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Optimal duration of prone positioning in patients with acute respiratory distress syndrome: a protocol for a systematic review and meta-regression analysis

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ABSTRACT

Introduction Several systematic reviews and meta-analyses have demonstrated that prolonged (≥16 hours) prone positioning can reduce the mortality associated with acute respiratory distress syndrome (ARDS). However, the effectiveness and optimal duration of prone positioning was not fully evaluated. To fill these gaps, we will first investigate the effectiveness of prone positioning compared with the conventional management of patients with ARDS, regarding outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Second, if statistical heterogeneity in effectiveness with regard to short-term mortality (intensive care unit death or ≤30-day mortality) is shown, we will conduct a meta-regression analysis to explore the association between duration and effectiveness, and determine the optimal duration of prone positioning.

Method and analysis Relevant studies are collected using PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials and the WHO International Clinical Trials Platform Search Portal. Randomised controlled trials comparing prone and supine positioning in adults with ARDS will be included in the meta-analysis. Two independent investigators will screen trials obtained by search eligibility and extract data from selected studies to standardised data recording forms. For each selected trial, the risk of bias and quality of evidence will be evaluated using the GRADE system. Meta-regression analyses will be performed to identify the most important factors associated with short-term mortality, and subgroup analysis will be used to analyse the following: duration of mechanical ventilation in the prone position per day, patient severity, tidal volume and cause of ARDS. If heterogeneity or inconsistency among the studies is detected, subgroup analysis will be conducted on factors that may cause heterogeneity.

Ethics and dissemination This study requires no ethical approval. The results obtained from this systematic review and meta-analysis will be disseminated through international conference presentations and publication in a peer-reviewed journal.

Strengths and limitations of this study

- One strength of this study is that it is a systematic review with meta-regression analysis comparing prone positioning to other positions for patients with acute respiratory distress syndrome undergoing mechanical ventilation.
- The Grading of Recommendations, Assessment, Development and Evaluation system will be used to assess the strength of the evidence base and allow clinicians to judge the quality of available evidence.
- We plan sensitivity analyses and meta-regression to examine the relationship between the duration of prone positioning and its efficacy.
- Non-English articles will not be included in our study due to language difficulties which may result in publication bias.
- A possible weakness may be the quantity and quality of the trials we identify.

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INTRODUCTION

More than 200 000 patients are diagnosed with acute respiratory distress syndrome (ARDS) each year accounting for 3.6 million hospital-days of annual admissions in the USA.[1] The prevalence of ARDS is approximately 10% of all intensive care unit (ICU) admissions[2] and treating ARDS comprises 5% of all hospital ventilator-days, resulting in enormous medical expenses, up to US$115 000/hospital stay.[3 4] Despite advances in the ventilator management of patients with ARDS,[5] mortality rates of patients with moderate to severe ARDS still remain as high as 30%–40%.[1 6]

Prone positioning has been used to manage patients with ARDS since a study

in 1976 reported improved oxygenation from prone positioning.[7] Physiological studies showed improved oxygenation after prone positioning in a majority of patients with ARDS,[8 9] but randomised controlled trials (RCTs) failed to show a significant reduction in mortality with prone positioning.[10–12] Of recent RCTs examining the efficacy of prone positioning for patients with ARDS,[13–15] the PROSEVA study[15] published in 2013, an RCT treating patients with severe ARDS with prolonged (≥16 hours) prone positioning, showed an improvement in mortality rates. Several systematic reviews and meta-analyses of studies including these RCTs indicate that prone positioning may reduce the mortality rates in patients with ARDS, especially those with severe hypoxaemia.[16–20] Although the duration of prone positioning appears to affect patient outcomes, the relationship between the duration and its efficacy, and the shortest duration needed to improve outcomes are unknown.

Previous systematic reviews and meta-analyses[17–21] have shown that prolonged prone positioning (≥10, 12 or 16 hours/day) may be effective in patients with ARDS. However, these studies did not conduct meta-regression analyses to investigate the potential heterogeneity of the results or meticulous subgroup analyses using a strict systematic approach such as the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[22] We will conduct meta-regression analyses to examine associations between effect sizes and variables that may influence short-term mortality, such as patient characteristics, duration of prone positioning, tidal volume and the use of neuromuscular blocking agents.

OBJECTIVE

The objective of this systematic review and meta regression analysis is to investigate the duration of prone positioning needed to improve outcomes using sensitivity analyses and meta-regression.

METHODS AND ANALYSES

This systematic review will be conducted according to the Cochrane Handbook for Systematic Review of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the GRADE system.[22–24] The logistics and reporting of this protocol will be in compliance with PRISMA-P.Meta-regression is thought to be meaningful only with more than 10 studies included in the analysis.[23]

Patient and public involvement

No patients were involved in the design of the study. We will submit our results to a peer-reviewed journal for publication to enable dissemination.

STUDY ELIGIBILITY

Type of studies

Published and unpublished RCTs and randomised crossover trials (the first-period only) between January 1980 and September 2017 were included, restricted to the English language. Quasi-experimental studies and cluster randomisations were excluded. We will only include RCTs with supine positioning or semirecumbent position (which could include lateral positioning as part of routine pressure care) for ARDS and acute lung injury. We will exclude studies examining rotational bed therapies.

