MKB: A NEW ANESTHETIC APPROACH TO FERAL CAT STERILIZATION SURGERY

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
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A combination of medetomidine (M), ketamine (K), and buprenorphine (B) (MKB) was evaluated as an injectable anesthetic in 240 feral cats undergoing ovariohysterectomy or castration surgery at a high-volume sterilization clinic. A selected dose of MKB (100 μg/kg M, 10 mg/kg K, 10 μg/kg B) was evaluated for efficacy in a weight-specific manner and was then extrapolated to a fixed dose to be used in all cats, regardless of true weight. The selected dose of MKB provided adequate duration of action, acceptable physiological parameters, and acceptable duration and quality of recovery; however, the fixed dose of MKB was ineffective and unreliable.

Cats were not intubated and breathed room air. Hemoglobin oxygen saturation (SpO_2), systolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and rectal temperature were measured and recorded. Atipamezole (A) (5 mg/mL) was administered following the completion of surgery to reverse the effects of medetomidine. The selected dose of MKB (100 μg/kg M, 10 mg/kg K, 10 μg/kg B) produced rapid onset of lateral recumbency (4.3 ± 4 minutes in males and 5.2 ± 5.6 minutes in females) and adequate duration of surgical anesthesia in both males and females.

SpO_2 significantly increased over time in both males (R: 36-99 %) (R = range) and females (R: 73-100 %). SpO_2 fell below 90% at least once in most cats. Blood pressure (R: 91-195 mm Hg) and heart rate (R: 77-176 beats/minute) in males did not change significantly as a factor of time, however, blood pressure (R: 38-190 mm Hg) and heart rate (R: 57-172 bpm) significantly decreased over time in females. There was no significant change in respiratory rate over time in males (R: 4-76 breaths/minute) or females (R: 4-56 breaths/minute). Rectal temperature significantly decreased throughout the duration of anesthesia in both males and females. Time from medetomidine reversal until sternal recumbency was 38.6 ± 38 minutes in males and 40.6 ± 78.2 minutes in females. Eleven cats (11%) required a second dose of the selected combination of MKB to maintain an adequate plane of surgical anesthesia and this was associated with significantly longer recovery times (62 ± 20.7 minutes in males and 103.8 ± 28.4 minutes in females). The selected dose of MKB was used to calculate a fixed volume to be used in all cats, regardless of true weight. Injection volumes of 0.7 mL and 0.8 mL of MKB were studied and proved to be ineffective at providing adequate anesthesia. There were no perioperative deaths associated with this study.

The selected dose of MKB fulfilled many of the demanding requirements associated with feral cat sterilization clinics, however, it was not possible to use a fixed volume, acceptable for use in all cats, regardless of true weight. The selected dose of MKB may be used more effectively in smaller clinics or settings in which it can be dosed in a weight-specific manner.

CHAPTER 1
INTRODUCTION

Feral Cat Populations

Feral cats are considered the "wild" offspring of domesticated cats; although a variety of alternate definitions exist. The classification of these animals is loosely defined and is often based upon opinion, rather than a universally accepted definition. Socialization status, recognition of ownership, and overall way life-style are often considered when defining a feral cat. The lines between loosely owned outdoor cats, tame strays, and feral cats are often blurred (Levy & Crawford 2004). Lack of consistency in terms of definition is further complicated by the idea that cats may change classification over time. Owned outdoor cats that wander or become lost may be considered stray. Stray cats that have lived an extensive amount of time in the wild may become untrusting of humans and be considered feral. Alternatively, a cat born in the wild, and deemed feral, may be adopted and over time become an acceptable companion animal. While the exact definition is undefined, for the purpose of this study, a feral cat is considered any free roaming cat that does not have a rightful owner, regardless of socialization status.

While it is impossible to say with certainty, it is estimated that there are between 60 and 100 million feral and abandoned cats in the United States today (Jessup 2004). Cats are often depicted as independent or anti-social animals; however, feral cats are known to congregate around a stable food source, forming a colony (Mahlow & Slater 1996; Centonze & Levy 2002). Feral cat colonies vary in size, but are often dependant upon the availability of food (Mahlow & Slater 1996). Colonies are generally closed societies with members remaining their entire life; with replacement coming from births, immigration, and illegal abandonment (Wolski 1982; Levy

et al. 2003). Human caretakers may provide food, a source of shelter, and some veterinary care (Centonze & Levy 2002).

In one study (Centonze & Levy 2002), 101 caretakers in north central Florida were surveyed in an effort to characterize 920 feral cats and the people who cared for them. Most colonies were located on the caretaker's property and contained less than 10 cats. Most (91%) caretakers reported caring for their colonies out of sympathy, affection, or a sense of responsibility for hungry or injured animals. Nearly all caretakers provided a consistent source of food, while 75% provided shelter and 37% provided or were willing to provide veterinary care. Most of the caretakers surveyed believed the cats they cared for had an excellent or good quality of life, and while many were too wild to be handled, they were still considered "like pets."

The Problem

Feral cat colonies are often a source of controversy as their right to exist is widely debated. Overpopulation of cats contributes to a variety of problems, resulting in heated arguments between people in favor of their survival, and those opposing it. While some feel these animals should be a focus of community efforts to sterilize, vaccinate, and return them to the wild, others simply feel that eradication is a more definitive solution. This issue is further complicated by the lack of scientific data demonstrating the most effective control strategy. Discussions about feral cats are often emotionally charged and perceptions based on personal experiences often substitute for missing objective scientific data (Stoskopf & Nutter 2004).

Although public opinion, attitude, and actions play a predominant role in the number of unwanted and abandoned animals, a domestic cat's high reproductive capacity creates additional problems. Free-roaming cats produce an average of 1.4 litters per year and have the potential to produce up to 3 litters per year (Stoskopf & Nutter 2004). Mean litter size of free-roaming cats

reported in one study was 4.1 ± 1.3 (Stoskopf & Nutter 2004). The overpopulation and prolific breeding ability of feral cats is of concern regarding public health, impact on wildlife, and animal welfare.

Public Health Considerations

Although disease carried by feral cats is a concern for public health officials, its zoonotic impact is unknown. Several unanswered questions include the degree to which infections circulate within a population; whether or not cats maintain or amplify infection after introduction from other reservoirs; and whether or not the existence of feral cat populations impact the likelihood of human exposure to pathogens (Case et al. 2006).

Feral cats may be carriers of infectious diseases transmissible to humans and other animals. *Toxoplasma gondii, Salmonella typhimurium, Escherichia coli*, and bacteria from the genera Rickettsia, Bartonella, and Coxiella; among others, are the causative agents responsible for numerous infectious diseases found in humans and domestic animals (Patronek 1998; Case et al. 2006; Dabritz et al. 2006). While the harboring and transmission of these infections by feral cats is of concern, public health officials are primarily concerned with the potential implications surrounding rabies.

Rabies is a fatal infectious disease that is transmitted to humans by the bites of infected animals. Non-bite exposures also exist by means of scratches, abrasions, open wounds, or mucous membranes exposed to virus-containing saliva or other forms of infected tissue (Fearneyhough 2001). In the United States, rabies is primarily a disease that affects and is maintained by wildlife populations (Krebs et al. 2005). Feral cats are of concern because they are generally unvaccinated and may become infected from contact with wild animals. The fact that feral cats are commonly regarded as domestic animals may, in itself, pose a serious threat. The Texas Department of Health reported that rabid domestic animals expose 5 times as many

people to rabies as the average infected wild animal (Clark 1988). Since the middle of the century, an average of one or two human rabies cases have been reported annually in the United States (Fearneyhough 2001). Transmission of rabies by wild animals, primarily bats, has accounted for more than 85% of reported cases in the United States since 1976 (Krebs et al. 1997). In most other countries, dogs remain the major species with rabies and the most common source of rabies transmission to humans (2003). An estimated 40,000 to 100,000 human deaths result worldwide from rabies (Rupprecht et al. 1995). While the incidence of rabies in free-roaming cats is not known, an increase in feline rabies cases in the United States, from 183 to 288, was reported in 1988 and 1995, respectively (Eng & Fishbein 1990; Krebs et al. 1996). During 2005, 49 states and Puerto Rico reported 6,417 cases of rabies in nonhuman animals and 1 case in a human being, representing a 6.2% decrease from the 6,836 cases in nonhuman animals and 8 cases in human beings reported in 2004 (Blanton et al. 2006).

Wildlife Vulnerability

Whether or not feral cats pose a threat to native wildlife species is an undefined and controversial issue. The notion that free-roaming cats are detrimental to wildlife populations is often accepted at face value due to limited studies and lack of definitive scientific proof. The debate surrounding feral cats and wildlife generally centers on three major issues: predatory behavior of feral cats on native wildlife species, the notion that cats are an introduced species that should not be allowed to remain in the wild, and the concept that cats are viewed as a domestic species and it is society's responsibility to keep them confined for their protection, as well as the protection of other species (Slater 2004).

Much of the evidence that implicates feral cats as the source for extinction or endangerment of wildlife species come from studies conducted on islands (Girardet et al. 2001; Veitch 2001; Bester et al. 2002; Nogales et al. 2004; Tantillo 2006). Cats have been introduced

to remote islands off the coasts of New Zealand, Australia, and South Africa where native wildlife evolved in the absence of predators (Patronek 1998). On many of these islands, cats were reported to have devastating effects on local species and were even responsible for their extinction (Veitch 2001). Results from these studies, however, have been inappropriately extrapolated to the United States, where the impact of feral cats on native wildlife species is not well documented or understood (Patronek 1998).

Whether or not feline predation is detrimental to wildlife populations remains unclear in many parts of the world. Few studies accurately report feral cat predation and concisely relate it to detrimental effects on wildlife (Tantillo 2006). Although studies documenting the negative impact of feral cats on island ecosystems and their subsequent recovery following the removal of cat populations exist, many references of cat predation are unsupported by factual data (Coman & Brunner 1972; Girardet et al. 2001; Veitch 2001; Bester et al. 2002; Nogales et al. 2004; Tantillo 2006). In one study (Coleman et al. 1997), a previously published "best guess" of the amount of birds killed by feral cats per year in Wisconsin was later self-cited in another publication and reported as "research" (Tantillo 2006). Examples such as these often go unnoticed, are cited by other authors, and are rarely critically evaluated (Tantillo 2006).

The predatory behavior of feral cats has been reported largely based upon casual observations, perpetuated rumor, and speculation (Bradt 1949). Even if carefully designed to be representative of the feline population, predation studies that rely on human observation and reporting are subject to a variety of bias (Patronek 1998). Tantillo points out several biases common to predation studies (Tantillo 2006). Fecal analyses may only highlight the dietary habits of animals whose excrements are easiest to find. Similarly, stomach contents of deceased cats may correlate with the manner and/or location of death. For example, cats killed by cars

along roadsides may prey upon roadside species more than a normally distributed population of cats. Furthermore, few studies address whether or not predatory behavior by feral cats is considered "additive," adding to a base level of predation and contributing to an increase in overall mortality; or "compensatory," where cat predation replaces other forms of mortality and merely compensates for mortality that would happen anyway (Tantillo 2006).

The uncertainty surrounding the impact or lack thereof, of feral cat populations on native wildlife species is cause for concern for wildlife conservationists, ecologists, researchers, and feral cat activists. Although further evidence is needed to more clearly define the ambiguity and bias surrounding wildlife vulnerability, the topic remains an unresolved issue.

Animal Welfare

Feral cats are frequently considered a nuisance to society as they often exhibit noisy courting and territorial behavior, fecundity, and urine spraying by males. Despite these misgivings, a general concern for their welfare and way of life is recognized (Zaunbrecher & Smith 1993). High neonatal and juvenile mortality rates are reported for feral cats (Nutter et al. 2004). In one study, colony-based observations found a kitten mortality rate of 48% three months following the initiation of the study, which contributed to a 75% cumulative kitten mortality rate at 6 months (Stoskopf & Nutter 2004). Kitten death was highly dependent upon environmental factors, but trauma accounted for most deaths in which cause could be confirmed (Nutter et al. 2004). In addition, feral cats, like wildlife, are susceptible to every day threats including dogs, cars, humans, disease, starvation, and climate. The potential for suffering is a cause for concern and warrants a solution to end overpopulation and its negative effects on the welfare of feral cats.

Current Methods of Control

A variety of population control methods have been tried and are ongoing, however, none have proved to be the most obvious choice. Two management schemes, removal and trap-neuter-

return (TNR), are strategies recognized in the attempt to control feral cat populations. Traditional animal control, or capture and removal, is often limited by resources and is rarely successful in extensive cat populations (Andersen et al. 2004). The population management technique of trap-neuter-return focuses on decreasing feral cat populations through sterilization as an alternative to conventional removal methods.

Removal Methods

Eradication in situ, removal for culling off-site, transferring to sanctuaries, and adoption are all examples of removal strategies employed in the quest to eliminate feral cat populations. Due to the magnitude of feral cat overpopulation, an effective control program must integrate environmental safety, affordability, sustainability, and public aesthetics (Levy & Crawford 2004)

Lethal eradication methods can be effective; however, they often present logistical barriers that compromise environmental safety and put non-target animals at risk (Veitch 2001; Bester et al. 2002). In addition, opposition is common as such removal techniques are often found unacceptable by the general public (Levy & Crawford 2004). Introduction of disease, poison, and hunting are examples of lethal eradication strategies. A combination of such tactics has been employed on at least 48 islands with the first successful campaign taking place on Stephens Island, New Zealand, in 1925 (Nogales et al. 2004). The majority of islands (75%, n=36) where eradication has been successful are less than 5 km^2 (Nogales et al. 2004). Therefore, these results cannot be appropriately extrapolated to larger islands and other mainland parts of the world where lethal eradication strategies may be considered.

Trapping efforts are generally orchestrated near or at colony sites where cats are humanely captured. Cats considered feral, sick, or injured may be culled, whereas socialized cats and kittens may be put up for adoption. While this appears to be the ideal solution, two problems exist within this strategy. Feral cats are naturally wary of unusual conditions in their environment

and may be reluctant to enter traps even if they are baited (Nutter et al. 2004). Therefore, total elimination is usually unsuccessful as several colony inhabitants will likely evade capture and ultimately repopulate the area (Mahlow & Slater 1996). Feral cats are territorial animals and their highest potential for population increase occurs when populations are low (Foley et al. 2005). This repopulation will likely attract immigrant cats and together they will breed to fulfill whatever the environmental niche can support. Cat population size tends to increase until a carrying capacity is reached (Foley et al. 2005).

While adoption is often considered the ideal outcome, an additional problem arises because there are simply not enough homes for the number of cats that need them. A proposed alternative to adoption is the creation of cat sanctuaries. Sanctuaries are refuges for homeless cats that serve as permanent homes where they are provided for, however, many of these facilities fill to maximum capacity almost immediately after opening (Levy & Crawford 2004). Additionally, sanctuary cats are not guaranteed proper care nor are they ensured a good quality of life (Slater 2004).

The effectiveness of removal methods rely on a variety of factors that often limit the success of a particular strategy. Public opposition and environmental safety concerns prevent eradication from becoming a feasible option in regard to population disposal. Similarly, removal by culling and adoption alone has proven to be ineffective and inadequate (Neville & Remfry 1984; Mahlow & Slater 1996; Levy & Crawford 2004). It has been shown that partially successful removal of feral cats produces a vacuum phenomenon in which population dynamics and territorial behavior encourage new animals to move into an unoccupied area (Zaunbrecher & Smith 1993; Patronek 1998; Gibson et al. 2002). Alternative strategies continue to be explored with the goal of reducing the problem of feral cat overpopulation.

Trap-Neuter-Return

The newest approach in feral cat population management is trap-neuter-return (TNR). The concept of TNR was introduced in Denmark and England in the 1970's and has spread in recent decades to the United States. Trap-neuter-return programs generally focus on unowned cats, being fed by caretakers, and are often considered more acceptable to the public than trap and destroy methods (Mahlow & Slater 1996). TNR involves trapping, sterilizing, and then returning feral cats to their initial capture site. Some TNR programs offer additional amenities including vaccination, parasite control, retroviral testing, and treatment of injury or illness. The primary goal of TNR programs is to reduce populations of feral cats, and therefore, their impact on society.

The long term goal of TNR is often extinction of a colony through natural attrition. The deaths of sterilized animals will ultimately result in a slow total population decline. A three-tiered approach of incorporating euthanasia of sick or injured animals, adoption of socialized cats, and TNR is considered to be most effective (Levy & Crawford 2004). TNR programs serve to prevent the birth of new litters, reduce the threat of feline and zoonotic diseases through vaccination, and improve the quality of life for homeless cats (Foley et al. 2005). Most feral populations are at a capacity for available resources (Gibson et al. 2002). Reducing the birth rate decreases the competition for food and shelter, therefore increasing survivability. In addition, animal stress is reduced with less fighting and competition for mates (Gibson et al. 2002).

There is a disagreement among veterinarians and members of animal protection groups about whether TNR programs should be discouraged, tolerated, or encouraged (Patronek 1998). While most advocates of TNR recognize its limitations, opposition arguments include mainstay topics such as concerns over zoonotic diseases, wildlife vulnerability, hidden costs of performing surgery, and the questionable quality of life following release. Additionally, the question arises

that if these animals are indeed considered wild, why should they be treated any differently than other wild animals (Mahlow & Slater 1996)? Evidence that TNR is an effective method for controlling cat populations is scarce (Zaunbrecher & Smith 1993; Levy et al. 2003). The concept of TNR has contributed to a decline in population over time when compared to control colonies in which cats are not neutered (Stoskopf & Nutter 2004). Several studies deliver varying results, illustrating both the potential benefits and limitations associated with TNR (Levy et al. 2003; Stoskopf & Nutter 2004; Natoli et al. 2006).

