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Outcomes of a Military Regional Multispecialty Synchronous Telehealth Platform and the Importance of the Dedicated Patient Presenter

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Abstract

Implementing a successful multispecialty synchronous telehealth program requires identifying and overcoming numerous barriers. One key aspect of synchronous telehealth involves the telehealth presenter; however, the impact that a dedicated patient presenter has supporting routine multispecialty synchronous telehealth is unknown.

Methods: We conducted a retrospective review of telehealth encounters conducted from a single regional medical center over a two-year period to 12 outlying health clinics which provided one of 3 levels of patient presenter support: category 1 locations had a dedicated telehealth registered nurse, category 2 locations had a nondedicated registered nurse or licensed vocational nurse, and category 3 locations were supported by an Army medic (military occupational specialty 68W).

Results: A total of 4,032 telehealth encounters occurred from January 2014 to December 2015 involving 26 distinct specialties located within a single regional medical center and 12 outlying health clinics which supported 60,232 beneficiaries. The 3 category 1 locations (3/12, 25%) supported the most telehealth encounters per month compared to either category 2 or category 3 locations ($P<.0001$). Category 1 and category 2 locations averaged a 239% and 122% year-to-year growth, respectively. Category 3 locations averaged a year-to-year decline of 11.7%.

Comment: This is the first study of which we are aware that has compared different patient presenter levels and evaluated its effect on telehealth activity. Regional medical centers initiating a multispecialty synchronous telehealth program should strongly consider hiring, educating, and placing dedicated presenters at patient originating sites.

Telehealth development and implementation within the military has continued to grow at a rapid pace. As part of the Army Campaign 2020, the US Army Medical Command (MEDCOM) has committed significant resources with the initiation of the Telehealth Service Line (THSL) in 2010 to develop and implement enterprise-level telehealth strategies.[1] While the majority of telehealth encounters in the military have either been specific for behavioral health or via an asynchronous or "store-and-forward" modality, telehealth can also encompass multispecialty synchronous or real-time patient interaction, remote patient monitoring, and mobile health.[2] For 2014-2016, the MEDCOM THSL directed efforts to expand a comprehensive patient-centered experience using a multispecialty synchronous platform; however, multiple barriers and challenges exist between regional medical centers and remote clinics where specialists and patients are located. One major challenge is creating a sustainable workflow process connecting both administrative and healthcare personnel at the originating site where the patient and presenter are located with the distant site where the specialist is located.[3] Unfortunately, there are no current dedicated telehealth positions on the US Army's organizational Table of Distribution and Allowances with the exception of the THSL headquarters located under the MEDCOM G-3/5/7 Patient Care Integration. Thus, regional health commands and local Army health clinics (AHCs) are left to determine how they can support telehealth. Many articles have discussed the roles and responsibilities of the telehealth presenter but we are unaware of specific reports describing differences in presenter capabilities and its effect on telehealth.[4-11] Herein, we report the results of a multispecialty synchronous telehealth program after developing 3 different categories of patient presenters. We also discuss specific aspects and lessons learned with dedicated patient presenters and their effect on regional telehealth efforts and workflow processes.

Methods

The primary objective of this retrospective review was to assess the number of clinical encounters per month in individual AHCs comparing 3 telehealth presenter categories. Secondary objectives assessed year-to-year telehealth activity and telehealth activity in locations prior to and after implementation of dedicated telehealth presenters. From January 2014 to December 2015, 98% (4,032/4,112) of synchronous telehealth encounters in Regional Health Command Europe (RHC-E) were conducted by healthcare providers located at the Landstuhl Regional Medical Center (K. H. W., unpublished data). Landstuhl Regional Medical Center (LRMC) is the regional strategic specialty medical platform supporting approximately 60,000 beneficiaries who are enrolled in 12 distant AHCs located in Germany, Italy, and Belgium (Figure 1). Prior to 2015, telehealth efforts in RHC-E were focused on behavioral health and surgical subspecialties. However, in part due to the reluctance of "frontline staff" to support telehealth as a routine component of patient care, the European Advancement for Regional Telehealth project was launched in late 2014, hiring 3 specifically trained telehealth presenters who supported a comprehensive medical, surgical, and behavioral health telemedicine platform.[3]

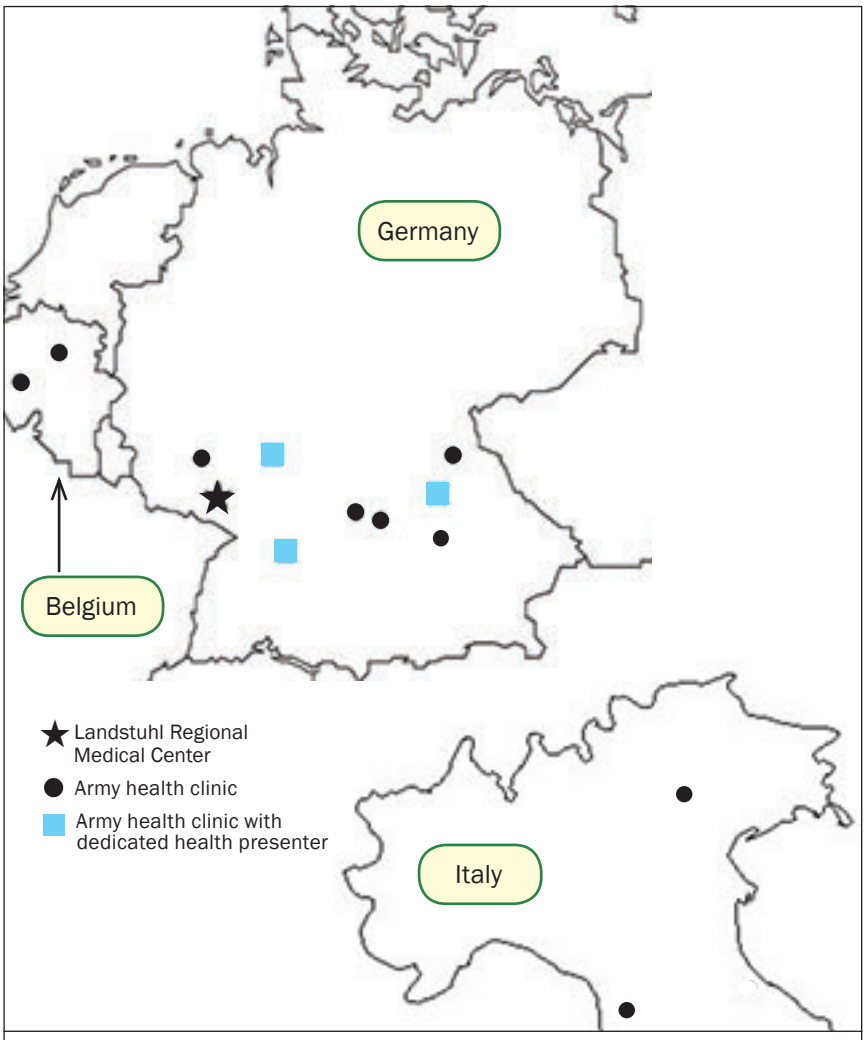

Figure 1. Locations of Army Regional Health Command–Europe Army health clinics.

One clear barrier at the initiation of regional telehealth efforts in 2013 centered on consistent patient presentation. Staffing the AHC primary care mission left few additional resources to support regional telehealth efforts, despite regional policies directing immediate priority to these efforts. Simply put, initial resistance to various pilot projects mirrored known telehealth barriers.[3] Secondary to these initial difficulties and lack of robust uptake, a GS-0610-10 position description was developed for a Registered Nurse (Clinical) Telehealth Nurse Care Coordinator (TNCC). Further, 3 categories for a telehealth patient presenter were established to model potential assets within the AHC: category 1 represented the dedicated registered nurse hired specifically to support a multispecialty telehealth platform within the AHC (ie, dedicated telehealth presenter); category 2 was a registered nurse or licensed vocational nurse (LVN) located within the clinic but telehealth was not their full time duty; category 3 was a military occupational specialty (MOS) 68W medic (Table 1). All clinics received an initial site visit, specific education, and competency assessment regarding the telehealth processes for each patient encounter. Hired in late 2014, Category 1 TNCCs spent an initial week with the regional telehealth team, individually met with each specialty service, developed service-specific standard operating procedures (SOPs) and presentations skills, engaged in weekly one-hour telehealth huddles with the regional telehealth nurse manager, and returned every 6 months for refresher training and new service development. Category 2 and 3 locations were assisted with telephonic, video teleconference, and in-person site visits as requested.

All telehealth visits regardless of location required written patient or parental consent. Synchronous telehealth visits conducted between patients and providers were performed on a secure, Health Insurance Portability and Accountability Act (HIPAA)-compliant video link. Each

AHC supporting telehealth had one standardized Polycom HDX 9000 Practitioner Cart (Polycom, Inc, San Jose, CA) which included an AMD-2500 General Exam Camera, AMD Fiberoptic Otoscope, and AMD Telephonic Stethoscope (AMD Global Telemedicine, Chelmsford, MA). All presenters, regardless of category, were trained on the use of all devices. Providers used a desktop computer installed with Polycom RealPresence software and camera (Polycom, Inc, San Jose, CA). Per current telehealth guidance, all clinic encounters at the patient site are coded as a 99499 visit with an originating site fee: HCPCS (Healthcare Common Procedure Coding System) Q3014.

Table 1. Telehealth presenter categories and Army health clinic (AHC) location.

TNCC category (**Nov** 2014-**Dec** 2015)	1	2	3
Skill level	Dedicated presenter (TNCC)	AHC nurse, LVN, or 68W medic	68W medic only
AHC location	Stuttgart (PCH) Vilseck (VSK) Wiesbaden (WBD)	Grafenwoehr (GFW) Katterbach (KTB) Shape (SHP) Vicenza (VCZ)	Baumholder (BHR) Brussels (BSL) Hoenfels (HHF) Illesheim (ILS) Livorno (LVO)
Median population (range)	8,236 (6,968-10,214)	6,157 (3,487-8,548)	1,884 (411-4,141)
Total population	25,418	24,349	10,465

TNCC indicates Telehealth Nurse Care Coordinator; LVN, licensed vocational nurse.

Briefly, patients arriving at their AHC for a telehealth visit follow standard clinic operating procedures (ie, checked-in, 2-patient identifier verification, placed in a HIPAA compliant exam room, vital signs obtained, medications reconciled, and consented for telehealth). At the allotted appointment time, both the originating site where the patient is located and the distant site (ie, LRMC specialist) dial-in to a video conference bridge. At that time, good audio and video is established, a unique access code is provided by the bridge technician to both parties, and the bridge technician signs out which "locks" the virtual exam room. Two-patient identifier, a 2016 Ambulatory Care National Patient Safety Goal, is established by the specialist and the appointment begins. Content such as educational slides for specific diagnoses can be virtually shared or emailed to the patient and presenter, respectively. At the request of the specialist, the presenter can perform a physical exam using a high-definition camera and peripheral medical devices to perform any aspect of the ear, eye, nose, throat, heart, lung, and skin exam. Category 1 dedicated telehealth presenters also have additional training for specialty-specific aspects of the history and physical exam (Table 2).

Table 2. Specialty-specific concepts used by category 1 TNCCs.

Specialty	Unique capabilities
Allergy/Immunology	Asthma control test; Allergen immunotherapy and omalizumab consent forms; spirometry,* peak flow measurement
Anesthesia/Preoperative	12-lead ECG, telestethoscope, Mallampati score
Cardiology	12-lead ECG, Holter event monitor*
Dermatology	Vibrent Teledermatology
Ear, Nose, and Throat	Fiberoptic laryngoscopy, whisper test, Weber and Rinne test
General surgery	Postoperative wound assessment, suture removal, dressing changes, wound VAC changes
Neurosurgery	Socrates, complete neurological exam, follow up xray
Occupational therapy	Goniometry, dynamometer
Orthopedics	Specialized shoulder exam (eg, Neers, O'Briens, Hawkins test), specialized knee exam, suture and splint removal, CAM boot, goniometry, follow up x-rays
Pediatric development	Head circumference
Plastic surgery	Body measurements for elective surgery
Podiatry	Suture/splint removal, CAM boot, goniometry for ankle range of motion
Pulmonary	Spirometry* and peak flow measurement
Sleep medicine	Epworth sleepiness scale, Friedman score, Mallampati score, neck circumference
Urology	Postoperative examination, Bladder ultrasound

*Depending on facility capabilities.
TNCC indicates Telehealth Nurse Care Coordinator; CAM, controlled ankle motion.

Study approval was obtained from the LRMC Human Research Protection Program. Descriptive statistics were used for demographic and AHC details. One-way ANOVA was used to assess differences for intra- and inter-TNCC category encounters. Population-corrected telehealth activity between locations was calculated using the 2-tailed Mann-Whitney U test. An α of less than 0.05 was considered statistically significant.

Results

From January 2014 and December 2015, 4,032 synchronous telehealth encounters occurred among 26 distinct specialties located within a single regional medical center and 12 outlying health clinics. Beneficiary population varied at each AHC with a median (range) of 4,184 (411-10,214) with a total beneficiary population of 60,232 (Table 1). The median (range) distance from outlying AHCs to LRMC was 366 (40-940) kilometers.

Regarding the 12 AHCs: from January to October 2014 (10 months) which was prior to hiring 3 category 1 dedicated patient presenters, 42% (5/12) were category 3 sites while

58% (7/12) were category 2 sites. From November 2014 through December 2015, the 5 category 3 sites remained category 3 while 43% (3/7) of category 2 sites were converted to category 1 sites with the hiring and placement of 3 dedicated telehealth registered nurses (Figure 2).

The 3 category 1 telehealth nurses worked in their respective clinics for the first 10 months of 2014 prior to being hired in a dedicated nurse presenter position, but were not engaged with patient presentation prior to being hired. Monthly telehealth encounters for November 2014 to December 2015 compared to the first 10 months of 2014 significantly increased in 75% (8/12) of clinics, was not significant in 25% (3/12) of clinics, and had significant decline in one clinic (Figure 2).

The 3 category 1 locations (3/12, 25%) performed the most telehealth encounters per month compared to either category 2 or category 3 locations (P<.0001) (Figure 3). There was no significant difference between the 3 category 1 locations in 2015 (P=.08) which observed an average year-to-year growth of 239.3%. Significant differences were observed within the 4 category 2 and 5 category 3 locations, respectively (P <.05), but category 2 locations supported significantly greater telehealth appointments compared to category 3 locations (P<.0001) with an average year-to-year growth of 122%. Category 3 locations had significant interclinic telehealth differences (P<.05) but experienced a year-to-year decline of 11.7% (Figure 3). Category 1 sites' activity as a percentage of all sites increased from an initial 34.9% to 75.7% from November 2014 to December 2015 (Figure 4).

Controlling for population size, 2 category 1 locations were not significantly different (P=.82). One category 1 site was not significantly different from one category 2 AHC (P=.45) and one category 3 AHC (P=.16). The percentage of the population utilizing telehealth per month did not exceed 1% with the exception of 2 category 1 sites (Vilseck and Wiesbaden) (Figure 5). For 2015, the mean (SD) percentage of the beneficiary population seen via telehealth at category 1, 2, and 3 sites were 7.04 (4.65) %, 3.0 (1.43) %, and 1.9 (1.22) %, respectively (P<.05). When comparing one AHC to another AHC there were a number of locations that were statistically distinct from one another (Table 3).

Estimated travel distance, travel expenses, and days missed if each patient visit was based on a single individual travelling to LRMC for their visit from November

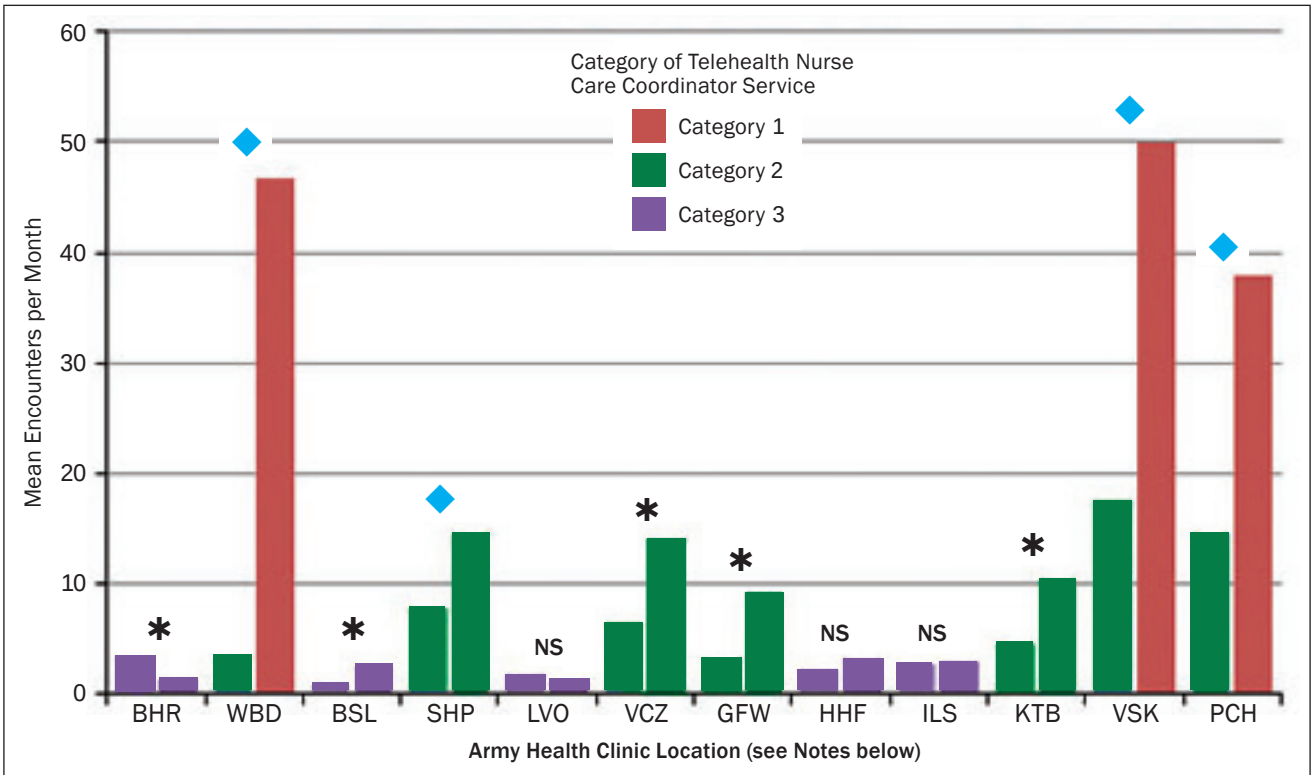

Figure 2. Comparison of mean telehealth encounters per month at Army health clinics prior to and after hiring 3 Category 1 telehealth nurses.

Notes: ✱ indicates P<.05; ◆ indicates P<.0001; NS indicates not significant.
Army health clinic locations and associated identifiers are listed in Table 1.

2014 through December 2015 equaled 1.65 million kilometers driven, $1.13 million in travel expenses, and 4,365 work days missed (Table 4).

COMMENT

Telehealth can encompass a number of modalities, but multispecialty synchronous or real-time telehealth currently provides the best patient satisfaction.[12] Further, synchronous telehealth fosters the patient-physician relationship through direct communication.[13] To be successful, sustainable, and robust, synchronous telehealth encounters require the provider, patient, and patient presenter. Previous studies have demonstrated how the patient presenter can streamline patient presentations for specialists, but we are unaware of any studies which have compared different levels of patient presenters.[14,15]

One of the main obstacles for telehealth is achieving the acceptance of patient originating sites.[3] It is clear that close working relationships between the medical neighborhood containing specialists and the primary care home is paramount. Herein, we observed that as the "dedication" and presenter category increased, so did the number of telehealth visits even when controlling for population size. Dedicated telehealth presenters functioned as local and, in many instances, subregional telehealth champions providing feedback to local providers in morning huddles, interacting weekly with the regional telehealth office, and refining workflow processes and examination skills with specialists (Table 2).

The decision to hire a dedicated telehealth presenter is often the subject of concern with questions about return of investment (ROI). These are appropriate questions, but travel expenses, school days missed, work days, decreased deferral to the network, and increased medical and surgical recapture should be included in ROI assessments, as well as work relative value units generated.

As a retrospective review, we acknowledge that there are a number of limitations of this study. First, perhaps the same outcomes could be obtained with a dedicated LVN or dedicated MOS 68W medic instead of the registered nurses who were hired. The purpose of the registered nurse was to allow significant expansion of the clinical exam under the training and guidance of the specialist. In fact, as part of the biannual training, category 1 nurses gained specialty-specific skills which would not be permitted with a lower skill level. Further, a registered nurse can conduct and document in the electronic health record any aspect of the physical exam required by the specialist.

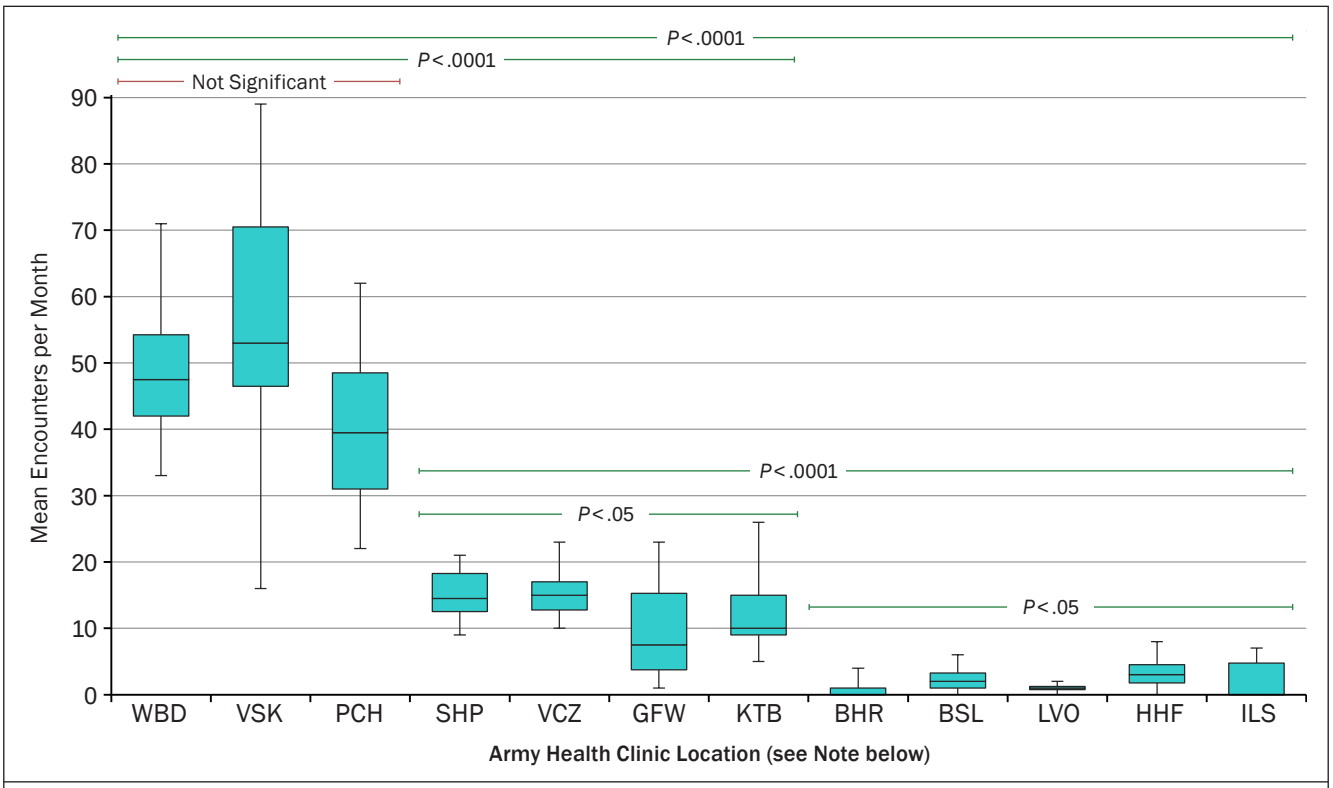

Figure 3. Mean and interquartile plot of monthly mean telehealth encounters within Army health clinics.
Note: Army health clinic locations and associated identifiers are listed in Table 1.

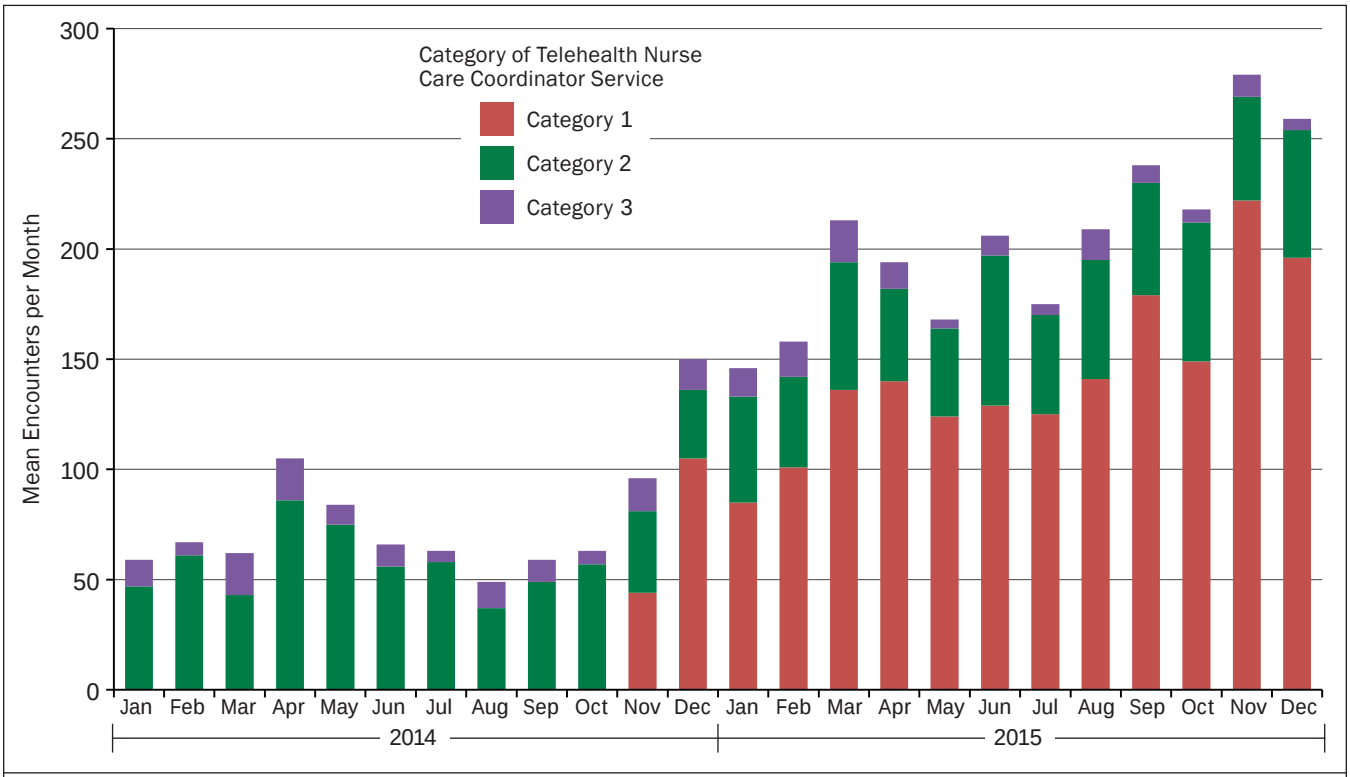

Figure 4. Number of telehealth encounters supported by month based on telehealth nurse category.

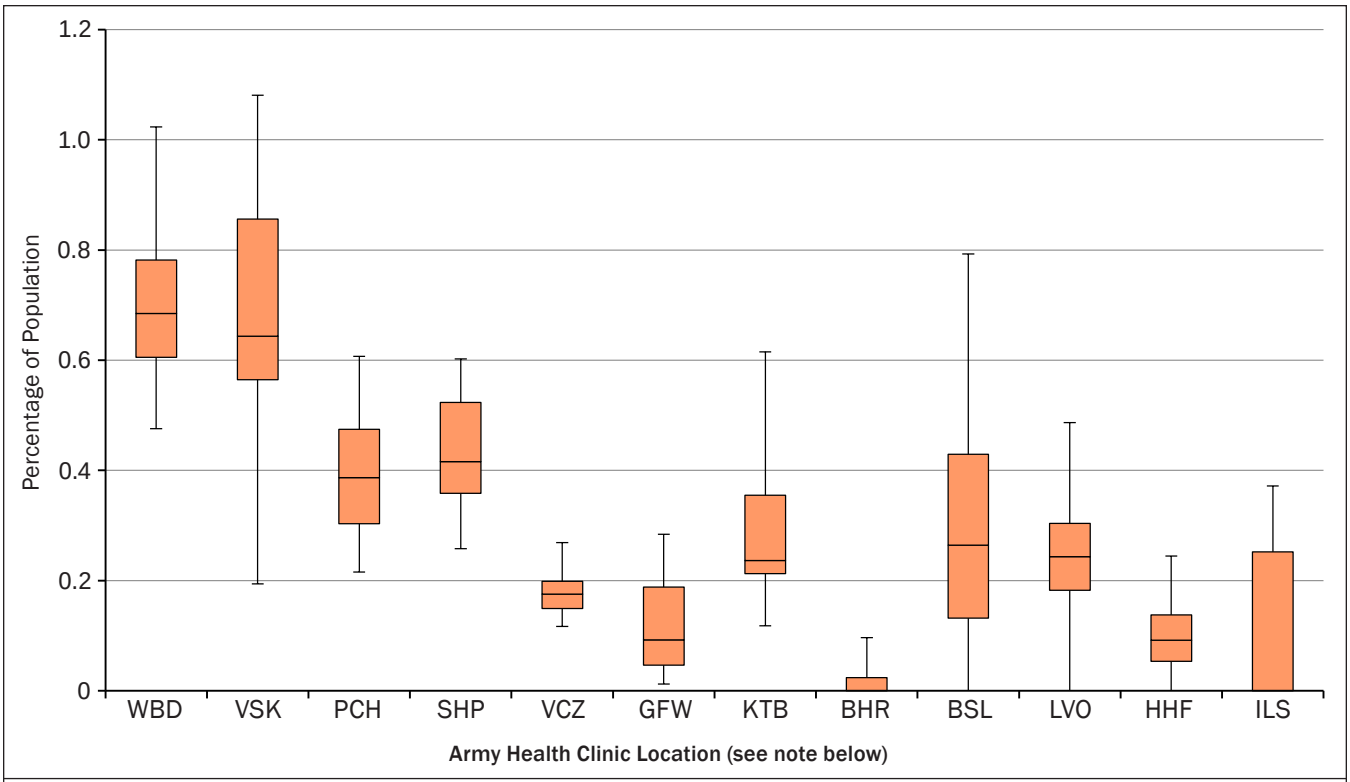

Figure 5. Percentage of population using telehealth monthly.
Note: Army health clinic locations and associated identifiers are listed in Table 1.

Second, the 3 AHCs with a category 1 registered nurse were the initial starting locations for each specialty, thereby increasing at least initial monthly activity. While overall telehealth activity increased in 5 category 2 and 3 locations, there were 2 locations which, when corrected for population size, were not statistically significant from one category 1 site: Shape and Brussels AHCs (Table 3). The Shape clinic specifically prioritized telehealth by identifying and placing a nurse in mid-2015 to be dedicated to the telehealth mission. Brussels AHC was the second smallest clinic site, resulting in a much smaller denominator which could significantly skew population-based percentage calculations as noted by its wider variation of monthly encounters (Figure 5).

Table 3. Population-corrected comparison between telehealth sites and monthly telehealth encounters (January-December 2015). Note: Army health clinic locations and associated identifiers are listed in Table 1.

	VSK	PCH	SHP	VCZ	GFW	KTB	BHR	BSL	LVO	HHF	ILS
WSD	0.82	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖
VSK		◆	✸	✖	✖	◆	✖	◆	◆	✖	✖
PCH			0.45	✖	✖	✸	✖	0.16	✸	✖	◆
SHP				✖	✖	◆	✖	0.051	◆	✖	◆
VCZ					0.06	✸	✖	0.24	0.17	✸	0.37
GFW						◆	✖	✸	0.09	0.89	0.37
KTB							✖	0.75	0.89	✖	✸
BHR								✖	✸	◆	0.93
BSL									0.27	◆	✸
LVO										✸	0.10
HHF											0.67

✸ indicates $P<.05$; ◆ indicates $P<.01$; ✖ indicates $P<.001$

Three category 1 presenters (authors I. B., R. S., and B. C.) were queried regarding their observations within their respective AHCs. One of the most important aspects is to ensure that there is an alternate presenter who, in case of personal illness or other reasons, is able to present patients. Regarding patients who are typically in a remote or small military installation, the opportunity to travel to the regional medical center located within a larger urban shopping location is a frequently identified factor. Some patients also have expressed the desire to visit the specialist in a typical "brick and mortar" location which is often the local host nation provider close to where the patient lives. Additional ancillary services such as pulmonary function testing, Wood's lamp, ultrasound, and computed tomography may not be available in some AHCs, resulting in the requirement for some patients to visit the host nation university hospital or LRMC. In a recent publication, it was noted that none of the outlying AHCs in RHC-E had the capability to perform pulmonary function testing, a basic component of asthma management.[16] Finally, there is no direct financial cost incurred by the Soldier's unit or AHC for the patient to see a host nation provider, as the costs are covered by TRICARE. Thus, an unexpected cost of increased telehealth activity is an increased likelihood of a recommendation that the patient travel to LRMC, thereby directly affecting the unit's budget. However, one published study from an LRMC specialty observed that telehealth resulted in less than one-quarter of new and follow up visits requiring an in-person visit, thereby saving costs and improving individual readiness.[16] On the other hand, difficulties with obtaining timely and translated medical records coupled with minimal time lost from work when using synchronous telehealth in an individual's local AHC is clearly nested in the Chief of the Army's priority of readiness.[17]

Table 4. Estimates of per month travel-related distances and per diem costs associated with documented encounter data.

Category	AHC Location[a]	No. of Encounters		Estimated Travel Costs		
		Before TNCC[b]	After TNCC[c]	Kilometers Traveled (roundtrip)	Missed Work Days	Per Diem Costs (USD)
1	WBD	3.1	46.6	9,981.6	46.6	3,443.6
	VSK	17.4	50.1	37,753.9	100.1	25,542.9
	PCH	14.6	37.9	15,702.4	37.9	9,210.2
Category 1 totals		35.1	134.6	63,437.9	184.6	38,196.7
2	SHP	7.7	14.5	10,875.0	29.0	9,551.9
	VCZ	6.4	14.1	22,514.3	42.2	18,292.9
	GFW	3.1	9.2	7,279.3	18.4	4,814.9
	KTB	4.6	10.4	5,613.6	20.7	4,008.1
Category 2 totals		21.8	48.2	46,282.2	110.3	36,667.8
3	BHR	3.3	1.3	102.9	0.6	35.5
	BSL	0.7	2.5	1,750.0	5.0	1,603.8
	LVO	1.8	1.1	2,250.0	5.4	1,847.7
	HHF	2.3	3.1	2,309.7	3.1	1,564.7
	ILS	2.7	2.8	1,526.6	2.8	1,083.8
Category 3 totals		10.8	10.8	7,939.2	16.9	6,135.5
Categories 1, 2, 3 totals		67.7	193.6	117,659.3	311.8	81,000.0
Estimated cost totals, Nov 2014-Dec 2015				1,647,230.2	4,365.2	1,134,000.0

AHC indicates Army health clinic; TNCC indicates telehealth nurse care coordinator.

Notes:
a. Army health clinic locations and associated identifiers are listed in Table 1.
b. Per month for the first 10 months of 2014.
c. Per month for 14 months, (November 2014 through December 2015).

Telehealth remains a top MEDCOM policy and has the ability to leverage technology to provide services and access to specialists that otherwise are limited or require extensive travel to reach. However, telehealth faces numerous obstacles and challenges, both from providers and staff at both originating and distant sites. We observed the direct impact of the dedicated patient presenter who, over 14 months, was the key to solving many challenges within the AHC, the regional telehealth office, and communication between patients and specialty providers. The telehealth presenter should be considered a vital member of the synchronous telehealth encounter, and we recommend that other regional medical centers developing multispecialty synchronous telehealth platforms ensure appropriate identification and hiring of dedicated patient presenters.

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A Retrospective Analysis: Do Bacterial Culture and Sensitivity Data Support Empiric Use of Piperacillin-Tazobactam and Antipseudomonal Fluoroquinolones in Hospitalized Patients?

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The mortality benefit of early recognition of infection with empiric initiation of antibiotics is well documented.[1] *Pseudomonas aeruginosa* has been a particularly problematic bacterial infection whose antibiotic resistance is increasing at an alarming rate.[2] Inappropriate empiric antibiotic coverage of *Pseudomonal* blood stream infections has shown mortality rates as high as 43.4%.[3] This high mortality rate, in addition to prior studies showing an increased mortality rate with empiric monotherapy,[4-6] has led to empiric combination antimicrobial coverage becoming the clinical standard for suspected infection with gram-negative bacteria. "Double coverage" for *Pseudomonas* infection usually includes the addition of an antipseudomonal fluoroquinolone or aminoglycoside to an antipseudomonal beta-lactam.

At our institution as well as other military and civilian medical centers, it is common to use the antipseudomonal beta lactam piperacillin-tazobactam in combination with a fluoroquinolone for empiric gram-negative coverage. Fluoroquinolones are commonly selected for double coverage due to the ease of dosing, decreased monitoring, and decreased toxicity (compared to aminoglycoside agents). Our institution provides an annual cumulative antimicrobial susceptibility report to estimate percentages of resistance of a particular organism to an antibiotic. Based on the William Beaumont Army Medical Center (WBAMC) 2015 antimicrobial susceptibility report,* 88% of *Pseudomonas* isolates were susceptible to piperacillin-tazobactam, 77% of isolates were susceptible to levofloxacin, and 79% of isolates were susceptible to ciprofloxacin. In order for our current strategy of double coverage to be effective, (ideally) the 12% of *Pseudomonas* isolates not susceptible to piperacillin-tazobactam would be susceptible to levofloxacin or ciprofloxacin.

We conducted a 6-month retrospective record review to determine whether there is bacterial culture data to support our initial empiric gram-negative double coverage with extended antipseudomonal beta-lactam (piperacillin-tazobactam) and fluoroquinolones (ciprofloxacin and levofloxacin) in our military hospital patient population.

Based on our institution's antiobiogram, a previous study showing no benefit in *Pseudomonas* coverage with use of an antipseudomonal fluoroquinolone and antipseudomonal beta-lactam,[7] along with our knowledge of mechanisms of resistance, led us to hypothesize that providing "double coverage" for empiric *Pseudomonas* coverage with floroquinolones in addition to piperacillin-tazobactam would provide no additional coverage.

Methods

We examined 6-months of culture and sensitivities data of *Pseudomonas* bacteria from urine, blood, sputum, wound, joint, or body fluid in our hospitalized patient population.

Exclusion criteria for our study were cultures from patients under the age of 18; concomitant gram-positive organisms; and gram-negative organisms other than *Pseudomonas, Proteus, Klebsiella,* and *E coli.* Isolates from same anatomical site or person were included as separate data points, only if these isolates are phenotypically different.

The terms "susceptible" and "resistant" are determined by standard Clinical and Laboratory Standards Institute (http://clsi.org/) guidelines, and criteria used by the WBAMC lab. Culture and sensitivities are reported as

*WBAMC Cumulative Antimicrobial Susceptibility Report: 1Jan2015-31Dec2015. Internal medical facility document not readily accesible by the general public.

"susceptible," "intermediate," or "resistant." Susceptible is defined as having been found as susceptible based on reported culture data. Given that intermediate sensitivities indicate the level of antibiotic needed to achieve the maximum inhibitory concentration approaches or exceeds the level of antibiotic that can ordinarily be achieved,[8] "resistant" included sensitivities reported as intermediate or resistant.

Over a 6-month period, 64 *Pseudomonas* isolates that were sensitive or resistant to levofloxacin, ciprofloxacin, and piperacillin-tazobactam were identified. The cultures that were identified as resistant to Piperacillin-tazobactam were then further evaluated for susceptibility to levofloxacin or ciprofloxacin.

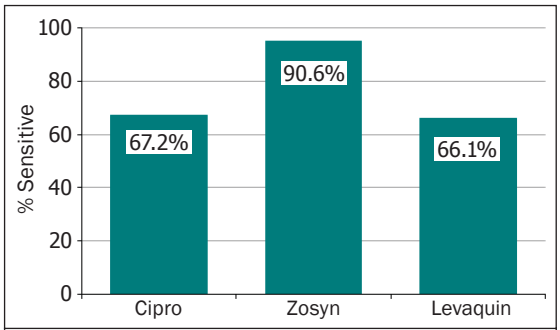
Results

A total of 64 isolates of *Pseudomonas* were identified during a 6-month period. Of these, 32 were from urine, 11 from sputum, 12 from wound cultures, 3 from blood, and 6 from body fluid cultures. Of the cultures, 57 isolates were of *Pseudomonas auerginosa* and 7 isolates of *Pseudomonas putida*.

Of the 64 isolates of *Pseudomonas* identified, 90.6% (58/64) of isolates were susceptible to piperacillin-tazobactam, 66.1% (42/64) to levofloxacin, and 67.2% (47/64) susceptible to ciprofloxacin. The results are graphically represented in the Figure. Four of the isolates were multidrug resistant organisms resistant to all fluoroquinolones and beta-lactams. Of the 6 isolates resistant to piperacillin-tazobactam, none of those isolates were susceptible to fluoroquinolones.

Comment

Our initial hypothesis questioning the efficacy of empiric double coverage of suspected pseudomonal infections was confirmed by our 6-month retrospective review. None of the 64 isolates cultured were resistant to piperacillin-tazobactam but sensitive to fluoroquinolones. This suggests there is no additional coverage or benefit conferred with empiric *Pseudomonas* double coverage with an antipseudomonal beta-lactam and an antipseudomonal fluoroquinolone in our hospital population. Fluoroquinolone use has associated with adverse effects including QT prolongation, photoxicity, tendon rupture, gastrointestinal discomfort, headache, confusion, and delirium.[9] These side effects, coupled with the fact that no antibacterial coverage improvement is achieved, would indicate that double coverage for suspected *Pseudomonal* infection within our hospital patient population would produce more harm than benefit.



Pseudomonas sensitivity.
Note: Cipro is ciprofloxacin; Zosyn is pipercilin-tazobactam; Levaquin is levofloxacin.

The resistance of *Pseudomonas* isolates to fluoroquinolones when concomitantly resistant to piperacillin-tazobactam is unsurprising when examining the mechanism by which resistance of the bacteria is developed. Fluoroquinolone resistance occurs with mutations to the AmpR gene that negatively regulate the Mex-EF-OprN efflux which can pump out fluoroquinolones, or changes in the quinolone target of type II topoisomerase or type IV topoisomerase. Beta-lactam resistance is also mediated in part by the AmpR gene by positively regulating AmpC production of beta-lactamase. AmpR is a major part of *Pseudomonas* genome, and is one of the few genes that may confer resistance to multiple antibiotic classes, including beta-lactams and fluoroquinolones.[10]

Although this study meets the 30-isolate standard set by the Clinical and Laboratory Standards Institute M39-A2 recommendations for cumulative antiobiogram preparation,[11] the study could be improved by an increased sample size, either through duration of retrospective review or enrollment of a larger population pool from which to extract *Pseudomonas* isolates. Also, future studies may seek to identify which antibiotics can confer the greatest additional antibacterial coverage in the setting of resistance to antibiotics used for empiric therapy, thereby creating a double coverage regimen that would provide benefit to the patient.

This study brings to the forefront inappropriate antibiotic use for a common hospital infection. Previously an afterthought, this empiric double coverage can lead to the emergence of new multidrug resistant antibiotics,[12] as well as exposing a patient to a medication with significant side effects with no concurrent medical advantage in therapy. Based on our institution's culture data, we advocate that each institution reevaluate the empiric double coverage of gram-negative bacteria with the addition of an antipseudomonal fluoroquinolone or amino-glycoside to an antipseudomonal beta-lactam based on their specific patient subset.

