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Early neuromuscular blocking agents for adults with acute respiratory distress syndrome: a systematic review, meta-analysis and meta-regression

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ABSTRACT

Objective To determine whether neuromuscular blocking agents (NMBAs) can decrease the mortality of patients with acute respiratory distress syndrome (ARDS) and improve their clinical outcomes.

Design Systematic review, meta-analysis and meta-regression.

Data sources PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrials.gov.

Methods Randomised controlled trials (RCTs) comparing the treatment effect of NMBAs with that of placebo (or traditional treatment) in patients with ARDS were carefully selected. The primary outcome was 90-day mortality. The secondary outcomes were 21–28 days mortality, NMBA-related complications (barotrauma, pneumothorax and intensive care unit (ICU)-acquired muscle weakness), days free of ventilation and days not in the ICU by day 28, Medical Research Council score, Acute Physiology and Chronic Health Evaluation II score and arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) (at 48 hours and 72 hours). Random-effects meta-regression was used to explore models involving potential moderators. Trial sequential analysis was performed to estimate the cumulative effect on mortality across RCTs.

Results NMBAs were not associated with reduced 90-day mortality (risk ratio (RR) 0.85; 95% CI 0.66 to 1.09; p=0.20). However, they decreased the 21–28 days mortality (RR 0.71; 95% CI 0.53 to 0.96; p=0.02) and the rates of pneumothorax (RR 0.46; 95% CI 0.28 to 0.77; p=0.003) and barotrauma (RR 0.56; 95% CI 0.37 to 0.86; p=0.008). In addition, NMBAs increased PaO_2/FiO_2 at 48 hours (mean difference (MD) 18.91; 95% CI 4.29 to 33.53; p=0.01) and 72 hours (MD 12.27; 95% CI 4.65 to 19.89; p=0.002). Meta-regression revealed an association between sample size (p=0.042) and short-term mortality. Publication year (p=0.050), sedation strategy (p=0.047) and sample size (p=0.046) were independently associated with PaO_2/FiO_2 at 48 hours.

Conclusions In summary, the results suggested that use of NMBAs might reduce 21–28 days mortality, NMBA-related complications and oxygenation. However, NMBAs did not reduce the 90-day mortality of patients with ARDS, which contradicts a previous meta-analysis.

PROSPERO registration number CRD42019139440.

Strengths and limitations of this study

- This study is a comprehensive systematic review, including meta-analysis and meta-regression, of the effectiveness of neuromuscular blocking agents for patients with acute respiratory distress syndrome; this study contains the most randomised controlled trials of any review on the topic.
- We used trial sequential analysis to analyse short-term and long-term mortality to increase the accuracy and stability of the results.
- The quality of studies included in the systematic review was generally low, which made it difficult to draw clear conclusions.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a sudden and dangerous illness caused by other sudden medical or surgical conditions, such as sepsis, injury, burn or severe pancreatitis.[1] The symptoms of ARDS include hypoxia, which is difficult to correct, and patients always need life support with a ventilator in an intensive care unit (ICU).[1–5] ARDS is typically associated with diseases and trauma conditions, which usually require multimodal treatment strategies that include both non-pharmacological and pharmacological therapies.[6] Although several treatments have been tested in patients with ARDS, this disease remains a highly lethal disease that affects almost three million people annually and accounts for 1/10 of all ICU admissions worldwide.[7]

In the 21st century, neuromuscular blocking agents (NMBAs) have played an important role as an adjuvant therapy in the ventilatory care of critically ill patients.[8–10] Among all pharmacology-based therapeutic strategies, only NMBAs are associated with a mortality reduction in patients with ARDS.[6] NMBAs could cause skeletal muscle relaxation by blocking the transmission of nerve impulses at neuromuscular junctions, and non-depolarising NMBAs are widely used in the clinic because their metabolism is

unrelated to renal or hepatic function.[8] Several trials published over the past 15 years have demonstrated that NMBAs could achieve better clinical results in patients with ARDS than placebo, especially in terms of oxygenation and mortality.[9 11–14] However, given the risk of neuromuscular dysfunction and other side effects, such as atelectasis and diaphragm paralysis, the use of NMBAs remains controversial and is usually not recommended in clinical guidelines for patients with ARDS.[10 15–20] Recently, a new randomised controlled trial (RCT) published by Moss *et al* showed that NMBAs did not decrease the 90-day mortality among patients with ARDS compared with those who did not receive NMBAs.[21] Subsequently, Chang *et al* performed a meta-analysis to assess the efficacy of NMBAs and found that NMBAs could decrease the 90-day mortality, even after adding the results of the Rose trial.[22] Although the outcomes of the study by Chang *et al* were similar to those in the previous meta-analysis,[23] their results may be limited. The 90-day mortality data used in the study by Chang were pooled with 28-day mortality data, which might have affected the accuracy of the results. Considering the possible errors in Chang's meta-analysis, it is necessary to conduct a new systematic review.

Furthermore, to guide drug therapy strategies for patients with ARDS, we performed this systematic review and meta-analysis to identify whether NMBAs could improve the clinical outcomes of patients with ARDS.

MATERIALS AND METHODS

This meta-analysis was constructed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Patient and public involvement

Patients and the public were not involved in planning the design and conducting, reporting or disseminating the results of our study.

Search strategy

We performed a systematic literature search to identify relevant studies in the PubMed, Embase, Cochrane Library, Web of Science and ClinicalTrial.gov databases from inception to 20 August 2020. Our search strategy combined concepts related to acute respiratory distress syndrome (ie, 'shock lung', 'ARDSs, human' and 'respiratory distress syndrome') and neuromuscular blocking agents (ie, 'neuromuscular blockade', 'neuromuscular block' and 'neuromuscular blockers') (see online supplemental table 1). We used the filters provided by the website of Cochrane Work to locate RCTs in PubMed and Embase. We applied no language restrictions, and we manually screened the search results to identify relevant RCTs and related pieces of literature. We studied the citations of each included article to find articles that met the inclusion criteria. Any uncertainty was resolved by discussion with the third researcher.

Study selection

Two reviewers (SS and HK) independently assessed each document for eligibility by screening the title, abstract and full text. All disagreements were resolved by discussion.

The inclusion criteria were as follows: (1) RCTs; (2) adult (aged over 18 years) patients who were diagnosed with ARDS by the consensus definition of the disease when the relevant study was published; (3) study groups that received NMBAs and control groups that received placebo without NMBAs and (4) studies that accurately and clearly provided any of the outcomes.

The exclusion criteria were as follows: (1) case reports, letters, systematic reviews, meta-analyses, professional opinions or cohort studies; (2) studies lacking risk ratios (RRs), 95% CIs or continuous variable outcomes that could be converted to the mean and SD; (3) incorrect statistical methods that cannot be corrected and (4) incomplete data and unclear outcomes.

Data extraction and risk of bias assessment

A double-entry procedure was performed by two authors (SS and HK). In addition, the results of the data extraction were verified by a third author (ZT). The risk of bias of each study was assessed by two researchers (SS and HK). Any uncertainty was resolved through discussion with another person. We extracted the following data from the qualified studies: year of publication, country, name of

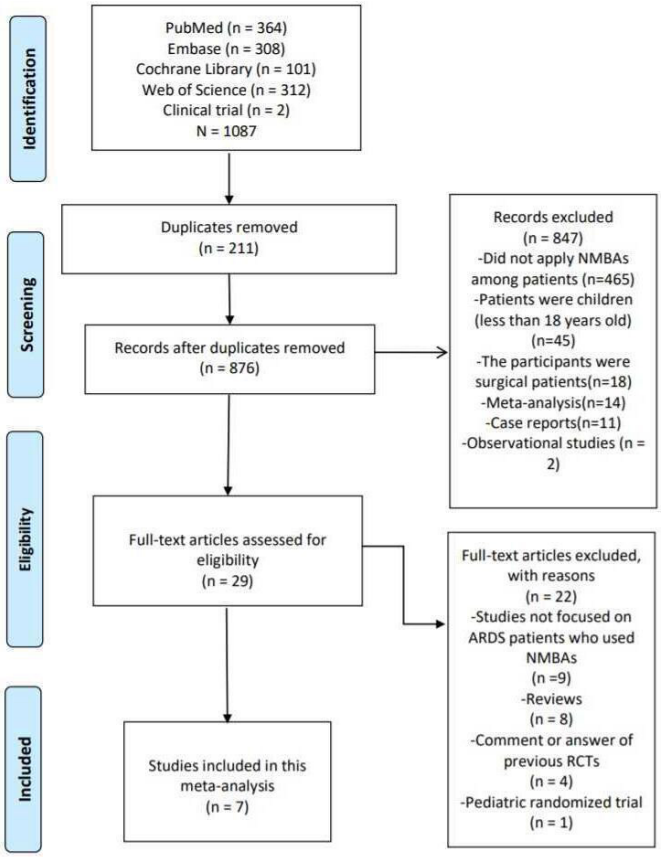

Figure 1 Screening process. NMBAs, neuromuscular blocking agents; RCTs, randomised controlled trials.

