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REVIEW

Can non-invasive positive pressure ventilation prevent endotracheal intubation in acute lung injury/acute respiratory distress syndrome? A meta-analysis

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ABSTRACT

The role of non-invasive positive pressure ventilation (NIPPV) in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is controversial. The aim of this study was to investigate whether NIPPV could prevent endotracheal intubation and decrease mortality rate in patients with ALI/ARDS. Randomized controlled trials (RCT) which reported endotracheal intubation and mortality rate in patients with ALI/ARDS treated by NIPPV were identified in Pubmed, Medline, Embase, Central Cochrane Controlled Trials Register, Chinese National Knowledge Infrastructure, reference lists and by manual searches. Fixed- and random-effects models were used to calculate pooled relative risks. This meta-analysis included six RCT involving 227 patients. The results showed that endotracheal intubation rate was lower in NIPPV (95% confidence interval (CI): 0.44–0.80, $z = 3.44$, $P = 0.0006$), but no significant difference was found either in intensive care unit (ICU) mortality (95% CI: 0.45–1.07, $z = 1.65$, $P = 0.10$) or in hospital mortality (95% CI: 0.17–1.58, $z = 1.16$, $P = 0.25$). Only two studies discussed the aetiology of ALI/ARDS as pulmonary or extra-pulmonary, and neither showed statistical heterogeneity ($I^2 = 0\%$, $\chi^2 = 0.31$, $P = 0.58$), nor a significant difference in endotracheal intubation rate (95% CI: 0.35–9.08, $z = 0.69$, $P = 0.49$). In conclusion, the early use of NIPPV can decrease the endotracheal intubation rate in patients with ALI/ARDS, but does not change the mortality of these patients.

Key words: acute lung injury, acute respiratory distress syndrome, meta-analysis, non-invasive ventilation, randomized controlled trial.

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; CPAP, continuous positive airway pressure; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; PaO_2/FiO_2, arterial partial pressure of oxygen to the fraction of inspired oxygen; PEEP, high positive end expiratory pressure; RCT, randomized controlled trial; RR, risk ratio; SpO_2; arterial oxygen saturation by pulse oximetry.

INTRODUCTION

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a type of acute diffuse, inflammatory lung injury, which leads to increased pulmonary vascular permeability, increased lung weight and loss of aerated lung tissue.[1] Multiple clinical disorders can cause ALI/ARDS, including pneumonia, sepsis, severe acute pancreatitis and trauma, with bacterial and viral lung infection the most common cause.[2,3] Despite the trend of decline in the last five decades, ALI/ARDS mortality remains very high and was reported to be about 26% in 2004–2005.[4]

Conventional therapies including invasive mechanical ventilation, antibiotics and fluid conservation have been widely used, particularly lung-protective ventilation, which decreases the mortality rate compared with high tidal volume ventilation and high positive end expiratory pressure (PEEP).[5,6] However, endotracheal ventilation is associated with significant complications, such as barotrauma, ventilator-associated pneumonia and tracheoesophageal fistula, leading to increased medical cost and social economic burden.[7–10]

Non-invasive positive pressure ventilation (NIPPV) is any type of positive ventilatory support applied without an endotracheal tube, including continuous positive airway pressure (CPAP).[11] Various studies have investigated the effectiveness and safety of NIPPV as the first-line therapy to avoid endotracheal intubation in patients with ALI/ARDS.[12–15] Rocker *et al.*[12] conducted an experiential cohort study using NIPPV in the initial treatment of 10 patients with ALI/ARDS, and reported an overall survival rate of 70% and success rate of 50%. Success in their study was defined as withdrawal of face mask ventilation without the need for further assisted ventilation for an

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additional 72 h. Several studies also demonstrated that NIPPV was successful in avoiding intubation and improving the ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2).[13,14] In contrast, another observational cohort study that involved 54 ALI patients treated with NIPPV reported a high failure rate, with more than two thirds of the subjects (38/54) having to undergo subsequent intubation and invasive mechanical ventilation.[15]

In 2006 and 2010, Agarwal *et al*. published two systematic reviews comparing NIPPV and standard oxygen therapy in patients with ALI/ARDS.[16,17] Surprisingly, the results were negative: in 2006, the risk ratio (RR) of intubation rate and mortality rate was −0.17 (95% confidence interval (CI): −0.38 to 0.04, $z = 1.59$, $P = 0.11$) and −0.04 (95% CI: −0.20 to 0.12, $z = 0.49$, $P = 0.62$), respectively. The results of the 2010 study were inconclusive because of the significant statistical heterogeneity in both intubation and mortality rate. Recommendations regarding the use of NIPPV in ALI/ARDS were limited because of the highly inconsistent findings.

