META-ANALYSIS

Meta-Analysis of Efficacy and Safety of Prone Enteral Nutrition in Critically Ill Ventilated Patients

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ABSTRACT

Objective • Assessing the safety and efficacy of enteral nutrition in critically ill patients receiving prone position ventilation is essential to optimize treatment strategies for critically ill patients. Systematically evaluate the effectiveness and safety of prone position enteral nutrition in critically ill ventilated patients, providing a reference for clinical decision-making.

Methods • We conducted a comprehensive search for relevant studies on the safety and efficacy of enteral nutrition in prone ventilation patients. Our search encompassed randomized controlled trials, quasi-experimental studies, and cohort studies, utilizing databases including PubMed, Embase, and Scopus. The search duration spanned from May 2000 to May 2023. Inclusion and exclusion criteria were applied to select eligible literature, followed by data extraction and quality assessment. We employed specific keywords and filters in our search strategy to ensure a robust selection of studies. Subsequently, statistical analysis was performed utilizing RevMan 5.2 software to synthesize and interpret the findings effectively.

Result • Five articles were ultimately included, with a total of 372 patients undergoing prone ventilation. The meta-analysis results showed that patients receiving enteral nutrition during prone and supine ventilation had higher levels of gastric residue incidence [RR = -0.01, 95% CI: (-0.08, 0.06), *P* = .77]. There was no significant difference in the incidence of vomiting/reflux between the prone position group and the control group [RR = 0.60, 95%CI: (0.15-2.45), *P* = .48]. Prone position ventilation had no significant effect on the incidence of ventilator-associated pneumonia (VAP) [RR = 1.00, 95%CI: (0.14-6.90), *P* = 1.00]. There was no significant difference in the rate of enteral nutrition interruption between the prone position group and the control group [RR = 0.65, 95%CI: (0.28-1.52), *P* = .32].

Conclusion • Enteral nutrition in critically ill patients receiving prone position ventilation was not associated with high levels of gastric residual, vomiting or reflux, ventilator-associated pneumonia, or increased incidence of enteral nutrition interruption. (*Altern Ther Health Med.* 2023;29(8):754-759).

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INTRODUCTION

The prone position (PP) refers to a patient transitioning from the supine position (SP) to the ventral position in order to enhance the expansion of the dorsal lung area and improve patient oxygenation.[1] Prone position ventilation is an important treatment method to improve the oxygenation status of critically ill patients by expanding the dorsal lung and has been applied to the treatment of various clinical hypoxemia patients.[2,3] Patients with prone position ventilation have increased body catabolism and energy consumption, resulting in a higher incidence of malnutrition, which is not conducive to their recovery.[4] Enteral nutrition is the preferred method of nutritional support for mechanically ventilated patients, which is of great significance in maintaining intestinal function and reducing secondary infections. The European Guidelines for Critical Care Nutrition recommend that patients with prone position ventilation should receive enteral nutrition as soon as possible. However, changes in posture and factors such as the use of analgesics and sedatives can affect gastrointestinal motility in patients undergoing prone ventilation, leading to increased abdominal pressure and delayed gastric emptying. During this period, enteral nutrition may increase the risk of feeding intolerance.[6] there is controversy over the safety and effectiveness of enteral nutrition in patients undergoing prone position ventilation, as it sheds light on a critical aspect of patient care that has been debated within the medical community. This study's findings provide valuable insights into this contentious topic, contributing to a deeper understanding of optimal nutritional management for critically ill patients in prone position ventilation. Although its effectiveness has been widely described in the literature, the use of prone position is not common in ICUs. Relevant studies have shown that for critically ill ventilated patients, the range of use of this protocol is 2.8% to 16.3%.[7] Factors such as the availability of resources, medical guidelines, and healthcare infrastructure could contribute to this range, reflecting the diverse approaches taken by different institutions or regions in managing prone ventilation patients and their nutritional needs. Linn et al. published a systematic review of enteral nutrition in adult prone-position ventilated patients in 2015, but this study only included four articles, of which only two compared the safety and effectiveness of enteral nutrition in supine and prone-position ventilated patients.[8]