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Table 1 Characteristics of included studies

Source	Country	Centres	Eligibility	Criteria for enrolment	Methods	Strategy of ventilation	Main outcome	Group	No of patients	Patient intervention	Sedation strategy
Gainnier (2004)[9]	France	Four ICUs	PaO_2/FIO_2 ratio of <150 at a PEEP of ≥5 cm H_2O	American-European consensus definition	Prospective study	Volume-assist/control (6–8 mL/kg ideal body weight)	The evolution of PaO_2/FIO_2 ratio during the 120 hours; days free of ventilation at day 28; days free of ventilation at day 60; ICU death; mortality at day 28; mortality at day 60; rates of barotrauma	NMBA	28	Bolus of 50 mg cisatracurium, followed by a continuous infusion at an initial rate of 5 μg·k·min for 48 hours	Sedation (midazolam and sufentanil) was used to obtain a Ramsay score of 6
								Control	28	An infusion of saline at a rate of 4 mL/hour for 48 hours	Sedation (midazolam and sufentanil) was used to obtain a Ramsay score of 6
Forel (2006)[12]	France	Three ICUs	PaO_2/FIO_2 ratio of <200 at a PEEP of ≥5 cm H_2O	American-European consensus definition	Prospective study	Volume-assist/control (4–8 mL/kg ideal body weight)	Inflammatory cytokines (tumour necrosis factor, interleukin (IL)–1, IL-6, and IL-8); PaO_2/FiO_2 ratio; Total PEEP; Pplat; ICU death Days free of ventilation at day 28; rates of barotrauma	NMBA	18	A bolus of 0.2 mg/kg was followed by a continuous infusion at an initial rate of 5 μg·k·min for 48 hours	Sedation with midazolam and sufentanil was used to obtain a Ramsay score of 6
								Control	18	An infusion of placebo (saline) at a rate of 4 mL/hour for 48 hours	Sedation with midazolam and sufentanil was used to obtain a Ramsay score of 6
Papazian (2010)[11]	France	Twenty ICUs	PaO_2/FIO_2 ratio of <150 at a PEEP of ≥5 cm H_2O	American-European consensus definition	Prospective study	Volume-assist/control (6–8 mL/kg ideal body weight)	The 90-day mortality; ICU death; Hospital death day-28 mortality; Days not in ICU at day 28; Days not in ICU at day 90; Days free of ventilation at day 28; days free of ventilation at day 90; rates of barotrauma	NMBA	177	A 3 mL rapid intravenous infusion of 15 mg of cisatracurium, followed by a continuous infusion of 37.5 mg/hour for 48 hours	Sedative medicine was used to obtain a Ramsay score of 6
								Control	162	A 3 mL rapid intravenous infusion of 15 mg of placebo, followed by a continuous infusion of 37.5 mg/hour for 48 hours	Sedative medicine was used to obtain a Ramsay score of 6
Lyu (2014)[13]	China	One ICU	PaO_2/FIO_2 ratio of <150 at a PEEP of ≥5 cm H_2O	The Berlin definition	Prospective study	Volume-assist/control (4–8 mL/kg ideal body weight)	APACHE II score; SOFA; PaO_2/FiO_2; $ScvO_2$; Lactate and C reactive protein levels; 21 days mortality	NMBA	48	0.1 mg/kg vecuronium up to 0.05 mg/kg·hour for continuous intravenous infusion for 24–48 hours	Patients were given adequate sedation and analgesia with midazolam and sufentanil.
								Control	48	Give patients regular treatment	Patients were given adequate sedation and analgesia with midazolam and sufentanil.
Yirao (2016)[28]	China	One ICU	PaO_2/FIO_2 ratio of <300 at a PEEP of ≥5 cm H_2O	The Berlin definition	Prospective study	Volume-assist/control (6 mL/kg ideal body weight)	Gender, age, APACHE II, PEEP, FiO_2, pH, PaO_2, $PaCO_2$, PaO_2/FiO_2, no of cases of pulmonary atelectasis, no of cases of ventilation in prone position; incidence of VAP, non-ICU hospitalisation time and non mechanical ventilation time within 28 days, 28 days mortality, 90 days mortality	NMBA	24	Vecuronium 1 μg/kg·hour was given to maintain muscle relaxation and eliminate spontaneous respiration	Patients were given adequate sedation and analgesia with midazolam + morphine or midazolam + fentanyl combined
								Control	17	Give patients regular treatment	Midazolam + morphine or midazolam + fentanyl combined with sedation and analgesia were given. Ramsay Sedation score was given daily and controlled at 2–4 points
Guervilly (2017)[14]	France	Two ICUs	PaO_2/FIO_2 ratio of <150 at a PEEP of ≥5 cm H_2O	The Berlin definition	Prospective study	Volume-assist/control (6 mL/kg ideal body weight)	Pplat; total PEEP; ICU mortality; driving pressure; Inspiratory and expiratory PL and ΔPL; PaO_2/FiO_2; days free of ventilation at day 28; days not in ICU at day 28	NMBA	13	A3 mL rapid intravenous infusion of 15 mg cisatracurium, followed by a continuous infusion of 37.5 mg/hour	Sedation with midazolam and sufentanil was used to obtain a Ramsay score of 6
								Control	11	Give patients regular treatment	Sedation with midazolam and sufentanil was used to obtain a Ramsay score of 6

Continued

Table 1 Continued

Source	Country	Centres	Eligibility	Criteria for enrolment	Methods	Strategy of ventilation	Main outcome	Group	No of patients	Patient intervention	Sedation strategy
Moss (2019)[21]	USA	Forty-eight ICUs	PaO_2/FiO_2 ratio of <150 at a PEEP of ≥8cm H_2O	–	Prospective study	Low tidal volume ventilation within 2 hours after randomisation and a high PEEP strategy for up to 5 days after randomisation	In-hospital death by day 90; In-hospital death by day 28; days free of ventilation at day 28; Days not in ICU at day 28; Days not in hospital at day 28; rates of barotrauma	NMBA	501	A bolus of 15 mg of cisatracurium, followed by a continuous infusion of 37.5 mg/hour for 48 hours	Deep sedation evaluated by the Richmond Agitation-Sedation Scale or the Riker Sedation Agitation Scale or the Ramsay Sedation Scale
								Control	505	Give patients regular treatment without routine NMBAs	Light sedation evaluated by the Richmond Agitation-Sedation Scale or the Riker Sedation Agitation Scale or the Ramsay Sedation Scale

APACHE II, Acute Physiology and Chronic Health Evaluation; FiO_2, fractional inspired oxygen; ICU, intensive care unit; NMBA, neuromuscular blocking agent; PaO_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

the first author, number of centres in each trial, criteria for enrolment, intervention description, outcomes, study methods, ventilation strategy, number of patients in each group, sedation strategy, outcome data, mean age, causes of ARDS, proportion of males and the Simplified Acute Physiology Score II score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2), tidal volume, plateau pressure (Pplat) and positive end-expiratory pressure (PEEP) at inclusion. If any data were inadequate, we emailed the corresponding authors. We used the Cochrane Collaboration risk of bias tool[24] to examine the risk of bias of the included trials and judge the risk of bias as 'low risk,' 'unclear' or 'high risk' in each domain specified by the tool.

Outcomes

The primary outcome was 90-day mortality. The secondary outcomes were 21–28 day mortality, days free of ventilation as of day 28, days not in the ICU as of day 28, NMBA-related complications (barotrauma, pneumothorax and ICU-acquired muscle weakness), Medical Research Council (MRC) score, APACHE II score and PaO_2/FiO_2 at 48 hours and 72 hours.

