Effect of Prone Positioning on Clinical Outcomes in Children With Acute Lung Injury

A Randomized Controlled Trial

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Context In uncontrolled clinical studies, prone positioning appeared to be safe and to improve oxygenation in pediatric patients with acute lung injury. However, the effect of prone positioning on clinical outcomes in children is not known.

Objective To test the hypothesis that at the end of 28 days infants and children with acute lung injury treated with prone positioning would have more ventilator-free days than those treated with supine positioning.

Design, Setting, and Patients Multicenter, randomized, controlled clinical trial conducted from August 28, 2001, to April 23, 2004, of 102 pediatric patients from 7 US pediatric intensive care units aged 2 weeks to 18 years who were treated with supine vs prone positioning. Randomization was concealed and group assignment was not blinded.

Intervention Patients were randomized to either supine or prone positioning within 48 hours of meeting acute lung injury criteria, with those patients in the prone group being positioned within 4 hours of randomization and remaining prone for 20 hours each day during the acute phase of their illness for a maximum of 7 days, after which they were positioned supine. Both groups were treated using lung protective ventilator and sedation protocols, extubation readiness testing, and hemodynamic, nutrition, and skin care guidelines.

Main Outcome Measure Ventilator-free days to day 28.

Results The trial was stopped at the planned interim analysis on the basis of the prespecified futility stopping rule. There were no differences in the number of ventilator-free days between the 2 groups (mean [SD], 15.8 [8.5] supine vs 15.6 [8.6] prone; mean difference, –0.2 days; 95% CI, –3.6 to 3.2; $P=.91$). After controlling for age, Pediatric Risk of Mortality III score, direct vs indirect acute lung injury, and mode of mechanical ventilation at enrollment, the adjusted difference in ventilator-free days was 0.3 days (95% CI, –3.0 to 3.5; $P=.87$). There were no differences in the secondary end points, including proportion alive and ventilator-free on day 28 ($P=.45$), mortality from all causes ($P>.99$), the time to recovery of lung injury ($P=.78$), organ-failure–free days ($P=.88$), and cognitive impairment ($P=.16$) or overall functional health ($P=.12$) at hospital discharge or on day 28.

Conclusion Prone positioning does not significantly reduce ventilator-free days or improve other clinical outcomes in pediatric patients with acute lung injury.

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ACUTE LUNG INJURY IS A MAJOR cause of acute respiratory failure in patients who are critically ill and is associated with several clinical disorders, including sepsis, pneumonia, and aspiration.[1] Although lifesaving, traditional ventilation strategies with higher tidal volumes and airway pressures can exacerbate lung inflammation and injury.[2] Acute lung injury produces parenchymal lung damage that is heterogeneous and may place the patient at risk for ventilator-associated lung injury. When patients are supine, the reduced volume of the nondependent-aerated lung is at risk for alveolar overdistention,[3] and the cyclical ventilation of the dependent lung at low volumes can cause recruitment-derecruitment with subsequent mechanical strain.[4] Prone positioning, as

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first suggested by Bryan,[5] is a maneuver that can improve ventilation-to-perfusion matching[6] and lung mechanics[7] in both adult and pediatric patients with severe impairment of gas exchange.[8-13] The improved oxygenation and regional changes in ventilation may result in decreased ventilator-associated lung injury[14] and facilitate patient recovery.

Although prone positioning is frequently used in the management of pediatric patients with acute lung injury,[15] there are no data that suggest improved clinical outcomes. Gattinoni et al[16] showed no effect of 7 hours per day of prone positioning with survival in adult patients with acute lung injury. Prone positioning improved oxygenation and a post hoc analysis suggested improved outcomes in those patients with severe acute lung injury. Using a similar study design, Guerin et al[17] extended the study population to include all adult patients with acute hypoxemic respiratory failure and found improved oxygenation but no difference in survival or ventilator days between the prone and supine groups. Both trials used prone positioning for relatively short periods each day, did not require a lower tidal volume approach, and did not include children. Therefore, we examined prolonged periods of prone ventilation combined with a lower tidal volume approach in children aged 2 weeks to 18 years with acute lung injury. We tested the hypothesis that children with acute lung injury treated with prone positioning would have more ventilator-free days than those treated with supine positioning.

METHODS

Patients were enrolled from August 28, 2001, to April 23, 2004, at 7 US pediatric intensive care units that participate in the Pediatric Acute Lung Injury and Sepsis Investigators network. The study design was approved by the institutional review board of each hospital. Written informed consent was obtained from the parent or legal guardian of each patient.