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Low Prevalence of Carbapenem-Resistant Enterobacteriaceae Among Wounded Military Personnel

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ABSTRACT

Multidrug-resistant organisms (MDROs) are a global health problem that affect both civilian and military populations. Among wounded warriors, MDROs further complicate the care of trauma-related infections, resulting in extended duration of hospitalization, as well as increased morbidity and mortality. During the wars in Iraq and Afghanistan, extended spectrum β-lactamase-producing Enterobacteriaceae were frequently isolated from wounded warriors. The potential emergence of difficult-to-treat carbapenem-resistant Enterobacteriaceae represented a serious challenge for clinicians. We examined carbapenem-resistant Enterobacteriaceae prevalence among wounded military personnel over a 6-year period (2009-2015). Among 4090 Enterobacteriaceae isolates collected, 16 (0.4%) were carbapenem-resistant, of which the majority was *Enterobacter aerogenes* (44%) followed by *Klebsiella pneumoniae* (37%), and *Escherichia coli* (19%). Five isolates (31%) collected from 2 patients were carbapenemase-producers with one associated with an infection. All 5 carbapenemase-producing isolates were resistant to all tested carbapenems and each carried one carbapenemase gene (4 with blaKPC-3 and 1 with blaNDM-1). Overall, although a large number of Enterobacteriaceae isolates were collected, only a small proportion was carbapenem-resistant and data indicate a lack of a cluster. Due to these limited numbers, it is difficult to make any conclusions regarding the association between carbapenem resistance, antibiotic exposure, and clinical outcomes.

Colonization and infection with multidrug-resistant organisms, including extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, are a global health problem and frequently complicate the care of wounded military personnel.[1-6] Examination of surveillance cultures collected from wounded military personnel on admission to Landstuhl Regional Medical Center (LRMC) in Germany and military hospitals in the United States recovered 2,065 colonizing isolates. The predominant organisms were *Escherichia coli* and *Klebsiella pneumoniae* (50% and 9%, respectively), of which 37% and 22% were ESBL-producers.[7]

Recently, the emergence of carbapenem-resistant Enterobacteriaceae (CRE) has become an additional threat associated with difficult-to-treat infections, high mortality rates, and potential for wide transmission.[8-17] In an analysis of healthcare-associated infections in the United States, 2%, 2%, and 8% of *E coli*, *Enterobacter* spp, and *K pneumoniae* associated with surgical site infections were resistant to carbapenems, respectively.[8] The rising prevalence of CREs has further complicated patient care in the military health system. Surveillance of Department of Defense (DoD)-managed medical facilities within the United States and overseas reported a mean annual CRE incident rate of 0.49 per 100,000 patient-years. It was noted that the proportion of CRE increased from 0.033% in 2005 to 0.052% in 2012, with a steady rise in the proportion of carbapenem-resistant *Klebsiella* spp between 2005 and 2010.[9] Furthermore, approximately 1% of *E coli* and 8% of *K pneumonia*e isolates recovered from US military personnel and Afghan nationals treated at a deployed US military hospital in Afghanistan were carbapenem-resistant.[18]

As more combat casualties are surviving grievous injuries, the rate of trauma-related infections has increased.[19] With complicated, polymicrobial wounds, the prevalence of multidrug-resistant organisms provides a challenge to clinicians treating wounded warriors. As carbapenems

are often used to treat gram-negative infections resistant to broad-spectrum antibiotics, the emergence of CREs is a cause for concern. As a result, we determined the prevalence of CREs among wounded military personnel and evaluated carbapenem resistance mechanisms.

Methods

As part of the US DoD-Department of Veterans Affairs, Trauma Infectious Disease Outcomes Study (TIDOS),[19] isolates were collected from military personnel injured during deployment and medically evacuated to LRMC before being transferred to a participating military hospital in the United States (the Walter Reed National Military Medical Center* or San Antonio Military Medical Center†). All collected isolates were stored in a microbiological repository. Our analysis was restricted to Enterobacteriaceae isolates collected between June 1, 2009, and April 31, 2015. Isolates were classified as infecting if they were recovered from infection work-ups. Surveillance specimens were obtained from groin/axilla swabs performed within 2 days of hospital admission either at LRMC or the participating military hospitals in the United States. Multidrug resistance was defined as resistance to at least 3 of 4 antibiotic classes, ESBL production, or carbapenemase production.[20] For the purpose of our study, carbapenem resistance was defined as resistance to all carbapenems tested (ie, meropenem, imipenem, doripenem, and ertapenem). Information related to infections, treatment, and outcomes was retrieved from the TIDOS infectious disease module,[19] which supplements the Department of Defense Trauma Registry.[21]

Table 1. PCR Oligonucleotide Primers for the Amplification of Carbapenemase Genes.

Gene	Primer Sequence (5'-3')	Product Size (base pair)
blaIMP	F: GGAATAGAGTGGCTTAAYTCTC R: GGTTTAAYAAAACAACCACC	232
blaSPM	F: AAAATCTGGGTACGCAAACG R: ACATTATCCGCTGGAACAGG	271
blaAIM	F: CTGAAGGTGTACGGAAACAC R: GTTCGGCCACCTCGAATTG	322
blaVIM	F: GATGGTGTTTGGTCGCATA R: CGAATGCGCAGCACCAG	390
blaOXA	F: GCGTGGTTAAGGATGAACAC R: CATCAAGTTCAACCCAACCG	438
blaGIM	F: TCGACACACCTTGGTCTGAA R: AACTTCCAACTTTGCCATGC	477
blaBIC	F: TATGCAGCTCCTTTAAGGGC R: TCATTGGCGGTGCCGTACAC	537
blaSIM	F: TACAAGGGATTCGGCATCG R: TAATGGCCTGTTCCCATGTG	570
blaNDM	F: GGTTTGGCGATCTGGTTTTC R: CGGAATGGCTCATCACGATC	621
blaDIM	F: GCTTGTCTTCGCTTGCTAACG R: CGTTCGGCTGGATTGATTTG	699
blaKPC	F: CGTCTAGTTCTGCTGTCTTG R: CTTGTCATCCTTGTTAGGCG	798

Isolate identities and antimicrobial susceptibilities were determined utilizing the BD Phoenix automated microbiology system and NMIC/ID-304 panels (BD Biosciences, Sparks, MD). As the BD Phoenix system does not report susceptibility results for certain bacteria/antibiotic combinations, E-test was also performed for all carbapenems.[22] Pulsed-field gel electrophoresis (PFGE) was conducted for genotyping in accordance with standard practices. Three multiplex PCRs for the detection of carbapenemase genes were performed using previously described primers (Table 1).[23] The PCRs were carried out with the following conditions: 5 minutes at 94ºC, 30 cycles of 30 seconds at 94ºC, 40 seconds at 56ºC, and 50 seconds at 72ºC, followed by 5 minutes at 72ºC.

The Neo-Rapid CARB Kit (Rosco Diagnostica, Taastrup, Denmark) was used to identify carbapenemase-producing isolates, which were sent to the Multidrug-Resistant Organism Repository and Surveillance Network (MRSN) for whole genome sequencing using the Illumina MiSeq platform. Paired-end sequencing of short (550 bp) and mate-paired sequencing of long (2-10 kilobase [kb]) genomic fragments was performed to obtain finished bacterial genomes. The genes encoding carbapenem resistance were identified along with other antibiotic resistance genes by BLASTN analysis using comprehensive web-based microbial annotation resources and pipelines developed internally by MRSN.

Results

A total of 4090 Enterobacteriaceae isolates were collected from June 2009 through April 2015 (Table 2). Examination of antimicrobial susceptibility determined that 1391 isolates (34%) were multidrug-resistant and 1302 (32%) were classified as infecting. *E coli* was the most common (51%), followed by *K pneumoniae* (13%) and *Enterobacter cloacae* (12%).

A total of 141 isolates (3.4% of 4090) were resistant to at least one carabapenem; however, only 16 isolates (0.4% of 4090) were resistant to all tested carbapenems (100% resistant to doripenem, ertapenem, imipenem, and meropenem) with 50% associated with infections (Table 2). *Enterobacter aerogenes* (44%) was predominant, followed by *K pneumoniae* (37%) and *E coli* (19%). All carbapenem-resistant isolates were ESBL-producers. Twelve isolates (75%) were susceptible to amikacin, 9

*Prior to their consolidation to become the Walter Reed National Medical Center in September 2011, both the Walter Reed Army Medical Center and the National Naval Medical Center received patients from LRMC.

†The Brooke Army Medical Center became part of the newly established San Antonio Military Medical Center in September 2011.

(56%) to gentamicin, 5 (31%) to nitrofurantoin, 4 (25%) to tetracycline, and 1 (6%) to tobramycin. All *E aerogenes* isolates were also susceptible to levofloxacin. The 16 isolates were recovered from 7 deployed military personnel, of which 6 were wounded in Afghanistan and one was injured in Naples, Italy. Except for one isolate obtained from LRMC, the carbapenem-resistant isolates were collected from surveillance swabs or clinical cultures obtained at military hospitals in the United States (94%). The proportion of the 16 isolates varied annually, with 3 (19%) collected in 2009 (June-December), 4 (25%) in 2010, none in 2011, 5 (31%) in 2012, 3 (19%) in 2013, and one (6%) in 2014.

Table 2. Most Common Enterobacteriaceae Collected from Wounded Military Personnel (2009-2014) with a Focus on Carbapenem Resistance.

Organisms[a]	Surveillance (%)	Infecting (%)	Total (%)
Escherichia coli	1608 (57.7)	495 (38.0)	2103 (51.4)
Resistant to ≥1 carbapenem	12 (0.7)	9 (1.8)	21 (1.0)
Carbapenem-resistant *E coli*[b]	**0**	**3 (0.6)**	**3 (0.1)**
Klebsiella pneumoniae	391 (14.0)	150 (11.5)	541 (13.2)
Resistant to ≥1 carbapenem	15 (3.8)	7 (4.7)	22 (4.1)
Carbapenem-resistant *K pneumoniae*[b]	**5 (1.3)**	**1 (0.7)**	**6 (1.1)**
Enterobacter cloacae	227 (8.1)	284 (21.8)	511 (12.5)
Resistant to ≥1 carbapenem	6 (2.6)	6 (2.1)	12 (2.3)
Carbapenem-resistant *E cloacae*[b]	**0**	**0**	**0**
Enterobacter aerogenes	232 (8.3)	125 (9.6)	357 (8.7)
Resistant to ≥1 carbapenem	17 (7.3)	20 (16.0)	37 (10.4)
Carbapenem-resistant *E aerogenes*[b]	**3 (1.3)**	**4 (3.2)**	**7 (2.0)**
Serratia marcescens	76 (2.7)	120 (9.2)	196 (4.8)
Resistant to ≥1 carbapenem	3 (3.9)	14 (11.7)	17 (8.7)
Carbapenem-resistant *S marcescens*[b]	**0**	**0**	**0**
Total Enterobacteriaceae[c]	2788	1302	4090
Total Enterobacteriaceae resistant to ≥1 carbapenem	70 (2.5)	71 (5.5)	141 (3.4)
Total Carbapenem-Resistant Enterobacteriaceae[b]	**8 (0.3)**	**8 (0.6)**	**16 (0.4)**

Notes:
a. The percentage of carbapenem-resistant isolates for each organism is calculated using the totals for that specific organism.
b. Carbapenem-resistant Enterobacteriaceae are defined as being resistant to all tested carbapenems (ie, meropenem, imipenem, doripenem, and ertapenem).
c. Only the top 5 organisms are presented so the total for the overall Enterobacteriaceae is greater than the sum of the columns.

Examination of PFGE results showed that all patients carried different strains of the Enterobacteriaceae organisms, indicating a lack of a cluster. Furthermore, no patients carried two or more different strains within the same genus. When serial isolates collected from patients were assessed, there were no genotypic changes.

Five *K pneumoniae* isolates were carbapenemase-producers, of which 4 were from surveillance cultures (3 from groin and one rectum) and one was associated with a pneumonia (collected from bronchoalveolar lavage). In addition, 4 were serial isolates from one patient collected at 2 separate facilities, including the infecting isolate recovered at Walter Reed National Military Medical Center 3 days after the patient's first positive groin culture at LRMC. One patient sustained a gunshot wound in the Afghanistan combat theater and the other was injured in a fall while stationed in Naples, Italy. The 5 carbapenemase-producing *K pneumoniae* isolates were sent to MRSN for further testing and carbapenemase genes were identified. The PCR results found that one isolate carried the blaNDM gene, while the remaining 4 isolates from a single patient carried a blaKPC gene.

Whole genome sequencing of the 5 carbapenemase-producing *K pneumoniae* isolates revealed that the 4 serial isolates (from the same patient) were genetically identical and represented a single clone (collected in 2012). Specifically, the 4 isolates belonged to MLST ST-258 and carried the carbapenemase gene blaKPC-3 on an approximately 78 kb plasmid that shared more than 98% homology to the previously described plasmid pKpQIL-LS6.[24] The single isolate from another patient belonged to MLST ST-11 (collected in 2014) and carried the carbapenemase gene blaNDM-1 on an approximately 73.5 kb plasmid that shared more than 95% homology to plasmid pS-300cz (Genbank Accession # KJ958927).

Two surveillance isolates amongst the serial carbapenemase-producing *K pneumoniae* isolates from one patient were collected prior to treatment with meropenem, suggesting that the strain already carried the resistance gene and that meropenem exposure did not induce carbapenem resistance. For this patient, a carbapenem-susceptible *K pneumoniae, Staphylococcus aureus,* and *Acinetobacter baumannii-calcoaceticus* complex isolates were associated with the same pneumonia along with the carbapenemase-producing *K pneumoniae.* Treating this patient with ampicillin-sulbactam, meropenem, and vancomycin cleared the infection during inpatient hospitalization.

Comment

Carbapenem-resistant Enterobacteriaceae are becoming more widespread in healthcare facilities in the United

States and have been associated with high rates of mortality.[8-11,25,26] While the rate of carbapenem resistance is still low, the rising prevalence is concerning. As a result, we examined isolates for carbapenem resistance collected from military personnel wounded during deployment in support of operations in Iraq and Afghanistan. Although a large number of Enterobacteriaceae isolates were collected from combat casualties over a study period of approximately 6 years, only 16 (0.4%) were carbapenem-resistant. The distribution of isolates across the study years and molecular typing findings indicate a lack of a carbapenem-resistant Enterobacteriaceae cluster with this wounded military population.

Prior to 2000, recovery of CREs was rare in the United States; however, within the past decade, an increase in the incidence of CREs has been observed. Specifically, according to the National Healthcare Safety Network, the proportion of CREs in US acute care hospitals rose from 1.2% in 2001 to 4.2% in 2011 with *Klebsiella* spp having the highest increases (1.6% to 10.4%, respectively).[25] Localized hospital outbreaks have also been reported in multiple states, including New York, Colorado, Illinois, and West Virginia.[26-31] It is notable that our analysis reports a lower proportion of CREs (0.4%) in combat casualties compared to findings from civilian US hospitals, and may be the result of environmental factors or the approach to infection control.

Nonetheless, the proportion of CREs in our analysis is higher than previous surveillance reports from DoD-managed medical facilities (overall proportion of 0.055% over a period of 2005 to 2012). With regards to specific organisms, the proportion of carbapenem-resistant *E coli*, *K pneumoniae*, and *Enterobacter* spp (*E aerogenes* and *E cloacae*) in our study (0.14%, 1.11%, and 0.81%, respectively) is also higher compared to the prior surveillance reports (0.041%, 0.116%, and 0.163%, respectively).[9]

Following recognition of increased carbapenem resistance due to widespread transmission of the blaNDM-1 gene, a military health system surveillance program was implemented in 2010, resulting in the screening by MRSN of all carbapenem-resistant isolates for the gene. Approximately 13 hospitals, including 5 in combat zones, submitted isolates for screening. In 2011, the first reported identification of the blaNDM-1 gene was identified in *Providencia stuartii* isolates recovered from an Afghan national burn patient treated at a US/coalition combat support hospital in Bagram, Afghanistan.[32,33] A low number of carbapenem-resistant *K pneumoniae* isolates (4.2%) have also been collected from hospitals in Iraq; however, none were found to carry the blaNDM-1 or blaKPC-3 genes.[34]

Five (0.1% of all Enterobacteriaceae isolates; 32% of CRE isolates) carbapenemase-producing *K pneumoniae* isolates were identified in our study. The 5 carbapenemase-producing isolates were recovered from 2 patients and one isolate was associated with an infection (ie, pneumonia). All 5 isolates were resistant to all tested carbapenems and each isolate carried one carbapenemase gene, indicating that carbapenem resistance was due to the presence of the resistance genes. Specifically, 4 isolates carried blaKPC-3 while blaNDM-1 was only identified with one isolate. The patient with the isolates carrying blaKPC-3 sustained injuries in Naples, Italy, and was treated initially at a Naples hospital. As a carbapenem-resistant ST258 *K pneumoniae* strain carrying blaKPC-3 has been previously reported in Italy,[24] there is the potential that the carbapenemase-producing *K pneumoniae* isolates were acquired through hospital transmission by the injured service member. To the best of our knowledge, this is the first report of *K pneumoniae* isolates carrying blaNDM-1 recovered from military personnel wounded in Afghanistan.

Due to the low numbers of CREs in our study, it is difficult to analyze the association between carbapenem resistance, antibiotic exposure, and clinical outcomes. It is also difficult to draw any conclusions regarding transmission patterns of CREs in this patient population. Nevertheless, as CREs are becoming widespread in both civilian and military health systems, surveillance should continue.

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Effects of Mandatory Screening Labs in Directing the Disposition of the Apparently Healthy Psychiatric Patient in the Emergency Department

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ABSTRACT

Objective: To determine whether mandatory psychiatric admission laboratory tests yield results that change the disposition of a patient with primary psychiatric complaint from admission to a psychiatric service to admission to a medical service.

Methods: This was a single center retrospective cohort chart review study approved by the facility Institutional Review Board in which we used a records database maintained by the emergency department's social workers to access the records of every patient that presented to our emergency department with a psychiatric chief complaint between the dates of December 1, 2011, and December 1, 2013. We focused on those that were admitted to either a psychiatric service or a medical service after a thorough evaluation by the department of social work and an emergency provider.

We applied our inclusion and exclusion criteria and reviewed the results of the mandatory psychiatric laboratory tests (complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, acetaminophen, aspirin, blood alcohol level, urinalysis, urine pregnancy test, urine drug screen) required for admission. Our independent variables were the compulsory psychiatric admission laboratory tests and our dependent variable was the admission to a medical service.

Results: Of 5,606 laboratory tests that were ordered and produced results for the 682 patients enrolled in our study, 51 results were considered clinically significant abnormal results, or results requiring treatment prior to psychiatric service admission, by the 2 reviewing emergency physicians. Only one of 682 psychiatric patients received a final disposition to a medical service based upon abnormal laboratory studies. That patient presented without any medical complaints but a chief complaint of "suicidal ideation," and was found to have diabetic ketoacidosis. Based on our data, the probability that an abnormal laboratory test will result in a change in disposition is 1/682=0.1% (95% CI: 0.0% to 0.9%).

Conclusion: Patients presenting to the emergency department with a psychiatric chief complaint and no physical complaints, abnormal vital signs, or abnormal physical exam findings have less than 1% probability that an abnormal laboratory study will change their disposition from a psychiatric admission to a medical admission.

Psychiatric complaints are the fastest growing condition evaluated in emergency departments (ED) in the United States, increasing by 15% in the last decade.[1] In 2012, the Carl R. Darnall Army Medical Center Emergency Department (Fort Hood, Texas) saw 3,686 patients with a mental health concern as a chief complaint, making up 4.8% of the emergency department patients seen that year.

When the American military entered combat operations in Afghanistan and Iraq over 14 years ago, military medical departments and the American government were woefully unprepared to handle the psychological strains that would be placed on some 2.2 million troops (and their families) who were deployed over the years. A 2008 report by the RAND Corporation estimated that more than 26% of troops have returned from these combat operations with mental health issues.[2] Along with the active duty service member, family members are seeking care for their own mental health issues in record numbers. In a 2002 study, Calhoun et al[3] determined that partners of Veterans diagnosed with posttraumatic

stress disorder (PTSD) experience more caregiver burden and have poorer psychological adjustment than partners of Veterans without PTSD. According to the Veteran's Administration, partners of Veterans with PTSD reported lower levels of happiness and less satisfaction in their lives with about half reporting having felt "on the verge of a nervous breakdown."[4] The psychological stress and ongoing struggle for adequate treatment for these service members and their families have led to a strain on the mental health care system at many of our military bases. Several recently published reports attest that service members interested in accessing mental health care often face long wait lists.[5] Although these wait times can vary considerably from one behavioral health clinic to another; the Department of Defense Mental Health Task Force noted that delays of 30 days for an initial mental health appointment are not uncommon. This gap in care leads many service members and their families to seek help for their mental health concerns at local EDs.

For adult psychiatric cases that present to the ED and are otherwise medically stable, mandatory screening labs add unnecessary costs, use limited resources, and extend emergency department stays without changing the final disposition of the patient. The screening labs that are required for psychiatric admission are often based on expert opinion and medical screening performed by psychiatrists, who are not trained to evaluate emergency patients for medical conditions, rather than emergency providers.[6] In a retrospective study of 212 patients, Korn et al[7] concluded that patients with a psychiatric chief complaint and normal physical exam findings may be safely referred to psychiatric services without the use of ancillary testing in the ED. In a similar study, Amin and Wang found that patients presenting to the ED with psychiatric chief complaints and benign histories and physical exams have a low likelihood of clinically significant laboratory findings.[1]

We conducted this study to determine if mandatory psychiatric admission laboratory tests yield results that change the disposition of a psychiatric patient from admission to a psychiatric service to admission to a medical service if that patient has presented with no medical complaints and no abnormal physical exam findings following examination by a trained emergency provider. We believe that if these mandatory laboratory results do not change the patient's admitting service, the use of laboratory testing for psychiatric patients should be performed only at the discretion of the evaluating emergency medicine provider, thus increasing patient throughput in the department, reducing risks to patients and staff, and decreasing costs in the healthcare system.

Methods

Study Design

We conducted a single center retrospective cohort chart review study.

Setting

This study was conducted at a Level III trauma center supporting more than 42,000 military personnel and more than 145,000 family members, retirees, and civilian emergencies. In 2012, the ED evaluated 77,403 patients, with 3,686 (4.8%) of those patients being psychiatric patients. The department has a full time staff of 8 licensed social workers that evaluate all psychiatric complaints and assist the emergency clinicians with the assessment and placement of these patients. The medical center has a 15-bed inpatient psychiatric ward and a 5 bed ICU, as well as the ability to admit psychiatric patients to 3 offsite inpatient psychiatric treatment facilities.

Selection of Participants

We conducted this study using a database maintained by the medical center Department of Social Work of all emergent psychiatric patient evaluations and their dispositions. The database records a patient's name, age, military unit, chief complaint, and disposition. Using SPSS software (IBM Inc, Armonk, NY) and the general rule for multivariate analysis, we powered our study for 30 subjects enrolled per independent variable. With 9 independent variables, we determined that we would have to enroll at least 270 patients to adequately power our study. We performed a post hoc analysis to ensure adequate power. We trained an emergency medicine second-year resident to apply our specific inclusion and exclusion criteria to all patients in the database. In addition to her training, our research resident was blinded to our hypothesis and was not involved in the development of our study to avoid data collection bias. We instructed her to pull paper medical records if electronic medical records were not complete and informed her that we would perform quality checks on her data collection and recording. She spent 3 months enrolling study participants that met criteria. She began by narrowing our search to all patients aged 18-65 years who presented with a psychiatric chief complaint at the ED and were admitted to a psychiatric or medical service from the ED during the period December 1, 2011 through December 1, 2013. From this patient group, she reviewed each medical chart for any physical complaints, vital sign abnormalities, or abnormal history and physical exam findings recorded by the nurse or emergency department provider. Patients who were not strictly psychiatric patients were eliminated. After eliminating all patients with concurrent medical complaints or physical exam or vital sign abnormalities, 682 patients remained enrolled in the study. After

data was collected, the primary investigator randomly reviewed 3 patient charts from each month to ensure our data collector had enrolled appropriate patients and collected accurate data.

Outcome Measures

Our primary outcome measure was the percentage of dispositions that changed from psychiatric admission to medical admission as a result of clinically significant laboratory abnormalities in the mandatory screening laboratory tests. To determine the percentage, we divided the total number of patients who underwent each mandatory laboratory test by the total number of patients whose disposition was changed to a medical admission based on an abnormality in each laboratory test. We also tabulated the total number of clinically significant laboratory abnormalities, defined as laboratory results that would require treatment per our hospital protocols, prior to disposition, but did not change the disposition of the patient. Our hypothesis was that the mandatory psychiatric admission laboratory tests do not yield results that change the disposition of a psychiatric patient from admission to a psychiatric service to admission to a medical service.

Method of Measurement and Data Collection

After finding the 682 patients that met our inclusion and exclusion criteria, the data research resident removed personal identifications from the data and recorded the laboratory results for each patient into an Excel spreadsheet. Normal laboratory results were recorded as "normal," and abnormal laboratory results were recorded as the actual laboratory value. If the research resident encountered missing electronic medical records, the paper hardcopy was pulled for review. Using this method, we had no incomplete charts or missing data points. The results of the mandatory psychiatric screening laboratory tests for the 682 study participants (complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid stimulating hormone (TSH), acetaminophen (APAP), aspirin (ASA), blood alcohol level (BAL), urinalysis (UA), urine pregnancy test (UHCG), urine drug screen (UDS)) were reviewed separately by 2 independent board certified emergency physicians for abnormalities that were clinically significant enough to require treatment in the department according to the hospital psychiatric admission protocols. The reviewing physicians were blinded to any change in disposition that resulted from the laboratory tests and were not involved in the development or execution of this study in any way. This study was conducted under a protocol reviewed and approved by the Institutional Review Board and in accordance with the approved protocol.

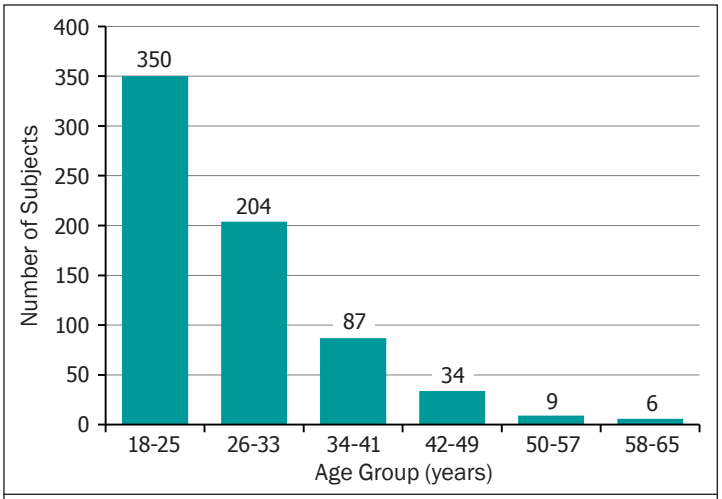

Figure 1. Number of subjects by age group.

Results

Six hundred eighty-two subjects met our criteria and were enrolled in the study. All of the patients presented with a chief psychiatric complaint (ie, "life stress," suicidal ideation, homicidal ideation, depression, anxiety), denied concurrent physical ailments, and had normal vital signs and nursing and provider assessments. Descriptive statistics of the subjects are presented in Figures 1 and 2.

Of 5,606 laboratory tests ordered and results received for these patients (682 UA, CMP, BAL, TSH, ASA, CBC, UDS, APAP, and 150 UHCG), as shown in Table 1, there were 59 that were considered clinically significant abnormal results by our 2 reviewing emergency physicians. These were laboratory values that, according to our hospital psychiatric admission criteria, would require treatment prior to psychiatric admission.

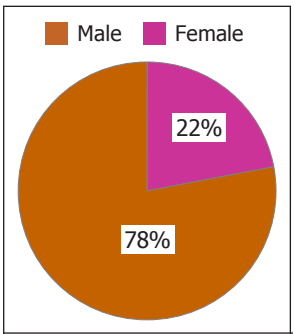

Figure 2. Percentages of subjects by gender.

Thirty patients had abnormal UAs and were started on treatment for asymptomatic urinary tract infections prior to admission to psychiatry. Five patients had hypokalemia on their CMP and were treated with K-Dur and admitted to psychiatry. The other 2 abnormal CMPs showed elevated creatine for which the patients received IV fluids and the repeat laboratory values returned to normal prior to psychiatric admission. The 7 patients with elevated BAL had repeat laboratory tests drawn until levels were under 100, meeting admission standards to psychiatry. Thyroxine free (free T4) levels were obtained on the 3

Table 1. Clinically significant abnormal laboratory tests and results that changed disposition.

	Laboratory Test								
	UA	CMP	BAL	TSH	ASA	CBC	UDS	APAP	UHCG
Number of laboratory tests ordered	682	682	682	682	682	682	682	682	150
Number of normal laboratory tests	651	674	675	680	681	682	682	682	150
Number of clinically significant abnormal laboratory tests	31	8	7	2	1	0	0	0	0
Number of dispositions changed due to laboratory results	1	1	0	0	0	0	0	0	0

UA indicates urinalysis; CMP, complete metabolic panel; BAL, blood alcohol level; TSH, thyroid stimulating hormone; ASA, aspirin; CBC, complete blood count; UDS, urine drug screen; APAP, acetaminophen; UHCG, urinary human chorionic gonadotropin.

patients with abnormal TSH and results were normal, eliminating concern for acute thyroid abnormalities. These patients were cleared for psychiatric admission with recommendations for repeat laboratory work upon discharge. Finally, the patient with elevated ASA had serial ASA levels drawn in the emergency department to confirm a downward trend prior to psychiatric admission.

Of 682 psychiatric patients, only one received a final disposition to a medical service based upon abnormal laboratory studies, a probability of 1/682=0.1% (95% CI: 0.0% to 0.9%). That patient was a 43-year-old male who presented without any medical complaints but a chief complaint of "suicidal ideation." This patient had an abnormal CMP (elevated glucose) and UA (glucose and ketones present) and was found, through his laboratory work, to have diabetic ketoacidosis (DKA). Upon diagnosis, he received IV fluids and insulin in the emergency department and was transferred to the intensive care unit. The probability that an abnormal laboratory test will result in a change in patient disposition is 1/682=0.1% (95% CI: 0.0% to 0.9%).

Using Fisher's Exact Test, we found that there was a statistically significant difference in the change in patient disposition between an abnormal and normal CMP (P=.013) and an abnormal and normal UA (P=.047).

Because many of our laboratory tests had no abnormal results (CBC, UDS, APAP, UHCG), we decided to investigate if the probability of an abnormal finding was truly "zero" and, if not, what the estimated probability is for an abnormal result in one of those laboratory tests in the future. Using the Modified Wald Equation and the rule of three, among the tests for which there were no abnormal results, the estimated probability of an abnormal laboratory finding in the future was 0.4% to 0.7% for the CBC, UDS, and APAP, and 2.0% to 3.1% (high limit of the 95% CI) for UHCG. This means that even though our data had some laboratory tests with no abnormal results, there is still a small probability that there will be abnormal results in future patients. The analysis results are presented in Table 2.

There were also laboratory tests for which there were abnormal results but no change in disposition (ASA, BAL, and TSH), and we estimated the probability of future abnormal results in those laboratory tests as well. Using the same Modified Wald Equation, we estimate the probability of a future abnormal result in the laboratory tests that already had abnormal results was up to 1.8% (high limit of the 95% CI), presented in Table 3. This means that there is continued probability of these laboratory tests resulting abnormally, but this does not change the probability that these abnormal results will alter disposition in the future.

Comment

Due in part to the demand placed on emergency departments and the prevailing evidence that mandatory psychiatric laboratory tests do not alter a patient's disposition,

Table 2. Estimated probability of a future significant abnormality in laboratory tests with no abnormal results.

	N	Abnormality	Normal	Probability of an Abnormality Occurring in the Future	95% CI	Rule of Three
CBC	682	0	682	0.0%	0.4% (-0.1% to 0.7%)	0.4%
APAP	682	0	682	0.0%	0.4% (-0.1% to 0.7%)	0.4%
UDS	682	0	682	0.0%	0.4% (-0.1% to 0.7%)	0.4%
UHCG	150	0	150	1.3%	1.8% (-0.5% to 3.1%)	2.0%

CBC indicates complete blood count; UDS, urine drug screen; APAP, acetaminophen; UHCG, urinary human chorionic gonadotropin.

Table 3. Estimated probability of a future significant abnormality in laboratory tests with abnormal results.

	N	Abnormality	Normal	Probability of an Abnormality Occurring in the Future	95% CI
BAL	682	7	675	1.0% (Modified Wald)	0.8% (0.3% to 1.8%)
TSH	682	2	680	0.3% (Modified Wald)	0.6% (0.0% to 1.2%)
ASA	682	1	681	0.1% (Modified Wald)	0.5% (-0.1% to 0.9%)

BAL indicates blood alcohol level; TSH, thyroid stimulating hormone; ASA, aspirin.

the American College of Emergency Physicians (ACEP) created a clinical policy in 2005 that provided a Level B and two Level C recommendations (recommendations for patient management that may identify a particular strategy that reflect moderate clinical certainty) against the routine testing of clinically stable adults that present to the emergency department with psychiatric symptoms.[8] Despite these recommendations and the results from prior studies, clinical practice has not changed in most emergency departments which is, in part, due to poor communication between the emergency medicine providers and the accepting psychiatrists.

Our results validate the findings from prior studies, such as Korn et al,[7] Parmar et al,[6] and Amin and Wang,[1] in the military population. Our study demonstrates that these mandatory screening laboratory tests change the disposition in psychiatric patients with no physical complaint or abnormal physical exam findings less than 1% of the time (high end of 95% CI). With only one exception, none of the performed tests altered a patient's disposition. Our study confirms that extensive screening laboratory tests for medically stable psychiatric patients are very unlikely to change the patient's disposition. Medicine accepts a reasonable miss-rate order to avoid over-testing and unnecessary treatments. Many decision-making rules, such as pulmonary embolism rule-out criteria, accept the risk of missing a positive at anything below 2%. We believe that our results, which show a less than 1% probability in a change of disposition, demonstrate that forgoing mandatory screening laboratory tests in these stable psychiatric patients is allowing an acceptable level of risk. This risk is further mitigated due to these patients being admitted to a hospital psychiatric ward where they will continue to be monitored and can be transferred or reevaluated quickly if their presentation changes.

In analyzing the individual laboratory tests for clinically significant abnormal results, we found many laboratory results are often returned as "normal." However, we know that "zero abnormal results" does not mean "zero risk," so we determined the future probability of an abnormal result in those laboratory tests with no abnormal results (CBC, APAP, UDS, UHCG) in our study and found that, with the exception of the UHCG, there was less than a 1% estimated probability. This is a miss rate of an abnormal finding that we in the medical field can be comfortable with. This means that we can, essentially, stop ordering these tests in stable psychiatric patients with a less than 1% chance of missing a clinically significant abnormal result in the future. In the laboratory studies with abnormal results that did not alter a patient disposition (BAL, TSH, ASA), there is a less than 2% estimated probability of a future abnormal result. This is a miss rate that we can also be comfortable with, as none of these abnormalities ultimately change the patient disposition. This study suggests that these 6 laboratory tests can be safely eliminated from our battery of mandatory tests, as none of them altered the patient disposition and there is less than 2% estimated risk for any clinically significant abnormal results in future testing. The urine pregnancy test was only ordered on female patients and a positive result did not alter the disposition at our hospital as all inpatient psychiatric facilities are capable of treating pregnant patients. This laboratory result may direct a treatment plan for the psychiatrist but does not alter the disposition of our medically stable psychiatric patient. We suggest that the UHCG can be ordered by the psychiatrist once the patient is admitted rather than in the emergency department where it does not alter the patient course.

Again, focusing on the utility of individual laboratory tests, the only ones with abnormalities that required a change in disposition were the CMP and the UA. Both of these laboratory tests were positive for elevated glucose, and the results initiated the workup for DKA in the only patient with a disposition change. The reviewing physicians believe the CMP results were cause enough to alter the disposition, but the UA results did not, on their own, result in the disposition change. This patient was a new-onset diabetic with no previous workup or diagnosis of diabetes and he denied any physical symptoms throughout his ED course, even after he was told of his diagnosis and began emergency treatment. These 2 laboratory results were significant and initiated a formal DKA workup due to the hyperglycemia found in each. These laboratory tests may be considered redundant or may be replaced by the finger-stick glucose test, which is much less expensive and faster to rule out DKA in the stable psychiatric patient. The non–life-threatening diagnoses found by these 2 laboratory tests were mild hypokalemia and asymptomatic urinary tract infections that required treatment prior to psychiatric admission, but add to our concerns for overtreatment of laboratory results in asymptomatic patients. From our results, we believe that the CMP and UA can be replaced by the finger-stick glucose testing to screen for hyperglycemia. With the elimination of these 2 laboratory tests, the probability of a disposition change will remain less than 1% and risk continues to be mitigated as these patients are all admitted to the hospital and monitored for symptom changes.

Our results, which would suggest that we only need a finger-stick glucose test to ensure no disposition change in stable psychiatric patients, differ from those of

Parmar et al[6] in which the laboratory results caught an acetaminophen overdose in a medically cleared patient. As a result, they recommended keeping the APAP level as a screen for suicidal patients.

With these results, a dialogue should begin within the hospital system, between the emergency and psychiatric departments, in the hopes of eliminating completely or reducing the number of mandatory tests required for a psychiatric admission. Because there is no standardized medical clearance for a psychiatric patient, it is important that each hospital system review the efficacy of the system they have in place. This study shows that extensive mandatory screening laboratory tests do not change the disposition of psychiatric patients presenting without medical complaint to a military hospital. In an era of fiscal limitations within the military and an emphasis on decreasing emergency department wait times, the departments of emergency medicine and psychiatry could use this study results, in conjunction with the 2005 guideline from ACEP and the results of prior studies on the matter, to streamline the process of psychiatric admissions within the military and reduce the medical screening laboratory tests required for medical clearance.

We hypothesized that a thorough history and physical exam would be sufficient to find an abnormality in a psychiatric patient without any medical complaints and that mandatory laboratory tests would not change the disposition. Our results show that, with one exception, history and physical exam alone can appropriately provide the disposition of medically stable psychiatric patients. Emergency providers and psychiatrists should work together to create appropriate testing strategies and admission criteria for psychiatric patients.

Limitations

Our study site had characteristics distinctive to the military in that our study population was a mean age of 28 years and over 75% male. The population consisted of a relatively healthy active duty population and their family members. Our study site was also unique in that it had multiple inpatient psychiatric facilities that were able to readily accept our patients, including the inpatient psychiatric ward of the study hospital. This made admitting a psychiatric patient relatively less difficult. This population and psychiatric disposition resources may not reflect all other institutions and may be skewed to the military hospitals across the country, however the ability for an emergency provider to appropriately evaluate psychiatric patients for an underlying medical condition should be universal to emergency departments. We believe that our observations, with regard to mandatory testing of psychiatric patients with no physical complaint or abnormal physical exam finding, are applicable to multiple emergency department settings.

We performed a retrospective cohort chart review study in which we used a second year emergency department resident to review all of the patient charts and record data over the course of 3 months. We believe that by having a single data collector performing this task over a short period of time, we decreased the possibility of multiple interpretations of the data collection process and data recording. Our data collector was blinded to our hypothesis to decrease data collection bias. She was also informed that we would perform random inspections of her data to ensure accuracy.[9] We pulled paper records of all charts that were not complete in the electronic medical records to ensure complete data collection. We also reviewed records that spanned a 2-year time period, attempting to get a better long-term picture and increase our data points.

Because this was a retrospective review and we only had written documentation of the patient encounter, we had to trust that documentation as fact. In reviewing provider and nursing notes, occasional documentation errors were found with regards to normal vital signs and laboratory findings. Abnormal laboratory results were recorded as normal and abnormal vital signs were recorded as normal. This brings to light the limitations of a retrospective study and, while our data collector did her best to fully evaluate patient documentation, we must acknowledge that due to human error, not all documentation made in patient charts may be accurate. We could see when abnormal results were recorded as normal but we could not see if abnormal physical exam findings were recorded as normal; this is always a possibility and a risk when trusting retrospective charts.

Finally, in reviewing retrospective data, we could not see the order in which the patient evaluation process occurred. In our department, these mandatory laboratory tests may be ordered in triage, prior to an emergency provider's evaluation, or by the provider after the bedside evaluation. If these laboratory tests are ordered in triage and results obtained prior to the physical evaluation, those results may guide some providers to a more focused and detailed history and physical examination with the possibility of discovering abnormalities, thereby excluding that patient from our study. Ideally, to truly test the emergency provider's ability to find a medical abnormality in a stable psychiatric patient, the patient would be evaluated without the provider's knowledge of the laboratory results so as not to guide the history and exam.

A prospective validation study, ideally with a more varied patient population, is recommended to more broadly apply our findings to other practice centers. A large prospective multicenter study at military hospitals is needed to derive and validate a clinical decision-making rule that can be used across the Department of Defense and in similar populations for screening of psychiatric patients with no physical complaint.

Conclusion

Of 682 patients evaluated with a psychiatric chief complaint and no medical complaint of abnormal physical exam findings, one patient disposition was changed from psychiatric admission to medical admission based on laboratory results alone. Our study validates the findings of previous studies and indicates that these mandatory screening laboratory tests rarely alter a patient's disposition after evaluation by an emergency trained provider. By eliminating these laboratory tests we accept a less than 1% miss rate. We believe this is further mitigated due to these patients all being admitted to the hospital.

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Resilience-Enhancing Relationships: What We Can Learn From Those With a History of Adverse Childhood Experiences

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Adverse childhood experiences (ACE) have long been recognized as antecedents to negative physical and mental health outcomes. Felitti and his colleagues, in their landmark ACE study,[1] discovered child maltreatment and household dysfunction to be associated with many of the leading causes of death in adults. Further reports from the ACE study linked childhood adversity to psychosocial problems that included suicide attempts,[2] alcohol abuse,[3] intimate partner violence,[4] depressive disorders,[5] hallucinations,[6] and generally poorer mental health functioning.[7] Since the initial work of Felitti et al, others have contributed to the growing understanding of the long-term consequences of childhood trauma. A study of young adults from economically disadvantaged, urban communities revealed that those with a high rate of ACEs were more likely to experience depressive symptoms, use drugs and engage in antisocial behavior.[8] Since the advent of the all-volunteer service, increased percentages of service members, particularly males, have described personal ACEs.[9] This is reflected in the high prevalence of ACEs seen in Soldiers who sought treatment for a wide array of behavioral health disorders while deployed to a combat zone, with many reporting having experienced 3 or more types of adversity.[10] Similarly, active duty Marines who reported a history of ACEs appeared to be at an increased risk for developing posttraumatic stress disorder after returning from a combat deployment.[11] Additional studies have correlated childhood adversity with a lifetime onset of posttraumatic stress disorder, conduct disorder, substance use disorders, suicidal ideation, and anxiety.[12-14] Furthermore, ACEs are believed to exacerbate the physical and psychological symptoms experienced by those with severe mental health disorders.[15,16] Much of the research on ACEs has shown that the more adversity a child experiences, the more likely they will develop physical or psychosocial problems as an adult. Nevertheless, embedded in these findings is the revelation that not everyone who endures hardships early in life is destined to become psychosocially dysfunctional. This evidence suggests that some people become resilient in the face of adversity and emerge from childhood trauma to lead psychologically healthy and highly successful professional lives. Thus resilience, characterized by achieving positive outcomes despite severe threats to growth or adaptation,[17] may mitigate the risk of developing the psychological distress and maladaptive behavior associated with ACEs. In fact, psychological resilience has been shown to protect against the risk of suicide related to childhood trauma and lessens the association between being emotionally neglected as a child and developing psychiatric symptoms as a young adult.[18,19] Furthermore, homeless adolescents with a history of ACEs who perceived themselves as resilient were found less likely to engage in risky behavior, were less lonely and more hopeful.[20] Becoming resilient can be achieved through various pathways.[21] While innate factors and environmental influences undoubtedly contribute to resilience, the Kauai longitudinal study on the resilience and recovery of at-risk children discovered that relationships with supportive adults mitigate the vulnerabilities of adversity and facilitate positive outcomes as adults.[22]

Resilience and Relationships

The power of human connections to shape individual growth and development has been espoused by many theoretical perspectives, but none more so than attachment theory. According to John Bowlby, "Attachment behavior is any form of behavior that results in a person attaining or maintaining proximity to some other clearly identified individual who is conceived as better able to cope with the world."[23] Accordingly, becoming securely attached has been shown to be positively associated with resilience.[24] Further support for the influence human relationships can exert in promoting, and in some cases restoring, healthy development can be found in the literature on resiliency in vulnerable populations. Research has established that older children who live under chronically adverse conditions tend to do better or recover more effectively when they have a relationship

with a competent adult.[25] Relatedly, Brooks proposed that developing caring relationships in schools, based on respect, encouragement, and attentiveness, may help young students elude the negative outcomes related to environmental threats.[26] This idea is congruent with the finding that at-risk adolescents desire supportive relationships with adults that foster the formation of a self-identity grounded in resilience and competence.[27] Furthermore, developing a sense of competence, a contributor to resilience, requires caring, competent adults to be actively involved in a child's life.[28] Importantly, resilience-enhancing relationships are not limited to primary caregivers. Extra-familial adults, such as teachers, coaches, clergy and mental health workers, have proven to be effective mentors that can serve as a protective factor for vulnerable children.[29] This may partially explain how mothers who were abused as children were able to break the cycle of abuse after receiving emotional support from foster parents and others when they were younger.[30] Although much resilience research focuses on children, a meta-analysis of the effectiveness of resilience-building programs conducted in occupational settings found many of the protective factors pertinent to children may also apply to adults and that direct resilience training is most beneficial,[31] suggesting that relating to the "coach" or trainer can enrich the learning process. Additionally, caring relationships in the workplace boost resilience and can be transformative during times of organizational change.[32] Interestingly, Laursen and Birmingham, in an ethnographic study of adolescents,[33] identified the foundational attributes of a caring relationship to include trust, attention, empathy, availability, affirmation, respect, and virtue. Sebastian Junger, one of the directors behind the acclaimed film *Restrepo* (http://restrepothemovie.com/), has written about the role social bonds play in helping to sustain Soldiers through the stress of a combat deployment and, conversely, how the absence of postdeployment social support elevates the risk of developing posttraumatic stress disorder.[34] One of the principal objectives of this study is to identify the characteristics of past and present supportive relationships that have helped individuals overcome adversity and contributed to them becoming resilient Soldiers.