In recent years, multiple original studies on related topics have emerged, but the sample size of a single study is small and some research conclusions are inconsistent. In addition, a retrospective study on critically ill ventilated patients who applied a prone position regimen found that 82.9% of patients had insufficient enteral feeding in the prone position, which contributed to negative energy and protein balance.[9]

In conclusion, the objective of this study was to systematically evaluate the effects of enteral nutrition in a prone position on gastric residues and clinical outcomes in critically ill patients. The purpose of this study is to provide a reference for clinical decision-making, and to evaluate the effect of enteral nutrition on gastrointestinal function and clinical outcome of patients with severe illness by comprehensively evaluating the effect of enteral nutrition on prone ventilation.This study was designed to provide valuable insights into clinical decision making and advance our understanding of the impact of enteral nutrition during prone ventilation.

MATERIALS AND METHODS

Retrieval Strategy

The literature search was conducted in May 2023 in three databases (PubMed, Scopus, and Embase), with indexed terms related to enteral nutrition and prone position. The main MesH used in the search is as follows: "prone position"+"prone position ventilation" AND "enteral nutrition"+"enteral nutrition," with no restrictions on the language or date of publication. The search strategy used in PubMed is shown in Figure 1, and the search was updated in May 2023.

Figure 1. PubMed Retrieval Strategy

#1 "prone position" [MeSH Terms]

#2 "position prone" [Title/Abstract] OR "prone positions" [Title/Abstract] OR "Prone" [Title/Abstract] OR "Position" [Title/Abstract] OR "Positions" [Title/Abstract] OR "Prone Positions" [Title/Abstract]

#3 #1 OR #2

#4 "enteral nutrition" [MeSH Terms]

#5 "nutrition enteral" [Title/Abstract] OR "enteral feeding" [Title/Abstract] / OR "feeding enteral" [Title/Abstract] OR "force feeding" [Title/Abstract] OR (("feeding" [All fields])) OR "force feedings" [Title/Abstract] OR "tube feeding" [Title/Abstract] OR "feeding tube" [Title/Abstract] OR "gastric feeding tubes"[Title/ Abstract] OR "feeding tube gastric" [Title/Abstract] OR (("feeding" [All Fields] OR "feedings" [All Fields] OR "feeds" [All Fields]) AND "tubes gastric" [Title/Abstract]) OR "Gastric Feeding Tube" [Title/Abstract] OR ((("tubes" [All Fields] OR "tubed" [All Fields] OR "tubes" [All Fields] OR "tubings" [All Fields]) AND "tastric feeding" [Title/Abstract]) AND "diet care" [All Fields] AND "Eating" [All Fields])

#6 #4 OR #5

#7 "randomized controlled trial" [Publication Type] OR "randomized" [Title/Abstract] OR "placebo" [Title/Abstract]

#8 #3 AND #6 AND #7

#9"Critical ventilation patients" [Title/Abstract] OR "Ventilation patients" [Title/Abstract]

#10 #8 AND #9

Criteria for inclusion and exclusion of literature

Inclusive criteria. 1. The types of studies were randomized controlled trials, quasi-experimental studies and cohort study; 2. The research subjects are patients who are ventilated in a prone position and receive enteral nutrition without limiting their gender, age, ethnicity, nationality, etiology, underlying diseases, etc.; 3. A clinical randomized controlled trial of enteral nutrition and parenteral nutrition in the treatment of critically ventilated patients; 4. All included studies must provide at least one of the following endpoint study indicators: systemic multiple organ failure, mortality, and infection rates.

Exclusion criteria. 1. Clinical randomized controlled trials of enteral and parenteral nutrition treatment inon-critically ill ventilated patients; 2. Repeated publications, conference papers, and poor-quality literature; 3. The full text cannot be obtained through various means; 4. Animal experiments; 5. Those who implement enteral nutrition methods that do not meet the standards.

