PROSPECTIVE ECONOMIC EVALUATION ALONGSIDE THE NASAL INTERMITTENT VENTILATION TRIAL

By

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To my husband, children and parents

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LIST OF ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
iCER	Incremental cost effectiveness ratio
nCPAP	Nasal continuous positive airway pressure
NEC	Necrotizing enterocolitis
NIPPV	Non-invasive positive pressure ventilation or nasal intermittent positive pressure ventilation
PDA	Patent ductus arteriosis
PMA	Post menstrual age
pRBC	Packed red blood cell
ROP	Retinopathy of prematurity

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Non-invasive ventilation strategies are commonly used as a means of avoiding intubation and its consequences in premature infants. Recently, a large randomized controlled trial compared the use of nasal continuous positive airway pressure (nCPAP) to nasal intermittent positive pressure ventilation (NIPPV) as a method to reduce bronchopulmonary dysplasia (BPD).[1] While no significant difference in the primary outcome was found, the economic implication of using one strategy over the other needed evaluation. We sought to determine the cost effectiveness of nCPAP compared to NIPPV for improvement in survival without BPD in infants with birth-weights less than 1,000 grams.

Using patient level data from the clinical trial, we undertook an economic evaluation. We measured costs from a third party payer perspective, with a time horizon through discharge, death or 44 weeks post-menstrual age. After directly comparing costs between treatment arms, we performed a formal economic evaluation using the primary outcome of the trial, survival without BPD.

The mean cost of hospitalization per infant was higher in the NIPPV group, $205,309, compared to the nCPAP group, $196,836. Similarly, there was a 69%

probability that NIPPV is both more expensive and less effective than nCPAP and only a 2.4% probability that it is less costly and more effective.

Although clinically equal in the trial, formal economic evaluation reveals that using NIPPV is an economically unfavorable strategy. This confirms that the resource implications of clinical therapies may be independent of the primary biological outcome of a trial, and should be routinely included in assessments of therapies.

CHAPTER 1
BACKGROUND

Ventilation of Premature Infants

In the United States 11.5% of infants are born prematurely, leading to an estimated societal cost of over $26 billion.[2,3] Premature infants are classified as those delivered prior to 37 weeks gestation. Given their early entry, these infants are at risk of numerous complications and require intensive care for an extended period of time. Respiratory difficulties are among the most common morbidities faced in this population and many premature infants require respiratory support during their first days to weeks of life. For the smallest infants, the mainstay of treatment is invasive ventilation such as intubation and mechanical ventilation.[4] However, the use of invasive ventilation increases lung injury, and in some cases, causes bronchopulmonary dysplasia (BPD), or even death.[5]

Bronchopulmonary dysplasia, a chronic lung disease characterized by premature infants who remain oxygen dependent at 36 weeks corrected gestational age, occurs in approximately 22% of premature infants.[6] The degree of injury and risk of death are directly related to the duration and intensity of the invasive ventilation. Consequently, neonatologists are searching for a way to decrease the amount of time premature infants spend on invasive assisted ventilation in order to decrease lung injury and potentially BPD as well as improve survival.

Non-Invasive Ventilation

Nasal continuous positive pressure (nCPAP) is one means to avoid invasive ventilation. nCPAP provides positive pressure by way of nasal mask or prongs to stent open the upper airway. Many studies have shown the use of nCPAP decreases the

need for, and risks associated with, invasive ventilation.[7–9] Therefore, neonatologists use nCPAP as a first line therapy to avoid intubation or as a bridge to discontinue use of invasive support.

Nasal intermittent positive pressure ventilation (NIPPV) provides the same continuous positive pressure as nCPAP with the addition of an intermittent peak inspiratory pressure. As a result, neonatologists have proposed NIPPV as an alternative to nCPAP, hoping it confers greater benefit than nCPAP. Studies completed thus far comparing nCPAP to NIPPV have mixed results.[10] Kirpalani, et al. undertook a large international, multi-center, randomized control trial testing the use of nCPAP vs. NIPPV to prevent BPD or death in infants with birth weights less than 1,000 grams.[1] In the study, the composite outcome of BPD or death was not significantly different between the groups (38.4% vs. 36.7%; $p = 0.56$).[1] This study is the largest to date with over 1,000 infants enrolled and raises the question of which non-invasive ventilation strategy to use if both are equally efficacious.

