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Prone versus supine position in mechanically ventilated children: a pilot study

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: It is known that mechanically ventilated patients in the prone position have improved oxygenation compared with those supine. We did a prospective, randomized, controlled trial to evaluate the effect of prone position during mechanical ventilation, on survival in critically ill children.

Material/Methods: Forty-two children needing mechanical ventilation for various illnesses were randomized to receive initial ventilation for four hours prone or supine by drawing lots. Initial severity of illness and blood gases in all children were noted. In a crossover design, after the initial four hours the children were turned over and ventilated in the alternate posture for an hour. Oxygenation parameters and mean airway pressures were noted at one hour, four hours, and five hours. Mortality, duration of ventilation, and the above parameters were compared in the two groups.

Results: Initial PRISM scores were similar in the two groups. Mortality in the prone group was less than in the supine group. The odds ratio of mortality was 0.20 (95% CI 0.05–0.75). Duration of ventilation was similar in the two groups. The oxygenation index was significantly lower in the prone group at one, four, and five hours after onset of ventilation.

Conclusions: Prone position in the first few hours of ventilation significantly improves gas exchange and oxygenation, reduces the mean airway pressures required to ventilate children, and may cause significant improvement in survival. Our study protocol allowed ventilator settings to be changed as needed during ventilation.

key words: **prone position • mechanically ventilated children**

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BACKGROUND

Bryan noted in 1974 that patients mechanically ventilated in the prone position had improved oxygenation compared with those in the supine position [1]. The mechanisms responsible are said to be uniform regional ventilation [2–4], better ventilation-perfusion matching [2,5,6], increased end expiratory lung volume [7–9], and alteration in chest wall mechanics [9]. Prone position has also been shown to reduce ventilator-induced lung injury in animal studies [10,11]. Curley, in a systematic review in 1999, showed improved oxygenation in 69% of patients with ARDS when ventilated prone [12]. Kornecki et al. [13] randomized children with acute respiratory failure in a crossover study design; group I received ventilation in a supine-prone sequence and group II in a prone-supine sequence. Oxygenation was found to be significantly superior in the prone position than in the supine position. Those patients who were initially prone had sustained benefit even after being turned to supine, whereas those who were initially supine had marked improvement on change of posture to prone. Prone ventilation, however, is not yet standard practice. Also, the effect of the prone position on survival of children has not been studied. In children with respiratory failure who need to be ventilated, it is reasonable to assume that optimized initial ventilation would lead to improved results in terms of shortened duration of ventilation and improved survival. Curley et al. [14] studied 25 pediatric patients between 2 months and 17 years of age with acute lung injury and demonstrated improvement in oxygenation without serious iatrogenic injury in the prone position. They concluded that their study provided a foundation for a prospective, randomized investigation on the effect of the prone position on clinical outcome in pediatric patients [14].

We hypothesized that prone ventilation would result in improved survival and carried out this prospective, randomized control study to test the hypothesis. We investigated the effects of 4 hours of initial prone ventilation compared with supine ventilation on ultimate mortality in patients ventilated for respiratory failure of different etiologies. We also carried out a one-hour crossover to study the changes in mean airway pressure brought about by change in position.

MATERIAL AND METHODS

The study was conducted in a level III pediatric intensive care unit (PICU) which admits critically ill patients (excluding trauma patients) less than 12 years of age who require extensive monitoring and ventilatory and circulatory support. Ten of the patients were neonates. As this was a preliminary study and there was no information on what change in mortality to expect, we planned to study 40 children without prior statistical analysis of sample size and study power.

Enrollment

All mechanically ventilated patients during the study period were considered eligible for study. The decision to ventilate was made on clinical grounds by the attending pediatrician. The criteria for ventilation included impending respiratory failure, extreme respiratory distress, and hypoventilation with decreasing saturations and rising $PaCO_2$. Informed consent from the parents or guardians of the child was obtained for participation in the study prior to ventilation. The ventilators used were VIP Bird, SLE 2000, and Newport Breeze, and allocation to the ventilator was dependent on the ventilator available at the time. The hospital research committee approved the research protocol. The study was conducted between October 2000 and November 2001.