Statistical synthesis and analysis

The values of the categorical variables represent the RR and 95% CI. We generated summary estimates of the mean and SD of the continuous outcomes. The meta-analysis was performed using Mantel-Haenszel (M-H) random-effect models or, if the heterogeneity was not significant, fixed-effects models. A correction factor (1.0) was applied to zero-event trials to enforce the effect of RR.[25] We assessed the heterogeneity among the trials by using I^2 testing (where a value >50% is regarded as indicative of substantial heterogeneity). If a primary or secondary outcome exhibited heterogeneity, we performed a subgroup analysis or sensitivity analysis to identify the source of heterogeneity. For the subgroup analysis, the following variables were selected before the study was performed: different inclusion criteria (PaO_2/FiO_2<150 mm Hg, PaO_2/FiO_2<200 mm Hg, or PaO_2/FiO_2<300 mm Hg); whether the patients were in the prone position; and whether lighter sedation was used in the control group than the NMBA group. All outcomes and subgroup analyses were planned a priori. We performed an interaction test in all subgroups to determine whether the difference between the subgroups was statistically significant. We judged the publication bias by creating a funnel plot and applying traditional statistical methods (Egger's test) when more than five trials were included.[26] The results were considered statistically significant at a p<0.05. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to judge the quality of evidence of the primary outcome and secondary outcomes. The statistical analyses were completed using Review Manager V.5.3, Stata V.15.1 and GRADE Profiler V.3.6.

Table 2 Characteristics of patients at inclusion

Author/year	PaO_2/FiO_2(mm Hg, NMBAs/placebo)	Tidal volume (mL/kg, NMBAs/placebo)	Pplat (cm H_2O, NMBAs/placebo)	PEEP (mm Hg, NMBAs/placebo)	Age, (yrs NMBAs/placebo)	SAPSII	APACHEII	Prone position	Males (%)
Gainnier (2004)[9]	130±34/ 119±31	7.1±1.1/ 7.4±1.9	27.1±6.2/ 26.1±4.0	11.1±2.8/ 10.9±2.4	59.8±17.5/ 61.5±14.6	41.8±10.4/ 5.4±10.5	–/–	Did not used in both group	75/71
Forel (2006)[12]	–/–	6.5±0.7/ 7.0±0.7	27.5±4.4/ 24.8±5.7	13.2±2.7/ 11.1±2.7	61±18/ 52±16	49±19/ 47±15	–/–	Did not used in both group	78/67
Papazian (2010)[11]	106±36/ 115±41	6.55±1.12/ 6.48±0.92	25.0±5.1/ 24.4±4.7	9.2±3.2/ 9.2±3.5	58±16/ 58±15	50±16/ 47±14	–/–	Used in both groups	–
Lyu (2014)*[13]	140.95±26.97/ 144.33±24.09†	–/–	–/–	–/–	58.4±8.2‡	–/–	18.20±3.59/ 19.37±4.14†	–	–
	77.68±11.21/ 80.61±12.82§	–/–	–/–	–/–	58.4±8.2‡	–/–	24.08±4.05/ 23.20±5.04§	–	–
Yirao (2016)[28]	176±63/ 165±53	–/–	–/–	8±3/6±2	35±16/50±16	–/–	21±8/20±8	Used in both groups	87.5/76.5
Guervilly (2017)¶[14]	158(131,185)/ 150(121,187)	6.2 (5.9, 6.8)/ 6.3 (6.0, 6.9)	23(19, 26)/ 21 (19, 25)	11 (10, 11.5)/ 10(9, 12)	72 (63; 79)/ 60 (52; 75)	47(37; 54)/ 48(42; 62)	–/–	–	69/91
Moss (2019)[21]	98.7±27.9/ 99.5±27.9	6.3±0.9/ 6.3±0.9	25.5±6.0/ 25.7±6.1	12.6±3.6/ 12.5±3.6	56.6±14.7/ 55.1±15.9	–	103.9±30.1/ 104.9±30.1**	Used in both groups	58.1/53.3

*Lyu *et al* divided patients into two group.
†Moderate group with PaO_2/FiO_2 ≤150 mm Hg.
‡In Lyu's trial, the average age of all patients was given, but the average age of NMBAs group and placebo group were not provide.
§Severe group with PaO_2/FiO_2 ≤100 mm Hg) to evaluate the effect of NMBAs in patients with ARDS.
¶Only the results of Guervilly were expressed as the median and interquartile range (25th and 75th percentiles).
**APACHE III was used in trial of Moss. Its scores range from 0 to 299, with higher scores indicating more severe illness.
'–', means unreported; APACHE II, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; NMBAs, neuromuscular blocking agents; PEEP, positive end-expiratory pressure; Pmean, mean pressure; Pplat, plateau pressure; SAPS, Simplified Acute Physiology Score.

Table 3 The risk of bias of eligible articles

Author/year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Gainner (2004)[9]	U*	U*	L	L†	L	L	U*
Forel (2006)[12]	U*	U*	H‡	L†	L	L	U*
Papazian (2010)[11]	L	L	L	L	L	L	U*
Lyu (2014)[13]	L	U*	U*	L	L	L	U*
Yirao (2016)[28]	L	L	H‡	L†	L	L	U*
Guervilly (2017)[14]	L	U*	H‡	L	L	L	U*
Moss (2019)[21]	L	L	H‡	L†	L	L	U*

*The relevant information in the text was not mentioned and could not be judged.
†Outcomes were less likely to be affected by single blind method (eg, mortality).
‡The article used the single blind method, that was, some participants (such as nurses) have broken the blindness.
H, high risk; L, low risk; U, unclear.

Meta-regression

A meta-regression was performed using a random-effects model to explore the potential source of heterogeneity in our study. The following variables were selected before the meta-regression was performed to explore the potential source of heterogeneity: publication year, race, baseline PaO_2/FiO_2, mean age, types of NMBAs, sedation strategy (whether lighter sedation was used in the control group than the NMBA group), whether the prone position was used, article sample size, proportion of ARDS cases arising from intrapulmonary causes, baseline PEEP, baseline Pplat and baseline tidal volume.

Trial sequential analysis

Trial sequential analysis (TSA) uses a combination of techniques to eliminate early false positive findings due to imprecise outcomes and repeated trials in a meta-analysis.[27] We applied the analysis to the 21–28 days mortality and 90-day mortality data. In this part, a Z-curve was constructed to represent mortality, and a conventional threshold of z=1.96 was used to identify whether the result was meaningful. We chose the O'Brien-Fleming alpha to construct adjusted trial sequential monitoring boundaries. The setting of the analysis was estimated using a two sided of 0.05 and a β of 0.20 (power:80%) to limit the type I and type II errors. The incidence rates of 35.2% and 41.8% in the control arm were selected because these rates were compatible with most large-scale RCTs included in this study. The estimated information size obtained by the TSA refers to the number of cases needed in a meta-analysis to obtain statistically significant differences, that is, the sample size necessary for the meta-analysis. TSA provides a termination standard for clinical trials by estimating the estimated information size, that is, when the cumulative number of cases in the meta-analysis reaches the expected amount of information

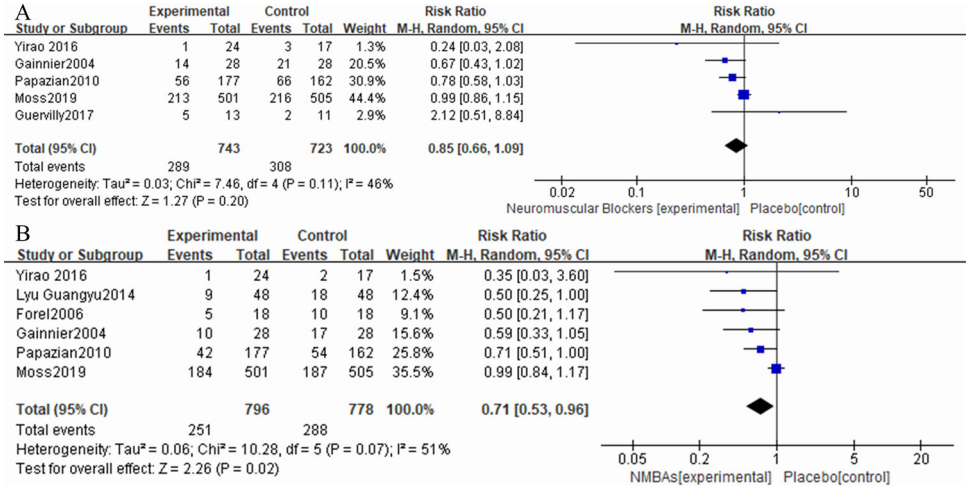

Figure 2 (A) Forest plot showing the 90-day mortality of acute respiratory distress syndrome patients. (B) Forest plot showing the 21–28 days mortality of acute respiratory distress syndrome patients. M-H, Mantel-Haenszel; NMBAs, neuromuscular blocking agents.