One limitation associated with TNR is the time necessary for results to become evident. In Rome, Italy, 8000 cats were neutered over the span of 10 years and reintroduced into their colonies (Natoli et al. 2006). While a significant decrease in overall population was observed (16-32%), it was not noted until at least 3 years from the time of neutering. While a decrease was observed, it was indicated that the results were not as great as originally hoped for. Immigration due to abandonment and spontaneous arrivals were found to be 21% in this study, offsetting the decrease from sterilization, and it was concluded that without proper education on overpopulation and abandonment.

Similar to the findings of Natoli and Maragliano, new arrivals as a result of illegal abandonment may hinder the success of a TNR program. One study revealed that the presence of highly visible, well-fed, established feral colonies encouraged illegal desertion of pet cats (Castillo & Clarke 2003). While TNR was shown to decrease the original population, the population at the end of the study was observed to increase as a result of illegal abandonment. This phenomenon is thought to be the result of cat owners' desperate attempts to "give the cat a chance," as opposed to relinquishment to an animal shelter, where high rates of euthanasia exist (Levy & Crawford 2004).

Conversely, the effects of TNR have also been shown to substantially reduce populations of feral cats. In Randolph County, North Carolina, USA, a study used 9 managed colonies to assess reproductive parameters in feral cats (Stoskopf & Nutter 2004). Of the 9 colonies, 6 participated in a TNR program. The remaining 3 colonies did not participate in a TNR program and were used as control groups. Of the surgically sterilized colonies, all 6 decreased in population (mean decrease of 36%) and continued to decline within the first 2 years. In the same 2 years, the remaining 3 control colonies, which were not sterilized, were found to increase in number by 47%. The study concluded that TNR may bring feral colonies to extinction, but is not a rapid solution.

Similarly, an 11-year study at the University of Central Florida (USA) found TNR to be highly successful at reducing the number of feral cats amongst several populations (Levy et al. 2003). Between 1991 and 1995 an original group of 155 study cats were sterilized, with the exception of 1 male cat. While records were not kept prior to 1991, observers estimated the cat population on campus may have reached 120 cats. Sterilization and adoption of socialized cats reduced the population to 68 by 1996 and only 23 cats remained on campus at the end of the study in 2003, representing a 66% reduction. Additionally, no known kittens were observed to be born on campus after 1995. The study concluded that long-term reduction of feral cat populations is feasible by TNR.

A separate study in north central Florida (USA) distributed a written survey to feral colony caretakers who participated in a local TNR Program (Centonze & Levy 2002). The survey reported 132 colonies being cared for with a total of 920 cats. At the time of the completed survey, caretakers had participated in monthly sterilization clinics for 1 to 9 months. Most colonies contained less than 10 cats with the largest colony containing 89 cats. The mean colony

size before participation in monthly sterilization clinics was 7 cats. The mean colony size following participation in a TNR program was 5.1 cats. Within less than one year of TNR participation, average colony size decreased by 27%, while the largest colony was observed to decrease in numbers from 89 to 24 cats. In conclusion, implementation of TNR was determined to decrease colony size and the number of cats overall, from 920 to 678, as a result of death, disappearance, adoption, and the prevention of new births.

In addition to halting reproduction, TNR has also been reported to offer additional benefits. One study reported improved body condition of feral cats 1 year after sterilization surgery (Scott et al. 2002). Body weight, body condition scoring (BCS), and falciform fat pad measurements were used to determine changes in feral cat body conditions before and after sterilization. Reported scores indicated more than half of feral cats were less than the ideal weight prior to surgery. Cats were found to increase in mean body weight by 40% and scored 1 point higher on the BCS scale (1-9) 1 year following participation in a TNR program. In addition, caretakers reported a decreased tendency to roam following neutering. Fighting amongst cats was also observed to decrease following sterilization.

The Gillis W. Long Hansen's Disease Center, a federal research facility and hospital located in Carville, Louisiana, USA, was the site of a well-established feral colony (Zaunbrecher & Smith 1993). In response to noise and odor complaints by hospital residents and staff, trap and removal methods were employed without success. A TNR study was designed and initiated. The colony was regarded as a nuisance prior to the study and implementation of TNR. After the initiation of the TNR program, not only was the population found to stabilize, but overall health and body condition was found to improve and complaints about territorial behavior and noise decreased. The overall attitude toward the feral cats had also changed. After participation in the

TNR program, cats attained a certain amount of status evoking a protective and possessive behavior from both patients and staff. The TNR program also incorporated the participation of several hospital patients that hand-delivered 18 cats to partake in the study, indicating support and endorsement for the project. Patients and staff soon regarded the feral cats as pets. TNR was determined to be effective, economically feasible, and a humane solution to the once negative attitude towards the colony. In this particular example, not only did colony health improve, but the overall attitude and approach to the colony was increasingly positive.

While it may not embody the gold standard for pet cats, TNR offers an alternative way of life for feral cats. TNR programs offer the opportunity for feral cats to live a good quality of life for an extended period of time as their population is diminished by way of adoption, natural attrition, and the prevention of new births.

Nonsurgical Contraception

Alternatives to surgical sterilization programs, using pharmacaceutical or immunological methods, are currently under investigation for use in feral cats. One example of non-surgical contraception is chemical castration, in which intratesticular or intraepididymal injections of a chemical agent (4.5 % solution of chlorhexidine digluconate) are used to cause infertility in males (Kutzler & Wood 2006). Similarly in females, mechanical barriers, such as intravaginal and intrauterine devices, can be implanted to disrupt fertility. (Kutzler & Wood 2006). Additionally, hormonal treatments, including progestins, androgens, or analogs of gonadotropin releasing hormone (GnRH) act either directly or indirectly to block reproductive hormone-mediated events and conception (Kutzler & Wood 2006).

Recently, the concept of immunocontraception has been investigated for a nonlethal and nonsurgical approach to controlling feral cat populations (Levy et al. 2004; Kutzler & Wood 2006; Purswell & Kolster 2006). Immunocontraception, via vaccination against GnRH, uses the

immune system to block fertility (Purswell & Kolster 2006). While immunocontraception is promising, there are also some drawbacks. In addition to finding the most appropriate antigen for a vaccine, appropriate delivery systems have proven to be a challenge. Oral vaccine baits raise the concern for non-target species and the implications of introducing a widely distributed oral contraceptive vaccine into the environment (Purswell & Kolster 2006). Additionally, animals generally require a series of immunizations for adequate immunity, some of which fail to respond and remain fertile (Levy et al. 2004). In order to be considered effective, immunocontraception vaccines for feral cats require long-term immunity for a large population, achieved with a single treatment, eliminating the need for repeat vaccines (Purswell & Kolster 2006).

While progress continues to be made, the development of non-surgical contraceptive strategies are complex and slow. Therefore, the use of surgical sterilization and TNR programs must be retained, at least for the present time, to control feral cat populations.

Operation Catnip®: A Trap-Neuter-Return Program

Operation Catnip® is a non-profit organization that holds monthly feral cat sterilization clinics at the University of Florida's College of Veterinary Medicine. Cats are presented the morning of each clinic confined in humane, wire mesh traps. Upon arrival, cats are assigned an identification number. After being anesthetized, cats encounter a series of stations in preparation for surgery. Eyes are lubricated, bladders are expressed, injectable antibiotics are administered, and appropriate surgery site preparation is performed. After sterilization is complete, all cats are vaccinated against feline rabies, feline leukemia virus, feline panleukopenia virus, herpes virus, and calicivirus. In addition, they receive topical treatment with selamectin for parasite control. The tip of the left ear is removed to permanently identify sterilized cats.

Operation Catnip® is considered a high-volume sterilization clinic, averaging between 100 and 200 surgeries at each monthly clinic. The largest clinic to date sterilized 230 feline participants. Each clinic is completed in a matter of hours and is comprised solely of volunteers, students, clinicians, and surgeons. In 2006, Operation Catnip sterilized 3,725 feral cats (Scott 2007).

Challenges of Working with Feral Cats

The challenges associated with feral cats include a variety of obstacles in regards to their capture and sterilization. Trapping is relatively easy and requires little to no training in order to safely transport and present feral cats for sterilization; however, some feral cats may evade trapping attempts. Providing an acclimation period to traps prior to capture may prove beneficial to colonies not used to human contact or particularly "trap-shy" cats. Additional methods are available, but are not practical as they require experience or the participation of a veterinarian; an example being net capture or sedative-laced food (Nutter et al. 2004).

Once trapped, feral cats present a unique problem because these animals, similar to wildlife, cannot be safely handled while conscious. Therefore, feral cats must be anesthetized within their traps. Anesthesia presents additional challenges in regard to administration. Feral cats are usually of unknown weight, age, and health status, which are influential in choosing any anesthetic regime. Similarly, unknown factors such as injury or illness may influence or even compromise the safety of anesthesia. An anesthetic protocol to be used in feral cats must consider the safety of both the handlers and the animals.

Properties of an Ideal Anesthetic

Injectable anesthetics permit immobilization while cats are confined within their traps, eliminating the potential for escape or contact with conscious animals that may prove to be dangerous. Intramuscular injections are the most efficient route of administration when

anesthetizing feral cats. An ideal anesthetic regime to be used in feral cats would be predictable, reliable, and offer a wide margin of safety. It would be suitable for both males and females of any age and physical condition. In addition, it would provide rapid onset, sufficient duration of surgical anesthesia, rapid return to normal function, and adequate post-operative analgesia.

Injectable anesthesia for use in feral cats also requires consideration of the injection volume. Ensuring a complete and accurate injection for feral cats restrained within their traps is difficult because restraining options are limited and often inefficient. Large drug volumes pose the risk of incomplete administration because cats may move upon injection. A small volume increases the likelihood for complete administration.

Feral Cat Anesthesia: Shortcomings of Current Methods

The current anesthetic protocol used in Operation Catnip® is an injectable combination of tiletamine, zolazepam, ketamine, and xylazine (TKX) given intramuscularly. TKX is considered an acceptable injectable anesthetic for use in feral cat sterilization and importantly, is associated with a low (0.35%) perioperative mortality rate (Williams et al. 2002). However, TKX possesses several limitations that have prompted the search for an alternative injectable anesthetic. Shortcomings include oxygen saturation levels that are below accepted values, prolonged recovery times, postoperative hypothermia, and likely inadequate post-operative analgesia (Cistola et al. 2004).

Tiletamine is a dissociative anesthetic, chemically related to ketamine. It provides analgesia and immobilization in a dose-dependent manner (Lin et al. 1993). Zolazepam is a benzodiazepine and provides muscle relaxation (Lin et al. 1993). Tiletamine and zolazepam are combined in a 1:1 ratio by mass and marketed under the trade name, Telazol® (Fort Dodge Animal Health, Fort Dodge, IO, USA) (Lin et al. 1993). Telazol® is not considered a good

combination for maintenance of anesthesia beyond its initial dose, as recoveries may be prolonged and the actions of zolazepam may outlast those of tiletamine (Pascoe 1992). This is a problem because the animal experiences a greater degree of tranquilization than anesthesia during recovery (Plumb 2005). Xylazine is used as a sedative analgesic and also provides good muscle relaxation and is approved for use in the dog and cat in the United States. Xylazine may cause significant cardiovascular depressant effects (Paddleford & Harvey 1999).

At the same inspired oxygen concentration, there is a tendency for arterial oxygen tensions to be less during general anesthesia than observed while conscious (McDonell 1996). Hemoglobin oxygen saturation (SpO_2) > 95% is considered normal and SpO_2 < 90% (defined as a PaO_2 of < 60 mmHg) equates to serious hypoxemia (Thurmon et al. 1996). In cats anesthetized with TKX, SpO_2 levels averaged 92 ± 3% in males and 90 ± 4% in females (Cistola et al. 2004). SpO_2 levels were also found to drop below 90% at least once in most cats (Cistola et al. 2004). TKX does not require animals to be intubated and room air (Fi = 0.21) is inspired. This is likely a contributing factor to low oxygen saturation levels seen in cats anesthetized with TKX. While low oxygen saturation is easily preventable and treatable, it is not feasible to administer supplemental oxygen to all cats participating in Operation Catnip® because equipment is limited and up to 50 cats may be anesthetized at one time. The exact repercussions of low SpO_2 levels in cats anesthetized with TKX are unknown, but prompt the search for alternative methods of anesthesia.

Prolonged recoveries are often seen with the use of TKX in cats. The sedative effects of xylazine last 1-2 hours, but complete recovery may take 2-4 hours (Paddleford & Harvey 1999). After surgery is complete, the effects of xylazine may be reversed using one of its antagonists, yohimbine. However, the time from reversal to sternal recumbency has been reported to be

prolonged (72 ± 42 minutes) in cats anesthetized with TKX (Cistola et al. 2004). The low specificity of yohimbine as an antagonist to xylazine may contribute to prolonged recovery times (Virtanen et al. 1989).

One side effect of Telazol is hypothermia (Plumb 2005). Normal body temperature for cats ranges from 37.8-39.5ºC (100-103.1ºF) (Plumb 2005). Cats administered TKX were reported to be hypothermic with temperatures dropping as low as 36.6 ± 0.8ºC (97.8 ± 1.4ºF) post-operatively (Cistola et al. 2004). Clinical hypothermia is associated with decreased liver and renal blood flow, resulting in reduced liver metabolism and renal excretion (Posner 2007). Subsequently, hypothermia-induced slowed metabolism of anesthetic drugs may account for prolonged recovery times seen in cats anesthetized with TKX. Another complication resulting from hypothermia is CNS depression, which may potentiate the effects of anesthetics and muscle relaxants (Short 1987). Additionally, hypothermic animals often shiver during recovery, increasing their metabolic requirements for oxygen. In humans, shivering in recovery is reported to be unpleasant (Kumar et al. 2005).

Feline post-operative pain has been under treated largely as a result of fear of side effects and lack of suitable pharmaceutical products (Robertson & Taylor 2004). It has been reported that cats undergoing ovariohysterectomy that are not provided with analgesics have more post-operative pain than cats that receive analgesics (Slingsby et al. 1998). While xylazine and ketamine may offer analgesic properties, TKX does not contain a recognized analgesic and therefore, post-operative pain control is likely inadequate. Due to the inadequacies surrounding TKX, alternative anesthetic regimes are desired.

Proposed Drug Combination

A combination of medetomidine, ketamine, and buprenorphine (MKB) has been proposed for use in feral cat sterilization surgery. Similar to TKX, this combination of drugs is combined and administered intramuscularly as a single injection. Medetomidine and its specific antagonist, atipamezole, are highly specific for alpha$_2$ adrenoceptors. Ketamine is classified as a dissociative anesthetic, offering a state of unconsciousness and somatic analgesia. Buprenorphine is an opioid analgesic used in pain management. It is hypothesized that the MKB combination may eliminate some of the inadequacies associated with TKX.

Alpha$_2$-Adrenoceptors

Adrenergic drugs affect receptors stimulated by norepinephrine or epinephrine. These drugs can act directly on the receptor (adrenoceptor or adrenoreceptor) by activating it, blocking neurotransmitter actions, or interrupting the release of norepinephrine. Norepinephrine releasing neurons are found in the central and sympathetic nervous system where they serve as links between ganglia and effector organs (Howland & Mycek 2000).

Adrenoceptors can be distinguished pharmacologically and are divided into two families, alpha (α) and beta (β). Alpha adrenoceptors are further subdivided into several classes, including alpha$_1$ and alpha$_2$, based on relative affinities for agonists, independent of their anatomical location (Berthelsen & Pettinger 1977; Wickberg 1978; Wikberg 1978). Alpha$_2$-adrenoceptors have been isolated in the central nervous system, gastrointestinal tract, uterus, kidney, and platelets and produce a variety of effects (Paddleford & Harvey 1999). Pharmacologic studies have revealed alpha$_2$-adrenoceptors to be located in either pre-synaptic or post-synaptic positions (Cullen 1996). Alpha$_2$-adrenoceptors located in the central nervous system regulate the neuronal release of norepinephrine and several other neurotransmitters that are intimately involved in the modulation of sympathetic outflow, cardiovascular and endocrine function, vigilance, emotion,

cognition, and nociception (Scheinin & MacDonald 1989). In most cell types, but not all, alpha$_2$-adrenoceptors regulate adenylate cyclase activity. Specifically, they are linked to a guanine nucleotide regulatory protein (G-protein), whereby receptor activation results in inhibition of adenylate cyclase activity and cAMP formation in target cells (Fain & Garcia-Sainz 1980). This leads to the inhibition of further release of norepinephrine from the neuron. When a sympathetic adrenergic nerve is stimulated, released norepinephrine crosses the synaptic cleft, interacting with alpha$_1$ receptors. A portion of the released norepinephrine "circles back" and reacts with alpha$_2$ receptors on the neuronal membrane. The stimulation of the alpha$_2$ receptor results in feedback inhibition for continued norepinephrine release from the stimulated adrenergic neuron. This inhibitory action decreases further output of the neuron and serves to reduce sympathetic output when sympathetic activity is high (Howland & Mycek 2000). Adrenoceptors are a natural target for the development of sedatives and anesthetics because their activation leads to reduced norepinephrine release and locus coeruleus activity, a site in the brain containing many norepinephrine releasing neurons (Stenberg et al. 1993). Norepinephrine is a neurotransmitter required for a variety of physiological effects and is necessary for the mediation of arousal and pain (Paddleford & Harvey 1999). If norepinephrine is blocked, the result is sedation and analgesia (Paddleford & Harvey 1999). Activation of alpha$_2$-adrenoceptors by specific agonists offer profound sedative-anesthetic effects in a variety of species (Scheinin et al. 1987).

Medetomidine

Medetomidine is one of the newer sedative drugs approved for veterinary use. It is classified as an adrenergic alpha$_2$-agonist (Cullen 1996). Intended for use in dogs and cats, it provides predictable and dose-dependant sedation and analgesia, mediated by receptor stimulation in the spinal cord and brain (Cullen 1996). Medetomidine is lipophilic and rapidly

eliminated (Paddleford & Harvey 1999). Its $alpha_2$ to $alpha_1$ receptor selectivity binding ratio is 1620, compared to 160 for xylazine (Virtanen 1989). $Alpha_2$ agonist drugs bind to $alpha_2$-adrenoceptors, altering their natural membranes and preventing the release of neurotransmitters (Paddleford & Harvey 1999). Medetomidine induces sedation and analgesia, and in high doses, has anesthetic properties (Savola et al. 1986; Virtanen et al. 1988). It has been shown to induce change in metabolites of various transmitters resulting in their decreased release, metabolism, and turnover (Virtanen et al. 1988).