Patients

Inclusion criteria were pediatric patients aged 2 weeks to 18 years who were intubated and mechanically ventilated with a ratio of partial pressure of arterial oxygen (Pa_{O_2}) to the fraction of inspired oxygen (F_{IO_2}) of 300 or less (adjusted to 253 in Salt Lake City, Utah, because of altitude), bilateral pulmonary infiltrates, and no clinical evidence of left atrial hypertension.[18] Patients were excluded if they were younger than 2 weeks of age (newborn physiology), less than 42 weeks postconceptual age (considered preterm), unable to tolerate a position change (persistent hypotension, cerebral hypertension), had respiratory failure from cardiac disease, had hypoxemia without bilateral infiltrates, had received a bone marrow or lung transplant, were supported with extracorporeal membrane oxygenation, had a nonpulmonary condition that could be exacerbated by the prone position, had participated in other clinical trials within the preceding 30 days, or if there was a decision to limit life support. Randomization was performed by using a permuted blocks design, stratified by center, with random block sizes. Allocation was concealed; each center received serially numbered, opaque, sealed envelopes containing study assignments.

Treatment Procedures

Eligible patients were randomized within 48 hours of meeting study criteria to either supine or prone positioning. The clinical and research teams were not blinded to treatment assignment. Patients randomized to the supine group remained supine. Patients randomized to the prone group were positioned prone within 4 hours of randomization and remained prone for 20 hours each day during the acute phase of their illness for a maximum of 7 days of treatment, after which they were positioned supine. When prone, individually sized cushions were used to splint the most compliant aspect of the chest wall over the sternum and unrestrain the diaphragmatic-abdomen component of the chest wall.[7]

The acute phase of illness was defined as the time interval between randomization and the time at which extubation readiness criteria were met; specifically, spontaneous breathing, oxygenation index (mean airway pressure/[Pa_{O_2}:F_{IO_2} ratio] × 100) of less than 6, and a decrease in ventilator support over the previous 12 hours.[19] Patients in both groups were assessed each morning while in the supine position. Thus, the length of prone positioning could be less than 20 hours on day 1. Other than positioning, both groups were treated with specific care algorithms, which included ventilator and sedation protocols, extubation readiness testing, as well as hemodynamic, nutrition, and skin care guidelines during the 28-day period.

Data Collection

At enrollment, admission functional health[20] and Pediatric Risk of Mortality III (PRISM III)[21] data were recorded. Race and ethnic group were categorized by the investigators. Circulatory, pulmonary, coagulation, hepatic, renal, and neurological system function was also monitored daily for 28 days.

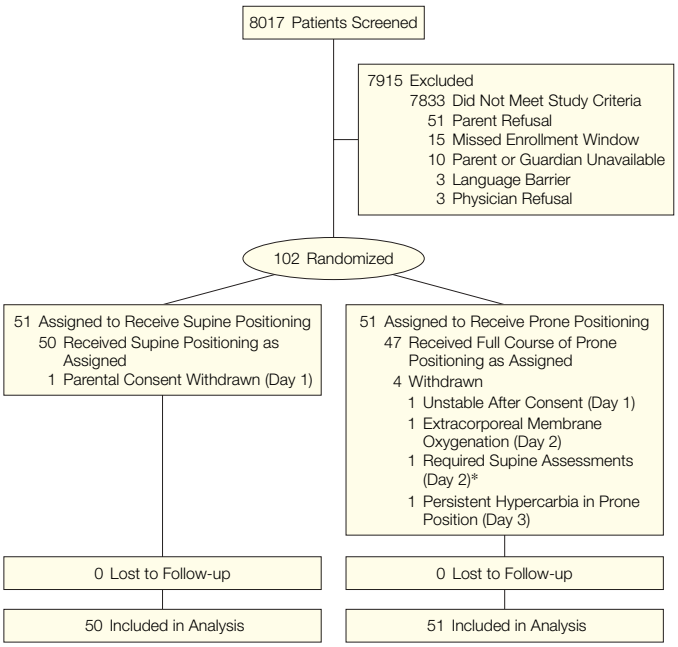
Patients randomized to prone positioning had their physiological values and arterial blood gases assessed before and 1 hour after each supine-to-prone and prone-to-supine turn. Days in which a patient exhibited an increase in the Pa_{O_2}:F_{IO_2} ratio of at least 20 or a decrease in oxygenation index of at least 10% after a supine-to-prone turn were classified a priori as responder days.[22] Patients who experienced more responder days than nonresponder days over the entire study period were considered overall responders; when equal, the patient's overall response was categorized by the day 1 response.[9]

Outcome Measures

The primary outcome measure was ventilator-free days, which were defined as the number of days a patient breathed without assistance for at least 48 consecutive hours from day 1 to day 28 after randomization.[23] Secondary end points included alive and ventilator-free on day 28, mortality from all causes,

the time to recovery of lung injury, organ-failure–free days, and functional health. Time to recovery of lung injury was defined as the number of days from randomization to meeting extubation readiness testing criteria for 24 consecutive hours through day 28. Organ-failure–free days were defined as the number of days from day 1 to day 28 in which a patient was without clinically significant nonpulmonary organ dysfunction. The Paediatric Logistic Organ Dysfunction score parameters[24] were used to define pediatric organ dysfunction. Functional health was defined as differences in cognitive impairment and overall functional health from intensive care admission to hospital discharge or day 28, whichever occurred first, using the Pediatric Cerebral Performance Category score and Pediatric Overall Performance Category score.[20]

Figure 1. Patient Flow Through Clinical Trial



*Prone positioning alone was stopped on day 2 in a patient with sickle cell disease because of splenic sequestration.