Table 4 The outcomes of the study

Outcomes or subgroup analysis	Studies	Study reference no	Patients	RR/MD (95% CI)	I^2	P value
Primary outcomes						
90 days mortality	5	(9, 11, 14, 21, 28)	1466	0.85 (0.66 to 1.09)	46%	0.2
Secondary outcomes						
21–28 days mortality	6	(9, 11–13, 21, 28)	1574	0.71 (0.53 to 0.96)	51%	0.02
Days free of ventilation at day 28	5	(9, 11, 12, 14, 21)	1461	0.54 (–0.47 to 1.56)	15%	0.3
Barotrauma*	4	(9, 11, 12, 21)	1439	0.56 (0.37 to 0.86)	0%	0.008
Pneumothorax†	2	(11–21)	1345	0.46 (0.28 to 0.77)	0%	0.003
ICU acquired muscle weakness	3	(11, 12, 21)	691	1.19 (0.99 to 1.44)	0%	0.07
Days not in the ICU at day 28	3	(11, 14, 21)	1369	0.16 (–1.00 to 1.31)	17%	0.79
APACHE II score	2	(13–28)	137	–2.07 (–3.17 to -0.97)	35%	2E-04
MRC score	2	(11–21)	1345	–2.24 (–6.24 to 1.76)	84%	0.27
PaO_2/FiO_2 at 48 hours	5	(9, 12–14, 21)	1218	18.91 (4.29 to 33.53)	59%	0.01
PaO_2/FiO_2 at 72 hours	4	(9, 11–12, 21)	1437	12.27 (4.65 to 19.89)	37%	0.002
Subgroup analysis of 21 to 28 day mortality (PaO_2/FiO_2)						
ARDS with PaO_2/FiO_2 <200 mm Hg	1	(12)	36	0.50 (0.21 to 1.17)	–	0.58§
ARDS with PaO_2/FiO_2 <300 mm Hg	1	(28)	41	0.35 (0.03 to 3.60)	–	
ARDS with PaO_2/FiO_2 <150 mm Hg	4	(9, 11, 13, 21)	1497	0.75 (0.54 to 1.02)	62%	
Subgroup analysis of 21–28 days mortality (prone position)						
Did not used prone position in both group	2	(9–12)	92	0.56 (0.35,0.90)	0%	0.13§
Used prone position in both group	4	(11, 13, 21, 28)	1386	0.86 (0.64,1.16)	45%	
Subgroup analysis of 21–28 days mortality (whether used lighter sedation in control group)						
Used lighter sedation in control group	2	(21–28)	1047	0.98 (0.84 to 1.16)	0%	0.005§
Used deep sedation in control group	4	(9, 11–13)	1574	0.63 (0.49 to 0.82)	0%	
Sensitive analysis						
90 days mortality†	4	(9, 11, 14, 28)	460	0.75 (0.56 to 1.00)	13%	0.05
21–28 days mortality‡	5	(9, 11–13, 28)	568	0.63 (0.48 to 0.81)	0%	4E-04
PaO_2/FiO_2 at 48 hours‡	4	(9, 12–14)	1182	13.08 (0.96 to 25.20)	46%	0.03

Barotrauma is defined as any new pneumothorax, pulmonary mediastinum, subcutaneous emphysema or pulmonary bulge larger than 2 cm in diameter.
*Pneumothorax refers to the entry of gas into the pleural cavity, causing a state of pneumothorax, called pneumothorax.
†Sensitive analysis of primary outcome.
‡Sensitive analysis of secondary outcomes.
§ Values of test of interaction between subgroups.
APACHE II, Acute Physiology and Chronic Health Evaluation II; FiO2, fractional inspired oxygen; ICU, intensive care unit; MD, mean difference; MRC score, The Medical Research Council score; PaO2, arterial oxygen tension; RR, risk ratio.

and similar clinical trials can be terminated to avoid wasting scientific research and medical resources. The software TSA 0.9.5.10 beta was used for the entire analysis.

RESULTS

After systematically searching five electronic databases, we obtained 1087 articles according to the search strategy as follows: PubMed (n=364), Embase (n=308), Cochrane library (n=101), Web of Science (n=312) and ClinicalTrial.gov (n=2). Among these articles, 211 studies were excluded because they were duplicates. Eight hundred and forty-seven studies were excluded because they did not meet our inclusion criteria after we reviewed their titles and abstracts. The remaining 29 studies were considered relevant, and we carefully screened the full articles. Nine studies did not focus on patients with ARDS, and eight reviews, four comments and one paediatric RCT were discarded. Ultimately, 7 RCTs involving a total of 1598 patients were included in this systematic review and meta-analysis. The screening process is shown in figure 1.

Study characteristics

The number of patients in a single trial ranged from 24 to 1006. In total, four trials were conducted by the same

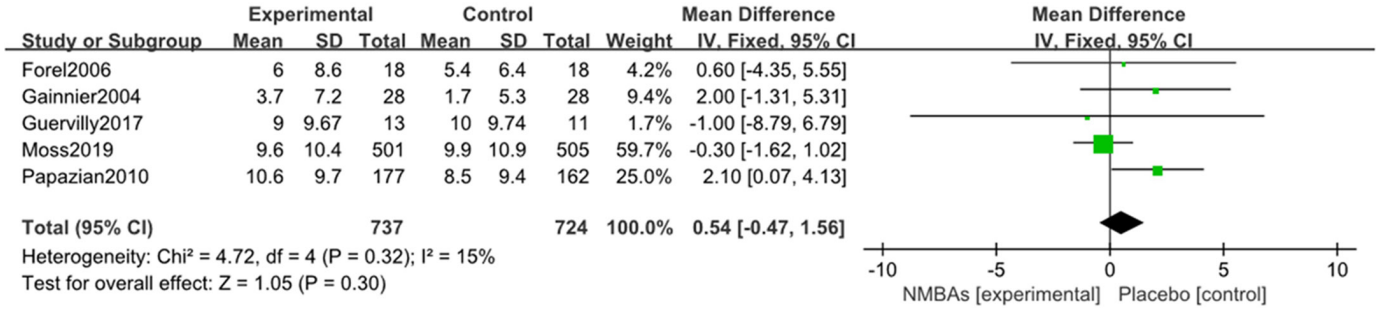

Figure 3 Forest plot showing the days free of ventilation at day 28 of acute respiratory distress syndrome patients. NMBAs, neuromuscular blocking agents.

research group in France.[9 11 12 14] Another two trials were conducted in China,[13 28] and the last trial was conducted in the USA.[21] Five eligible studies included patients with moderate to severe ARDS whose PaO_2/FiO_2 was less than 150 mm Hg.[9 11 13 14 21] However, in the studies by Yirao *et al*[28] and Forel *et al*[12] the PaO_2/FiO_2 values were <300 mm Hg and <200 mm Hg, respectively. In the trial by Moss *et al*,[21] the baseline PEEP was greater than 8 cmH_2O, but in the remaining trials, the PEEP threshold was 5 cmH_2O.[9 11–14 28] The mean PEEP value of the patients at inclusion in the Rose trial[21] was 12.6 cmH_2O, but in Gainner's trial,[9] the mean was 11.0 cmH_2O. The prone position was applied in three eligible studies,[11 21 28] and the proportion of patients who were treated in the prone position did not statistically significantly differ among these three studies. In addition, on average, the included patients were younger in the study by Yirao *et al*[28] (mean age=42.5 years) and older in the study by Guerville *et al*[14] (mean age=66 years) than those in the other trials. The characteristics of the studies are presented in table 1, and the details of the characteristics of the patients at inclusion are shown in table 2.

Risk of bias

Regarding the bias of the individual trials, three trials were judged to have an unclear risk of bias.[9 11 13] The remaining trials were assessed as having a high risk of bias because of deficits in the blinding methods[12 14 21 28] (table 3). Further details are shown in online supplemental figures 1 and 2.