A clinical evaluation by seven veterinary clinics in Finland determined the recommended dose of medetomidine to be between 50-150 μg/kg for various clinical procedures in cats in which sedation was needed (Vaha-Vahe 1989a). Doses ranging between 80 and 110 μg/kg were used for examinations, clinical procedures, and minor surgical operations in cats (Vaha-Vahe 1989a). The preferred route of administration was intramuscular injection (Vaha-Vahe 1989b; Vaha-Vahe 1989a). Cats administered 10 μg/kg of medetomidine show stupor-like sedation with loss of reflexes (Stenberg et al. 1993). Sedation for up to 90 minutes and analgesia for 20-50 minutes is reported with 80 μg/kg (Vaha-Vahe 1990). Medetomidine has been shown to reduce dose requirements for other anesthetics in animals when used concomitantly (Segal et al. 1988). An advantage of medetomidine is that the sedative and depressant effects associated with it can be fully and rapidly reversed with its specific antagonist, atipamezole.

Medetomidine: Cardiovascular and Respiratory Effects

Medetomidine produces marked changes in the cardiovascular system, mostly through stimulation of central receptors, increasing vagal tone and decreasing sympathetic activity, resulting in bradycardia and hypotension (Cullen 1996). The autonomic nervous system, under control by the central nervous system, is the principal means by which heart rate is controlled (Berne et al. 2004). Drug lipophilicity is a major determinant of the rate of diffusion across

biological membranes (Gaynor & Muir 2002). Medetomidine is highly lipophilic and therefore, its ease of penetration into the central nervous system is reflected by its rapid onset of cardiovascular effects (Savola 1989). After medetomidine administration, peripheral vascular resistance increases due to alpha$_2$ adrenoceptor-mediated events (Paddleford & Harvey 1999). Stimulation of postsynaptic receptors located in venous and arterial walls results in vasoconstriction, whereas stimulation of presynaptic receptors inhibits norepinephrine release, reducing sympathetic tone, and contributing to bradycardia (Ruffolo 1985). In cats, medetomidine induces a biphasic effect on blood pressure by increasing it transiently before a decrease to pre-injection control values or less is seen. Heart rate decreases immediately following injection (Savola et al. 1986; Savola 1989). Prior administration of atropine did not eliminate the hypotensive or bradycardic actions associated with medetomidine, nor was it found to modify the initial hypertensive phase (Savola 1989). Medetomidine consistently produces marked bradycardia in cats and heart rate may decrease by as much as 50% of pre-injection values (Vaha-Vahe 1989b; Vaha-Vahe 1989a; Cullen 1996). Cats administered 20 µg/kg of medetomidine IM showed a 58% decrease in heart rate from baseline values 15 minutes following administration (Lamont et al. 2001). Medetomidine-induced changes in heart rate are primarily due to centrally mediated effects and peripheral receptor stimulation; there is no evidence for a direct action of alpha$_2$ agonists on heart muscle (Day & Muir 1993).

Medetomidine has been reported to cause a decrease in arterial PaO_2 in cats (Duke et al. 1994). Venous desaturation also occurs and is likely the result of increased tissue oxygen extraction associated with decreased cardiac output (Gaynor & Muir 2002). Medetomidine depresses the respiratory center, decreasing sensitivity to increases in $PaCO_2$ (Muir et al. 2000).

When large doses of medetomidine are administered, the respiratory threshold for $PaCO_2$ values increase, resulting in marked respiratory depression (Muir et al. 2000).

Medetomidine: Side Effects

The other most common adverse effects observed clinically with the use of medetomidine are vomiting, muscle twitching, and hypothermia (Cullen 1996). In one study of 678 cats, 65% vomited after IM administration of medetomidine, using doses ranging between 80-100 μg/kg (Vaha-Vahe 1989b). In addition, pale mucous membranes are often witnessed as a result of medetomidine's profound vasoconstrictive effects (Muir et al. 2000). Inhibition of gastric secretions have also been reported with the use of medetomidine (Cullen 1996).

Atimpamezole

A major advantage of the use of $alpha_2$ agonists, like medetomidine, is that specific antagonists have been developed to fully reverse their physiological effects. Atipamezole is a potent $alpha_2$ antagonist and is the most selective drug currently available for clinical use in veterinary anesthesia (Paddleford & Harvey 1999). Its $alpha_2$ to $alpha_1$ receptor specificity is 8526, compared to 40 for yohimbine, and it has virtually no effect on other receptors (Virtanen et al. 1989). Atimpamezole has been shown to effectively antagonize the cardiovascular, respiratory, gastrointestinal, and hypothermic effects of medetomidine (Savola 1989; Cullen 1996). In one study, mean arterial pressure and heart rate values were completely restored following administration of atipamezole during maximal hypotensive and bradycardic phases induced by medetomidine (Savola 1989). In dogs, a transient decrease in mean arterial pressure of between 8% and 20% was found after intramuscular injection of atipamezole (Vainio 1990).

In cats, the most effective dose of atipamezole was found to be 2-4 times (on a mg basis) the medetomidine dose administered IM (Cullen 1996). Atipamezole can be administered intravenously, intramuscularly, or subcutaneously and its half-life is twice that of medetomidine,

minimizing the risk for sedation relapse after atipamezole administration (Paddleford & Harvey 1999; Bollen & Saxtorph 2006). Atipamezole reverses the undesirable depressant effects of medetomidine and is useful for rapidly returning animals to normal function.

Atipamezole: Side Effects

Adverse effects accompanying atipamezole reversal of medetomidine include urination, salivation, and muscle tremors (Vaha-Vahe 1990). Extremely high doses may induce signs of CNS stimulation, extreme excitement, panting, and vomiting (Paddleford & Harvey 1999). Following IV administration, tachycardia and hypotension have occurred and therefore slow IV or IM administration is recommended (Paddleford & Harvey 1999).

Dissociative Anesthesia

Dissociative anesthesia derives its name from its unique ability to simultaneously depress one area of the central nervous system, while stimulating another (Evans et al. 1972). Dissociative anesthetics produce unique effects in which animals are assumed to feel dissociated, or apart, from their body (Bill 2006). It is this effect that allows dissociative drugs to provide analgesia and anesthesia without disrupting vital physiological functions (Evans et al. 1972). One advantage to using dissociative anesthesia in cats is that their airway remains patent, eliminating the need for endotracheal intubation (Beck et al. 1971). Dissociative anesthesia differs further from other anesthetics in that its use often results in emergence reactions and hallucinatory behavior, unlike sluggish recoveries characteristic of most other agents (Wright 1982). These reactions are thought to be the result of CNS over stimulation. The consequences of feline hallucinations are not known, but post-anesthetic personality changes have been reported (Haskins et al. 1975).

Ketamine

Ketamine hydrochloride is classified as a short-acting dissociative anesthetic that is used for chemical restraint, anesthesia induction, and surgical anesthesia in cats (Saywer et al. 1993). It is a rapid-acting general anesthetic that has significant analgesic activity and lacks cardiopulmonary depressant effects (Plumb 2005). In the past, ketamine has been recommended for most surgical procedures in cats, including abdominal surgery (Evans et al. 1972).

The functional disorganization associated with ketamine is the reason for its classification as a dissociative (Hanna et al. 1988). Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist (Thurmon et al. 1996). By inhibiting NMDA receptors, it is thought that ketamine may prevent nociceptive stimulation (Woolf & Thompson 1991). While its exact mechanism remains unclear, ketamine induces anesthesia by selectively interrupting CNS reactivity to various sensory impulses, without blocking sensory input at spinal or brain stem levels (Wright 1982). This mechanism is unique as most anesthetic properties cause complete CNS depression.

After injection, patients enter a cataleptic state, similar to a trance, in which loss of voluntary motion and muscle rigidity are often seen (Evans et al. 1972). Lack of complete muscular relaxation makes ketamine unsuitable as a sole anesthetic agent (Bill 2006). In cats, ketamine only provides loss of clinical reaction to pain during its maximal effect (Haskins et al. 1975). Additional doses of ketamine do not enhance muscle-relaxing effects, but do prolong recovery (Arnbjerg 1979).

Recommended doses vary depending on desired depth of anesthesia, route of administration, and the use of other anesthetics concomitantly. In cats, ketamine can be given in doses ranging from 2-33 mg/kg, although doses of 50 mg/kg have been used without fatalities (Arnbjerg 1979; Wright 1982). Ketamine produces dose-related unconsciousness and analgesia

with a rapid onset of action (Thurmon et al. 1996). Following intramuscular injection, cats become recumbent in 1 to 8 minutes (Lumb & Jones 1973). After intramuscular injection, peak drug levels occur within approximately 10 minutes with the highest concentrations found in the brain, liver, lung and fat (Plumb 2005). Duration of anesthesia is approximately 30 to 45 minutes (Lumb & Jones 1973). In one study, small doses (4 and 8 mg/kg) of ketamine caused slow induction times and produced circulatory stimulation, catatonia, and bizarre behavior. Larger doses (32 and 64 mg/kg) caused circulatory depression, respiratory depression, and prolonged recovery times (Child et al. 1972).

Ketamine is excreted in the urine and a cat's reduced ability to excrete the drug due to compromised renal function may prolong recovery (Haskins et al. 1975). Ketamine is rapidly biotransformed to its only known metabolite, norketamine, in the cat (Chang & Glazko 1974; Heavner & Bloedow 1979). The elimination half-life of ketamine in the cat is approximately 1 hour (Plumb 2005). Recovery from symptoms associated with ketamine may not be complete within 10 hours, but most cats can stand unassisted within 2 hours (Evans et al. 1972)

Ketamine offers many advantages. The route of administration is versatile as it can be administered subcutaneously, intravenously, intramuscularly, orally, and rectally (Wright 1982; Hanna et al. 1988; Wetzel & Ramsay 1998). Additionally, ketamine may aid in the prevention of post-operative pain as it has shown to exhibit weak visceral analgesic properties (Saywer et al. 1993). Finally, ketamine has gained favor for use in animal surgical procedures because of its apparent lack of depressant effects on the cardiovascular and respiration systems when used in small doses (Child et al. 1972; Haskins et al. 1975)

Ketamine: Cardiovascular and Respiratory Effects

Ketamine stimulates the heart and lacks the depressant effects prevalent in other anesthetics (Wright 1982). The effects of ketamine on the cardiovascular system include

increased cardiac output, heart rate, mean aortic pressure, pulmonary artery pressure, systemic arterial blood pressure, and central venous pressure (Wong & Jenkins 1975; Plumb 2005). An increase in heart rate and blood pressure has been reported in a clinical setting, but the increase in heart rate is not proportional to the dose of ketamine given (Arnbjerg 1979).

Ketamine causes dose-dependent respiratory depression (Wright 1982). Apneustic breathing is defined as sustained tonic contraction of the respiratory muscles, resulting in prolonged inspiration. Ketamine is capable of inducing an apneustic respiratory pattern, and may be the result of its ability to alter the functional organization of the respiratory controller (Pokorski et al. 1987). Respiratory rates and/or tidal volumes were decreased by ketamine in cats and occasionally transient apnea has been reported (Wright 1982).

Ketamine: Side Effects

Ketamine has a pH of 3.5 and tissue irritation may occur during intramuscular injection as a result of its acidic properties (Wright 1982). Pedal reflexes remain intact and purposeless movements, of varying degree, are often seen unrelated to specific noxious stimuli (Evans et al. 1972). Cat's eyes remain open after ketamine administration and need to be protected with an ophthalmic lubricant (Plumb 2005). Reduced body temperature may be seen with high doses of ketamine (Arnbjerg 1979). Body temperatures decrease on average 1.6ºC after therapeutic doses (Plumb 2005). Due to its dissociative effects, hallucinatory behavior may be observed during emergence from ketamine anesthesia (Thurmon et al. 1996). Cats should be placed in areas with little visual or auditory stimulation to aid in a smoother recovery. Additional emergence reactions include ataxia, increased motor activity, sensitivity to touch, avoidance behavior of an invisible object, and violent recovery (Plumb 2005). Sialorrhea, or excessive salivation, is also commonly seen with ketamine use (Evans et al. 1972). Most cats recover from these symptoms within several hours without further reoccurrence (Wright 1982).

Medetomidine and Ketamine Combination

There are a number of reports using a combination of medetomidine and ketamine in cats for anesthetic purposes (Verstegen et al. 1989; Verstegen et al. 1990; Verstegen et al. 1991a; Dobromylskyj 1996; Wiese & Muir 2006). Used in combination, the centrally stimulating effects of ketamine have been reported to balance the depressive effects of alpha$_2$-agonists (Verstegen et al. 1991a). The tendency for ketamine to increase heart rate may assist in counteracting negative cardiovascular effects associated with medetomidine (Verstegen et al. 1991a).

In cats, the use of medetomidine (80-100 μg/kg) with a low dose of ketamine (7 mg/kg) proved to be sufficient for short acting (20-40 minutes) surgical anesthesia (Vaha-Vahe 1989b). Verstegen et al (1991) found that medetomidine (80 μg/kg) greatly potentiated the effects of low doses (5-7.5 mg/kg) of ketamine, providing suitable surgical anesthesia for 59 minutes. Intramuscular administration of medetomidine (80 μg/kg) combined with ketamine at doses of 2.5, 5, 7, 7.5 and 10 mg/kg produced anesthesia in less than 4 minutes and the duration ranged between 36 and 99 minutes, dependent upon the dose of ketamine (Verstegen et al. 1990; Verstegen et al. 1991a). When increasing the dose of ketamine from 2.5 to 10 mg/kg, the duration of anesthesia was significantly extended (Verstegen et al. 1991a). Although the duration of action was found to be closely related to the dose of ketamine, the quality of anesthesia was similar in all groups. Verstegen and others reported the advantages of the medetomidine/ketamine combination over that of the xylazine/ketamine combination to be the need for a lower dose of ketamine, a longer duration of action, and better analgesia (Verstegen et al. 1990). It was concluded that medetomidine combined with low doses of ketamine forms a suitable combination for anesthesia in cats.

Medetomidine and Ketamine Combination: Cardiovascular and Respiratory Effects

Bradycardia in cats is evident with medetomidine/ketamine combinations. In one study, varying doses of ketamine were combined with 80 μg/kg of medetomidine and evaluated. When the dose of ketamine was increased from 2.5 to 10 mg/kg a change from bradycardia to mild tachycardia was observed (Verstegen et al. 1991a).

In the same study, additional anesthetic drug combinations were evaluated, including combining ketamine with acepromazine or xylazine. Bradypnoea was seen in all groups receiving ketamine, regardless of its anesthetic pairing (Verstegen et al. 1991a). Verstegen et al (1990) observed no respiratory depression in cats anesthetized with 80 μg/kg of medetomidine and 5 mg/kg of ketamine (Verstegen et al. 1990). However, periods of apnea were observed in cats anesthetized with 80 μg/kg of medetomidine and 10 mg/kg of ketamine (Verstegen et al. 1991a).

Medetomidine and Ketamine Combination: Side Effects

The most common side effects seen with the concomitant use of medetomidine and ketamine are vomiting, excitability, and apnea (Verstegen et al. 1990; Verstegen et al. 1991a).

Analgesia

NSAIDS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in pain management in both humans and animals as they are easy to administer, inexpensive, offer a long duration of action, and are not controlled substances (Papich 2000). NSAIDs, however, are not widely used in cats due to potential toxic effects. Due to their deficiency of certain metabolic pathways, particularly hepatic glucoronidation, cats are prone to decreased NSAID metabolism (Lascelles et al. 2007). This prolongs the duration of effect and may ultimately result in drug accumulation. Slow clearance may result in hyperthermia, metabolic acidosis, and kidney or liver injury (Davis

& Donnelly 1968). Severe adverse effects associated with NSAIDs also include gastrointestinal ulceration, perforation, and bleeding or renal ischemia (Papich 2000). NSAID use should be based on confirming normal renal function prior to use; and doing so in feral cats is not feasible. Hypotension during anesthesia can contribute to the renal toxicity of NSAIDs and blood pressure is rarely measured during feral cat procedures. Additionally, dehydration due to trapping may make some cats more susceptible to NSAID toxicity. Because feral cats do not participate in follow up examinations post-operatively, NSAID use is inappropriate. Alternative methods of pharmacologic analgesia should be sought for use in feral cats.

Opioids

Opioids are defined as any natural or synthetic drug that produces analgesia without loss of proprioception or consciousness (Gaynor & Muir 2002). An important advantage for opioid analgesics is that they can be administered without fear of the potential side effects associated with NSAIDS (Papich 2000). Opioid drugs are highly effective and remarkably safe (Papich 2000). They are generally characterized by rapid and extensive distribution as they are highly lipophilic drugs (Papich 2000). Opioids exert their effects by interaction with opioid receptors located on cell membranes and are currently one the most effective systemic means of controlling post-operative pain (Gaynor & Muir 2002)There are three known opioid receptor classifications: mu, kappa, and delta; however, more types likely exist (Gaynor & Muir 2002; Evers & Maze 2004). Receptors are located throughout the body and drugs acting on them produce a variety of effects on tissue and organ systems (Pascoe 2000). Opioid drugs are classified as agonist, partial agonist, antagonist, or agonist-antagonist based on their affinity for specific opioid receptors (Gaynor & Muir 2002).

Buprenorphine

Effective pain control is important in regards to the development of an anesthetic regime. The concomitant use of medetomidine and ketamine has been reported to offer analgesic properties. In one study, cats administered a combination of medetomidine and ketamine were shown to have less post-operative pain after ovariohysterectomy when compared to other anesthetic regimes (Slingsby et al. 1998). However, the short duration of action associated with these drugs likely limits their use as sole analgesics (Paddleford & Harvey 1999). In addition, any potential analgesic effects of medetomidine are reversed.