Even though the two strategies of non-invasive ventilation (nCPAP and NIPPV) may be equally efficacious, their use may have differing costs. Therefore, cost may help neonatologists decide which treatment to use in premature infants. Consequently, we undertook an economic evaluation of the NIPPV trial to determine the cost-effectiveness of the two therapies.

CHAPTER 2
METHODS

Overview of the NIPPV Trial

The NIPPV study group lead by Kirapalani undertook a trial comparing noninvasive ventilation strategies in preterm infants. Infants less than 30 weeks gestation and less than 1,000g birth weight who required non-invasive ventilation were enrolled from 36 sites in 10 countries including the United States, Canada, the United Kingdom, Ireland, Netherlands, Sweden, Belgium, Austria, Singapore, and Qatar. In total, 1009 patients were randomized to receive either nCPAP or NIPPV at the time they needed non-invasive respiratory support within the first 28 days of life. The primary outcome was reported as a composite of death or bronchopulmonary dysplasia (BPD) as defined by a supplemental oxygen requirement at 36 weeks post-menstrual age (PMA) or a positive oxygen reduction test. Infants were followed until 44 weeks PMA, discharge or death, whichever occurred first. The study had 80% power to determine a 20% relative risk reduction in the primary outcome.

Framing of the Economic Evaluation

The prospectively planned economic evaluation was completed alongside the clinical trial using individual, patient-level data. The third-party payer perspective was used with time horizon through discharge, death or 44 weeks PMA. This was equivalent to the endpoint used in the NIPPV trial. Either United States costs or Canadian costs were applied according to the payer system that mostly closely matched that of the local medical system. Conversion to 2013 currency was completed using country specific health consumer price indices.[12–14] Finally, country specific currency was converted to US dollars similar to previous evaluations.[11,15,16]

Resource Utilization, Costs and Effects

Resource utilization data was collected from the case report forms provided from the NIPPV trial. First, from these forms, the total number of hospital days and acuity was determined. Patients were assigned an acuity based on respiratory support. Next, using the acuity, a per diem rate for hospital services was assigned. Hospital per diem costs included nursing and other support staff time, diagnostic procedures, nutrition (both enteral and parenteral), respiratory support, hospital overhead and equipment. Physician per diem costs covered physician time and services. These were calculated in a similar manner as hospital per diem fees by classification of care day by acuity. Acuity for physician fees was based on respiratory support, age and route of nutrition. Per diem costs used in the analysis are seen in Table 2-1. Using the combination of costs for physician per diem and hospital per diem a total cost for hospitalization was determined for each patient as well as an average for each arm of the study (NIPPV vs. nCPAP).

The primary outcome from the clinical trial was used to calculate the incremental cost-effectiveness ratio. The inverse of the published outcome, survival without BPD at 36 weeks corrected gestational age was used as the measure of effectiveness for the evaluation.

Statistical Considerations

First, we completed a direct cost comparison by calculating the mean costs for each treatment arm as outlined above. Second, we calculated the incremental cost-effectiveness ratio (iCER) as the difference in mean costs between the two study arms, divided by the difference in mean effect between the two study arms. We assessed uncertainty using deterministic and probabilistic sensitivity analyses, including

nonparametric bootstrapping. To accomplish this, simulated repetitions of the data set were obtained, and mean costs, mean effects and the iCER was calculated. A total of 1,000 simulated repetitions were performed.[17–19]

Table 2-1. Costs for hospital and physician per diem[20,21]