Primary outcome

Ninety-day mortality

Five trials involving a total of 1466 patients examined the 90-day mortality.[9 11 14 21 28] Overall, these trials demonstrated that NMBAs did not decrease the 90-day mortality (RR 0.85; 95% CI 0.66 to 1.09; p=0.20). The statistical heterogeneity was acceptable (I^2=46%) (figure 2A) (table 4). Due to the importance of this outcome, we

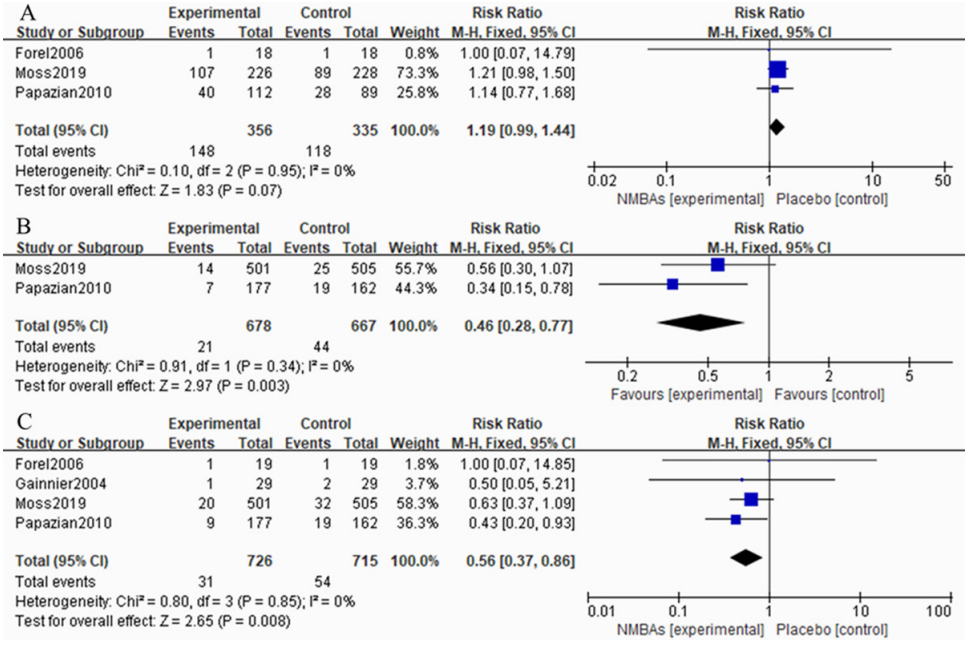

Figure 4 (A) Forest plot showing the occurrence of ICU acquire muscle weakness of acute respiratory distress syndrome patients. (B) Forest plot showing the rate of pneumothorax of acute respiratory distress syndrome patients. (C) Forest plot showing the rate of barotrauma of acute respiratory distress syndrome patients. ICU, intensive care unit; M-H, Mantel-Haenszel; NMBAs, neuromuscular blocking agents.

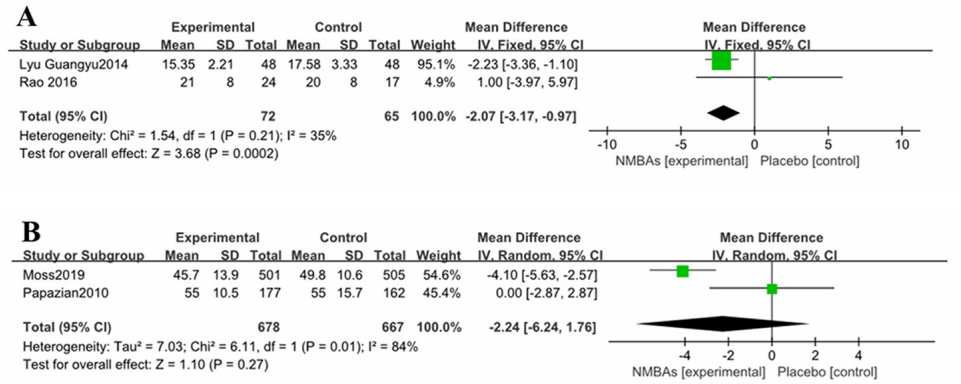

Figure 5 (A) APACHE score. (B) MRC score. APACHE, Acute Physiology and Chronic Health Evaluation; MRC, Medical Research Council; NMBAs, neuromuscular blocking agents.

analysed the possible sources of heterogeneity by a meta-regression.

Secondary outcomes

Twenty-one-day to 28-day mortality

Six RCTs published over the past 15 years were eligible for inclusion in this analysis.[9 11–13 21 28] Further information is provided in figure 2B. NMBAs were associated with a reduced 21–28 days mortality in the M-H random-effects model (RR 0.71; 95% CI 0.53 to 0.96; p=0.02; I²=51%) (table 4).

Days free of ventilation at day 28

Five trials[9 11 12 14 21] involving a total of 737 participants in the interventional groups (table 4) and 724 patients in the control groups reported the number of days free of ventilation at day 28. Our meta-analysis indicated that there was no significant intergroup difference in the number of days free of ventilation at day 28 (mean difference (MD) 0.54; 95% CI −0.47 to −1.56; p=0.30), and there was no heterogeneity among the five trials (I²=15%). All details are shown in figure 3.

NMBA-related complications (barotrauma, pneumothorax and ICU-acquired muscle weakness)

Four studies involving 1439 patients reported barotrauma.[9 11 12 21] Two studies reported the rate of pneumothorax in a total of 1345 patients.[11 21] In addition, three eligible studies provided the rate of ICU-acquired muscle weakness in a total of 691 patients.[11 12 21] A fixed-effects model was applied to NMBA-related complications. For the zero-event trials, we added 1.0 as a correction factor.[9 12 25] Compared with the non-NMBA treatment, NMBAs did not increase the occurrence of ICU-acquired muscle weakness (RR 1.19; 95% CI 0.99 to 1.44; I²=0%; p=0.07)[11 12 28] (figure 4A) (table 4). Using NMBAs in patients with ARDS may improve survival outcomes by reducing the rates of pneumothorax[11 21] (RR 0.46; 95% CI 0.28 to 0.77; p=0.003; I²=0%) and barotrauma[9 11 12 21] (RR 0.56; 95% CI 0.37 to 0.86; p=0.008; I²=0%) (figure 4B,C) (table 4).

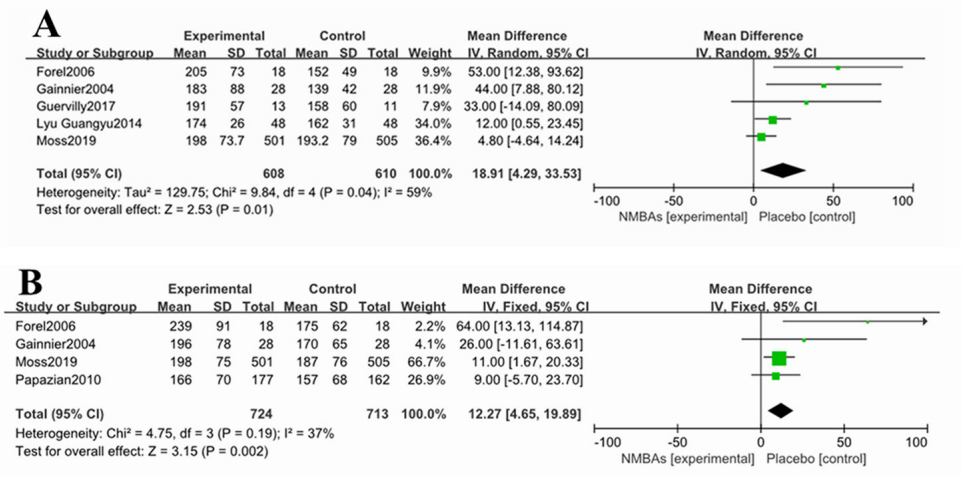

Figure 6 (A) Forest plot showing the PaO_2/FiO_2 at 48 hours. (B) Forest plot showing the PaO_2/FiO_2 at 72 hours. FiO_2, fractional inspired oxygen; NMBAs, neuromuscular blocking agents; PaO_2, arterial oxygen tension.