Therefore, to further investigate whether NIPPV have advantages in reducing the rate of endotracheal intubation and mortality in ALI/ARDS, we used a meta-analysis to systematically compare NIPPV with conventional standard oxygen therapy.

METHODS

Search strategies

A comprehensive search in Pubmed, Ovid Medline, Ovid Embase, Ovid Central Cochrane Controlled Trials Register and Chinese National Knowledge Infrastructure from 1947 to October 2013 was conducted. The following search strategies were used: first, we limited the search to 'randomized controlled trials (RCTs)', and then we used the key words including 'acute respiratory distress syndrome/ARDS', 'acute lung injury/ALI', 'acute respiratory failure/insufficiency', 'acute hypoxemic respiratory failure/insufficiency' or 'acute hypoxemic respiratory distress' and 'nippv', 'bipap', 'cpap', 'niv', 'nipsv', 'noninvasive positive-pressure ventilation', 'noninvasive positive pressure ventilation', 'non invasive positive-pressure ventilation', 'bi-level positive-airway pressure', 'bi-level positive airway pressure', 'continuous positive airway pressure', 'noninvasive ventilation', 'non invasive ventilation', 'noninvasive pressure-support ventilation', 'non invasive pressure-support ventilation', 'mask ventilation', 'nasal ventilation' or 'positive-pressure respiration'. We also reviewed the references listed in the identified articles and performed a manual search of the related articles to identify all relevant and eligible articles and to minimize publication bias.

Inclusion and exclusion criteria

Relevant clinical trials were selected based on the following criteria: (i) study design was RCT; (ii) patients with any causes of ALI/ARDS were defined by the American-European Consensus Conference in 1994,[18] that is acute onset, bilateral pulmonary infiltrates on frontal chest radiograph, $PaO_2/FiO_2 \leq 200$ mm Hg for ARDS and ≤300 mm Hg for ALI and no evidence of left atrial hypertension (pulmonary artery wedge pressure ≤18 mm Hg); (iii) intervention was NIPPV compared against standard oxygen therapy (high-concentration oxygen delivered by a Venturi mask or a face mask to achieve arterial oxygen saturation by pulse oximetry (SpO_2) greater than 90%) and (iv) outcome measures included endotracheal intubation rate (which referred to the rate of endotracheal intubation actually performed, rather than the rate of meeting the endotracheal intubation criteria) and intensive care unit (ICU) or hospital mortality rate. We did not include non-randomized controlled trials, observational studies, cohort studies and case control studies in our meta-analysis.

Study selection

Study selection was conducted by two investigators independently in two phases. First, articles were screened according to titles and abstracts. Second, eligible articles were reviewed in full texts and selected according to the study inclusion criteria. Any disagreement was solved by mutual consensus in the presence of a third investigator.

Data extraction

The two investigators extracted data independently from each eligible study, using a standardized data extraction form.[19] The corresponding authors of eligible articles were contacted via e-mail to request any missing data information. The data extracted included: author, publication year, study design, number of patient, patient demographic characteristics (age, gender, etc.), inclusion and exclusion criteria, causes of ALI/ARDS, interventions (NIPPV: ventilator type, interface, mode and pressure range; standard oxygen therapy: type of mask), outcome measures and study results (endotracheal intubation rate, and ICU or hospital mortality rate). Differences in opinion were resolved by reaching a consensus or by consulting a third investigator.

Patients

In all six trials included, patients were divided into two groups based on treatment strategies (NIPPV or standard oxygen therapy) once they participated in the trial. In terms of endotracheal intubation rate, we divided patients with ALI/ARDS into pulmonary aetiology and extra-pulmonary aetiology to investigate whether different causes would influence the effectiveness of NIPPV.