In the proposed combination, MKB includes a drug specifically for pain control, buprenorphine. Buprenorphine is the most popular opioid analgesic used in small animal species in the UK and is widely used in other parts of Europe, Australia, and South Africa (Watson et al. 1996; Capner et al. 1999; Joubert 2001). In clinical studies, it has provided better analgesia than other opioids and is considered highly suitable for perioperative pain management in cats (Dobbins et al. 2002; Robertson & Taylor 2004).

Buprenorphine is classified as a partial mu-opioid agonist (Howland & Mycek 2000). Mu-receptors are responsible for euphoria, sedation, analgesia, and respiratory depression (Papich 2000). Partial mu-opioid agonist implies that buprenorphine does not produce the same effects as a full agonist, such a morphine (Pascoe 2000). However, buprenorphine has produced better analgesia in clinical studies in cats when compared with morphine (Stanway et al. 2002).

Agonists acting on receptor sites inhibit pain transmission or modulate pain sensation by inhibiting neurotransmitters associated with pain production (Papich 2000). Use of buprenorphine in cats is associated with euphoria, and often purring combined with rolling and kneading of the front paws (Robertson et al. 2005). The euphoric effects associated with mu-opiate receptors help to relieve anxiety and stress for cats in an unfamiliar environment (Papich

2000). Another advantage to using buprenorphine is its long acting effects, which may exceed 6 hours in cats (Pascoe 2000; Robertson et al. 2005). The recommended dose for buprenorphine ranges from 5-20 μg/kg in cats and can be administered intramuscularly, intravenously, subcutaneously, transmucosally, and orally (Pascoe 2000; Robertson et al. 2005). Thermal threshold responses have been used to evaluate the efficacy of buprenorphine. Cats that received 10 μg/kg of buprenorphine intramuscularly increased thermal threshold from 4 to 12 hours following administration (Robertson et al. 2003). Another study concluded that thermal threshold only increased 45 minutes after a subcutaneous injection of buprenorphine (20 μg/kg) (Steagall et al. 2006). This suggests that the route of administration of buprenorphine may impact its effectiveness. Routes that lead to slow uptake may not achieve sufficient concentration gradients to drive the drug into the biophase (Steagall et al. 2007). No difference was seen in pain scores between control groups, who did not receive any analgesics, and cats administered 6 μg/kg of buprenorphine intramuscularly after ovariohysterectomy (Slingsby & Waterman-Pearson 1998).

Buprenorphine: Side Effects

In animals, well documented effects of excitement and dysphoria exist in conjunction with opioid use (Papich 2000). Cats are ordinarily the species considered to be more prone to excitatory effects associated with opioid administration (Papich 2000). However, many of the studies concluding these reactions were used in healthy, alert animals in which doses of opioids in excess of those required for analgesia were administered. These effects seem to be less apparent when opioids are administered to animals in pain (Papich 2000). Buprenorphine, on the other hand, is rarely seen to cause dysphoria in cats (Robertson & Taylor 2004).

The use of opioid analgesics often raises concerns regarding clinical hyperthermia, or the elevation of body temperature above normal range. In cats, hyperthermia is considered to be ≥ 39.3ºC (103ºF) (Tilley & Smith 2004). The effects of severe hyperthermia are primarily related

to an increase in metabolic activity and cellular oxygen consumption and generalized cellular necrosis associated with the denaturation of proteins, enzymes, and cell membranes (Niedfeldt & Robertson 2006). Doses of buprenorphine ranging between 10-20 µg/kg were not found to cause hyperthermia in cats when compared with other opioid analgesics (Niedfeldt & Robertson 2006; Posner 2007).

An additional side effect associated with buprenorphine use in cats is excessive mydriasis, or pupil dilation (Robertson & Taylor 2004). Precautions need to be taken when approaching the animal as they may not see clearly. In addition, they should be kept away from bright lights while their pupils are excessively dilated. Buprenorphine rarely causes dysphoria or vomiting in cats (Robertson & Taylor 2004). Buprenorphine is highly effective, easily administered, long-acting and considered highly suitable for pain management in cats (Robertson & Taylor 2004).

Opioid and Alpha$_2$ Agonists

Interestingly, a close association between opioid and alpha$_2$-adenoceptors has been identified (Unnerstall et al. 1984). Enhanced antinociception occurs following simultaneous administration of agonists at specific sites in the spinal cord (Ossipov et al. 1989; Ossipov et al. 1990; Omote et al. 1991). Alpha$_2$ agonists and mu-opioid agonists produce similar pharmacological effects in the CNS because their receptors are located in the same area of the brain, are connected to the same signal transducer, and the same effector mechanism is used by both agonists (Paddleford & Harvey 1999). Heightened effects of opioid and alpha$_2$ agonist combinations may prove to be useful in potentiating their anesthetic and analgesic properties for use in feral cat sterilization surgery.

Summary

The overpopulation of feral cats has contributed to a variety of problems including animal welfare concerns, detriment to wildlife, and public health considerations. These issues have

sharply divided veterinarians, ecologists and conservationists, as well as the general public. In the quest for a solution, some control methods have proven to be ineffective, while others offer considerable promise. Currently, there is no obvious answer as to what the most effective management strategy is. Trap-neuter-return programs offer an alternative to lethal eradication methods and are bridging the gap until other solutions become available. Due to the unique situation feral cats present, successful anesthesia in high-volume clinics is challenging. The currently used anesthetic protocol, TKX, possesses limitations that have prompted the search for a superior alternative. The purpose of this study was to evaluate a combination of medetomidine, ketamine, and buprenorphine (MKB) for use in large-scale feral cat sterilization clinics.

CHAPTER 2
MATERIALS AND METHODS

Animals

Feral cats admitted to trap-neuter-return programs in Alachua County (Operation Catnip® and Maddie's Outdoor Cat Program®) were used in this study. Cats were captured from their colonies using humane traps and were transported to the University of Florida's College of Veterinary Medicine by colony caregivers for sterilization. Over a 2-year study period, a total of 240 cats and kittens were anesthetized using a combination of medetomidine, ketamine, and buprenorphine (MKB). Cats selected for the study were of unknown health status and because of this; all researchers were required to wear gloves and be vaccinated for rabies.

Overview

All anesthetic and surgical procedures were approved by the University of Florida Institutional Animal Care and Use Committee. Cats arrived on the morning of surgery in wire traps or plastic crates. Upon arrival, cats were assigned an identification number and a medical record to document anesthetic and surgical details. Cats were sterilized, vaccinated, and had the tip of their left ear removed for identification purposes. Cats were sent home later the same day. Caretakers were instructed to release the cats to their colonies the following day.

Cat Selection

Every attempt was made to choose apparently healthy cats free from obvious signs of upper respiratory infection or other advanced disease. Cats with evidence of trauma, fecal staining from diarrhea or signs of dehydration were avoided. Most cats were judged to be adults ($\geq$ 1 year of age) (n = 238), although kittens under 6 months of age (n = 2) were included in the study.

Anesthetic Drugs

Medetomidine HCl (M) 1 mg/ml (Domitor®, Orion Corporation, Espoo, Finland), ketamine HCl (K) 100 mg/ml (Ketaject®, Phoenix Pharmaceuticals Inc, St. Joseph, MO, USA), and buprenorphine HCl (B) 0.3 mg/ml (Buprenex®, Reckitt Benckiser Healthcare, Hull, England, UK) were used in this study. Atipamezole HCl (A) 5 mg/ml (Antisedan®, Orion Corporation, Espoo, Finland) was used to reverse the effects of medetomidine following the completion of surgery.

Experimental Design

This study was divided into three separate phases. Phase 1 was a dose-finding study to determine the optimal combination of medetomidine, ketamine, and buprenorphine to be used in feral cat ovariohysterectomy and castration surgeries. The route of administration and dose of atipamezole was modified based upon clinical observations and length of recovery. Each cat was instrumented non-invasively with monitoring equipment for measurement of the following physiological parameters: heart rate (HR), respiratory rate (RR), blood pressure (BP), and hemoglobin oxygen saturation (SpO_2). Time intervals including time to lateral recumbency, surgical duration, and time from reversal to sternal recumbency were recorded. The preliminary trials (Phase 1) continued until a satisfactory combination of MKB was achieved. The criteria required for the selected dose of MKB included adequate duration of action, acceptable physiological parameters, and rapid return to normal function.

Phase 2 of this study evaluated the physiological parameters of the selected combination acquired in Phase 1. A total of 100 cats were to be anesthetized using the selected MKB combination. Each cat was instrumented with non-invasive monitoring equipment that allowed HR, RR, BP, and SpO_2 to be recorded. Time to lateral recumbency, surgical duration, and time from reversal to sternal recumbency were also recorded.

In Phase 3 of this study, a fixed dose was created using an average estimated body weight of 3 kg/cat. A mixture of MKB was generated using the selected dosing regime evaluated in Phase 2. From this mixture, a fixed volume was calculated to be used in each cat, regardless of true weight. Physiological parameters were not monitored during Phase 3; although time to lateral recumbency, surgical duration, and time from reversal to sternal recumbency intervals were recorded. Adjustments to the calculated MKB fixed volume were made based upon anesthetic requirements and overall assessment. If anesthesia was found to be inadequate, the fixed volume was increased in 0.1 mL increments. A fixed volume of atipamezole was calculated based on the volume of medetomidine in the fixed anesthetic combination. Adjustments to atipamezole were made based upon the volume of MKB, clinical observations, and the total time of recovery.

Pre-operative Preparation

Cats were weighed in their traps on a pediatric scale. Ten empty traps were weighed and determined to have an average weight of 2.4 ± 0.1 kg. The estimated trap weight of 2.4 kg was used consistently throughout this study, although actual trap weight was found to vary slightly. An approximate body weight was calculated by subtracting the average trap weight (2.4 kg) from the total weight of the cat plus the trap. This weight was used for MKB dose calculations.

Induction of Anesthesia

Cats were restrained at one end of the trap by passing a wire comb through the wire meshing of the trap. A 22-gauge, 1-inch needle was used to administer an intramuscular injection of MKB. The target injection site was into the paralumbar muscles, although this route of administration could not be confirmed.

Drug Administration Phase 1: Dose Finding Study

In Phase 1, several different anesthetic combinations were performed, varying the dose of each drug and route of administration of the reversal agent. Previous evaluations of MKB (Verstegen et al. 1991a) were the basis of the preliminary dosing regimes for the initial trials in this study. Based upon duration of action and the physiological parameters, adjustments were made in order to achieve optimum results. The drug combinations performed in Phase 1 are shown in Table 2-1.

Each of the three drugs (M, K, and B) were measured separately and then combined into a single syringe immediately prior to injection. Each cat was administered a single intramuscular injection of MKB. If the initial dose of MKB was found to be insufficient, an additional dose of 10 μg/kg of medetomidine was injected intramuscularly and recorded. Insufficient effect was defined as: the cat was still responsive to toe pinch through the trap 10 minutes post-injection. If the depth of anesthesia was still found to be insufficient (at t = 15 minutes), an additional dose of 2.5 mg/kg of ketamine was injected intramuscularly. If anesthesia remained inadequate, a face mask was placed on the cat and isoflurane vaporized in oxygen was administered, via a non-rebreathing Bain anesthetic circuit, for the duration of surgery.

Dependent upon the conditions of the trial, atipamezole was given intramuscularly or subcutaneously at a volume of 0.125 or 0.25 times the initial volume of medetomidine. If cats were not sternal 1 hour post-injection, a second dose of atipamezole was administered. This dose was of equal volume and delivered intramuscularly, regardless of the initial route of atipamezole administration.

Drug Administration Phase 2: Selected Dose Study

Physiological parameters in cats given the selected drug combination from Phase 1 were evaluated in Phase 2. Each of the three drugs (M, K, and B) were calculated based upon each

cat's estimated weight (cat plus trap weight – average trap weight) and combined in a single syringe prior to injection. The selected dosing regime is shown in Table 2-2.

If the initial dose of MKB was found to be insufficient (at t =10 minutes), an additional dose of 20 µg/kg of medetomidine was injected intramuscularly. If anesthesia remained inadequate (at t =15 minutes) an additional dose of 2.5 mg/kg of ketamine was injected intramuscularly. If anesthesia continued to be insufficient, a face mask was placed on the cat and isoflurane gas vaporized in oxygen was administered via a non-rebreathing Bain anesthetic circuit, for the duration of surgery. At the completion of surgery, each cat received a subcutaneous (intrascapular) dose of atipamezole to reverse the effects of medetomidine.

Drug Administration Phase 3: Fixed Dose Study

In Phase 3, the selected dosing regime (100 µg/kg M, 10 mg/kg K, 10 µg/kg B) was calculated for a 3 kg cat (Table 2-4). A mixture of MKB was calculated to accommodate 20 cats (Table 2-5). In a sterile 30 mL vial, 6.0 mL medetomidine, 6.0 mL ketamine, and 2.0 mL of buprenorphine were mixed together. From this vial, an injection volume of 0.7 mL was withdrawn (Table 2-4). If anesthesia was found to be inadequate, the fixed volume was increased by 0.1 mL (0.8 mL). The fixed volume was administered to all cats, regardless of true weight. The MKB injection was administered intramuscularly. The target site was the paralumbar muscles, although this could not be confirmed.

Subcutaneous atipamezole was administered post-operatively to reverse the effects of medetomidine. The injection volume of atipamezole was 0.08 mL (0.4 mg) as calculated by the initital volume of medetomidine (Table 2-6). If cats did not achieve sternal recumbency by 1-hour following the injection of atipamezole, an additional 0.4 mg (0.08 mL) of atipamezole was given into the paralumbar muscle intramuscularly.

Cats that received the 0.8 mL (0.344 mg M, 34.4 mg K, 0.034 mg B) dose of MKB participated in the high-volume clinic (Operation Catnip®) without time interval, physiological measurement, or monitoring. Additionally, weights were not recorded. This was the first simulation of what would normally take place in a high volume clinic using the MKB protocol in mass. Due to the volume of cats anesthetized simultaneously, every effort was made to note the need for supplemental anesthesia, although actual numbers may be higher.

Clinical Procedures: Evaluation of Anesthetic Effects

Following injection, loss of reaction to toe pinch was tested from outside the trap. Once determined to be unresponsive, each cat was carefully removed from its trap and its sex was determined. Palprebral reflex, jaw tone, and overall muscle relaxation were evaluated and recorded. These criteria were used to determine adequacy of anesthesia before, during, and after surgical procedures.

Clinical Procedures: Hemoglobin Oxygen Saturation

A pulse oximeter sensor (Nellcor Puritan Bennett NPB-40, Nellcor Puritan Bennett Inc, Pleasanton, CA, USA) was placed on the cat's tongue for the purpose of monitoring oxygen hemoglobin saturation (SpO_2) levels and pulse rate. If readings could not be obtained from the tongue, digits or an ear were used in an attempt to obtain additional readings.

Clinical Procedures: Evaluation of Cardiovascular Function

Blood pressure was measured using a Doppler probe (Ultrasonic Doppler Flow Detector, Model 811-B and 811-L, Parks Medical Electronics Inc, Aloha, OR, USA). The hair over the caudal carpus was shaved. Ultrasound gel was applied to the doppler probe, placed directly over the digital arteries, and secured with zinc oxide tape. A small (size 3) blood pressure cuff (Critikon Inc, Southington, CT, USA) was applied proximally and attached to a sphygmomanometer (Welch Allyn, Beaverton, OR, USA) from which systolic blood pressure

values were obtained. The size of each cuff was determined by cuff width encompassing 48-50% of the circumference of the forelimb where it was applied.

Heart rate and systolic blood pressure were measured and recorded at 5 minute intervals throughout the duration of anesthesia. Pulse oximetry readings were only accepted if consistent with the pulse rate counted from the Doppler probe and the heart rate obtained by palpation.

Clinical Procedures: Evaluation of Respiratory Function

Respiratory rate was determined visually (counted for 30 seconds). Clear surgical drapes facilitated observation of chest movements during ovariohysterectomy surgeries. If clear surgical drapes were not used, respiratory rate was determined by palpation. Respiratory rate was conducted at 5 minute intervals throughout the duration of anesthesia.

Clinical Procedures: Temperature

Rectal temperature was measured using a standard electronic digital thermometer (MABIS Healthcare, Inc., Waukegan, IL, USA). Temperature was determined at the time of induction, at the completion of surgery, and 5 minutes following the reversal of medetomidine.

Clinical Procedures: Pre-surgical

A sterile petroleum-based ophthalmic lubricant (Akorn, Inc., Buffalo Grove, IL, USA) was applied to both eyes and each cat was administered a long-acting penicillin injection (Extended Action Penicillin G Benzathine and Penicillin G Procaine, G.C. Hanford Manufacturing Company, Syracuse, NY, USA) subcutaneously. Prior to surgery, approximately 1 cm of the distal tip of the left ear was removed using a sterile hemostat and surgical scissors. This step was used as the first indicator of anesthesia efficacy in our study. Finally, the hair was clipped from the surgery site and the skin was prepared using alternating providine iodine and alcohol scrubs.

Clinical Procedures: Post-operative

After surgery was complete, each cat was vaccinated against rabies, feline leukemia virus, feline panleukopenia virus, herpes virus, and calicivirus (FVRCP) (Rabvac® 3TF Fort Dodge Laboratories, Fort Dodge, IO, USA; Fel-O-Guard™ Plus 3 + Lv-K, Fort Dodge Laboratories, Fort Dodge, IO, USA). The rabies vaccine was administered subcutaneously in the right hind leg. The feline leukemia/FVRCP combination vaccine was administered subcutaneously in the left hind leg. In addition, each cat received a single dose of selamectin (Revolution®) (Pfizer Animal Health, Exton, PA, USA) administered topically for parasite control.

Quality of Recovery

Following the completion of surgery and the subsequent reversal of medetomidine, a Quality of Recovery Score (QRS) was assigned and recorded according to predetermined guidelines (Table 2-3).