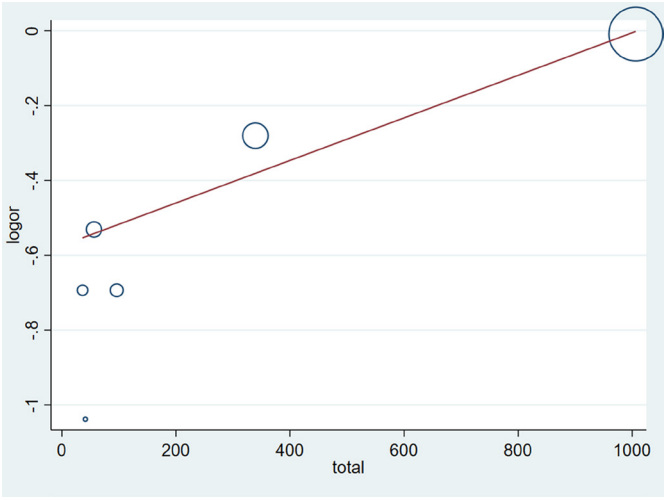

Figure 7 Meta-regression of 21–28 days mortality (sample size).

Days not in the ICU at day 28

Three studies involving 1369 patients reported the days not in the ICU at day 28.[11 14 21] The treatment regimens involving NMBAs were not helpful in increasing the days not spent in the ICU as of day 28 (MD 0.16; 95% CI −1.00 to −1.31; p=0.79), and there was no heterogeneity among the trials (I^2=17%) (see online supplemental figure 3) (table 4).

APACHE II score and MRC score

Two studies involving a total of 137 patients reported the APACHE II scores.[13 28] These scores significantly differed between the two groups, and the level of heterogeneity was acceptable (MD −2.07; 95% CI −3.17 to −0.97; p=0.0002; I^2=35%) (figure 5A). Two studies included 1345 patients reported the MRC score.[11 21] We found no statistically significant difference between the two groups in terms of the MRC scores (MD −2.24; 95% CI −6.24 to 1.76; p=0.27; I^2=84%) (figure 5B).

PaO_2/FiO_2 at 48 hrs and 72 hrs

A random-effects model was used because significant heterogeneity was present. There was a significant effect of NMBAs on PaO_2/FiO_2 at 48 hrs[9 12–14 21] (MD 18.91; 95% CI 4.29 to 33.53; p=0.01; I^2=59%) (figure 6A). After we excluded Forel's trial, the heterogeneity of PaO_2/FiO_2 at 48 hours was acceptable[12] (MD 13.08, CI 0.96 to 25.20; p=0.03; I^2=46%). Four studies involving a total of 1437 patients were eligible for the PaO_2/FiO_2 at 72 hours analysis.[9 11 12 21] There was a significant increase in PaO_2/FiO_2 at 72 hours with mild heterogeneity (MD 12.27; 95% CI 4.65 to 19.89; p=0.002; I^2=37%) (figure 6B) (table 4).

Meta-regression

In the meta-regression, we did not find the potential source of heterogeneity in the 90-day mortality data. Regarding the 21–28 days mortality, the meta-regression analysis showed that the difference in the sample size was associated with heterogeneity (p=0.042) (figure 7). Furthermore, the following variables were found to be independently associated with PaO_2/FiO_2 at 48 hours: publication year (p=0.050), article sample size (p=0.046) and sedation strategy (p=0.047) (see online supplemental figure 4) (table 5).

Subgroup analysis and sensitivity analysis

We performed a sensitivity analysis by sequentially omitting each trial to identify the possible main sources of heterogeneity in the 90 day mortality and 21–28 day mortality data. We found that when we omitted the Rose trial,[21] the heterogeneity of the 90-day mortality decreased from 46% to 13% (RR 0.75; 95% CI 0.56 to 1.00; p=0.05; I^2=13%) (see online supplemental figure 5). Similarly, the heterogeneity of the 21–28 day mortality disappeared when the Rose trial[21] was excluded (RR 0.63; 95% CI 0.48 to 0.81; p=0.0004) (see online supplemental figure 6). There is no significant change in the global RR of 90-day mortality or 21–28 days mortality compared with before.

Table 5 Meta-regression

Outcomes	Year	Race	Baseline PaO_2/FiO_2	Mean age	Type of NMBA	Pulmonary disease	Article sample size	Baseline PEEP	Baseline pplat	Baseline tidal volume	Whether lighter sedation was applied	Whether prone position was applied
90 days mortality	0.118	0.357	0.273	0.434	0.357	0.15	0.15	0.619	0.21	0.405	0.208	0.452
21*–28 days mortality	0.061	0.299	0.379	0.744	0.299	0.163	0.042†	0.681	0.13	0.161	–	0.089
PaO_2/FiO_2 at 48 hours	0.050†	0.97	0.952	0.396	0.97	0.976	0.046†	0.956	0.088	0.803	0.047†	0.21

*Since we did a subgroup analysis of the results and the p value was meaningful, we did not do the corresponding meta-regression.
†The results were statistically significant.
FiO_2, fractional inspired oxygen; NMBAs, neuromuscular blocking agents; PaO_2, arterial oxygen tension; PEEP, positive end-expiratory pressure.

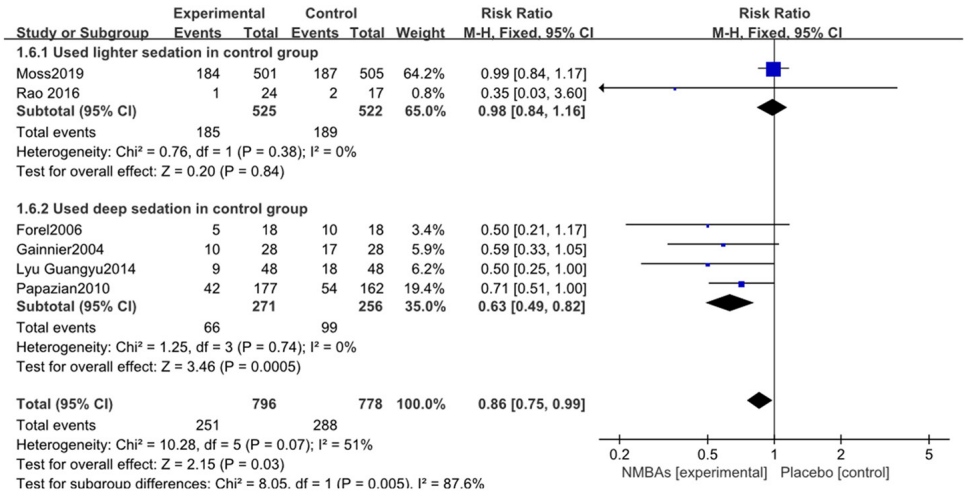

Figure 8 Subgroup analysis of 21–28 days mortality (whether used lighter sedation in control group). M-H, Mantel-Haenszel; NMBAs, neuromuscular blocking agents.

According to the different inclusion criteria and the treatment strategies for patients with ARDS, the articles reporting the 21–28 days mortality were divided into three subgroups as we mentioned above. The interaction test of 21–28 days mortality showed that there might be differences between the subgroups of various kinds of sedation strategy in the control group (p=0.005) (figure 8). Different inclusion criteria (ARDS patients with PaO_2/FiO_2 <150 mm Hg,[9 11 13 21] PaO_2/FiO_2<200 mm Hg,[12] and PaO_2/FiO_2<300 mm Hg[28] and whether prone position was used among patients were not the source of heterogeneity (see online supplemental figure 7A,B. Further details are shown in table 4.

Publication bias

Regarding the outcome of the 21–28 days mortality,[9 11–13 21] studies comparing NMBAs and placebo were absent near the bottom right of the plot, revealing the possibility of publication bias in the 21–28 days mortality (figure 9). Egger's test also provided evidence of possible publication bias in the 21–28 days mortality (p=0.05; 95% CI −3.42 to −1.37). Studies reporting the days free of ventilation at day 28 were also absent near the bottom right of the funnel plot, but Egger's test did not reveal any evidence of substantial publication bias (p=0.491) (see online supplemental figure 8).[9 11 12 14 21] Regarding PaO_2/FiO_2 at 48 hours, there may be publication bias, which was proven by Egger's test (p=0.008) (see online supplemental figure 9). Moreover, there was no publication bias in the 90-day mortality according to funnel plot and Egger's test (p=0.474)[9 11 14 21 28] (see online supplemental figure 10).