Statistical Analysis

To ensure adequate power for the interim and final analyses, we conservatively based our sample estimate on a dichotomous outcome—the proportion of patients who were alive and ventilator-free at the end of 28 days. We used data from our phase 1 study[9] in which 25 consecutive prone-positioned patients were matched (on acute lung injury trigger, age, and closest PRISM III score on admission and oxygenation index at enrollment) 1:2 to a historical control group derived from the pediatric acute respiratory distress syndrome data set.[19] After we excluded bone marrow transplant recipients from the analysis, 18 (90%) of 20 prone-positioned patients were alive and ventilator-free on day 28 compared with 26 (65%) of 40 matched supine-positioned patients. Prone-positioned patients also experienced more ventilator-free days (mean [SD], 15 [9] days) than supine-positioned patients (mean [SD], 8 [9] days). Assuming 10% noncompliance in each group, we calculated that a sample size of 90 patients per group was required to yield 90% power to detect the noncompliance-adjusted difference of 87.5% $[(90\% \times 90\%) + (65\% \times 10\%)]$ vs 67.5% $[(65\% \times 90\%) + (90\% \times 10\%)]$ in the proportion of patients alive and ventilator-free on day 28, using a fixed sample size χ^2 test (nQuery Advisor 3.0, Statistical Solutions, Boston, Mass).

A single interim analysis was planned after 50% of patients had completed their participation in the study using the O'Brien-Fleming stopping rule,[25] with a priori boundaries of $P<.006$ ($|Z|>2.74$) to reject the null hypothesis (efficacy boundary, if large treatment differences appear before the end of the study) and $P>.52$ ($|Z|<0.70$) to accept the null hypothesis (futility boundary, if there is little chance of finding a significant difference between groups). Allowing for this interim analysis with possible early stopping, a sample size of 90 patients per group provided 88% power to detect the difference of 87.5% vs 67.5% in proportion of patients alive and ventilator-free on day 28 between treatment groups using a χ^2 test, and 82% power to detect a difference of at least 4 ventilator-free days between treatment groups via a *t* test, assuming a common SD of 9 days for each group (East 3.1, Cytel Software Corporation, Cambridge, Mass). Thus, this study was adequately powered to detect the hypothesized difference of at least 4 ventilator-free days or a 20% or more difference in the proportion of patients who were ventilator-free and alive on day 28.

The primary analyses were performed on an intention-to-treat basis. We used the 2-sample *t* test, χ^2 test, or Fisher exact test to compare baseline characteristics. The *t* test was used to compare the number of ventilator-free days between the 2 groups. Multiple linear regression analysis was then used to control for age, PRISM III score, mode of mechanical ventilation at enrollment, and direct vs indirect cause of lung injury. Center was not included in regression models because it did not appreciably affect treatment group comparisons and center effects were not statistically significant. No lack of fit, deviation from the homoscedasticity assumption, or outliers were indicated in the residual plots against variables in the

Table 1. Patient Characteristics at Enrollment*

Characteristic	Supine Group (n = 51)	Prone Group (n = 51)
Age, median (IQR), y	2.1 (0.3-11.0)	2.0 (0.3-8.2)
Age, No. (%), y		
<2	25 (49)	25 (49)
2-8	10 (20)	13 (25)
>8	16 (31)	13 (25)
Female sex, No. (%)	21 (41)	27 (53)
Race/ethnicity, No. (%)†		
White	28 (56)	27 (54)
Black	6 (12)	5 (10)
Hispanic	10 (20)	14 (28)
Asian	4 (8)	0
>1 Group	2 (4)	4 (8)
Score, median (IQR)‡		
PCPC	1 (1-2)	1 (1-2)
POPC	1 (1-2)	1 (1-2)
Pediatric Risk of Mortality III scores, mean (SD)§	11 (9)	11 (8)
Risk of mortality, median (IQR), %	3 (2-12)	6 (1-23)
No. of nonpulmonary organ or system failures, median (IQR)‖	2 (1-2)	2 (1-2)
Pa_{O_2}:FI_{O_2} ratio, mean (SD)¶	105 (48)	94 (41)
≤200, No. (%)	49 (96)	50 (98)
Cause of lung injury, No. (%)		
Pneumonia	28 (55)	29 (57)
Bronchiolitis with pneumonia	8 (16)	6 (12)
Sepsis	7 (14)	8 (17)
Aspiration	6 (12)	5 (10)
Other#	2 (4)	3 (6)
Direct pulmonary injury, No. (%)**	44 (86)	42 (82)

Abbreviations: FI_{O_2}, fraction of inspired oxygen; IQR, interquartile range; Pa_{O_2}, partial pressure of arterial oxygen; PCPC, Pediatric Cerebral Performance Category; POPC, Pediatric Overall Performance Category.