Data

Least square mean (LSM) and true mean for physiological data were reported. The least LSM is identical to the true mean assuming no missing data and the number of replications is the same in each group. Because our data did not meet these criteria, both were reported for comparison.

Statistical Analysis

SAS PROC MIXED (SAS Institute Inc., Cary, NC, 27513-2414, USA) was used to evaluate physiological parameters in support of missing data. SAS PROC MIXED assumes data are missing at random, which is suspected for the majority of absent records in this study, although cannot be confirmed. Missing data was the result of equipment error, human error, or the result of other unforeseen complications.

Individual anesthetic records were kept for each cat. Male and female data were compared. Physiological variables (BP, RR, SPO_2, HR, and rectal temperature), the time from MKB injection until lateral recumbency, the time from MKB injection until the start of surgery, surgical duration, the time from atipamezole administration to sternal recumbency, and the total time recumbent were compared between males and females. Body weight, the need for additional MKB, and the need for additional atipamezole were also compared between males and females. In cats requiring additional MKB, time from reversal to sternal recumbency, total time recumbent, and additional atipamezole requirements were compared and analyzed amongst males and females, as well.

Weight, MKB injection to time of lateral recumbency, MKB injection to start of surgery, surgical duration, time of reversal to sternal recumbency, and total time recumbent were compared by means of an unpaired t-test. Physiological variables (BP, RR, HR, SPO_2) were compared separately over time by means of a two-factor ANOVA (Time-fixed; Subject-random) test. Temperatures were compared over time using split-plot repeated measures ANOVA with post hoc time comparisons by means of Bonferroni's t-test. The effect of multiple doses of MKB on the total time recumbent was evaluated using a two-way ANOVA test (SAS PROC MIXED, SAS Institute Inc., Cary, NC, 27513-2414, USA). Reversal to sternal time was compared between cats that did or did not require additional MKB by means of an unpaired t-test.

The significance in the difference between physiological parameters upon the completion of surgery and 5 minutes following atipamezole administration were compared in all cats. Changes in physiological variables (BP, RR, HR, SPO_2) before and after the reversal of medetomidine were analyzed using split-plot repeated measures ANOVA. The α-priori significance level used throughout this study was $P < 0.05$.

Finally, the associations between sex and additional MKB, and sex and the need for additional reversal were evaluated using a 2 x 2 contingency table and a chi-square test. Similarly, the need for additional MKB and the need for additional reversal were evaluated using a 2 x 2 contingency table and a chi-square test for males and females separately. If expected values were < 5, then a minimum chi-square test was used instead of chi-square.

Table 2-1. Dose-finding study

	n =	M	K	B	A	A
		µg/kg	mg/kg	µg/kg	(x M volume)	Route of Administration
Trial 1	10	80	7.5	10	0.25	IM
Trial 2	10	80	10	10	0.25	IM
Trial 3	15	100	7.5	10	0.25	IM
Trial 4	3	100	10	10	0.25	IM
Trial 5	4	110	7.5	10	0.125	IM
Trial 6	8	110	7.5	10	0.25	IM
Trial 7	9	110	7.5	10	0.25	SC
Trial 8	10	100	10	10	0.25	SC

Table 2-2. Selected dosing regime

Drug	Dose	Route of Administration
Medetomidine (M)	100 µg/kg	IM
Ketamine (K)	10 mg/kg	IM
Buprenorphine (B)	10 µg/kg	IM
Atipamezole (A)	0.25 x M volume	SC

Table 2-3. Quality of recovery scores

QRS	Scoring Guidelines
3	Good: Smooth Recovery, No Excitement, < 45 min Reversal to Sternal Time
2	Acceptable: Mild Excitement and/or <1hr Reversal to Sternal Time
1	Unacceptable: Severe Excitement, 2nd Reversal, and/or >1hr Reversal to Sternal Time

Table 2-4. Fixed dose calculation

Drug	Dose	Concentration	mL/kg	mL/3kg
Medetomidine (M)	100 ug/kg	1 mg/ml	0.1	0.3
Ketamine (K)	10 mg/kg	100 mg/ml	0.1	0.3
Buprenorphine (B)	10 ug/kg	0.3 mg/ml	0.033	0.1

Table 2-5. MKB mixture calculation (20 Cats)

	mL/3 kg	x # of Cats	Total (mL)
Medetomidine (M)	0.3	20	6
Ketamine (K)	0.3	20	6
Buprenorphine (B)	0.1	20	2

Table 2-6. Atipamezole fixed dose calculation

Volume of (M) x 0.25
0.3 mL x 0.25 = 0.075 mL

CHAPTER 3
RESULTS

Phase 1-Dose-Finding Study

During Phase 1 of this study, 69 cats (41 males, 28 females) were anesthetized with MKB in 8 separate trial experiments (Table 3-1). All cats were of acceptable body condition and appeared healthy at the time of the procedure. Pregnancy (n = 3) and bilateral cryptorchidism (n =1) were observed in a small number of cats. In addition, one male was found to be previously castrated.

Drug combinations in groups 1, 2, and 3 provided good anesthesia, however, duration of action was inadequate for surgery completion. Duration of action in groups 1, 2, and 3 were 35 ± 16 minutes (M: 36 minutes; R: 14-62 minutes) (Median, Range), 41 ± 14 minutes (M: 45 minutes, R: 19-67 minutes), and 38 ± 25 minutes (M: 30 minutes; R: 15-105 minutes), respectively. In group 4 duration of action was sufficient (62 ± 26 minutes) (M: 75 minutes; R: 32-79 minutes) and physiological parameters were acceptable, but recoveries were violent and considered unacceptable in every cat (n = 3). In groups 5, 6, and 7 depth of anesthesia was good, but the duration of action was inconsistent and was not considered acceptable. The duration of action in groups 5, 6, and 7 were 50 ± 28 minutes (M: 46 minutes; R: 26-84 minutes), 30 ± 6 minutes (M: 30 minutes; R: 21-40 minutes), 35 ± 6 minutes (M: 35 minutes, R: 26-47 minutes), respectively.

The dose of atipamezole and route of administration in groups 1, 2, 3, and 4 provided acceptable recovery times (≤ 1 hour). In group 5, the reversal dose was decreased by one-half to see if a smaller dose would be sufficient. This protocol was found to result in delayed recoveries (≥ 1 hour) and all cats (n = 4) required an additional injection of atipamezole. The reversal volume and route of administration in groups 6 and 7 were satisfactory, with group 7 providing

an alternate option for atipamezole administration (subcutaneous injection). Cats that received subcutaneous atipamezole in group 7 were observed to have longer (28 ± 15 minutes; M: 31 minutes, R: 5-50 minutes), yet acceptable, recoveries compared to group 4 (17 ± 13 minutes; M: 14, R: 5-36 minutes). Recoveries in group 7 had no incidence of excitement or violent behavior.

Group 4 was considered the best with respect to adequate depth of anesthesia and duration of action, however, recoveries were unacceptable. The recovery process appeared to take place undesirably fast, and was accompanied by excitement and violent behavior. Based on these observations, group 8 combined the MKB doses from group 4 (100 μg/kg M, 10 mg/kg K, 10 μg/kg B) with the reversal dose and route of administration from group 7 (1.25 mg (0.25 mL) x M; subcutaneously). This protocol was carried out in 10 cats and exhibited superior qualities when compared to previous trials. Duration of action was sufficient (33 ± 11 minutes; M: 30, R: 15-57) and time to sternal recumbency (34 ± 24 minutes; M: 25; R: 5-74 minutes) was adequate, uneventful, and within acceptable recovery parameters. The protocol executed in group 8 was considered to have the best potential for our needs, and therefore, was chosen for further investigation.

Phase 1-Dose-Finding Study: Side Effects

In Phase 1, 4 cats displayed severe respiratory depression. All 4 cats received the same dose of MKB (110 μg/kg M, 7.5 mg/kg K, 10 μg/kg B).

Phase 2-Selected Dose Study: Animals

One hundred and one cats (53 males, 48 females) were anesthetized with the selected dose of MKB (100 μg/kg M, 10 mg/kg K, 10 μg/kg B). Ninety-nine cats were identified as adults and 2 cats were approximately 6 weeks of age. Two cats were pregnant and 2 cats were lactating at the time of surgery. Three cats were found to be previously sterilized (1 male, 2 females), therefore, a total of 98 cats (52 males, 46 females) were sterilized using the selected dose of

MKB. With one exception, all cats were considered to be free from obvious signs of disease or trauma. One cat displayed signs of marked dehydration, diarrhea, and intestinal parasites upon examination following MKB administration. There was evidence of external parasites, such as fleas, on most cats.

There was no significant difference in the weight of male cats (3.2 ± 0.2 kg) compared with female cats (2.9 ± 0.1) (P = 0.15). Cat weights ranged between 0.93 kg and 6.31 kg and therefore, the volume of the MKB combination was between 0.22 mL and 1.4 mL, respectively.

Phase 2-Selected Dose Study: Time Intervals

Lateral recumbency was achieved in 4.3 ± 4 minutes and 5.2 ± 5.6 minutes (mean ± SD) after the injection of MKB in male and female cats, respectively. There was no significant difference in lateral recumbency times between males and females (P = 0.35). Eight cats (2 males, 6 females) vomited following anesthetic injection, however, the transition to lateral recumbency was free from signs of CNS excitement. The time from MKB injection until the start of surgery was significantly longer in females (23 ± 6.2 minutes) than in males (16.1 ± 5.2 minutes) (P < 0.0001) due to longer surgical preparation requirements. Similarly, the surgical duration was significantly longer in female cats (29.6 ± 18.7 minutes) compared to male cats (3.2 ± 2.5 minutes) (P < 0.0001).

The time from the injection of the reversal agent atipamezole until the onset of sternal recumbency was not significantly (P = 0.9) different between males (38.6 ± 38 minutes) and females (40.6 ± 78.2 minutes). There was also no difference (P = 0.6) in time to sternal recumbency in cats that received a second dose of MKB (n =11).

The total time recumbent (including preparation, surgery, and recovery) was significantly longer in females (86.9 ± 27.1 minutes) than in males (64.7 ± 36.2 minutes) (P = 0.0009). The total time recumbent was significantly different (P = 0.008) in males (62 ± 20.7 minutes) and

females (103.8 ± 28.4 minutes) who required a second dose of MKB (7 males, 4 females), however, there was no interaction observed between the two (total time recumbent and the need for additional MKB) (P = 0.34).

There was no difference (P = 0.4) in the frequency of additional MKB requirements in male (n = 7) and female (n = 4) cats. Similarly, there was no difference (P = 0.4) in the frequency of cats (6 males, 8 females) requiring a second dose of the reversal agent, atipamezole. There was also no association (P = 0.3) between cats that required a second dose of MKB and cats that required a second dose of reversal agent.

Phase 2-Selected Dose Study: Physiological Variables

Physiological variables (BP, HR, SpO_2, and RR) were measured immediately after removal from the trap, throughout the surgical procedure, and 5 minutes following the reversal of medetomidine. The feral nature of the cats prohibited further monitoring beyond this point. Physiological data are missing intermittingly as a result of equipment error, human error, or other unforeseen complications. Absent data are believed to be missing at random, although this cannot be confirmed.

Male and female data were assessed separately over time. The average range of data collections were between 5 and 35 minutes in males and between 5 and 85 minutes in females. Data were collected every 5 minutes using set time intervals. The start point and the length of these intervals were determined by the time of lateral recumbency and the surgical duration. Following the reversal of medetomidine, physiological parameters were collected for an additional 5 minutes in all cats when possible. Some measurements were unable to be obtained in cats with unusually short recovery times.

In males, a relationship between blood pressure (R: 91-195 mm Hg) and time could not be made (P = 0.52) with > 95% confidence. Blood pressure (R: 38-190 mm Hg) decreased

significantly over time ($P < 0.0001$) in female cats. One female cat was hypotensive (< 60 mm Hg) at least once throughout the duration of anesthesia. Twenty-two cats (7 females, 15 males) were hypertensive (> 160 mm Hg) at least once throughout the duration of anesthesia. Normotension was observed following the administration of medetomidine and throughout the duration of surgery in most cats (Figure 3-1 and Figure 3-2).

In males, heart rate (R: 77-176 beats/minute) did not significantly ($P = 0.32$) change over time (Figure 3-3). No observation of tachycardia (> 180 beats/minute) was observed in any cat. Conversely, heart rate (R: 57-172 bpm) significantly decreased ($P < 0.0001$) as a factor of time in female cats (Figure 3-4). One female was observed to be bradycardic (< 60 beats/minute) throughout the duration of anesthesia.

Severe hemoglobin desaturation was observed in both males (R: 36-99 %) and females (R: 73-100 %) 5 minutes following the administration of MKB. Hemoglobin saturation was 81.1 ± 1.9% and 86.3 ± 1.1 % 5 minutes following MKB administration in males and females, respectively. Hemoglobin oxygen saturation, however, significantly increased over time in both males ($P = 0.0003$) and females ($P < 0.0001$) (Figure 3-5 and Figure 3-6). There was no change in respiratory rate over time in males (R: 4-76 breaths/minute) ($P = 0.13$) or females (R: 4-56 breaths/minute) ($P = 0.14$) (Figure 3-7 and Figure 3-8). Apneustic breathing was observed in 3 cats and periods of apnea (longer than 1 minute) were observed in 1 cat.

Oral mucus membrane color was also evaluated. Most cats contained pink membranes and were considered clinically acceptable. In addition, capillary refill time was evaluated in most cats and noted to be less than 2 seconds.

Rectal body temperature was measured at three separate times throughout the procedure: following MKB induction (start), at the completion of surgery (pre-reversal), and 5 minutes

following the reversal of medetomidine (post-reversal) (Figure 3-9). Rectal temperature was lower in females ($P < 0.0001$) at all three points in time and temperature decreased over time in both males and females ($P < 0.0001$). Start, pre-reversal, and post-reversal temperatures in males were 38.9 ± 0.6ºC, 38.2 ± 0.7ºC, 37.9 ± 0.7ºC, respectively. Start, pre-reversal, and post-reversal temperatures in females were 38.7 ± 0.5ºC, 36.8 ± 1.1ºC, 36.7 ± 1.2ºC, respectively. No male temperatures were below 34ºC (93.2ºF). One female had a temperature of 33.1ºC (91.4ºF) and was considered hypothermic.

Phase 2-Selected Dose Study: Physiological Variables before and after Reversal

Physiological parameters obtained following the completion of surgery (pre-reversal) and 5 minutes following the reversal of medetomidine (post-reversal) were compared. Male ($P < 0.0001$) and female ($P < 0.0001$) blood pressures changed significantly over the 5 minute reversal period, but did not change differently over the 5 minute reversal period ($P = 0.37$). Blood pressures in females ($P < 0.0001$) were less than blood pressures in males ($P < 0.0001$) both prior to the reversal of medetomidine and following the reversal of medetomidine (Figure 3-10). Blood pressure was significantly lower post-reversal ($P = 0.0003$) when compared to pre-reversal values ($P < 0.0001$) in both males and females.

Heart rate increased following the reversal of medetomidine in males ($P < 0.0001$) and females ($P < 0.0001$) when compared to immediate pre-reversal values (Figure 3-11). Pre-reversal heart rates in males were greater than in females ($P = 0.0006$), however, there was no difference between male and female heart rates following the reversal of medetomidine ($P = 0.25$).

Following the reversal of medetomidine, hemoglobin oxygen saturation significantly increased in males ($P = 0.0001$) and females ($P = 0.03$). Oxygen saturation value pre-reversal ($P < 0.0001$) and post-reversal ($P = 0.002$) were significantly lower in males when compared to

females at both time points (Figure 3-12). There were no differences in respiratory rates in males or females over time (P = 0.7).

Temperatures immediately following treatment with MKB were 38.9 ± 0.6ºC (102ºF ± 1.1) in males and 38.7 ± 0.5ºC (101.7 ± 0.9ºF) in females. Following the completion of surgery, temperatures dropped to 38.1 ± 0.7ºC (100.8 ± 1.3ºF) and 36.7 ± 1.1ºC (98.4 ± 1.9ºF) in males and females, respectively. Temperature was significantly lower (P < 0.0001) in males (37.9 ± 0.7ºC) (100.2 ± 1.2ºF), but not in females (36.6 ± 1.2ºC) (98.2ºF) (P = 0.16) following reversal. Females, however, had lower temperature values at both pre-reversal and post-reversal recordings (P < 0.0001) compared to males (Figure 3-13).

Phase 2-Selected Dose Study: Rescue Anesthesia (Isoflurane)

A total of 11 cats (2 males, 9 females) required supplemental anesthesia which constitutes approximately 11% of the study population. Females required supplemental anesthesia significantly more often (P = 0.02) than males. Rescue anesthesia in the 2 males was required at the time of induction, following a second dose of MKB that proved to be insufficient. Of the 9 females that required supplemental anesthesia (isoflurane) 5 of them required it after 45 minutes of successful anesthesia (timed from the initial injection).

Phase 2-Selected Dose Study: Quality of Recovery Scores

Quality of Recovery Scores (QRS) (Table 3-2) were assigned following the completion of surgery and subsequent reversal of medetomidine. Recovery times in males and females were 38.6 ± 38 minutes (M: 30 minutes; R: 5-207 minutes) and 40.6 ± 78.2 minutes (M: 22 minutes, R: 4-130 minutes) in males and females, respectively. Ninety-eight cats (51 males, 47 females) were scored for quality of recovery (QRS). Fifty-nine cats (28 males, 31 females) received a QRS of 3 (good) and 15 cats (12 males, 3 females) received a QRS of 2 (acceptable). The remaining 24 cats received a QRS of 1 (unacceptable), mainly due to prolonged recovery times

(n = 20). Only 4 cats (2 males, 2 females) were considered to have an unacceptable QRS as a result of overly excited or violent behavior. Approximately 75% of cats achieved an acceptable or good QRS.

