BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021408
Article Type:	Protocol
Date Submitted by the Author:	01-Jan-2018
Complete List of Authors:	Kamo, Tetsuro; Keio University School of Medicine, Department of Pulmonary Medicine; Saiseikai Utsunomiya Byoin, Department of Pulmonary Medicine, Intensive Care Medicine Aoki, Yoshitaka; Shizuoka Kenritsu Sogo Byoin, Department of Anesthesiology and Intensive Care Medicine Fukuda, Tatsuma; The University of Tokyo, 4) Department of Emergency and Critical Care Medicine, Graduate School of Medicine; Beth Israel Deaconess Medical Center, Department of Emergency Medicine Kurahashi, Kiyoyasu; Kokusai Iryo Fukushi Daigaku Mita Byoin, Department of Anesthesiology and Intensive Care Medicine Yasuda, Hideto; Kameda Medical Center, Department of Intensive Care Medicine; Keio University School of Medicine, Department of Preventive Medicine and Public Health Sanui, Masamitsu; Jichi Ika Daigaku Fuzoku Saitama Iryo Center, Department of Anesthesiology and Critical Care Medicine Nango, Eishu; Tokyo-Kita Medical Center, Department of General Medicine Abe, Takayuki; Keio University Hospital, Department of Preventive Medicine and Public Health; Keio University Hospital, Biostatistics Unit at Clinical and Translational Research Center Lefor, Alan; Jichi Medical University, Department of Surgery Hashimoto, Satoru; Kyoto Prefectural University of Medicine, Department of Anesthesiology and Intensive Care Medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, prone position, acute respiratory distress syndrome, INTENSIVE & CRITICAL CARE, acute lung injury

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

Tetsuro Kamo,[1,2] Yoshitaka Aoki,[3] Tatsuma Fukuda,[4,5] Kiyoyasu Kurahashi,[6] Hideto Yasuda,[7,8] Masamitsu Sanui,[9] Eishu Nango,[10] Takayuki Abe, [11,12] Alan Kawarai Lefor,[13] Satoru Hashimoto,[14]

1) Department of Pulmonary Medicine, Intensive Care Medicine, Saiseikai Utsunomiya hospital, Tochigi, Japan
2) Department of Pulmonary Medicine, Keio University School of Medicine, Tokyo, Japan
3) Department of Anesthesiology and Intensive Care Medicine, Shizuoka General Hospital, Shizuoka, Japan
4) Department of Emergency and Critical Care Medicine, Graduate School of Medicine, The University of Tokyo

5) Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston

6) Department of Anesthesiology and Intensive Care Medicine, School of Medicine, International University of Health and Welfare

7) Department of Intensive Care Medicine, Kameda Medical Center, Chiba, Japan

8) Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo Japan

9) Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan

10) Department of General Medicine, Tokyo- Kita Medical Center, Tokyo, Japan

11) Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo

12) Biostatistics Unit at Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan

13) Department of Surgery, Jichi Medical University, Tochigi, Japan

14) Department of Anesthesiology and Intensive Care, Kyoto Prefectural University of

Medicine, Kyoto, Japan

Corresponding author:

Masamitsu Sanui, M.D., Ph.D.

Department of Anesthesiology and Critical Care Medicine,

Jichi Medical University Saitama Medical Center

1-847, Amanuma-cho, Omiya-ku

Saitama, Saitama 330-8503, Japan

Tel.: +81 48 647 2111

Fax: +81 48 648 5188

E-mail: msanui@mac.com

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 system (GRADE). Second, if statistical heterogeneity in effectiveness with regard to short-term mortality (ICU 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 World Health Organization International Clinical Trials Platform Search Portal. Randomized 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 standardized 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 analyze 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.

Trial registration number: PROSPERO CRD42017078340

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 the other positionings for patients with

acute respiratory distress syndrome undergoing mechanical ventilation.

- The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system will be used to assess the strength of the evidence base and allow clinician to judge the quality of the available evidence.
- We plan sensitivity analyses and meta-regression to examine the relationship betwee the duration of prone positioning and its efficacy.
- Non-English articles will not be included in our study due to language difficulties and this may cause publication bias to some extent.
- A possible of weakness may be the quantity and quality of the trials we identify.