Methods

The study protocol was approved by the Institutional Review Board at Tripler Army Medical Center. Investigators adhered to the policies for protection of human subjects as prescribed in 45 CFR §46 and entailed a 2-part protocol. First, we used a correlational design to explore the relationship between adverse childhood experiences and resilience in adulthood followed by semistructured interviews to identify characteristics of supportive relationships that contributed to individuals becoming resilient adults in spite of childhood adversity. A convenience sample of 250 active duty service members, recruited at the Soldier Readiness Processing Center at Schofield Barracks in Hawaii, completed a 3-part survey that included basic demographic information, the ACE questionnaire, and the Connor-Davidson Resilience Scale (CD-RISC). The ACE questionnaire used in this study is an adaptation of the survey used in the seminal ACE Study.[1] It contains 10 questions written to elicit dichotomous yes/no responses to capture the respondent's exposure, prior to age 18, to child maltreatment, domestic violence, parental separation/divorce, having a member of the household who was mentally ill, abused substances, or was incarcerated. In addition to identifying specific types of adverse childhood experiences, each affirmative response is tallied to determine a total ACE score. Although the ACE data are collected retrospectively, answers to the ACE questions have demonstrated good test-retest reliability indicating that responses tend to be generally stable.[35] The CD-RISC is a valid and reliable self-reported measure of resilience consisting of 25 items rated on a 5-point scale (0-4) with higher scores indicative of greater resilience.[36] In our current study, we achieved a Cronbach α coefficient of 0.93. Except for those individuals who further volunteered to be interviewed, participant responses contained no personally identifiable information. Confidentiality was strictly guarded for those who voluntarily provided their name and a point-of-contact.

Inclusion criteria for the qualitative portion of the study consisted of reporting at least 3 adverse childhood experiences, demonstrating high resilience as evidenced by scoring 80 or higher on the CD-RISC and, based on their response to question two of the CD-RISC, having a close and secure relationship they could turn to in times of stress. From the 36 volunteers who met our criteria, we selected a purposive sample of 25 that reflected a representative mix of demographic characteristics. The semistructured interviews consisted of a series of open-ended questions with probing follow-up queries designed to capture descriptions of the personal characteristics and behavior exhibited by individuals with whom participants had a current or past supportive relationship. Interviews were recorded in process and specific descriptors using verbatim participant quotes documented. To control for interviewer bias, another member of the research team listened to the recorded interview and transcribed key descriptive quotes as well. Finally, a third researcher reviewed the 2 independent interview summaries for inter-rater reliability, only material documented on both summaries was considered reliable and included in the final analysis. The data were organized

into descriptive themes, defined as characteristics or actions, and frequencies tabulated. The statistical application SPSS v.22 (IBM Corporation, Armonk, New York) was used to calculate the frequency distributions of demographic characteristics, the prevalence of each adverse childhood event, and correlations between ACEs and resilience. Significance was set at .05. The Tripler Army Medical Center Institutional Review Board granted approval to conduct this study.

RESULTS

Demographics

As described in Table 1, the 250 participants were predominantly male with a moderate number of women. They were relatively young with an average age of 27 years. The sample was rather diverse with many self-identifying as Caucasian, followed by Hispanic, African American, Asian, Pacific Islander and Native American. Most were married while a significant number reported being single. Only a few were divorced. They were fairly well-educated as a majority were high school graduates or had completed some college courses and a significant number had earned at least a 2-year college degree. Some had completed postgraduate education or earned technical degrees or certifications. The overwhelming majority were enlisted service members with almost half serving in the junior grades of E1-E4. A substantial number were junior noncommissioned officers (NCO) (E5-E6) with a few senior NCOs (E7-E9) represented. Commissioned and warrant officers comprised a modest percentage of the sample. Half worked in support positions or in the medical field, while many of the others served in the combat arms specialties. On average, they had almost 6 years of time-in-service with a wide range of 3 months to 28 years of military experience. Interestingly, most had not deployed to a combat zone. The subset of 25 that participated in interviews was similar across most demographic variables but were more likely to be married, more junior in rank, and less likely to have deployed to a combat zone.

Table 1. Demographic Characteristics of Study Population.

Demographic Variables	Survey Only (n=225)	Interviewees (n=25)	Total (n=250)
Mean Age (years)	27.12	27.52	27.16
Mean Time-In-Service (years)	5.7	5.5	5.7
Gender			
Female	33 (14.7%)	6 (24%)	39 (15.6%)
Male	192 (85.3%)	19 (76%)	211 (84.4%)
Race			
African-American	43 (19.1%)	3 (12.0%)	46 (18.4%)
Asian	17 (7.6%)	3 (12.0%)	20 (8.0%)
Caucasian	99 (44.0%)	13 (52%)	112 (44.8%)
Hispanic	46 (20.4%)	4 (16.0%)	50 (20.0%)
Native American	3 (1.3%)	1 (4%)	4 (1.6%)
Pacific Islander	14 (6.2%)	1 (4%)	15 (6%)
Other	3 (1.3%)	0 (0%)	3 (1.2%)
Marital Status			
Single	83 (36.9%)	6 (24.0%)	89 (35.6%)
Married	132 (58.7%)	19 (76%)	151 (60.4%)
Divorced	9 (4%)	0 (0%)	9 (3.6%)
Unknown	1 (0.4%)	0 (0%)	1 (0.4%)
Education			
High School	68 (30.2%)	7 (28.0%)	75 (30.0%)
Some College	72 (32.4%)	10 (40.0%)	83 (33.2%)
Tech Certification	8 (3.6%)	0 (0%)	8 (3.2%)
Associates Degree	31 (13.8%)	5 (20.0%)	36 (14.4%)
Bachelor's Degree	33 (14.7%)	2 (8.0%)	35 (14.0%)
Master's Degree	7 (3.1%)	1 (4.0%)	8 (3.2%)
Doctorate	2 (0.9%)	0 (0%)	2 (0.8%)
Unknown	3 (1.3%)	0 (0%)	3 (1.2%)
Rank			
E1–E4	106 (47.1%)	15 (60.0%)	121 (48.4%)
E5–E6	79 (35.1%)	5 (20.0%)	84 (33.6%)
E7–E9	8 (3.6%)	3 (12.0%)	11 (4.4%)
Officer	32 (14.2%)	2 (8.0%)	34 (13.6%)
MOS			
Combat Arms	97 (43.1%)	12 (48.0%)	109 (43.6%)
Combat Support	34 (15.1%)	2 (8.0%)	36 (14.4%)
Combat Service Support	63 (28.0%)	3 (12.0%)	66 (26.4%)
Medical	18 (8.0%)	5 (20.0%)	23 (9.2%)
Unknown	13 (5.8%)	3 (12.0%)	16 (6.4%)
Combat Deployment			
No	127 (56.4%)	17 (68%)	144 (57.6%)
Yes	98 (43.6%)	8 (32%)	106 (42.4%)

Adverse Childhood Experiences

In total, ACE scores ranged from 0 to 10 with a mean of 2.9 (SD=2.6). As detailed in Table 2, the vast majority of Soldiers reported experiencing at least one form of childhood adversity with half enduring 3 or more. Of the 7 individuals who reported 9 or more types of adverse experiences, only one met the inclusion threshold for resiliency but that individual did not volunteer to be interviewed. Having parents that divorced or separated was the most commonly reported disruption to one's childhood. Experiencing child maltreatment, in its various forms, was reported by a significant number but with a relatively small percentage reporting being sexually abused. Many indicated growing-up in a household with someone who abused alcohol or other substances. A little over a quarter lived with a mentally ill family member. A considerable number had a member of the household incarcerated and one-fifth witnessed the trauma of

domestic violence. Predictably, given our criteria to be included in the study's qualitative phase, the 25 individuals who were interviewed reported experiencing childhood trauma in greater percentages across all measures. We found no statistically significant relationships between ACEs and any demographic variable.

Resilience

Scores on the CD-RISC ranged from 34 to 100 with a mean of 78.28 (SD=13.74) and a median of 79. A weak but statistically significant negative relationship was found between total number of ACEs and current resilience as measured by the CD-RISC (r=-.138, P=.029). Further analysis using the χ^2 test for independence with Yates Continuity Correction was conducted to examine the relationship between a high number of ACEs (3 or more) and high resilience scores (80 or higher on the CD-RISC) and also found a statistically significant, weak, negative correlation (χ^2=10.9, P=.001, φ=-.217). When high CD-RISC scores (80 or higher) were analyzed in relation to each ACE, statistically significant negative correlations were established with psychological abuse (χ^2=11.8, P=.001, φ=-.225), physical abuse (χ^2=6.3, P=.01, φ=-.167), domestic violence (χ^2=6.0, P=.015, φ=-.164) and household member mental illness (χ^2=5.5, P=.019, φ=-.157). Therefore, individuals who were physically or psychologically abused, who witnessed their maternal figure being abused, or grew-up with a mentally ill family member tended to be less resilient as measured by the CD-RISC. All other adverse childhood experiences were not significantly associated, at least statistically, with current resilience.

Table 2. Prevalence of Adverse Childhood Experiences.

Adverse Childhood Experience Items	Survey Only (n=225)	Interviewees (n=25)	Total (n=250)
Psychological abuse: insulted, humiliated, demeaned, sworn at, feared physical abuse.	92 (40.9%)	20 (80.0%)	112 (44.8%)
Physical abuse: pushed, grabbed, slapped, targeted with thrown objects, struck leaving marks or resulting in injury.	77 (34.2%)	18 (72.0%)	95 (38.0%)
Sexual abuse: touched, fondled, and/or forced to touch others in a sexual way; oral, anal, or vaginal intercourse.	25 (11.1%)	9 (36.0%)	34 (13.6%)
Emotional neglect: not loved, made to feel unimportant, not looked after, did not feel close or supported.	46 (20.4%)	11 (44.0%)	57 (22.8%)
Physical neglect: not enough to eat, wore dirty clothes, not protected, parents too high or drunk to provide care or seek medical care for you if needed.	28 (12.4%)	7 (28.0%)	35 (14.0%)
Parental divorce/separation: parents ever separated or divorced.	118 (52.4%)	17 (68.0%)	135 (54.0%)
Domestic violence: directed towards mother or stepmother.	43 (19.1%)	7 (28.0%)	50 (20.0%)
Substance abuse: lived with a problem drinker, alcoholic, or drug abuser.	75 (33.3%)	20 (80.0%)	95 (38.0%)
Mental illness: household member was depressed, had a mental illness, or attempted suicide.	55 (24.4%)	11 (44.0%)	66 (26.4%)
Incarceration: household member went to prison.	45 (20.0%)	11 (44.0%)	56 (22.4%)
Number of ACEs Reported per Individual			
0	56 (24.9%)	0 (0%)	56 (22.4%)
1-2	70 (31.1%)	0 (0%)	70 (28.0%)
3-4	44 (19.5%)	9 (36.0%)	53 (21.2%)
5-6	36 (16.0%)	9 (36.0%)	45 (18.0%)
7-8	12 (5.3%)	7 (28.0%)	19 (7.6%)
9-10	7 (3.1%)	0 (0%)	7 (2.8%)

Relationship Characteristics

All 25 interviewees described having current and past supportive relationships that helped them become resilient. An individual's spouse (44%) or mother (24%) were the most frequently identified current sources of support followed by extra-familial relationships with peers or supervisors such as their platoon sergeant (20%). Some (12%) reported gaining strength from their relationship with a spiritual or religious entity. Similarly, family members, mostly the mother but also fathers, grandparents, siblings and an uncle, were described as prominent adult relationships during childhood or adolescence by 68%. People outside of the family, such as a foster parent, teacher, neighbor and friends, were, and in some instances remain, influential in the lives of almost a third (32%) of the sample. As seen in the Figure, 9 characteristics reliably emerged from the descriptions of those who were identified as supportive and having contributed to the development of resilience. The characteristics with representative descriptions are:

Available

Always there
Just being there
Always going to be there
(and in several instances) No matter what
Would be there
Was always there for me

Communicator

Listens	Good listener
Willing to listen	Listened to me
Would listen before giving advice	
Talked to me like an adult	
Just talking things out	Could sit down and talk
Talks to me	No yelling

Caring

Showed me she cares	Cares about me
Would go out of his way to show he cared	
Very nurturing and loving	
Constantly checking up on me	
Willing to help	

Role Model

A role model to me	Led by example
Inspiring	Respected
Looked up to	Always positive
Displayed courage and confidence	

Trustworthy

Trusted	Can confide in him
Can tell her anything	Earned my trust
Honest	100% faithful

Coach

Taught me a lot	Pushed me to be greater
Encouraged me	Pushed me to not give up
Gave me tips on how to do things,	
Showed me the Army thinking process	
Taught me to be more responsible	

Guardian

Provided security	Tried to protect me
Made sure I had a place to stay	
Would stand up for us	
Always had my back	Always put us first
My mental shield	

Nonjudgmental

Didn't judge me at first sight	
Tried to understand	Never judged me
Put herself in my shoes	Unbiased
He understands what I've been through	
Accepted me	

Firm

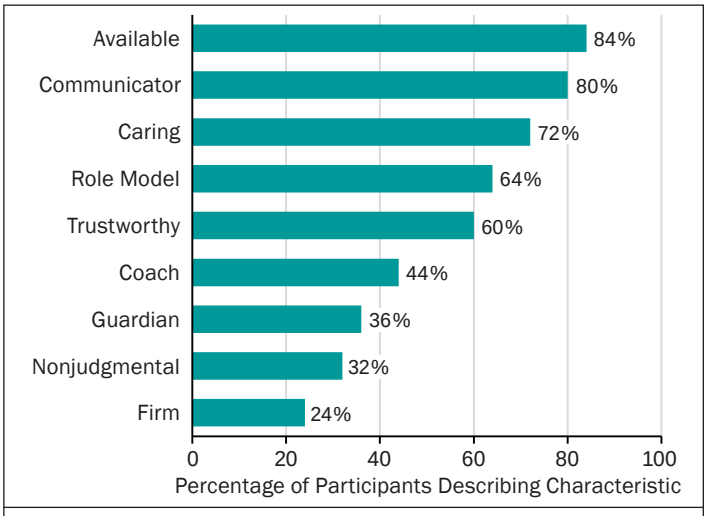
Direct and stern	Tough love
Very forceful	Kicks me in the ass
Tells me when I'm being a baby, to man up	

COMMENT

Our findings show that a substantial number of Soldiers may come from challenging backgrounds as this active duty sample reported experiencing childhood adversity at a rate comparable to that reported by a clinical sample of deployed Soldiers[10] and exceeding that found in the general population.[37] Moreover, anyone could possibly have a history of ACEs as no specific demographic group was found to be more likely to have grown-up in adverse conditions. The large percentage of Soldiers that acknowledged having ACEs underscores the Kauai study's finding that joining the military is seen as an opportunity to escape family adversity.[21] Therefore, the military may disproportionately attract recruits with a difficult upbringing, resulting in a significant number of military personnel at-risk for the psychosocial problems associated with adverse childhood experiences. Consequently, it is in the best interests of the military services to understand the needs of these potentially vulnerable service members and to provide leadership and support services to help them achieve success in their pursuit of a better life.

Although the strength of the relationship is admittedly weak, our findings suggest that enduring maltreatment or household dysfunction as a child can have a deleterious effect on how resilient one becomes as an adult. This may be particularly true for those individuals who were physically or psychologically abused, witnessed domestic violence, or lived with a mentally ill family member. That said, our findings also indicate that the damage ACEs can inflict may be mitigated by a relationship with a supportive adult.

Being considered supportive by others can be accomplished by manifesting certain personal qualities. First, and apparently foremost, is being available. Knowing that someone who is viewed as "better able to cope with the world" will be there when needed establishes



Characteristics of people as described during participant interviews who were identified as supportive and having contributed to the participant's resilience.

a secure base from which to engage the external world without fear of being abandoned. In addition, maximizing the benefits of "being there" depends, in part, on exercising good communication skills that begin with a willingness to listen. A great deal of support appears to derive from being allowed to express oneself before receiving unsolicited advice or, in a more negative vein, disapproval from others. Listening, however, is contingent upon others being willing to open-up. While the experience of being "cared for" is subjective, demonstrating that one cares and can be trusted and nonjudgmental fosters a sense of safety that encourages a person to talk who may otherwise be reluctant to reveal their innermost thoughts due to their family history. Further, a relationship built on trust provides an opportunity to impart wisdom, teach life skills, and promote self-efficacy that cultivate a sense of competency leading to enhanced resilience. There are, nonetheless, times when firmly, and judiciously, enforcing socially acceptable conduct is necessary to keep someone who may be at-risk for maladaptive behavior on the right track. Being a respected role model who conveys humility, confidence, and positivity and leads by example appears to facilitate the process.

Our results, however, should be considered within the context of limitations inherent in our approach. Using a correlational design does not allow us to conclude that growing-up with ACEs causes one to be less resilient as an adult, only that the two situations are associated with one another. Also, relying on a convenience sample of volunteers creates the risk of a selection bias that reduces our confidence in generalizing our findings beyond the sample. Furthermore, we only achieved face validity in defining the characteristics of a supportive relationship. Additional specificity is required to reach more precise operational definitions.

Implications

Our findings support the conclusions made by others that supportive relationships do make a positive difference in the lives of those who experienced childhood adversity by contributing to resilience in adulthood. Further, being experienced as supportive entails several prominent characteristics that include availability, communication that emphasizes listening, caring, trustworthiness, and being a respected role model who is willing to coach and, as necessary, provide firm guidance on behaving in socially acceptable ways without being judgmental. While these qualities seem fundamentally applicable to all human interactions, they may be most meaningful in our family relationships. A supportive family member, either a spouse, mother, or other relative, was most frequently identified as being instrumental in helping to overcome adversity and contributing to resilience. Therefore, incorporating these evidence-based characteristics into family advocacy prevention classes may be useful in strengthening marriages as well as provide a simple model for healthy parent/child relationships. Moreover, since a wide-array of extra-familial relationships were also deemed supportive, these attributes can be developed into a skill set for military leaders to apply in mentoring vulnerable Soldiers and used to inform the training of junior leaders during their initial leadership schools. Providing supportive leadership based on the characteristics found in this current research could augment the Army's efforts to enhance psychological resilience through the Comprehensive Soldier and Family Fitness Program.[38] Future research should continue to focus on those who developed grit despite childhood adversity to further refine the attributes of a supportive relationship and to determine if there is a critical developmental point in which the benefits of a supportive relationship can be optimized.

Conclusions

Much research has clearly established that adverse childhood experiences can lead to an adulthood plagued by multiple physical and psychosocial maladies. Nevertheless, there is mounting evidence to show that supportive relationships can mitigate the negative effect of childhood trauma by helping to build resilience. More specifically, relationships based on a constellation of seemingly simple actions and basic human qualities contribute to the development of the resiliency necessary to overcome current and future adversity. Given the number of Soldiers who may have experienced childhood adversity, military leaders, in addition to being technically and tactically proficient, may become more effective mentors by integrating these qualities into their leadership style. Perhaps we should consider applying these supportive attributes in all the relationships in which we hope to make a meaningful difference.

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A Randomized Comparison Between Neurostimulation and Ultrasound-Guided Lateral Femoral Cutaneous Nerve Block

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Abstract

Background: This prospective, randomized trial compared neurostimulation (NS) and ultrasound (US) guided lateral femoral cutaneous nerve (LFCN) block. We hypothesized that US would result in a shorter total anesthesia-related time (sum of performance and onset times).

Methods: Twenty-one volunteers were enrolled. The right lower limb was randomized to an NS- or US-guided LFCN block. The alternate technique was employed for the left lower limb. With NS, paresthesias were sought in the lateral thigh at a stimulatory threshold of 0.6 mA (pulse width=0.3 ms; frequency=2 Hz) or lower. With US, local anesthetic was deposited under the inguinal ligament, ventral to the iliopsoas muscle. In both groups, 5 mL of lidocaine 2% were used to anesthetize the nerve. During the procedure of the block, the performance time and number of needle passes were recorded. Subsequently, a blinded observer assessed sensory block in the lateral thigh every minute until 20 minutes. Success was defined as loss of pinprick sensation at a point midway between the anterior superior iliac spine and the lateral knee line. The blinded observer also assessed the areas of sensory block in the anterior, medial, lateral, and posterior aspects of the thigh and mapped this distribution onto a corresponding grid.

Results: Both modalities provided comparable success rates (76.2%-95.2%), performance times (162.1 to 231.3 seconds), onset times (300.0 to 307.5 seconds) and total anesthesia related-times (480.1 to 554.0 seconds). However US required fewer needle passes (3.2±2.9 vs 9.5±12.2; $P=.009$). There were no intergroup differences in terms of the distribution of the anesthetized cutaneous areas. However considerable variability was encountered between individuals and between the 2 sides of a same subject. The most common areas of sensory loss included the central lateral two-eighths anteriorly and the central antero-inferior three-eighths laterally.

Conclusion: Ultrasound guidance and NS provide similar success rates and total anesthesia-related times for LFCN block. The territory of the LFCN displays wide inter- and intra-individual variability.

Meralgia paresthetica, a painful mononeuropathy of the lateral femoral cutaneous nerve (LFCN), can result from injury, compression or mechanical irritation of the latter.[1] Lateral femoral cutaneous nerve block plays an instrumental role in the diagnosis and management of meralgia paresthetica.[1] Techniques for LFCN block include blind infiltration, neurostimulation (NS), and utrasound (US)-guidance.[2-4] In a randomized crossover study, blind infiltration was compared to NS.[2] The latter resulted in a greater success rate (100% vs 40%; $P<.001$) coupled with a shorter onset time ($P<.02$).[2] Although several recent reports[3-4] have advocated US for LFCN block, to date, no RCT has compared NS- and US-guided techniques.

In this randomized, volunteer study, we set out to compare NS- and US-guided LFCN blocks. We hypothesized that US would provide shorter performance and onset times. Thus, the primary outcome was the total anesthesia-related time (ie, the sum of performance and onset times). We also aimed to describe the triplanar sensory distribution of the LFCN after local anesthetic blocks.

Material and Methods

The current trial was registered at Clinicaltrials.gov (Identifier: NCT02577510) on October 14, 2015. After obtaining ethics committee approval (Defence Research and Development Canada Human Research Ethics Committee) and written informed consent, we enrolled 21 volunteers. Inclusion criteria were age between 18 and 60 years, American Society of Anesthesiologists (ASA) physical status I to II, and body mass index between 20 kg/m^2 and 40 kg/m^2. Exclusion criteria included

coagulopathy, pregnancy, breast feeding, hepatic or renal failure, allergy to local anesthetic (LA), prior surgery in the inguinal area, and neuropathy impacting sensation of the lateral thigh.

All LFCN blocks were performed by 2 operators (authors G. G. and R. J. F.) experienced with the NS and US techniques. They were carried out in a medical facility with access to resuscitative equipment and drugs. Volunteers were positioned supine. Using a computer-generated sequence of random numbers and a sealed envelope technique, the right lower limb was randomized to an NS- or US -guided LFCN block. The alternate technique was employed for the left lower limb.

The NS technique was modified from the earlier description of Shannon et al.[2] After disinfection and draping, a skin wheal (using 0.5 mL of lidocaine 1%) was raised 2 cm medial to the anterior superior iliac spine (ASIS) and 1 cm caudal to the inguinal ligament (Figure 1). A 22-gauge block needle (SonoPlex Stimcannula, Pajunk Mediztechnologie, Geisingen, Germany) attached to a nerve stimulator (MultiStimSwitch, Pajunk Mediztechnologie, Geisingen, Germany) set at a current of 1.5 mA (pulse width=0.3 ms; frequency=2 Hz) was then inserted. Paresthesias were sought along the lateral aspect of the thigh. If sensory stimulation was not found with the initial insertion, the needle was advanced superficially in a fan-like pattern towards the ASIS. After confirming the presence of paresthesia at a threshold of 0.6 mA or lower, 5 mL of lidocaine 2% were injected to anesthetize the LFCN.

The US technique was performed according to the description of Hara et al.[5] After skin disinfection and draping, a 6-13 MHz linear US probe (probe SL3323, MyLabTouch, Esoate, Genova, Italy) was applied in a sterile fashion medially to the ASIS and caudally to the inguinal ligament, in order to obtain a short axis view of the iliopsoas muscle. A skin wheal was raised with 0.5 mL of lidocaine 1%. Using an out-of-plane technique, a 22-gauge block needle was advanced until its tip was positioned just ventral to the iliopsoas muscle. Five mL of lidocaine 2% were deposited in this location (Figure 2).

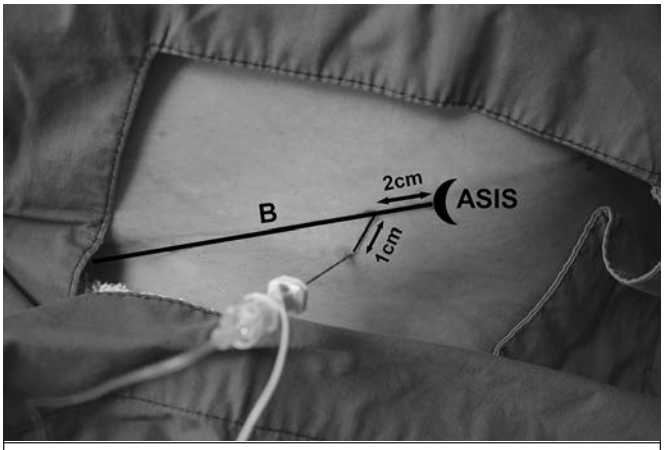

Figure 1. Needle in position for a block of the lateral femoral cutaneous nerve using the nerve stimulation technique. A line has been drawn (B) between the anterior superior iliac spine (ASIS) and the pubic tubercle. The skin puncture site is 2 cm medial along this line and 1 cm caudal to it.

For the US group, the imaging time was defined as the time interval between contact of the US probe with the patient and the acquisition of a satisfactory picture. For both groups, the performance time was defined as the temporal interval between the start of the procedure (skin-probe contact for the US group and skin wheal for the NS group) and the end of LA injection through the block needle. Imaging and performance times were

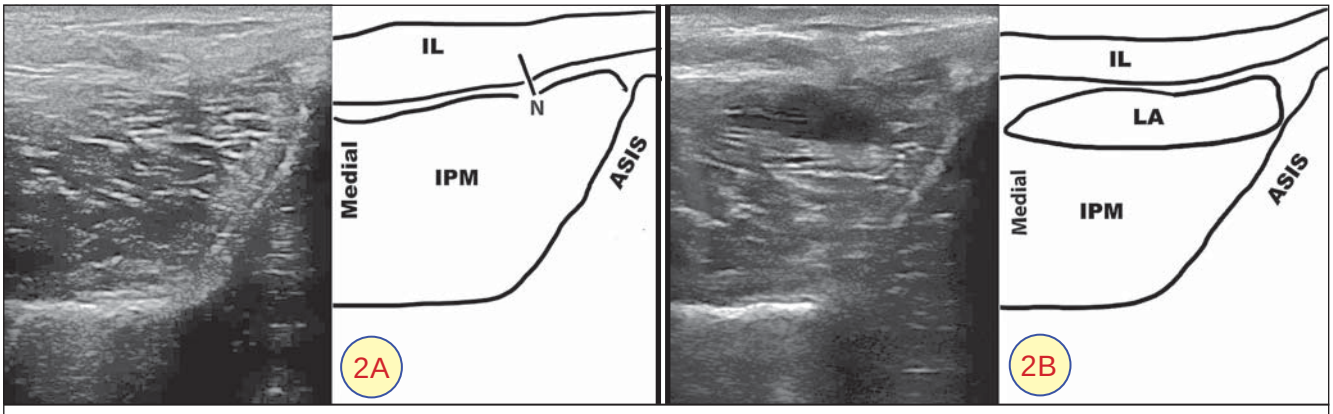

Figure 2. Ultrasound guided block of the lateral femoral cutaneous nerve.
2A: an out-of-plane needle (N) has been placed through the inguinal ligament (IL), ventral to the iliopsoas muscle (IPM), one centimeter medial to the anterior superior iliac spine (ASIS).
2B: 5 mL of local anesthetic (LA) has been injected, spreading under the inguinal ligament (IL) and ventral to the iliopsoas muscle (IPM).

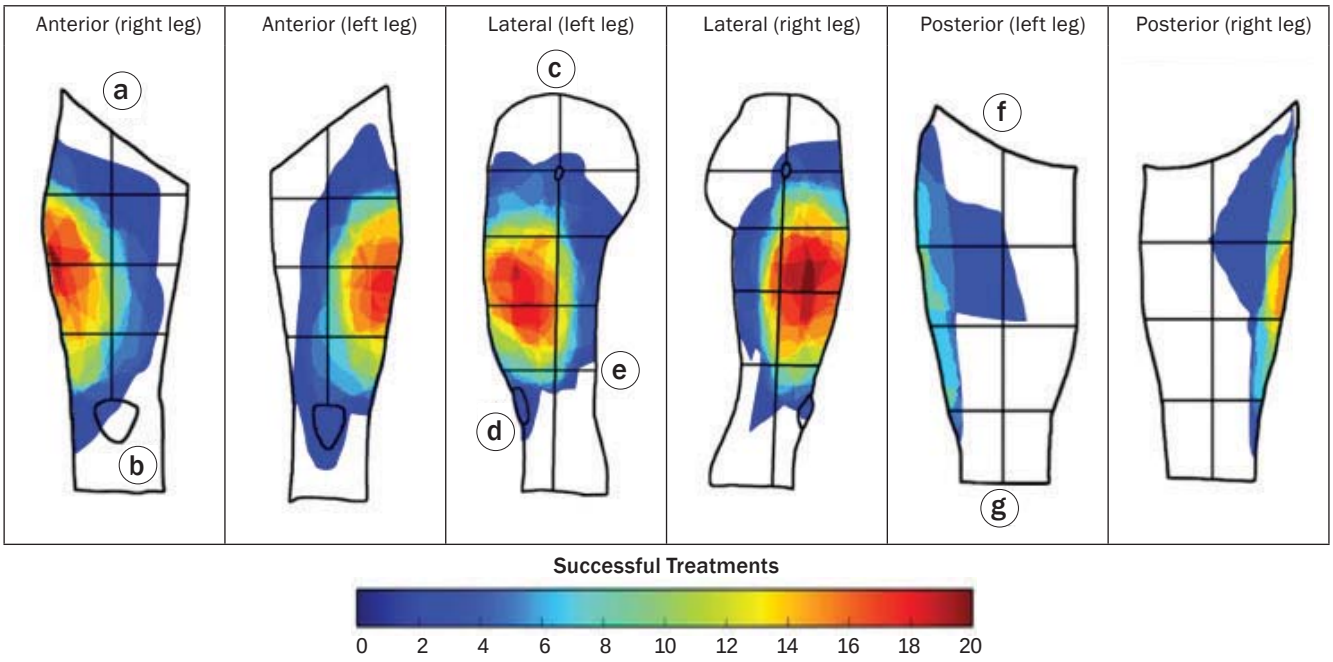

Figure 3A. Sensory area distribution maps observed for successful nerve blocks. Overlapping areas shared between patients are denoted by the area color.

Legend: a. Anterior superior Illiac spine
b. Patella (anterior view)
c. Greater trochanter
d. Patella (lateral view)
e. Lateral joint line
f. Gluteal fold
g. Popliteal crease

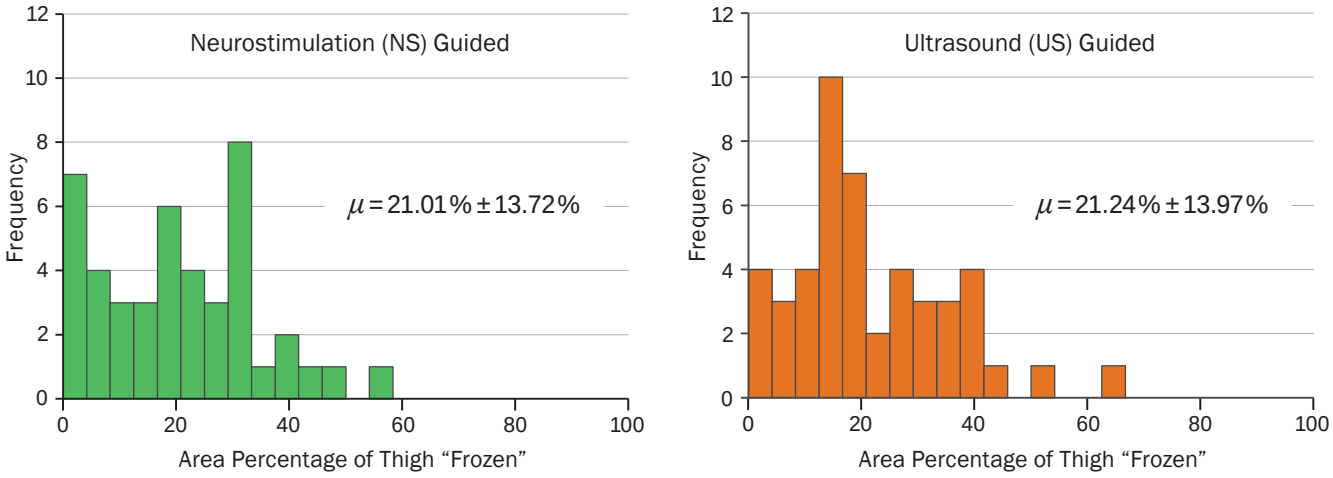

Figure 3B. Histogram of frozen areas (reported as a percentage of patient thigh surface area) experienced by patients for successful NS and US treatments. Average freeze area percentage for each treatment protocol are shown.

recorded by the (nonblinded) investigator assisting the primary operator. The number of needle passes was also recorded by the nonblinded assistant. The initial needle insertion counted as the first pass. Any subsequent needle advancement that was preceded by a retraction of at least 10 mm counted as an additional pass.[6]

After LA injection through the block needle, LFCN block was tested over the lateral aspect of the thigh. Measurements were carried out every minute until 20 minutes by a blinded observer. Block success was defined as loss of sensation to pinprick at a point midway between the ASIS and the lateral knee line.[2] Onset time was defined as the temporal interval required to achieve success. Thus total anesthesia-related time equaled the sum of performance and onset times.

In addition to recording anthropometric data, the blinded observer also assessed incidental femoral block (knee extension) at 20 minutes and procedural pain using a

visual analog scale (0 cm indicates no pain; 10 cm indicates worst imaginable pain).

For those patients with successful LFCN blocks at 20 minutes, the blinded assessor proceeded to determine the extent of the sensory loss in all directions from the reference point. A mark was made where sensation was deemed to have normalized, and the distribution was transferred to the respective grid (Figure 3). Using washable markers, the grids were premarked into quartiles (based on length) in all views, and then further subdivided into eighths. Anteriorly, quartiles were calculated by dividing the distance from the ASIS to superior patella into equal fourths, and then further subdivided into eighths with a bisecting line drawn superiorly from the midpoint of the patella. Laterally, the distance from the superior edge of the greater trochanter to the lateral joint line of the knee was divided into quartiles, and then further subdivided into eighths with a bisecting line drawn superiorly from the midpoint of the lateral joint line. Posteriorly, the distance between the gluteal and popliteal folds was divided into fourths, and then further subdivided into eighths with a bisecting line drawn superiorly from the midpoint of the popliteal fossa.

Table 1. Volunteer Characteristics

Age (years)	40.3 (10.0)
Sex (male/female)	17/4
Body mass index	26.7 (3.5)

Continuous variables are presented as means (SD). Categorical variables are presented as count.

Statistical Analysis

We expected similar success rates for both groups. Our research hypothesis was that performance and onset times would be different. Therefore, the main outcome was the total anesthesia-related time (sum of performance and onset times). According to Shannon et al,[2] the total anesthesia-related time with NS is 10.1±4.7 minutes. Using a paired *t* test to compare both techniques, a 30% difference in total time represented an effect size of 0.74 and required a total of 17 subjects undergoing bilateral blocks in order to achieve a 2-tailed α error of 0.05 and a β error of 0.2. Since onset and total anesthesia-related times can only be calculated for successful blocks, and since we expected an 85% success rate with NS, 20 subjects were needed to account for block failure. Because 21 volunteers inquired about study participation, we decided to enroll all 21 subjects.

Statistical analysis was performed using SPSS Version 21 statistical software (IBM, Armonk, New York). For continuous data, normality was first assessed with the Lilliefors test and then analyzed using a paired *t* test. Data that did not have a normal distribution, as well as ordinal data, was analyzed using Wilcoxon's signed ranks or McNemar's test. All *P* values presented were 2-sided and values inferior to .05 were considered significant.

For territorial mapping of the LFCN, initial digitization was handled with a digital scanner. We used a combination of guided curve detection (as implemented in GraphClick (Arizona-Software.ch, Neuchatel, Switzerland)) and our own implementation of the flood fill algorithm to segment images between FROZEN and UNFROZEN. All images were area-normalized, allowing for comparison between subjects of different physical sizes. Subsequently, images were aligned within ±one degree. Treatment heat-maps (Figure 3) were generated using Matplotlib (http://matplotlib.org). Statistics for the sensor distribution were computed using the open source python module SciPy (http://scipy.org).

Results

All LFCN blocks were performed over a period of 2 days (November 7-8, 2015).

Demographic data are presented in Table 1. Both techniques provided similar success rates (76.2%-95.2%), performance times (162.1-231.3 seconds), onset times (300.0-307.5 seconds), total anesthesia related-times (480.1-554.0 seconds) and procedural pain scores (4.0-4.6). However US required fewer needle passes (3.2±2.9 vs 9.5±12.2; *P*=.009) (Table 2). At 20 minutes, one volunteer (US group) displayed incidental femoral nerve blockade.

No statistical differences were detected when comparing the distribution of sensory loss between US and NS-guided LFCN blocks. The overall average surface area coverage was similar, with normative distribution observed in the available sample size. However considerable variability was encountered between individuals

Table 2. Block Performance Data.

	Ultrasound (N=21)	**Nerve Stimulation** (N=21)	***P* value**
Imaging time	22.5 (19.6)	NA	NA
Performance time	162.1 (125.8)	231.3 (210.9)	.138
Onset time	307.5 (157.8)	300.0 (236.0)	.920
Total anesthesia-related time	480.1 (251.9)	554.0 (366.9)	.443
Success rate (%)	20.0 (95.2)	16.0 (76.2)	.125
Number of passes	3.2 (2.9)	9.5 (12.2)	.009
Block-related pain (VAS score)	4.6 (2.2)	4.0 (2.2)	.139
Incidental femoral block	1.0 (4.8)	0 (0)	>.999

All time variables are in seconds.
Continuous variables are presented as means (SD). Categorical variables are presented as count (percentage).
NA indicates not applicable; VAS, visual analog scale.

and between the 2 sides of a same subject (Figure 3). The most common areas of sensory loss included the central lateral two-eighths anteriorly and the central antero-inferior three-eighths laterally.

Comment

In this randomized trial, we compared NS- and US-guided LFCN blocks. Our results reveal that both modalities result in similar success rates and total anesthesia-related times. We speculate that the lack of intergroup differences stem from the superficial position of the LFCN. Although US confers significant advantages for brachial plexus, femoral, and sciatic nerve blocks,[7-8] its benefits may not extend to smaller neural structures. For instance, Tran et al[9] reported comparable success rates (80%-85%) and onset times for US and landmark-guided superficial cervical plexus blocks. Similarly, Fredrickson et al[10] found no differences in success rate (80%-89%) for ankle blocks performed with the conventional infiltrative method (using 30 mL of ropivacaine 0.5%) or US. Furthermore, in 18 volunteers randomized to a landmark-based deep peroneal nerve block on one side and a US technique on the other, Antonakakis et al[11] observed similar sensory and motor block between 20 and 60 minutes.

We attribute our 76.2%-95.2% success rates to anatomical variations of the LFCN. Instead of being a singular structure, the latter can divide into multiple branches proximal to the inguinal ligament in 28% of cases.[12] For these subjects, NS would provide limited success as paresthesias may only reflect needle tip proximity with an end branch and not the parent trunk. Furthermore the LFCN can be found dorsal, ventral, or lateral to the ASIS.[13-15] In the event that the nerve is ventral to the latter, subinguinal LA deposition (with US guidance) would result in failure.

The technique employed in our US group requires discussion. In the literature, most descriptions pertaining to US guidance have painstakingly identified the LFCN prior to targeting it with LA. In contrast, Hara et al[5] simply used US to inject LA under the inguinal ligament, ventral to the iliopsoas muscle. In 2011, these authors compared their subinguinal method to a nerve-targeting US technique. A significantly higher success rate was achieved with the former (95.9% vs 74.5%; P=.0027).[5] Thus, in the current trial, we opted for the subinguinal technique because it represents the best evidence-based option available. Similarly, for the control group, we purposefully selected NS instead of blind LA infiltration.[2]

The interindividual variability in the sensory distribution of the LFCN has been previously described. Corujo et al[16] reported that in 40.9% of patients, the LFCN displayed a "typical" territory (lateral thigh without extension past the midline of the anterior thigh). However, in 45.5% of the subjects, the sensory distribution of the LFCN encompassed both lateral and anterior aspects of the thigh. Conversely, in 13.6% of the subjects, it was confined to a small, circumscribed area on the lateral thigh.[16] In 16 patients, Hopkins et al[17] found that, after a successful LFCN block, the area of sensory loss was frequently "pear-drop shaped" with its apex lying over or distal to the greater trochanter and its body extending distally and anteriorly towards the knee. However, there existed no region of the thigh that was consistently anesthetized in all 16 subjects.[17] In addition to confirming previous reports by Corujo et al[16] and Hopkins et al[17] pertaining to interindividual variability, our results also reveal for the first time that the sensory innervation of the LFCN can vary within the same individual between right and left lower limbs.