Type of participants

This study will include adults with ARDS or acute lung injury from any cause, as defined by the North-American–European Consensus Conference on ARDS[25] and the Berlin definition,[7] aged 16 years or older, undergoing mechanical ventilation. Cointerventions in addition to prone positioning will be permitted. We excluded studies of neonates or paediatric patients (ie, younger than 16 years), and also excluded duplicated studies or data, studies using specific treatment options including high-frequency oscillatory ventilation,[26 27] inhaled nitric oxide,[28] extracorporeal membrane oxygenation and studies without sufficient data regarding outcomes.[29]

Type of interventions and comparators

The intervention of interest is the initiation of prone positioning, regardless of the duration. The comparator group will contain all positions other than prone positioning during mechanical ventilation.

Type of outcomes

The following outcome measures will be evaluated: the primary outcomes are short-time mortality (ICU deaths or ≤30-day mortality) and endotracheal tube malfunction (unplanned extubation, dislocation or obstruction of the endotracheal tube). Secondary outcomes are the number of ventilator-free days up to 28 days, the incidence of ventilator-associated pneumonia and decubitus ulcers.

INFORMATION SOURCES

Two investigators (TK, YA) will search for the eligible trials from the following databases:

1. The Cochrane Central Register of Controlled Trials.
2. Ovid/MEDLINE.
3. Embase.
4. The WHO International Clinical Trials Platform Search Portal.

We will also check the reference lists in the relevant sections of international guidelines.[30] We will search the reference lists of relevant studies and studies cited in studies using Web of Science.[31]

SEARCH STRATEGY

Investigators will search the keywords ‘prone position’ AND ‘ARDS’, ‘adult respiratory distress syndrome’, ‘ALI’

or 'acute lung injury'. We will also perform a MeSH term search using the following terms: 'respiratory distress syndrome, adult', or 'acute lung injury' or 'lung injury' AND 'Prone position'. Searches will be performed from 18 July to 31 July 2018. The detailed strategy and details of the dates performed are shown in box 1.

Study records and data management

Literature selected from each database will be extracted into Microsoft Excel files and duplicates will be removed by sorting the data alphabetically according to author. The results of all processes (first and second screenings) are entered into the same data file. All full-text files will be managed with Papers bibliographic software. For studies lacking information, we will directly contact the corresponding author of each study to request the information.

Meta-analysis and meta-regression analysis will be conducted with Review Manager (RevMan) software V.5.3.5[32] and the graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[33] All data will be managed by the primary investigator (TK).

Selection process

Two investigators (TK, YA) will screen titles and abstracts as the first screening process, and the full text as secondary screening for relevant studies and will then independently extract data from included studies to standardised data forms. HY will supervise the process of systematic review. TA will supervise the process of analysis as a biostatistician. MS and SH are consultants on clinically relevant issues.

Data collection process

After the second screening, data will be extracted from each study by two investigators (TK, YA) using two tools: the Cochrane Data Collection Form (RCTs only)[34] and Review Manager (RevMan) software V.5.3.5.[32]

Risk of bias in individual studies

Investigators will assess the risk of bias in each selected study based on a modified version of the Cochrane risk-of-bias instrument.[35] The risk of bias will be evaluated for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other relevant potential bias (cross over). Two investigators (TK, YA) will independently conduct study selection, data extraction and risk of bias assessment. Two investigators will resolve disagreements between the two investigators through discussion, with a third reviewer available for adjudication if needed (HY).

Data analysis

Data synthesis

Statistical analyses will be performed using Comprehensive Meta-Analysis using Review Manager (RevMan) 5.5.5.[32] We will use a fixed-effect meta-analysis except

Box 1

(A) Ovid/MEDLINE

1. exp Lung Injury/
2. Acute respiratory distresss.mp.
3. Adult Respiratory distresss.mp.
4. ARDS.mp.
5. acute lung injury.mp.
6. acute lung injuries.mp.
7. shock lung.mp.
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. exp Prone Position/
10. prone* position*.mp.
11. #9 OR #10
12. #8 AND #11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomi?ed.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. drug therapy.sh.
21. groups.ab.
22. or/13-22
23. exp animals/ not humans.sh.
24. 22 not 23 #25 and/12,24

(B) Embase

1. 'adult respiratory distress syndrome'/exp
2. 'acute lung injury'/exp
3. 'lung injury'/exp
4. 'acute respiratory distress' OR 'adult respiratory distress' OR ards OR 'acute lung injury' OR 'acute lung injuries' OR 'shock lung'
5. OR/#1-#4
6. 'prone position'/exp
7. prone* AND position*
8. OR/#6-#7
9. #5 AND #8
10. 'controlled clinical trial'/exp
11. 'randomized controlled trial'/exp
12. randomized:ab,ti
13. randomly:ab,ti
14. trial:ab,ti
15. placebo:ab,ti
16. groups:ab,ti
17. OR/#10-#16
18. 'animal'/exp
19. 'invertebrate'/exp
20. 'animal experiment'
21. 'animal model'
22. 'animal tissue'
23. 'animal cell'
24. nonhuman
25. OR/#18-#24
26. human
27. 'human cell'
28. OR/#24-#25
29. #25 AND #28
30. #25 NOT #29
31. #17 NOT #30
32. #9 AND #31