Data Collection

On enrollment into the study, medical history and pediatric risk of mortality (PRISM II) data [15] were recorded as per study protocol. Randomization was done by drawing lots, and the children were placed supine or prone according to this random allocation. All patients were intubated while lying supine and were connected to the ventilator. The ventilator settings were adjusted according to the requirements of the child. They were then turned to the position to which they had been randomized. The children were turned prone by simply rolling them over. Two to four persons were involved in changing the posture depending on size of the patient, with at least one person taking care of the intravascular lines and the endotracheal tube. The ventilated children were sedated with midazolam and paralyzed with pancuronium if required. The patients were ventilated for four hours in the position to which they had been allotted. Those patients who were randomized to receive ventilation in the prone position were turned to the supine position, and those who were randomized to supine ventilation were turned to the prone at the end of 4 hours. After an hour, that is 5 hours into study period, all patients were placed in the supine position. Arterial blood gas analysis, fraction of inspired oxygen (FiO_2), peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), inspiratory time (Ti), and ventilator breath rate were recorded at onset before placing them in the allotted position and again at one hour, four hours, and five hours into the study.

Mean airway pressure (mPaw) was calculated by the following method [16]:

$$mPaw = K\ (PIP - PEEP)\ (Ti / Te + Ti) + PEEP$$

K is a wave-form constant =0.5 to1 and we used K =1, Ti is inspiratory time, and Te is expiratory time = (60 / ventilator rate) – Ti.

Oxygenation Index (OI) is an index of oxygenation impairment calculated as:

$$OI = mPaw \times FiO_2 \times 100 / PaO_2$$

Oxygenation Index was chosen because, in addition to the PaO_2/FiO_2 ratio, it relates to mean airway pressure, which also can affect oxygenation [13].

General support

Synchronized intermittent mandatory ventilation with pressure control was applied to all children in the study. The primary ventilatory strategy in our unit is to limit peak inspiratory pressures and to allow permissive hypercapnia as long as arterial pH is greater than 7.2 and oxygen saturation is maintained above 85%. The details of management of ventilation were left to the discretion of the attending clinician, as was done in the study by Kornecki et al. [13]. Inotropes and sedation were used as required.

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Table 1. Underlying diagnosis in children studied.

Diagnosis	No. of prone cases (no. of neonates)	No. of supine cases (no. of neonates)
Multi-organ failure ± sepsis	13 (5)	10 (4)
Hyaline membrane disease	1 (1)	3 (3)
Primary lung disease: – pneumonia, bronchiolitis	3 (0)	3 (0)
Central nervous system disorder: – meningitis, encephalopathy, status epilepticus	5 (1)	2 (1)
Congenital heart disease	0 (0)	2 (2)

Table 2. Baseline characteristics in the two groups: prone and supine.

Characteristics	Prone Mean (SEM)	Supine Mean (SEM)	p value
Age (in months)	7.5 (3.4)	21.4 (10.3)	0.19
PRISM Score	19.1 (1.9)	21.6 (1.9)	0.36
PaO_2 / FiO_2	255.4 (56.6)	139.6 (37.3)	0.1
$PaCO_2$	32.7 (3.3)	40.5 (3.2)	0.1

Table 3. Baseline characteristics in the two groups: median values and 10th and 90th percentile ranges.

	Prone	Supine	Statistical significance p>0.05*
Median PaO_2/ FiO_2 (10th–90th percentile)	160 (43–554)	100 (45–312)	NS
Median $PaCO_2$ (10th–90th percentile)	30 (14–48)	37 (24–61.1)	NS

* The test of significance was performed comparing medians, 10th percentiles, and 90th percentiles in the two groups.

Outcome measures

Primary outcome measures of the study were mortality and duration of ventilation in hours in the two study groups. Secondary outcome measures were in $PaCO_2$, PaO_2/FiO_2, HCO_3, mean airway pressures, and oxygenation index at 1 hour, 4 hours, and 5 hours after initial positioning.