Our protocol contains some limitations. Firstly, our findings are specific to the 5 mL-injectate. We cannot rule out potential differences between NS and US with larger LA volumes. However larger injectates may increase the risk of incidental femoral nerve block, thereby hindering the diagnostic value of LFCN block for meralgia paresthetica. Secondly, the 4.8% rate of femoral block (US group) suggests that even volumes as small as 5 mL can result in LA migration from the LFCN to the femoral nerve. Thus dose-finding studies are required for LFCN block. Thirdly, the benefits derived from the US subinguinal technique (decreased needle passes) apply solely to LFCN blocks with LA. Neuroablative procedures, such as pulsed radiofrequency, would still require targeted identification of the LFCN (with NS or US). Finally, there exists no standard method to delineate neural sensory distribution. Any mapping technique inherently carries a certain amount of imprecision. Nonetheless, future studies could employ 3-dimensional scanning technology to determine the sensory topography for various nerves blocks.

In conclusion, US and NS provide similar success rates and total anesthesia-related times for LFCN block. The territory of the LFCN displays wide inter- and intra-individual variability: the most common distributions in the thigh encompass the central lateral two-eighths anteriorly and the central antero-inferior three-eighths laterally.

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Occlusion Training: Pilot Study for Postoperative Lower Extremity Rehabilitation Following Primary Total Knee Arthroplasty

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Abstract

With continued emphasis on the value of healthcare, factors such as quality of life and patient reported outcomes are critical in evaluating high-demand procedures such as knee replacement surgery. Equally important to the surgery itself is maximizing the effectiveness and efficiency of the treatment, both preoperatively and postoperatively, which can significantly affect the final outcome. Technical outcomes of total knee replacement are generally considered excellent; however, many patients continue to have postoperative pain, functional limitations, and low treatment satisfaction. The recovery process can be difficult and is often prolonged in older patient populations. Blood flow restriction (BFR) training is a resistance exercise performed with a venous tourniquet that stimulates local changes in muscle at low resistance. Herein we report on 3 patients who participated in BFR exercises as an adjunct to their normal physical therapy following total knee arthroplasty.

Total knee arthroplasty (TKA) is a commonly performed procedure proven to provide functional improvement and pain relief for most patients with advanced knee arthritis.[1] Although outcomes of total knee replacement are typically excellent, up to 20% of patients continue to have postoperative pain, functional limitations, and low treatment satisfaction.[2-4] Postoperative health-related quality of life and patient satisfaction is now a key goal of surgery and important measure of operative outcomes.[5] Quadriceps activation has been shown to be negatively affected following TKA and its function has been directly correlated with outcomes.[6-8] Postoperative rehabilitation protocols focus specifically on improving quadriceps strength in order to improve postoperative pain and functional outcomes.[6] Blood flow restriction (BFR) training is a form of exercise that uses brief periods of partially restricted venous blood flow during low load resistance training to improve muscular strength and endurance. These loads are typically 20% to 30% of a patient's single repetition maximum.[7-8] This technique has been used with promising results in a wide spectrum of patients, from high intensity athletes to the elderly.[8-12] Occlusion training has recently gained increased attention in the rehabilitation community where it has produced significant strength gains and in turn earlier, faster rehabilitation.[9-10] We present 3 cases of active patients with a primary diagnosis of osteoarthritis who underwent primary TKA and participated in BFR training as part of their postoperative rehabilitation.

Materials and Methods

All patients were identified and cleared by their operating surgeon to participate in BFR training as an adjunct to their standard physical therapy. Patients were given the opportunity to participate in these therapy adjuncts at the suggestion of their operating surgeon following postoperative rehabilitation and restoration of adequate range of motion as determined by the operating surgeon.

Patients participated in BFR training 3 times a week, during which each person was asked to perform leg extension, leg press, and reverse press during each session under occlusion conditions. The weight was determined based on that individual's one-repetition maxium (1RM). This was calculated by performing a warm-up at 50% of the predicted 1RM, followed by an attempt at an 80% load. If successful, after a one minute rest, the patient repeated the exercise at the same load for as many repetitions as could safely be performed. If the first repetition of 80% was unsuccessful, the weight was decreased, and the process repeated. Each exercise was repeated after one minute of rest. Tourniquet pressure was set at 80% of the limb occlusion pressure. This was determined by first inflating the cuff until the pulse in the dorsalis pedis was lost using an ultrasound probe. Tourniquet pressure averaged between 100 and 150 mmHg for the 3 patients.

Each exercise was performed in 4 sets, with each set to failure, and a 30-second rest between sets. When the

patient was able to perform any one set for more than 120 seconds before muscle failure, the weight for that exercise was increased by 10% to allow for progression. At no time did the occlusion training proceed for greater than 30 minutes consecutively.

Isokinetic muscle testing was performed at the baseline evaluation and at the conclusion of each patient's physical therapy period using a Biodex System 3 isokinetic dynamometer (Biodex Medical Systems, Inc, Shirley, NY 11967). For each patient, peak torque was calculated as a measure of maximum strength attained throughout the range of motion. Total work, a measure of muscular endurance, was calculated as the amount of work performed throughout the range of motion. These measurements were taken at 90 degrees/second of both extension and flexion.

Results

Case 1

A 44-year-old male with left knee pain and radiographic osteoarthritic changes to his medial and patellofemoral compartments with neutral alignment underwent an uncomplicated primary cruciate retaining TKA. Following examination and radiographic work-up, he underwent a course of nonoperative treatment for his osteoarthritis that failed to provide satisfactory long-term relief. As such, he was indicated for a left total knee arthroplasty. Six weeks following his procedure, his pain was well controlled. He had appropriate wound healing and regained his range of motion although he had persistent weakness. His personal goals were to fish, spend time with his children, and continue to serve in his role as an active duty service member in the Army. After participating in 8 weeks of blood flow restriction training, he achieved a 359.3% increase in peak torque during extension and 17.8% increase in flexion peak torque at 90 degrees/second as shown in Figure 1.

Case 2

A 51-year-old male police officer presented with activity-limiting chronic right osteoarthritic knee pain that failed nonoperative treatment modalities. Radiographs revealed significant medial joint space narrowing and degenerative changes of the patellofemoral articulation with a 7 degree varus deformity. The patient underwent primary cruciate retaining TKA followed by our routine postoperative physical therapy program. However, 4-months postoperatively he expressed apprehension in returning to his job as a patrolman due to his continued quadriceps weakness and resultant functional disability. He was subsequently enrolled in a BFR training regimen that included leg extensions, leg press, and standing reverse leg press to improve his quadriceps strength deficit. After an 8-week BFR program, he demonstrated a 57% increase in peak torque in extension and 2.8% in flexion at 90 degrees/second as shown in Figure 2 and was able to return to his work related activities.

Case 3

A 60-year-old male presented with chronic right knee pain that limited his abilities to perform activities of daily living. Radiographs demonstrated tricompartmental osteoarthritis, most severe in medial joint space

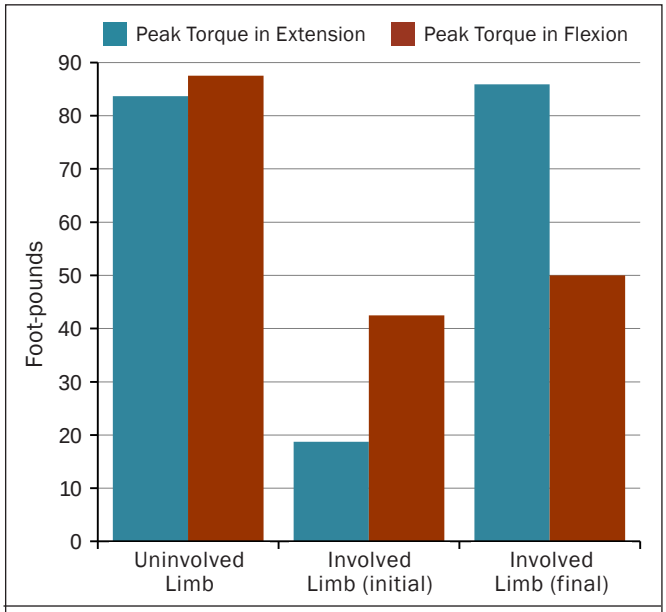

Figure 1. Case 1 change in peak torque achieved at 90 degrees/second following 8 weeks of blood flow restriction training.

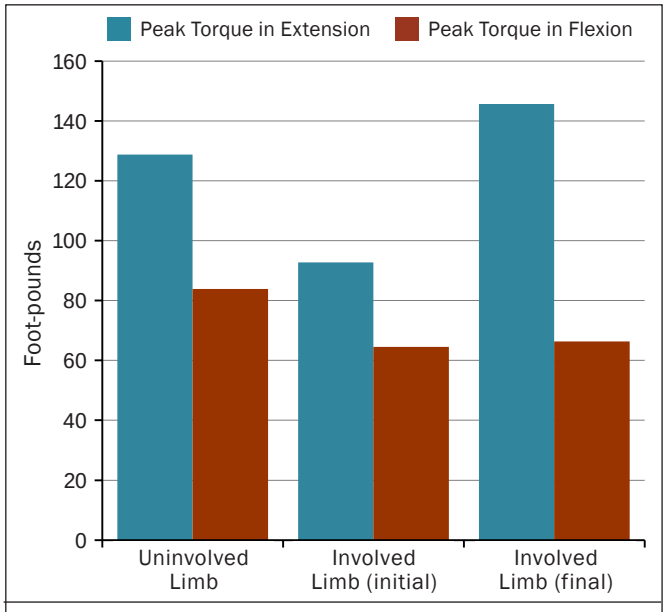

Figure 2. Case 2 change in peak torque demonstrated at 90 degrees/second following 8 weeks of blood flow restriction training.

narrowing and a 7 degree varus deformity. He subsequently failed nonoperative treatment and was indicated for a primary cruciate retaining TKA. His course was complicated by limited range of motion postoperatively. He was indicated for manipulation under anesthesia 20 days after his index procedure. His range of motion was 2 to 100 degrees of flexion after his manipulation. One month after his manipulation, he was referred to physical therapy for BFR due to continued inability to regain his quadriceps strength. After participating in 8 weeks of BFR training, he experienced an increase in peak torque of 84.1% in extension and 126.9% in flexion at 90 degrees/second as shown in Figure 3.

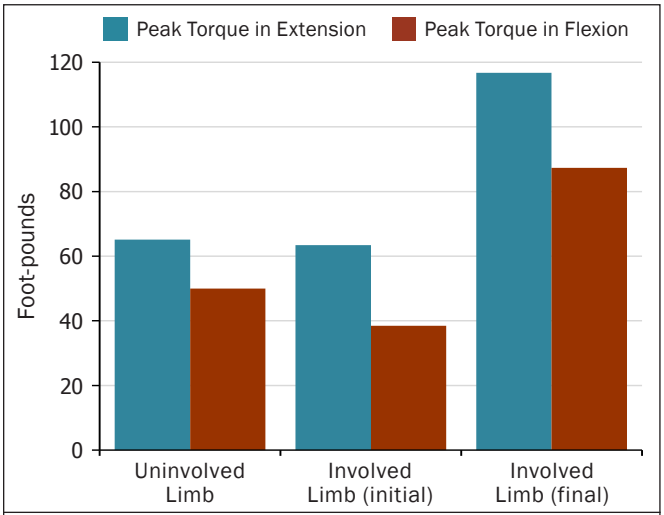

Figure 3. Case 3 change in peak torque demonstrated at 90 degrees/second following 8 weeks of blood flow restriction training.

Comment

In this case series, we report data on 3 patients who underwent total knee arthroplasty and had postoperative functional deficits and physical exam findings indicative of quadriceps weakness. All 3 patients had persistent weakness despite being enrolled in our standard postoperative physical therapy regimen which emphasizes range of motion and quadriceps strength. After participation in an 8-week program of BFR training, all 3 had objective improvements in their quadriceps strength and in all 3 cases exceeded the peak torque measurements of their uninvolved limb as measured prior to initiation of BFR therapy. To our knowledge, this is the first report of the use of BFR therapy following total knee arthroplasty.

As mentioned previously, quadriceps weakness following total knee arthroplasty is well described in the literature. Mizner et al[13] demonstrated a 62% decrease from 10 days preoperative to 27 days postoperatively, and other studies have shown decreased strength compared to healthy controls at time points out to 2 years postoperatively.[14,15] These studies suggest that the weakness is pervasive throughout the full arc of motion of the knee and strength oftentimes never fully reassumes its preoperative level. To demonstrate the importance of this weakness, clinical studies have documented a positive correlation between quadriceps strength and scoring on multiple validated patient-reported outcome measures.[15-17] Given this information, there is certainly a role for novel rehabilitation tactics that improve our ability to rehabilitate postoperative muscle weakness.

Low-load resistance training with blood flow restriction has been shown to elicit substantial increases in muscle mass and strength. While the exact mechanism of action is not yet fully understood, studies suggest that following BFR training there are increased levels of anabolic growth hormones and increased activation of signaling pathways, such as mTOR, that regulate muscle hypertrophy and proliferation of myogenic stem cells.[7,18-20] Further research is required to determine the significance of these factors, though it is clear that BFR therapy results in physiologic changes when compared to standard resistance training.

While there were no adverse events related to therapy in our series, the sample was too small to support any significant conclusions. We did not initiate therapy prior to 6 weeks postoperatively in any patient as the effect of BFR training on wound healing is unknown. The most catastrophic adverse events described in the literature related to BFR training are deep venous thrombosis (DVT), pulmonary embolism, rhabdomyolysis, and exacerbation of ischemic heart disease, all of which occur at less than 1% in the literature.[21] Another study looking specifically at DVTs reported a rate of 0.055% and further demonstrated that there we no increases in hematologic clotting factors after BFR training.[22] Furthermore, although literature has demonstrated that intraoperative occlusive tourniquet use has been associated with decreased quadriceps function postoperatively, the pressures used in BFR training are subocclusive and significantly lower than those used in these studies.[23]

A major limitation of this series is the lack of patient-reported outcomes measurements recorded before and after the implementation of blood flow restriction training and lack of a comparison population. Further clinical studies utilizing validated patient-reported questionnaires in addition to functional outcome measures would allow for a more accurate comparison assessing both the short- and long-term consequences of knee injury and osteoarthritis and the potential benefits of blood flow restriction training in the postoperative period. Further studies with larger cohorts should be undertaken

to better characterize these risks. Furthermore, as this series of patients is small, we are unable to make definitive treatment recommendations. Larger clinical studies are required to better elucidate the benefits and risks of occlusion training following primary TKA. Possible areas for future research would also include the use of BFR training preoperatively as preoperative quadriceps strength has also been associated with better postoperative outcomes.[24] Lastly, as we recognize the potentially devastating complications associated with wound healing complications, this intervention should be used with caution in the acute postoperative period and only in those patients with uncomplicated postoperative courses.

This series represents our early success using BFR training for postoperative TKA patients. While we recognize the limitations of this series, we believe that BFR training may provide patients the opportunity to regain their strength more quickly and completely, and potentially decrease their total duration of physical therapy. Further investigation into this therapeutic modality is clearly warranted.

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Martial Arts-Based High Intensity Interval Training as a Component of Warfighter Rehabilitation and Tactical Athlete Fitness

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The demands on today's Warfighter have created unique challenges to training and equipping Soldiers for military operations. Rarely are large numbers of Soldiers and their equipment marched over great distances relying upon the physical endurance of the troops to reach strategic objectives. Since the onset of hostilities following the attacks of September 11, 2001, military engagements have involved Soldiers transported to and from the area of combat operations by personnel carriers or aircraft with their success and survival far more dependent on individual speed, strength, and tactical agility than upon their 2-mile run time. In addition to the changing physical demands of modern warfare, increasing fiscal scrutiny while maintaining a brisk operations tempo have driven military leadership to question both the effectiveness and cost of current physical training methods. A number of studies have demonstrated high rates of overuse injuries associated with the long-distance marching within our initial entry trainees, further adding to the cost of basic training, delaying combat readiness, and causing the discharge of a number of recruits before they reach their operational unit. International studies have demonstrated that decreased running mileage can have a profound effect on the number of overuse injuries while maintaining physical fitness among trainees.[1] Given the disproportionately high rate of these overuse injuries among female recruits, modification to current training methods is necessary to fully accomplish current advances in the integration of women into combat career fields.

Soldiers in today's military engagements must be equipped with speed, strength, and agility, which are primarily anaerobic functions. Additionally, Soldiers must have middle-distance running and strength endurance—primarily aerobic functions. Thus, a fully optimized Soldier must have peak fitness, both anaerobic and aerobic. The reality of the changing physical demands placed on Soldiers and the legitimate shortcomings of traditional endurance training suggests further advances, applicable for austere environments, are needed in the current methods of physical training across the military.

Recent data suggests these requirements can be met using martial arts-based high intensity internal training (MA-HIIT) by providing optimal aerobic fitness and both extremity and core muscle strength with minimal resource needs in an environment that fosters esprit-de-corps. In addition to a number of health and fitness benefits, HIIT has also been shown to increase aerobic fitness without impeding strength gains when combined with resistance strength training. Though there are a number of recognized safety concerns with martial arts, various safety precautions can be taken to mitigate the risk of injury to apply this type of physical training broadly across the military. Integrating martial arts into HIIT principles could provide a cost-effective and efficient way to train both basic trainees and operational military units to meet the high demands of present-day military operations. This article highlights the known risks and benefits associated with a martial arts-based, high intensity interval training program for consideration to be incorporated into training, fitness, and rehabilitation of Warfighters.

High Intensity Interval Training

High intensity interval training has become a well-known and well-studied method of improving cardiopulmonary and skeletal muscle function with several known metabolic benefits. Enthusiasts use HIIT as a form of both individual fitness and competitive athletic training, integrating it into a variety of different athletic activities. Additional research has broadened the use of HIIT by modifying workouts to achieve activity-specific outcomes all along the aerobic-anaerobic spectrum. The training consists of "repeated short (less than 45 seconds) to long (2 to 4 minute) bouts of rather high-intensity exercise interspersed with recovery periods."[2] Optimal cardiovascular and peripheral tissue adaptions are believed to occur when the athlete is performing at or close to their VO_{2max} over long periods of time. This can be achieved through a variety of different exercises, including short-distance sprints, stationary or road cycling, or martial arts. Documented benefits of HIIT are not limited to physiologic and metabolic function, as workouts are commonly much shorter in duration than

traditional lower-intensity, high-volume workouts, saving both time and money for participants.[2,3]

Mixed Martial Arts

Mixed martial arts (MMA) is a sport derived from a mixture of modern and traditional combat sports that incorporates punches and kicks from western boxing, kick-boxing, and muay thai, stand-up grappling from judo, Greco-Roman and freestyle wrestling, and ground fighting from jujitsu, judo, and freestyle wrestling. This admixture of various combat sport traditions grew in popularity under a variety of different names, including ultimate fighting, toughman fighting, extreme fighting, and mixed martial arts. The physical requirements of MMA are characterized by high-intensity and explosive movements over short time intervals combined with the strength and power of the contenders to deliver high velocity blows and control or grapple their opponents to achieve dominant positioning and submission holds. Mixed martial arts fights usually last 3 to 5 rounds for 5 minutes each. The winner is decided by knockout, technical knockout, or submission; or the judges decides the winner if time runs out.[4,5] As the sport has grown in popularity, the use of MMA-based workouts has also increased. We recommend a regimen of modified MMA exercises that excludes floor combat skills and live-sparring, integrated with HIIT that we hereafter refer to as martial arts-based high intensity interval training (MA-HIIT).

Drawbacks to Implementing Martial Arts-Based High Intensity Interval Training Programs

Implementing an MA-HIIT fitness regimen broadly across the military would come with a number of recognized risks, some of which are presented in Table 1. Prominent members within the sports medicine community have long voiced concerns over the safety of martial arts overall and western boxing in particular.[6,12] Some have argued that the sole intent of boxing is to inflict physical damage on the opponent and as such is "immoral violence."[12] In truth, there is evidence to support the premise that professional boxers do suffer from permanent brain damage with up to 87% of boxers demonstrating deficits on 2 or more neurophysiological tests.[8] With the rise in popularity, and subsequent profitability of mixed martial arts, this opposition has since been extended to all forms of "extreme" fighting, with calls for reform in the American Medical Association's position on such sports.[13]

Given the rise in popularity and involvement of a wide range of ages, physicians have taken a closer look at the risks associated with the sport. Studies of tournament-style fighting demonstrates a wide range of injuries. Thirty eight percent of taekwondo tournament fighters have evidence of head and neck injury, as well as fractures and one reported fatality.[14] With the exception of cutaneous hematomas and bruising, musculoskeletal injuries are the most common type of injury seen in MMA fighters.[9] Given that there is a broad range of martials arts forms and styles, each with varying degrees of intensity and contact, coupled with the fact that many martial artists never compete in tournaments, Zetaruk et al[10] compared the injuries in different types of popular martial arts during both periods of normal training and tournament competition. Their results demonstrate the obvious correlation between the degree of contact and injury severity among martial arts. Taekwondo, for example, portrayed a 3-fold increase in risk of injury than Shotokan karate (a low-impact form of karate) and Tai chi, which has no opponent present, confers a very minimal risk of injury even though many participants are about the age of 65. In the context of normal practice and interspersed tournament play, martial artists sustained varying degrees of injury with 59% of students in taekwondo sustaining time loss injuries, 51% in aikido, 38% in kung fu, 30% in Shotokan karate, and only 14% of students in tai chi.[10] They also found that participants who had been practicing for 3 or more years and were aged 18 years or older had a higher risk of sustaining injury, indicating that more experienced and stronger participants were more capable of inflicting injuries on opponents. The implementation of a fitness regimen infused with low contact martial arts would require measured risk analysis with reasonable preventive measures

Table 1. Unfavorable findings and opinions regarding MA-HIIT published in the literature.

Reference	Summary
Lundberg[6]	Boxing is dangerous and immoral.
Weisenthal et al[7]	CrossFit participants showed 20% injury rate, most commonly of the shoulder, lower back and knee. Decreased injury rates seen when trainer present.
Casson et al[8]	87% of boxers in study demonstrated signs of brain injury on at least 2 different neurophysiological studies.
James[9]	Besides bruising and cutaneous hematomas, muscle and joint injury are the most common type of injury in MMA.
Zetaruk et al[10]	There is a threefold greater risk of injury in taekwondo than in Shotokan karate. There is a decreased number of injuries in MA participants less than 18 years old and an increase risk of injury in participants with greater than 3 years of experience.
Bergeron et al[11]	CrossFit may be associated with increased risk of rhabdomyolysis, overuse injuries, muscle strain, ligamentous injury, and stress fractures.

to address known injury risks and widespread concerns about the implications of martial arts and western boxing.

The health and fitness market has also seen a rise in a variety of extreme conditioning programs (ECP) such as CrossFit, P90x and Insanity that are similar in intensity to MA-HIIT. A number of concerns have been voiced regarding such programs due to the relative intensity of the workouts. In 2011, the Consortium for Health and Military Performance and American College of Sports Medicine consensus paper on extreme ECPs among military personnel states that ECPs may be associated with increased risk of rhabdomyolysis, overuse injuries, muscle strain, ligamentous injury, and stress fractures.[11] Another survey of CrossFit athletes showed that the most common injuries were to the shoulder, low back, and knee with an overall injury rate of 20%.[15] These data give reason to implement preventive measures to mitigate the risk of injury possible in MA-HIIT that are discussed later in this review.

Martial arts have grown in popularity in the western world as a form of physical fitness regimen and as competitive sports with appeal across a broad age-range for both sexes. As physicians are charged with oversight of our society's medical wellbeing, there are a number of reasons for medical professionals to have measured concern with the promotion of combat sports and high intensity fitness regimens. Thus, the advantages of this type of training as well as an expansive discussion of methods to mitigate known risks must also be considered to perform a thorough, evidence-based risk benefit analysis of such training.

Benefits of a High Intensity Interval Training Program

There are several well-studied advantages to both martial arts and HIIT, some of which are presented in Table 2. We suggest that integrating martial arts-based exercises with HIIT principles would yield additive benefits to create an optimized training program for the unique demands of military members. Such benefits include observed cardiovascular and metabolic improvements, injury prevention rates, increased team building within participants, and the low relative costs of these regimens.

A number of studies have investigated the functional performance outcomes of HIIT in variety of settings. HIIT has been shown to increase VO_{2max} and O_2 consumption and improve exercise-induced cardiac output, translating to improved overall exercise performance.[16,17,19] Much of the enthusiasm for HIIT in the physical training community stems from the possibility to decrease adaptive interference when improvement in both aerobic and anaerobic function is desired. Many experts hold that muscle hypertrophy, strength, and power from resistance training (ie, low-repetition, heavy-weight lifting) are inhibited with high-volume endurance training (ie, long-distance jogging or cycling).[18,38] Thus, in the context of the Warfighter or "tactical athlete" who must optimize both power and endurance, this dynamic would create a tradeoff between these 2 metrics of performance. Essentially, the Soldier can either be relatively weak with high long-distance endurance or strong with relatively low long-distance endurance. A study by Laird et al[18] recently challenged this theory. Twenty-eight recreationally active women were enrolled in either a concurrent sprint interval and resistance training (CST) group or a control group of resistance training (RT) alone. The results demonstrated significant but equal improvements in one repetition max back squat, maximal isometric force, average peak anaerobic power testing, and zero incline treadmill velocity. More importantly, the results showed no evidence of interference of strength adaptations in the CST group and simultaneous improvements in both anaerobic and aerobic function when HIIT and resistance training are used concurrently.[18] Smith et al[17] further validated the aerobic improvements achieved by HIIT in a group of men and women subjects who underwent a 10-week cycle of high intensity power training.

Metabolic improvements in HIIT have been demonstrated in a number of studies investigating cellular adaptations explaining functional gains in both strength and endurance. Burgomaster et al[20] observed an increase in the maximal activity of citrate synthase leading to increased muscle oxidative potential and twice the endurance capacity in cyclers who performed 6 sessions of 15-minute sprint cycling over a 2-week time period. These data demonstrate that workouts consisting of intense, short duration, sprint-style intervals can significantly improve endurance capacity and muscle oxidative potential at or above that of long-distance aerobic training regimens over similar time periods. Additionally, Ni Cheilleachair et al[21] observed similar results in a group of competitive male rowers finding that HIIT performed twice weekly, in addition to baseline aerobic exercise, demonstrates improved endurance performance in rowers and is more effective than slow-paced, long-distance training at improving associated aerobic physiological variables including power output and lactate threshold. Investigation by Gibala and McGee[22] showed that a short-term HIIT program produced marked increases in oxidative enzyme expression, oxidative capacity, improved endurance capacity, and changes in carbohydrate metabolism that are comparable to traditional endurance training with a fraction of the training time. Research has also extended beyond exercise science demonstrating even

Table 2. Positive findings and opinions regarding MA-HIIT published in the literature.

Reference	Summary
Coswig et al[5]	MMA sparring matches achieve moderate to high intensity, yet promote only low to moderate muscle damage or inflammation based on serum levels of creatinine kindase, IgA, glucose, and cortisol.
Hwang et al[16]	8-week HIIT program is associated with improvement in cardiac ejection fraction which was positively related to exercise-induced improvements in peak 0_2 consumptions.
Smith et al[17]	High intensity power training caused increased VO_{2max} and aerobic fitness.
Laird et al[18]	HIIT does not interfere with strength adaptations while improving aerobic fitness.
Astorino et al[19]	HIIT regimens increase VO_{2max} which is related to an increase in cardiac output.
Burgomaster et al[20]	2 weeks of HIIT showed increased citrate synthase maximal activity and doubled endurance capacity during cycling exercise at 80% VO_{2max}.
Ni Cheilleachair et al[21]	HIIT performed twice weekly in addition to aerobic exercise demonstrates improved endurance performance in rowers and is more effective than long, slow-distance training at improving associated aerobic physiological variables including power output at lactate threshold.
Gibala and McGee[22]	Short-term high-intensity interval training shows marked increase in oxidative enzyme expression, improved oxidative capacity, improved endurance capacity and changes in carbohydrate metabolism that are comparable to traditional endurance training with a fraction of the training time.
Cho et al[23]	HIIT regimen in mice alleviates whole body insulin resistance associated with obesity.
Richards et al[24]	16 minute sessions of very high-intensity, sprint interval exercise training distributed over 2 weeks increased insulin sensitivity.
Drigny et al[25]	HIIT regimens in patients with metabolic syndrome was associated with decreased BMI, reduced waist circumference, and decreased QTd EKG parameters.
Byun et al[26]	Basic taekwondo movements are associated with statistically significant improvements in children's posture.
Bu et al[27]	Tai Chi studies have demonstrated stress reduction, improved agility and balance, posture control, lower extremity strength improvement and decreased musculoskeletal decline seen in aging individuals.
Yan et al[28]	12-week Tai Chi regimen is associated with clinically significant improvements in pain, stiffness, and physical function in patients with knee osteoarthritis.
Yang et al[29]	Tai Chi shows beneficial effects by improving motor function, balance, and functional mobility in people with Parkinson's disease compared to other active therapies.
Woodward[30]	Martial arts are likely associated with decreased number of falls in elderly, improved relaxation, self-esteem, mind-body coordination, decreased depression and sleep disruption, increased self-esteem in cancer patients, and possibly an adjuvant therapy for symptom control in ADHD patients.
Tong et al[31]	Core muscle strength improvements are associated with improved endurance running performance.
Jones et al[32]	Amount of unit training in terms of running distance and amount of weight-bearing physical training was associated with increased risk of over-use injury.
Santtila et al[33]	HIIT would be an effective method of training recruits because of observed aerobic improvements and low injury rates compared to traditional methods.
Hak et al[34]	Injury rates similar in CrossFit as Olympic weight lifting, power lifting, and gymnastics. Shoulder and spine injuries are the most common. No incidences of rhabdomyolysis
Poston et al[35]	There is no increased risk of rhabdomyolysis in CrossFit/HIFT participants compared to long distance running.
Dibble et al[36]	HIIT consisting of resistance training produces increased muscle volume, muscle force, and functional status in Parkinson's disease patients when compared to standard exercise programs.
Dibble et al[37]	High intensity eccentric resistance training improves muscle force, bradykinesia, and quality of life in Parkinson's disease patients to a greater degree than standard exercise programs.

broader effects of HIIT programs. Cho et al[23] saw an improvement in whole-body insulin resistance associated with obesity in laboratory mice after exposing them to HIIT regimens. Richards et al[24] saw similar results in a test group of healthy adults after 2 weeks of sprint interval training. Drigny et al looked at the effect of HIIT on patients with metabolic syndrome. Improvements were seen in a number of physiologic metrics associated with metabolic syndrome including body mass index (BMI), waist circumference and a decrease in echocardiogram QT dispersion parameters which has been hypothesized to be associated with metabolic syndrome secondary to hyper-sympathetic nervous syndrome at baseline.[25]

Benefits of Martial Arts

The focus on posture, balance and mind-body control has demonstrated a variety of both emotional and physical benefits for those who practice martial arts. Byun et al[26] studied the effects of a regimented treatment program of noncontact taekwondo movements on a group of children with postural deficiencies. The children showed significant improvement in posture afterwards,

demonstrating the effect of martial arts training on core muscle strengthening. Tia chi, a no-contact, no-opponent style of martial arts often practiced by a wide range of ages including the elderly, has been associated with a variety of health benefits including stress reduction, improved agility and balance, posture control, and lower extremity strength improvement and has been associated with decreased musculoskeletal decline in aging individuals.[27] A meta-analysis of the effects of a 12-week regimen of tai chi in patients with symptomatic knee osteoarthritis showed improvement in pain, stiffness, and physical function.[28] The effect of tai chi on neurodegenerative processes and balance in the elderly has also shown beneficial effects in improving motor function, balance, and overall functional mobility in people with Parkinson's disease when compared to other active therapies.[29] Woodward et al[30] further studied the broad effects of martial arts on health status, suggesting that martial arts are likely associated with decreased number of falls in the elderly, relaxation, mind-body coordination, decreased depression and sleep disruption, increased self-esteem in cancer patients, and possibly an adjuvant therapy for symptom control in patients with attention-deficit hyperactivity disorder. Given the wide variety of health benefits and symptom improvements seen in patients practicing martial arts, especially in tai chi studies, further investigation is needed to determine the efficacy of this approach as well as to define the specific training regimens needed to achieve such results. Even without such available data, the evidence presented by the studies cited above clearly supports the potential of martial arts to cost-effectively produce significant health improvements for a variety of patients.

Benefits of a Martial Arts-Based High Intensity Interval Training Program

The integration of martial arts-based workouts into HIIT principles is based on the number of benefits demonstrated in the literature for both martial arts and HIIT. Tong et al[31] studied the effect of core muscle strengthening in addition to HIIT on endurance running economy, showing that the addition of core strengthening exercises, such as MA-HIIT, can add to the aerobic improvements seen in HIIT. Coswig et al[5] used time-motion responses and biological parameters of fatigue and physiological stress to characterize the effect of athletes participating in sparring matches outside of actual competition fights. They found that MMA sparring achieves moderate to high intensity yet only low to moderate muscle damage and inflammation based on serum levels of creatinine kinase, IgA, glucose, and cortisol. These data show MMA sparring is an efficient way to simulate the intensity of a live fight with low physiological effect. This further supports the hypothesis that martial arts-based drills and sparring are a practical method to achieve the level of intensity required for HIIT.

When compared to traditional methodology of training military personnel, MA-HIIT provides an effective manner by which to prepare Soldiers for the demands of modern warfare, decreases overuse injuries, and substantially lowers the cost of preliminary military training. Several authors have detailed the physical challenges faced by today's Warfighters unique to that of past conflicts.[39-41] Mala et al[39] described the "anaerobic battlefield" in which Soldiers are often engaged in high-intensity combat activities such as moving under fire, evacuating casualties, and reacting to contact with enemy fire, often in close-range urban settings. During recent conflicts, such as Operation Iraqi Freedom and Operation Enduring Freedom, troops were often transported with personnel carriers or airborne insertion. This is in sharp contrast to traditional warfare where infantry Soldiers had to travel on foot over long distances while carrying their personal equipment and weapons to wage assaults. Once inserted into in an objective, Soldiers today perform anaerobic bursts of sprinting, climbing, pulling, or crawling while carrying a large amount of heavy gear. Turner et al[40] suggests that HIIT combined with strength and power training and decreasing running volume would deliver the results needed to optimize the modern day Warfighter for such tasks. This shift in battlefield requirements has yet to be fully realized in the way Soldiers are physically trained in preparation for deployments. The dynamics of modern warfare necessitate a training program that develops anaerobic total body power and explosiveness while maintaining the cardiovascular capacity to support it.[38,39]

In addition to the evolving demands of modern warfare, the recent advances taken to integrate women into combat career fields requires training programs that accommodate the exercise physiology unique to women. Women, on average, have lower body mass, lower bone mass, greater body fat, and less lean body mass then men. Due to the low levels of circulating testosterone, women have less muscle mass and smaller ratio of fast twitch to slow twitch fibers. The circulatory and oxygen delivery capacity of women is further limited by smaller hearts, less circulating intravascular volume, and lower hemoglobin than men.[42] Even in the context of such physiologic challenges to optimizing the female tactical athlete, several studies demonstrate that strategic strength and conditioning regimens can significantly decrease the sex-based differences in physical performance.[43-45] Kraemer et al[44] demonstrate that periodical resistance

training significantly decreases observed strength difference in men and women. Additionally, they demonstrated that increased aerobic fitness resulted in improved functional strength such as repetitive box lifts. Through the ability to accomplish both aerobic fitness and concurrent resistance training, MA-HIIT would facilitate both muscular hypertrophy and improve functional strength to optimize the capability of women to effectively participate in combat career fields.[43,44]

One of the strongest factors catalyzing change in military training across several nations is the rate of injuries seen in traditional training methods consisting of large volume endurance exercises (ie, long-distance running or marching) and the associated high cost of these injuries.[46] In 1993, Jones et al[32] studied the epidemiology of military training injuries, finding that 37% of basic trainees incurred lower extremity injuries, 28.4% of which were overuse injuries (stress fractures, Achilles tendonitis, or patellofemoral syndrome). More importantly, they found that the amount of unit training in terms of running distance was positively correlated with overuse injury. Later, in 2001, Knapik et al[47] expanded on these findings showing that overuse injuries accounted for 75% and 78% of male and female injuries respectively and that women were twice as likely to sustain training-related injuries as men. It was previously thought that encouraging pretraining in recruits would reduce the large number of overuse injuries seen in basic trainees. Swissa et al[48] explored this theory and found that no correlation existed between pre-basic training activity and the number of stress fractures reported. This further highlights the need for high-quality, evidence-based training programs in the military. Even among highly trained Naval Special Warfare Sea, Air, and Land (SEAL) operators that routinely engage in high-risk, tactical missions and training, 20% of all their injuries occur during physical conditioning.[49] In the face of these high injury-rates, HIIT has been recognized as an adequate method to train basic trainees primarily due to the decreased rates of injury as well as the positive effect on aerobic fitness.[33] In summary, the high rates of overuse and musculoskeletal injuries in both basic trainees and special operations force units would be decreased while increasing physical performance by implementing MA-HIIT into military physical training programs.

The ability to actually address the well-known causes of overuse injuries has proven more difficult than expected, yet there have been several studies demonstrating effective techniques to do so if implemented appropriately. Chalupa et al[46] found that Soldiers participating in the Army physical readiness program (APRP) had reduced overuse and musculoskeletal injuries including tarsal bone and femoral neck stress fractures. The primary differences in the APRP from traditional training is a decreased amount of long-distance endurance running and integration of interval training. Additionally, researchers found that the Israeli military was able to reduce high rates of stress fractures in Soldiers by decreasing the total distance marched or ran and increasing the number of hours slept per night by trainees.[1] Given the clear association between overuse injuries in the military and total distances ran by trainees, MA-HIIT would provide an effective way to improve aerobic fitness while decreasing long-distance training to minimize overuse injuries.

Strategies to Mitigate Potential Risks of MA-HIIT

Given the relative intensity of MA-HIIT and the known risks associated with it, there are several measures that can be taken to mitigate such risks. We recommend against using exercises that incorporate live strikes to the head and groin or choke and submission holds which would largely decrease the known risks of head and neck injury in combat sports.[10,50] We also recommend the use of protective gear such as gel gloves and proper punching pads or bags.[30] Attention should be given to proper technique, as there is data to suggest that adherence to correct form and prescribed workout regimen with the use of a trained instructor or instructor-participant decreases injury.[9,15,51] Additionally, in agreement with several other sources,[11,34] we recommend periodization with a proper familiarization period, individualizing workouts to Soldiers' abilities, frequent inspection of workout equipment and facilities, and monitoring profile rates that suggest evidence of overtraining within units. We also recommend the strict adherence to known principles of exercise (ie, PROVERBS* and FITT†) to encouraged successful, well-balanced and injury-free physical training. Though MA-HIIT is likely associated with several risks of injury, implementing rather simple methods to decrease such risks enables MA-HIIT to be both effective and safe for broad use across the military.

Risk/Benefit Analysis

After sufficient review of the available literature pertaining to the use of MA-HIIT, the recognized risks and benefits associated with this type of physical training program can be compared. The main risks for participants largely consist of musculoskeletal injury given the dynamic exercises used. Using appropriate oversight and

*Progression, Regularity, Overload, Variety, Recovery, Balance, Specificity. Source: US Army Fitness Handbook (http://www.physicallytrained.com/army-fitness-handbook-1-physical-fitness-principles/).

†Frequency, Intensity, Time, Type (http://stretchcoach.com/articles/fitt-principle/).

technical instruction with periods of familiarization for participants, these risks can be decreased. Though some believe there to be a risk of rhabdomyolysis secondary to the intensity of the training, several sources point out there is little to no evidence to support such claims, suggesting the overall intensity of MA-HIIT confers minimal risk on participants.[34,35] Many of the injuries associated with competitive martial arts are mitigated by not striking opponents and using safety equipment. The numerous studies demonstrating benefits in HIIT, such as improvements in aerobic fitness without impairing strength training and lower rates of overuse injury secondary to lower mileage make it an optimal model of physical training. A decrease in the number of overuse injuries alone could potentially save the military millions of dollars annually. Additionally, MA-HIIT betters equips the Warfighter for the anaerobic demands of modern warfare with the cardiovascular reserve to sustain prolonged engagements. Given the known risks and benefits of MA-HIIT, this program would provide substantial improvement to existing training programs and should be used to train military personnel. Since 2010, the Center for the Intrepid and the Department of Orthopaedic Surgery at Brooke Army Medical Center have incorporated a martial arts-based high intensity interval training program in the rehabilitation of over 500 wounded warriors with extremity war injuries, both amputees and limb-salvage patients, with oversight by Orthopaedic Sports Medicine specialists trained in martial arts.

Conclusion

Martial arts-based high intensity interval training, overseen by a qualified instructor and following known principles of exercise and sports medicine provides an optimal training program for today's Warfighter, as well as rehabilitation/reintegration of the wounded warrior. Implementation of MA-HIIT across the military has the potential to provide a time and cost effective method of training that would improve existing levels of physical performance and likely decrease overuse injury rates in the military. Further well-formulated, prospective studies are necessary to provide more data for the implementation of MA-HIIT programs across both military and civilian organizations.

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Martial Arts-Based High Intensity Interval Training in the Rehabilitation of Combat Amputees

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The US armed forces are currently engaged in the longest active period of continuous armed conflict in US history. The advancements in tactical combat casualty care, rapid medical evacuation, and improvements in personal body armor and armored vehicles have resulted in unprecedented survival rates. The second-order effect of the improved survival of combat injuries is the increased clinical burden of extremity injuries, including amputations.[1] These unique features of casualty care within Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF), coupled with the widespread use of a myriad of improvised explosive devices (IEDs)/roadside bombs have given rise to the almost 1,700 individuals with major limb amputations from 2001 to 2015.[2-5]

The long-term nature of musculoskeletal combat injuries has a profound effect on service members' potential for continued military service as well as their quality of life after separation from service. In a cohort from 2001-2005, 69% of unfit-for-duty conditions were orthopaedic/musculoskeletal. In the midst of OIF and OEF, many advances were made with regards to rehabilitation and reintegration of service members with severe extremity injury, regardless of limb-salvage or amputation. Unfortunately, the return to duty rate postamputation is low, on average 8.8% for lower extremity amputations and 8% for upper extremity amputations.[6,7] Furthermore, regardless of whether the medical disposition of the injured service member is return to duty, continuation on active duty in another military occupational specialty, or separation from military service, their emotional wellness remains significantly degraded. An estimated 28.7% to 35% of combat amputees have comorbid depressive symptoms.[8,9] The toll that a traumatic amputation has on a Soldier's physical and mental wellbeing cannot be overstated. In a study of resource utilization in the care of combat injuries, "extremity injuries require the longest average inpatient stay, were responsible for 64% of total inpatient resource utilization and ultimately disabled 64% of those injured."[10] It is clear that extremity injuries represent the largest clinical burden of the current and recent past military conflicts, the most severe of which are combat amputations. Military orthopaedic surgeons are now charged with providing the highest level of treatment and rehabilitation for posttraumatic combat amputees to ensure they regain the highest possible quality of life regardless of the overwhelming challenges they face, while also retaining these critical lessons learned for the betterment of casualties from future wars.

Treating the combat amputee requires careful consideration of a number of characteristics unique to these patients when compared to amputees amongst the general population. Of the amputations performed in the US general population, over 80% are due to nontraumatic causes, the majority of which being vascular and oncologic disease.[11] These patients are typically older, have several comorbidities, are less active at baseline, and have decreased functional demands when compared to posttraumatic amputees, especially those of the military.[12] In fact, nearly half of the patients that receive an amputation secondary to vascular disease will die within 5 years of the operation.[13] Posttraumatic amputees, on the other hand, are often younger, in better physical and cardiovascular condition at the time of injury, desire more active lifestyles, and have a higher survival rate following amputation.[14] Many combat amputees also sustain other injuries associated with their combat trauma. As many as 16% of amputees have lost more than one extremity, 39% also have long bone fractures, 45% have active infections, and 12% have peripheral nerve injuries.[15] Additionally, posttraumatic stress disorder is commonly associated with patients with orthopaedic combat injuries.[6] Taking into consideration the characteristics unique to the posttraumatic combat amputee is essential in providing comprehensive rehabilitative care with several nuances that differ from standard noncombat amputee care.