INTRODUCTION

More than 200,000 patients are diagnosed with ARDS each year accounting for 3.6 million hospital-days of annual admissions in the United States [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 $ 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 remains 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 randomized 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, a 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 hypoxemia [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-Analysis (PRISMA) statement, and the GRADE system [22-24]. The logistics and reporting of this protocol will be in compliance with the PRISMA-P. This protocol is registered with PROSPERO prospective register of systematic reviewers (CRD42017078340). Meta-regression is thought to be meaningful only with more than 10 studies included in the analysis [23].

STUDY ELIGIBILITY

Type of studies

Published and unpublished RCTs and randomized crossover trials (the first-period only) between January 1980 and September 2017 were included with the language restricted to English. Quasi-experimental studies and cluster randomization were excluded. We will only include RCTs with supine positioning or semi-recumbent 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 18 years or older, undergoing mechanical ventilation. Co-interventions in addition to prone positioning will be permitted. We excluded studies of neonates or pediatric patients (i.e. younger than 18 years), and also excluded duplicated studies or data, studies using specific treatment options including high frequency oscillatory ventilation (HFOV) [26, 27], inhaled nitric oxide [28],

extracorporeal membrane oxygenation (ECMO) 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 positioning other than prone positioning during mechanical ventilation.

Type of outcomes

The following outcome measures will be evaluated: the primary outcome is 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 (CENTRAL)

2. Ovid/MEDLINE

3. EMBASE (Excerpta Medica Database)

4. The World Health Organization International Clinical Trials Platform Search Portal (ICTRP)

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 use 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

on 29th September 2017. The detailed strategy and details of the dates performed are shown in Table 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 standardized data forms. HY supervises the process of systematic review. TA supervises 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 is 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 used a fixed-effect meta-analysis except 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% confidence intervals (CIs). Pooled effect estimates will be stated with 95% confidence intervals 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 standard deviation 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 was assessed by examination of forest plots and the I^2 statistics [38]. We considered statistical heterogeneity to be low for $I^2 \leq 40\%$, moderate for $I^2 = 30\text{-}60\%$, substantial for $I^2 = 50\text{-}90\%$, and considerable for $I^2 = 75\text{-}100\%$. Cochran's Q statistic will be used for quantifying heterogeneity. The statistical analysis for publication bias was 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 planned 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 oxygenation index; PaO_2/FIO_2 ratio [< 150 mmHg vs ≥ 150 mmHg], 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 extra-pulmonary)

We planned 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 (≤ 8ml/kg of ideal body weight or > 8ml/kg of ideal body weight)
- Using neuromuscular blocking agents or none

Participant characteristics

- Mean age
- SAPS Ⅱ score
- Severity of hypoxemia; 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. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315;629-34.].

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).

Contributors: Conception and design of research (TK, YA, TF, KK, HY and MS); tested the feasibility of the study (TK, YA, EN, TA and MS); wrote the manuscript (TK); approved final manuscript (MS, AKF and SH).

Competing interests: None declared.

Funding: This research was not supported by any grants.

References

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685-93.

2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Syndrome in Intensive Care Units in 50 countries. *JAMA* 2016;315:788-800.

3. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;174:538-44.

4. Esteban A, Ferguson ND, Meade MO, et al; VENTILA Group. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;177:170-7.

5. Cochi SE, Kempker JA, Annangi S, et al. Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013. *Ann Am Thorac Soc* 2016;13:1742-51.

6. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976;4:13-4.

7. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.

8. Albert RK, Leasa D, Sanderson M, et al. The prone position improves arterial oxygenation and reduces shunt in oleicacid-induced acute lung injury. *Am Rev Respir Dis* 1987; 135:628–33.

9. Chatte G, Sab JM, Dubois JM, et al. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997; 155:473–8.

10. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004;292:2379-87.

11. Voggenreiter G, Aufmokolk M, Stiletto RJ, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a retrospective randomized trial. *J Trauma* 2005;59:333-41.