Quality assessment

For the assessment of risk of bias in estimating the study outcomes, we used the Cochrane risk of bias tool.[19] Each study was assessed for: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of

participants and personnel (performance bias); (iv) blinding of related outcomes assessment (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias) and (vii) other bias. Two investigators conducted the quality assessment for the study methodology, independently and in duplicate. Any disagreement was resolved by mutual consensus in the presence of the third investigator.

Statistical analysis

Categorical variables were reported as frequency and proportion. We tested the heterogeneities of the enrolled studies, including clinical, methodological and statistical heterogeneity, using the χ^2 test with $P < 0.1$, indicating significant heterogeneity. Statistical heterogeneity was also supposed to be significant when $I^2 > 50\%$. In the presence of statistical heterogeneity, the random-effects model was applied; otherwise, the fixed-effects model was used. We calculated the RR for the dichotomous data and 95% CI for interval estimation. Data analyses were performed using the Cochrane systematic review software Review Manager (RevMan; Version 5.1.7 for windows, Rigshospitalet, Copenhagen, Denmark; The Nordic Cochrane Centre 2008). Mann–Whitney *U*-test was used for hypothesis test with the significant *z*-value and *P*-value set at 0.05. Results of the hypothesis tests were displayed in Forest plots. Sensitivity analysis was conducted to substitute alternative decisions or ranges of values for decisions that were arbitrary or unclear.

RESULTS

We identified 857 studies from electronic databases (Fig. 1), of which, 556 were discarded for not being RCT and 229 were discarded for not comparing the NIPPV against standard oxygen therapy. Then we searched the remaining 72 studies for full-text review, and six studies[20–25] were included in the final analysis. The 66 studies discarded did not meet the ALI/ARDS criteria, did not recruit adult patients or did not report endotracheal intubation rate.

Study description

All six trials were prospective and randomized, and provided data on endotracheal intubation. Of the six trials included in the final analysis, five reported ICU mortality,[20,21,23–25] and only three further described hospital mortality.[21,22,24] Two trials were multicenter studies.[21,24] Two trials used concealed randomization.[20,21] None of the six trials were blinded. Three trials specifically involved patients with ARDS,[22,24,25] whereas the other three included patients with various causes of acute hypoxemic respiratory failure but provided data on ARDS patients separately. Only two studies discussed the aetiologies of ALI/ARDS as pulmonary or extra-pulmonary and provided endotracheal intubation rate in each group.[20,24] Details of causes of ARDS, non-invasive ventilators, NIPPV interfaces and modes and outcomes are summarized in Table 1. Quality assessment of the six included trials showed that although none of the six trials had blinding of participants or personnel, or blinding of outcome assessment, no bias in selection, attrition or reporting was identified.

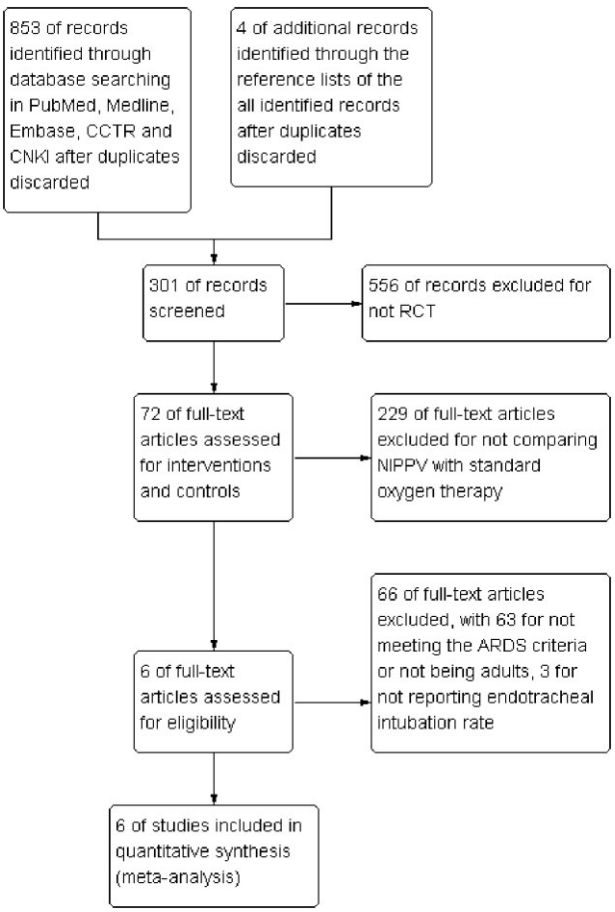

Figure 1 Study flow diagram. ARDS, acute respiratory distress syndrome; CCTR, Ovid Central Cochrane Controlled Trials Register; CNKI, Chinese National Knowledge Infrastructure; NIPPV, non-invasive positive pressure ventilation; RCT, randomized controlled trial.