Statistical analysis

Characteristics of the study population are expressed as mean (±SEM) and median (10th and 90th percentiles). Patient characteristics and secondary outcomes measures were compared using the student's test. In cases of non-normality, log transformation and square root transformation (for negative values) was done as appropriate. A p value of ≤0.05 was considered statistically significant. Mortality and outcome were compared using the chi-square test. Odds ratio (OR) with confidence intervals was calculated.

Results

Forty-two patients were enrolled in the study and 22 patients were randomized to receive prone ventilation and 20 patients to supine ventilation. Table 1 shows the different diagnoses in these 42 patients. Multi-organ failure was the most common reason for ventilation. Table 2 shows the baseline characteristics of the two groups randomized to receive prone and supine ventilation. The mean age in the prone children was 7.54 months and that in the supine group was 21.4 months. The difference was not statistically significant (p=0.19). The mean PRISM scores at the onset of ventilation in prone-ventilated patients were 19.1 and 21.6 in those ventilated supine (p=0.36). The median PRISM score in the prone group was 19, with an interquartile range of 12–23, and in the supine group 21, with an interquartile range of 14–28. When tested, there was no statistical difference in the medians or the upper and lower values of the interquartile range between the groups. The mean PaO_2/FiO_2 ratio in the two groups was similar (p=0.1). Table 3 shows the median values for PaO_2/FiO_2 and CO_2 at the onset of ventilation and also the 10th and 90th percentile values. There was no statistical difference in the median nor in either of the percentile values between the groups. Most patients had normal CO_2 at onset of ventilation. These findings reflect the fact that the groups were well randomized and initial severity of illness by PRISM in both groups was similar. Table 4 shows the duration of ventilation required for the prone group compared with the supine group as well as the mortality during hospital stay. No significant difference in duration of ventilation was noted.

Table 4. Primary outcome measures.

	Prone (n=22)	Supine (n=20)	
Duration of Ventilation in hours (SEM)	68.2 (21.9)	58.1 (10.9)	p value =0.4
Mortality in% (n)	22.7 (5.0)	60.0 (12.0)	Odds Ratio of Mortality 0.20 (95% CI 0.05–0.75)

Table 5. Secondary outcome measures.

Parameters	Time	ProneMean (SEM)	SupineMean (SEM)	p value
PaO_2/FiO_2	Baseline	255.4 (56.6)	139.6 (37.3)	0.1
	1 hour	453.9 (89.9)	247.6 (94.1)	0.003
	4 hours	452.9 (106.9)	319.9 (108.3)	0.3
	5 hours	386.7 (94.1)	203.5 (30.2)	0.07
Mean Airway Pressure	Baseline	6.6 (0.4)	7.5 (0.4)	0.13
	1 hour	6.8 (0.4)	7.7 (0.4)	0.11
	4 hours	6.5 (0.4)	8.3 (0.6)	0.02
	5 hours	6.6 (0.5)	8.6 (0.7)	0.01
$PaCO_2$	Baseline	32.7 (3.3)	40.5 (3.2)	0.1
	1 hour	29.3 (2.7)	34.6 (2.4)	0.15
	4 hours	34.8 (2.5)	35.9 (3.3)	0.7
	5 hours	29.5 (1.9)	43.4 (5.8)	0.02
Oxygenation index	Baseline	6.6 (1.3)	9.4 (1.2)	0.12
	1 hour	2.9 (0.5)	7.5 (1.2)	0.0004
	4 hours	3.3 (0.6)	6.3 (1.2)	0.015
	5 hours	3.5 (0.7)	8.5 (2.3)	0.02
HCO3	Baseline	13.9 (1.5)	15.5 (1.6)	0.4
	1 hour	15.3 (1.5)	16. 3(1.4)	0.63
	4 hours	16.6 (1.2)	17.6 (1.3)	0.58
	5 hours	16.5 (1.5)	18.5 (1.4)	0.32

Three patients in each group left the PICU against medical advice (LAMA) or were referred out for procedures such as cardiac surgery. These six patients were included among survivors in the analysis based on intention to treat. Analysis was also done after excluding the 6 (3 prone, 3 supine) and this did not affect the conclusion.