Continued

Box 1 Continued

(C) Cochrane Central Register of Controlled Trials
1. MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees
2. MeSH descriptor: [Acute Lung Injury] explode all trees
3. MeSH descriptor: [Lung Injury] explode all trees
4. Acute respiratory distress:ti,ab,kw or Adult respiratory distress:ti,ab,kw or ARDS:ti,ab,kw or acute lung injury:ti,ab,kw or acute lung injuries:ti,ab,kw or shock lung:ti,ab,kw
5. #1 or #2 or #3 or #4
6. MeSH descriptor: [Prone Position] explode all trees
7. prone* position*:ti,ab,kw
8. #6 or #7
9. #5 and #8
10. #9 and in Trials

(D) The World Health Organization International Clinical Trials Platform Search Portal
1. Respiratory Distress Syndrome
2. Acute Lung Injury
3. Lung Injury
4. #1 OR #2 OR #3
5. prone

when we identified statistical heterogeneity, and then used a random-effects model.

Continuous data

Continuous data will be presented as a mean difference with 95% CIs. Pooled effect estimates will be stated with 95% CIs quantitatively and illustrated in a forest plot along with tables where necessary.[36] The data reported as medians will be converted to means and the range/4 will be converted to SD if possible.[37]

Categorical data

For categorical data, results will be expressed as a pooled relative risk with 95% CI.

Assessment of heterogeneity

Inconsistency (heterogeneity) among included studies will be assessed by examination of forest plots and the I^2 statistics.[38] We will be considered statistical heterogeneity to be low for $I^2 \leq 40\%$, moderate for $I^2=30\%–60\%$, substantial for $I^2=50\%–90\%$ and considerable for $I^2=75\%–100\%$. Cochran's Q statistic will be used for quantifying heterogeneity. The statistical analysis for publication bias will be planned for outcomes with at least 10 included studies.[23] If there are any kinds of heterogeneity, they will be investigated through sensitivity analyses and meta-regression to explore the potential sources of heterogeneity.

Subgroup analysis

If heterogeneity or inconsistency among the studies is detected, subgroup analyses will be conducted on the main factors that may cause heterogeneity.

We plan to undertake the following subgroup analyses.

- Duration of ventilation in the prone position per day (<8 hours/day vs ≥8 hours/day).
- Outcomes according to severity (using an index of oxygenation; arterial oxygen tension/fractional inspired oxygen ratio (P/F ratio) (<150 mm Hg vs ≥150 mm Hg), severity of illness score; Simplified Acute Physiology Score II (SAPS II) (<50 vs ≥50)).
- Tidal volume (<8 mL/kg of ideal body weight vs ≥8 mL/kg of ideal body weight).
- Cause of ARDS (pulmonary or extrapulmonary).

We plan to explore differences in outcomes in these subgroups if the number of collected studies are sufficient.

Sensitivity analysis

We will perform sensitivity analysis depending on study characteristics identified during the review process using fixed-effect model analysis. We will exclude studies with one or more 'low' or 'very low' from the sensitivity analysis. The remaining studies will be used for sensitivity analysis.

Meta-regression

If there is any statistically significant heterogeneity, or if considerable methodological heterogeneity is noted, investigators will explore the relationship between the duration of prone positioning and the short-term mortality by using random-effects meta-regression. We will perform meta-regression analysis by using the following factors as covariates.

Intervention characteristics:

- Duration of prone positioning (hours).
- Tidal volume (≤8 mL/kg of ideal body weight or >8 mL/kg of ideal body weight).
- Using neuromuscular blocking agents or none.

Participant characteristics:

- Mean age.
- SAPS II score.
- Severity of hypoxaemia; P/F ratio.

If studies are insufficient to justify meta-regression techniques, we will conduct meta-regression analysis by limiting the covariates.

Assessment of reporting bias

A funnel plot will be used to investigate the possibility of publication bias if >10 studies are available (RevMan).[39] Egger's test will be performed on each study group to evaluate asymmetry in funnel plots.[40]

Assessment of evidence in cumulative evidence

We will assess and rate the quality of evidence for each outcome across studies using four levels (high, moderate, low or very low) according to the GRADE criteria.[41]

The quality of evidence will be decreased by any one of the following limitations: risk of bias, imprecision, inconsistency, indirectness and publication bias. Two investigators (TK, YA) will independently conduct study selection, data extraction and risk of bias assessment. Investigators will resolve disagreements between the two investigators through discussion, with a third reviewer available for adjudication if needed (HY).

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Contributors TF and MS contributed to the conception of the study. TK, YA, TF, KK and HY designed the model and the framework of the systematic review and will analyse the data under supervisions of MS, EN and TA. TK wrote the protocol in consultation with YA, MS, AKL and SH. All authors were involved in the critical revision, for the intellectual content, and read and approved the final manuscript.

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