*Because of rounding, percentages may not all total 100. There were no statistically significant differences between treatment groups for any of these variables.

†Race and ethnicity could not be determined for 2 patients (1 in supine group and 1 in prone group).

‡PCPC score ranges from 1 (normal cognitive development) to 6 (brain death) and POPC score ranges from 1 (good overall performance) to 6 (brain death).[20]

§Scores range from 0 to 74, with higher scores indicating higher probability of death.[21]

‖Patients were monitored for neurological, cardiovascular, renal, hematological, and hepatic failure.[24]

¶Arterial blood gases in both groups were assessed in the supine position. Pa_{O_2}:FI_{O_2} values from Salt Lake City were normalized for altitude. Data reflect the lowest Pa_{O_2}:FI_{O_2} ratio on the day of enrollment.

#Includes acute chest syndrome, pulmonary hemorrhage, and neurogenic pulmonary edema.

**Direct pulmonary injury originates from pulmonary disease.[26]

model or against selected variables not in the model. A quantile normal plot of the residuals revealed no clear deviation from normality. The secondary outcomes and adverse events were compared using the 2-sample *t* test for continuous variables and χ^2 test or Fisher exact test for categorical variables, except that the time to recovery of lung injury was analyzed using the log-rank test. Although 2-sample *t* tests are known to be robust for deviation from normality for the sample sizes in the current study, Wilcoxon rank sum tests were also performed because they may be more powerful than *t* tests for nonnormal data. The *P* values for Wilcoxon rank sum tests were not reported unless the significance result differed from *t* tests. All analyses were performed with SAS software version 9.0 (SAS Institute, Cary, NC). A 2-sided $P<.05$ indicated statistical significance.

RESULTS

The data and safety monitoring board stopped the trial at the interim analysis, after 102 patients had been enrolled, on the basis of the prespecified futility stopping rule. At this time, based on the 94 patients who had completed the 28-day study period (47 in the prone group and 47 in the supine group), comparison of the primary outcome variable (ventilator-free days) either via *t* test ($P=.87$) or multiple linear regression ($P=.55$) crossed the a priori futility boundary for early stopping with acceptance of the null hypothesis of no difference between groups. An identical conclusion was reached using the comparison between proportions of patients alive and ventilator-free on day 28 (χ^2 test $P=.60$). At the interim analysis, it was calculated that if the study had continued to the planned enrollment of 180 patients, the probability of demonstrating a difference in ventilator-free days between treatment groups was less than 1% under the alternative hypothesis based on the observed unadjusted ventilator-free day treatment group differences. Analyses report on data from all 102 patients enrolled.

Study Population

Of the 8017 pediatric patients who were intubated, ventilated, and screened for the study, 184 met acute lung injury criteria and 102 were enrolled and randomized, 51 patients to each group (FIGURE 1). The baseline characteristics and respiratory variables at enrollment were similar between the 2 groups (TABLE 1 and TABLE 2). More patients in the prone-positioned group were initially supported on high-frequency oscillatory ventilation (12% supine and 29% prone; χ^2 test $P=.03$). This difference was no longer significant after the implementation of study protocols when patients in both groups with an oxygenation index of more than 20 were transitioned to high-frequency oscillatory ventilation.

Outcomes

The primary outcome, number of ventilator-free days, was not significantly different between the 2 groups (mean [SD], 15.8 [8.5] for supine and 15.6 [8.6] for prone; 2-sample *t* test $P=.91$; prone-to-supine mean difference, –0.2 days; 95% confidence interval [CI], –3.6 to 3.2) (TABLE 3 and FIGURE 2). After controlling for age, PRISM III score, direct vs indirect cause of acute lung injury, and mode of mechanical ventilation at enrollment in a multiple linear regression analysis, the adjusted prone-to-supine mean difference was 0.3 days (95% CI, –3.0 to 3.5; Wald test $P=.87$). In addition, we found no evidence that age was a confounder (when excluding age from model, prone-to-supine mean difference was 0.4 days, similar to that when age was included in the model; 95% CI, –2.9 to 3.7) or effect modifier of the association between prone vs supine positioning and ventilator-free days (F test for position by age interaction $P=.53$). In particular, the mean (SD) ventilator-free days for patients in the supine and prone position for the 3 age groups were for less than 2 years, 18.7 (7.1) vs 18.6 (7.6) days (mean difference, –0.1 days; 95% CI, –4.4 to 4.1); for 2 to 8 years, 14.6 (8.3) vs 11.5 (8.3) days (mean difference, –3.1 days; 95% CI, –10.4 to 4.1); for more than

8 years, 12.2 (9.4) vs 14.0 (9.2) days (mean difference, 1.8 days; 95% CI, –5.3 to 9.0).