Phase 2-Selected Dose Study: Side Effects

Under MKB anesthesia, apneustic breathing (holding of breath upon inspiration) was observed in male (n = 3), but not female cats. Additionally, rapid shallow breaths were observed in 6 anesthetized male cats. Eight males responded to the stimulus of castration surgery (tension on the spermatic cord) by hind limb movements, while spontaneous movement was observed in 3 females. Spontaneous movements were defined as movement that did not occur in response to a noxious stimulus; when it was noted, cats were checked by squeezing their toe and no response was elicited. Spontaneous movement included paw extension and ear flicking. Post-induction apnea (n = 1), post-operative retching (n = 1), and pawing at the mouth post-reversal (n = 6) were also observed.

Phase 3-Fixed Dose Study (0.7 mL): Animals

Based on an average calculated weight of 3 kg/cat and the selected dosing regime achieved in Phase 1 and tested in Phase 2, a fixed-dose of MKB was extrapolated and performed in Phase 3.

Two fixed volumes of MKB were evaluated in this study. Thirty-six cats (16 males, 20 females) were anesthetized using an MKB fixed dose volume of 0.7 mL (0.3 mg M, 30 mg K, 0.03 mg B). Seven cats were pregnant and one female was previously spayed.

The average weight for both male and female cats was 2.8 ± 0.6 kg. Based on the fixed dose, the average cat received an overdose of MKB (107 µg/kg M, 10.7 mg/ kg K, 10.7 µg/kg B). This represented a 7% increase in the total amount of medetomidine, ketamine, and buprenorphine given in excess. The average weight for cats < 3 kg (n = 25) was 2.4 ± 0.3 kg.

Based on the fixed dose volume, cats weighing less than 3 kg were overdosed (125µg/kg M, 12.5 mg/kg K, 12.5 µg/kg B) on average by 25% for MKB. The smallest cat weighed 1.8 kg. Based on the fixed dose, this cat was overdosed (166 µg/kg M, 16.6 mg/kg K, 16.6 µg/kg B) as well. This represents a 66% increase in the amount of MKB given in excess. Approximately 30% of cats (n = 11) weighed over 3.0 kg. The average weight for cats weighing > 3 kg was 3.56 ± 0.4 kg. Cats weighing over 3 kg were under dosed (84 µg/kg M, 8.42 mg/kg K, 8.42 µg/kg B) by -16% .

Seven cats (2 males, 5 females) needed an additional injection (0.1 mL; 0.043 mg M, 4.3 mg K, 0.0042 mg B) of MKB. Four of the 7 cats that required an additional injection of MKB weighed ≥ 3.0 kg. Similarly, 7 cats (2 males, 5 females) required an additional injection of the reversal agent atipamezole, including 3 cats (1 male, 2 females) that received a second dose of MKB. One female cat required a third injection of atipamezole approximately 2 hours following the initial atipamezole injection. That cat achieved sternal recumbency approximately 10 minutes following the third injection of atipamezole.

Phase 3-Fixed Dose Study (0.7 mL): Time Intervals

Time to lateral recumbency was 7 ± 5 minutes and 4 ± 3 minutes in males and females, respectively. Surgical duration was longer in females (43 ± 18 minutes) than in males (7 ± 4 minutes). Time from reversal to sternal recumbency was 31 ± 20 minutes in males and 31 ± 31 minutes in females. Total time recumbent was 64 ± 20 minutes and 117 ± 46 minutes in males and females, respectively.

Phase 3-Fixed Dose Study (0.7 mL): Side Effects

Apnea or severe respiratory depression was observed in several cats (n = 6). The weight of these cats (4 females, 2 males) was 2.9 ± 0.5 kg (M: 2.9 kg, R: 2.34-3.9 kg). One cat vomited following injection of MKB.

Phase 3-Fixed Dose Study (0.7 mL): Rescue Anesthesia

Thirteen cats (2 males, 11 females) required supplemental anesthesia. Of the 13 cats, 7 weighed more than 3.0 kg. Cats were further divided into those requiring inhaled supplemental anesthesia before (n = 7) 45 minutes of successful anesthesia and after (n = 6) 45 minutes of successful anesthesia. Approximately 36% of the total population receiving the fixed dose required supplemental anesthesia. In conclusion, this number was far greater than our initial goal of less than 10% of the population requiring rescue anesthesia, and therefore the volume of MKB was increased.

Phase 3-Fixed Dose Study (0.8 mL):

Thirty-four cats (9 males, 25 females) were anesthetized using a fixed MKB volume of 0.8 mL (0.344 mg M, 34.4 mg K, 0.034 mg B). Physiological parameters were not monitored and time intervals were not recorded.

Excessive requirements for MKB (n =3) or the need for supplemental isoflurane anesthesia (n = 9) were observed. Because cats were monitored as a whole, and not individually, this number may be higher as a result of missed data. Three cats vomited following the initial injection of MKB.

The initial injection of MKB was performed by an anesthetist unfamiliar with MKB and its volume in 28 cats. In 4 of the cats (14%), the anesthetist reported difficulty injecting a larger drug volume compared to the usual TKX protocol (0.25 mL). Two of the 4 cats with difficult injections required supplemental anesthesia.

Apnea or severe respiratory depression was observed in most cats and was more recurrent in cats anesthetized with MKB (fixed volume) in Phase 3, compared to those anesthetized in Phase 2 (weight-specific). Because individual medical records were not kept for each cat, an

exact number is not available, although it is believed that more than half of the cats anesthetized with the 0.8 mL fixed volume of MKB displayed clinical signs of respiratory distress.

Summary

Based on preliminary findings in Phase 1, a selected dosing regime was chosen to be used in 100 feral cats. In Phase 2, cats anesthetized with the selected protocol were closely monitored, recording physiological parameters and time intervals of interest throughout the surgical procedure. The selected dose in Phase 2 provided an anesthetic combination that offered acceptable physiological parameters and the potential for a fixed-volume derivative. In Phase 3, a calculated a fixed volume of MKB (0.7 mL) based upon an average calculated value for a feral cat's weight (3.0 kg) was found to provide inadequate anesthesia. Based on these observations, the decision was made to increase (0.8 mL) the fixed volume of MKB. The 0.8 mL of MKB was considered undesirable as a high percentage (30%) of cats required rescue anesthesia. In addition, apnea or respiratory depression was observed in most cats. There was no perioperative mortality for cats anesthetized with MKB.

In conclusion, the selected dose of MKB used is Phase 2 offered potential when used in a weight-specific manner, although failed to meet the goals set out at the start of the study when extrapolated to a fixed dose to be used in all cats, regardless of true weight. In addition, the adverse physiological effects observed with the fixed-dose results were less than desirable, making the studied fixed dose of MKB an unsuitable combination for use in feral cats of unknown weight.

Table 3-1. Dose-finding study groups

	n =	M	K	B	A	A
		µg/kg	mg/kg	µg/kg	(x M volume)	Route of Administration
Group 1	10	80	7.5	10	0.25	IM
Group 2	10	80	10	10	0.25	IM
Group 3	15	100	7.5	10	0.25	IM
Group 4	3	100	10	10	0.25	IM
Group 5	4	110	7.5	10	0.125	IM
Group 6	8	110	7.5	10	0.25	IM
Group 7	9	110	7.5	10	0.25	SC
Group 8	10	100	10	10	0.25	SC

Table 3-2. Quality of recovery scores

QRS	Scoring Guidelines
3	Good: Smooth Recovery, No Excitement, < 45 minutes Reversal to Sternal Time
2	Acceptable: Mild Excitement and/or <1hr Reversal to Sternal Time
1	Unacceptable: Severe Excitement, 2nd Reversal, and/or >1hr Reversal to Sternal Time