We found that mortality was almost three times higher among those who were ventilated supine. The odds ratio of mortality was 0.20 (95% CI 0.05–0.75). Table 5 shows the mean PaO_2/FiO_2 one hour after ventilation. Though mean PaO_2/FiO_2 was similar in the two groups at the baseline, at one hour in prone-ventilated children it was significantly higher (mean PaO_2/FiO_2=450) than the supine-ventilated children (mean PaO_2/FiO_2=247). This suggests that improved oxygenation and improved gas exchange was achieved in the prone-ventilated children. $PaCO_2$ was not different in the two groups. The PaO_2/FiO_2 ratio was not significantly different at 4 and 5 hours, but the mean airway pressure (MAP) used at these times was much less in the prone group. We took the MAP in the two groups to see if prone-ventilated children needed less mean airway pressure. At the onset and at one hour, mean airway pressure was not significantly different, but at four hours it was significantly less in the prone group. The oxygenation index as a measure of oxygenation impairment was calculated. The baseline value was similar in the two groups, but it was significantly less in prone-ventilated children at one hour, four hours, and five hours. This illustrates that children in the prone position were able to maintain blood gases with less FiO_2 and lower mean airway pressure.

Table 5 also includes the 5-hour readings (after crossover into the alternate position for an hour). We found that those who were prone and then turned to the supine position maintained their saturations at lower MAP than those who were supine and then turned to the prone. The supine group continued to require high pressures. This suggests that those initially ventilated prone sustained these benefits even one hour after being turned supine but those who were supine did not show marked improvement on being turned prone.

Discussion

Chatte et al. [17] have previously shown that a short, four-hour period of prone ventilation resulted in improved oxygenation. Murdoch and Storman have also demonstrated improvement in saturation with only thirty minutes of prone position in children [18]. Our findings go one step further and suggest that early prone ventilation and the resultant improved oxygenation makes a difference in the final outcome in terms of survival. We found that children who were randomized to receive initial prone ventilation had significantly less mortality compared with those ventilated supine. Survival in the prone group was 63.6% compared with 25% in the supine group. The odds ratio of mortality was 0.20 (95% CI 0.05–0.75). The fact that the baseline characteristics of patients in the prone and supine groups and mean PRISM scores before ventilation were similar suggests that these were well-randomized groups. The better results seen in the prone group may be attributed to the initial prone ventilation.

In our study we found that children who had been ventilated prone had better oxygenation and required less FiO_2 and airway pressure to maintain oxygenation. The composite value of oxygenation is the oxygenation index ($OI=FiO_2 \times MAP \times 100/PaO_2$), which was significantly less in the prone group at one and four hours. We found that PaO_2/FiO_2 was significantly less at 1 hour. This would have resulted in better saturation of blood as seen on the saturation monitor and prompted the lowering of MAP on the ventilator. Subsequently, at 4 and 5 hours PaO_2/FiO_2 is not significantly different, but the MAP used is significantly lower.

In our protocol we took a cue from a crossover study from Kornecki et al. [13]. Children were turned to the alternate position for one hour after the end of four-hour ventilation in the randomized position. At the end of fifth hour we found that babies initially prone continued to maintain lower mean airway pressures and had better oxygenation indexes, while those supine needed higher mean airway pressures and had poorer oxygenation indexes. It is possible that had the prone position (in those initially supine) been maintained for a longer period of time, say four hours, benefits may have become apparent. In retrospect, we feel that the crossover part of our study was not called for to answer the question of improved survival we were looking for. The crossover aspect of our study helps to suggest that initial ventilation in prone position and thence optimized lung function in the early part of ventilation is crucial for survival. In fact, the benefit of an initial prone position persists even after tuning the patient to the supine position.

