Different Duration of Prone Position Treatment for Patients with Acute Respiratory Distress Syndrome in Intensive Care Unit Patients: A Prospective Randomized Clinical Study

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Article

Different Duration of Prone Position Treatment for Patients with Acute Respiratory Distress Syndrome in Intensive Care Unit Patients: A Prospective Randomized Clinical Study

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Abstract

Introduction: Prolonged prone positioning, exceeding 16 hours, has been associated with decreased mortality rates among patients diagnosed with moderate to severe acute respiratory distress syndrome (ARDS). Extending the duration of prone positioning may confer greater therapeutic benefits. This study aims to assess the clinical disparities between 16-hour and 24-hour prone positioning therapy in patients with moderate to severe ARDS. **Methods:** This prospective randomized clinical trial was conducted in the intensive care unit of a university-affiliated tertiary medical center. Patients were randomly assigned to receive either 16-hour or 24-hour prone positioning therapy. All participants followed a protocol incorporating low tidal volume and protective lung strategies. **Results:** Forty-five patients diagnosed with moderate to severe ARDS requiring mechanical ventilation, 21 were allocated to the 16-hour prone positioning group, while 24 were assigned to the 24-hour group. Findings revealed no significant differences in PaO_2 / FiO_2 ratios, driving pressure, or serum lactate levels between the two groups. The first session of prone positioning has significantly higher PaO_2 / FiO_2 improvement than the second session of prone positioning (). The 24-hour group displayed a tendency toward requiring fewer prone positioning sessions compared to the 16-hour group. Secondary endpoint did not significantly differ between the two groups. **Conclusions:** There is a trend suggesting that the 24-hour prone positioning group necessitates fewer sessions than the 16-hour group, potentially reducing clinical workload. The first session of prone position has better improvement of oxygenation than the second session of prone position.

Keywords: acute respiratory distress syndrome; driving pressure; lung protective strategies; oxygenation; prone position

1. Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening disease, patients with ARDS usually need mechanical ventilation. Treatment options for ARDS include low tidal volume ventilation, steroids, extracorporeal membrane oxygenation (ECMO), and prone positioning [1,2]. Prone positioning has been shown to recruit and stabilize dependent lung segments [3], resulting in improving oxygenation and reducing mortality rates in moderate to severe ARDS cases. Current guidelines suggest a minimum duration of 16 hours for prone positioning therapy [4]. Studies indicated that longer durations may confer greater benefits [5,6]. However, the optimal duration of prone positioning remains uncertain. In light of this, our study aims to compare the clinical outcomes

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associated with 16-hour versus 24-hour prone positioning sessions for patients diagnosed with moderate to severe ARDS.

2. Materials and Methods

2.1. Enrollment

The study was conducted over a three-year period, spanning from July 2020 to July 2023, within the adult intensive care unit (ICU). Eligible participants were individuals aged 20 or above, diagnosed with moderate to severe ARDS and managed under protective lung ventilation protocols (tidal volume 4-8 ml/kg, plateau pressure ≤ 30 cmH_2O, PaO_2/FiO_2 ratio < 150 mmHg, Positive end-expiratory pressure (PEEP) ≥ 5 cmH_2O, FiO_2 > 60%), and anticipated to survive for at least 24 hours. Exclusion criteria included patients who underwent abdominal surgery with an open abdominal wound, experienced massive hemoptysis, suffered from intracranial hemorrhage, were pregnant, or had spine or pelvic fractures. This prospective, randomized clinical study obtained approval from the human investigation and research committee of Kaohsiung Veterans General Hospital (VGHKS19-CT11-14). Before enrolling the first patient, the study was registered on clinicaltrials.gov (NCT04391387). This study performed in accordance with the Declaration of Helsinki. There are no conflicts of interest.

2.2. Randomization

After obtaining informed consent from the patients or their next of kin, participants were randomly assigned to one of two study groups using a software-generated randomization schedule. Randomization was allocated with 1:1 principle. Sequential numbers were put in sealed containers. Caregivers remained blinded to the randomization sequence. Upon assignment, arterial blood gas, serum lactate, and driving pressure measurements were taken. Residents and ICU nurses turn the subjects into the prone position after administering sedation and opioid therapy.