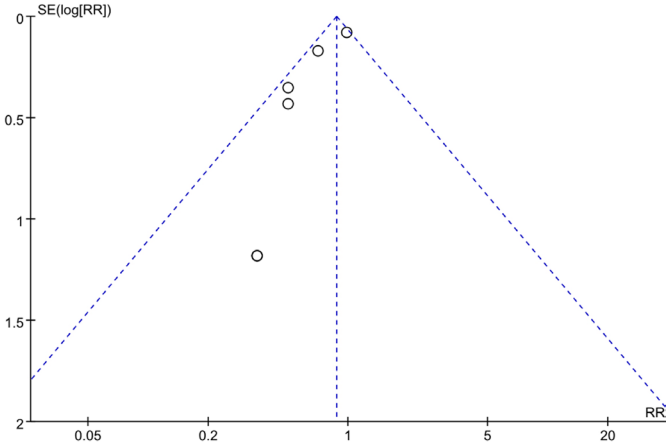

Figure 9 Funnel plot for 21–28 days mortality of acute respiratory distress syndrome patients. RR, risk ratio.

Quality of the evidence in this meta-analysis

The principles of the GRADE system indicated that the quality of the evidence related to mortality was low due to the limitations of inconsistency, imprecision and publication bias (table 6). The quality of the secondary outcomes is shown in online supplemental tables 2–6.

TSA of mortality

Regarding the outcome of the 21–28 days mortality, the TSA analysis revealed that the cumulative Z-curve crossed the conventional boundary to determine significance but did not cross the trial sequential monitoring boundary for benefit and estimated information size, indicating that this may be a false positive result and needs to be further investigated in future RCTs (figure 10A). The Z-curve of the 90-day mortality did not cross the conventional boundary, indicating that this result may be a false negative result and the estimated information size is 3334 patients (figure 10B). The definitions of the TSA are shown in online supplemental table 7.

DISCUSSION

Statement of principal findings

This meta-analysis revealed that NMBAs did not reduce the 90-day mortality or MRC scores and did not increase the number of days free of ventilation at day 28 or days not in the ICU at day 28. However, the results of this study suggest that the use of NMBAs may decrease mortality

Table 6 GRADE system: mortality for acute respiratory distress syndrome patients

Mortality for patients with ARDS						
Patient or population: patients with ARDS						
Settings: mortality						
Intervention: NMBAs						
	Illustrative comparative risks* (95% CI)					
	Assumed risk	Corresponding risk				
Outcomes	Control	Mortality	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
90 day mortality	Study population 426 per 1000 Moderate 407 per 1000	 362 per 1000 (281 to 464) 346 per 1000 (269 to 444)	RR 0.85 (0.66 to 1.09)	1466 (5 studies)	⊕⊕⊖⊖ low†‡	
21–28 days mortality	Study population 370 per 1000 Moderate 375 per 1000	 263 per 1000 (196 to 355) 266 per 1000 (199 to 360)	RR 0.71 (0.53 to 0.96)	1574 (6 studies)	⊕⊕⊖⊖ low§¶	

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†The results of Rose trial and Rao's trial were different from the previous study.
‡There were only 41 patients in Rao's study.
§Two-thirds of the trials involved fewer than 150 patients (36, 41, 96 and 56, respectively).
¶There was publication bias among those trials through Egger's test.
ARDS, acute respiratory distress syndrome; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NMBAs, neuromuscular blocking agents; RR, risk ratio.

at days 21–28, APACHE II scores, and the occurrence of barotrauma and pneumothorax without increasing ICU-acquired muscle weakness. Finally, the PaO_2/FiO_2 results at 48 hours and 72 hours indicated that the use of NMBAs could improve oxygenation after treatment.

Discussion of the important differences in the results

Compared with a previous meta-analysis,[23 29] our study included Moss *et al*' trial[21] and Yirao *et al*'s trial,[28] which had a larger number of participants than previous studies. Due to the dominance of the latest published trial,[21] our results differed from those of previous meta-analyses,[23 29] and heterogeneity was inevitable. Besides, our study included more outcomes that these authors did not assess (such as APACHE II score and rate of pneumothorax), which are important for judging the severity of the underlying condition of patients. According to the TSA analysis, the 90-day mortality might be a false negative result, which need more RCTs to judge this outcome in the future. Compared with the study by Chang, we corrected the 90-day mortality data and obtained the opposite results.[22]

Based on the sensitivity analysis and subgroup analysis, the heterogeneity was speculated to be attributable to the differences in study design. First, the control group in the Rose trial[21] received lighter sedation than the control groups in other trials following the current recommendations for current clinical practice.[30 31] A previous study reported a reduction in infection complications in patients receiving a reduced dosage of sedatives, especially in terms of ventilator-acquired pneumonia.[32] In addition, deep sedation can increase the incidence of reverse triggering, which is associated with a poor prognosis in patients with ARDS.[33] Second, a detailed comparison of the seven studies was performed in terms of the eligibility criteria and exclusion criteria,[9 11–14 21 28] and most criteria were similar among the different studies. Interestingly, the Rose trial[21] employed the ratio of arterial blood oxygen saturation ($SpaO_2$) to the FiO_2 as the diagnostic criterion for ARDS in the case the PaO_2/FiO_2 results were unavailable. Although Chen *et al*[34] suggested that the clinical characteristics and prognosis were quite similar between patients with ARDS diagnosed by $SpaO_2/FiO_2$ and those diagnosed by PaO_2/FiO_2, $SpaO_2$ monitoring could enable the early diagnosis of ARDS and timely application of protective ventilation since $SpaO_2$ allows the continuous monitoring of oxygen without excessive arterial blood draws. Thus, patients ith ARDS diagnosed by $SpaO_2/FiO_2$ may receive more timely treatment and have fewer complications than those diagnosed by PaO_2/FiO_2. Third, compared with other RCTs, in the Rose trial,[21] more patients (17%) in the control arm received NMBAs, which might have affected the