The proportion of patients alive and ventilator-free on day 28 was 86% in the supine and 80% in the prone group (risk ratio [RR], 0.93; 95% CI, 0.78-1.11; χ^2 test $P=.45$). The mortality rate was 8% in both groups (RR, 0.98; 95% CI, 0.26-3.71; Fisher exact $P>.99$). There were no significant differences in the other secondary end points of time to recovery of lung injury, organ-failure–free days, and functional outcomes (Table 3) or sedative use (TABLE 4) between the 2 groups. There were also no significant differences in the number of survivors who were oxygen dependent on day 28 (20% supine and 26% prone, χ^2 test $P=.49$).

Prone Positioning and Oxygenation

Patients who were randomized to the prone-positioned group were positioned within a median 28 hours of meeting study criteria (interquartile range, 18-39 hours) and within a median 2.3 hours of randomization (interquartile range, 1.6-3.5 hours). Patients remained prone for a mean 18 (SD, 4) hours per day for 4 days (range, 1-7 days), which accounted for a mean 79% (SD, 9%) of the acute phase of illness. The Pa_{O_2}:F_{IO_2} ratio and oxygenation index response to positioning are shown in FIGURE 3.

Table 2. Respiratory Values at Baseline, Study Day 1, and Average in Acute Phase*

Variable	Baseline†		Study Day 1†		Average in Acute Phase†	
	Supine (n = 51)	Prone (n = 51)	Supine (n = 50)	Prone (n = 50)	Supine (n = 50)	Prone (n = 50)
Pa_{O_2}:F_{IO_2} ratio						
No. of patients	51	51	49	50	49	50
Mean (SD)	147 (60)	153 (65)	157 (63)	159 (74)	176 (62)	183 (69)
Oxygenation index						
No. of patients	51	51	49	50	49	50
Mean (SD)	15 (12)	18 (18)	14 (11)	15 (12)	12 (9)	11 (9)
Pa_{O_2}, mm Hg						
No. of patients	51	51	49	50	49	50
Mean (SD)	76 (26)	84 (32)	76 (25)	78 (29)	78 (18)	80 (19)
Pa_{CO_2}, mm Hg						
No. of patients	51	51	49	50	49	50
Mean (SD)	48 (12)	46 (10)	50 (12)	54 (13)	53 (12)	56 (13)
Arterial pH						
No. of patients	51	51	49	50	49	50
Mean (SD)	7.37 (0.08)	7.39 (0.07)	7.38 (0.06)	7.36 (0.10)	7.40 (0.06)	7.38 (0.07)
Tidal volume, mL/kg of ideal body weight						
No. of patients	34	27	39	34	42	42
Mean (SD)	7.7 (2.1)	7.6 (2.9)	6.6 (1.4)	6.3 (1.3)	6.8 (1.0)‡	6.2 (1.1)‡
Mean airway pressure						
Conventional mechanical ventilation, cm H_2O						
No. of patients	45	36	39	34	42	42
Mean (SD)	15 (5)	16 (5)	14 (4)	14 (5)	13 (4)	12 (4)
High-frequency oscillatory ventilation, cm H_2O						
No. of patients	6	15	11	16	16	17
Mean (SD)	26 (7)	26 (6)	29 (6)	25 (6)	27 (4)§	23 (5)§
Supported on high-frequency oscillatory ventilation, %	12‖	29‖	22	32	24	27
No. of patients	51	51	50	50	50	50
Minute ventilation, L/min						
No. of patients	34	27	39	34	42	42
Median (IQR)	1.8 (1.0-5.7)	1.6 (1.1-4.4)	1.6 (0.9-3.6)	1.8 (0.7-3.8)	1.6 (1.0-3.2)	1.6 (0.6-2.8)
F_{IO_2}						
No. of patients	51	51	50	50	50	50
Mean (SD)	0.58 (0.19)	0.61 (0.19)	0.54 (0.17)	0.55 (0.18)	0.49 (0.13)	0.49 (0.14)
PEEP, cm H_2O						
No. of patients	45	36	39	34	42	42
Mean (SD)	8.4 (3.4)	9.5 (3.2)	7.8 (3.2)	8.4 (3.1)	7.7 (2.7)	7.2 (2.2)

Abbreviations: F_{IO_2}, fraction of inspired oxygen; IQR, interquartile range; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2}, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

*Patients in both groups were assessed in the supine position. Pa_{O_2}:F_{IO_2} values from Salt Lake City were normalized for altitude.

†Baseline is before the institution of study protocols; day 1 is the first 10 AM assessment; average in acute phase was calculated as the average of the morning (10 AM) assessments in the acute phase.

‡Significantly different between the 2 groups (2-sample t test $P = .02$).

§Significantly different between the 2 groups (2-sample t test $P = .04$; Wilcoxon rank sum test $P = .08$).

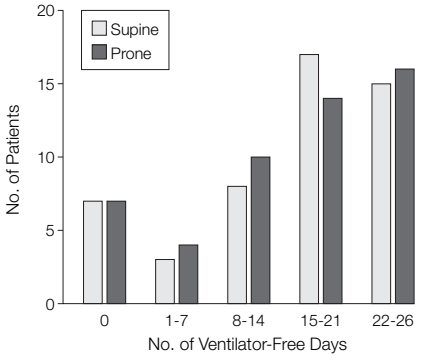
‖Significantly different between the 2 groups at baseline (χ^2 test $P = .03$).