Following prone positioning, arterial blood gas, driving pressure, and serum lactate levels were assessed at the first hour, 8^{th} hour, 16^{th} hour and 24^{th} hour. These parameters were re-evaluated 8 hours after discontinuation of prone positioning. If patients achieved a PaO_2/FiO_2 ratio≥ 150 mmHg on FiO_2 ≤ 0.6 and PEEP ≤ 10 cmH_2O in the supine position, the next session of prone positioning therapy was discontinued [7]. Conversely, if patients did not meet these criteria, the next session of prone positioning therapy was initiated, with subsequent arterial blood gas, driving pressure, and serum lactate checks.

Demographic data collected at randomization included primary ICU admission diagnosis, age, gender, body mass index (BMI), number of organ failures, Acute Physiology and Chronic Health Evaluation (APACHE) II score, serum lactate and arterial blood gas levels, days between ARDS onset and prone positioning, and pulmonary or extra-pulmonary causes of ARDS.

Furthermore, specific medications administered during the study period, such as steroids (methylprednisolone, hydrocortisone, dexamethasone, prednisolone), antibiotics, sedatives, muscle relaxants, and opioids, were recorded.

The protective lung strategy for ventilator settings entailed maintaining a tidal volume of 4-8 ml per predicted body weight, with plateau pressure kept ≤ 30 cmH_2O [8].

2.3. Observations

Patients were monitored daily for the occurrence of pressure sores, endotracheal tube obstruction, tube dislodgement, ventilator-associated pneumonia (VAP), and the need for rescue use of ECMO. Monitoring of patients continued throughout the duration of prone position therapy, extending until the cessation of the final session.

2.4. Definitions

The diagnosis of ARDS follows the Berlin definition, which includes the following criteria [9]:

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1. Acute onset of infiltrates resulting from a known clinical insult or new/worsening respiratory symptoms within 7 days.
2. Bilateral opacity observed on chest imaging, not fully explained by effusions, lobar/lung collapse, or nodules.
3. Respiratory failure not fully explained by cardiac failure or fluid overload.
4. Utilization of a minimum PEEP of at least 5 cmH_2O.

The severity of ARDS is determined by the PaO_2/FiO_2 ratio: mild ARDS (200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg), moderate ARDS (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg), and severe ARDS (PaO_2/FiO_2 ≤ 100 mmHg).

Driving pressure is calculated as the difference between plateau pressure and PEEP, with plateau pressure defined as the pressure after the inspiratory pause.

A positive response to prone position therapy is indicated by an increase in the PaO_2/FiO_2 ratio of ≥20% following prone positioning. Mortality is defined as death at discharge.

Diagnosis of VAP required the agreement of two pulmonologists. All radiographs were reviewed independently by each pulmonologist, without knowledge of clinical details. The diagnosis followed a modified version of the criteria of The National Nosocomial Infection Surveillance (NNIS) system developed by the Centers for Disease Control [10].

2.5. Outcomes

The primary outcomes measured in this study were the changes in the PaO_2/FiO_2 ratio following each prone positioning session, variations in driving pressure and serum lactate levels. Secondary outcomes included the number of prone positioning sessions required, lengths of ICU and hospital stays, duration of mechanical ventilation, occurrences of pressure sores, tube dislodgement, endotracheal tube obstruction, incidents of ventilator-associated pneumonia, and mortality rates.

2.6. Statistical Analysis

The statistical analysis was performed using SPSS version 29.0 (SPSS, Inc., Chicago, IL). A comparison between the two treatment groups was conducted based on the intent-to-treat principle. Data were presented as mean ± standard deviation, percentage, or median with interquartile ranges (IQRs). Student's t-test was employed for comparing continuous variables with a normal distribution, while the Mann-Whitney U test was utilized for continuous variables with a non-normal distribution. Dichotomous variables were compared using either the Chi-square test or Fisher's exact test, depending on the expected frequency of occurrence. Differences in primary outcomes were analyzed using two-way analysis of variance (ANOVA), followed by post hoc analysis with Bonferroni method. Difference of PaO_2/FiO_2 ratio change among different sessions of prone positioning was analyzed using two-way ANOVA. All p-values were two-tailed, and significance was considered at $p < 0.05$.