Literature Screening and Data Extraction

In the literature screening and data extraction phase, we planned to search for relevant literature from May 2000 to May 2023 by searching the PubMed, Embase, and Scopus databases. We will use randomized controlled trials, quasi-experimental studies, and cohort studies to evaluate the safety and efficacy of enteral nutrition in patients ventilated in the prone position. Our search terms and strategies will cover keywords related to enteral nutrition, prone position ventilation, and critically ill patients to ensure access to the research literature as comprehensive as possible.

Extract and organize information from all preliminarily retrieved relevant literature according to the abovementioned inclusion and exclusion criteria. Researchers who have received evidence-based training will independently screen and extract literature according to the inclusion and exclusion criteria, and conduct cross-checking. We have taken multiple steps to resolve these conflicts. First, each researcher independently performed literature screening and data extraction to avoid subjective bias. We then cross-check and review each other's work to detect and correct possible errors early. If we disagree, we engage in discussions to gain insight into each other's positions and try to reach consensus. If there is still disagreement, we seek the assistance of a third researcher, usually an experienced expert, to provide a neutral opinion. Repeatedly screen all literature that meets the research criteria according to the above criteria, and eliminate those that do not meet the secondary screening. Finally, count the research literature that ultimately meets the inclusion criteria.

Literature quality evaluation

Quality evaluation of randomized controlled trials was conducted using the bias risk assessment tool recommended in Cochrane Evaluation Manual 5.1.0.[10] The evaluation content includes the generation of random sequence, the hiding of allocation scheme, the blinding of research objects and interveners, the blinding of evaluators, the integrity of result data, the selective reporting of results and other biased items. The researchers make the judgment of "low-risk bias" and "high-risk bias unclear" for each item. If the research fully meets the above criteria, the likelihood of various biases occurring is low, with a quality level of A; if partially met, the likelihood of bias occurring is moderate, with a quality level of B; if not completely met, the likelihood of bias occurring is high, with a quality level of C. These bias assessment items cover important factors such as randomness, blinding, and result reporting, and play a key role in the overall quality assessment. They help to judge the reliability of a study and the possibility of bias, so as to accurately assess the credibility of a study.