Since the onset of the hostilities following the attacks of September 11, 2001, several advances related to the

rehabilitation of the combat amputee have been developed to achieve maximum function in these patients. Research shows a number of positive aspects of exercise routines relevant to combat amputees including improved health outcomes of quality of life, functional capacity and mood states, decreased metabolic cost of ambulation, and reduced anxiety.[16-18] Previous studies have shown that participation in sports can help amputees cope with their perceived physical impairments by providing adaptive athletic opportunities that maximize engagement in new activities while minimizing disability.

Additionally, pursuing sports as an amputee allows patients to discover the options available to them regarding different types of activities and prostheses, as well as gain the motor control necessary to control the prosthetic limb for athletic participation.[12] One study showed that rehabilitation programs with the use of the prosthesis to achieve activity correlates with improved overall quality of life and satisfaction with the prosthesis.[19] Specifically, measures of quality of life and self-esteem are higher in amputees who participate in sports as well as "enhanced psychological well-being, self-confidence, and coping behavior."[12] Amputee participation in athletics leads to improvements in the cardiopulmonary system, muscle force generation, and lean body mass, as well as decreased rehabilitation time.[12] Using sports to develop a physical fitness regimen for combat amputees is a component of the culturally competent care process for veterans that is proving to be essential to their overall rehabilitation.[12]

High intensity interval training (HIIT) has become a popular evidence-based approach to developing cardiovascular fitness as well as improving muscular strength. The HIIT programs emphasize short, repetitive intervals of less than 4 minutes of explosive exercises, allowing the trainee to exercise at or close to VO_{2max} over a significant period of time.[20] Several studies demonstrate that HIIT can lead to improvements in cardiopulmonary fitness, musculoskeletal strength, and several metabolic parameters. The training regimens are modifiable to optimize activity-specific improvements at various points along the aerobic-anaerobic spectrum. A number of different exercises can be used within the HIIT model including sprints, seated rows, cycling, and martial arts. Recently, researchers have investigated the utility of modifying HIIT principles to maximize the fitness requirements of men and women in the armed forces into a program called martial arts-based high intensity interval training or MA-HIIT.[21]

Benefits of an integrated MA-HIIT program include "observed cardiovascular and metabolic improvements, decreased injury rates, increased team building within participants, and the low relative costs of these regimens."[21] The numerous studies demonstrating the benefits of HIIT, such as improvements in aerobic fitness without impairing strength training and lower rates of military training overuse injury secondary to lower running mileage make MA-HIIT an optimal model of physical training in the military. Additionally, MA-HIIT better equips the warfighter for the anaerobic demands of the modern battlefield with the cardiovascular reserve to sustain prolonged combat engagements.[21]

Although conceived as a way to optimize fitness and resilience of the fighting force in general, MA-HIIT is also being used to optimize the rehabilitation of combat amputees. Since 2010, the Center for the Intrepid and the Department of Orthopaedic Surgery at the San Antonio Military Medical Center have used a martial arts-based high intensity interval training program to rehabilitate over 500 combat veterans who sustained severe extremity injuries, both amputees and limb salvage patients, as demonstrated in the Figure. Patients receive coaching during MA-HIIT sessions by Orthopaedic Sports Medicine specialists trained in martial arts. While several combat amputees have thrived in this program and were

A combat amputee undergoing martial arts-based high intensity interval training at the Center for the Intrepid at San Antonio Military Medical Center.

very positive in their assessments of its results, there remains a dearth of scientific evidence-based practices from which to derive best practices on the use of MA-HIIT for rehabilitating these combat injured patients. Though some authors advocate gradual orientation to exercise regimens and limiting amputees to moderate or low intensity exercises, little empiric evidence exists to support these reservations.[22] In fact, one study showed similar injury rates among amputees and able bodied players competing in noncontact football.[12] Patients that begin a rehabilitation program sooner after their amputation achieve better walking ability postoperatively.[23] Though more studies are needed to explore the effectiveness of MA-HIIT on this subset of traumatic amputees, the potential of providing a comprehensive and effective rehabilitation program remains promising given the current body of knowledge.

The combat amputee has several barriers to successful rehabilitation to premorbid function that are unique to young, healthy, and motivated patients who underwent extremely traumatic injuries. MA-HIIT programs offer an excellent method to achieve and maintain maximal cardiovascular fitness and musculoskeletal strength while providing the opportunity for patients to become more aware and confident of their control of their residual limb and/or prosthesis. Additionally, working together with other amputees overcoming similar challenges to their recovery embodies the warrior ethos and encourages comradery amongst wounded warriors and their care providers. Creating a rehabilitative program that adequately addresses the challenges unique to combat amputees while providing the mental and physical training necessary can likely be achieved through implementing MA-HIIT. However, more well-designed studies are necessary before adequate definitive data is available to support creation of a formal, evidence-based program incorporating MA-HIIT into an overall rehabilitative treatment regimen for amputees.

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Characteristics of US Combat Veterans (2001-2011) Who Remain on Active Duty After Upper Extremity Amputations

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ABSTRACT

Objectives: Return to duty following traumatic amputations has been extensively studied in those with lower extremity amputation. As upper extremity amputations occur less frequently, the issue of return to duty for those with upper extremity amputations has received relatively little research. The purpose of this study was to determine the rate at which service members remain on active duty at least one year after having sustained traumatic upper extremity amputations during Operation Iraqi Freedom, Operation Enduring Freedom, and other overseas contingency operations of the Global War on Terrorism.

Design: Retrospective.

Setting: Military, Academic Level 1 trauma center.

Patients: One hundred eighteen patients who sustained combat-related upper extremity amputations between October 2001 and December 2011.

Intervention: Data was obtained from the medical record for these 118 patients.

Main Outcome Measurements: Percentage of service member remaining on active duty one year following an upper extremity amputation, and evaluation of demographic and injury related factors associated with retention.

Results: The overall rate for the upper extremity amputees studied at one year from injury who remained on active duty was 47%. Officers were more likely to remain on active duty than their enlisted counterparts (P=.021) and patients who sustained burns were also more likely to remain on active duty than patients with similar amputation types without concomitant burn injuries ($P = .039$).

Conclusions: The rate of service members with traumatic upper extremity amputations who were still on active duty status 1-year postinjury was 47%. The presence of burns and rank were significant factors when examining retention on active duty. Further study on war casualties who sustain upper-extremity traumatic amputations with and without burns is required to optimize outcomes in this population.

Since 2001, overseas contingency operations (OCOs) in support of the Global War on Terrorism have led to a large population of combat-related amputees.[1] In contrast to America's previous conflicts, the majority of combat-related injuries and combat-related amputations in Iraq and Afghanistan have been the result of explosions (78% and 93%, respectively).[1-3] Gunshot wounds from those combat areas accounted for 18% and 3.7%, respectively, in the same time period.[1-3] Nearly 90% of service members wounded in these conflicts survived their initial injury as compared to 75% during the Vietnam War.[4,5] Decreased mortality rates for those wounded on the battlefield can be attributed in part to advancements in body armor, casualty evacuation, and tactical combat casualty care.[4-7] Therefore, the percentage of service members with multiple limb amputations has increased proportionately as greater numbers of service members are able to survive these previously life-threatening injuries.[8] Review of the data of the Military Orthopaedic Trauma Registry (MOTR) within the Department of Defense Joint Trauma System as of October 1, 2012, found that 1,559 patients with major amputations, defined as a hand, arm, leg, or foot, had been treated at military treatment facilities, including 481 with multiple amputations and 272 with upper extremity amputations.

A larger body of research has been conducted on amputations involving the lower extremity as such amputations

are far more common than those involving the upper extremity (86% compared to 14%).[1] The ability to return to duty has been evaluated as an indicator of a service member's functional outcome.[6,9-11] This has led to greater amounts of resources devoted to research, prosthetic development, and rehabilitation processes that benefit lower extremity amputees and increase return to duty rates.[6,10-12] However, upper extremity amputees have higher disability rates compared with lower extremity amputees.[12] Despite this, relatively little research has been focused on upper limb amputations.

The purpose of our study was to determine the return to duty rate at one-year postinjury for service members who sustained upper extremity amputations and remain on active duty, and to determine if there are specific characteristics associated with higher retention rates.

Patients and Methods

Following receipt of institutional review board approval, we searched the Department of Defense Trauma Registry (DoDTR) and the MOTR using ICD-9 codes to identify all US military service members who sustained combat-related, upper extremity amputations from October 7, 2001, to December 18, 2011. Upper extremity amputations were defined as any limb loss from digital to shoulder disarticulation. All US military service members who were treated for combat-related upper extremity amputation at the San Antonio Military Medical Center (SAMMC) were included. All nontraumatic, noncombat related amputations that occurred during this time period were excluded from the research. Non-US military personnel, including civilian contractors and foreign nationals, were also excluded from the study. Electronic medical records at SAMMC were then manually searched.

The data extracted from the inpatient and outpatient medical records included rank at the time of injury, military occupation specialty (MOS) or area of concentration, age, branch of service, mechanism of injury, injury type, Maximum Abbreviated Injury Severity score and Injury Severity Score (ISS), hand dominance, ICD-9 codes, single or multiple amputations, laterality of amputation, definitive level of amputation, prosthetic use, type of prosthetic used, and a range of comorbidities.

Army Regulation 40-501[13] defines the Medical Retention Determination Point (MRDP) as the point in treatment and rehabilitation (not to exceed 1 year from date of injury) at which the service member's progress is stabilized sufficiently to determine that he/she is unlikely to carry out the tasks required by their military rank and specialty. Therefore, for this study we defined "retention" as the absence of initiation of a medical evaluation board (MEB) within 365 days of injury. The Medical Evaluation Board Internal Tracking Tool was queried to determine the date of medical board initiation.

IBM SPSS Statistics 20 was used to perform the statistical calculations. The χ^2 test was used to determine statistical significance for parametric data, and the Fisher exact test was used in instances where the expected count was less than 5 to compare categorical data. All continuous variables were tested for normality to determine the appropriate test. The variable ISS score was normally distributed and used a Student's *t* test. All others were calculated using the Mann-Whitney *U* test. Statistical significance was set at $P \leq .05$.

Results

Of the 118 service members who met the initial inclusion criteria (combat amputation, ICD-9 code, time period) from the DoDTR/MOTR, 83 were included in the final statistical analysis. Reasons for exclusion included: (1) amputations performed less than one year prior to the conclusion of data collection (August 1, 2012), and had not yet reached the MRDP, (2) lack of definitive amputation, (3) lack of treatment at SAMMC, and (4) incomplete medical records (Table 1). Of the 83 subjects who met final inclusion criteria, 39 remained on active duty one year postinjury, and 44 had initiated a MEB. This yields an initial retention rate of 47%.

Of the demographic characteristics available for analysis (Table 2), only rank was correlated significantly with retention ($P = .021$). At one year from injury, MEB processions had been initiated for 66% of junior enlisted personnel, 45% of senior enlisted personnel, and only 15% of officers. Of the comorbid conditions identified among our patient population (Table 3), there was a demonstrated paradoxical relationship with burn injuries. Medical board proceedings were initiated for 8 of the 23 service members (35%) who sustained burns as well as an amputation, while 36 of 60 patients (60%) who sustained an amputation without any burns entered the MEB process, nearly twice the rate of those who were burned ($P = .039$). Factors which did not demonstrate statistical significance included branch of service, MOS (Table 2), injury type, laterality of amputation, amputation level (Table 4), hand dominance, or prosthetic use (Table 5).

Table 1. Reasons for exclusion of candidates from final study population (N=35).

Reason for Exclusion	Number n(%N)
No definitive amputation	19 (54%)
Limited documentation	3 (9%)
Other	13 (37%)

Table 2. Demographics of study population (N=83).

	Active Duty n (%N)	MEB n (%N)	*P* Value
Average Age (range in years)			.053
18-23	12 (14%)	24 (30%)	
24-29	12 (14%)	12 (14%)	
30+	15 (18%)	8 (10%)	
Gender			.95
Male	38 (46%)	44 (53%)	
Female	1 (1%)	0 (0%)	
Branch of Service			.28
Army	33 (40%)	36 (43%)	
Marine	4 (5%)	7 (8%)	
Air Force	2 (2%)	0 (0%)	
Navy	0 (0%)	1 (1%)	
Rank			.021
Junior Enlisted: E1-E4	13 (16%)	26 (31%)	
Senior Enlisted: E5-E9	16 (19%)	13 (16%)	
Commisioned Officer: W01-06	6 (7%)	1 (1%)	
Rank Unknown	4 (5%)	4 (5%)	
MOS			.44
11A - Infantry Officer	3 (4%)	0 (0%)	
11B - Infantry Enlisted	7 (8%)	13 (16%)	
12B - Combat Engineer	0 (0%)	1 (1%)	
13B - Field Artillery	1 (1%)	2 (2%)	
19K - Armor Crewman	1 (1%)	2 (2%)	
21B - Engineer (Combat)	2 (2%)	3 (4%)	
31B - Military Police	2 (2%)	1 (1%)	
Other	13 (16%)	11 (13%)	
Missing	10 (12%)	11 (13%)	

Table 3. Comorbidities among study population (N=83).

	Active Duty n (%N)	MEB n (%N)	*P* Value
Traumatic Brain Injury	15 (18%)	11 (13%)	.18
Spinal Cord Injury	2 (2%)	1 (1%)	.9
Burns	15 (18%)	8 (10%)	.039
Fractures	31 (37%)	34 (41%)	.81
Soft Tissue	37 (45%)	42 (51%)	.7
Nerve	6 (7%)	6 (7%)	.82
Polytrauma	34 (41%)	42 (51%)	.34
Behavioral Health Diagnosis	21 (25%)	27 (33%)	.48

COMMENT

This study yielded a statistically significant difference in whether a subject remained on active duty based on rank (P=.021) and on comorbidity of burns (P=.039).

Increased retention rates with increasing rank is consistent with previous studies.[6,10,11] One possible explanation is that those who have achieved higher ranks in their military careers have, on average, invested a significant amount of time in the military and may remain dedicated

Table 4. Injury characteristics of study population (N=83).

	Active Duty n (%N)	MEB n (%N)	*P* Value
Mechanism of Injury			.52
Explosive Device	36 (43%)	43 (52%)	
Gunshot Wound	3 (4%)	1 (1%)	
Type of Injury			.54
Penetrating	25 (30%)	31 (37%)	
Blunt	11 (13%)	12 (14%)	
Burn	3 (4%)	1 (1%)	
Amputee #			1
Single	24 (29%)	27 (33%)	
Multiple	15 (18%)	17 (20%)	
Laterality			.48
Unilateral Upper	24 (29%)	27 (33%)	
1 Upper 2 Lower	8 (10%)	9 (11%)	
1 Upper 1 Lower	1 (1%)	4 (5%)	
Bilateral Upper	6 (7%)	3 (4%)	
Quad	0 (0%)	1 (1%)	
Amputation Level			.48
Digital	22 (27%)	19 (23%)	
Ray Resection	2 (2%)	1 (1%)	
Wrist Disarticulation	2 (2%)	2 (2%)	
Transradial	5 (6%)	8 (10%)	
Elbow Disarticulation	1 (1%)	1 (1%)	
Transhumeral	3 (4%)	11 (13%)	
Shoulder Disarticulation	1 (1%)	0 (0%)	
Digital & Transradial	1 (1%)	1 (1%)	
Digital & Elbow Disarticulation	0 (0%)	1 (1%)	
Digital & Transhumeral	1 (1%)	1 (1%)	
Elbow Disarticulation & Transhumeral	1 (1%)	0 (0%)	

Table 5. Prosthetic type and use among study population (N=83).

	Active Duty n (%N)	MEB n (%N)	*P* Value
Hand Dominance			.46
Right	30 (36%)	32 (39%)	
Left	4 (5%)	7 (8%)	
Unknown	5 (6%)	5 (6%)	
Prosthetic Use			.32
Used	17 (20%)	24 (29%)	
Not Used	20 (24%)	18 (22%)	
Unknown	2 (2%)	2 (2%)	
Type of Prosthetic			.55
Body Powered	5 (8%)	5 (8%)	
Myoelectric	8 (12%)	18 (28%)	
Hybrid	2 (3%)	4 (6%)	
Other	9 (14%)	14 (22%)	

to fulfilling their obligation for various reasons. In addition, those who have achieved a higher rank are less likely to be required to hold positions that require physical labor and the fine use of one or both upper extremities.

Amputees who had sustained burns were more likely to remain on active duty than those who were not burned (65% compared to 40%). One possible explanation is access to early rehabilitation through the integrated rehabilitation program at the US Army Institute for Surgical Research Burn Center. All amputees receive out-patient rehabilitation at the Center for the Intrepid, an integrated rehabilitation center. However, patients treated in the Burn Center began rehabilitation as inpatients. This is in contrast to amputees without burns who were treated without an integrated rehabilitation program. Therefore, the only difference is the time of exposure to integrated rehabilitation. The observation that burn victims were more likely to remain on active duty requires further study.

When analyzing specific types of prosthetics used, it was noted that most prosthetic users used more than one type of prosthetic. While none of the type of prosthetics (body-powered, myoelectric, hybrid or other) yielded statistically significant differences in whether a service member remained on active duty, it should be noted that the more costly and technologically advanced myoelectric prosthetics did not increase the retention rates within our study. Determining the cause for decreased retention rates in those using myoelectric prosthetics merits further study.

The major limitation of our study is its retrospective nature, thus we are able to show associations only. Respective studies are dependent upon the quality of the medical documentation reviewed. During the course of the research, multiple discrepancies in the medical records examined were noted. To minimize errors, two researchers were utilized to provide a second examination of the collected data and ensure congruency with the medical records.

A second weakness in this study was the process used to determine retention status. The MEB initiation date is often accepted in military medicine literature as a preliminary return to duty date, but it can by no means be considered a final determination of return to duty. We are unable to determine if our subjects initiated MEB proceedings after the Medical Retention Decision Point. However, given the scope of our review included a 10-year period, it is consistent that nearly half of upper-extremity amputees are able to perform well enough to be retained beyond the MRDP.

Lastly, this study included only US service members treated at SAMMC after sustaining combat-related traumatic upper extremity amputations. Adhering to these criteria yielded a relatively small sample size of 118 patients. This decreases the external validity of our study.

Some strengths of this study include the length of time utilized (10 years), which encompasses a greater portion of current conflict than most previous research in this area. As the study was conducted at one of the only three military amputee care centers, the small population of this study is reflective of the overall size of the population. This study, therefore, may be thought of as an initial study examining the characteristics of upper extremity amputees who remain on active duty one year post injury.

Initially, 47% of veterans of overseas contingency operations in support of the Global War on Terrorism (primarily OIF and OEF) who were treated at San Antonio Military Medical Center remained on active duty one year after combat-related, traumatic upper extremity amputations. The characteristics that correlated significantly with retention included rank and the presence of burns. Increased active duty rate among burn victims may, in part, be due to earlier exposure to integrated rehabilitation. This potential relationship warrants future study. No other statistically significant correlations were found.

Other studies on upper extremity amputees have demonstrated long-term return to duty rates as low as 12%.[12] Our study provides characteristics of those patients who remain on active duty at one year from their injury. The gap between the status of these patients at one year and the final return to duty rates provide areas for exploration:

- What changes between the medical decision making point and the final disposition?
- When service members leave the rehabilitative environment, are they still able to access appropriate resources when they face setbacks?
- Is there a disconnect between the resources available and service members' understanding of what they may access?
- Could additional resources bridge the gap between one year retention and full return to duty?

Further research is necessary to define the prosthetic needs of amputee service members who wish to remain on active duty following an upper extremity amputation. Further qualitative research should also be conducted with this population to determine other factors that may

affect a service member's desire and his/her ability to remain on active military service following an upper extremity amputation.

Treatment of combat casualties in a patient-centered, integrated performance unit model such as a musculoskeletal specialty home within the Patient Centered Medical Neighborhood is supported and warrants further research.

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Temporospatial Angiogenesis-Associated Gene Expression Profiles in Rat Ischemic Skin Flaps

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Abstract

Objectives: Emerging therapies designed to improve soft tissue flap survival include the use of angiogenic factors. However, endogenous expression patterns for these factors have not been characterized. The purpose of this study was to identify spatial and temporal variations in expression patterns of angiogenesis-associated genes in ischemic rat skin flaps.

Study Design: This is an observational animal study characterizing spatial and temporal angiogenesis associated gene expression patterns in rat ischemic skin flaps.

Methods: Dorsal skin flaps were created on 15 male Sprague-Dawley rats. The flap tissue was harvested and sectioned at 1, 3, or 7 days postsurgery. Total RNA was isolated, amplified, labeled with biotin, and hybridized to microarrays containing probes for 113 angiogenesis-associated genes. Microarray analysis revealed unique spatial and temporal patterns with statistically significant gene modulation over the length of the flap ($P<.05$).

Results: The molecular analysis performed in this study correlates with the hemodynamic profile previously published. Expression patterns associated with blood flow were markedly different from patterns associated with stasis and avascularity.

Conclusions: To our knowledge, this study is the first to characterize endogenous spatial and temporal angiogenesis-associated gene expression in rat ischemic skin flaps. Further characterization of expression patterns may allow clinicians to differentiate ischemic tissue that may be rescued via pharmacological or surgical intervention from tissue destined to succumb. Additionally, comparison of the expression profiles observed in this study with profiles generated from pharmacologically treated rats may suggest mechanisms for enhanced healing.

Pedicle soft tissue flaps represent a ubiquitous treatment modality in plastic and reconstructive surgery, yet flap necrosis remains a major complication. Partial or complete flap necrosis can lead to infection, delayed wound healing, dehiscence, fistula formation, wound contracture, and poor cosmesis.[1,2] A common model for studying necrosis is the rat dorsal ischemic skin flap. The first description of a dorsal pedicle soft tissue flap model in the rat was by McFarlane in 1965.[3] Numerous investigators have sought to improve the survival of rat ischemic skin flaps using a wide range of surgical techniques, topical and systemic drugs, and angiogenic factors. It is widely recognized that angiogenesis is a key process in wound healing. Thus, multiple points along the angiogenesis pathway have evoked interest as therapeutic targets.[4-7] Although emerging therapies designed to improve the survival of ischemic tissue include the use of angiogenic factors, endogenous expression patterns for these factors have not been well characterized. Such information could influence strategies for therapeutic intervention. In this article, lower-case abbreviations refer to genes, while gene products are denoted in capital letters.

While growth factors are critically important in angiogenesis, the process involves a functionally diverse set of genes. Vascular endothelial growth factor and fibroblast growth factor-2 (FGF2), two growth factors that act at multiple points in angiogenesis, are among the most studied angiogenic factors.[5,7-11] Vascular endothelial growth factor (VEGF) participates in the initial steps of angiogenesis by inducing nitric oxide synthase activity in endothelial cells leading to vasodilatation and by increasing vascular permeability.[12] Further in the process of angiogenesis, VEGF acts as a specific mitogen for endothelial cells, while fibroblast growth factors induce proliferation more broadly. Platelet derived growth factor (PDGF) is a mitogen for mesenchymal cells in multiple phases of wound healing. This growth factor is important for the recruitment of pericytes in the development of stable, mature vessels.[13] Additionally, PDGF may promote vessel maturation by directly inhibiting endothelial cells from entering the cell cycle,[14] and it also induces VEGF mRNA in fibroblasts.[15] Cadherin-5 (CDH5) is an endothelial specific adhesion molecule and major component of endothelial adherins junctions.[16] The integrity

of endothelial adherins junctions mediates endothelial motility, vascular morphogenesis, and permeability.[16] Adherins junctions may also be important in the integration of mechanical and chemical cellular signals.[16]

Angiogenesis is also under negative control. For example, leukocyte cell derived chemotaxin 1, also known as chondromodulin-I, inhibits angiogenesis in avascular tissues such as cartilage and avascular compartments in the eye.[17,18] A combination of angiogenesis inhibitors restricts formation of vessels in the eye despite the presence of potent promoters of angiogenesis such as VEGF and FGF2.[18] One of the most important endogenous inhibitors of angiogenesis is pigment epithelium derived factor, also known as serine peptidase inhibitor, clade F, member 1.[19] This anti-angiogenic factor is produced by multiple cell types, and its inhibitory effect results from stimulation of endothelial apoptosis.[19] Tissue inhibitors of metalloproteinases (TIMPs) inhibit angiogenesis by preventing metalloproteinase induced matrix degradation.[20] However, TIMPs also exert negative control on angiogenesis via other mechanisms. For example, TIMP3 interferes with VEGF binding its receptor, preventing its stimulatory effect.[20]

Materials and Methods

All procedures were reviewed and approved by the Dwight David Eisenhower Army Medical Center Animal Care and Use Committee and were performed in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International. Research was conducted in compliance with the Animal Welfare Act (Pub L 89-544, 80 Stat 350 (1966)) and other federal statutes and regulations pertaining to animals and experiments that involve animals and adhered to principles stated in the *Guide for the Care and Use of Laboratory Animals* (NRC, 1996).

A total of 15 male Sprague-Dawley rats (Harlan Sprague-Dawley) weighing approximately 350 grams were used for this study. The rats were housed in an environmentally controlled room on a 12-hour light-dark cycle and were fed standard rat chow and water ad libitum. Animals were housed in pairs throughout a one-week acclimation period until surgery. Following surgery, the animals were housed individually to prevent injury to skin flaps from cannibalism and normal socialization activities.

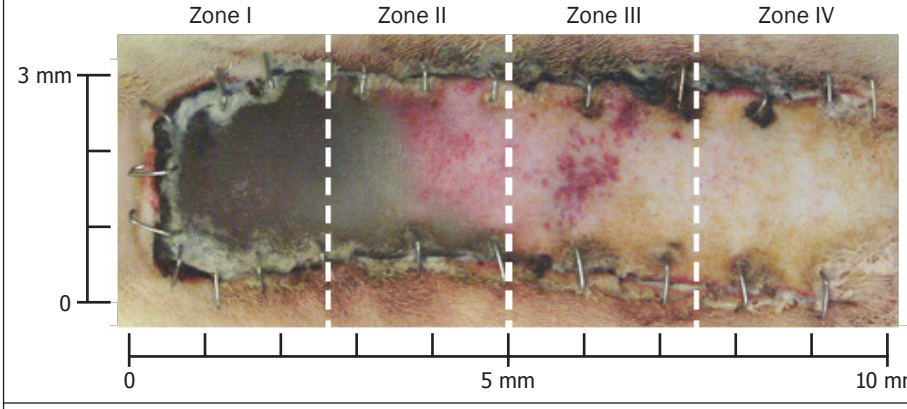
Modified McFarlane flaps measuring 3 cm x 10 cm were created on the dorsal skin of the rats. The myocutaneous flaps were elevated from the underlying fascia then returned to their native positions and secured with staples. The rats were divided into 3 groups based on a terminal evaluation interval of 1, 3, or 7 days.

RNA Isolation

Following euthanasia, flaps were harvested, photographed, and sectioned transversely into four 3 cm x 2.5 cm zones and stored at -80°C. The zone closest to the flap base was defined as Zone IV; the zone furthest from the flap base was defined as Zone I, as shown in the Figure. Total RNA was isolated from the skin flaps, using a monophase phenol and guanidine thiocyanate isolation reagent according to the manufacturer's instructions (TriPure, Boerhringer Mannheim, Indianapolis, IN). Briefly, 100 mg of tissue was immersed in 1 mL of Tripure, homogenized, and centrifuged at 12,000g for 10 minutes at 4°C. Homogenized samples were incubated for 5 minutes at room temperature, followed by an addition of 0.2 mL of chloroform. The mixture was vigorously shaken and incubated for another 15 minutes. Samples were then centrifuged at 12,000g for 15 minutes at 4°C. After centrifugation, the solution contained 3 phases. The upper aqueous phase contained the RNA, while the lower organic phase and cloudy interphase contained DNA and proteins. Total RNA was recovered from the upper phase by isopropanol precipitation. The RNA was resuspended in molecular biology grade water, and the quantity and purity of the isolated RNA was analyzed on a Bioanalyzer 2100 (Agilent Technologies, Cold Spring, NY). The RNA was then stored at -80°C until processed.

RNA Amplification and Labeling

Total RNA (25-100 ng) was reverse transcribed into complementary DNA (cDNA) using the target Amp



Modified McFarlane Skin Flap Design. Flaps wre harvested at the appropriate time points and sectioned transversely into 3 cm x 2.5 cm zones; zone I is the furthest from the caudal flap base.

1-Round Biotin-aRNA Amplification Kit 104. The resulting cDNA was then used to generate biotin-U labeled aRNA as instructed by the manufacturer (Epicentre, Madison, WI). The biotin labeled aRNA was purified using Qiagen RNeasy Mini Kit according to the manufacturer's protocol (Qiagen, Valencia, CA) and 2 µg of labeled aRNA was used to hybridize to the Angiogenesis specific arrays. Hybtube format rat angiogenesis arrays (ORN24.2, SuperArray, Frederick, MD) containing 128 positions and 113 unique angiogenesis-associated oligonucleotide probes were processed according to the manufacturer's instructions. The resulting images were captured using time-lapse image acquisition at a rate of one image per 10 minutes for a total of 40 minutes (Kodak ImageStation 2000MM, Kodak, New Haven, CT).

Web-based software (GEArray Analysis Suite 2.0, SuperArray BioScience Corp, Frederick, MD) was used to analyze the signal intensity produced for each gene. To account for background differences among microarrays, the lowest average density spot on each array was found and the average intensity across the spot was used as a background correction factor. Interquartile normalization of the signal intensity was used, ranking the absolute intensity of each signal then dividing it by the mean intensity of the genes that fell between the 25% and 75% quartiles. Each zone-time point group (4 flap zones, 3 time points) contained 5 microarrays. For each zone, differences in the mean normalized signal intensity were compared over 2 time intervals: early (from day 1 to day 3) and late (from day 3 to day 7). A Student's *t* test was performed for each comparison. Differences in mean normalized signal intensity were deemed statistically significant for *P* values less than .05.

Results

In an earlier study,[21] researchers in our lab used orthogonal polarization spectral imaging to define and report mean areas of flap avascularity, areas of stasis exhibiting vessels without flow, and unaffected areas showing vessels with blood flow. At day 1, the mean area of avascularity was completely contained within the distal 2.5 cm of the flap (Zone I). By day 3, Zone I was completely avascular. At days 3 and 7, the transition from avascularity to stasis fell between 2.5 cm and 5 cm from the distal flap margin (within Zone II). At all time points, the total affected area (the area of the flap exhibiting stasis or avascularity) fell within Zone II.

Statistically significant ($P<.05$) changes in signal intensity were observed within all 4 zones over the early (day 1 to day 3) and late (day 3 to day 7) time intervals. In Zone I, more genes showed large changes in signal intensity during the early time interval, while more modest gene modulation occurred from day 3 to day 7. In Zone II the expression profile over the early time interval showed few genes with large magnitude changes in signal intensity, while gene modulation over the late time interval was much more robust. Fold-changes in signal intensity for the 112 genes are presented in Table 1. Table 2 lists mean normalized signal intensity for selected genes.

Comment

Immediately after flap elevation, pedicle skin flaps become dependent upon collateral circulation through vessels contiguous with intact vessels in the flap base.[22] A minimum blood flow of 0.04 cc per gram of tissue per minute is required to maintain viability.[23] However, skin cells can survive up to 12 hours of complete avascularity at body temperature.[22] Necrosis ultimately ensues in areas where flow is inadequate and does not improve before cells perish.[22] In modified McFarlane skin flaps, a distal flap segment is destined to become necrotic, and a larger proximal segment will have adequate blood flow irrespective of experimental conditions. The interposed segment is most interesting, because it can either become necrotic or be rescued, depending on the experimental parameters. Distinct areas of modified McFarlane flaps have been defined using orthogonal polarization spectral imaging, a noninvasive technique for visualizing soft tissue microcirculation without the use of dyes.[5,21,24,25] Hart et al defined an area of necrosis devoid of blood vessels, an area of stasis exhibiting vessels without flow, and an unaffected area showing vessels with blood flow.[21] The area of stasis, containing vessels yet absent of blood flow, represents the area of the flap susceptible to pharmacological intervention. Hart et al showed that the total affected area remained relatively constant over time while the mean area of necrosis increased at the expense of the area of stasis.[21] While the progression of necrosis in ischemic rat skin flaps has been studied, endogenous expression patterns for angiogenesis-associated genes remain uncharacterized.[21]

Angiogenesis-associated gene expression profiles generated in the present study correlated with the progressive proximal extension of the avascular segment noted in the previously reported orthogonal polarization spectral imaging analysis.[21] In the area exhibiting near complete avascularity by day 1 (Zone I), robust gene modulation occurred during early time interval. Platelet endothelial cell adhesion molecule (PECAM-1) and CDH5 are among the genes that showed significant modulation ($P<.05$) in this area. Both of these genes are associated with the vasodilatation and endothelial permeability seen during the initiation of angiogenesis.

Table 1 (part 1 of 3). Early and late fold changes in signal intensity by zone.

Genebank ID	Gene Name	Symbol	Fold Change Zone 1		Fold Change Zone 2		Fold Change Zone 3		Fold Change Zone 4	
			Early	Late	Early	Late	Early	Late	Early	Late
NM_053546	Angiopoietin 1	Adra2b	-2.45	-3.54*	-1.46	-2.88*	-1.50	-1.70	-1.06	-1.09
NM_138505	Adrenergic receptor, alpha 2b	Aggf1	1.39	1.01	2.05	1.36	-1.61	1.21	1.36	2.05
XM_226709	Angiogenic factor with G patch and FHA domains 1	Akt1	-1.68	-1.65	1.19	-1.95	-2.33	1.34	1.16	1.48
NM_033230	Thymoma viral proto-oncogene 1	Angpt1	1.70	1.63	1.41	1.03	-2.42	1.89	-1.40	1.36
XM_344544	Angiopoietin 2	Angpt2	2.23	1.11	2.68	2.70	-2.45	1.67	1.44	3.21
NM_199115	Angiopoietin-like 4	Angptl4	1.73	1.61	1.09	3.30	-1.27	1.45	-1.54	-1.21
NM_031012	Alanyl (membrane) aminopeptidase	Anpep	-2.41	-2.46	-1.70	-1.64	-2.07	1.25	-1.66*	1.44
XM_220907	ADP-ribosylation factor-like 12	Arl12	-1.68	-1.13	-1.35	1.34	1.03	-2.41	2.03	1.14
XM_343260	Brain-specific angiogenesis inhibitor 1	Bai1	1.75	1.59	1.45	3.24	-2.67	-1.70	-1.84	1.37
NM_019205	Chemokine (C-C motif) ligand 11	Ccl11	-2.05*	1.20	-1.21	1.20	1.43	1.46	1.08	-2.86
NM_031530	Chemokine (C-C motif) ligand 2	Ccl2	1.62	1.20	2.09*	2.77	-2.78	-1.55	1.30	2.31
XM_226213	Cadherin 5	Cdh5	-4.52*	-7.65*	1.00	-3.21*	-1.09	-3.03*	1.66	-2.55
XM_241632	Procollagen, type XVIII, alpha 1	Col18a1	5.36	5.47	2.26	11.45	1.77	-1.21	1.36	-1.80*
XM_343607	Procollagen, type IV, alpha 3	Col4a3	1.35	1.18	1.55	2.44	-1.88	1.64	-1.71	-1.33
NM_017104	Colony stimulating factor 3 (granulocyte)	Csf3	-1.20	-1.25	1.00	2.10	-1.18	1.89	1.28	-1.80
NM_022266	Connective tissue growth factor	Ctgf	2.22	-2.20	1.11	1.07	-2.29	-1.57	-2.29	1.42
NM_030845	Chemokine (C-X-C motif) ligand 1	Cxcl1	-1.27	1.05	-1.31	1.08	-1.68	-1.04	1.11	1.46
NM_139089	Chemokine (C-X-C motif) ligand 10	Cxcl10	-1.42	-1.81	-1.42	-1.01	-3.13	-1.56	-1.67	1.42
NM_182952	Chemokine (C-X-C motif) ligand 11	Cxcl11	-2.54	-6.70	1.32	-1.38	2.47	1.78	3.48	-2.86
NM_053647	Chemokine (C-X-C motif) ligand 2	Cxcl2	-1.68	-1.66	1.74	1.11	-2.86	-1.22	1.07	1.80
NM_001007729	Chemokine (C-X-C motif) ligand 4	Cxcl4	8.85	7.19	1.34	13.23	-1.47	-1.73	-1.19	1.11
NM_022214	Chemokine (C-X-C motif) ligand 5	Cxcl5	-1.42	1.28	-1.54*	-1.16	-1.39	-1.10	2.18	1.10
NM_145672	Chemokine (C-X-C motif) ligand 9	Cxcl9	-6.80*	-4.13	-1.29	-2.24	-1.31	-2.55 *	2.37	-1.92
NM_001012122	Endothelial cell growth factor 1 (platelet-derived)	Ecgf1	-9.52	-7.19	-2.50*	-5.74*	-1.38	1.00	-1.59*	1.26
NM_017301	Endothelial differentiation sphingolipid GPCR 1	Edg1	1.70*	1.52	1.49	2.38	1.56	1.15	-1.35	1.21
NM_053599	Ephrin A1	Efna1	1.68	-1.19	1.42	1.82	-2.74	-2.64	-1.56	1.39
XM_234903	Ephrin A2	Efna2	2.56*	1.83	1.18	3.91	-3.17	-1.07	-1.84	1.16
XM_574979	Ephrin A3	Efna3	1.56	1.59	1.46	1.37	-2.12	2.10	-1.51	1.75*
NM_012842	Epidermal growth factor	Egf	-2.00	-1.73	-4.11	-4.76	-1.01	2.10 *	-2.06	1.23
NM_001010968	Endoglin	Eng	-1.59	-1.37	-1.49	-1.76	1.24	-1.05	1.71*	1.05
NM_023090	Endothelial PAS domain protein 1	Epas1	-5.63*	-3.00*	-5.06*	-5.61*	-1.38	1.11	-1.85*	1.05
NM_021689	Epiregulin	Ereg	-3.91*	-3.75*	-2.43*	-3.19*	-1.10	1.18	-1.49	-1.87
NM_022924	Coagulation factor II	F2	1.82	1.20	-1.73	1.80	-1.32	-1.24	-2.18	1.43
NM_012846	Fibroblast growth factor 1	Fgf1	1.41	1.77	-1.12	1.63	-1.91	-1.60	-1.89	1.16
NM_019305	Fibroblast growth factor 2	Fgf2	1.18	-1.02	1.04	2.28	-1.43	1.05	-1.24	1.42
NM_131908	Fibroblast growth factor 6	Fgf6	2.53*	2.04	1.11	1.63	1.35	1.85 *	-1.39	1.14
NM_053429	Fibroblast growth factor receptor 3	Fgfr3	1.30	1.18	1.27	1.41	-2.66*	1.23	-2.32	-1.13
NM_031761	C-fos induced growth factor	Figf	1.95	2.93	1.32	1.11	-2.20	1.50	-1.49	1.11
NM_019306	FMS-like tyrosine kinase 1	Flt1	8.41	7.19	1.03	20.09	-1.23	1.40	-1.33	1.06
NM_173838	Frizzled homolog 5 (Drosophila)	Fzd5	1.43	1.41	-1.25	-1.31	-1.32	2.43 *	-1.53	1.03
NM_001013119	Guanine nucleotide binding protein, alpha 13	Gna13	-1.76	-2.19	-1.96	2.00	1.06	-1.29	-1.32	-1.02
NM_022696	Heart and neural crest derivatives expressed transcript 2	Hand2	-1.34	1.05	-1.18	1.79	-1.07	-1.06	-1.33	1.20
NM_017017	Hepatocyte growth factor	Hgf	1.54	1.21	1.35	2.35	-1.81	-2.46	-1.77	1.69

*Statistically significant (P<.05)

Table 1 (continued, part 2 of 3). Early and late fold changes in signal intensity by zone.

Genebank ID	Gene Name	Symbol	Fold Change Zone 1		Fold Change Zone 2		Fold Change Zone 3		Fold Change Zone 4	
			Early	Late	Early	Late	Early	Late	Early	Late
NM_024359	Hypoxia inducible factor 1, alpha subunit	Hif1a	1.74	1.28	1.06	1.91	1.13	-1.15	1.15	1.37
NM_001014786	Interferon-alpha 1	Ifna1	-2.34	-2.83*	-2.18	-1.60	1.09	1.22	-1.67	-1.09
NM_138880	Interferon gamma	Ifng	1.50	1.48	1.62	5.12	-1.55	1.16	-1.61	1.03
NM_178866	Insulin-like growth factor 1	Igf1	1.98	2.18	-1.46	2.59	1.14	1.77	-1.20	-1.08
NM_012854	Interleukin 10	Il10	20.62	15.31	1.03	33.20	-2.01	1.13	1.08	1.07
NM_053390	Interleukin 12a	Il12a	-3.08*	-2.35*	-1.38	-2.87*	1.01	-1.26	-1.33	-1.10
NM_019165	Interleukin 18	Il18	1.43	-1.37	-1.95	-1.53	1.30	1.29	-1.40	1.22
NM_031512	Interleukin 1 beta	Il1b	10.84	5.74	1.41	17.16	-1.74	-1.42	-1.30	1.80
NM_012589	Interleukin 6	Il6	1.06	-1.11	1.02	1.58	-1.02	-1.05	-1.36	1.33
XM_230950	Integrin alpha V	Itgav	-10.16*	-12.68*	-3.59	-16.39*	-1.83	-2.07	1.10	-1.37
NM_153720	Integrin beta 3	Itgb3	-1.71	-3.73*	-1.06	-1.24	2.68*	1.21	2.26	-1.79
NM_019147	Jagged 1	Jag1	-1.68	-1.41	-1.36	-1.74	2.46*	1.80	1.23	-1.16
NM_013062	Kinase insert domain protein receptor	Kdr	-1.55	1.43	1.72	1.65	1.68	1.52*	1.15	-1.24
XM_215963	Laminin, alpha 5	Lama5	1.27	-1.12	1.05	1.39	2.05*	1.06	1.33	1.01
NM_030854	Leukocyte cell derived chemotaxin 1	Lect1	15.72	13.15*	2.74	42.73	-2.41	-2.25	-1.16	-1.50*
NM_013076	Leptin	Lep	5.51	4.80	1.13	11.05	-1.00	1.08	-1.12	1.22
NM_031020	Mitogen activated protein kinase 14	Mapk14	-1.35	-1.06	1.47	1.05	1.88*	1.26	1.36	1.24
NM_030859	Midkine	Mdk	2.66	2.38	1.41	5.29	-1.53	1.08	-1.24	-1.05
XM_222317	Matrix metalloproteinase 19	Mmp19	1.20	1.69*	1.36	1.23	1.11	1.82*	-1.06	-1.12
NM_031054	Matrix metallopeptidase 2	Mmp2	1.93	2.43*	2.22*	2.56*	1.15	2.08*	1.02	-1.19
NM_031055	Matrix metallopeptidase 9	Mmp9	1.16	1.29	-1.41	-1.39	-1.81*	1.73*	-1.46	1.43
NM_001002827	Notch homolog 4	Notch4	2.10	3.62*	1.97*	3.11*	1.18	1.46*	-1.22	1.12
NM_031545	Natriuretic peptide precursor type B	Nppb	1.65	1.24	1.96*	1.70*	-1.71	-1.31	-1.62	1.39
NM_012613	Natriuretic peptide receptor 1	Npr1	-1.02	2.14	1.25	1.00	-1.47	1.30	-1.73	-1.08
NM_145098	Neuropilin 1	Nrp1	-2.51	1.10	1.07	-2.07	-1.09	-1.03	-1.50	-1.57
NM_030869	Neuropilin 2	Nrp2	7.95	4.05	2.10*	9.90	-1.16	-1.50	1.12	-1.27
NM_181363	Nudix (nucleoside diphosphate linked moiety X)-type motif 6	Nudt6	-3.20*	-2.40*	-1.49*	-2.96*	-1.13	1.25	-1.59*	-1.69*
NM_012801	Platelet derived growth factor, alpha	Pdgfa	1.27	1.52	1.46	2.06	1.85	1.06	2.09*	-1.56
XM_343293	Platelet derived growth factor, B polypeptide	Pdgfb	2.04	-1.47	1.30	1.41	-1.98	-1.58	-1.87	1.64*
NM_031591	Platelet/endothelial cell adhesion molecule	Pecam	3.06*	1.74	1.87*	2.88*	-1.96	-1.59	-1.82	1.36
NM_053595	Placental growth factor	Pgf	-1.22	-1.28	-1.34	-1.03	1.01	-1.42	1.22	1.02
NM_013085	Plasminogen activator, urokinase	Plau	1.23	-1.14	1.18	1.08	-1.44*	-1.40*	-1.16	1.07
XM_574314	Plasminogen	Plg	-3.15*	-3.12*	1.90*	-1.68	2.73*	-1.53	2.29	-2.17
NM_001002278	Protein O-fucosyltransferase 1	Pofut1	1.13	-1.00	1.19	-2.00*	-1.36	1.36	-1.14	-1.06
NM_138852	Prokineticin 2	Prok2	2.65	1.63	1.06	1.07	-1.19	1.69*	-1.12	-1.09
NM_031606	Phosphatase and tensin homolog	Pten	2.74	1.34	1.39	1.54	-2.26	-1.98	-2.10	-1.78
NM_017043	Prostaglandin-endoperoxide synthase 1	Ptgs1	2.77*	2.94*	1.59	3.82	-1.20	-1.71	-1.03	1.19
NM_017232	Prostaglandin-endoperoxide synthase 2	Ptgs2	-2.05	-1.58	-1.30	-2.08	1.61	1.15	1.17	1.25
NM_017066	Pleiotrophin	Ptn	1.15	2.41	1.36	1.20	1.13	1.13	-1.18	-1.05
XM_341781	SAPS domain family, member 1	Saps1	-1.58	-1.75*	-1.20	-2.64*	1.31	1.13	1.03	-1.03
NM_177927	Serine (or cysteine) peptidase inhibitor, clade F, member 1	Serpinf1	-3.82*	-7.67*	-3.51*	-5.27*	1.83*	-1.36	2.80	-1.94
NM_207605	SH2 domain protein 2A	Sh2d2a	-2.21	-1.88*	-1.13	-2.88	1.06	-1.37	1.62*	-1.23

*Statistically significant (P<.05)

Table 1 (continued, part 3 of 3). Early and late fold changes in signal intensity by zone.