3. Results

3.1. Demographics

Forty-nine patients initially meeting the inclusion criteria were enrolled in the study. However, two patients did not provide consent, one had undergone abdominal surgery with an open wound, and another had intracranial hemorrhage with increased intracranial pressure. Consequently, 45 patients were included, with 21 receiving 16-hour prone position therapy and 24 receiving 24-hour therapy. The flow chart for all patients is presented in Figure 1. All the patients completed study. The study ended when investigation and research expiration date reached. This study analyzed data with intent-to-treat principle.

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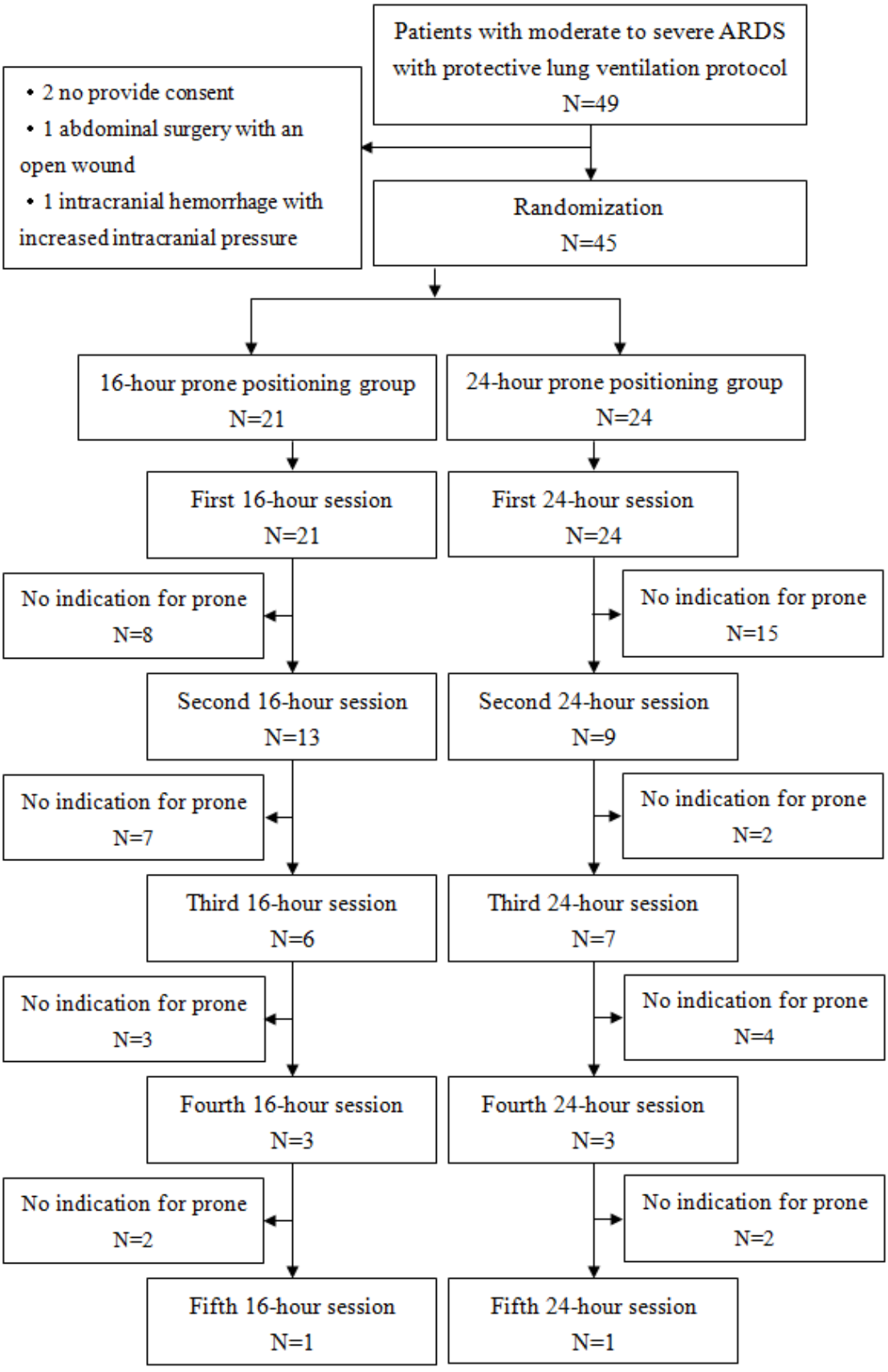