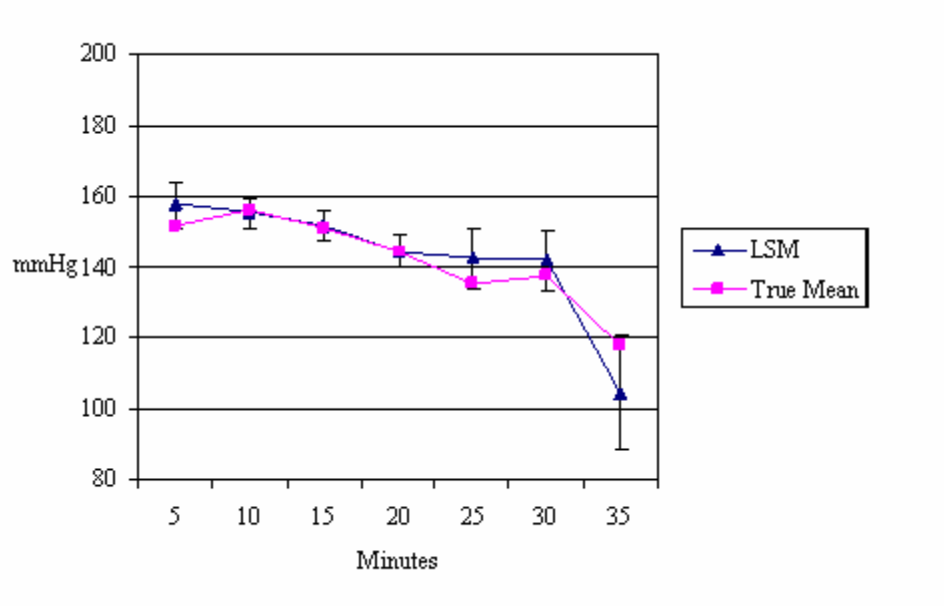

Figure 3-1. Blood pressure in male cats over time

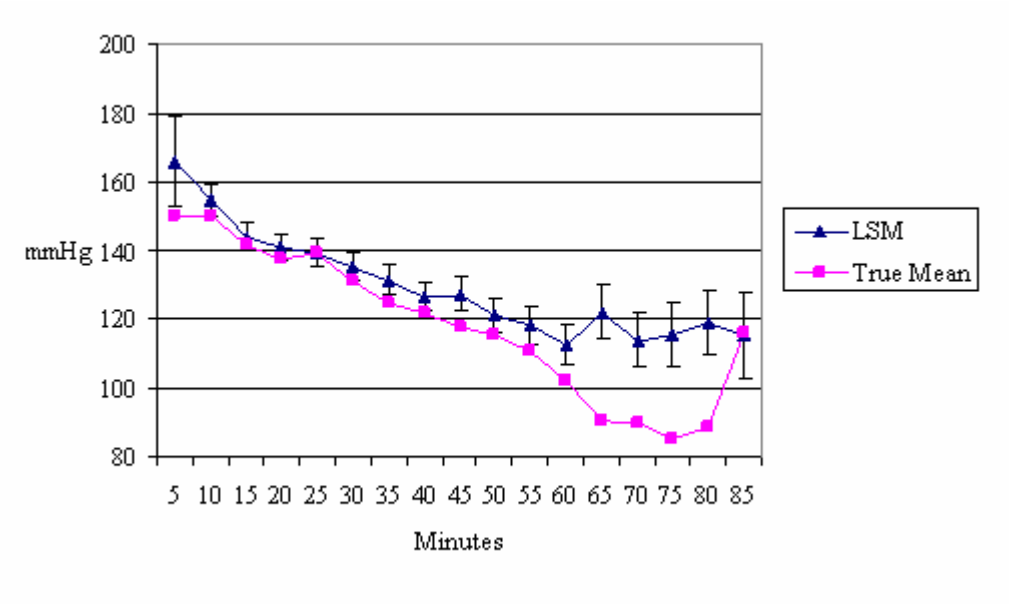

Figure 3-2. Blood pressure in female cats over time

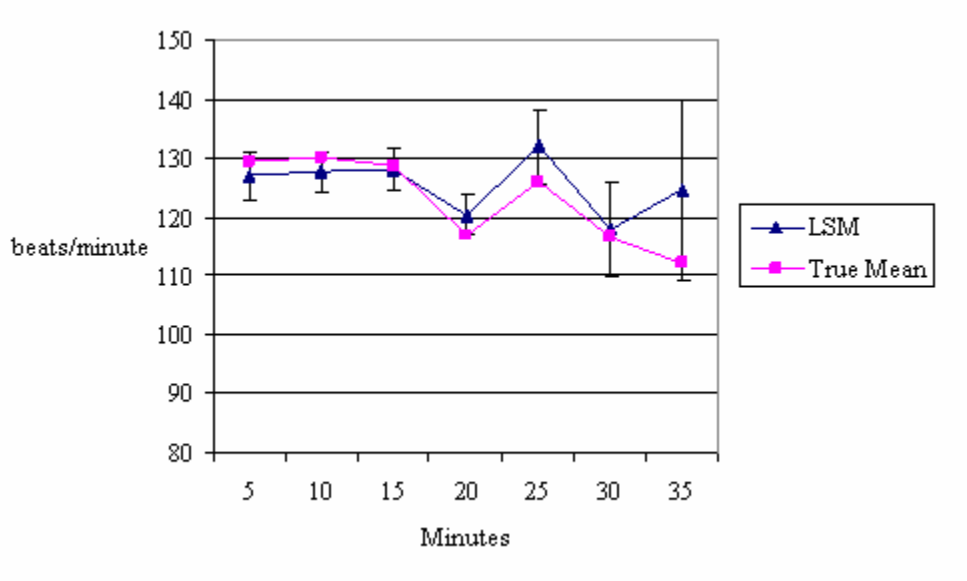

Figure 3-3. Heart rate in male cats over time

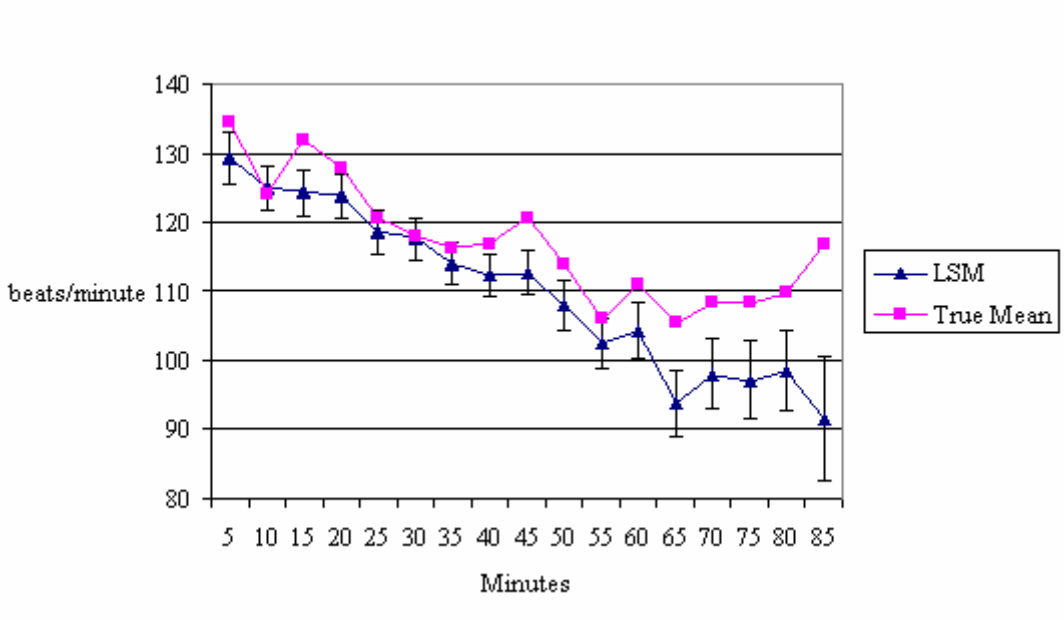

Figure 3-4. Heart rate in female cats over time

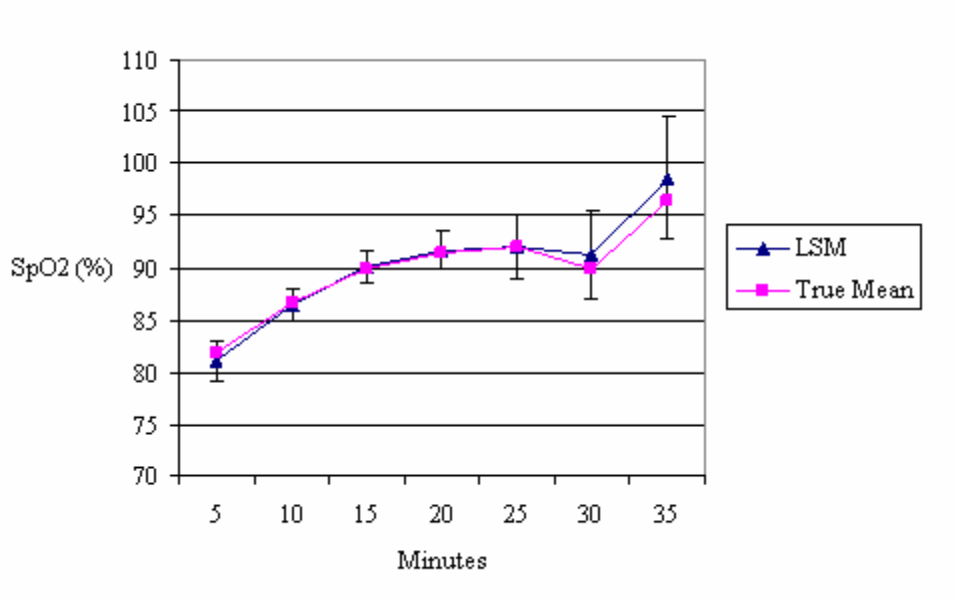

Figure 3-5. Sp O2 (%) in male cats over time

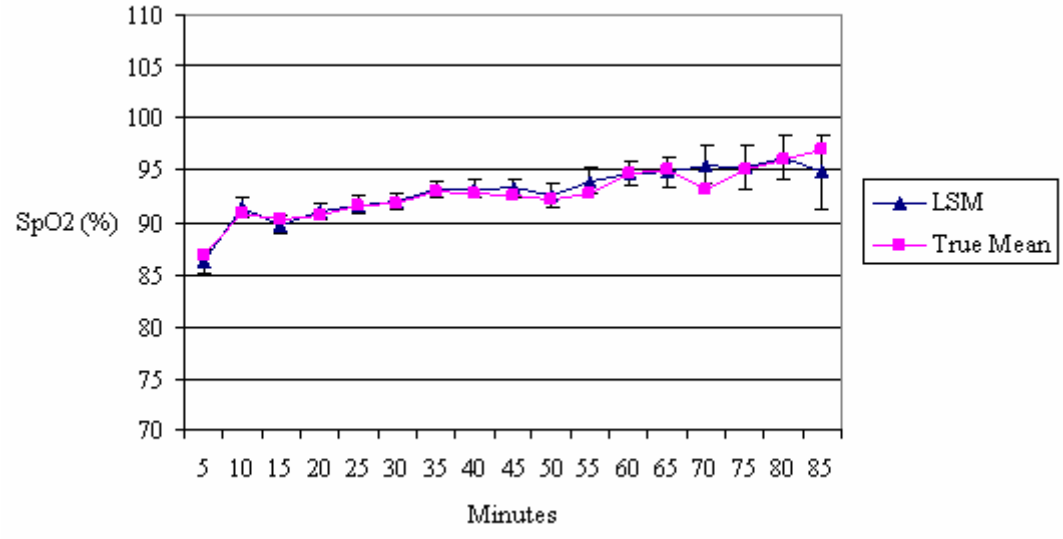

Figure 3-6. Sp O2 (%) in female cats over time

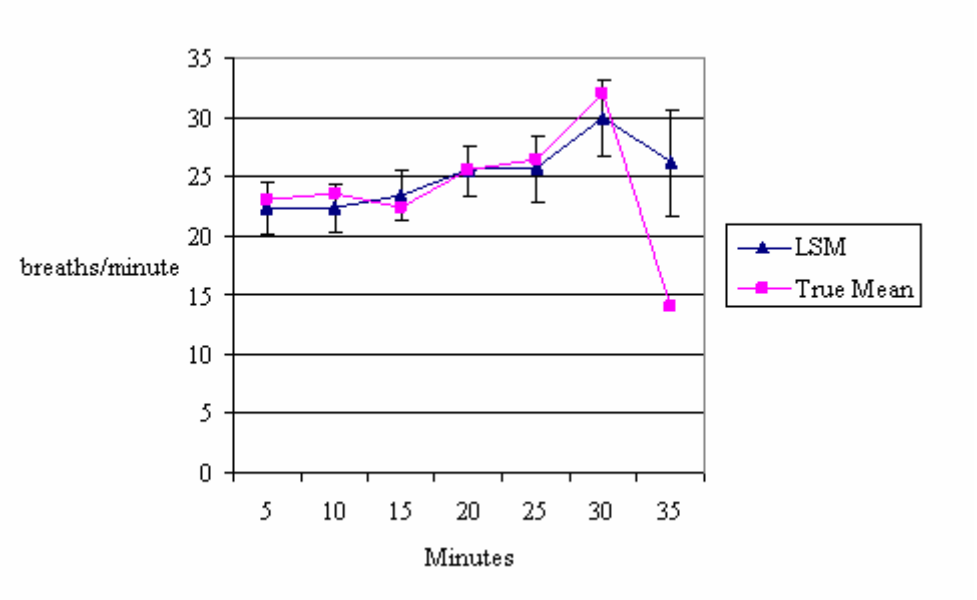

Figure 3-7. Respiratory rate in male cats over time

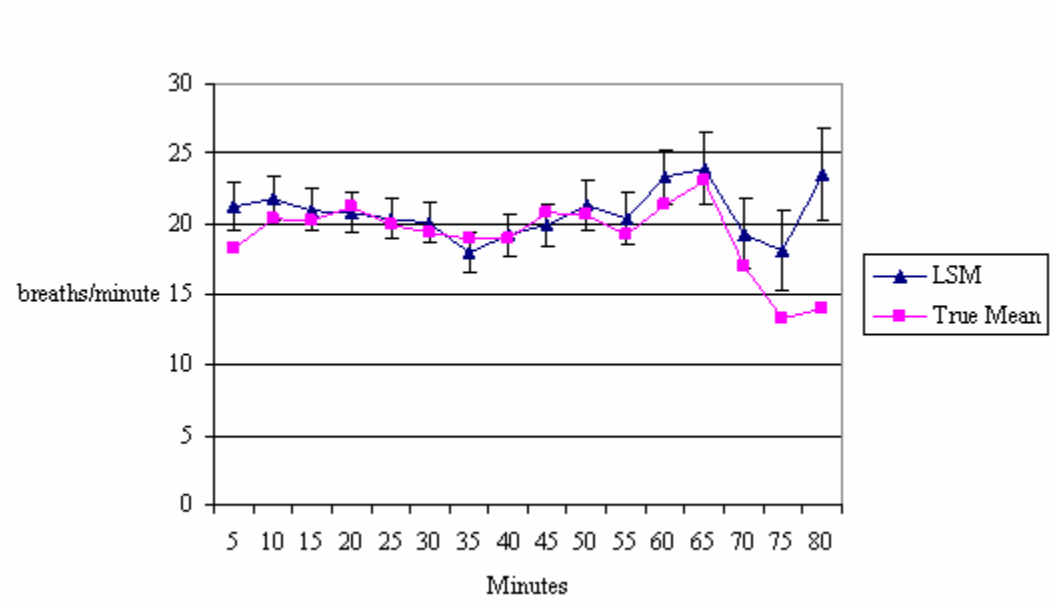

Figure 3-8. Respiratory rate in female cats over time

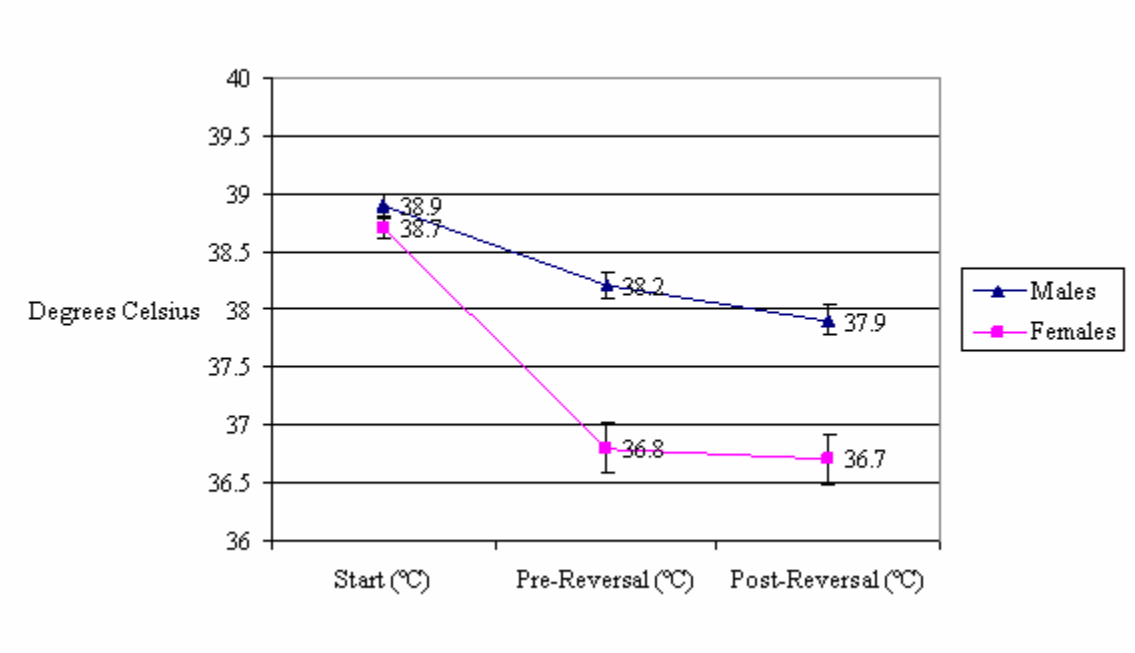

Figure 3-9. Temperature over time

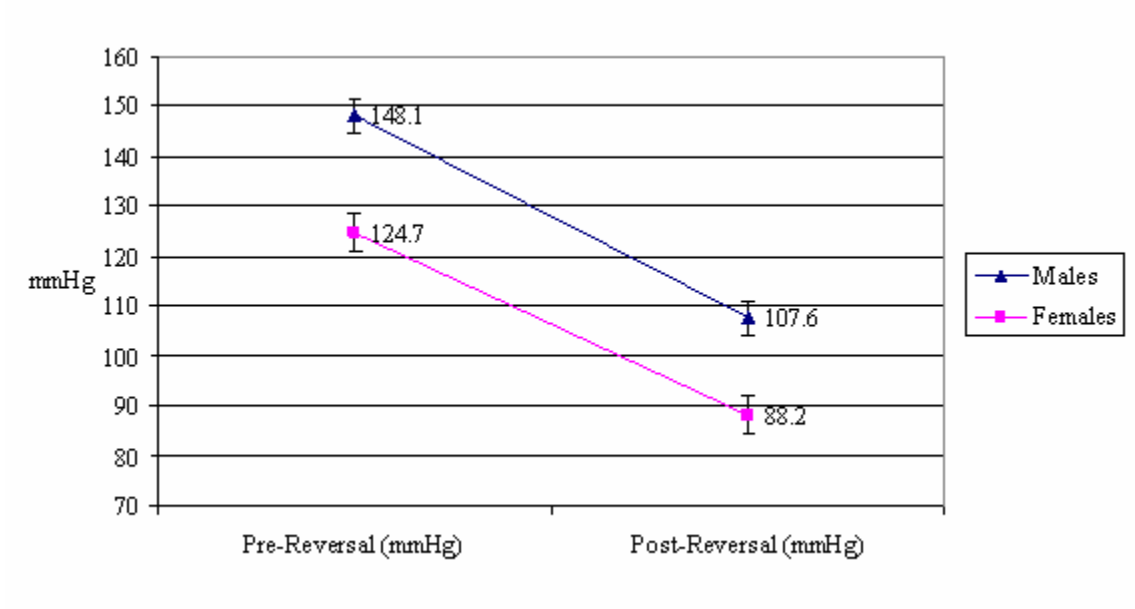

Figure 3-10. Blood pressure before and after reversal

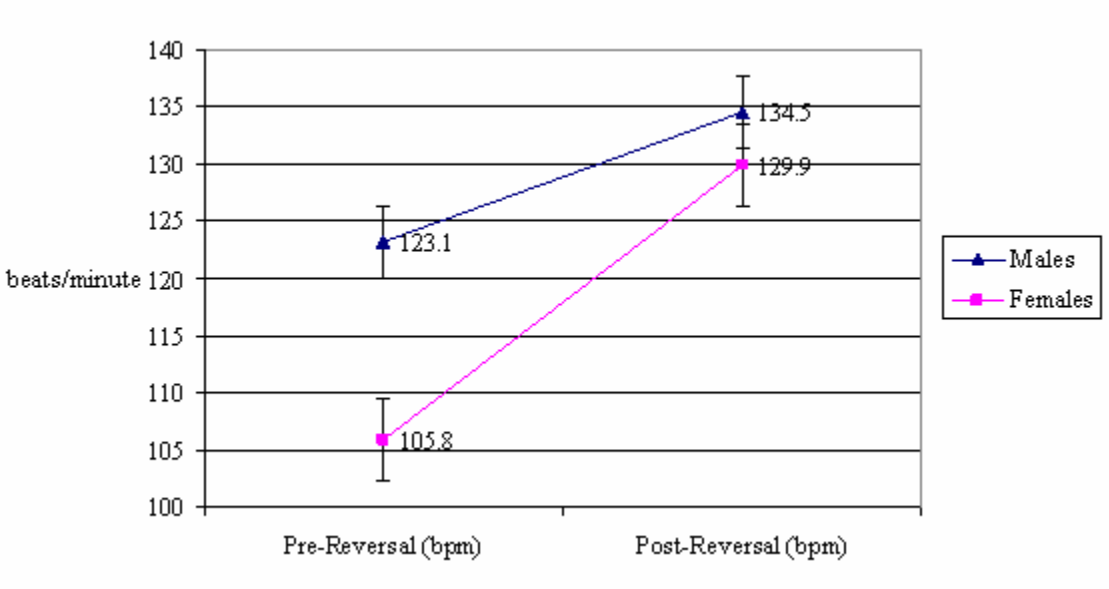

Figure 3-11. Heart rate before and after reversal

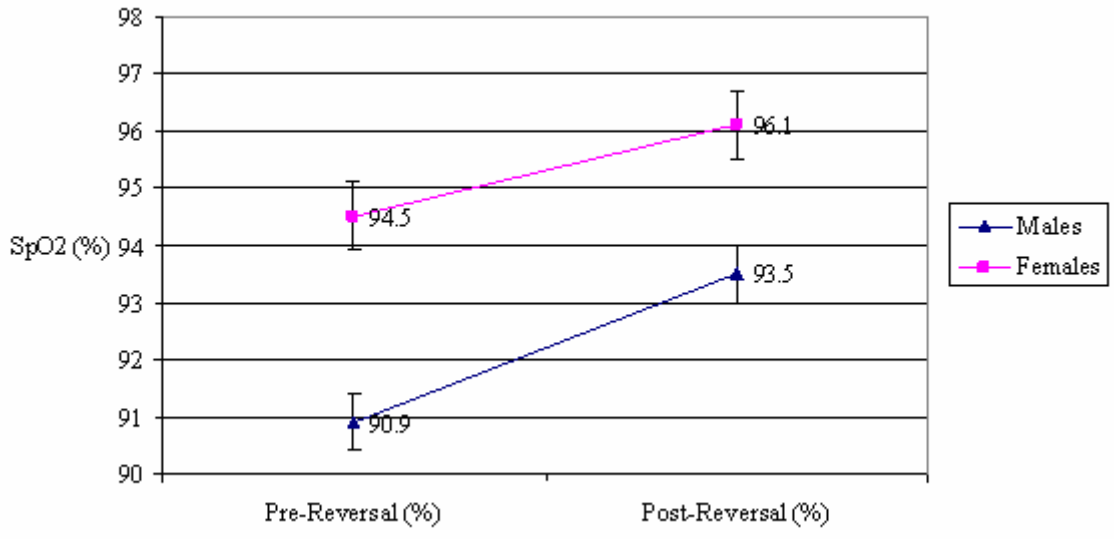

Figure 3-12. SpO2 (%) Before and after reversal

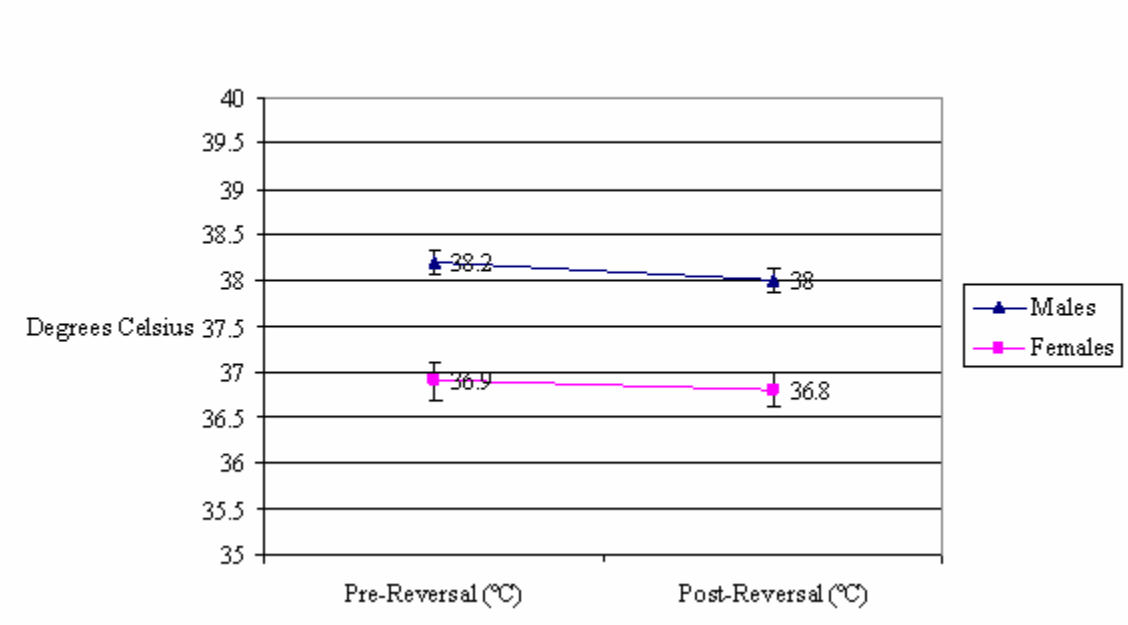

Figure 3-13. Temperature before and after reversal

CHAPTER 4
DISCUSSION

Feral cat sterilization clinics are an integral component of Trap-Neuter-Return programs. Such programs present a variety of challenges and rely heavily on the efficacy, predictability, and safety of an anesthetic regime. Not only must anesthesia protocols be adequate to perform all surgeries, they must also safely and effectively render cats unconscious while still in their traps. An anesthetic protocol for use in large feral cat clinics must be injectable, provide adequate duration of action, support acceptable physiological parameters, have a wide margin of safety, and allow rapid return to normal function. In addition, postoperative analgesia must be adequate. TKX, the current anesthetic regime used in Operation Catnip® , accommodates many of the demands associated with feral cat anesthesia, however, it also posses inadequacies. An attempt to improve the TKX protocol through the study of MKB was the purpose of this study. While MKB may compensate for some of the limitations associated with TKX, the doses of MKB used in this study exhibited its own shortcomings.