Genebank ID	Gene Name	Symbol	Fold Change Zone I		Fold Change Zone II		Fold Change Zone III		Fold Change Zone IV	
			Early	Late	Early	Late	Early	Late	Early	Late
NM_021692	MAD homolog 5 (Drosophila)	Smad5	-1.82	-1.78	-1.67	-3.15*	1.19	1.44	-1.09	-1.07
NM_133386	Sphingosine kinase 1	Sphk1	2.04	1.36	1.21	1.45	-1.97	-1.18	-1.91*	1.19
XM_214279	Stabilin 1	Stab1	1.96*	1.08	-1.29	1.33	1.35	-1.52*	-1.02	-1.12
XM_238531	Stabilin 2	Stab2	-1.15	-1.73*	-1.05	-1.67*	-1.09	1.10	1.22	1.19
XM_341009	T-box 1	Tbx1	1.24	-1.03	1.37	1.46	-1.61*	-1.50	-1.05	1.16
XM_220811	T-box 4	Tbx4	1.69	1.42	1.22	-2.79*	-1.92*	-1.28	-1.16	1.14
XM_342863	Endothelial-specific receptor tyrosine kinase	Tek	1.36	1.29	-1.12	-1.62	-1.19	1.25	-1.10	-1.14
NM_012671	Transforming growth factor alpha	Tgfa	1.20	1.34	1.42	1.40	1.07	1.35	1.18	-1.20
NM_021578	Transforming growth factor, beta 1	Tgfb1	1.24	1.48	-1.47	-1.91*	-1.42	1.18	-1.20	-1.22
NM_031131	Transforming growth factor, beta 2	Tgfb2	1.49	-1.20	1.10	1.18	-1.37	-1.38	-1.68	1.52
NM_013174	Transforming growth factor, beta 3	Tgfb3	1.34	-1.19	1.06	1.69	-1.40	-1.61	-1.27	1.35
NM_012775	Transforming growth factor, beta receptor 1	Tgfbr1	-3.99*	-6.20*	-1.74	-5.92*	-1.82	-1.86	-1.04	-1.12
XM_214778	Thrombospondin 2	Thbs2	-2.11	-2.30*	-1.04	-1.62	1.69	-1.04	1.58	-1.01
XM_233462	Tyrosine kinase with Ig-like and EGF-like domains 1	Tie1	1.15	1.57	-1.06	-1.06	1.36	1.20	1.11	1.01
NM_053819	Tissue inhibitor of metallopeptidase 1	Timp1	1.73*	1.02	1.30	-1.67	-1.83*	-1.01	-1.01	1.07
NM_021989	Tissue inhibitor of metalloproteinase 2	Timp2	-1.29	2.34	-1.16	1.13	1.54	2.08*	-1.24	1.43
NM_012886	Tissue inhibitor of metalloproteinase 3	Timp3	-1.24	-1.44	-1.08	-1.60	1.87	4.44	-1.27	1.88
XM_235768	Transmembrane serine protease 6	Tmprss6	1.57	1.74*	1.13	1.46	-1.10	1.00	-1.43	1.37
NM_012675	Tumor necrosis factor (TNF superfamily, member 2)	Tnf	-1.04	1.56	-1.11	-1.22	-1.61*	-1.63	-1.30	1.63
NM_181086	Tumor necrosis factor receptor superfamily, member 12a	Tnfrsf12a	-1.36	-1.12	-2.49*	-2.42*	-2.70	2.46	-1.92	2.24
NM_001001513	Tumor necrosis factor ligand superfamily member 12	Tnfsf12	-3.75*	-3.57*	-2.60	-5.13*	-2.19*	1.00	-1.39	1.41
NM_145765	Tumor necrosis factor (ligand) superfamily, member 15	Tnfsf15	1.11	1.10	1.10	-1.88*	1.14	1.17	-1.18	-1.07
NM_134388	Troponin T1, skeletal, slow	Tnnt1	-2.14	-1.6	-1.93	-2.27*	-1.52	1.00	1.09	1.24
NM_031836	Vascular endothelial growth factor A	Vegfa	1.62	1.33	1.41	1.18	-1.74	1.14	-1.02	1.14
NM_053549	Vascular endothelial growth factor B	Vegfb	1.75*	1.15	1.17	1.16	-1.03	1.78	-1.02	1.08
NM_053653	Vascular endothelial growth factor C	Vegfc	1.39	1.43	1.23	3.76*	-2.02	-1.12	-1.57	2.38
NM_001013167	WAS protein family, member 2	Wasf2	2.02	1.63	1.28	2.40	-2.05	-1.36	-2.03	1.84

*Statistically significant (P<.05)

During the late time interval, changes in signal intensity in Zone I were much less pronounced, presumably because few cells in the distal zone retained normal cellular function. However, complete absence of RNA was neither expected nor observed. Even when the dermal flap surface appears black, viable cells may exist across the thickness of the flap. Zone II, which did not exhibit avascularity during the early time interval, showed a relatively modest pattern of gene modulation from day 1 to day 3. Once the avascular segment extended into Zone II (in the late time interval), this area exhibited a more robust expression pattern, analogous to early observations in Zone I. Furthermore, some of the same genes modulated early in Zone I were modulated later in Zone II. For example, the following genes exhibited statistically significant (P<.05) modulation early in Zone I and late in Zone II: CDH5, PECAM-1, SERPINF1, TGFBR1, Endothelial cell growth factor-1 (Ecgf1), Endothelial PAS domain protein-1 (Epas1), Epiregulin (Ereg), Interleukin 12a (Il12a), Integrin αV (Itgav), Nudix-type motif 6n (Nudt6), and Tumor necrosis factor ligand superfamily member-12 (Tnfsf12). As shown in Table 1, other genes followed this trend: Il1b, Lect1, Procollagen type XVIII α1 (Col18a1), Chemokine (C-X-C motif) ligand-4 (Cxcl4), FMS-like tyrosine kinase-1 (Flt1), Interleukin-10 (Il10).

Overall, the expression patterns observed, in the context of the previously reported proximal progression of avascularity, suggest that necrosis may trigger modulation of numerous genes in adjacent tissue during the normal healing of pedicle soft tissue wounds. This speculation

Table 2. Mean Normalized Signal Intensity for Selected Genes.

	Tgfbr1 mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	98.5±38.5	24.7±24.3	15.9±11.7
Zone II	81.0±36.3	46.6±33.3	13.7±16.3
Zone III	27.3±15.5	15.0±2.5	14.7±10.3
Zone IV	15.4±3.5	14.8±5.4	13.7±6.8

	Epas mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	6.79±3.17	1.21±0.99	2.26±1.85
Zone II	10.4±7.2	2.06±0.94	1.86±1.75
Zone III	9.37±4.12	6.80±1.31	10.4±3.57
Zone IV	11.1±4.52	6.00±1.84	11.6±5.92

	Nrp2 mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	0.69±0.19	5.53±4.71	2.81±2.58
Zone II	0.65±0.13	1.37±0.37	6.45±7.19
Zone III	1.44±0.54	1.24±0.67	0.96±0.19
Zone IV	1.07±0.29	1.20±0.55	0.85±0.14

	Serpinf1 mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	25.5±5.38	6.66±11.69	3.32±3.97
Zone II	15.6±8.58	4.43±2.75	2.95±3.69
Zone III	2.00±0.88	3.66±1.23	1.47±1.14
Zone IV	1.83±1.66	5.14±3.89	0.95±0.17

	Vegfa mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	0.46±0.19	0.78±0.37	0.64±0.31
Zone II	0.57±0.11	0.81±0.43	0.67±0.36
Zone III	0.52±0.33	0.30±0.13	0.59±0.18
Zone IV	0.53±0.15	0.52±0.57	0.60±0.31

	Vegfc mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	0.71±0.14	0.99±0.85	1.02±0.88
Zone II	0.75±0.30	0.92±0.40	2.82±1.87
Zone III	0.51±0.50	0.25±0.16	0.46±0.26
Zone IV	0.47±0.19	0.30±0.28	1.11±0.90

	Fgf2 mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	0.67±0.07	0.79±0.34	0.65±0.59
Zone II	0.43±0.21	0.44±0.19	0.97±0.67
Zone III	0.37±0.15	0.25±0.06	0.38±0.06
Zone IV	0.38±0.26	0.30±0.15	0.53±0.24

	Pdgfa mean normalized signal intensity±sd		
	Day 1	Day 3	Day 7
Zone I	2.66±0.65	3.37±5.31	4.03±4.16
Zone II	1.80±1.65	2.63±1.65	3.71±4.54
Zone III	2.37±2.17	4.38±1.22	2.50±2.19
Zone IV	2.25±0.99	4.71±2.12	1.45±1.32

is supported by the observed modulation of cytokines as viable tissue succumbed to necrosis in the stasis zone. Modulation of immunoregulatory molecules may be expected adjacent to necrotic tissue since necrosis is known to elicit an intense immune response.[27] In the present study, Il10 and Il1β exhibited some of the largest magnitude changes in expression. Large magnitude modulation of these 2 genes occurred in Zones I and II at time points when avascularity was present and relatively minor in the area of blood flow (Zones III and IV). IL-1β, a signature proinflammatory cytokine of macrophages, has been shown to be essential for angiogenesis in multiple settings including rheumatoid arthritis, endometriosis, myocardial infarction, and wound healing.[28-31] However, IL-1β influences on angiogenesis may be complex, since it has also been shown to inhibit one of the most potent angiogenic factors, VEGF-D.[32] IL-10 is an anti-inflammatory cytokine that functions primarily to limit inflammation but also promotes growth and maturation of multiple cell types including vascular endothelial cells.[33]

In addition to immunoregulatory molecules, adhesion molecules also showed large magnitude modulation in this study. Integrin αvβ3 is an adhesion receptor expressed in wound granulation tissue but not in normal skin.[34] Antagonists of Integrin αvβ3 block angiogenesis induced by FGF-2 or tumor necrosis factor-α (TNF-α) and promote tumor regression by inducing apoptosis of endothelial cells in angiogenic vessels.[34,35] Both Integrin αv (Itgav) and Integrin β3 (Itgb3) subunits exhibited statistically significant modulation in this study, with the αv subunit showing more than 10-fold reduction in signal intensity over the early time interval in the necrotic zone.

Few transcription factors that initiate programs of angiogenesis-associated gene expression showed statistically

significant modulation in this study, and none showed large magnitude changes. A well-known stimulus for gene expression is hypoxia. Although oxygen tension was not measured in this study, an oxygen gradient was expected to exist along the length of the flap. The most distal aspect of the flap most likely had the lowest partial pressure of oxygen, owing to early loss of blood flow. In a hypoxic state, the hypoxia inducible factor-1α (HIF-1α) protein exhibits a diminished degradation rate, permitting association with HIF-1β.[36] This functional transcription factor complex initiates a program of hypoxia-inducible gene expression.[36] In the present study, expression levels of HIF-1α were low across the length of the flap at all time points, and there were no statistically significant changes in HIF-1α signal intensity. It is possible that the time-points that we examined were too late to detect changes in signal intensity in the range exhibited by this transcription factor.

Results from this study will provide a basis for comparison for ongoing research involving ischemic skin flap healing in diabetic rats and ischemic rat skin flaps treated with pharmacological agents. Identification of the molecular basis for derangement or pharmacological enhancement of angiogenesis may be possible. Future studies should also aim at identifying the cell types expressing important angiogenic factors using techniques such as laser capture microdissection. Further characterization of the complex sequence of events that occurs during the skin flap healing process may provide new directions for adjunctive therapies.

Conclusion

In a previous study,[21] researchers in our lab defined distinct zones in ischemic rat skin flaps using orthogonal polarization spectral imaging. We now correlate these zones with spatial and temporal variations in angiogenesis associated gene expression. Future experiments will focus on differences in expression profiles between treatment and nontreatment groups in diabetic and nondiabetic rats.

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Resistance to Abrasion of Extrinsic Porcelain Esthetic Characterization Techniques

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Abstract

Statement of Problem: A novel esthetic porcelain characterization technique involves mixing an appropriate amount of ceramic colorants with clear, low-fusing porcelain (LFP), applying the mixture on the external surfaces, and firing the combined components onto the surface of restorations in a porcelain oven. This method may provide better esthetic qualities and toothbrush abrasion resistance compared to the conventional techniques of applying color-corrective porcelain colorants alone, or applying a clear glaze layer over the colorants. However, there is no scientific literature to support this claim.

Purpose: This research evaluated toothbrush abrasion resistance of a novel porcelain esthetic characterization technique by subjecting specimens to various durations of simulated toothbrush abrasion. The results were compared to those obtained using the conventional characterization techniques of colorant application only or colorant followed by placement of a clear over-glaze.

Method and Materials: Four experimental groups, all of which were a leucite reinforced ceramic of E TC1 (Vita A1) shade, were prepared and fired in a porcelain oven according to the manufacturer's instructions. Group S (stain only) was characterized by application of surface colorants to provide a definitive shade of Vita A3.5. Group GS (glaze over stain) was characterized by application of a layer of glaze over the existing colorant layer as used for Group S. Group SL (stain+LFP) was characterized by application of a mixture of colorants and clear low-fusing add-on porcelain to provide a definitive shade of Vita A3.5. Group C (Control) was used as a control without any surface characterization. The 4 groups were subjected to mechanical toothbrushing using a 1:1 water-to-toothpaste solution for a simulated duration of 32 years of clinical use. The amount of wear was measured at time intervals simulating every 4 years of toothbrushing. These parameters were evaluated longitudinally for all groups as well as compared at similar time points among groups.

Results: In this study, the novel external characterization technique (stain+LFP: Group SL) did not significantly enhance the wear resistance against toothbrush abrasion. Instead, the average wear of the applied extrinsic porcelain was 2 to 3 times more than Group S (stain only) and Group GS (glaze over stain). Application of a glaze layer over the colorants (Group GS) showed a significant improvement on wear resistance. Despite its superior physical properties, the leucite reinforced ceramic core (Group C) showed 2 to 4 times more wear when compared with other test groups.

Conclusion: A conventional external esthetic characterization technique of applying a glaze layer over the colorants (Group GS) significantly enhanced the surface wear resistance to toothbrush abrasion when compared with other techniques involving application of colorants only (Group S) or mixture of colorant and LFP (Group SL). The underlying core ceramic had significantly less wear resistance compared with all externally characterized specimens. The novel esthetic characterization technique showed more wear and less color stability, and is thus not advocated as the "best" method for surface characterization.

Clinical Implications: Application of a glaze layer provides a more wear resistant surface from toothbrush abrasion when adjusting or extrinsically characterizing leucite reinforced ceramic restorations. Without the glaze layer, the restoration is subjected to a 2 to 4 times faster rate and amount of wear leading to possible shade mismatch.

Although ceramic restorations are considered to be color-stable, a gradual change in shade may be noticed starting a few years after placement.[1] While there could be any number of reasons for this change, removal of a thin layer of colorants by toothbrush abrasion may be a contributing factor. According to Aker et al, toothbrush abrasion was found to gradually remove the colorant layer applied to the surface of metal ceramic crowns.[2] The colorant layer was completely removed after 10 to 12 years of simulated toothbrushing, while colorants having a glaze overcoat were removed after 30 years of simulated toothbrushing because the layer of clear glaze had to be worn away before the colorant layer could be affected.[2,3] In another study, most of the colorant layer was removed after 11 years of simulated brushing resulting in a significantly rough surface and shade mismatch.[4]

A novel dental ceramic characterization technique was introduced by a master dental laboratory technician during hands-on training at the US Army Prosthodontic Residency Program to fabricate longer lasting esthetic dental restorations with improved wear resistance properties

and color stability. The method involves mixing an appropriate amount of ceramic colorants with incisal, or clear, low-fusing porcelain (LFP). The mixture is then applied to the external ceramic surfaces and fired. Dental laboratory technicians can characterize dental restorations faster since this technique requires only one firing cycle, whereas conventional characterization technique involves 2 separate cycles of firing colorants and glaze layer. The master technician also claims that suspending colorants throughout the matrix of clear porcelain creates more esthetic and natural looking restorations by increasing the depth of perception. The wear resistant property and color stability using this novel technique have not been published in the dental literature, but may surpass those of placing and firing a separate colorant layer, then covering it with a low fusing glaze (Figure 1).

The effects of toothbrush abrasion on dental restorations are studied in vitro using a reciprocating, mechanical device to hold toothbrushes against the restoration surface in a slurry mixture of water and dentifrice to simulate the in vivo state. This condition simulates a three body wear system that involves frictional contact among toothbrush bristles, dentifrice slurry, and the restorative material.[5] Furthermore, there are additional factors that are related to toothbrush and dentifrice abrasion. The combination of the effects of dentifrice, toothbrush, brushing force, brushing habits, and pH of the slurry solution contribute to abrasion of tooth and restoration surfaces.[4,6] The effect of brushing force on wear of dental ceramics has been studied using an in vitro 3-body wear test.[7] Studies have shown a direct relationship between brushing force and the amount of wear.[7] In addition, De Boer et al showed that abrasion is linearly correlated to the number of strokes.[6]

Aker et al reported that 1 hour of brushing or 16,000 brush strokes in the toothbrushing machine was projected to be equal to brushing each tooth 22 strokes twice a day, 365 days a year.[2] In addition, Bergvall et al estimated 14,000 strokes per year whereas Heath and Wilson estimated 20 000 strokes per year.[8,9] Another study reported that, on average, one surface of a tooth receives 19 strokes each time of brushing resulting in approximately 14,000 strokes per year.[10] More strokes were used to brush the mandibular than the maxillary teeth, more for the labial and buccal than for occlusal and lingual surfaces.[10,11] These studies imply that the labial surface of anterior teeth or restorations will receive more brush strokes compared to other tooth surfaces in the mouth, hence enhancing the adverse effects of toothbrush abrasion in the esthetic zone.

Materials and Methods

Ceramic Specimen Preparation

One master specimen (14.5 mm by 11.5 mm by 3.0 mm) was cut from a 3 mm thick clear plastic vacuum matrix material (Biostar, Great Lakes Orthodontics). Four dimples, approximately 50 μm deep, were carved on the corners of the master specimen. An impression of the master specimen was made in a disposable plastic box (Plastic Boxes Clear/Blue 1", #1011740LL, Zahn Dental) using polyvinyl siloxane impression material (Extrude, Light Body, #29177, Kerr Dental). Melted dental dipping wax (Bellewax, Kerr Dental) was flowed into the impression and allowed to cool to room temperature and harden. A total of 16 wax-patterns of the master specimen were generated in this manner. The wax-patterns were sprued and invested in a phosphate-bonded investment (Microstar Dental, LLC) for 15 minutes, allowed to harden, and then transferred into a burn-out oven (Infinity L30, Jelrus) preheated to 1600°F. After 60 minutes in the oven, 2 ceramic ingots with Vita A1 shade (IPS Empress, E TC1 Esthetic Ingot, Ivoclar Vivadent) were pressed into the investment in a porcelain oven (EP 500; Ivoclar Vivadent) according to manufacturer's instructions. Thus, a total of 16 leucite-reinforced ceramic blocks were fabricated from the wax-patterns. The shade of each processed specimen was measured with a calibrated intraoral dental spectrophotometer (VITA Easyshade, Vident). The spectrophotometer was secured on a stand with clamps and the specimens were raised on a flat platform perpendicular to the probe. The initial surface characteristics as well as the thickness of the materials above the plane connecting 3 of the 4 dimple bottoms of each specimen were obtained by using a scanning profilometer (Taylor Hobson Pneumo, Taylor Hobson Precision) before the application of the surface colorants. The dimple bottoms were not covered with surface colorants because they served as reference points for comparing within each specimen throughout clinically simulated toothbrushing (CST) (Figure 2).

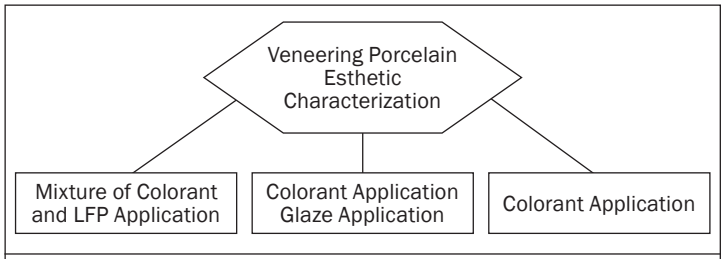

Figure 1. Different techniques of ceramic esthetic characterization by application of components to surface of existing ceramic restoration.

Surface colorants (IPS Empress Universal stain A2/A3/A3.5, Ivoclar Vivadent) were applied to the specimens in Group S and Group SL to achieve the definitive shade

of Vita A3.5. These specimens were then fired in a porcelain oven at the manufacturer recommended temperature. A clear glaze layer (IPS Empress Universal Glaze, Ivoclar Vivadent) was applied only to the 4 specimens in Group GS and then fired in the same porcelain oven. A mixture of clear, add-on low-fusing porcelain (IPS Empress Add-On, Ivoclar Vivadent) and color corrective porcelain colorants was made and applied to the 4 specimens in Group SL. The specimens were fired in the same porcelain oven. The specimens in Group C were used as a control without any external esthetic characterization.

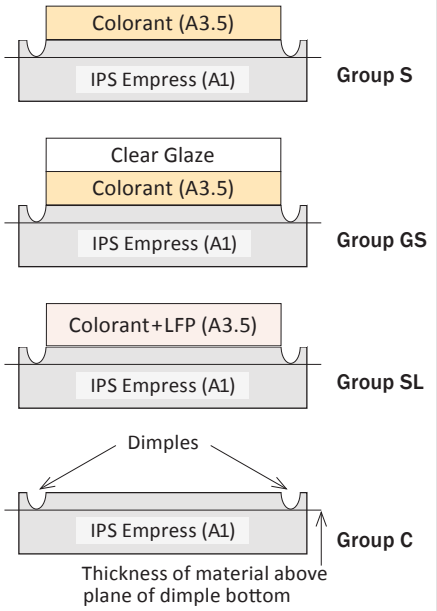

Figure 2. Schematic diagram portraying each specimen group with composition in cross section.

The prepared specimens were scanned again using the surface profilometer. The scanned, 3-dimensional images of each specimen were compared with the correlated images scanned before the characterization (Figure 3).

Toothbrush Abrasion of the Ceramic Groups

Specimen holders for the toothbrushing machine were made by placing 2 specimens on a 2 mm-thick clear plastic block and pressing down a heated 0.6 mm-thick vacuum matrix material (Biostar, Great Lakes Orthodontics) on the top of the specimens.

The middle portion of the vacuum matrix material was cut out while protecting the dimples (Figure 4). A toothbrushing machine (V-8 Cross Brushing Apparatus, Sabri Enterprises) that holds up to 8 manual toothbrushes (47 Tufts Medium Toothbrush, Ranir Co.) simulated toothbrush abrasion on the groups under a slurry solution composed of 37.5 g of neutral toothpaste (Sparkling White Cinnamon Mint Toothpaste, Colgate Oral Pharmaceuticals) and 37.5 ml of distilled water. The force applied on each brush was adjusted to 200 gf (1.96 N). The toothbrushing machine was adjusted to provide 19,000 reciprocal strokes (defined as 1 cycle of downward and upward motion) to the specimens to simulate one year of clinical use. The number of reciprocal strokes and force applied was determined based on 8 published abrasion studies (Table 1).

Initial measurements of the surface profile were recorded before subjecting the specimens to simulated toothbrush abrasion. The specimens were then placed in the toothbrushing machine and the abrasion process was started. After each 76,000 strokes, the specimens were removed and tested and rotated 180°. In addition, the slurry solution and toothbrushes were replaced every 76,000 reciprocal strokes.

Surface Profilimetry

Three dimensional images of the scanned specimens were produced using profilometer software (Talymap Software, Taylor Hobson Precision). The 3-dimensional images were properly oriented and leveled using a reference plane formed by connecting the bottom of 3 specific dimples. Then, a surface profile of the leveled images, diagonally connecting 2 specific dimples, was produced for every 4 years of simulated toothbrushing up to 32 years of CST (Figure 5).

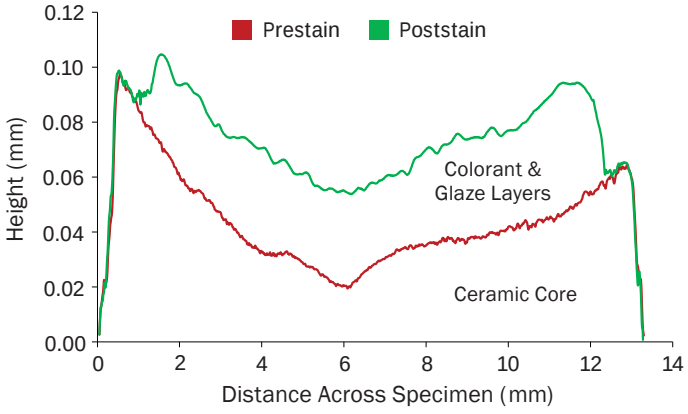

Figure 3. Group GS: glaze layer over colorant layer.

The surface profiles were exported to Microsoft Excel (2003) and a superimposed image was produced for each group (Figure 6).

The average height loss over time and percentage loss of colorant layer in each group over time were calculated using the digitized areas under these curves. First, unnecessary areas under the incline of the dimples as well as the shoulder areas between the top of the dimples to the beginning of the colorant layer were removed (Figures 7 and 8). In order to calculate the average height of colorant layer above the ceramic core, the average height of the core above the bottom of the dimples was subtracted from the

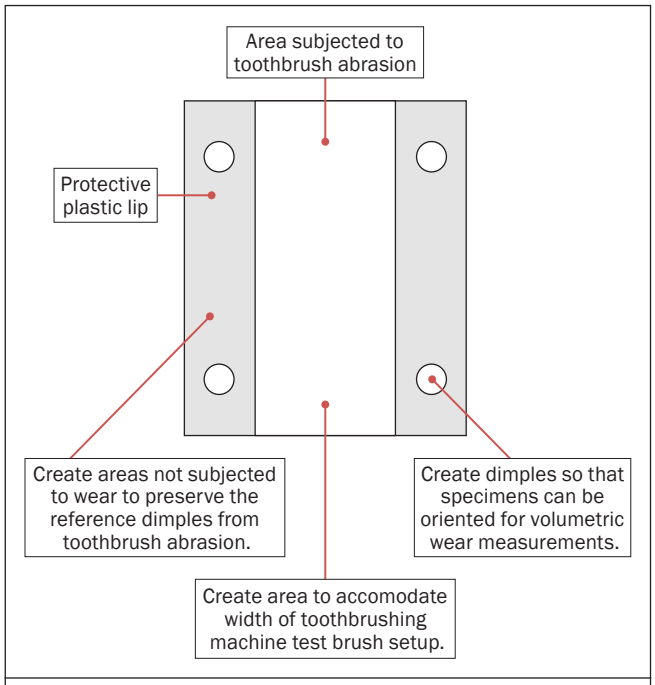

Figure 4. Design of specimen holder.

average height of the colorant layer from the bottom of the dimples (Figure 8). This method was applied to calculate initial thickness of characterization layers in Groups S, GS, and SL. The average initial thickness of colorants in Group S was 16 µm. The average initial thickness of colorants and glaze layer in Group GS was 34 µm. The initial thickness of glaze layer above colorants was 18 µm. The average initial thickness of mixture of colorants and LFP was 40 µm.

The average height of colorant layer was calculated every 4 years until 32 years of CST. The average height loss as well as percentage loss was calculated every 4 years of CST. The average height loss and percentage loss over time was plotted.

Statistical Analysis

For each data, repeated measures analysis of variance (ANOVA) were used to test the null hypothesis that there was no interaction between groups (stain only, Group S; glaze over stain, Group GS; stain+LFP, Group SL; Control, Group C) and time (0, 4, 8, 12, 16, 20, 24, 28, 32 years). If no significant interaction was found, profiles for each group were assumed to be parallel. In this case, the next step was to (1) test the main effect for "group", which was the null hypothesis that the group profiles were coincident, and (2) test the main effect for "time", which was the null hypothesis that the group profiles were level. Failure to reject the null hypothesis in (1) would have shown that there was no difference among groups, regardless of time. Failure to reject the null hypothesis in (2) would have shown that there was no difference with regard to time, regardless of group. All 3 of these tests were performed at the 0.05 significance level.

In this study, the group-by-time interaction was statistically significant. Therefore, the 4 groups were compared separately at each of the time points, and the time points were compared separately within each of the 4 groups. Each of the tests of the group effect and each of the tests of the time effect were performed at a Bonferroni-adjusted significance level of 0.05/(number of tests performed), so that the family-wise error rate for the tests of the 2 factors (group and time) could be controlled at the 0.05 level.

Regardless of whether there was significant interaction or not, the Tukey-Kramer method of multiple comparisons for repeated measures designs was used to perform all possible pair-wise comparisons among groups and among time points, using the same significance level as the test of the corresponding main effect.

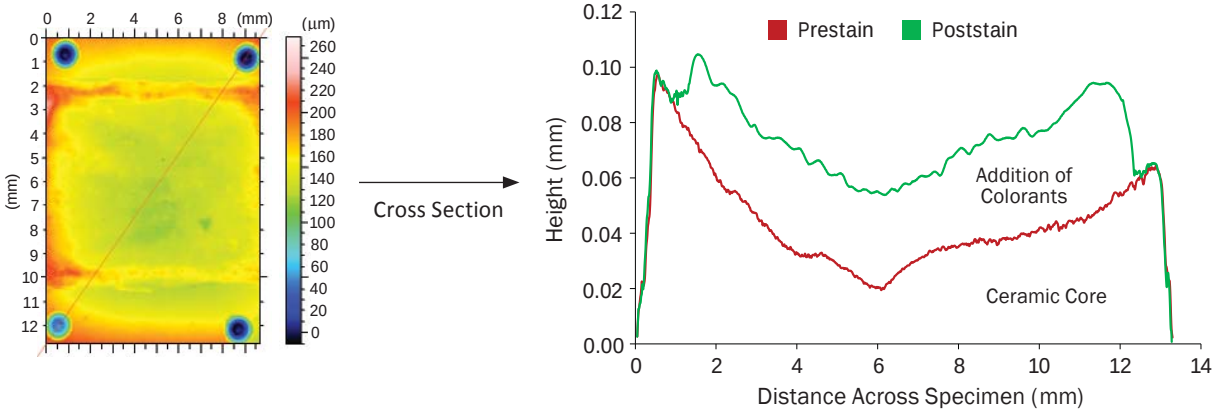

Figure 5. Cross-sectional image generated every 4 years of clinical simulation of toothbrushing for each specimen.

RESULTS

Average Height Loss (µm)

The novel external characterization technique (stain+LFP, Group SL) did not significantly enhance the wear resistance against toothbrush abrasion when compared with conventional techniques. Instead, the average height loss of the applied extrinsic porcelain was 2 to 3 times more than Group S (stain only) and Group GS (glaze over stain) after 32 years of CST.

Table 1. Summary of previously published studies on toothbrush abrasion.

Study	Number of Reciprocal Strokes/Year	Weight (g) Applied	Dentifrice Water Ratio	Slurry Replacement Cycle	Substrate
Aker[2]	7,920	450	1:1	None	Porcelain
Bativala[4]	14,118	250	1:1	None	Porcelain
Bergwall[8]	7,000	450	1:1	None	Acrylic Resin
Cannon[12]	N/A	250	1:1	None	Porcelain
Goldstein[13]	10,000	283	1:1	None	Composite
Heath[9]	10,000	N/A	N/A	N/A	N/A
Kanter[14]	4,320	N/A	N/A	N/A	Composite
Tanoue[15]	10,000	350	1:1	20,000 strokes	Composite
Wictorin[16]	7,380	450	1:1	None	Acrylic Resin
Wang[17]	23,809	200	N/A	N/A	Composite
Average	10,505	335	1:1	N/A	N/A

Application of a glaze layer over the colorants (Group GS) showed a significant improvement on wear resistance, starting as early as the 12-year mark, when compared with Group SL (stain+LFP) and Group S (stain only). After 32 years of CST, only 9 µm (average height loss), or 27% (average percentage loss), of the initial applied glaze layer (Group GS) had been abraded away, whereas 15 µm (81%) loss was observed in the colorant layer (Group S) and 24 µm (52%) loss was observed when the colorants were mixed with LFP (Group SL). This result was consistent with the protective effect of a glaze layer against toothbrush abrasion.[4]

Merely applying and firing colorants (Group S) showed a significant improvement in wear resistance as early as 12 years of CST when compared with the novel

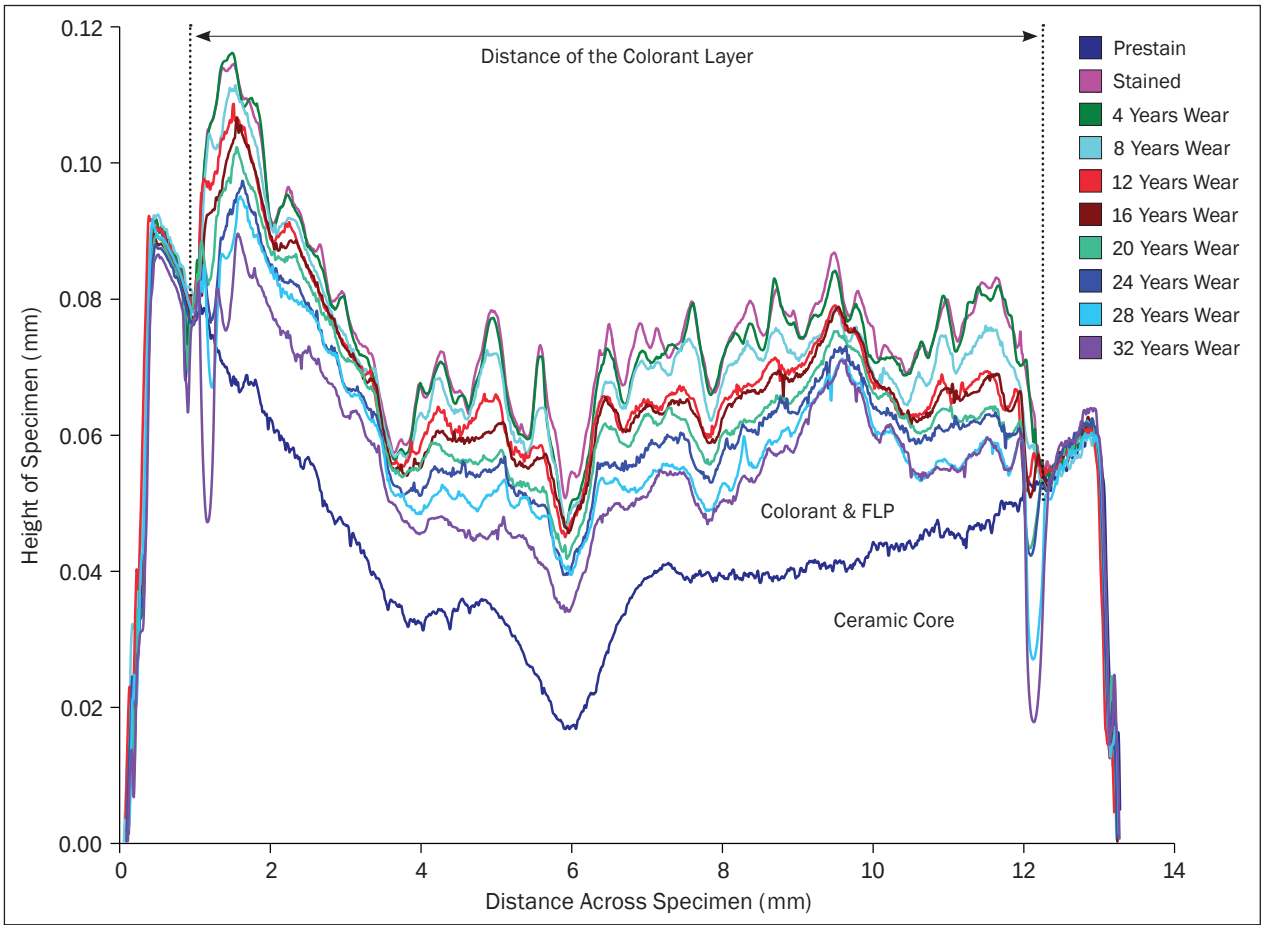

Figure 6. Superimposed cross-sectional views over time.

technique (Group SL). Despite its superior physical properties, the leucite reinforced ceramic core (Group C) showed 2 to 4 times more wear over 32 years of CST when compared with other test groups. Statistically significant height loss of the ceramic core was observed, starting as early as the 8-year mark, when compared with other test groups.

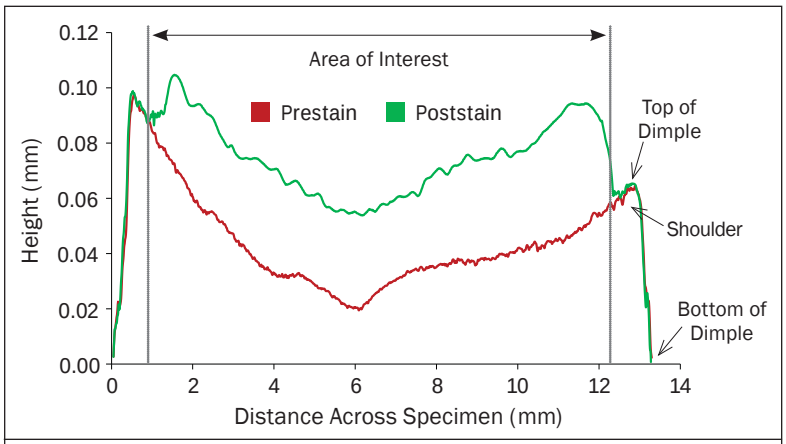

Figure 7. Area of interest defined.

Although average height loss among the characterized specimens showed a positive relationship with increased duration of simulated toothbrushing, each group demonstrated different rates of wear. For example, the least average height loss (9±1.74 µm) among the characterized specimens was observed in Group GS (glaze over stain) after 32 years of CST. The largest average height loss (35±2.74 µm) was observed in Group C (Control). Group S (stain only) had a lower average height loss (13±2.47 µm) when compared with Group SL (stain+LFP) (21±2.28 µm) (Figure 9, Table 2).

Average Percentage Stain Loss

Average percentage loss among the characterized specimens also showed a positive relationship with increased duration of simulated toothbrushing. Each group demonstrated a different rate of percentage loss. For example, Group S (stain only) showed 80%±12% of the original external colorants gradually removed after 32 years of CST. Group SL (stain+LFP) showed 52%±7% of the external colorant layer gradually abraded away. Group GS (glaze over stain) showed only 27%±6% of the external glaze and colorant layer abraded away over 32 years of CST (Figure 10, Table 3).

Group GS (glaze over stain) demonstrated a significantly reduced percentage loss, starting as early as the 12-year point, when compared with other test groups. Overall, this group showed the least amount of percentage loss of the characterized surface over 32 years of CST (Figure 10).

Group SL (stain+LFP) showed a significantly smaller percentage loss starting at the 16-year mark when compared with Group S (stain only). This finding was due to increased initial thickness of the characterization layer in Group SL that was 2 times thicker than the colorant layer in Group S. The average thickness of the colorants in Group S (stain only) was 16 µm compared with that of 40 µm in Group SL (stain+LFP).

COMMENT

In this study, using the novel external characteristic technique of mixing LFP with colorants (Group SL) did not enhance the wear resistance against simulated toothbrush abrasion. Instead, the average height and percentage loss were 2 to 3 times greater when compared to Group S (stain only) and Group GS (glaze over stain). This substantial wear of the LFP and colorant mixture may have resulted from its less dense and more porous surface characteristics compared with a stained and glazed surface. Therefore, the novel esthetic characterization technique may lead to more adverse effects

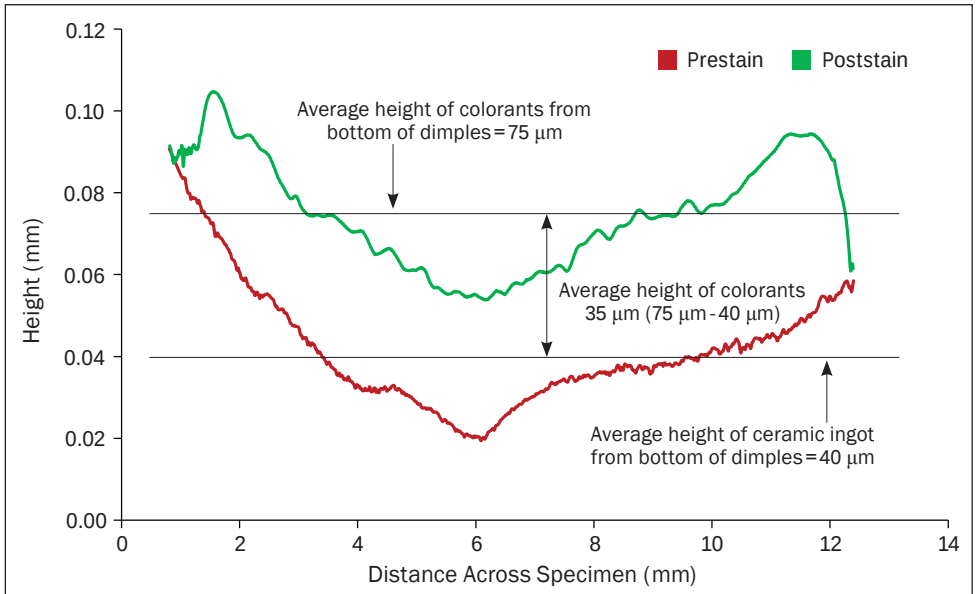

Figure 8. Area of interest after removal of unnecessary areas.

rather than improving the physical and esthetic qualities of a restoration.

Application of a glaze layer over the colorants (Group GS) improved the wear resistance compared with other characterization techniques. After 32 years of CST, only 9 µm (average height loss), or 27% (average percentage loss), of the initial applied glaze layer (Group GS) was abraded away, whereas 15 µm (81%) loss was observed in the colorant layer (Group S) and 24 µm (52%) loss was observed when the colorants were mixed with LFP (Group SL). These results were consistent with the protective effect of a glaze layer against toothbrush abrasion.[2,4] Therefore, application of a clear glaze layer over the colorants is recommended to enhance the wear resistance against toothbrush abrasion.