Figure 1.

At randomization, demographic characteristics such as gender, age, BMI, number of organ failures, APACHE II score, use of sedation, muscle relaxants, vasopressors, or steroids, time from

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ARDS onset to prone position therapy, pulmonary or extra-pulmonary cause of ARDS, and serum lactate levels were similar between the two groups (Table 1).

Table 1. The demographic characteristics of patients in the 16-hour group and the 24-hour group before the initiation of prone positioning therapy.

Characteristic	**16-hour** (N=21)	**24-hour** (N=24)	P value
Gender (M/F)	11/10	10/14	0.47
Age, year	71.1± 13.6	69.0 ± 11.2	0.59
BMI (kg/m^2)	23.2 ± 3.3	24.9 ± 6.3	0.27
Organ failure number	2.3 ± 1.2	2.3 ± 1.1	1.00
APACHE II score	26.6 ± 7.3	27.4 ± 7.7	0.72
Sedation (%)	21 (100)	24 (100)	0.99
Muscle relaxant (%)	18 (85.7)	24 (100)	0.06
Vasopressor (%)	18 (85.7)	17 (70.8)	0.22
Steroid (%)	17 (81.0)	20 (83.3)	0.81
ARDS to prone day	1.1 ± 1.9	1.0 ± 1.3	0.91
Pulmonary ARDS (%)	16 (76.2)	20 (83.3)	0.55
Extrapulmonary ARDS (%)	5 (23.8)	4 (16.7)	0.55
Serum lactate (mmole/L)	3.6 ± 3.5	2.1 ± 1.1	0.08

Definition of abbreviations: M/F, Male/Female; BMI, body mass index; APACHE, Acute Physiologic and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome.

No statistical differences were observed in respiratory parameters before the study period (Table 2), indicating homogeneity between the two groups.

Table 2. The disparity in ventilator parameters between the 16-hour group and the 24-hour group before the initiation of prone positioning therapy.

Characteristic	**16-hour** (N=21)	**24-hour** (N=24)	P value
PaO_2/ FiO_2 (mmHg)	79.3 ± 31.9	89.7 ± 30.5	0.27
PaO_2 (mmHg)	75.4 ± 28.9	78.9 ± 23.4	0.67
$PaCO_2$ (mmHg)	46.3 ± 28.9	53.3 ± 18.5	0.12
pH	7.4 ± 0.1	7.3 ± 0.1	0.13
Respiratory rate (breath/minute)	23.1 ± 4.9	22.1 ± 5.8	0.55
Tidal Volume (mL)	456.4 ± 120.4	462.8 ± 117.2	0.86
PEEP (cmH_2O)	12.0 ± 3.1	11.5 ± 2.6	0.53
Compliance (mL/cmH_2O)	23.8 ± 8.9	23.2 ± 8.8	0.82
Driving pressure (cmH_2O)	19.5 ± 4.5	21.0 ± 4.2	0.25
Mean airway pressure (mmHg)	19.2 ± 3.1	19.3 ± 3.6	0.92

Definition of abbreviations: PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure.