Per diem	Country	Respiratory support	Day of life	Cost in 2013 US dollars
Hospital per diem	United States	Mechanical ventilation	All	$2,499.78
		nCPAP or NIPPV	All	$2,132.24
		Nasal cannula	All	$962.91
		Room air	All	$825.71
	Canada	Mechanical ventilation	All	$2,831.75
		nCPAP or NIPPV	All	$2,831.75
		Nasal cannula	All	$1,968.59
		Room air	All	$1,968.59
Physician per diem	United States	Mechanical ventilation	1	$934.27
		nCPAP or NIPPV	1	$934.27
		Nasal cannula	1	$342.27
		Room air	1	$342.27
		Mechanical ventilation	2-28	$384.80
		nCPAP or NIPPV	2-28	$384.80
		Nasal cannula and PMA less than or equal to 31 weeks	2-28	$137.45
		Room air and PMA less than or equal to 31 weeks	2-28	$137.45
		Nasal cannula and PMA 31 1/7 - 35 weeks	2-28	$124.86
		Room air and PMA 31 1/7 - 35 weeks	2-28	$124.86
		Nasal cannula and PMA equal to or more than 35 1/7 weeks	2-28	$116.70
		Room air and PMA equal to or more than 35 1/7 weeks	2-28	$116.70
		Mechanical ventilation	29 and up	$396.71
		nCPAP or NIPPV	29 and up	$396.71
		Nasal cannula and PMA less than or equal to 31 weeks	29 and up	$137.45
		Room air and PMA less than or equal to 31 weeks	29 and up	$137.45
		Nasal cannula and PMA 31 1/7 - 35 weeks	29 and up	$124.86
		Room air and PMA 31 1/7 - 35 weeks	29 and up	$124.86
		Nasal cannula and PMA equal to or more than 35 1/7 weeks	29 and up	$116.70
		Room air and PMA equal to or more than 35 1/7 weeks	29 and up	$116.70
	Canada	Mechanical ventilation	1	$440.34

Table 2-1. Continued

Per diem	Country	Respiratory support	Day of life	Cost in 2013 US dollars
Physician per diem (continued)	Canada (continued)	nCPAP or NIPPV	1	$440.34
		Nasal cannula and on parental nutrition	1	$302.15
		Nasal cannula and no parental nutrition	1	$190.90
		Room air and on parental nutrition	1	$302.15
		Room air and no parental nutrition	1	$190.90
		Mechanical ventilation	2-30	$220.11
		nCPAP or NIPPV	2-30	$220.11
		Nasal cannula and on parental nutrition	2 or more	$151.04
		Nasal cannula and no parental nutrition	2 or more	$95.45
		Room air and on parental nutrition	2 or more	$151.04
		Room air and no parental nutrition	2 or more	$95.45
		Mechanical ventilation	31 and up	$109.96
		nCPAP or NIPPV	31 and up	$109.96

CHAPTER 3
RESULTS

Outcome of NIPPV Trial

In total, 1,009 patients were enrolled in the NIPPV trial, with 504 in the NIPPV group and 505 in the nCPAP group. Seven patients in the NIPPV group were excluded secondary to not receiving an oxygen reduction test and 15 patients in the nCPAP group (13 missing oxygen reduction test and 2 withdrew consent) were excluded, leaving 987 for analysis. With the exception of male sex (p=0.04), the baseline characteristics of the nCPAP group and NIPPV group were not different.[1] No significant difference was observed for the primary outcome, death or BPD, between the two groups (38.4% vs. 36.7%; p=0.56). Additionally no significant differences were seen in the secondary outcomes including: air leaks, pulmonary hemorrhage, patent ductus arteriosis (PDA), PDA ligation, nosocomial sepsis, meningitis, culture confirmed meningitis, pneumonia, any retinopathy of prematurity (ROP), severe ROP, brain injury, nasal trauma, confirmed necrotizing enterocolitis (NEC), death before discharge, reintubation after randomization.[1]

Resource Utilization

Resources used by each group from the time of randomization to the primary endpoint (death, discharge or 44 PMA) are summarized in Table 3-1. Resource utilization for medications and procedures between the two groups did not differ significantly. As seen in Table 3-2, there was a trend towards a longer hospitalization in the NIPPV group (91 days) when compared to the nCPAP group (88 days). When further broken down, the NIPPV group remained on non-invasive ventilation, defined as nasal CPAP or NIPPV, longer than the nCPAP group. On average, the NIPPV group

used non-invasive ventilation support for 32 days compared to the nCPAP group's use of 29 days (p=0.04) (Table 3-2).

Direct Cost Comparison

Table 3-3 shows the average costs for hospital per diem and physician per diem fees which did differ significantly. The NIPPV group had higher per diem hospital and per diem physician costs on average compared to the nCPAP group. When totaled, the nCPAP infants' average cost per hospitalization was less, $196,837, than the NIPPV group, $205,309, although this did not reach statistical significance (p value = 0.11).

Cost Effectiveness Analysis

The incremental cost effectiveness ratio (iCER) plot (Figure 3-1) shows the cost effectiveness analysis. The mean cost difference and mean effectiveness difference for each of the 1,000 bootstrap replications are shown. From this plot we see that 69% of the replications lie in the upper left quadrant, which represents the dominated situation of increased cost and decreased effect. Moreover, 3% of the plots lie in the lower right quadrant, dominant, which indicates that it is unlikely NIPPV is both less costly and more effective than the use of nCPAP (Figure 3-1).