A total of 227 patients with ALI/ARDS were studied, among which, 115 (50.7%) received NIPPV and 112 (49.3%) received standard oxygen therapy. Baseline characteristics of the patients with ALI/ARDS enrolled were described in three trials,[22,24,25] whereas the data in the other three trials were mixed in different subgroups, such as pneumonia, cardiogenic pulmonary oedema and thoracic trauma (Table 2). Sensitivity analysis showed that none of these six trials was excluded for low quality or dubious decisions.

Heterogeneity

No statistical heterogeneity was found either in endotracheal intubation rate ($I^2 = 43\%$, $\chi^2 = 8.82$, $P = 0.12$) between NIPPV and standard oxygen therapy in all ALI/ARDS patients without considering the aetiologies (Fig. 2), or in ICU mortality rate ($I^2 = 0\%$, $\chi^2 = 3.11$, $P = 0.54$) (Fig. 3), whereas significant

Table 1 Details of the six studies reviewed

First author, year	Population	Aetiology of ALI/ARDS	Interventions		NIPPV ventilator	NIPPV interface	NIPPV mode	Pressure range (cmH_2O)	Outcomes[†]
			Experimental group	Control group					
Antonelli *et al.* 2000[20]	15	Complicated pneumonia, extra-pulmonary sepsis, massive blood transfusion and acute pancreatitis	NIV	Standard treatment with supplemental oxygen administration	Puritan Bennett 7200 or Servo 990C Siemens	Full face mask	BiPAP	IPAP:14–20 EPAP:5–10	1.2
Delclaux *et al.* 2000[21]	81	Pneumonia, aspiration, near-drowning, SIRS, others	Oxygen therapy plus CPAP	Oxygen therapy alone	Vital Flow 100 CPAP Flow Generator	Full face mask	CPAP	CPAP:5–10	1.2.3
Auriant *et al.* 2001[22]	48	Interstitial pulmonary oedema, atelectasis, pneumonia	NPPV with standard treatment	Standard treatment with oxygen supplementation	BiPAP Vision; Respironics Inc.	Nasal mask	BiPAP	NM	1.3
Ferrer *et al.* 2003[23]	15	NM	NIV	Oxygen therapy with high concentration sources	BiPAP Vision; Respironics Inc.	Face mask or nasal mask	BiPAP	IPAP: 10–24 EPAP: 4–12	1.2
Zhan *et al.* 2012[24]	40	Pulmonary infection, acute pancreatitis, multiple trauma, sepsis, drowning, carbonic oxide poisoning, haemorrhagic shock	NPPV	High-concentration oxygen therapy	BiPAP Vision; Respironics Inc.	Face mask	BiPAP	IPAP: Tidal volume >6 mL/kg or reach the maximum tolerated level EPAP: 4–13	1.2.3
Zhi *et al.* 2012[25]	28	Severe pneumonia, trauma, severe acute pancreatitis, haemorrhagic shock, toxication, septic shock, others	NPPV	Oxygen therapy	BiPAP Vision	Full face mask	CPAP	CPAP: 8–16	1.2

[†] Outcomes can be entered into meta-analysis: 1. endotracheal intubation rate. 2. ICU mortality rate. 3. hospital mortality rate.

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BiPAP, bilevel positive airway pressure; cmH_2O, centimeters of water; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; NIPPV, non-invasive positive pressure ventilation; NIV, non-invasive ventilation; NM, not mentioned; NPPV, non-invasive positive pressure ventilation; SIRS, systemic inflammatory response syndrome.