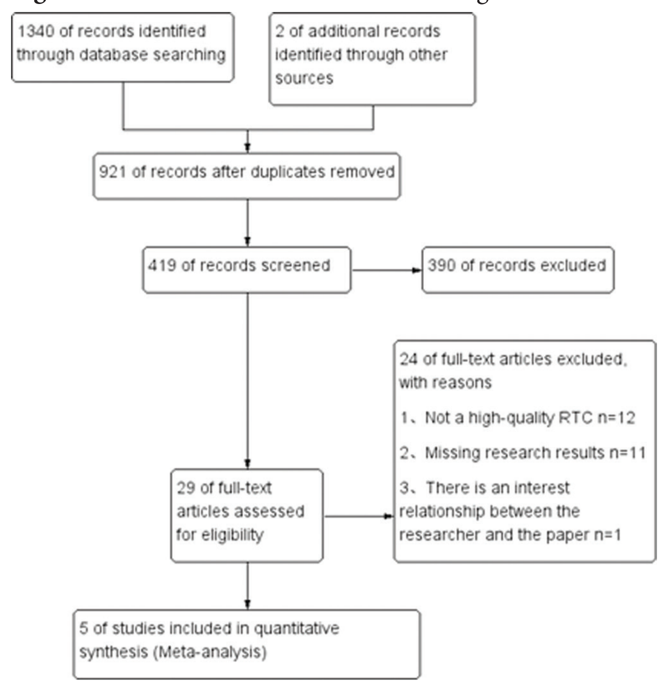
Statistical analysis

Meta-analysis was conducted using RevMan 5.2 software. Heterogeneity evaluation of the literature included in the study was conducted using I^2 statistics and χ^2. If χ^2 tested $P < .10$ or $I^2 > 50\%$, it indicates significant heterogeneity. In this case, a random effects model was used for consolidation analysis, otherwise a fixed effects model was used. The counting data used ratio (RR) and its 95% confidence interval (CI) as the effect indicators for the study. To ensure the stability of the results, sensitivity analysis was conducted by excluding individual studies and reanalysis. Individual studies were excluded one by one and re-analyzed. This process was designed to examine the impact of each independent study on the overall results. By excluding a particular study individually, we can observe its effect on the pooled effect estimate and thus determine whether that study has a significant effect on the overall conclusion. In addition, the degree of publication bias was evaluated by observing the funnel plot. The funnel plot is a graphical tool used in meta-analyses to assess publication bias. It reveals the impact of unpublished studies by presenting the relationship between study effect size and precision. It is usually symmetrical in shape and asymmetry may imply the presence of unpublished studies. By looking at the funnel plot, we can judge the impact of publication bias on the results of the meta-analysis.

Table 1. Basic characteristics of included literature (n = 5)

Included in the literature	The type of research	Example number	Intestinal nutrition pathway	Time of ventilation in each PP (h)	High-level GRV judgment criteria
Xie BF et al.[11]	cohort study	60	Nasogastric tubes or nasoenteral tubes	12	Every 6 h GRV ≥ 150 ml
Savio et al.[12]	cohort study	47	nasogastric tube	12	Every 6 h GRV ≥ 250 ml
Chen SS et al.[13]	RTC	35		6	Every 8.5 h GRV ≥ 100 ml
van der Voort et al.[14]	RTC	19		6	Every 6 h GRV ≥ 150 ml
Lucchini et al.[15]	cohort study	25		12	-

Figure 2. Flow Chart of Literature Screening



RESULTS

Literature search results

A preliminary search yielded 1340 articles, and 2 related articles were supplemented through other means（The other two papers could not be found in the database）, totaling 1342. After removing duplicate literature through EndNote X9 software, 419 articles were obtained. After reading the title, abstract, and full text, 414 articles that did not meet the inclusion criteria were excluded, and ultimately five articles were included. The included articles' screening process and research overview are shown in Figure 2 and Table 1[11-15]. The risk of bias was evaluated using the evaluation table recommended by the Co Crane evaluator manual for the literature included in the study. All included studies were of high quality, and implementation bias, measurement bias, and follow-up bias all had lower bias risks (Figure 3).

Figure 3. Summary of risk bias

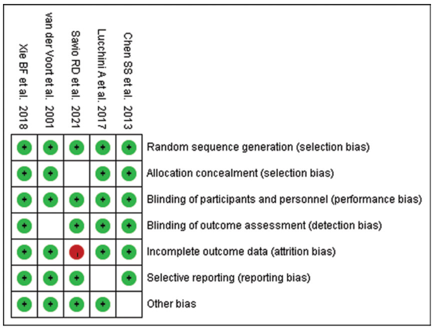


Figure 4. Incidence of HGR in prone position

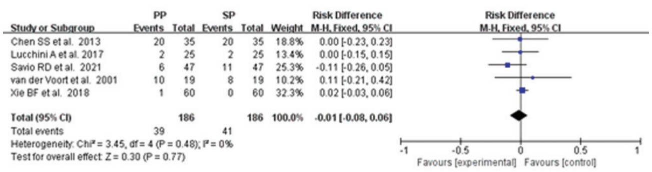


Figure 5. A funnel plot of HGR incidence

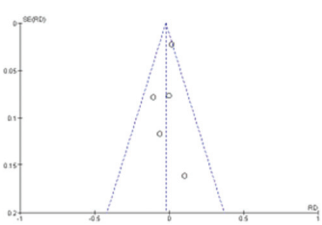


Figure 6. Incidence of HGR in prone position

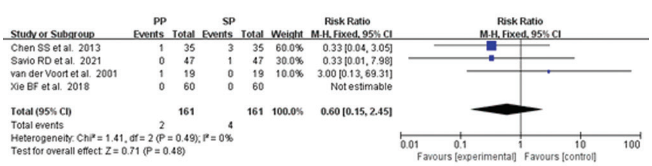
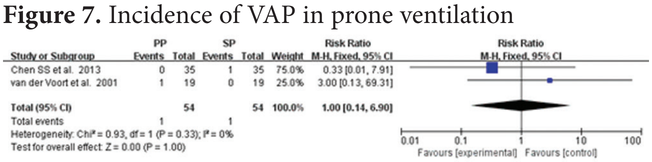