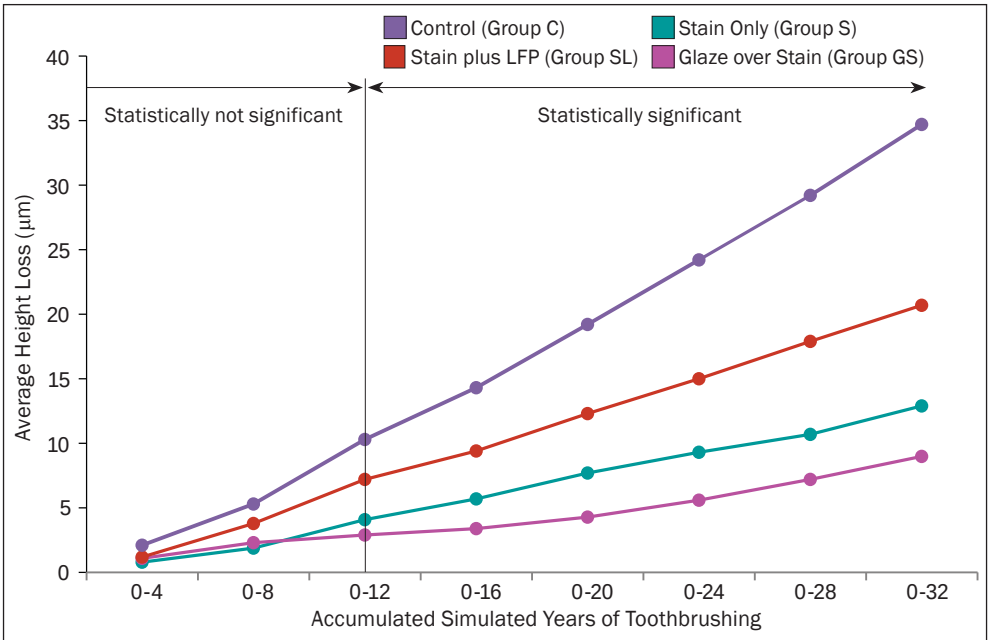

Figure 9. Average accumulated height loss (µm) of external porcelain characterization layer over 32 years of clinically simulated toothbrushing.
Note: n = 4 specimens per group. SD values not included to enhance clarity (refer to Table 2).

Table 2. Average accumulated height loss over accumulated years of clinically simulated toothbrushing (CST).

Accumulated Years of CST	Accumulated Height loss (µm)											
	Group S[a]			Group GS[b]			Group SL[c]			Group C[d]		
	Avg	SD	CV	Avg	SD	CV	Avg	SD	CV	Avg	SD	CV
0-4	0.8	0.5	57	1.1	0.3	27	1.2	0.3	24	2.1	0.5	23
0-8	1.9	0.5	25	2.3	0.6	28	3.8	0.7	18	5.3	0.2	5
0-12	4.1	0.5	12	2.9	0.4	16	7.2	1.1	15	10.3	1.2	11
0-16	5.7	0.5	10	3.4	0.2	5	9.4	1.1	11	14.3	0.3	2
0-20	7.7	0.4	5	4.3	0.4	9	12.3	1.5	12	19.2	1.2	6
0-24	9.3	0.8	8	5.6	0.5	10	15.0	1.5	10	24.2	1.4	6
0-28	10.7	1.4	13	7.2	1.5	21	17.9	1.7	10	29.2	2.2	8
0-32	12.9	2.5	19	9.0	1.7	19	20.7	2.3	11	34.7	2.7	8

a: stain only
b: glaze over stain
c: stain+LFP
d: Control
Note: CV indicates Coefficient of variation

Despite its superior physical properties, the leucite-reinforced core ceramic (Group C) showed 2 to 4 times more wear over 32 years of CST compared with the extrinsic colorants and glaze. Lower wear resistance of the ceramic core may be due to higher crack growth pattern of the leucite-reinforced ceramics in an aqueous slurry solution with neutral pH when they are subjected to mechanical toothbrushing. The increase in solubility of leucite crystals may be another explanation of this undesired property of the ceramic core. Further research should be conducted to investigate the correlation between the solubility of leucite-reinforced ceramics and the potential of a higher wear rate compared with dental ceramics without leucite crystals.

A pilot study was conducted for up to 32 years of CST using 2 specimens in each group in order to determine the number of specimens needed in each group for this experiment. Eight specimens per group were determined to be necessary based on the results from the pilot study. Although only 4 specimens per group were used in this experiment due to limited time and resources, statistically significant differences among groups were found. Experimental modifications, such as rotating the specimens 180° every 4 years of CST, using flat toothbrush bristles, and using more abrasive toothpastes, were made from the pilot study to facilitate even patterns of wear. A larger sample might have provided additional precision to detect differences among groups with shorter periods of follow-up corresponding to those that are more commonly found in clinical studies.

Parameters including the force applied to the specimens, number of reciprocal strokes in 1 year of CST, and the area of the toothbrush bristles had be considered. In an attempt to correlate these factors, Equation 1 was formulated:

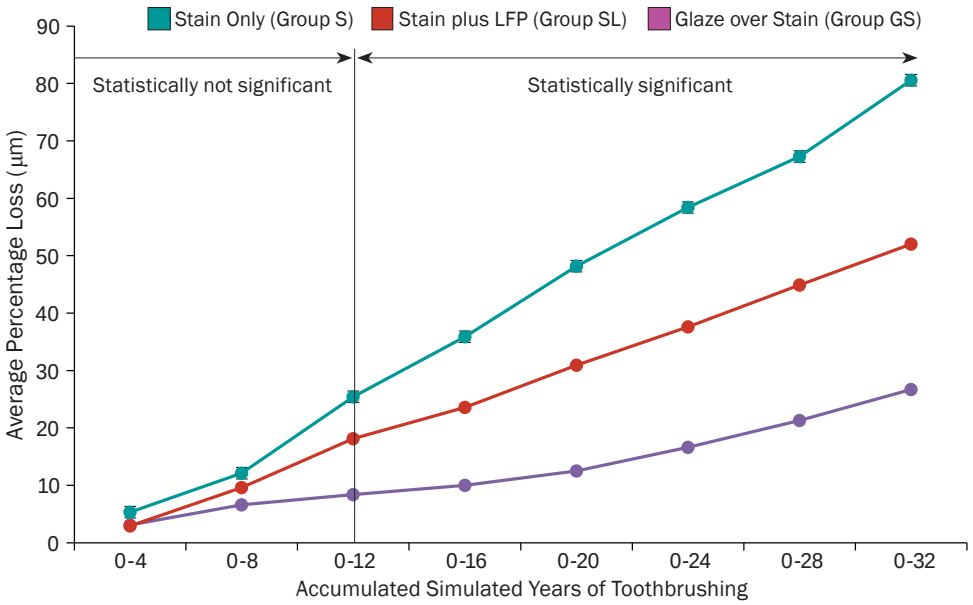

Figure 10. Average accumulated percentage loss of external porcelain characterization layer over 32 years of clinically simulated toothbrushing.
Note: n = 4 specimens per group. SD values not included to enhance clarity (refer to Table 2).

$$PD = \frac{F \times [Lb \times S]}{[Lb \times Wb]} = \frac{F \times S}{Wb}$$

where:

PD = pressure applied times distance traveled (work)

F = weight applied to the toothbrush (N)

Lb = length of bristles (mm)

Wb = width of bristles (mm)

S = number of reciprocal strokes for 1 year of CST

This equation shows that the weight (grams-force) applied on the toothbrush and the total distance the toothbrush bristles traveled on a specimen in 1 year of CST has an inverse relationship with the area of the bristles that are in contact with the specimen. For example, the average parameters of 8 different abrasion studies from Table 1 are shown below:

Average weight applied to toothbrush = 335 gf (3.29 N)

Average number of reciprocal strokes for 1 year of CST = 10,505 strokes

Length of bristles = 25 mm

Width of bristles = 8 mm

PD = (335 g × 10,505 reciprocal strokes × 25 mm)/(8 mm × 25 mm) =

(87,979,375 gf reciprocal strokes mm)/(200 mm^2) =

439,897 gf strokes/mm

A researcher can calculate the appropriate number of reciprocal strokes in 1 year of CST with different parameters using 439,897 gf strokes/mm as a constant value. In this study, the number of reciprocal strokes was calculated to be 19,000 per year since the maximum amount of force the toothbrushing machine could generate was 200 gf (1.96 N), which was 135 gf (1.32 N) less than the average force applied on the toothbrush. Therefore, the number of reciprocal strokes was increased to compensate for the decrease in force applied on the toothbrush using Equation 1.

CONCLUSIONS

A conventional external esthetic characterization technique of applying a glaze layer over the colorants (Group GS) significantly enhanced the surface wear resistance to toothbrush abrasion, and improved the surface color stability when compared with other techniques involving application of colorants only (Group S) or mixture of colorant and LFP (Group SL). The underlying core ceramic had significantly less wear resistance properties compared with all externally characterized specimens. The novel esthetic characterization technique showed more wear and is thus not advocated as the "best" method for surface characterization.

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Table 3. Statistical analysis of average accumulated height loss between groups over time

Time (years)	Height Loss (n=4 specimens per group)					
	IPS Empress vs Group GS[a]	IPS Empress vs Group SL[b]	IPS Empress vs Group S[c]	Group GS[a] vs Group SL[b]	Group GS[a] vs Group S[c]	Group SL[b] vs Group S[c]
4	1.000	1.000	0.989	1.000	1.000	1.000
8	0.003[d]	0.877	<0.001[d]	0.890	1.000	0.557
12	<0.001[d]	0.002[d]	<0.001[d]	<0.001[d]	0.994	0.002[d]
16	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	0.130	<0.001[d]
20	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]
24	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]
28	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]
32	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]

a: glaze over stain c: stain only
b: stain+LFP d: indicates statistical significance with $P < .05$

Effect of Smokeless Tobacco on Surface Roughness of Dental Restorations

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ABSTRACT

Clinical Relevance: Surface alterations of dental restorations can result in increased plaque biofilm. This leads to increased risk of premature restoration failure. Smokeless tobacco, in common use by some US military personnel, represents a potential source for surface alteration. If smokeless tobacco causes an untoward effect, selection of a more resistant restorative material could increase restoration longevity, thus minimizing lost work time and costs associated with replacement of failed restorations.

Purpose: Comparatively assess the effect of smokeless tobacco/salivary substitute mixture on altering surface roughness of amalgam, composite resin, and resin modified glass ionomer (RMGI) restorations.

Materials and Methods: Sixty cubic restorations (3 groups of 20) were fabricated using a 4 mm by 3 mm Teflon mold. One examiner assessed the restorations at time points representing zero days, one day, one week, 2 weeks, one month, and 3 months. The data obtained were collected using a surface profilometer, measured in micrometers. Data were statistically analyzed using 2-way analysis of variance (ANOVA) test. A difference was significant if $P < .05$.

Results: Confidence levels with a 95% overall rating received a clinically acceptable classification. The 2-way ANOVA test detected significant differences between baseline, one day, one week, 2 weeks, one month, and 3-month data for surface roughness ($P<.05$). With respect to time and restoration type, results proved statistically significant with $P<.0001$. All restorations were statistically significant with respect to change in surface roughness with RMGIs showing the greatest surface roughness alteration.

Conclusion: Smokeless tobacco mixed with a salivary substitute altered restoration surface roughness over time. Resin-modified glass isonomer restorations demonstrate the greatest alteration of surface roughness, with amalgam restorations showing the least. Amalgam remains the preferential restorative material in patients who use smokeless tobacco.

Despite notable progress in reducing the prevalence of cigarette smoking in the military, smokeless tobacco use continues to increase.[1] Based on data from the Millennium Cohort Study, deployment and combat exposure in the US military are associated with an increased level of smokeless tobacco use and smoking.[2] According to the Murtha Cancer Center, Department of Defense Cancer Center of Excellence, the prevalence of smokeless tobacco use in the military is almost 4 times greater compared to use in the US civilian population.[3] Symptoms of posttraumatic stress disorder also increase the odds for use.[2]

Dental caries is one of the most prevalent diseases causing the demineralization of tooth structure. Streptococcus species are the predominant oral bacterial acids produced.[4] Defective restorations lead to additional loss of tooth structure due to restoration and caries removal. Factors contributing to restoration defects include: marginal leakage, polymerization shrinkage, or plaque build-up due to high surface roughness.

Three restorative materials presently used for class V lesions include amalgam, resin composite, and resin-modified glass ionomer (RMGI). Amalgam continues to serve as an excellent and versatile material in dentistry for more than 150 years, with an estimated 100 million Americans having amalgam restorations.[5]

Amalgam is the material of choice for larger carious lesions in posterior teeth due to its strength, durability, ease of use, and low cost.[6] Amalgams were commonly placed in class V preparations due to their hydrophilic quality, decreasing the need for moisture control. Amalgam limitations include poor esthetics and increased tooth structure removal for mechanical retention.

Composite restorations increased in popularity as a result of their tooth-like appearance and ability to conserve tooth structure, and now represent the preferred restoration among patients in the United States. Improvements such as refinement of filler materials with wear properties comparable to human enamel have made resin materials more predictably reliable in clinical use.[7] Composite resins are more technique sensitive, require bonding agents to maintain retention, and typically fail sooner than amalgams.

Resin-modified glass ionomers (RMGIs) have the same ion-releasing glass filler particles seen in conventional GIs, but smaller. They are synthesized by reacting methacrylate with polyacrylic acid.[8] The setting reaction for RMGIs is dual cure and light activated, as well as an acid-base reaction after absorption of water. They are excellent for class V restorations due to their fluoride releasing properties in these nonesthetic regions. Their "smart behavior," which can change their behavior in response to various stimuli such as stress, heat, moisture, electricity, and pH, helps to prevent dimensional changes in moist environments.[9]

Compared to other restorative materials, one advantage of glass isonomers is that they may be placed in cavities without the need for bonding agents.[10] Despite these positive biocompatible features, their weakness lies in the lack of sufficient strength and toughness.[8] To improve some of these weak glass ionomer properties, the creation of RMGIs improved flexural strength through the introduction of hydrophilic monomers and polymers like hydroxylethyl methacrylate.[11]

Resin composites and RMGIs are the most common types of adhesive materials used to restore cervical lesions.[12] Ideal esthetic properties of composite resins and the fluoride releasing properties of RMGIs make these 2 restorations a good fit. The more comparable modulus of elasticity of both restorations compared to enamel also allows for ideal abfractive properties. Amalgams have a solid record of longevity far outlasting those of composite resins and RMGIs with less inclination to recurrent decay. Understanding these properties help dentists decide which restorative material to use when treating deploying Soldiers who use smokeless tobacco.

Smokeless tobacco, which contains high sugar content and acidic properties, also contributes to caries onset, destruction of enamel and other tooth structures.[13] As a result, smokeless tobacco use could result in a greater number of early failures of restorations, especially class V cervical restorations.

Various studies investigated the influence of surface structure and composition of dental restorative materials on bacterial adhesion.[14] The overall conclusion from these studies is that surface roughness is positively correlated with plaque accumulation.[15] Findings also demonstrate that increased surface roughness would prompt nonuniform stress distribution, mainly due to the shape differences in the surface layer.[16] Ultimately, this leads to craze lines, cracks, or even fractures in the restoration causing inflammation of the dental pulp if not properly treated. Mecholsky et al[17] developed the theory that initiation of cracks starts at stress concentration points caused by surface roughness.

Given the relatively high rate of smokeless tobacco use in the armed forces, it is critical to understand how different dental materials respond to smokeless tobacco

Materials to test the effect of smokeless tobacco exposure on surface roughness.

Material	Type	Contents	Manufacturer
Amalgam	Valiant PhD (regular set)	59% Ag, 13% Cu, 43% Hg, 28% Sn	Kerr Charlotte, NC
Composite resin	Filtek Supreme Ultra Universal	Bis-GMA, UDMA, TEGDMA, Bis-EMA (6) resins, silica filler, zirconia filler	3M ESPE St. Paul, MN
Resin modified glass ionomer	Fuji II LC	Silicate glass powder, polyalkenoic acid, HEMA, UDMA	GC America Alsip, IL
Copenhagen Tobacco	long cut, straight	Water, tobacco, sodium chloride binders, natural and artificial flavors, ammonium chloride, ethyl alcohol, ammonium sodium carbonate preservatives (10 mg)	US Smokeless Tobacco Company Nashville, TN
Surface profilometer	Surface Roughness Tester, Surftest SJ-210	2.4 in color graphic LCD, calculation results assessed profiles, load and amplitude curves	Mitutoyo Corporation Japan
Dykstra EMS Embedding Mold	Stepped Microtome Catalog # 70907	Teflon	Electron Microscopy Sciences Hatfield, PA
Curing Light	Mini LED #303677-019	Power module, handpiece, eyeshield	Acteon North America Mount Laurel, NJ
Simulated salivary extract	Hanks Balanced Salt Solution, 1X	10 mL	Corning Cellgro Manassas, VA
Matrix Strips	DuPont Mylar 10 cm by 0.95 cm MFG#20 95-8205	Plastic strips measure 4 in by 3/8 in by 0.002 in	Patterson Dental Supply Montreal, Quebec
Laboratory incubator	Heratherm Oven Model # 3700-87	97.2°F temperature	Thermo Scientific Anaheim, CA
Reclosable container & lid	0.55 liter clear plastic	None	Solo Cup Operating Corporation Highland Park, IL

exposure. To answer this question, the present study evaluated the effect of smokeless tobacco/salivary extract on 3 commonly used dental materials with differing surface roughness (Ra, µm).

Materials and Methods

Sixty restorations, divided into equal groups of twenty (20 amalgam, 20 RMGI, and 20 composite resin), were used to evaluate effects of smokeless tobacco and salivary extract solution combined liquid extract (Copenhagen long cut straight and Hanks Balanced Salt Solution) on the surface roughness of different restorations. Materials used, compositions, and product manufacturers used are listed in the Table.

Specimen Preparation

The restorative materials called for the preparation of 20 cubic specimens each, using a 4 mm x 3 mm Heliotest Teflon mold (Electron Microscopy Science, Hat field, PA) (Figure 1). The prepared materials slightly overfilled the molds. Careful preparation of the composite resin and RMGI occurred with proper isolation and light cure with the use of a Mylar strip (DuPont Mylar, Montreal, Quebec) to help remove voids and excess material. A LED light cure unit (Mini LED, Acteon North America, Mount Laurel, NJ) with a light intensity of 665 mW/cm cured and polymerized the composite and RMGI according to the manufacturers' instructions. Amalgams fully set over the 24-hour setting period. Figure 2 shows restoration placement in the embedding molds.

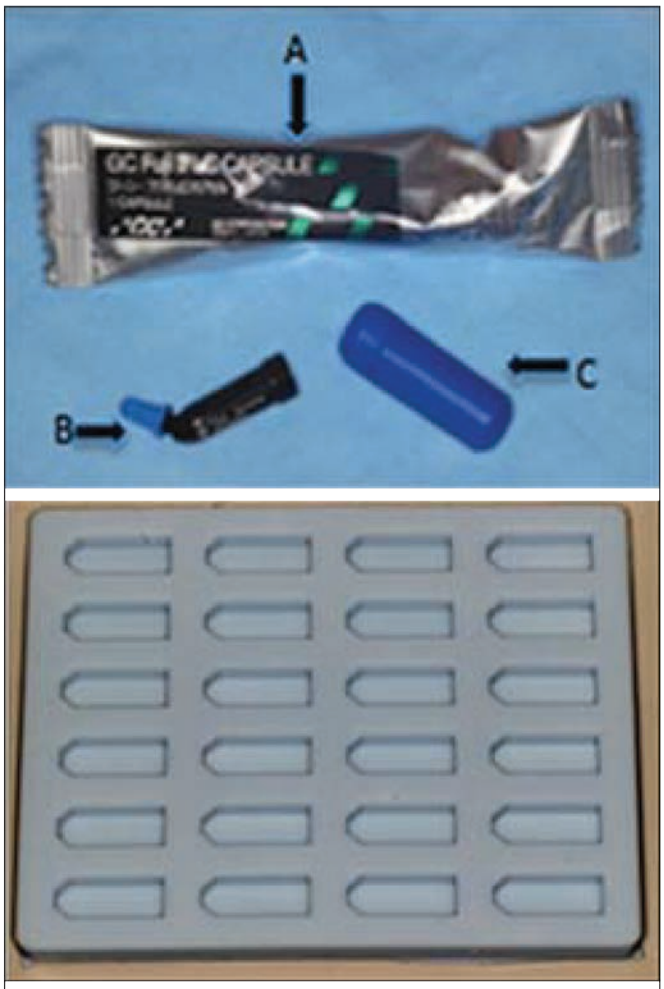

Figure 1. Top - restoration materials: (A) RGMI; (B) Composite; (C) Amalgam. Bottom - sample embedding mold.

Following specimen preparation, all restorations were polished, then soaked in normal saline at 37°C for 24 hours. Preparations were blotted dry and initial measurements taken with a surface profilometer (Mitutoyo Surftest SJ-210) to determine baseline surface roughness. Baseline measurements represent control values.

The examiner stored specimens in a 97.2°F Heratherm laboratory incubator (Thermo Scientific, Anaheim, CA) during the duration of the experiment to represent the average temperature of the human mouth. Ten mg of the Copenhagen smokeless tobacco (Figure 3) and 10 ml of the salivary substitute liquid mix fully covered each type of restorative material for 24 hours a day (Figure 4). The examiner measured the surface roughness after 6 hours (representing one day), 2 days (representing one week), 3.5 days (representing 2 weeks), 6 days (representing one month), and 15 days (representing 2 months). The need to evaluate the surface degradation at shorter time intervals occurred due to the limited time constraints. The surface profilometer (Figure 5), an instrument which measures a surface's profile in order to quantify its roughness, helped evaluate and quantify the surface roughness of the restorations. The average surface roughness (Ra) is the average value of the height of the surface profile above and below the centerline throughout the determined sampling length.[18]

In total, 60 prepared specimens divided into 3 groups were evaluated: Group 1, Valiant PhD (n=20); Group 2, Filtek Supreme Ultra Universal (n=20); and Group 3, Fuji II LC (n=20).

Evaluation and Data Collection

One independent examiner placed and evaluated all restorations and collected data. The examiner accurately calibrated the Surftest SJ-210 surface profilometer by measuring the precision roughness specimen supplied with the profilometer set per manufacturer guidelines. The examiner also adjusted the gain to ensure the measured value equaled the nominal Ra value of the precision roughness specimen.

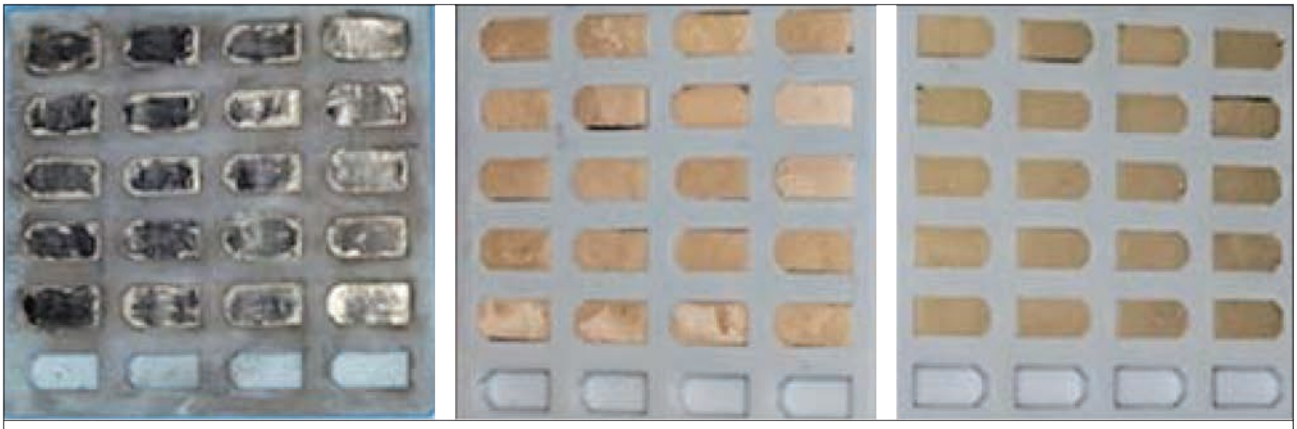

Figure 2. Amalgam (left), composite resin (center), and glass ionomer (right) restoration materials in embedding molds.

A calibrated surface profilometer found the average surface roughness (Ra, in micrometers) of the specimen. An initial roughness measurement represented the roughness value, unless the profilometer could not read an initial roughness value. If this occurred, the examiner moved the profilometer to an area where the device could obtain a reading. If the surface was too rough to gain a second reading, a null value was annotated.

Statistical Methods

A 2-way ANOVA test, using the same materials, analyzed intragroup comparisons between baseline and varying timelines. Evaluating row and column factors tested statistical significance of results with respect to time, restoration, and the interaction between the 2 factors. The alpha value was set at 0.05. Data are represented as means (±SEM) and experimental manipulations were performed in a parallel manner. Dunnett's multiple comparisons test indicated the data collected were dis-tributed normally and are statistically significant. Graph Pad Prism statistical software was used for all statistical analyses.

Results

No restorations were lost due to misplacement or extreme chemical wear. Fifty-two readings were discarded because the profilometer could not read the roughness measurement range for specific time points. Initial illegible readings presented at hour 222 of data collection. Despite illegible readings at a specific time point, restorations presented a legible reading on the next available measurement period.

Time

When evaluating the change percentage of surface roughness over time, all restorations showed a steady to large change in roughness. Amalgams showed an overall 20% increase during the modeled 2-month testing period. Figure 6 portrays a small increase in surface roughness from baseline to completion of the data collection. There was a steady movement with a slight change over time. The highest surface roughness recording appeared at the simulated one month and one day mark (186 hours) and the lowest surface roughness recording appeared at baseline.

The RMGI showed the greatest overall percentage change with a 237% increase over the represented 2-month period. Figure 6 shows a large increase over time from baseline to completion. The highest surface roughness recording appeared at the modeled 2-month period (360 hours) and the lowest recording appeared at baseline. Composites showed the most fluctuation with an overall 31% decrease over the represented simulated 2-month period as shown in Figure 6. The highest surface roughness recording emerged at the one-week mark (45 hours) and the lowest recording emerged just short of one month.

All of the results followed suit with the hypothesis showing statistical significance for an increase in surface roughness overall. The total percentage

Figure 3. Copenhagen Long Cut Straight smokeless tobacco.

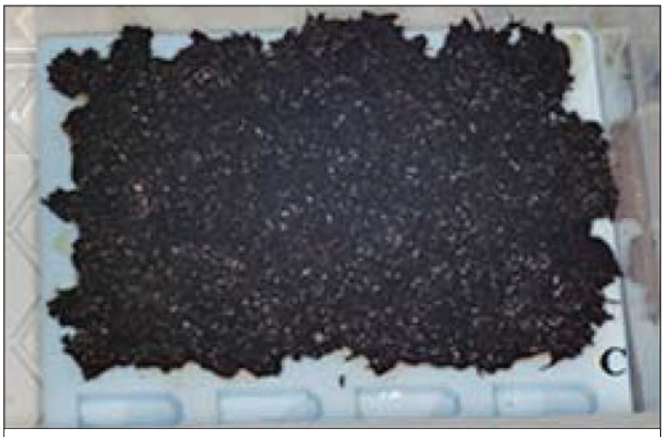

Figure 4. The embedding mold filled with RMGI restoration material covered with the smokeless tobacco/salivary substitute mix. The other 2 embedding molds were covered in a similar manner.

of variation for all restorations combined showed a row factor of 0.7672, yielding $P<.0001$ suggesting the results are statistically significant and stay within the confidence interval.

Restorations

Examination of the restorations from a clinical standpoint revealed a significant change in color and clinical roughness existed for all restorations. The RMGIs showed a distinct staining and change in surface texture (Figure 7). The percentage of total variation for the column factor was 67.73, yielding $P<.0001$, satisfying the confidence interval.

Interaction of Time with Respect to Restoration

Data shows that the amalgam restoration did not change surface roughness much over time, compared to the gradual, then rapid rise in surface roughness detected in the glass ionomer material. With regard to the effect of time with respect to the restoration, data shows statistical significance with a total percentage of variation of 4.2%. Surface roughness measurements of different restoration types yielded statistically significant variances among them after smokeless tobacco exposure ($F(60, 3425)=1.607$; $P<.005$). There was a significant interaction between time and restoration type ($F(2, 3425)=4255$; $P<.0001$).

Figure 5. Surface roughness tester (Surftest SJ-210 profilometer.

The P value ($P<.0001$) satisfied the confidence interval of greater than 95%. The 2-way ANOVA evaluated comparisons of specimen mean scores. The ANOVA revealed statistically significant variances for all restoration types with respect to time ($F(120, 3425)=4.398$; $P<.0001$).

Comment

Studies have shown an increased use of smokeless tobacco, especially among deployed military personnel.[2] Reasons for smokeless tobacco use include helping to stimulate moisture in the mouth, addiction to nicotine, and peer pressure. Ingredients found in smokeless tobacco include: polonium 210, N-nitrosamines, formaldehyde, nicotine, cadmium, cyanide, arsenic, benzene, and lead, to name a few. Natural and artificial flavors, preservatives, and sugars are also added. Polynuclear aromatic hydrocarbons, polonium 210, and N-nitrosamines represent the chemical carcinogens.[19] Another study shows 70% of tobacco-specific N-nitrosamines becomes extracted from one dip of snuff when kept in the mouth for 30 minutes.[20]

The pH of smokeless tobacco ranges from 5.84 to 8.1 with a nicotinic content ranging from 0.42% to 2.73%.[21] Although the average pH is more neutral to basic, the large amount of sugar, preservatives, and chemical carcinogens of smokeless tobacco have an association with gingival recession, tooth wear, and dental caries in users.[22] Long-term clinical success of dental restorations depends on various factors, including the physical properties of the material, clinical proficiency of the treating dentist, and proper maintenance and patient care. Understanding whether there is a change in surface roughness is important because, according to Yalcin and Gurgan, "irregularities in surface texture enhance bacterial adhesion, and roughened materials may suffer from increased staining."[23] Increased bacterial adhesion increases the incidence of recurrent decay and defective restorations.

The 3 restorative materials used in this study showed varying results most likely due to the differences in their material structure. Due to their organic matrix, resin materials are more prone to chemical alteration compared to metal or ceramic restorations.[14] This could explain why the amalgam group showed the smallest change in surface roughness compared to the composite resin and RMGI groups.

Studies comparing amalgam and resin-based composites as restorative materials suggest amalgam has greater

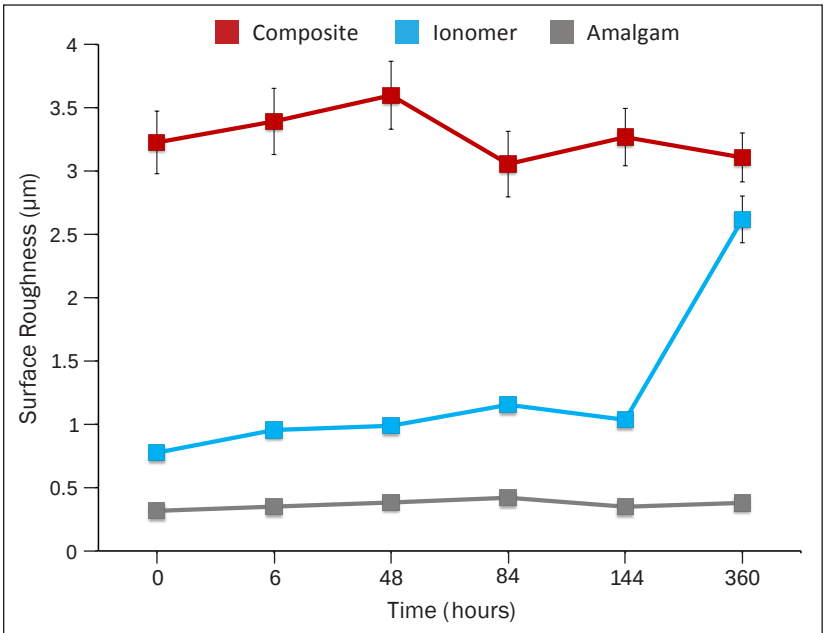

Figure 6. Change in surface roughness over time for each tested material.

longevity than resin-based composites. One randomized clinical trial[24] revealed the risk of experiencing secondary caries as 3.5 times greater with composites. Amalgam outperformed resin-based–composites, showing a 94.4% amalgam survival rate at 7 years compared with 85.8% for resin-based composites at 7 years. Improved survival rates of amalgams may be attributed to the less technique sensitive nature of placing them, expansion of amalgam upon setting which decreases onset of marginal leakage, and a greater ability to withstand occlusal forces.

The RMGI showed the greatest change in surface roughness with a statistically significant steady and gradual increase noted throughout the entire 360 hours of testing. This increase also showed clinical evidence with visible roughness and staining. The large sensitivity of RMGI to smokeless tobacco may be attributed to a weak organic matrix. While RMGIs perform well with retention and postsensitivity, it is not reliable in terms of marginal characteristics, surface properties, and color stability.[25] For this reason, RMGI may not be the restoration of choice for a patient using smokeless tobacco.

Smokeless tobacco also had a significant effect on the surface roughness of composite resin. The results for this material fluctuated differently from the amalgam and RMGI. Values for the surface roughness remained steady for the first half of the experiment until a sharp drop in roughness was measured around the halfway point. From that point on, the roughness continued to gradually increase. This is the only restoration which reacted contrary to initial clinical expectations clinically. Despite the clinical variability, statistics showed a significant overall increase in roughness.

Composite resins may have reacted with such clinical variability due to human error. Future studies may benefit from an extended time period of testing, which may help show a larger data set of the clinical exposure of the restoration composition change. In a previous study observing the effect of in-office bleaching agents carbamide peroxide and hydrogen peroxide,[14] results showed a slight increase in the surface roughness of the composite resin tested, but the increase in this experiment did not show statistical significance.

Filtek Supreme Ultra Universal, the nanofil resin used in this study, has a well-rounded appeal because of its equal mix of esthetics and strength. Its translucency is also appealing. Composite resins, in this experiment, did not show the high resistance to smokeless tobacco of amalgam, but it also did not show the large change

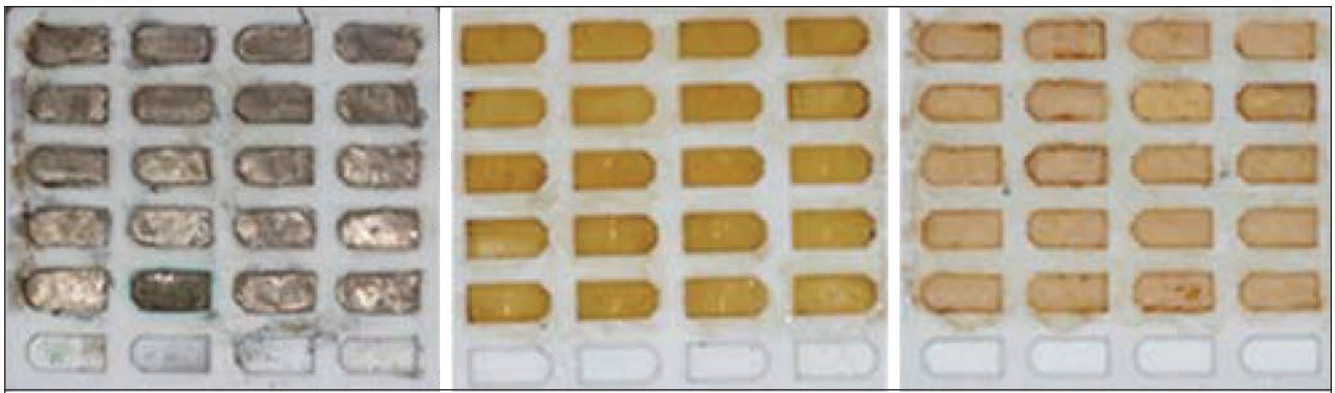

Figure 7. Amalgam (left), composite resin (center), and glass ionomer (right) restoration materials after 360 hours of testing.

in roughness in comparison to RMGIs. Additional testing focusing on the relationship smokeless tobacco has on the composite resin may be helpful in gaining more understanding.

When reviewing and evaluating overall experiment results, it is important to remember that this study only takes into account the effect a smokeless tobacco mix has on the surface roughness of dental restorations solely from a chemical perspective. Objectively, smokeless tobacco use has more than just a chemical effect. The largest effect is abrasive in nature. The natural state of the tobacco is a graininess, which contributes the abrasive effects. Additional studies accounting for both chemical and abrasive effects of smokeless tobacco will provide an even greater understanding of this topic. In retrospect, the gold standard for truly measuring the surface roughness of a specimen would be use of a scanning electron microscope (SEM).

Nonetheless, the results of this study demonstrate distinct, measurable differences among common dental restoration materials when exposed to smokeless tobacco. These findings provide a framework for future studies such as SEM experiments. Additionally, the results presented here add to the literature to better inform dental clinicians, particularly those treating military personnel, when selecting restoration materials.

Conclusion

Both quantitative and clinical observations show the distinct effect that smokeless tobacco/salivary substitute mix has on surface roughness of common dental restorations. Amalgam (Valiant PhD), which represents the oldest and strongest restoration, showed the smallest change over time. The RMGI (Fuji II) showed the greatest percentage of surface roughness change with a distinct clinical staining over a period equivalent to 2 months.

Acknowledgments

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Placement and Replacement Rates of Amalgam and Composite Restorations on Posterior Teeth in a Military Population

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ABSTRACT

Objective: Replacement rates of direct dental restorations have been reported to be 37% to 70%, occupying a large proportion of a general dentist's time. Variations in the rate of initial placement and replacement of direct den-tal restorations may be associated with material placed (amalgam or composite), age, caries risk of the patient, and other factors. The purpose of this research was to clarify where the majority of patient care time is spent as a restorative Army dentist regarding either the initial placement or replacement of failed restorations; and how the location, caries risk, and material used (amalgam or composite) affects replacement rates.

Methods: This retrospective cross-sectional study gathered data from 600 randomly selected military patient dental records. All paper records were reviewed and cross checked with the digital record and digital x-ray-databases. Record review was limited to all direct dental restorations placed in the posterior dentition within the past 2 years (March 2011 to March 2013). Statistical analysis was accomplished using chi-square tests and logistic regression analyses.

Results: Of the 600 charts reviewed, 525 were male, 75 were female, with an average age of 26 years (SD = 6), ranging from 17 to 54 years. A third of the patients were classified as high, moderate, and low caries risk, respectively. The total number of posterior direct dental restorations placed was 2,117. Initial restorations totaled 1,429 (67.5%), and replacement restorations placed totaled 688 (32.5%). Four hundred forty-one of the 688 direct dental restorations replaced were amalgam (64%), the 247 remaining direct restorations replaced were composite (36%). Mandibular first molar dental restorations were replaced the most often (23.1%) while mandibular first premolar restorations were replaced the least often (0.9%). Older patients were more likely to have replacement of an existing restoration.

Conclusions: Military dentists spend about one-third (32.5%) of their time replacing existing direct dental restorations. The majority of direct dental restorations placed and replaced were amalgam. No significant difference was found between composite and amalgam restorations. Location was shown to be significant with first molars and second molar restorations failing with the highest frequency. There was no significant difference found between male and female patients. As patient's age increased, the number of replacement restorations also increased.

In the past several decades, major changes have occurred in both dental treatment philosophies (surgical vs medical model)[1] and direct dental restorative materials (amalgam and composite)[2] which have the potential to change the longevity of directly placed dental restorations. The most frequently cited reason for replacing direct dental restorations is secondary caries.[3-11] Therefore, it stands to reason that if one lowers the caries risk of the patient by using Anderson's medical model[1] or Featherstone's CAMBRA approach (caries management by risk assessment),[12,13] the placed dental restoration will fare better and last longer.

Similarly, using the dental restorative materials with the greatest longevity potential and caries resistant properties would be beneficial. The 2 most commonly placed direct dental restorations are resin composite and amalgam. Reasons for choosing either amalgam or composite for direct dental restorations may include cost, esthetics, ease of use, caries risk of the patient, and the material of preference (either for the patient or doctor).[14,15] There is an ongoing debate in the literature over which restorative dental material has better longevity in the oral cavity.[2,4,8,11,14,16] It should be noted that, regardless of the current debate, amalgam has a longer history of success, but the longevity of properly placed resin composite, is greatly improving.

The US Department of Health and Human Services estimates that "60 to 70 percent of restorative work is

replacement of existing restorations."[17] Composite restorations have become the material of choice, being placed as direct restorations more frequently by practitioners than at any time in the past.[18] Are we compromising longevity and retention for esthetics? Or, have materials and methods changed so much that composites can now be used interchangeably with amalgam in most if not all clinical situations?[2]

In a military population the idea of placing a functional, lasting, and retentive dental restoration is critical.[19] Today's Soldiers experience a myriad of environments and their access to care is a constantly changing variable. Oral health is directly reflected in wellness and military readiness. This research seeks to improve upon existing treatment philosophies and aid in improving Soldier care.

The purpose of this research is to show where the majority of patient care time is spent by a restorative Army dentist on either the initial placement or replacement of failed restorations, and how the size, location, caries risk, and material used (amalgam or composite) affects replacement rates. The following scientific hypothesis will be tested: more than 50% of restorative work done by military dentists is replacing existing restorations; composite restorations fail more frequently; and permanent mandibular first molars require the replacement of existing restorations the most often.

Methods

For this research project, 600 dental records were selected (using an online random number generator) from the over 12,000 active dental records maintained at the Schofield Barracks Dental Clinic. To ensure records were randomly chosen and that no record was looked at twice, 60 records at a time were selected from each of the 10 color jackets used to sort records in the clinic. Once those 60 records were reviewed from each of the 10 sections a total of 600 patient charts had been reviewed.

The paper records were assessed concurrently with our digital record (CDA) and digital x-rays (DEVAA) databases for information confirming the types of dental restorations and restoration replacement rates. Record review was limited to all direct dental restorations placed in the posterior dentition within the previous 2 years (March 2011-March 2013). This data mining included looking at restorative materials (amalgam vs composite) being placed, replaced, and treatment planned within the past 2 years; the age, gender, and caries risk of the patient; restoration location; and the size (number of surfaces) of the restorations.

Exclusion criteria included any patient record that did not have direct dental restorations in the posterior of the mouth placed, replaced, or treatment planned in the past 2 years, and patients who did not have an annual exam with recent caries risk annotated in the past 2 years.

Statistical Analysis

Chi-square tests and logistic regression analyses were used to assess whether replacements are associated with factors such as age, risk of caries (high, moderate, or low), and material used (amalgam vs composite). Analyses were also done to evaluate whether type of restoration differs by location of tooth (eg, upper vs lower, or molar vs premolar).

Results

A total of 600 charts were reviewed; 525 of male patients, 75 female patients, with an average age of 26 years (SD= 6), ranging from 17 to 54 years. Patients were evenly divided among high, moderate, and low caries risk. As shown in Figure 1, there was no significant difference associated with gender and caries risk.

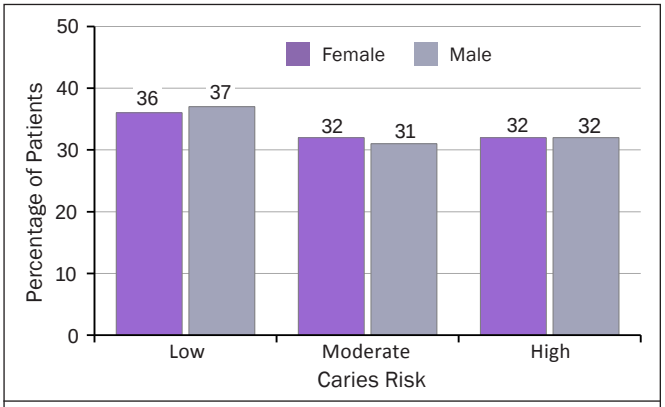

Figure 1. Caries risk by gender.