12. Gattinoni L, Tognoni G, Pessenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med.2001;345:568-73.

13. Taccone P, Pesenti A, Latini R, et al. Prone-positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA*

2009;302:1977-84.

14. Chan MC, Hsu JY, Liu HH, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community acquired pneumonia. *J Formos Med Assoc* 2007;106:708-16.

15. Guérin C, Reignier J, Richard JC, et al; Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.

16. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med* 2010;36:585-99.

17. Lee JM, Bae W, Lee YJ, et al. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014;42:1252-62.

18. Hu SL, He HL, Pan C, et al. The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *Crit Care* 2014;18:109.

19. Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in

adults. *Cochrane Database Syst Rev* 2015:CD008095.

20. Sud S, Friedrich JO, Adhikari NK, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2014;186:E381-90.
21. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014;40:332-41.
22. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.
23. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Oxford, England: Cochrane Collaboration; 2011. handbook.cochrane.org.
24. Moher D, Liberati A, Tetzlaff J, et al; Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
25. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus

Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.

26. Demory D, Michelet P, Arnal JM, et al. High-frequency oscillatory ventilation following prone positioning prevents a further impairment in oxygenation. *Crit Care Med* 2007;35:106-11.
27. Papazian L, Gainnier M, Marin V, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. *Crit Care Med* 2005;33:2162-71.
28. Massimo Borelli, Laura Lampati, Ettore Vascotto, et al. Hemodynamic and gas exchange response to inhaled nitric oxide and prone positioning in acute respiratory distress syndrome patients. *Crit Care Med* 2000;28:2707-12.
29. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008;34:1487-91.
30. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care

Medicine Clinical Practice Guideline; Mechanical Ventilation in Adult Patients with Acute Respiratory Syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63.

31. *Web of Science*. http://www.webofknowledge.com (accessed 7 Sep 2017)

32. RevMan 5 download and installion. Secondary RevMan 5 download and installion. http://tech.cochrane.org/revman/download (accessed 7 Sep 2017)

33. Ihaka R, R Gentleman. R: A language for data analysis and graphics. *J Comput. Graph. Stat.,* 1996;5:299-314. http://www.r-project.org/ (accessed 7 Sep 2017)

34. Cochrane Handbook for Systematic Reviews of Interventions. http://training.cochrane.org/handbook. (accessed 7 Sep 2017).

35. Higgins JP, Altman DG, Gøtzsche PC, et al; The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

36. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;46:139-45.

37. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of sample. *BMC Med Res Methodol* 2005;20:5-13.

38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

39. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. *BMJ* 2011;343:d4002.

40. Egger M, Davey Smith G, Shneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315;629-34.

41. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401-6.

Table1 Search strategy

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

C) CENTRAL
#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 (ICTRP)

#1 Respiratory Distress Syndrome

#2 Acute Lung Injury

#3 Lung Injury

#4 #1 OR #2 OR #3

#5 prone

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021408.R1
Article Type:	Protocol
Date Submitted by the Author:	03-May-2018
Complete List of Authors:	Kamo, Tetsuro; Keio University School of Medicine, Department of Pulmonary Medicine; Saiseikai Utsunomiya Byoin, Department of Pulmonary Medicine, Intensive Care Medicine Aoki, Yoshitaka; Shizuoka Kenritsu Sogo Byoin, Department of Anesthesiology and Intensive Care Medicine Fukuda, Tatsuma; The University of Tokyo, 4) Department of Emergency and Critical Care Medicine, Graduate School of Medicine; Beth Israel Deaconess Medical Center, Department of Emergency Medicine Kurahashi, Kiyoyasu; Kokusai Iryo Fukushi Daigaku Mita Byoin, Department of Anesthesiology and Intensive Care Medicine Yasuda, Hideto; Kameda Medical Center, Department of Intensive Care Medicine; Keio University School of Medicine, Department of Preventive Medicine and Public Health Sanui, Masamitsu; Jichi Ika Daigaku Fuzoku Saitama Iryo Center, Department of Anesthesiology and Critical Care Medicine Nango, Eishu; Tokyo-Kita Medical Center, Department of General Medicine Abe, Takayuki; Keio University Hospital, Department of Preventive Medicine and Public Health; Keio University Hospital, Biostatistics Unit at Clinical and Translational Research Center Lefor, Alan; Jichi Medical University, Department of Surgery Hashimoto, Satoru; Kyoto Prefectural University of Medicine, Department of Anesthesiology and Intensive Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Respiratory medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, prone position, acute respiratory distress syndrome, INTENSIVE & CRITICAL CARE, acute lung injury