Table 3. Primary and Secondary Outcome Variables*

Outcome	Supine (n = 50)	Prone (n = 51)	*P* Value†
No. of ventilator-free days from 1-28 d, mean (SD)	15.8 (8.5)	15.6 (8.6)	.91
Alive and ventilator-free on day 28, No. (%)	43 (86)	41 (80)	.45
Mortality, No. (%)	4 (8)	4 (8)	>.99
No. of days to recovery of lung injury, median (IQR)‡	5 (3-9)	4 (2-9)	.78
No. of days without failure of circulatory, neurological, coagulation, hepatic, and renal organs from 1-28 d, median (IQR)§	17 (7-22)	16 (9-22)	.88
Worse score from PICU admission to hospital discharge (or day 28), No. (%)‖			
PCPC	11 (22)	6 (12)	.16
POPC	14 (29)	8 (16)	.12

Abbreviations: IQR, interquartile range; PCPC, Pediatric Cerebral Performance Category; PICU, pediatric intensive care unit; POPC, Pediatric Overall Performance Category.
*All patients were included in the intention-to-treat analysis except 1 patient in the supine group for whom parental consent was withdrawn.
†*P* values are based on the *t* test for number of ventilator-free days and number of days without nonpulmonary organ failures, log-rank test for number of days to recovery of lung injury, Fisher exact test for mortality, and χ^2 test for the remaining outcomes.
‡In survivors, number of days from randomization to achieve an oxygenation criterion; oxygenation index of 6 or less for 24 consecutive hours through day 28.
§Patients were monitored daily for 28 days for neurological, cardiovascular, renal, hematological, and hepatic failure. This variable was not available for 10 patients (6 supine and 4 prone) who transferred to other acute care facilities during the 28-day study period.
‖POPC and PCPC were not available for 1 patient in the supine group. One patient in the prone group, with a static baseline to hospital discharge PCPC/POPC, died during a subsequent readmission from a nonpulmonary problem.

Figure 2. Number of Ventilator-Free Days in the Supine- and Prone-Positioned Groups



No significant differences were found between the 2 groups (2-sample *t* test *P* = .91).

Sixty-four percent of 202 daily pronation procedures resulted in a PaO_2:FIO_2 ratio increase of at least 20 mm Hg, or an oxygenation index decrease of at least 10%. Based on the patient's multiple day oxygenation response, 90% of patients in the prone group were categorized as overall responders to prone positioning. The number of ventilator-free days was not significantly different between overall responders and nonresponders to prone positioning (2-sample *t* test *P* = .85).

Protocol Deviations and Adverse Events

All positioning and adjunctive therapy protocols were stopped during the acute phase in 4 patients (3 in the prone group and 1 in the supine group) (Figure 1). In the prone group, 1 patient became hemodynamically unstable after consent had been obtained (day 1), 1 patient did not respond to conventional therapies and was cannulated for extracorporeal membrane oxygenation (day 2), and 1 patient demonstrated persistent hypercarbia in the prone position (day 3). One parent in the supine group withdrew consent on day 1. Prone positioning alone was stopped on day 2 in a patient with sickle cell disease because of splenic sequestration. Except for 1 patient in the supine group for whom parental consent was withdrawn, all patients were included in the intention-to-treat analysis.

Position-Related Complications

All position-related adverse events are listed in TABLE 5. Five patients experienced serious study-related events, 4 in the prone group and 1 in the supine group (Fisher exact *P* = .36). In the prone group, 3 patients experienced hypercarbia and 1 patient's endotracheal tube was twisted and partially obstructed during a head turn while prone. All 4 of these patients were on high-frequency oscillatory ventilation at the time of the event and all 4 survived. The single study-related serious adverse event in the supine group was a stage IV pressure ulcer[28,29]; the patient did survive.

COMMENT

In this randomized trial of 102 pediatric patients with acute lung injury, there were no significant differences in the number of ventilator-free days, mortality, time to recovery of lung injury, organ-failure–free days, or functional outcome between the prone and supine groups. Although we examined prolonged periods of prone ventilation combined with a lower tidal volume approach in children with acute lung injury, our results are similar to previously reported studies in the adult population.[16,17]

As described in several nonrandomized studies,[9,10,12] most of our patients who were positioned prone did exhibit an improvement in oxygenation; however, these improvements were not associated with a decrease in the duration of ventilator support. Our 20-hour per day protocol was much longer than the 7- and 8-hour protocols that were previously tested in adult patients.[16,17] This study was designed so that patients could be afforded the potential lung-protective effects of prone ventilation early and throughout the acute phase of illness. This goal was achieved as patients were positioned prone on average 28 hours after meeting eligibility criteria and were treated in the prone position for 79% of the acute phase of illness. Although patients in this trial received early and prolonged use of the prone position, we were unable to demonstrate beneficial effects on clinical outcomes.