Animal studies have shown that ventilation-induced lung injury is delayed when animals are prone ventilated [11]. Broccard et al. have also shown attenuated ventilator-induced lung injury in prone-ventilated dogs [10]. Improved oxygenation was also noted in 12 of 16 patients with acute lung injury after 2 hours of prone ventilation. In 2000, Curley et al. [14] placed 25 children with acute lung injury and acute respiratory distress syndrome in prone position for 20 hours per day until clinical improvement or death occurred. 84% of the children responded with improved oxygenation.

Previous studies have been done to see the effect of the prone position on ventilation-perfusion matching [2,6] and respiratory mechanics [9]. We have not measured all the above parameters. These may have been responsible for the better outcome in prone-ventilated children. We found lower mean airway pressure in prone-ventilated children. It is possible that improved survival may be related to improved lung function and reduced ventilator-induced lung injury due to lower mean airway pressure needed.

At the same time we were doing our study in children on the benefits of prone ventilation between October 2000 and November 2001, Gattinoni and colleagues were completing and writing up a similar study in adults [19,20]. This was a large multicenter study involving over 300 patients and they found no improvement in survival in the prone position. A major methodological difference in the study by Gattinoni et al. is that they kept their ventilator settings steady during the period of prone position in order to standardize the assessment of changes in gas exchange induced by the maneuver [19,20]. In our study we let the treating physician adjust ventilator setting according to the requirements of individual patients and thus to lower ventilator settings if ventilatory requirements came down. Prone patients in our study needed lower pressures for ventilation, and this could have been crucial. Slutsky has noted that ventilator-induced lung injury and not hypoxemia itself may be the cause of increased mortality in ARDS patients [21]. A consortium sponsored by the National Institutes of Health (NIH) reported that reducing the tidal volume from 12 to 6 ml per kilogram decreased mortality by 22 percent among patients with acute respiratory distress syndrome [22]. The implication of this finding is that by inducing iatrogenic lung injury during mechanical ventilation, clinicians have inadvertently been contributing to the high mortality associated with ventilation [21]. Others have previously reported that the benefit of the prone position is that it helps in lung recruitment and so less pressure is needed for ventilation [23,24]. This was also seen in our study. In the multi-center study of Gattinoni et al. the protocol did not allow changes in ventilator setting, so perhaps they were not able to give the patients the benefit of prone position. In the light of the findings of the NIH study that reducing tidal volume [22] can lower mortality and the lower MAP and mortality seen in our prone patients, we feel that our study, though small, has important implications for the design of other studies investigating prone ventilation.

The method of prone positioning is controversial, with some authors proposing the use of pillows or special portable devices to keep the abdomen suspended to allow free movement of the diaphragm [13,23]. Mure and Lindahl in 2001 suggested that keeping the abdomen free in the prone position may not be required [3]. We did not use any means to suspend the abdomen, but still found improvement in oxygenation.

Our study suffers from a number of drawbacks. The sample size is small and, although the patients were well randomized, neither the clinicians nor the patients were blinded to the intervention. The very nature of the study made it impractical to carry it out in a double-blinded manner. The drawback is mitigated by the fact that the outcome measures noted were not subjective but very objective, in the form of mortality, duration of ventilation, arterial blood gases, and mean airway pressures. Observer bias is less likely to cause errors in objective measurements. In retrospect we feel that the crossover design, as we did it, only confounded rather than clarified issues and would be best avoided in further studies in the field. We also feel that we should not have stopped recording the parameters at five hours, but continued for at least 48 hours.

Curley et al. in 2000 have suggested that it is safe to study the ventilation of children in the prone position [14]. Our findings, if substantiated by larger studies, would make it unethical to ventilate children supine. However, on account of the small size of this study, it is important that a larger study be conducted to validate our findings before such far-reaching recommendations to the standard practice of ventilation are made.

CONCLUSIONS

Our study suggests that the prone position in the first few hours of ventilation significantly improves gas exchange and oxygenation, reduces the mean airway pressures required to ventilate children, and may cause significant improvement in survival. We believe that reducing the airway pressure used for ventilation is crucial to achieve this benefit in survival.

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