Figure 7. Incidence of VAP in prone ventilation



Meta analysis results

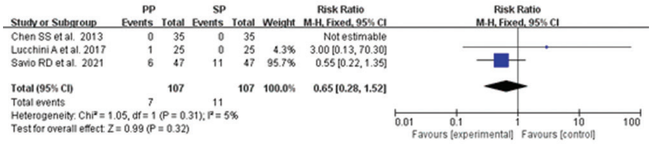
Effect of prone position ventilation on the incidence of HGR. Five studies with a total of 186 patients in the prone position ventilation group and 186 patients in the control group were included to assess the effect of prone position ventilation on the incidence of vomiting/reflux. The included studies were meta-analysed using Review Manager 5.2 software to obtain forest plots (Figure 4) and funnel plots (Figure 5) of the impact of prone ventilation on the mortality rate of critically ill patients. Forest plots are commonly used graphs in meta-analyses to present effect sizes and confidence intervals across multiple studies so that readers can intuitively understand the variation and consistency across studies. Each study is presented as a line segment, the length represents the effect estimate, the confidence interval is shown as a horizontal line, and comparing the different line segments can reveal differences and overall trends.The incidence of HGR was a two categorical variable, and the relative risk (RR) and 95% confidence interval (CI) were used for statistical analysis. The results showed low inter group heterogeneity (P = .48, I^2 = 0%), so a fixed effects model was used to calculate. This means that there are small differences between the results of the different studies included, which can indicate that the studies are consistent in some respects and the results are stable. The results showed that the incidence of HGR in patients in the prone ventilation group and the supine control group was 21.0% (39/186) and 22.0% (41/186), respectively, with no statistical difference [RR = -0.01, 95% CI: (-0.08, 0.06), P = .77]. The findings imply that there is no clear advantage or disadvantage with respect to the risk of this specific adverse event when selecting the ventilation position. This has important implications for clinical decision making in medical practice and the care management of critically ill patients.

Effect of prone position ventilation on the incidence of vomiting/reflux. Four studies with a total of 164 patients in the prone position ventilation group and 160 patients in the control group were included to assess the effect of prone position ventilation on the incidence of vomiting/reflux.The included studies were analyzed through software and a meta-analysis forest map was obtained for the impact of prone position ventilation on mechanical ventilation time in ARDS patients (Figure 6). The results showed that the heterogeneity test showed small intergroup heterogeneity (P = .49, I^2 = 0%). This means that there are small differences between the results of the different studies included, which can indicate that the studies are consistent in some respects and the results are stable. Using a fixed effects model, the results showed that there was no significant difference in the incidence of vomiting/reflux between the prone ventilation group and the supine position group [RR = 0.60, 95% CI: (0.15, 2.45), P = .48]. The results imply that there is no clear difference in the risk of this adverse event when ventilation position is considered. These findings have important implications for decision makers and clinical nursing staff in the management of ventilation in critically ill patients.

Effect of prone position ventilation on the incidence of VAP. Two studies with a total of 54 patients in the prone position ventilation group and 54 patients in the control group were included to evaluate the effect of prone position ventilation on the incidence of VAP. The included studies were analyzed using software to obtain a meta-analysis forest map of the impact of prone ventilation on the incidence of VAP (Figure 7). The results showed that there was no statistically significant difference in the incidence of VAP between the two groups [RR = 1.00, 95% CI (0.14, 6.90), P = 1.00]. Despite the inclusion of two studies in this study, the results of our analysis failed to show a clear effect of prone position ventilation on the incidence of VAP. However, the small sample size may have limited our ability to detect potential differences.