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

Tetsuro Kamo,[1,2] Yoshitaka Aoki,[3] Tatsuma Fukuda,[4,5] Kiyoyasu Kurahashi,[6] Hideto Yasuda,[7,8] Masamitsu Sanui,[9] Eishu Nango,[10] Takayuki Abe, [11,12] Alan Kawarai Lefor,[13] Satoru Hashimoto,[14]

1) Department of Pulmonary Medicine, Intensive Care Medicine, Saiseikai Utsunomiya hospital, Tochigi, Japan
2) Department of Pulmonary Medicine, Keio University School of Medicine, Tokyo, Japan
3) Department of Anesthesiology and Intensive Care Medicine, Shizuoka General Hospital, Shizuoka, Japan
4) Department of Emergency and Critical Care Medicine, Graduate School of Medicine, The University of Tokyo

5) Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston

6) Department of Anesthesiology and Intensive Care Medicine, School of Medicine, International University of Health and Welfare

7) Department of Intensive Care Medicine, Kameda Medical Center, Chiba, Japan

8) Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo Japan

9) Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan

10) Department of General Medicine, Tokyo- Kita Medical Center, Tokyo, Japan

11) Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo

12) Biostatistics Unit at Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan

13) Department of Surgery, Jichi Medical University, Tochigi, Japan

14) Department of Anesthesiology and Intensive Care, Kyoto Prefectural University of

Medicine, Kyoto, Japan

Corresponding author:

Masamitsu Sanui, M.D., Ph.D.

Department of Anesthesiology and Critical Care Medicine,

Jichi Medical University Saitama Medical Center

1-847, Amanuma-cho, Omiya-ku

Saitama, Saitama 330-8503, Japan

Tel.: +81 48 647 2111

Fax: +81 48 648 5188

E-mail: msanui@mac.com

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 system (GRADE). Second, if statistical heterogeneity in effectiveness with regard to short-term mortality (ICU 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 World Health Organization International Clinical Trials Platform Search Portal. Randomized 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 standardized 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 analyze 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.

Trial registration number: PROSPERO CRD42017078340

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 the other positionings for patients with

acute respiratory distress syndrome undergoing mechanical ventilation.

- The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system will be used to assess the strength of the evidence base and allow clinician to judge the quality of the available evidence.
- We plan sensitivity analyses and meta-regression to examine the relationship betwee the duration of prone positioning and its efficacy.
- Non-English articles will not be included in our study due to language difficulties and this may cause publication bias to some extent.
- A possible of weakness may be the quantity and quality of the trials we identify.

INTRODUCTION

More than 200,000 patients are diagnosed with ARDS each year accounting for 3.6 million hospital-days of annual admissions in the United States [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 $ 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 remains 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 randomized 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, a 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 hypoxemia [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-Analysis (PRISMA) statement, and the GRADE system [22-24]. The logistics and reporting of this protocol will be in compliance with the PRISMA-P. This protocol is registered with PROSPERO prospective register of systematic reviewers (CRD42017078340). Meta-regression is thought to be meaningful only with more than 10 studies included in the analysis [23].

STUDY ELIGIBILITY

Type of studies

Published and unpublished RCTs and randomized crossover trials (the first-period only) between January 1980 and September 2017 were included with the language restricted to English. Quasi-experimental studies and cluster randomization were excluded. We will only include RCTs with supine positioning or semi-recumbent 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. Co-interventions in addition to prone positioning will be permitted. We excluded studies of neonates or pediatric patients (i.e. younger than 16 years), and also excluded duplicated studies or data, studies using specific treatment options including high frequency oscillatory ventilation (HFOV) [26, 27], inhaled nitric oxide [28],

extracorporeal membrane oxygenation (ECMO) 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 positioning other than prone positioning during mechanical ventilation.