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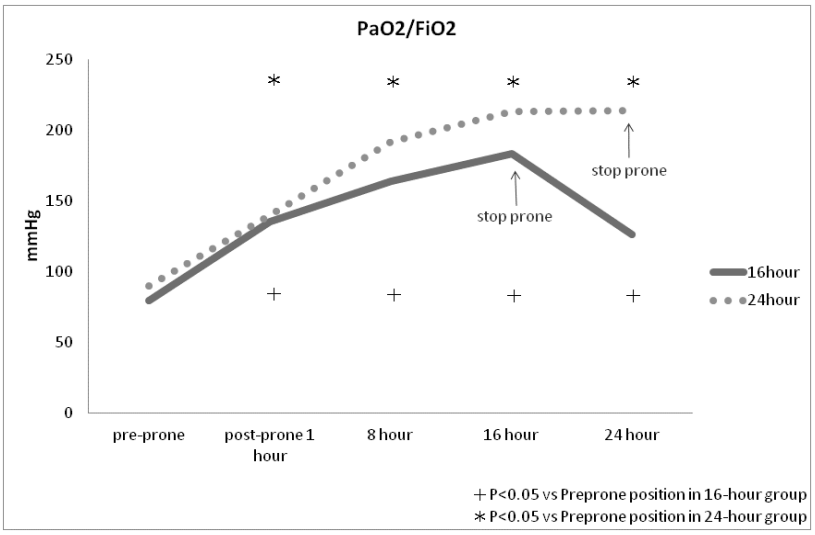
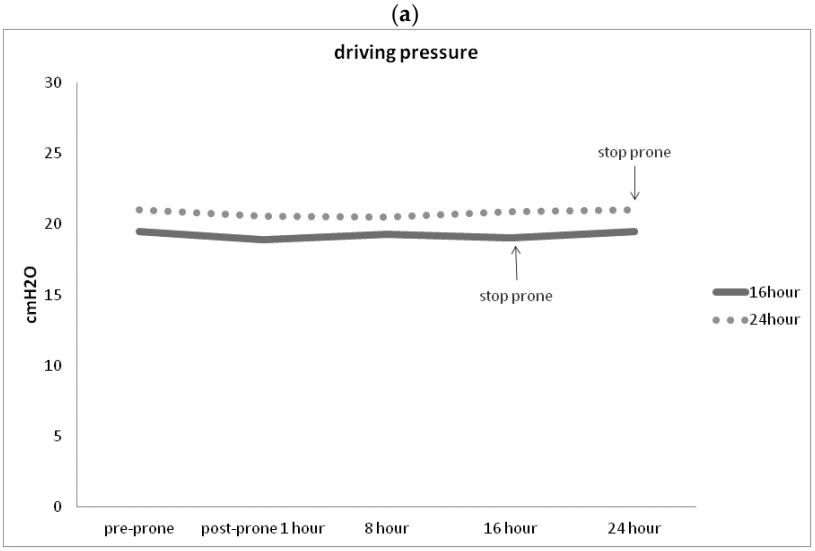
3.2. Primary Endpoints

Both groups demonstrated a significant improvement in PaO_2/FiO_2 following prone position therapy (Figure 2A), while there was no significant change in driving pressure (Figure 2B) or serum lactate levels (Figure 2C) during prone postioning. Notably, PaO_2/FiO_2 significantly increased within the first hour of prone positioning, but often decreased upon transitioning from prone to supine position (Figure 2A). There were no significant differences of PaO_2/FiO_2 driving pressure or serum lactate levels between 16-hour group and 24 hour-group (Figure 2 A,B,C).



(a)



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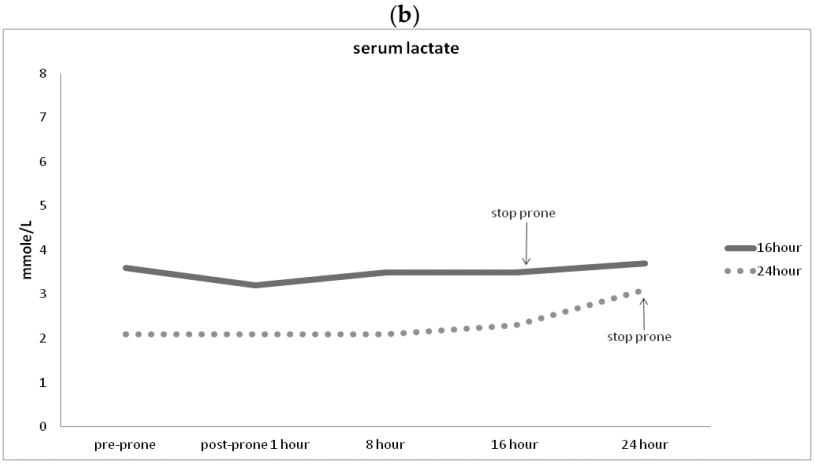

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Figure 2.