Effect of prone position ventilation on EN interruption rate. Three studies with a total of 107 patients in the prone position ventilation group and 107 patients in the control group were included to assess the effect of prone position ventilation on EN interruption rates.The included studies were analyzed by software and obtained a meta-analysis forest map of the impact of prone position ventilation on EN interruption rate (Figure 8). The results showed that there was no statistically significant difference in the interruption rate of EN between the two groups [RR = 0.65, 95% CI (0.28, 1.52), *P* = .32]. Although the results of our analysis showed no significant effect of prone position ventilation on the rate of enteral nutrition interruption, it is important to note that these results may have been affected by the limited sample size. Larger and more diverse studies may help to more fully assess the effects of prone position ventilation on enteral nutrition.

Figure 8. A Meta-analysis of the EN interruption rates



DISCUSSION

The first time prone ventilation was used for the treatment of critically ill patients can be traced back to 1976.[16] At that time, experiments carried out by PIEHL and others found that prone ventilation can improve oxygenation of patients. Since then, many studies have begun to explain the pathophysiological mechanism behind this result. It is generally believed that prone ventilation improves gas exchange in the lungs. When the body changes from supine to prone, A series of anatomical and physiological changes occur in the chest, most of which are related to gravity.[17] Firstly, after being compressed, the chest wall is forced to extend towards the abdomen and back. The pressure on the part that extends towards the abdomen remains unchanged due to the presence of the abdominal cavity, while the elasticity of the dorsal side of the chest wall is reduced due to the limitations of the spine and muscle groups. The overall effect is a decrease in chest wall compliance when lying prone. Secondly, the distribution of ventilated alveoli varies between prone and supine positions. When the human body is in a horizontal supine position, the degree of lung expansion is uneven due to the lungs' weight. This means that the tissue in the gravity-dependent area of the lungs is forced to compress under the influence of gravity, resulting in an exponential decrease in ventilation compared to the non gravity dependent area. At the same time, under the influence of gravity, the non gravity dependent area of lung tissue is also less than that in the gravity dependent area of lung tissue. Obviously, Changes in body position can significantly impact this distribution.[18,19] In addition, the heart's position also affects lung tissue's ventilation status.[20] When in a supine position, the heart continuously compresses the lung tissue, especially the left lower lobe, causing poor ventilation of the lung tissue in that area. However, when in a prone position, the pressure exerted by the heart is transferred from the lung tissue to the sternum, thereby relieving the pressure on the lungs. Due to the increased sensitivity of patients to the aforementioned anatomical and physiological changes, inflammation, edema, and consolidation of the lungs result in a continuous increase in lung weight, reaching 2-3 times that of normal lung tissue.[21] In this state, changes in posture have a more significant impact on the effectiveness of mechanical ventilation.

The prone position ventilation mechanism involves multiple physiological changes, some of which contribute to improved oxygenation. In the prone position, alveolar recruitment at the base of the lung increases, resulting in improved ventilation/perfusion matching, which can reduce hypoventilation in the basal region of the lung. In addition, the prone position can increase lung compliance and make the lung more prone to inflation, thereby improving ventilation efficiency. On the other hand, this position also reduces the risk of pulmonary edema because fluid flows more easily through the lungs and does not accumulate at the base of the lung under gravity.

According to relevant literature reports, 70% to 80% of ARDS patients improve oxygenation through prone position ventilation, and the mechanism behind this phenomenon has not been fully elucidated. Possible reasons include the following two points: (1) Compared to horizontal supine position.[22-23] When the body becomes prone, the number of alveoli involved in ventilation increases, and the increased alveoli are replenished by the alveoli originally located in the drooping area (back), resulting in an increase in ventilation/blood flow ratio and improved oxygenation; (2) The decrease in chest wall compliance during prone position may have adverse effects on lung diastolic function, but it can result in a more uniform distribution of ventilated alveoli, which clearly outweighs this adverse effect.