Type of outcomes

The following outcome measures will be evaluated: the primary outcome is 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 (CENTRAL)

2. Ovid/MEDLINE

3. EMBASE (Excerpta Medica Database)

4. The World Health Organization International Clinical Trials Platform Search Portal (ICTRP)

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 use 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

on 29th September 2017. The detailed strategy and details of the dates performed are shown in Table 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 standardized data forms. HY supervises the process of systematic review. TA supervises 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 is 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 used a fixed-effect meta-analysis except 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% confidence intervals (CIs). Pooled effect estimates will be stated with 95% confidence intervals 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 standard deviation 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 was assessed by examination of forest plots and the I^2 statistics [38]. We considered statistical heterogeneity to be low for $I^2 \leq 40\%$, moderate for $I^2 = 30\text{-}60\%$, substantial for $I^2 = 50\text{-}90\%$, and considerable for $I^2 = 75\text{-}100\%$. Cochran's Q statistic will be used for quantifying heterogeneity. The statistical analysis for publication bias was 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 planned 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 oxygenation index; PaO_2/FIO_2 ratio [< 150 mmHg vs ≥ 150 mmHg], 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 extra-pulmonary)

We planned 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 (≤ 8ml/kg of ideal body weight or > 8ml/kg of ideal body weight)
- Using neuromuscular blocking agents or none

Participant characteristics

- Mean age
- SAPS Ⅱ score
- Severity of hypoxemia; 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. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315;629-34.].

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).

Authors' contributions

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 analyze 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.

Funding sources/sponsors

None

Conflicts of interest

No one has conflicts of interest in the study.

References

References

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685-93.

2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Syndrome in Intensive Care Units in 50 countries. *JAMA* 2016;315:788-800.

3. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;174:538-44.

4. Esteban A, Ferguson ND, Meade MO, et al; VENTILA Group. Evolution of

mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;177:170-7.

5. Cochi SE, Kempker JA, Annangi S, et al. Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013. *Ann Am Thorac Soc* 2016;13:1742-51.
6. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976;4:13-4.
7. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
8. Albert RK, Leasa D, Sanderson M, et al. The prone position improves arterial oxygenation and reduces shunt in oleicacid-induced acute lung injury. *Am Rev Respir Dis* 1987; 135:628–33.
9. Chatte G, Sab JM, Dubois JM, et al. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997; 155:473–8.
10. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in

hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004;292:2379-87.

11. Voggenreiter G, Aufmokolk M, Stiletto RJ, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a retrospective randomized trial. *J Trauma* 2005;59:333-41.

12. Gattinoni L, Tognoni G, Pessenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med.2001;345:568-73.

13. Taccone P, Pesenti A, Latini R, et al. Prone-positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009;302:1977-84.

14. Chan MC, Hsu JY, Liu HH, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community acquired pneumonia. *J Formos Med Assoc* 2007;106:708-16.

15. Guérin C, Reignier J, Richard JC, et al; Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.

16. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients

with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med* 2010;36:585-99.

17. Lee JM, Bae W, Lee YJ, et al. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014;42:1252-62.
18. Hu SL, He HL, Pan C, et al. The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *Crit Care* 2014;18:109.
19. Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. *Cochrane Database Syst Rev* 2015:CD008095.
20. Sud S, Friedrich JO, Adhikari NK, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2014;186:E381-90.
21. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014;40:332-41.

22. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.

23. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Oxford, England: Cochrane Collaboration; 2011. handbook.cochrane.org.

24. Moher D, Liberati A, Tetzlaff J, et al; Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.

25. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.

26. Demory D, Michelet P, Arnal JM, et al. High-frequency oscillatory ventilation following prone positioning prevents a further impairment in oxygenation. *Crit Care Med* 2007;35:106-11.

27. Papazian L, Gainnier M, Marin V, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress

syndrome. *Crit Care Med* 2005;33:2162-71.

28. Massimo Borelli, Laura Lampati, Ettore Vascotto, et al. Hemodynamic and gas exchange response to inhaled nitric oxide and prone positioning in acute respiratory distress syndrome patients. *Crit Care Med* 2000;28:2707-12.

29. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008;34:1487-91.

30. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline; Mechanical Ventilation in Adult Patients with Acute Respiratory Syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63.

31. *Web of Science*. http://www.webofknowledge.com (accessed 7 Sep 2017)

32. RevMan 5 download and installion. Secondary RevMan 5 download and installion. http://tech.cochrane.org/revman/download (accessed 7 Sep 2017)

33. Ihaka R, R Gentleman. R: A language for data analysis and graphics. *J Comput. Graph. Stat.,* 1996;5:299-314. http://www.r-project.org/ (accessed 7 Sep 2017)

34. Cochrane Handbook for Systematic Reviews of Interventions. http://training.cochrane.org/handbook. (accessed 7 Sep 2017).

35. Higgins JP, Altman DG, Gøtzsche PC, et al; The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

36. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;46:139-45.

37. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of sample. *BMC Med Res Methodol* 2005;20:5-13.

38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

39. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. *BMJ* 2011;343:d4002.

40. Egger M, Davey Smith G, Shneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315;629-34.

41. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the

quality of evidence. *J Clin Epidemiol* 2011;64:401-6.

Table1

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

C) CENTRAL

#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 (ICTRP)

#1 Respiratory Distress Syndrome

#2 Acute Lung Injury

#3 Lung Injury

#4 #1 OR #2 OR #3

#5 prone

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page1,line10-17
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page5, line46
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 3, line 16-44
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 1, line 23-31
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐	☒	
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 7, line 6 to page8, line50

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page8, line56 to page9, lne14
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page9, line50 to page10,line 26
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page11,line55 to page12, line36
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page12,line43 to page 13,line10
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page13,line13 to line47
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page13,line53 to page14,line14
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page14,line20 to line 31
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page16, line43 to page17,line 30
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page11, line 33 to line 48
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page14, line34 to page15,line13
DATA					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page15, line 22
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page16, line 13 to line41
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page16, line44 to page18,line58
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page19, line6 to line21
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page19, line29 to 34.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021408.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Jul-2018
Complete List of Authors:	Kamo, Tetsuro; Keio University School of Medicine, Department of Pulmonary Medicine; Saiseikai Utsunomiya Byoin, Department of Pulmonary Medicine, Intensive Care Medicine Aoki, Yoshitaka; Shizuoka Kenritsu Sogo Byoin, Department of Anesthesiology and Intensive Care Medicine Fukuda, Tatsuma; The University of Tokyo, 4) Department of Emergency and Critical Care Medicine, Graduate School of Medicine; Beth Israel Deaconess Medical Center, Department of Emergency Medicine Kurahashi, Kiyoyasu; Kokusai Iryo Fukushi Daigaku Mita Byoin, Department of Anesthesiology and Intensive Care Medicine Yasuda, Hideto; Kameda Medical Center, Department of Intensive Care Medicine; Keio University School of Medicine, Department of Preventive Medicine and Public Health Sanui, Masamitsu; Jichi Ika Daigaku Fuzoku Saitama Iryo Center, Department of Anesthesiology and Critical Care Medicine Nango, Eishu; Tokyo-Kita Medical Center, Department of General Medicine Abe, Takayuki; Keio University Hospital, Department of Preventive Medicine and Public Health; Keio University Hospital, Biostatistics Unit at Clinical and Translational Research Center Lefor, Alan; Jichi Medical University, Department of Surgery Hashimoto, Satoru; Kyoto Prefectural University of Medicine, Department of Anesthesiology and Intensive Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Respiratory medicine, Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Thoracic medicine < INTERNAL MEDICINE, Respiratory physiology < THORACIC MEDICINE

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

Tetsuro Kamo,[1,2] Yoshitaka Aoki,[3] Tatsuma Fukuda,[4,5] Kiyoyasu Kurahashi,[6] Hideto Yasuda,[7,8] Masamitsu Sanui,[9] Eishu Nango,[10] Takayuki Abe, [11,12] Alan Kawarai Lefor,[13] Satoru Hashimoto,[14]