Ninety percent of prone-positioned patients were categorized as responders by some improvement in oxygenation efficiency. The mechanism by which prone positioning leads to an improvement in oxygenation is not fully understood, es-

pecially in a patient who is developmentally immature. In infancy, chest wall compliance is nearly 3 times that of the lung.[30] By the second year of life, the increase in chest wall stiffness is such that the chest wall and lung have similar compliance as in adults. By 8 years, the height of the chest wall is similar to that of an adult. Pelosi et al[7] reported that thoracoabdominal compliance decreases in the prone position and the magnitude of this change is associated with the observed change in oxygenation; that is, the greater the decrease in thoracoabdominal compliance, the greater the improvement in oxygenation with prone positioning. Given the demonstration that improved oxygenation with prone positioning is associated with the magnitude of supine-prone difference in chest wall compliance in adults,[7] we predicted that prone positioning would be more effective for improving oxygenation and clinical outcomes in the younger patients enrolled in our clinical trial. Our results did not support this prediction.

The primary outcome for this study was ventilator-free days, a composite outcome that reflects both survival and duration of mechanical ventilation.[23] We selected this outcome variable because we hypothesized that prone positioning would simultaneously reduce mortality and shorten the duration of ventilation. Compared with previous studies investigating acute lung injury in adult patients,[2,16,17,31-33] we report lower mortality and more ventilator-free days. Aside from age and excluding patients after bone marrow transplant, our patient population was similar to previous studies investigating prone positioning in adult patients.[16,17]

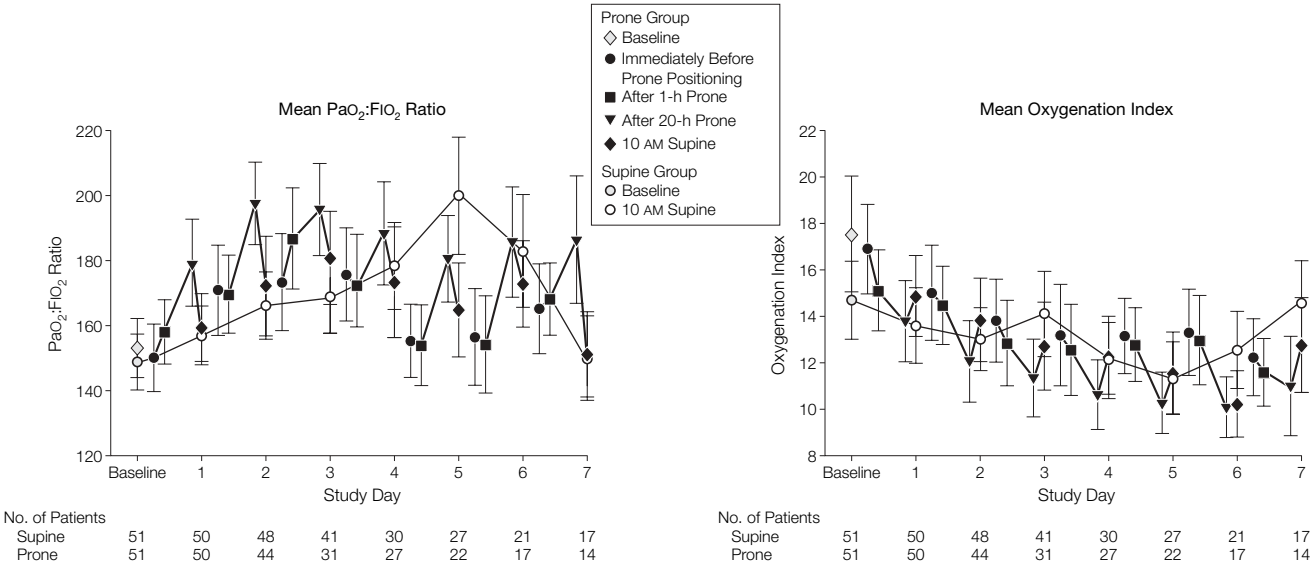
To evaluate the nonpulmonary effects of the prone position, a number of secondary outcomes were analyzed. Nonpulmonary organ-failure–free days, an outcome that provides insight into the lethal multiple organ dysfunction related to acute lung injury,[34] were not significantly different between the 2 groups. This may be related to the small number of patients who were septic in our study, a population that consistently manifests the largest number of organ failures in clinical trials.[1] Furthermore,

Table 4. Sedation Use During the Acute Phase*

	Median (Interquartile Range)	
	Supine Group (n = 50)	Prone Group (n = 50)
Average†		
Morphine equivalents	2.9 (1.6-4.7)	3.3 (1.5-5.2)
Midazolam equivalents	2.5 (1.2-4.2)	2.1 (1.2-4.2)
Sedation score	57 (43-86)	60 (34-87)
Total‡		
Morphine equivalents	12.2 (4.9-24.3)	9.9 (4.5-23.1)
Midazolam equivalents	12.1 (3.4-21.4)	8.7 (3.0-14.5)
Sedation score	262 (100-478)	199 (93-435)