Prone position ventilation is an important auxiliary treatment method for improving patients' oxygenation status.[24] In this study, the duration of each prone position ventilation varied among patients. In theory, the longer the ventilation time in the prone position, the more sedative, analgesic, muscle relaxant, and vasoactive drugs are used, and the more significant the impact on gastrointestinal function will be. The more complications of enteral nutrition, the higher the risk of feeding intolerance.[4] At present, the duration of prone position ventilation is not uniform, and relevant studies suggest that the ventilation time in each prone position should be ≥ 12 hours. Up to now, research on the duration of prone position ventilation has mostly focused on patient oxygenation status and mortality as outcome indicators, with few studies analyzing the impact of prone position ventilation duration on patient gastrointestinal function. In the future, research can be conducted on the tolerance of patients to enteral nutrition and the effectiveness of feeding based on the duration of ventilation in different prone positions.

Although the RCT studies included in this study have a high quality, there are still various impacts such as case selection, trial design, treatment measures, and mechanical ventilation methods, especially changes in diagnostic criteria for critically ill cases. Implementing lung protective ventilation and lung recruitment strategies can all bias the efficacy of patients. In addition, only 5 high-quality RCT studies were included in this study, with a relatively small number, There may be a risk of publication bias and insufficient evidence, so in the future, more large-scale and high-quality RCT studies are needed to evaluate the impact of prone ventilation on the prognosis of critically ill patients.

Prone ventilation is an effective adjunctive therapy to improve oxygenation status in critically ill patients by improving lung gas exchange and ventilation/blood flow ratio to increase oxygenation levels. Although the mechanism has not been fully elucidated, its effectiveness has been demonstrated in clinical practice. However, the effect of prone ventilation duration on patient prognosis and gastrointestinal function still needs further study. Current studies have focused on indicators such as oxygenation status and case fatality, and more large-scale randomized controlled trials are needed to assess their impact in the future.

The findings of this study have important clinical relevance, especially in the care of critically ill patients. Improved oxygenation may not only relieve dyspnea, but may also have a profound impact on patient outcomes and overall prognosis. Adequate oxygen supply can support cell metabolism and organ function, help to reduce the occurrence of organ dysfunction and complications, and thus improve the recovery process of patients. Particularly in clinical conditions such as acute respiratory distress syndrome, improved oxygenation may help reduce mortality, reduce the duration of mechanical ventilation, and promote early weaning.

However, there are still some challenges and caveats to be noted when implementing prone position ventilation. First, monitoring and maintenance of the patient in the prone position may be more difficult, requiring special attention to pulmonary pressure and position-related discomfort. Second, repositioning of patients may require additional human and time costs, especially in critical situations. In addition, some patients may not be suitable for prone position ventilation due to anatomical structure, cardiovascular instability, and other factors, which requires careful screening and judgment. Therefore, when implementing prone position ventilation in the clinical setting, the patient's condition, monitoring requirements, and operating techniques should be comprehensively considered to ensure safety and effectiveness.

In conclusion, prone position ventilation shows potential value as an adjuvant therapy to improve oxygenation in critically ill patients. We observed that prone position ventilation can improve oxygenation through multiple mechanisms, such as increasing alveolar recruitment, optimizing ventilation/perfusion matching, increasing lung compliance, reducing pulmonary edema, and causing pulmonary blood flow redistribution. However, we must also recognize that the number of current studies is limited, potential publication bias, and methodological heterogeneity may have affected the stability of our conclusions.

Nonetheless, these findings still provide positive clinical guidance for prone position ventilation as part of the care of critically ill patients. This non-invasive approach to intervention offers a promising avenue to improve oxygenation, especially in clinical situations such as acute respiratory distress syndrome. However, further large-scale, multicenter clinical studies are needed to validate and consolidate these preliminary findings in order to obtain a more complete understanding of the actual effects of prone position ventilation in critically ill patients. In conclusion, although more in-depth research is still needed, prone position ventilation as an intervention to improve oxygenation provides a promising new approach for the treatment of critically ill patients.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

BZ, JT and QW designed the study and performed the experiments, YT and JB collected the data, YT, JB and TL analyzed the data, BZ, JT and QW prepared the manuscript. All authors read and approved the final manuscript. BZ and JT contributed equally to this work.

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