Additionally, a decreasing trend was observed in the change of PaO_2/FiO_2 between pre- and post-prone positioning. With subsequent sessions, there was a significantly higher change of PaO_2/FiO_2 ratio in the first session compared to the second session of prone positioning (24-hour group: first session 135± 112.8 mmHg vs second session 42.6± 50.5 mmHg, $P < 0.05$, 16-hour group first session 104.4± 84.9 mmHg vs second session 20.4± 91.6 mmHg, $P < 0.05$) (Figure 3).

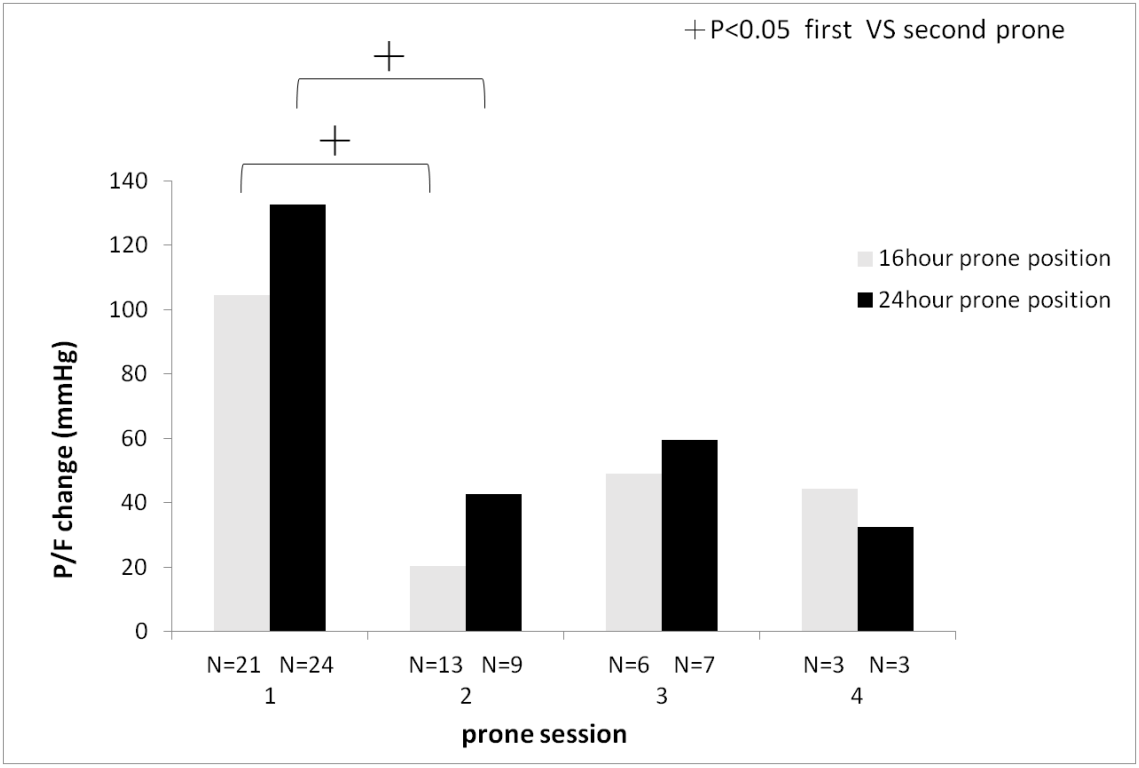

Figure 3.