*All opiates were converted to morphine equivalents using the following conversions to equal 1 mg of morphine sulfate: 15-µg fentanyl citrate, 0.15-mg hydromorphone hydrochloride, 0.3-mg methadone hydrochloride, and 20-mg codeine. All benzodiazepines were converted to midazolam equivalents using the following conversions to equal 1 mg of midazolam: 2-mg diazepam and 0.33-mg lorazepam. For the sedation scoring, 1 point was given for each of the following: morphine or midazolam equivalents of 0.1 mg/kg of body weight, pentobarbital of 2 mg/kg, chloral hydrate of 50 mg/kg, any propofol use, or any phenobarbitol use. Use of any antihistamines received a point score of 0.5.[27] There were no statistically significant differences between treatment groups for any of these variables (2-sample *t* test).
†Average calculated per patient per day (mg/kg body weight per day).
‡Total is sum (mg/kg of body weight) during the acute phase.

Figure 3. Mean PaO_2:FIO_2 Ratio and Oxygenation Index During the Acute Phase



Baseline reflects supine values in both groups before the implementation of ventilator protocols. Each calculation includes data from all patients, regardless of how many measurements were available from each patient on that day. The number of patients who contributed at least 1 measurement to the calculation are included. The morning supine PaO_2:FIO_2 ratio and oxygenation index were not significantly different between the 2 groups for any of the acute phase days (2-sample *t* test $P \geq .15$). Error bars indicate SE.

Table 5. Position-Related Adverse Events

	Events (No. of Patients)	
	Supine Group (n = 50)	Prone Group (n = 51)
Inadvertent endotracheal tube extubation	5 (5)	4 (3)
Plugged endotracheal tube	0	2 (2)
Endotracheal reintubation (after passing the extubation readiness test for upper airway obstruction)	5 (4)	6 (6)
Transient desaturation	6 (2)	5 (3)*
Transient hypercarbia	0	4 (3)
Bradycardic episode	0	4 (1)
Pneumothorax or pneumomediastinum	3 (2)	0
Pressure ulcer stage		
II	12 (7)	12 (9)
III	0	1 (1)
IV	1 (1)	0
Loss of arterial access	0	1 (1)
Paraphimosis	0	1 (1)
Abdominal ascites	0	1 (1)
Circumoral rash	0	1 (1)

*Two of the 5 transient desaturation events occurred in 1 patient while in the supine position.

the use of a lung-protective ventilator protocol limited the potential for differences in treatment outside of the positioning protocols.

Our study design also included assessment of functional health, which provided additional insights. Not all pediatric patients who survived acute lung injury returned to their previous level of function. Specifically, 11% of survivors experienced worsening cerebral function and 16% of survivors had worsening overall functional ability. To our knowledge, this is the first study of acute lung injury describing the impact of acute lung injury on functional outcomes in the pediatric population.

Little is known about the relationship between acute phase management (specifically, optimal levels of oxygenation in the acute phase) and functional outcomes in patients with acute lung injury. In pediatrics, several functional outcome and quality of life measures are now available. Future interventional studies should concentrate on looking past the immediate outcome of the episode of illness and focus on the patient's functional capacity and quality of survival.[35]

There are limitations to this clinical trial. First, it was not possible to blind clinicians to group assignment, so observer bias may have been introduced. However, several aspects of the trial design should have limited this potential bias, including the use of algorithms for most aspects of clinical care as well as the use of objective outcome measures (available from the authors upon request). Second, this study was not designed to show equivalence between prone and supine positioning. Our trial design included a futility stopping boundary because we thought it would be inappropriate to continue to randomize patients into a study in which there was little chance of finding statistically significant differences in the main clinical outcomes. Stopping the study for futility at the planned interim analysis could have caused a type II error (false-negative result); that is, failing to detect a prone positioning possible benefit of 3.5 ventilator-free days or possible harm of 3.0 ventilator-free days as indicated from the 95% CI. Third, given the smaller total sample size induced by stopping early, we might not have observed a rare position-related complication in the study.

Shortcomings of previous clinical studies of prone positioning have included the lack of treatment algorithms for adjunctive care of study patients that might impact primary or secondary study outcomes. In this trial, carefully designed protocols to define ventilator management, extubation readiness, and the use of sedative agents were implemented to minimize variation in the daily management of both groups. Despite careful control of these cointerventions, pediatric patients positioned prone did not demonstrate improved clinical outcomes. Although we can rule out a large beneficial treatment effect, we cannot exclude a small treatment effect, including a small negative effect. However, based on the interim analysis performed at the study midpoint, the results of this trial do not support the continued use of prone positioning as a therapeutic intervention to improve the outcomes in pediatric patients with acute lung injury.

Author Contributions: Dr Curley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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