Table 3-1. Resource utilization

Parameter	NIPPV (n=497)	nCPAP (n=490)	p-value
Length of Stay	91.01 (33.06)	88.16 (31.06)	0.16
Antibiotics	20.31 (17.75)	19.74 (17.50)	0.62
Antifungals	16.48 (17.29)	14.88 (14.59)	0.34
Surfactant	1.14 (0.38)	1.13 (0.36)	0.80
Indomethacin	2.85 (1.50)	2.89 (1.70)	0.86
Ibuprofen	3.43 (1.61)	3.36 (1.99)	0.83
Caffeine	48.75 (22.38)	48.73 (22.61)	0.99
Loop diuertics	6.60 (8.99)	7.55 (0.66)	0.25
Thiazide diuretics	25.33 (23.44)	25.93 (22.45)	0.84
Corticosteroids	10.12 (13.17)	10.07 (12.47)	0.56
Inhaled steroids	20.34 (23.44)	17.91 (22.85)	0.62
Inhaled bronchodilators	18.09 (21.68)	19.56 (24.40)	0.64
Inhaled nitric oxide	7.48 (7.54)	9.65 (18.09)	0.61
Vitamin A	10.83 (6.26)	11.84 (6.89)	0.39
pRBC transfusion	4.50 (3.98)	4.49 (3.92)	0.97
Perenteral nutrition	26.48 (22.14)	25.39 (21.29)	0.43
Surgery for NEC	9.32 (20.60)	6.88 (16.13)	0.55
Chest X-ray	9.54 (8.64)	6.62 (8.73)	0.91
Abdominal X-ray	5.23 (5.29)	5.42 (5.73)	0.63
Echocardiogram	2.73 (2.13)	2.83 (2.36)	0.58

Table 3-2. Length of stay and respiratory support

	NIPPV mean days (std. dev)	nCPAP mean days (std. dev)	p value
Length of stay	91 (33)	88 (31)	0.16
Mechanical ventilation	13 (18)	13 (18)	0.86
nCPAP or NIPPV	32 (19)	29 (19)	0.04
Nasal cannula	13 (15)	13 (15)	0.74
Room air	5 (11)	7 (12)	0.15

Table 3-3. Direct cost comparison

	NIPPV group mean (SD)	nCPAP group mean (SD)	p-value
Physician per diem	$17,231 ($9,942)	$16,588 ($9,582)	0.30
Hospital per diem	$186,696 ($81,260)	$179,456 ($77,007)	0.15
Total cost	$205,309 ($84,681)	$196,837 ($9,203)	0.11