1) Department of Pulmonary Medicine, Intensive Care Medicine, Saiseikai Utsunomiya hospital, Tochigi, Japan
2) Department of Pulmonary Medicine, Keio University School of Medicine, Tokyo, Japan
3) Department of Anesthesiology and Intensive Care Medicine, Shizuoka General Hospital, Shizuoka, Japan
4) Department of Emergency and Critical Care Medicine, Graduate School of

Medicine, The University of Tokyo

5) Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston

6) Department of Anesthesiology and Intensive Care Medicine, School of Medicine, International University of Health and Welfare

7) Department of Intensive Care Medicine, Kameda Medical Center, Chiba, Japan

8) Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo Japan

9) Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan

10) Department of General Medicine, Tokyo- Kita Medical Center, Tokyo, Japan

11) Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo

12) Biostatistics Unit at Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan

13) Department of Surgery, Jichi Medical University, Tochigi, Japan

14) Department of Anesthesiology and Intensive Care, Kyoto Prefectural University of Medicine, Kyoto, Japan

Corresponding author:

Masamitsu Sanui, M.D., Ph.D.

Department of Anesthesiology and Critical Care Medicine,

Jichi Medical University Saitama Medical Center

1-847, Amanuma-cho, Omiya-ku

Saitama, Saitama 330-8503, Japan

Tel.: +81 48 647 2111

Fax: +81 48 648 5188

E-mail: msanui@mac.com

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 system (GRADE). Second, if statistical heterogeneity in effectiveness with regard to short-term mortality (ICU 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 World Health Organization International Clinical Trials Platform Search Portal. Randomized 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 standardized 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 analyze 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.

Trial registration number: PROSPERO CRD42017078340

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 ARDS undergoing mechanical ventilation.
- The GRADE (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.

INTRODUCTION

More than 200,000 patients are diagnosed with adult respiratory distress syndrome (ARDS) each year accounting for 3.6 million hospital-days of annual admissions in the United States [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 $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 randomized 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, a 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 hypoxemia [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-Analysis (PRISMA) statement, and the GRADE system [22-24]. The logistics and reporting of this protocol will be in compliance with PRISMA-P. This protocol is registered with the PROSPERO prospective register of systematic reviewers (CRD42017078340). Meta-regression is thought to be meaningful only with more than 10 studies included in the analysis [23].

Patient and public involvement statement

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 randomized crossover trials (the first-period only) between January 1980 and September 2017 were included, restricted to the English language. Quasi-experimental studies and cluster randomizations were excluded. We will only include RCTs with supine positioning or semi-recumbent 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. Co-interventions in addition to prone positioning will be permitted. We excluded studies of neonates or pediatric patients (i.e. younger than 16 years), and also excluded duplicated studies or data, studies using specific treatment options including high

frequency oscillatory ventilation (HFOV) [26, 27], inhaled nitric oxide [28], extracorporeal membrane oxygenation (ECMO) 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 outcome is 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 (CENTRAL)

2. Ovid/MEDLINE

3. EMBASE (Excerpta Medica Database)

4. The World Health Organization International Clinical Trials Platform Search Portal (ICTRP)

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 use 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 in from July 18 to July 31, 2018. The detailed strategy and details of the dates performed are shown in Table 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 standardized data forms. HY supervises the process of systematic review. TA supervises 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 used a fixed-effect meta-analysis except 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% confidence intervals (CIs). Pooled effect estimates will be stated with 95% confidence intervals 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 standard deviation 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 was assessed by examination of forest plots and the I^2 statistics [38]. We considered statistical heterogeneity to be low for $I^2 \leq 40\%$, moderate for $I^2 = 30\text{-}60\%$, substantial for $I^2 = 50\text{-}90\%$, and considerable for $I^2 = 75\text{-}100\%$. Cochran's Q statistic will be used for quantifying heterogeneity. The statistical analysis for publication bias was 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 planned 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 oxygenation index; PaO_2/FIO_2 ratio [< 150 mmHg vs ≥ 150 mmHg], 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 extra-pulmonary)

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 (≤ 8ml/kg of ideal body weight or > 8ml/kg of ideal body weight)
- Using neuromuscular blocking agents or none

Participant characteristics

- Mean age

- SAPS Ⅱ score
- Severity of hypoxemia; 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. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315;629-34.].