The preliminary trials of this study led to a MKB combination of considerable promise. In Phase 1 of this study, superior components from two trial groups (4 and 7) were combined. It was hypothesized that if the duration of action achieved in group 4 could be maintained while the recoveries could be slowed down and still provide acceptable recovery times, the overall product would provide adequate anesthesia and smoother recoveries, as seen in group 7. The anesthetic and physiological effects of the selected dose were considered acceptable and even resolved some of the limitations associated with TKX. However, when tested in a high-volume setting, the MKB fixed volume offered less than desirable anesthetic effects; these including the frequent need for additional MKB injections, rescue anesthesia with isoflurane gas, and repeated reversal injections. In addition, apnea and respiratory depression were more pronounced and occurred

with a higher incidence in cats that received the fixed volume dose of MKB compared to those dosed in a weight specific manor in Phase 2.

One study reported anesthetic-related deaths to be 0.24% (0.21-0.27%) in cats (n = 79, 178) sedated or anesthetized for a variety of surgical procedures using a wide range of drug combinations (Brodbelt 2006). None of the cats (n =240) in this study died prior to being released back to their colonies. The absence of perioperative mortality is thought to contribute to a wide margin of safety associated with the use of MKB. The MKB protocol used in this study was considered relatively easy to administer, although the large injection volume may have compromised the ability to accurately deliver full doses in some cats. Approximately 11 % of cats in Phase 2 and 13% of cats in Phase 3 required a supplemental injection of MKB. This may have been the result of a large injection volume preventing a complete and accurate injection or perhaps, more simply, the administration of a dose insufficient at providing adequate anesthesia. Both of these factors may have contributed to the need for supplemental anesthesia. Female cats had a greater need for rescue anesthesia compared to males. This is likely the result of lengthier preparation and surgical procedures when compared to males.

Hemoglobin desaturation, particularly in the first five minutes following MKB administration, was common in both male and female cats; however, it was more apparent in male cats. One male cat was observed to report an oxygen saturation value of 36 % following MKB administration. Respiratory depression and periods of apnea (temporary suspension in breathing for more than 1 minute) were consistent with previous studies of similar medetomidine and ketamine combinations (80µg/kg M; 10 mg/kg K), in which apnea was observed in 8 out of 10 cats (Verstegen et al. 1989; Verstegen et al. 1991a).

Low SpO_2 values may be caused by anything that decreases the delivery of oxygen to the tissues including hypoxemia, vasoconstriction, or low cardiac output (Thurmon et al. 1996). Cardiac output (CO) is defined as the quantity of blood pumped by the heart each minute and varies dependent upon heart rate (HR) and stroke volume (SV) (Berne et al. 2004). The relationship between cardiac output and heart rate is linear (CO = HR x SV). Low SpO_2 values may be the result of patient factors or detection limitations. Because pulse oximetry relies on peripheral blood flow, the accuracy of readings may be affected as a result of the vasoconstriction or decreased heart rate observed following the administration of medetomidine (Haskins 1996). The observed hemoglobin desaturation, especially as seen following the injection of MKB, may have been the result of equipment inaccuracies or simply, the known depressant cardiovascular effects of medetomidine. Cats were not intubated in this study and spontaneously breathed room air. This was likely a contributing factor to low oxygen saturation levels seen in cats anesthetized with both TKX and MKB. A study assessing a combination of MKB with a significantly lower dose of medetomidine (40 μg/kg) observed an overall SpO_2 value of 94 ± 4% (Cistola et al 2002). A higher dose of medetomidine, such as the amount used in this study, may have affected SpO_2 values as a result of increased vasoconstriction. An increase in vasoconstriction may have contributed to either (1) a decrease in oxygen delivery to tissues or (2) a decrease in the accuracy of pulse oximetry readings. SpO_2 values were observed to increase over time in MKB treated cats. It is hypothesized that the increase in SpO_2 values over time was a result of the metabolism of medetomidine, lowering plasma concentration values, and exhibiting less total effect (vasoconstriction). A steady decrease in vasoconstriction may have contributed to increased oxygen delivery, resulting in higher SpO_2 values over time. Alternatively, decreased vasoconstriction may have provided more accurate pulse oximetry

readings in which earlier readings, when medetomidine plasma concentrations were higher, would be considered less precise. The true cause for the observed increase in SpO_2 values is unknown. Once the amount of deoxygenated hemoglobin exceeds 5 g/100 mL, the blood changes from a red color to a blue color (cyanosis) (Thurmon et al. 1996). Despite low pulse oximetry readings, oral mucous membrane color remained pink and was clinically acceptable in most cats. Pale mucous membranes were noted and hypothesized to be the result of drug-induced vasoconstriction following the administration of medetomidine. While low oxygen saturation is preventable and easily treated by providing supplemental oxygen, it is not feasible to administer to all cats due to the number of cats needing simultaneous administration and equipment limitations. Additionally, the challenge of identifying cats at risk of hypoxia and supplementing them as needed, should not be underestimated when many cats are anesthetized simultaneously. Hypoxia may result in abnormal organ function and/or cellular damage (Thurmon et al. 1996). The exact repercussions of low SpO_2 levels in cats anesthetized with MKB are unknown and may result in injury not apparent in the immediate post-operative period.

Normal heart rates in cats range between 145 and 200 beats per minute (Muir et al 2000). Following the administration of MKB, heart rate was significantly lower compared to normal values, although true baseline values of conscious animals could not be determined in this study. Ninety-one percent of cats in this study were observed to have lower than normal heart rate values. In one study, heart rate in cats administered solely medetomidine (80 μg/kg-110 μg/kg) decreased to about 50% of starting values within 15-30 minutes (Vaha-Vahe 1989a). While baseline values were not obtained in this study, it is believed that the measured values following induction were more than 50% of their starting values as a result of the cardiovascular stimulating effects of ketamine. In combination, it is thought that the centrally stimulating effects

of ketamine counteract the depressive effects of alpha$_2$ agonist compounds (Verstegen et al. 1989). In this study, heart rate was not observed to change in males over time, but was considered below normal throughout the duration of anesthesia. Female heart rates, on the other hand, were observed to continually decrease over time to below normal values under anesthesia. Decreased heart rate is believed to be the result of the bradycardic effects of medetomidine; however, one study concluded that medetomidine in cats did not conclusively demonstrate specific bradycardic action as a lowered state of vigilance could, in itself, decrease heart rate (Stenberg et al. 1987). The observed bradycardia was believed to be a direct result of medetomidine as these effects were reversed following the administration of atipamezole. While the results of this study exhibited below normal heart rate values in anesthetized cats, one study conversely found a similar dose of medetomidine and ketamine (80 μg/kg M; 10 mg/kg K), without buprenorphine, to result in tachycardia between 10 and 30 minutes following injection. Buprenorphine has been shown to decrease both blood pressure and heart rate in cats, suggesting buprenorphine may have had an affect on heart rate in this study (Benson & Tranquilli 1992). It is hypothesized that the analgesic properties of burpenorphine may have prevented an increase in heart rate and blood pressure by blocking nociceptive input in response to surgical stimulus. Some clinicians prefer to preemptively use anticholinergic drugs, such as atropine, in patients administered alpha$_2$-adrenergic drugs, however, others disagree (Paddleford & Harvey 1999). They argue that (1) the bradycardia is a normal physiological response to vasoconstriction and increased blood pressure, (2) anticholinergic drugs may increase myocardial work and oxygen consumption due to an increased heart rate, and (3) it may not be physiologically appropriate to have an increased heart rate in the face of severe vasoconstriction (Paddleford & Harvey 1999).

Normal systolic blood pressures in cats range between 110 and 160 mm Hg (Muir et al 2000). Normotension was observed following the administration of MKB and throughout the duration of anesthesia in most cats. However, twenty-three cats were observed to have systolic blood pressures rise above 160 mm Hg at least once following treatment with MKB, while 7 cats were observed to fall below 110 mm Hg at least once following treatment with MKB. Whether or not blood pressure was related to physiological stress is unknown, however, blood pressure was not observed to rise consistently in response to surgical stimulation. In males, a relationship between blood pressure and time could not be made with > 95 % confidence. A Type II statistical error is suspected as this observation may be the result of missing data points (at 5, 10, and 15 minutes only 10%, 60%, and 64% of data were available, respectively). Actual blood pressures may be higher than reported as the technique used in this study may underestimate systolic blood pressure by approximately 15% in cats (Grandy et al. 1992). In addition, there are no published reports assessing the accuracy of the Doppler technique when systolic blood pressure is in excess of 200 mm Hg (Dobromylskyj 1996). Values did not exceed 200 mm Hg in this study, but some values were close (195 mm Hg). Blood pressures significantly decreased in both males and females following the reversal of medetomidine. It is hypothesized that reversing the vasconstrictive effects of medetomidine resulted in a decrease in vascular resistance, and therefore a decrease in blood pressure.

Neither blood pressure nor heart rate was observed to increase at any time during the surgical procedure. Similarly, in another study, a comparable combination , although using a lesser dose of medetomidine (80 μg/kg), with ketamine (10 mg/kg) reported no reflex responses to traction of the ovarian pedicles (Verstegen et al. 1989). Based on these observations in Phase

2, it is assumed that anesthesia was adequate in the majority of cats because changes suggestive of response to nociceptive stimuli, as measured by physiological variables, were not detected.

Some opioids have been associated with an increase in body temperature in cats (Robertson & Taylor 2004). Alternatively, opioids have actually been found to lower the threshold for shivering, a thermoregulatory event that is meant to increase heat production, which can further contribute to heat loss (Posner 2006). Post-anesthetic rectal temperatures were not observed to rise significantly following buprenorphine administration in cats in a previous study (Niedfeldt & Robertson 2006). While temperatures were only collected during times of lateral recumbency in this study, no indication of measured hyperthermia (temperatures ≥ 103 ºF) or clinical evidence (panting) was noted. In fact, hypothermia was observed. The effects of anesthesia on thermoregulation are multifactorial and include the loss of normal behavioral responses and an altering of normal thermoregulatory responses (Posner 2006). Temperatures in TKX treated cats (38.0 ± 0.8ºC (100 ± 1.4ºF) in males and 36.6 ± 0.8ºC (97.8 ± 1.4ºF) in females) and MKB treated cats (38.1 ± 0.7ºC (100.7 ± 1.3ºF) in males and 36.7 ± 1.1ºC (98.3 ± 2ºF) in females) were similar at the time of reversal (Cistola et al. 2004). Loss of core body temperature occurs in three phases, the first of which is due to the redistribution of heat from the core to the periphery, where it is then easily lost (Posner 2006). Higher body temperatures found in MKB cats may be attributed to the vasoconstrictive properties of medetomidine as arteriovenous vasculature present in the skin contribute to thermoregulation (Posner 2006). The subsequent vasoconstriction of these shunts likely prevents heat loss from the core (Posner 2006). Core temperatures may actually have been lower than measured, as rectal temperature tends to lag behind changes in core body temperature (Posner 2006). Nevertheless, even mild hypothermia can substantially prolong recovery times by decreasing hepatic and renal blood

flow, therefore slowing the metabolism of anesthetic drugs (Posner 2006). Medetomidine elimination appears to rely heavily on biotransformation and is likely regulated by hepatic blood flow, thus, maintenance of these metabolic processes is essential (Salonen 1989). The application of external heat sources during surgery and recovery may reduce the severity of prolonged recoveries and decrease recovery times; however, a logistical barrier arises when high numbers of cats are undergoing surgery and recovery, simultaneously. In addition, the ability to apply external heat sources from outside the trap is limited which will likely compromise effectiveness.

No observations of licking or biting at incision sites were noted. In addition, body posture and overall demeanor appeared to be comfortable and relaxed in most cats.

Immediate post-operative analgesia was assumed to be adequate as several studies have noted the efficacy of buprenorphine up to 6 hours (Pascoe 2000; Robertson et al. 2005). There are no validated methods for pain assessment in cats, which makes evaluation and treatment difficult, however, pain can be managed on the basis of previous experience and intuition (Cambridge et al. 2000).

Overall, the recovery times observed with MKB were shorter compared to TKX with reversal to sternal recumbency times of 72 ± 42 minutes in cats administered TKX and 34 ± 33 minutes in cats administered MKB in Phase 2 of this study (Cistola et al. 2004). Atipamezole administration appeared to completely reverse the effects of medetomidine, as evident by the significant increase in heart rate and decrease in blood pressure following reversal. Fourteen cats required a second injection of the reversal agent. In dogs, the manufacturer recommends giving the same volume of atipamezole as medetomidine (5 mg/ml A: 1 mg/ml M) to reverse its effects (2007). In this study, a quarter of the volume of medetomidine was administered. This dose was sufficient in most cats; however, approximately 14% of the cats required additional reversal

agent injections. Perhaps a larger volume of atipamezole would have prevented the need for a second reversal, although the side effects associated with an increased volume of atipamezole are unknown and should be considered. An unusually fast recovery, as observed in Phase 1 of this study, is unfavorable and could result with a larger dose of atipamezole. Relapse to sedation is not believed to be the cause for the need for second reversal injections, as the half-life of atipamezole is twice that of medetomidine (Paddleford & Harvey 1999). Interestingly, there was no relationship between cats that received supplemental doses of MKB and cats that required an additional reversal agent injection. This may suggest that the initial atipamezole-medetomidine ratio was inadequate at providing acceptable recoveries in some cats. An atipamezole-medetomidine dose ratio (in mg) of 4:1 or 8:1 resulted in speedier return to normal vigilance patterns than a 2:1 ratio in cats receiving only medetomidine (Stenberg et al. 1993). However, one study that combined ketamine with medetomidine recommended a dose ratio of 2.5:1 as it prevents the undesirable tachycardia and CNS stimulation seen with higher doses of atipamezole (Verstegen et al. 1991b).

The selected dose in Phase 2 provided adequate duration of action in most cats. The number of cats requiring isoflurane supplementation was considered clinically acceptable. Approximately 11% of our study population required supplemental anesthesia. This was close to our initially set goal of less than 10% of the population

requiring rescue anesthesia and the decision was made to initiate a fixed volume.

Both fixed dose volumes (0.7 mL and 0.8 mL) of MKB were found to be inefficient at providing acceptable surgical anesthesia. Additionally, apnea and severe respiratory depression were observed in most cats. In Phase 3, twenty-one cats (30%) required inhaled supplemental anesthesia at some point throughout the surgical procedure. It is hypothesized that some of these

cats may have weighed > 3.0 kg and that individual anesthetic requirements were simply unmet. Furthermore, the 0.8 mL fixed dose was the first time anesthetists, other than those directly associated with this study, used the MKB protocol. In 14% of the injections, the anesthetist reported difficulty injecting the larger drug volume compared to the usual TKX protocol (.25 mL). Half of the cats with noted difficult injections required supplemental anesthesia. It is hypothesized that these cats did not receive the full dose of MKB as they required supplemental anesthesia shortly after the initial MKB injection.

For those weighing ≤ 3.0 kg, it remains unclear as to the differences observed in the fixed dose of MKB compared to the selected dose studied in Phase 2. Data on the number of cats anesthetized with TKX that require supplemental anesthesia are not available; but, this information would be useful in future studies to compare the failure rates between the two protocols. Regardless, the frequency of supplemental anesthesia and obvious physiological depressant effects observed with the fixed dose of MKB are considered unacceptable and this protocol is not recommended. If the individual weight of a feral cat could be verified prior to an anesthesia regime, it is believed that a higher rate of success and usefulness would be observed with the current combination of MKB. However, this would require increased time and labor considerations.

The studied combination of MKB appears to offer several advantages. Medetomidine potentiates the effects of ketamine and the disadvantages associated with the two drugs may be offset by one another. Medetomidine makes up for the poor muscle relaxing and analgesic effects of ketamine, while the cardiovascular stimulating effects of ketamine compensate for the bradycardic tendencies of medetomidine (Verstegen et al. 1989). The use of the medetomidine's specific antagonist, atipamezole, allows for the complete and rapid reversal of the depressant

effects exhibited by medetomidine. In addition, the combination of medetomidine and atipamezole may limit undesirable effects of less selective or less specific agonist/antagonist combinations.

In conclusion, MKB appears to fulfill many of the demanding requirements necessary for feral cat anesthesia when true weight is considered. In Phase 2, MKB provided a completely injectable regime that was predictable, offered an acceptable duration of action, and provided a rapid return to normal function. The major shortcoming of MKB in this study was the inability to determine an effective fixed dose volume to be used in all cats, regardless of true weight. Additionally, based on the high incidence of severe respiratory depression observed in cats administered the fixed volume, it cannot be recommended. Moreover, it was determined that increasing the fixed dose volume further would be without regard for the safety of the animal. Although this study failed to produce an effective MKB fixed dose to be used in high volume sterilization clinics, it is believed that MKB offers considerable promise in feral cat anesthesia.

Slight changes in Operation Catnip® may enhance the effectiveness of MKB and may be of interest in further investigations. It is believed that the MKB combination in this study would be more effective if given in a weight-specific manor. The addition of a weight station would enable a dose to be calculated for each individual cat, eliminating the need for a universal fixed volume. Several categories of fixed volumes designed to accommodate weight classes (0-1 kg, 1-2 kg, 2-3 kg, and > 3 kg) may prove to be beneficial. The addition of a weight station would, however, add additional labor and time constraints. If an MKB dosing regime does not take weight into consideration, it is possible that MKB will never be considered appropriate for use in high-volume clinics. However, the studied combination of MKB may be suitable for smaller clinics with fewer surgeries performed and shorter duration of action requirements.

There are approximately 1,440 combinations of MKB (based on relative doses of each drug used in cats). This study is believed to have narrowed the findings for an effective combination of MKB, although an exact fixed dose was not accomplished. Further research is required to determine whether or not a specific combination of MKB has the ability to produce a fixed volume that fulfills the unique demands of feral cat anesthesia and subsequent sterilization procedures.

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BIOGRAPHICAL SKETCH

Kelly Ann Meyer was born on October 30, 1981 in Chicago, Illinois, to Paula and Edward Meyer. An only child, she moved to Florida shortly after being born. Kelly graduated from Seminole High School in Seminole, Florida, in 2000. In April 2005, she earned her B.S. from the University of Florida in animal sciences and began working toward her M.S. degree shortly thereafter.

Kelly's passion has always been animals and their well-being. She continues to pursue her goal of becoming a Doctor of Veterinary Medicine.