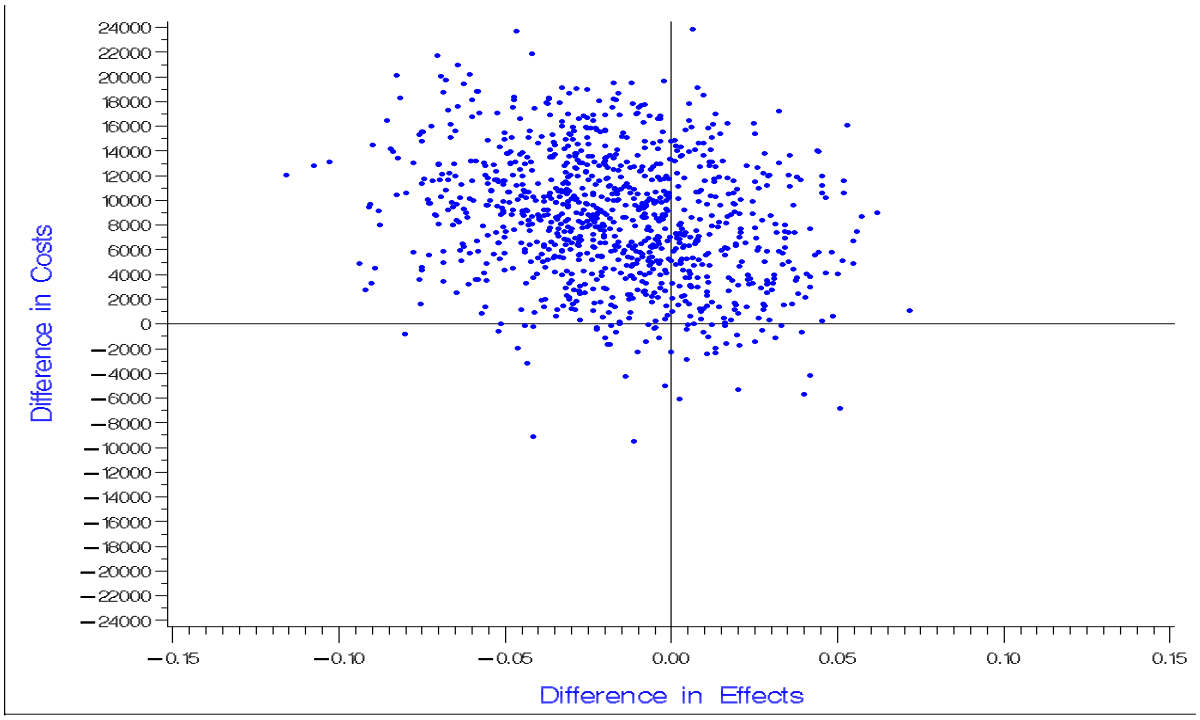

Figure 3-1. Incremental cost effectiveness ratio (iCER) plot

CHAPTER 4
DISCUSSION AND CONCLUSIONS

Economics of Non-Invasive Ventilation

For this economic evaluation, we used patient-level data from a multi-center randomized controlled trial. This evaluation analyzed costs in relation to the type of non-invasive ventilation received during hospitalization until the time of discharge, death or 44 weeks post-menstrual age. These costs were then evaluated in terms of outcome for the complete analysis. For infants assigned to the NIPPV group, overall costs were higher compared to the nCPAP group. When these costs were put in perspective with the outcomes of the NIPPV trial, NIPPV appears to be dominated by nCPAP. In other words, NIPPV is more costly and slightly less effective when compared to nCPAP (i.e., economically unfavorable).

Limitations

Due to limitations in gathering cost data, some patient data required imputation of costs outside their country of origin. When this occurred we chose to impute costs from Canada. We chose Canada because the health care payer system most similarly represents that found in the other countries (United Kingdom, Ireland, Sweden, Netherlands, Belgium, Austria, Singapore and Qatar). However, using costs from all countries, individually, would have allowed for better understanding of the relationship between resource utilization and cost of health care. The disadvantages of not using home country costs in this international setting include differences in outcome patterns, practice variation and comparing prices across the countries.[17] Although this may reduce the ability to generalize these findings to the other countries in the trial, this practice of applying a single country's costs is widely accepted in economic

evaluations.[25] Future analysis of this data set will include home country costs were they are able to be obtained. Additionally subgroup analysis by country will be differentiate individual country's costs in terms of patient outcome.

Second, for this analysis, we have chosen the third party payer perspective in which societal costs are not accounted for. Ideally, the societal costs would be included as they could contribute significantly to the total cost of prematurity. Future studies being designed by this author will address this issue with re-analysis of this data set.

Finally, additional resources such as operations, radiographic studies, procedures and medications were not included in the costs for this analysis. This approach was taken as most of the countries represented use a system of bundled services. In these cases no additional fees are charged for studies and medications. Although theoretically there is additional cost associated with these procedures it is difficult to determine what this cost may be in the setting of bundled billing. Additionally, given that resource utilization between the groups was not significantly different it is unlikely that this will significantly change the result. Again, future analysis of this data set will include costs for major procedures, surgeries, radiographic studies and medications to determine if this has an impact in the overall result.

Conclusion

This prospectively planned economic evaluation calls into question the use of NIPPV as a non-invasive strategy over traditional nCPAP. Although a newer technology and equally clinically efficacious to nCPAP, NIPPV is economically unfavorable in the patient population studied, i.e., those less than 30 weeks gestational age requiring non-invasive support. This study further supports the idea that clinical

outcomes are not always in line with resource and economic implications, advocating for concurrent economic evaluations in all clinical trials.

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BIOGRAPHICAL SKETCH

Meredith Mowitz received her medical degree from The University of Vermont in 2007. After completing her pediatric residency (2007-2010) she was selected to remain as chief pediatric resident at the University of Florida (2010-2011). She then went on to complete her neonatology fellowship at the University of Florida, while earning her Master of Science in Clinical and Translational Science, both completed in 2014.