3.3. Secondary Clinical Outcomes

Secondary clinical outcomes, including the number of prone positioning sessions, changes in PaO_2/FiO_2 after discontinuation of prone positioning, incidence of tube dislodgement, endotracheal tube obstruction, pressure sores, ICU days, ventilator days, hospital days, and occurrences of VAP, are summarized in Table 3. Patients undergoing 24-hour prone position therapy exhibited a tendency towards a lower rate of repeated prone positioning sessions compared to those receiving 16-hour therapy (37.5% vs. 61.9%, p=0.06) (Table 3), although this difference did not reach statistical significance. No significant differences in complications such as pressure sores, tube dislodgement, endotracheal tube obstruction, or VAP were observed between the two groups. The mortality rate was not significantly different between the 16-hour group (57.1%) and the 24-hour group (54.2%), with both groups showing a high responder rate (95.2% vs. 95.8%). Additionally, there was no significant difference in the need for rescue ECMO use. The 30-day outcomes, including the length of ICU-free days, ventilator-free days, and survival while liberated from the ventilator, did not exhibit any significant differences (Table 3).

Table 3. The variation in clinical outcomes between the 16-hour group and the 24-hour group following prone positioning.

Characteristic	**16-hour** (N=21)	**24-hour** (N=24)	P value
Session >1 of prone position (%)	13 (61.9)	9 (37.5)	0.06

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Change of P/F after stopping prone position (mmHg)	111.4 ± 134.7	74.8 ± 71.9	0.28
Tube dislodgement (%)	1 (4.8)	0 (0)	0.28
Endotracheal tube obstruction (%)	1 (4.8)	2 (8.3)	0.63
Pressure sore (%)	1 (4.8)	4 (16.7)	0.13
Ventilator-associated pneumonia (%)	1 (4.8)	3 (12.5)	0.35
Weaning ventilator (%)	9 (42.9)	9 (37.5)	0.71
Mortality (%)	12 (57.1)	13 (54.2)	0.86
Change of $PaCO_2$ (mmHg)	3.2 ± 10.9	9.6 ± 15.3	0.12
Change of P/F after prone position (mmHg)	104.4 ± 84.9	123.1 ± 105.2	0.52
PaO_2/ FiO_2 responder (%)	20 (95.2)	23 (95.8)	0.88
Rescue ECMO (%)	0 (0)	0 (0)	0.99
30-day outcomes			
ICU-free days	18.2 ± 7.7	14.4 ± 7.2	0.28
Ventilator-free days	16.1 ± 9.1	9.7 ± 7.3	0.16
Alive and liberated from ventilator (%)	8 (38.1)	7 (29.2)	0.53

Definition of abbreviations: IQR, interquartile range; P/F, PaO_2/ FiO_2; ICU, intensive care unit; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; ECMO, Extracorporeal Membrane Oxygenation.

4. Discussion

This study reveals that prone position therapy effectively enhances oxygenation for patients with moderate to severe ARDS in both 16-hour and 24-hour treatment groups. Early session of prone positioning has higher PaO_2/FiO_2 ratio improvement. However, it does not significantly improve driving pressure or serum lactate levels. Notably, the 24-hour duration of prone positioning demonstrates a tendency toward requiring fewer therapy sessions compared to the 16-hour duration.

In prior research, the increase in PaO_2 ranged from 23 to 78 mmHg, with PaO_2/FiO_2 improving by 21 to 161 mmHg [11]. Our study shows a PaO_2/FiO_2 increase of 114.1 mmHg. The improvement results from a reduction in shunt and ventilation-perfusion heterogeneity that occurs because the lungs, which anatomically resemble a cone, fit into their cylinder-like thorax endosure with less distortion when patients are prone versus supine [12–15].

Driving pressure correlates with global lung strain [16,17] and is recognized as a risk factor for ARDS in mechanically ventilated patients [18]. Reductions in driving pressure have been strongly linked to improved survival in ARDS cases [16]. However, our study did not show reduced driving pressure significantly during prone positioning, one study found that driving pressure did not significantly change during prone positioning for ARDS patients [19], which aligns with the findings of our study. Prone positioning exceeding 12 hours reduces mortality for patients with moderate to severe ARDS [20], but it's not directly related to driving pressure.