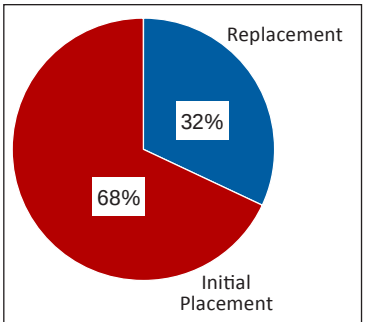

Figure 2. Posterior direct dental restorations.

The total number of direct dental restorations (composite and amalgam) placed in the posterior dentition from the 600 reviewed patient charts was 2,117. Initial restorations totaled 1,429 (68%), and replacement restorations placed totaled 688 (32%) (Figure 2).

As shown in Figure 3, of the 1,429 initial direct restorations initially placed, 1,026 were amalgam (71.8%) and 403 were composite (28.2%). A total of 441 of the 688 direct dental restorations replaced were amalgam (64%). The 247 remaining direct restorations replaced were composite (36%).

Younger patients were more likely than older patients to have an initial restoration placed. As patients increased in age, there was markedly less initial placement of restorations and more replacement of restorations. As shown in Figure 4, this transition typically occurred among patients aged 30-40 years.

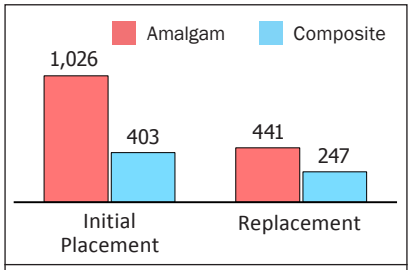

Figure 3. Distribution of restorative materials used in initial and replacement restorations.

As shown in Figure 5, restorations located on first and second molars were replaced the most often. Mandibular first molars were replaced most frequently, accounting for 23.1% (159 restorations) of all restorations replaced. Maxillary first molars were a close second, with a replacement rate of 22% (152 restorations). In order, from most often replaced to least often, the remaining locations were mandibular second molars, maxillary second molars, maxillary second premolars, maxillary first premolars, mandibular second premolars, and mandibular first premolars.

Five hundred twenty-five of the 600 randomly chosen charts were male patients (88%) and 75 were female patients (13%). This aligns well with the overall distribution of gender in the Army. In 2013, Defense Manpower Research showed enlisted strength to be 86.8% male and 13.2% female, while officers were 84.5% male and 15.5% female.[20] Therefore, the random sample used for this research closely reflects an average sampling of the Army. Female patients were noted to be about 2 years older on average than male patients, 27.5 vs 25.6 years. As mentioned earlier, a comparison of the distribution of caries risk by gender reveals no significant differences (Figure 1). However, the data showed that men were more likely than women to have an initial restoration placed, and that amalgam was more likely to be used for replacement restorations for males than for females (83% vs 71%, P=.007). Figure 6 presents those distributions.

The age range of our random patient sample of 600 was 17-54 years of age. There is a close to significant difference by age (P=.055), which is partly because younger patients are more likely to be classified as high caries risk than older patients (eg, 37% of patients aged 17-25 years are high risk vs 26% of patients aged 26-54 years) (Figure 7).

Another significant difference is that younger patients were more likely than older patients to have amalgam for initial restorations (79% of patients aged 17-21 years vs 49% of patients aged 36-55 years) (Figure 8).

Comment

Previous research has demonstrated that practicing general dentists spend a majority of their time replacing restorations, with a replacement rate between 37% and 70%.[2-10] However, the results from this research show that the majority of the military dentist's time (over two-thirds) is spent placing initial restorations. The hypothesis that more than 50% of an Army dentist's time is spent replacing restorations was shown not to be true. The authors believe that this is directly related to the unique subpopulation being treated by the Army dentist. Factors leading to this result could include the age of the patients (average age of 26 years), prevalent high caries risk of patients (almost one-third of all patients seen), poor oral hygiene of patients (often associated with stress), and the high intake of fermentable carbohydrates (snacks, sodas, energy drinks; all common for Soldiers to consume). The average civilian practice sees patients that are, on average, older, lower caries risk, and often represent a highly motivated patient group with excellent oral hygiene.

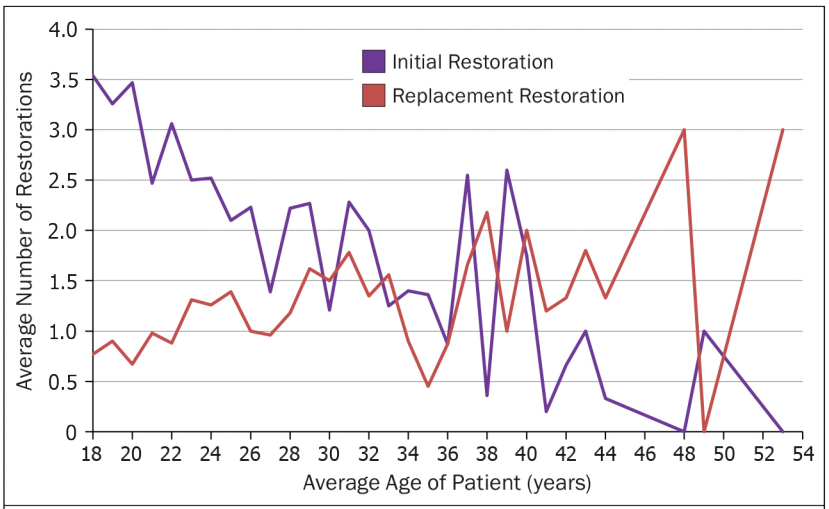

Figure 4. Comparison of initial restorations and replacement restorations by average ages of the study population.

This research indicated that in the Army, the majority of direct dental restorations being replaced are amalgams (64%). It should be noted that the vast majority of restorations being initially placed in the Army are also amalgams. In fact, within the confines of this research, of the 1,429 initial direct restorations placed and reviewed, 1,026 were amalgams (71.8%)

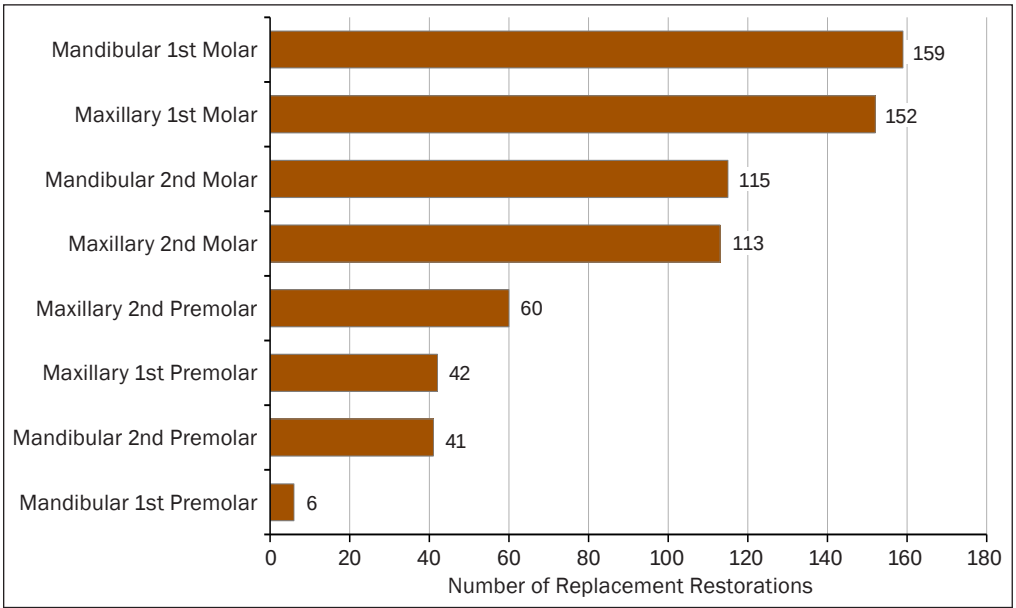

Figure 5. Distribution of replacement restorations by location.

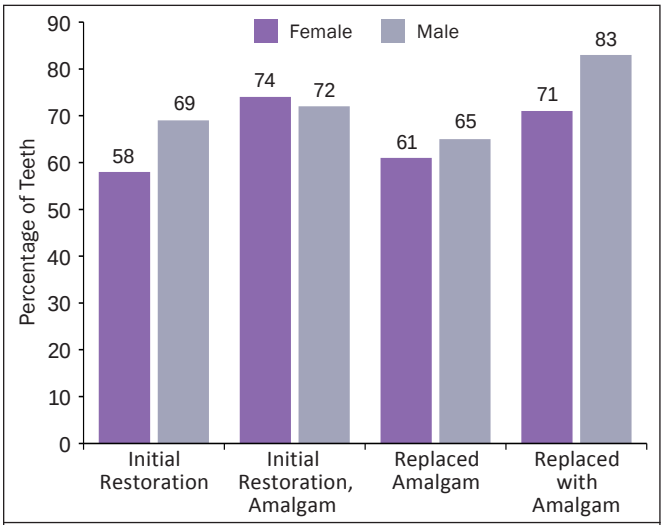

Figure 6. Distribution by gender of initial restorations and use of amalgam in restorations.

and 403 were composites (28.2%). Therefore, the minority of restorations placed in the Army are composites (28.2%), and a slightly larger minority of restorations replaced (36%) are composites. Considering this, it is apparent that a larger percentage of composites are being replaced in comparison to composites that are being initially placed within the Army's large group practice. This may represent a higher failure rate of composite restorations, even though fewer overall are being placed and replaced than amalgam restorations.

Older research shows that amalgam restorations routinely last longer than composite, exhibiting better wear, durability, and longevity.[2,15,16] However, newer research concludes that there is now no evident difference between amalgam and composite in longevity/failure rates.[21] It is interesting to note that higher failure rates were associated with both older patients and an increase in the number of surfaces being restored.[21] This newer research, which shows that amalgam and composite are becoming more equivalent, more accurately reflects the newer materials and methods being used by today's dentists.

A relational trend is present in the analysis of patient age and replacement rates of dental restoration. As patients age, there is a shift from initial placement of restorations to replacement of restorations. In the military, the vast majority of the population seeking dental treatment is young, which is part of the reason why more initial restorations are being placed. The average civilian dentist will be placing many more replacement restorations across an older (on average) patient base. Therefore, the implication is that civilian dentists with older patient bases will spend more time replacing restorations.

The data did confirm the hypothesis that location of the restoration affected the replacement rate. Restorations placed the on the permanent mandibular first molars were replaced the most often, at 159 restorations or 23.1%. The maxillary first molars were replaced at almost the exact same rate at 22% (152 restorations). The mandibular and maxillary second molars had very similar replacement rates to each other (16.7% and 16.4%) and came in at the 3rd and 4th most replaced locations, respectively. The posterior tooth that had replacement restorations completed the least often was the mandibular first premolar which had only 6 restorations (0.9%) replaced.

High caries risk patients should be treated medically because surgical replacement of missing tooth structure is insufficient treatment on its own. The disease process (caries) should be addressed. If the treating dentist "drills and fills" without regard for treating the active infectious disease, then those restorations will likely fail and require replacement in the future. Anderson et al[1]

addressed this concern in 1993 when they suggested dentists follow 7 steps for high caries patients:

1. Caries control and diet analysis
2. Use of sealants
3. Use of chlorhexidine and fluoride varnish
4. Use of xylitol gum
5. Use of fluoride rinse
6. Recall after the end of treatment, and bacteriologic testing
7. Definitive restorations of temporaries

The above protocol described by Anderson's medical model is still applicable today. Featherstone et al[12,13] described a newer technique for high caries management in 2003: caries management by risk assessment (CAMBRA). According to this model, dental caries progression or reversal depends upon the balance between demineralization and remineralization of tooth structure. The "caries balance" is determined by the relative weight of the sums of pathological factors and protective factors. If a patient is well advised of this and decreases the unfavorable factors (frequency and amount of fermentable carbohydrates, bacterial load, and poor saliva quality) while increasing the protective/favorable factors (saliva, sealants, antibacterials, fluoride, and an effective diet), the balance will shift towards remineralization of tooth structure and overall caries risk will decrease. If the techniques mentioned here are employed correctly by dentists and patients, replacement rates of dental restorations would go down as caries is consistently found to be the primary reason for replacing restorations.

This research revealed that military dentists place and replace direct dental restorations with amalgam more frequently than with composite. Why is amalgam the material of choice in the Army? Amalgam costs less, is more forgiving when placing in difficult environments, is less technique sensitive, has an excellent record, and is proven to be durable. Composite, having improved greatly in the areas of durability, fracture resistance, and longevity, is still very technique sensitive. In addition, compared to amalgam, composite requires up to 2.5× more time to properly place a composite restoration.[14] A poorly placed, incompletely cured composite will not last as long as, or function as well as, an amalgam restoration. The belief held by many dentists that high risk caries patients should not receive composite restorations is another reason that amalgam restorations are favored

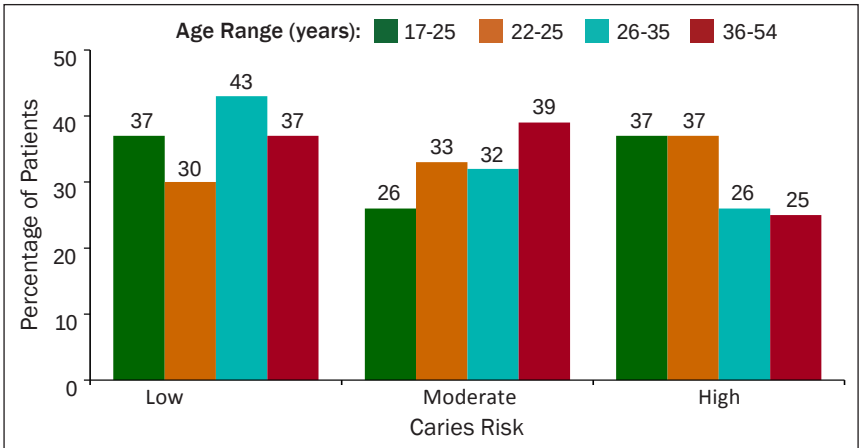

Figure 7. Caries risk by age group.

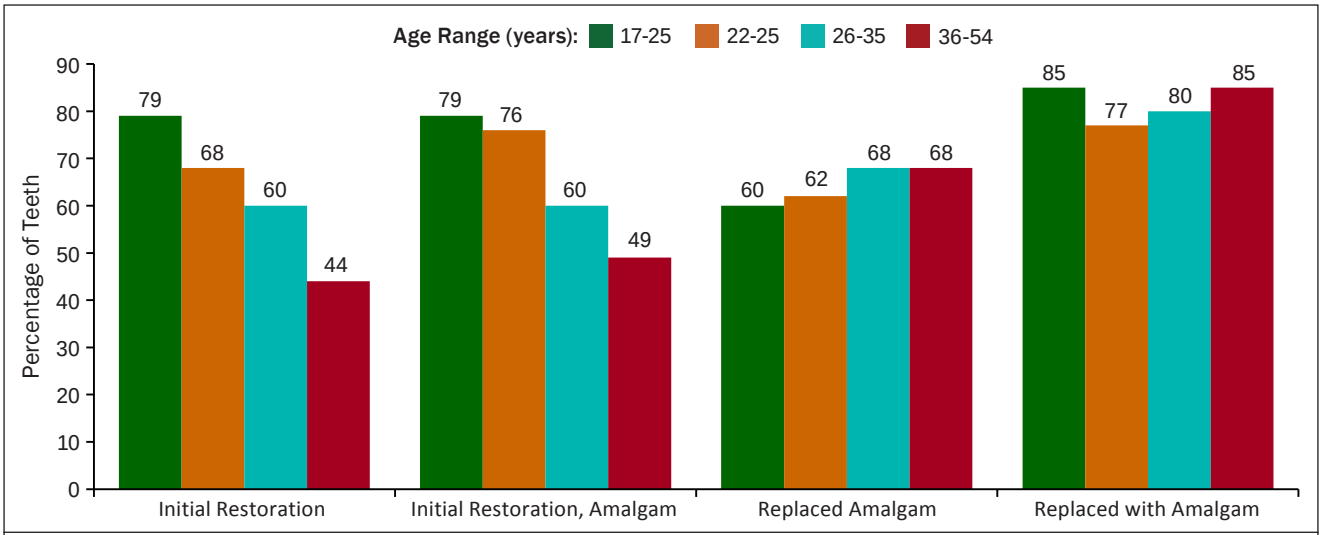

Figure 8. Distribution by age group of initial restorations and use of amalgam in restorations.

by Army dentists. In the less than ideal environments in which the military often finds itself, amalgam continues to have an advantage over composite. In summary, some advantages of amalgam:

- cost,
- time,
- ease of placement,
- BHA free,
- forgiving nature of the material,
- longevity;

while some advantages of composite include:

- esthetics,
- mercury free,
- improving durability, and
- longevity.

Conclusion

As materials and methods for use of composite resin as a dental restorative material continue to improve, clinical performance will continue to improve as well. The choice of restorative material may be considered less consequential in the future, and dental professionals will need to focus more on preventive treatment, such as CAMBRA, to decrease caries risk, decrease replacement rates, and increase restoration longevity.

Military dentists spend 32.5% of their time replacing existing direct dental restorations, and the majority of the direct dental restorations placed and replaced are amalgam. No significant difference was found between composite and amalgam restorations. Location was shown to be significant with first molars and second molar restorations failing with the highest frequency. There was no significant difference found between male and female patients. As patients' ages increased, the number of replacement restorations also increased.

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Improving Coding Accuracy in an Academic Practice

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Abstract

Practice management has become an increasingly important component of graduate medical education. This applies to every practice environment; private, academic, and military. One of the most critical aspects of practice management is documentation and coding for physician services, as they directly affect the financial success of any practice. Our quality improvement project aimed to implement a new and innovative method for teaching billing and coding in a longitudinal fashion in a family medicine residency. We hypothesized that implementation of a new teaching strategy would increase coding accuracy rates among residents and faculty.

Methods

Design: single group, pretest-posttest.

Setting: military family medicine residency clinic.

Study populations: 7 faculty physicians and 18 resident physicians participated as learners in the project.

Educational intervention: monthly structured coding learning sessions in the academic curriculum that involved learner-presented cases, small group case review, and large group discussion.

Main outcome measures: overall coding accuracy (compliance) percentage and coding accuracy per year group for the subjects that were able to participate longitudinally.

Statistical tests used: average coding accuracy for population; paired *t* test to assess improvement between 2 intervention periods, both aggregate and by year group.

Results

Overall coding accuracy rates remained stable over the course of time regardless of the modality of the educational intervention. A paired *t* test was conducted to compare coding accuracy rates at baseline (mean (M)=26.4%, SD=10%) to accuracy rates after all educational interventions were complete (M=26.8%, SD=12%); t_{24}=-0.127, P=.90.

Conclusions

Didactic teaching and small group discussion sessions did not improve overall coding accuracy in a residency practice. Future interventions could focus on educating providers at the individual level.

Practice management has become an increasingly important component of graduate medical education. Lessons learned in training will carry forward to every practice environment; private, academic, and military. One of the most critical aspects of practice management is documentation and coding for physician services, as they directly affect the financial success of any practice. This importance is also emphasized by the Accreditation Council for Graduate Medical Education mandate for training in coding and billing. Current (2015) program requirements for training in family medicine necessitate 100 hours (or one month) of health system management instruction, including current billing practices and determining value in the marketplace.[1]

The need for improved training in coding is recognized by residents and faculty alike. A survey of 600 residents at the University of Louisville demonstrated that residents identified deficits in their coding and billing knowledge. Further, knowledge deficits on healthcare care costs did not improve with subsequent years of training.[2] A survey of 60 surgical residents and 46 attending physicians from 5 training programs revealed that 82% of residents and 89% of attending physicians felt they had not been adequately trained in documenting and coding for physician services. Ninety-two percent of residents in this survey thought expertise in documentation and coding would improve their practice, and 85% thought it an important part of residency training.[3]

Coding accuracy has a significant effect on the financial success of academic medical centers, where initial coding is performed by resident physicians. Under-coding errors can lead to decreased financial recoupment for a

practice. An internal medicine residency program affiliated with the Mayo Clinic conducted a study to develop an instrument for billing in resident clinics, compare billing practices among residents of different training levels, and estimate financial losses from inaccurate resident billing. The authors found higher rates of coding errors among junior residents compared to senior residents. The rates of under billing was 74.2% for PGY-1, 48.8% for PGY-2, and 42.9% for PGY-3 residents, respectively ($P<.01$). Further, there was significantly less overbilling among PGY-1 residents compared with PGY-2 and PGY-3 residents (9.7% versus 24.4% and 17.9%, respectively ($P<.05$). Based on the 100 chart sample, the authors estimated that in a residency class of 48 residents, approximately $450,368.64 annually was lost to inaccurate coding, 50% of which was attributable to the PGY-1 level.[4] In an effort to improve resident knowledge on incentive-based reimbursement, Carter et al designed an educational intervention with emergency medicine residents. Residents attended a one-hour lecture, were given a pocket card on documentation, received biweekly newsletters, and received weekly case-specific feedback from their billing department. These interventions resulted in an increase in total relative value units (RVUs) per hour, from 3.17 to 3.71 ($P=.0001$). With an average of 70,000 patient encounters per year, the authors estimated a projected billing increase of $1.5 million from this educational intervention.[5]

Several educational experiences have been successfully directed toward residents at improving coding accuracy. Benke et al evaluated the effect of a single 90-minute training session covering basic coding procedures and common errors at an ENT program with 14 practitioners with varying coding experience. Those inexperienced with coding (10 providers) showed an improved error rate of 8%, however, this error rate was significantly lower than that of more experienced coding practitioners.[6] In an effort to improve generalized practice management knowledge, a surgery program implemented a multifaceted approach. Surgery and medicine residents attended a series of 10 monthly lectures covering various aspects of practice management. In addition, surgical residents met monthly for didactic sessions with the business office to discuss billing and coding. Finally, the coding team and program director provided real time outpatient visit coding feedback. Surgical coding compliance among residents increased from 33% to 88% over a 12-month period.[7]

Objective

Our quality improvement project aimed to implement a new and innovative method for teaching billing and coding in longitudinal fashion in a family medicine residency.

Methods

Design, Setting, Study Population

This study received institutional approval as a quality improvement project. It was conducted as a local quality improvement initiative within a family medicine residency clinic. Ten faculty physicians and 24 resident physicians participated in monthly educational sessions about coding rules and regulations for outpatient encounters. Seven faculty and 18 residents were present over both academic years spanned by this project.

Intervention

We implemented 2 different educational interventions over a 12-month period. Initially, the educational sessions were learner-presented cases followed by large group discussion. Every 4 weeks, 3 residents and one faculty member were identified by the authors as having a chart coding "error." The deficient encounters were selected from a series of charts identified by the clinic coders as common errors by the resident and faculty providers in the clinic. The selected residents and faculty were placed in coding "time out" and were instructed to sit with the coders to review their errors. The coders then provided one-on-one instruction regarding the appropriate way to code the encounter. During morning report once monthly, the selected providers then summarized the encounter, how the encounter was initially coded, and instructed the group on the appropriate coding or how improve documentation to justify their coding. The coders were present during this session to answer any questions generated by the large group discussion. The providers were subsequently released from "time out" and a new group of residents and faculty were chosen for the following cycle.

Over the second 6-month period, we changed the format of the educational sessions. In lieu of learner-presented cases, we facilitated small group case reviews followed by large group discussion. Each month, the authors identified common coding errors in the practice as reviewed with the clinic coding staff. Three outpatient encounters were selected and distributed to 3 small groups during the monthly educational sessions. Each small group received a different encounter with both patient and provider identifying information removed. Residents and faculty worked together in teams to discuss the appropriate diagnosis, current procedural terminology (CPT) code, and evaluation and management (E/M) code to assign to the encounter. Small groups then presented to the large group, while the authors facilitated discussion, highlighted teaching points, and emphasized proper coding practice. Again, coding staff attended to answer any questions or provide clarifying points from the large

group discussion. Of note, on arrival at the residency program, providers are given a coding "cheat sheet" for coding requirements for common family medicine encounters and procedures.

Outcomes

Coding accuracy rates were assessed monthly for individual providers. Prior to, and for the duration of this project, coders were collocated in the clinic. As standard practice, the coders reviewed 50% to 60% of total outpatient clinical encounters for all providers and were readily available for any questions. A monthly provider/coder comparison chart was already generated at the hospital level with provider diagnosis, CPT, and E/M codes followed by the correction after coder review. This report was obtained and reviewed every month by the authors. Encounters were considered "accurate" or "compliant" if the provider assigned E/M code matched the correct coder assigned E/M code. SPSS Statistics (IBM Corp, Armonk, NY) was used to conduct paired *t* test to assess for overall coding accuracy for the large group. Paired *t* test and ANOVA was used to assess subgroups as organized into faculty and residency class year.

Results

As this study crossed 2 academic years, only those who were present for the entire intervention period were included in the data analysis, shown in Table 1. All listed participants were present during both the preintervention and postintervention time periods.

Table 1. Provider Role.

Provider	Number of Participants
Intern/R2	8
R2/R3	10
Faculty	7

To ensure a large enough sample, a 3-month period, starting the month prior to the first educational intervention, was used as the baseline. Table 2 shows the results of the total group coding accuracy rates before and after the educational intervention period. The average coding accuracy for the learners in this study for this baseline period was 26.44% (mean (M)=26.44, SD=10.25) for 1,420 encounters. A 2-month period at the completion of the 2 interventions was evaluated for our comparison data. Average coding accuracy for the 899 encounters during this period was 26.79% (M=26.79, SD=11.38), t_{24}=-0.127, *P*=.90. This suggests no significant coding accuracy differences after the first intervention.

The average change in coding accuracy between educational intervention by year group was also assessed; first year residents who progressed to second year residents (R1/2), second year residents who progressed to third year residents, and faculty. The data is shown in Table 3.

A one-way between subjects ANOVA was conducted to compare the effects of the educational interventions within and between each of these subgroups. There were no significant differences between the groups ($F_{2,22}$=1.50, *P*=.25). Among all levels of learners, no group showed significant benefit from the training. Also, none of the groups had benefits in coding accuracy rates compared to each other.

Comment

There was no improvement in coding accuracy (as reflected in correct E/M) after the 2 intervention periods. There was no statistically significant difference when the data was aggregated and when individual year groups were assessed. Ideally, we would be able to assess long-term individual performance data in an educational practice. However, academic environment restrictions prevented this assessment at the individual level. Interns work in clinic on average once weekly, with increasing weekly clinics per year group. Thus the number of encounters, particularly from the interns, during the assessment period was small.

Although the upper level residents and faculty generated more clinical encounters, many individuals in these subgroups were not present in the residency program during the preintervention and postintervention period. As a consequence, only 8 upper level residents and 7 faculty formed the additional subgroups. Thus, participation in the educational interventions is a potential confounder. The educational sessions occurred during morning report, which is mandatory but may not be attended based on current rotation, vacation, etc. Attendance at each session was not recorded to subsequently note any potential trends in coding accuracy (ie, correlation between number of sessions attended and change in accuracy at an individual level).

Table 2. Coding Accuracy Rates Before and After Educational Intervention.

	Before Intervention		After Intervention		n	95% CI for Mean Difference	*t*	*df*
	M	SD	M	SD				
Outcome	26.44%	10.25	26.79%	11.38	25	-6.11 to 5.40	-0.127 (*P*=.90)	24

Table 3. Change by Year Group in Coding Accuracy After Educational Interventions.

Learner	N	Mean Coding Accuracy Change After Educational Interventions	SD	SE	95% CI for Mean	
					Lower Bound	Upper Bound
R1/R2	8	-3.86	13.61	4.81	-15.24	7.51
R2/R3	10	6.13	15.02	4.75	-4.61	16.88
Faculty	7	-3.08	11.44	4.32	-13.65	7.50

Prior studies demonstrated improvement after focused individual educational sessions and large group training.[4-7] It is unclear why these same methods were not effective in this project. In addition to the limitations listed above, it may be due to the fact that this is a military environment. Anecdotally, military providers have less incentive for "accurate" coding as they do not receive direct compensation for physician services. We hypothesize that due to the absence of financial incentive, providers have less motivation to learn and practice coding and billing skills.

There was also some resistance during this project based on perceptions of the role of the physician and frustration with the electronic medical record. During this quality improvement process the authors learned of implementation by the local coders of the Army Leveling Tool, resulting in down-coding of several conditions based on disease complexity, despite documentation provided. Although the coding staff understood and implemented the tool, experienced faculty providers had never been educated into its purpose or use. Therefore, it was conceptually more difficult to understand and teach residents ways to improve documentation and coding skills in the absence of experience or "corporate knowledge."

Over the last decade, the AMEDD has brought more emphasis to quality of care and population health measures, as compared to the previously emphasized RVU/FTE metric. However, decisions regarding staffing/personnel, space allocation, and density of clinic schedules are still largely based on a productivity metric. However, military facilities largely provide inadequate coding and billing education support to primary care providers. Low coding accuracy rates likely reflect poor knowledge or competency levels at the individual provider level. Leaders should consider that these low accuracy rates likely lead to inaccurate data management and assessment at the upper echelons, and may increase the work-load burden on front-line providers.

We were not able to define and measure a successful intervention to improve individual provider coding knowledge and competency. We recommend that other academic and clinical programs within the AMEDD experiment with other teaching and learning modalities. We suspect that more personal and individual educational interventions would be more beneficial. This would require increased administrative support resources and time, but could provide specific and timely feedback on errors.

Future interventions could also include a more detailed analysis of coding error to determine the types of coding errors on which to focus training.

Conclusion

Practice management, specifically documentation and coding for physician services, is an important facet of resident education. While this study did not demonstrate an improvement in coding accuracy using individual and small group sessions and subsequently small group sessions with facilitated large group discussion, a combination of educational strategies is likely beneficial. Programs should tailor their approach based on practice structure and learning needs.

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Winging of the Scapula Diagnosed as Parsonage-Turner Syndrome: A Case Report

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Abstract

A 24-year-old active duty female Soldier complained of right shoulder burning, stinging, electrical shock-like pain with radiation to the right hand after completing a ruck march. She also complained of swelling and feelings of her cold right hand. Examination showed a deficit in the deltoid, upper trapezius, supraspinatus, and also right winging of the scapula. She also exhibited weakness to right arm, weak right hand grip, and decreased sensation over the dorsal right hand. The right hand was also noticed to be colder to touch than the left one. She had tenderness to palpation over right paracervical muscles from C3 to C7. A previous magnetic resonance arthrogram of the right shoulder revealed no findings. The cervical magnetic resonance imagery showed mild disc protrusion at C5-C6 without spinal cord impingement. Based on the history and the physical findings, the patient was diagnosed with Parsonage-Turner syndrome.

Parsonage-Turner syndrome is a rare syndrome of unknown etiology affecting the brachial plexus. It is considered a rare disorder with an incidence of 2 per 100,000. Patients affected range from 3 months to 75 years of age with highest incidence between 30-70 years old.[1,2]

It is also known as brachial plexus neuritis, neuralgic amyotrophy, brachial plexitis, brachial plexus neuropathy, or shoulder girdle syndrome or neuritis.[1,3] Parsonage-Turner syndrome (PTS) is characterized by the inflammation of nerves that innervate the muscles of the chest, shoulders and arms. Viral illness or autoimmune responses have been considered the most common risk factors for PTS, although it can also be idiopathic and hereditary.[1,3,4]

It is a peripheral nervous system disorder that presents with acute upper extremity pain and multifocal paresis, and it may have a complicated recovery course in many of those affected.[2,3] The syndrome may be associated with scapular winging. The variable location and the severity of symptoms depend on which parts of the plexus are affected. The long thoracic, suprascapular, and the axillary nerves are most affected. Even if it mostly affects the upper trunk, the lower trunk can be affected as well.[3] Muscles most commonly affected include the deltoid, supraspinatus, infraspinatus, serratus anterior, biceps, and triceps.[5]

Parsonage-Turner syndrome varies in presentation and nerve involvement. It is usually characterized by the sudden onset of severe shoulder and upper arm pain followed by motor involvement several days later. The pain may extend to the trapezius, upper arm, forearm and hand.[1,2] If paralysis is present, it may persist for months but recovery is usually complete.[1]

Case Report

A 24-year-old female Soldier presented to the emergency department (ED) as a return visit for right shoulder pain. The first visit was 4 weeks prior after slipping and trying to catch herself with her right arm. She was seen in same ED 2 weeks after the injury and diagnosed with rotator cuff dysfunction after negative shoulder x-rays. On this subsequent return visit, she was complaining of worsening right shoulder pain with burning, stinging, and electrical shock-like pain with radiation from the posterior/lateral shoulder to the upper right back. She also complained of numbness over the deltoid and dorsal fingers, cold like sensation, swelling and weakness of the right arm, but denied any neck pain or trauma.

Neurological exam showed 4/5 strength in deltoid, biceps, and supraspinatus. Tendon reflexes were equal bilaterally. She had decreased sensation over the dorsal right hand with lack of discrimination sharp/dull. The hand was also cooler to touch and had mild swelling.

Clinical examination of the right shoulder revealed a normal but painful passive range of motion. Active mobilization of the right shoulder showed scapular winging. Rotator cuff muscle weakness was absent, other than the one noted with supraspinatus. Middle deltoid atrophy was noted. Vascular examination was normal.

Previous ED chart and follow up orthopedics and physical therapy visits were reviewed. Patient had a right shoulder arthrogram that was read as negative. She was

referred to physical therapy and during treatment she noticed worsening pain and weakness. Concerned for spinal cord impingement, patient was sent to ED for further evaluation.

The magnetic resonance imagery (MRI) of the cervical spine obtained on the repeat ED visit showed mild disc protrusion at C5-C6 without spinal cord impingement.

Findings were discussed with the neurologist on call. Parsonage-Turner syndrome was suspected. Patient was released home with opioids and short term steroid course. Upon further review during subsequent visits, patient was referred to an out of network neurologist and her case was lost to follow up.

Comment

Parsonage-Turner syndrome may involve several nerve trunks and vary in presentation, thus being often misdiagnosed as cervical disc disease or rotator cuff dysfunction/tear.[4] Diagnosis is based on the history and physical findings.[1,4] The characteristic presentation is an acute, severe neurogenic pain in the shoulder or arm lasting for several days or weeks, followed by muscle weakness, atrophy, and sensory loss as the pain diminishes.[4,5] Pain is the most common presenting symptom in almost 95% of patients, mostly aggravated by movement of the shoulder, but not by neck movements.[5]

The symptoms do not always correlate with a single nerve root distribution and are often described as patchy, with involvement of multiple muscles and dermatomal regions that do not coincide with a single or specific neurologic source.[4]

In addition to motor nerve symptoms, sensory nerve involvement occurs in up to 78% of cases with patchy paresthesia and hypoesthesia.[4,5] Most frequently, the sensory loss is incomplete and occurs over the lateral shoulder and upper arm or the radial surface of the forearm.[5]

Autonomic dysfunction in the form of trophic skin and nail changes, edema, temperature dysregulation, and increased sweating is less frequently seen.[4,5]

Electrodiagnostic studies and neuroimaging have high sensitivity for detecting which nerve trunks are involved and the degree of muscle denervation. However, they lack specificity, they cannot display the anatomic detail needed for precise localization and treatment planning, and they are usually performed more than 3 weeks from clinical onset.[1]

The duration of pain lasts for 1 to 2 weeks or longer. Once initial pain subsides, weakness and muscle atrophy may develop.[2,5]

Testing passive shoulder range of motion may be difficult in patients with PTS secondary to guarding. To make an accurate diagnosis, it is critical to complete a thorough neurologic and musculoskeletal examination of both the symptomatic and the asymptomatic extremities, including testing manual muscle strength, range of motion, sensation, and reflexes as well as evaluating the shoulder for signs of impingement, adhesive capsulitis, rotator cuff injury, and scapular dyskinesis.[5]

Magnetic resonance imagery remains the test of choice for diagnosis. Cervical MRI may reveal cervical disc disease or nerve root compression. Shoulder MRI may identify other causes of shoulder pain, including rotator cuff tears, labral tears, shoulder impingement, nerve entrapment, or mass lesions. Abnormalities signifying denervation may be detected on MRI in cases of early PTS, such as diffuse high signal intensity, or atrophy and fatty infiltration in later stages of PTS.

Magnetic resonance imaging may not be sensitive enough to detect early (within the first 2 to 3 weeks) changes in PTS. However, magnetic resonance neurography may show not only early hyperintense thickening of the involved areas of the brachial plexus,[5] but also nerve inflammation and muscle denervation in addition to assessing response to therapy.[1]

The best treatment for PTS remains unknown. There is some evidence stating that early use of oral corticosteroids shortens the time of intense pain and hastens motor nerve recovery. In addition, pain may be treated with a combination of nonsteroidal anti-inflammatory drugs and opioids.[4] Laboratory studies are of no benefit and do not help with diagnosis determination.[5]

The prognosis of PTS for the majority of patients is good, with an estimated three quarters of all patients making a complete recovery within 2 years.[2] However, some of the patients may still experience pain, and may develop adhesive capsulitis and shoulder subluxation years after the diagnosis was made.[5]

Conclusion

Parsonage-Turner syndrome is an under-recognized condition. It should be considered as a diagnosis in the setting of an abrupt onset of upper extremity pain followed by progressive neurologic deficits including

weakness, atrophy and occasional sensory abnormalities. Treatment with a multidisciplinary approach that includes both physical therapy and multiple medications is acceptable with a goal of maintaining range of motion and preventing loss of function. In addition, other therapies such as nerve stimulators and acupuncture should be considered, based on the patient's response.[5] If conservative treatment fails, early (within 6 months) surgical treatment such as neurolysis, nerve grafts, and nerve transfers may be considered.[5]

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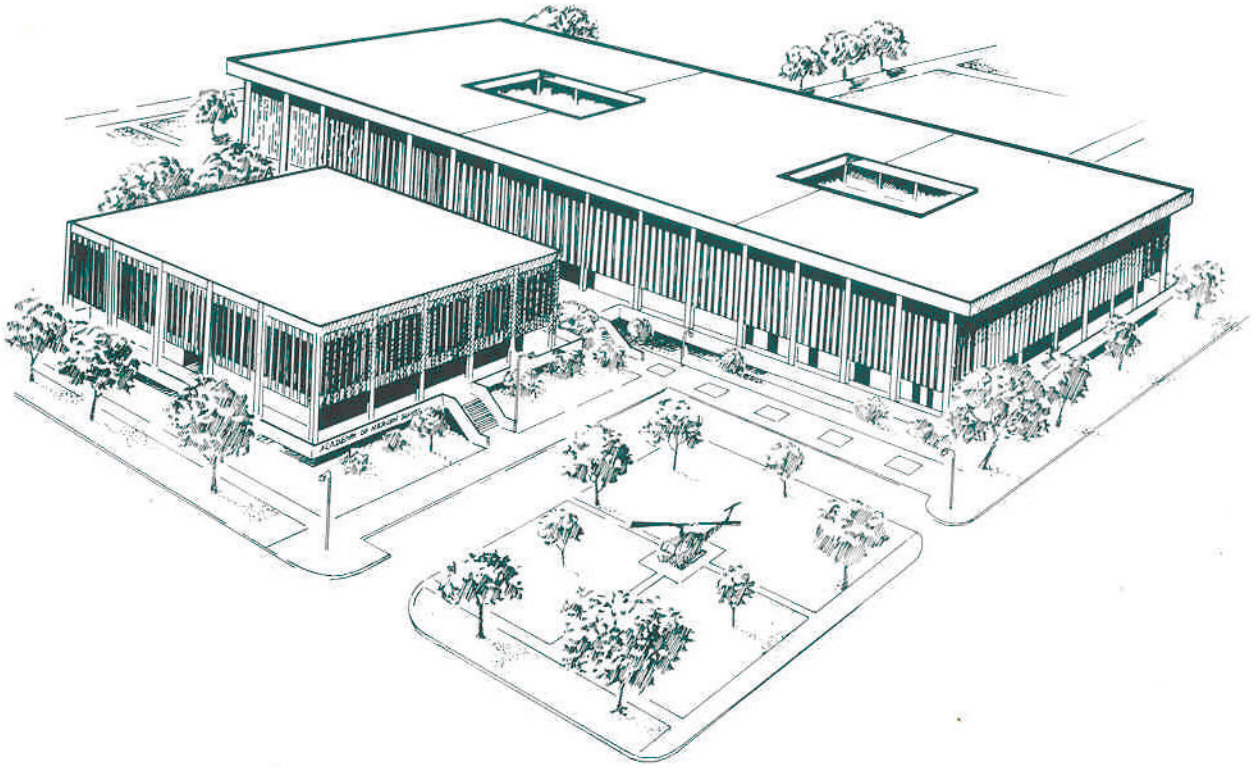

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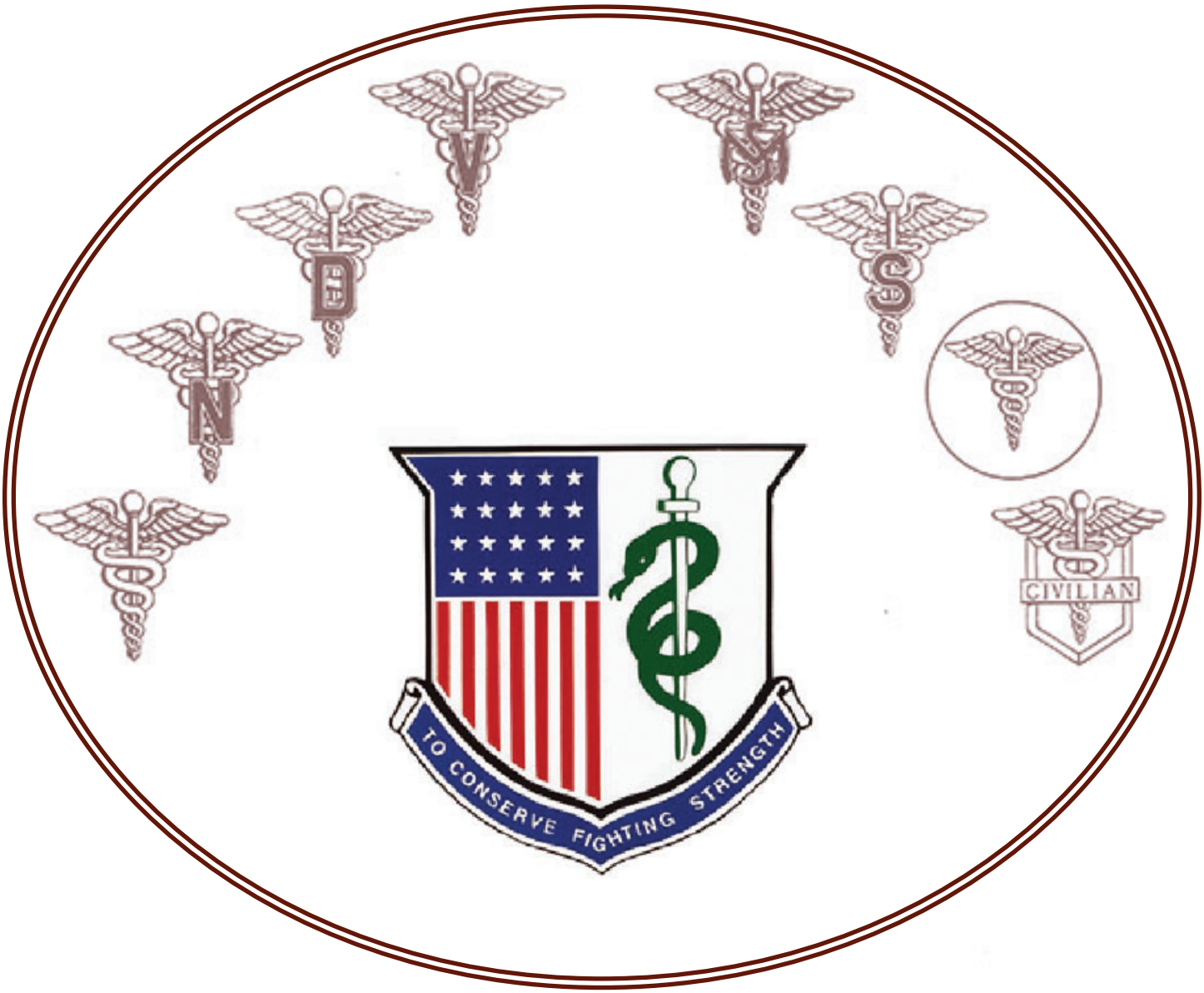

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