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).

Authors' contributions

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 analyze 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.

Funding sources/sponsor

None

Conflicts of interest

No one has conflicts of interest in the study.

References

References

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685-93.

2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Syndrome in Intensive Care Units in 50 countries. *JAMA* 2016;315:788-800.

3. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care*

Med 2006;174:538-44.

4. Esteban A, Ferguson ND, Meade MO, et al; VENTILA Group. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;177:170-7.

5. Cochi SE, Kempker JA, Annangi S, et al. Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013. *Ann Am Thorac Soc* 2016;13:1742-51.

6. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976;4:13-4.

7. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.

8. Albert RK, Leasa D, Sanderson M, et al. The prone position improves arterial oxygenation and reduces shunt in oleicacid-induced acute lung injury. *Am Rev Respir Dis* 1987; 135:628–33.

9. Chatte G, Sab JM, Dubois JM, et al. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997; 155:473–8.

10. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004;292:2379-87.

11. Voggenreiter G, Aufmokolk M, Stiletto RJ, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a retrospective randomized trial. *J Trauma* 2005;59:333-41.

12. Gattinoni L, Tognoni G, Pessenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med.2001;345:568-73.

13. Taccone P, Pesenti A, Latini R, et al. Prone-positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009;302:1977-84.

14. Chan MC, Hsu JY, Liu HH, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community acquired pneumonia. *J Formos Med Assoc*

2007;106:708-16.

15. Guérin C, Reignier J, Richard JC, et al; Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.

16. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med* 2010;36:585-99.

17. Lee JM, Bae W, Lee YJ, et al. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014;42:1252-62.

18. Hu SL, He HL, Pan C, et al. The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *Crit Care* 2014;18:109.

19. Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. *Cochrane Database Syst Rev* 2015:CD008095.

20. Sud S, Friedrich JO, Adhikari NK, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress

syndrome: a systematic review and meta-analysis. *CMAJ* 2014;186:E381-90.

21. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014;40:332-41.

22. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.

23. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Oxford, England: Cochrane Collaboration; 2011. handbook.cochrane.org.

24. Moher D, Liberati A, Tetzlaff J, et al; Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.

25. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.

26. Demory D, Michelet P, Arnal JM, et al. High-frequency oscillatory ventilation

following prone positioning prevents a further impairment in oxygenation. *Crit Care Med* 2007;35:106-11.

27. Papazian L, Gainnier M, Marin V, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. *Crit Care Med* 2005;33:2162-71.

28. Massimo Borelli, Laura Lampati, Ettore Vascotto, et al. Hemodynamic and gas exchange response to inhaled nitric oxide and prone positioning in acute respiratory distress syndrome patients. *Crit Care Med* 2000;28:2707-12.

29. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008;34:1487-91.

30. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline; Mechanical Ventilation in Adult Patients with Acute Respiratory Syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63.

31. *Web of Science*. http://www.webofknowledge.com (accessed 7 Sep 2017)

32. RevMan 5 download and installion. Secondary RevMan 5 download and installion. http://tech.cochrane.org/revman/download (accessed 7 Sep 2017)

33. Ihaka R, R Gentleman. R: A language for data analysis and graphics. *J Comput. Graph. Stat.,* 1996;5:299-314. http://www.r-project.org/ (accessed 7 Sep 2017)

34. Cochrane Handbook for Systematic Reviews of Interventions. http://training.cochrane.org/handbook. (accessed 7 Sep 2017).

35. Higgins JP, Altman DG, Gøtzsche PC, et al; The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

36. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;46:139-45.

37. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of sample. *BMC Med Res Methodol* 2005;20:5-13.

38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

39. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and

interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. *BMJ* 2011;343:d4002.

40. Egger M, Davey Smith G, Shneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315;629-34.

41. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401-6.

Table1

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

A) 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

B) CENTRAL

#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 (ICTRP)

#1 Respiratory Distress Syndrome

#2 Acute Lung Injury

#3 Lung Injury

#4 #1 OR #2 OR #3

#5 prone