While prone positioning significantly enhances oxygenation, it does not notably affect serum lactate levels. Lactate levels are influenced by various factors, including underlying diseases, medications, cellular metabolism, tissue perfusion, and regional areas of ischemia [21]. A decrease in lactate levels reflects both improved microcirculation and increased lactate clearance, rather than solely increased oxygen delivery. Yoshida T et al. also reported that prone position did not significantly lower serum lactate levels (supine: 15 mg/dl vs prone: 13 mg/dl) [22], consistent with our study.

Interestingly, the initial prone positioning session yields a significantly higher increase in PaO_2/FiO_2 compared to subsequent sessions. Prone position may be effective in improving oxygenation when initiated early (< 3 days) during the exudative phase, when congestive and compressive atelectasis are predominant features as opposed to the intermediate phase of ARDS (>1 week) [23,24].

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The majority of observational studies report no improvement in partial pressure of carbon dioxide ($PaCO_2$) [11], similar to our findings. However, clinical outcomes tend to be more favorable when prone positioning results in a decreased $PaCO_2$ at the same minute ventilation [25].

This study indicates that the 16-hour prone position group tends to undergo more repeated prone position therapy sessions. This trend arises from the observation that most patients who discontinued prone position therapy exhibited signs of worsening oxygenation, with their PaO_2/FiO_2 dropping below 150 mmHg, prompting the resumption of prone positioning therapy. In contrast, 24-hour prone position therapy demonstrates prolonged improvement in oxygenation. The longer duration of prone positioning confers the benefit of reducing the need for repeated therapy sessions, thereby decreasing clinical workload.

The response rate of prone position therapy is high up to 95.5% in this study. Lee DL et al showed that responders had a significantly shorter elapsed time from ARDS to prone position ventilation (8.4±2.9 vs 15.2±5.7 days, $P<0.05$), with a total response rate of 63.6% in that study [26]. The average elapsed time from ARDS to the first prone position is one day in our study. L'Her E et al. conducted early prone position therapy during the first 24 hours and demonstrated that the response rate is 96% [27], similar to our study.

Prone position therapy is associated with a higher incidence of pressure sores compared to the supine position, with age over 60 and a BMI above 28.4 being identified as risk factors for pressure sores [28]. Additionally, endotracheal tube obstruction is another prevalent complication associated with prone positioning. Lee JM et al. demonstrated that prone positioning increased the risk of endotracheal tube obstruction by 2.16-fold (95% CI, 1.53-3.05, $P < 0.001$), based on a previous meta-analysis of 11 randomized controlled studies [29]. However, our study found no significant difference in complications between the 16-hour and 24-hour groups of patients, which is consistent with recent report by Page DB et al [30].

This study has several limitations. The small sample size may limit the significance of some parameters. Additionally, being a single-center non-blinded randomized controlled study, further research involving multiple centers and nations is warranted.

5. Conclusions

Prone positioning ventilation significantly enhances oxygenation in patients with moderate to severe ARDS after just one hour of therapy. Early initiation of prone positioning yields better oxygenation improvement. The 24-hour prone positioning group tends to require fewer therapy sessions. Notably, there are no significant differences in oxygenation, driving pressure, serum lactate, mortality, or complications between the 16-hour and 24-hour groups.

Author Contributions: C. H.: Conceptualization, Methodology and Writing—original draft. **S. L.**: Investigation, Data curation. **C. Y.**: Investigation, Data curation. **S. S.**: Writing—review and editing. **S. K.**: Formal analysis. **K. C.**: Resources. All authors have read and agreed to publish version of manuscript.

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Institutional Review Board Statements: the study was conducted in accordance with declaration of Helsinki and approved by the human investigation and research committee of Kaohsiung Veterans General Hospital (VGHKS19-CT11-14).

Informed Consent Statement: Informed consent was obtained from all individual participants include in this study.

Data Availability Statement: All the data are available.

Conflicts of Interest: The authors declare no conflicts of interest.

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