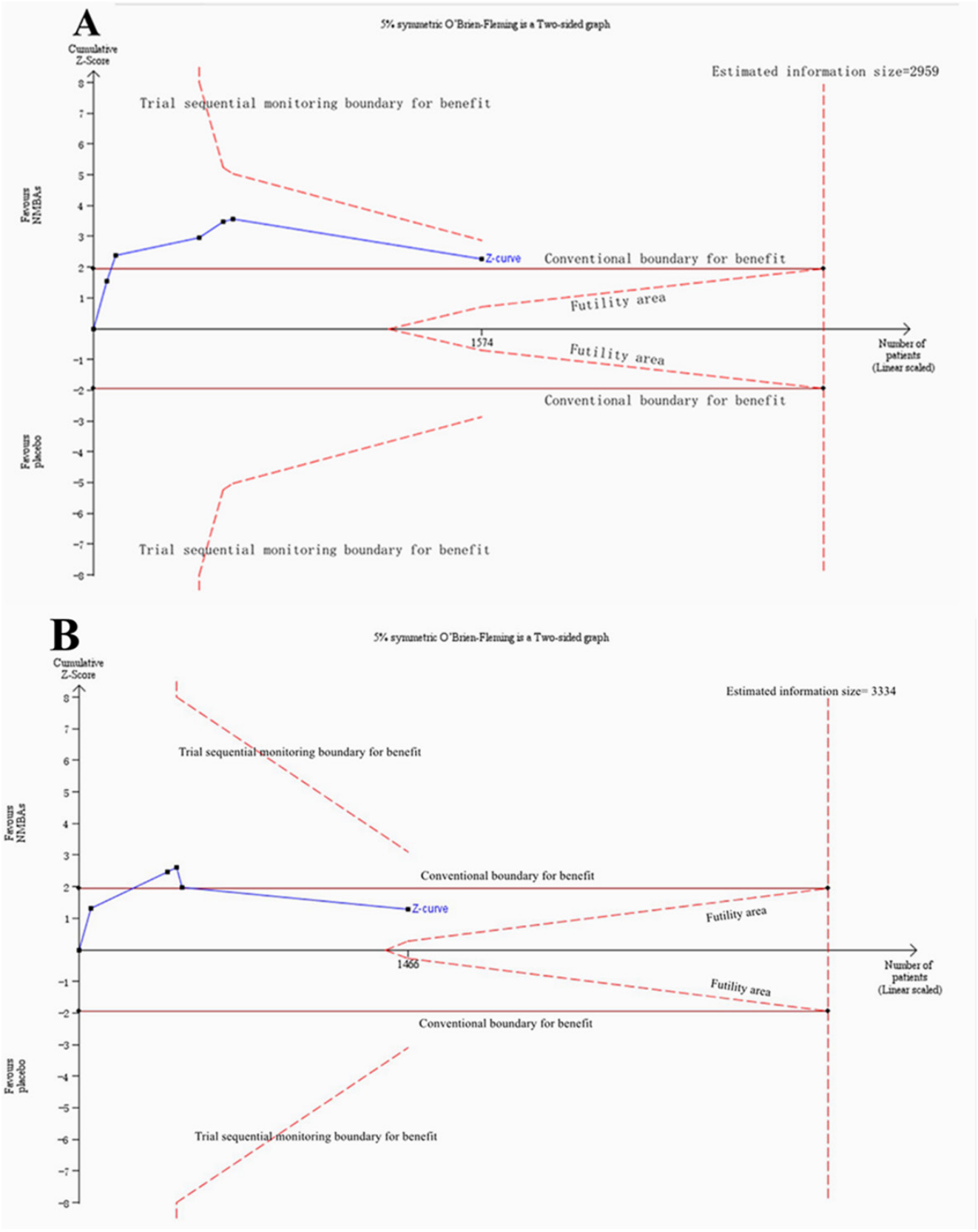

Figure 10 (A) TSA of 21–28 days mortality. The cumulative Z-curve of 21–28 days mortality surpassed the traditional boundary for statistical significance, none of the trial sequential monitoring boundaries have been surpassed in the TSA illustrated the positive effects of NMBAs on 21–28 days mortality could be a false positive effect and needs to be confirmed by including more RCTs. (B) TSA of 90-day mortality. The Z-curve did not cross the conventional boundary and estimated information size, which showed that 90-day mortality could be a false positive effect. NMBAs, neuromuscular blocking agents; RCTs, randomised controlled trials; TSA, trial sequential analysis.

mortality results. Moreover, the Rose trial used a modified protocol with higher PEEP than other RCTs, which used the protocol issued by the National Institutes of Health in the ARDS group.[35] A recent study published in 2018 showed that compared with low PEEP, high PEEP might offset the need of paralysis by rendering spontaneous effort less injurious and reducing the vertical gradient of the negative fluctuation of inspiratory local pleural pressure.[36] Therefore, the lung-protective ventilation with high PEEP in the Rose trial might have reduced the possible transpulmonary pressure swings in these two group, rendering NMBAs unnecessary.[36 37]

Additionally, our results indicated that NMBAs may decrease mortality at days 21–28, while no similar effect was observed in the 90-day mortality. The pathogenesis of ARDS is divided into the following three stages: the exudative phase, the repair phase and the proliferative phase.[38] Innate immune cell-mediated alveolar endothelial and epithelial barrier damage and protein-rich oedema accumulation in the pulmonary interstitium and alveoli are the most significant features during the exudative phase.[38] NMBAs are mainly used in the early stage when the inflammatory response is the most severe among patients.[39 40] NMBAs may restrain the release of inflammatory factors (eg, interleukin (IL)-1β, IL-6 and IL-8) and block nicotinic acetylcholine receptor α1 to achieve their anti-inflammatory effect and improve the clinical outcomes of respiratory patients in critical condition.[12 41 42] After the inflammatory stage, NMBAs may be reduced due to side effects, such as ICU-acquired muscle weakness, which may explain why NMBAs could only relieve short-term mortality among patients with ARDS.[16] In clinical practice, NMBAs are used only when patients with ARDS cannot be treated successfully with a ventilator and are not recommended for mild patients wih ARDS.[16] In addition to protective ventilation, sedation is often used in moderate to severe patients with ARDS, and the depth is controlled by a sedation scale.[2] Although sedation is recommended for patients with mechanical ventilation, the optimal degree of sedation and the best time to maintain sedation are still unclear.[43] Recent studies have found that sedation, especially deep sedation, may be related to post-traumatic stress disorder, cognitive dysfunction and other adverse reactions.[44 45] Meanwhile, in the Rose trial,[21] the use of cisatracurium was found to be associated with a high risk of severe adverse cardiovascular events (eg, hypotension and bradycardia), which was speculated to be associated with deep sedation. Therefore, the heterogeneity of the 21–28 days mortality could be explained by different sedation strategies as confirmed in the subgroup analysis (p=0.005). The meta-regression indicated that the sample size was associated with the 21–28 days mortality. Four eligible trials included in this outcome analysis were small sample studies.[9 12 13 28] We cannot ignore the possibility of a 'small sample effect,' and their sampling error should be fully considered.[46] In addition, according to the TSA, although the cumulative Z-curve of the 21–28 days mortality exceeded the traditional boundary and the results were statistically significant, none of the trial sequential monitoring boundaries was surpassed. Therefore, the result was inconclusive when adjusted for sequential testing based on an accumulating number of participants and the fact that the required information size has not been achieved. Thus, the effects of NMBAs on 21–28 days mortality could be a false positive effect and needs to be further confirmed by additional RCTs.

According to our analysis, NMBAs can contribute to a reduction in the incidence of NMBA-related complications and APACHE II score in patients with ARDS. To date, the mechanisms underlying the beneficial effects of NMBAs on oxygenation and patient prognosis have not been well illustrated, but it is generally believed that NMBAs could reduce oxygen consumption, carbon dioxide production, lactic acid accumulation and transpulmonary pressure by paralysing overworked respiratory muscles.[41 47–49] In addition, it has been reported that NMBAs can directly reduce ventilator-induced lung injury (atelectrauma and volutrauma) by preventing patient-ventilator desynchrony, thus allowing the ventilator to deliver the optimal amounts of oxygen and air into the lungs.[50] In the evaluated meta-regression model, the publication year was independently associated with FiO_2/FiO_2 at 48 hours. Increasing experience with mechanical ventilation and NMBAs may be a factor explaining this association during the studied time frame. Additionally, the sedation strategy may be a source of heterogeneity. Sedation therapy could protect organ function and improve oxygenation by reducing the respiratory rate, airway resistance and stress response.[51]

Strengths and limitations of this study

The uniqueness of this study lies in the analysis of RCTs with reasonable quality and strict designs; our study obtained novel results by including the largest number of studies and correct data. TSA software was applied in this study to assess the robustness of the relevant outcomes. Moreover, we conducted subgroup and meta-regression analyses to explore the relationship between the efficacy of NMBAs and important clinical variables. However, there are some limitations. First, although we systematically searched for relevant trials, it is still possible that certain unpublished articles and data were overlooked. Second, in addition to the possible sources of heterogeneity mentioned here, other factors that were not analysed may also lead to heterogeneity, such as the start time and duration of NMBAs. Third, due to the inadequate numbers of trials, the funnel plots presented in this study may fail to accurately reflect publication bias, which could be corrected by including additional RCTs in the future.

Unanswered questions and future research

Protective ventilation strategies represent an important treatment for patients with ARDS, and NMBAs are the most commonly used adjunctive therapy.[40 52 53] Sedation is commonly used to allow patients with ARDS to tolerate temporary hypoxia for therapeutic purposes and may improve their tolerance to mechanical ventilation.[54–56]

If the depth of sedation is not well controlled, excessive sedation could create or prolong the need for ventilation.[57–63] Therefore, we concluded that an individualised approach to the combined application of mechanical ventilation, NMBAs and sedation should be adopted, and the exact scheme should be adjusted based on the experience of the physicians. Moreover, it is necessary to conduct large-scale, multicentre prospective trials to identify the optimal dose and duration of NMBAs and explore the balance between the doses of NMBAs and sedation in patients with ARDS in the future.

CONCLUSION

In conclusion, although our study demonstrated that the use of NMBAs may reduce short-term mortality, NMBA-related complications, and APACHE II scores and may be associated with increased PaO_2/FiO_2 within the first 48 hours and 72 hours among patients with ARDS, long-term survival was not significantly improved. Therefore, NMBAs should not be considered a regular treatment regimen for moderate to severe patients with ARDS. Considering the limitations of the available studies, additional high-quality RCTs should be performed to guide the optimisation of clinical therapeutic strategies for NMBAs in the future.

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