Table 2 Baseline characteristics of patients in the six studies included

First author, year	Total patients (N)†	Aetiology of acute respiratory failure†	Patients with ALI/ARDS (n)†	Age (mean ± SD, y)†	Female no. (%)†	APACHE or score (mean ± SD)	Respiratory rate (mean ± SD, breaths/min)	pH (mean ± SD)	PaO_2/FiO_2 (mean ± SD, mm Hg)	$PaCO_2$ (mean ± SD, mm Hg)
Antonelli *et al.* 2000[20]	20	Pneumonia, cardiogenic pulmonary oedema, ARDS, mucus plugging or atelectasis, pulmonary embolism	8	45 ± 19	7 (70)	APACHE II 17 ± 5	38 ± 3	7.46 ± 0.05	129 ± 30	42 ± 10
Delclaux *et al.* 2000[21]	40	Pneumonia, aspiration, near-drowning, SIRS, others	40	56 (19–85)‡	23 (39)	SAPS II 32 (6–87)‡	34 (20–60)‡	7.42 (7.21–7.62)‡	140 (59–288)‡	37 (23–61)‡
Auriant *et al.* 2001[22]	24	Interstitial pulmonary oedema, atelectasis, pneumonia	24	58.9 ± 10	NM	SAPS II 16.9 ± 5.4	27.1 ± 7.2	7.42 ± 0.02	126.8 ± 42.1	34.2 ± 13.3
Ferrer *et al.* 2003[23]	51	Pneumonia, cardiogenic pulmonary oedema, thoracic trauma, ARDS, acute severe asthma, postoperative respiratory failure, usual interstitial pneumonitis	7	61 ± 17	21 (41)	SAPS II 34 ± 10	37 ± 6	7.42 ± 0.06	102 ± 21	37 ± 7
Zhan *et al.* 2012[24]	21	Pulmonary infection, acute pancreatitis, multiple trauma, sepsis, drowning, carbonic oxide poisoning, haemorrhagic shock	21	43.8 ± 13.7	5 (23.8)	APACHE II 11.8 ± 6.3	28.8 ± 7.2	7.44 ± 0.08	225.4 ± 17.4	31.3 ± 6.0
Zhi *et al.* 2012[25]	28	Severe pneumonia, trauma, severe acute pancreatitis, haemorrhagic shock, toxication, septic shock, others	28	47.9 ± 16.8	4 (26.7)	APACHE II 18.15 ± 3.33	NM	NM	139.06 ± 48.85	NM

† Data on all patients who received non-invasive positive pressure ventilation.

‡ In this report, this value was reported as median and 5th–95th percentile.

SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; ARDS, acute respiratory distress syndrome; SIRS, systemic inflammatory response syndrome; NM, not mentioned.

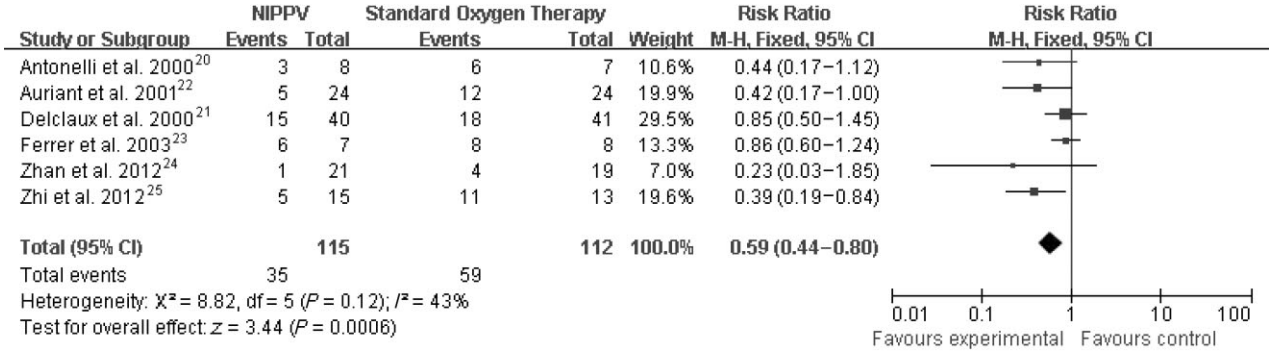

Figure 2 Endotracheal intubation rate: NIPPV versus standard oxygen therapy. CI, confidence interval; M.-H., Mantel-Haenszel; NIPPV, non-invasive positive pressure ventilation.

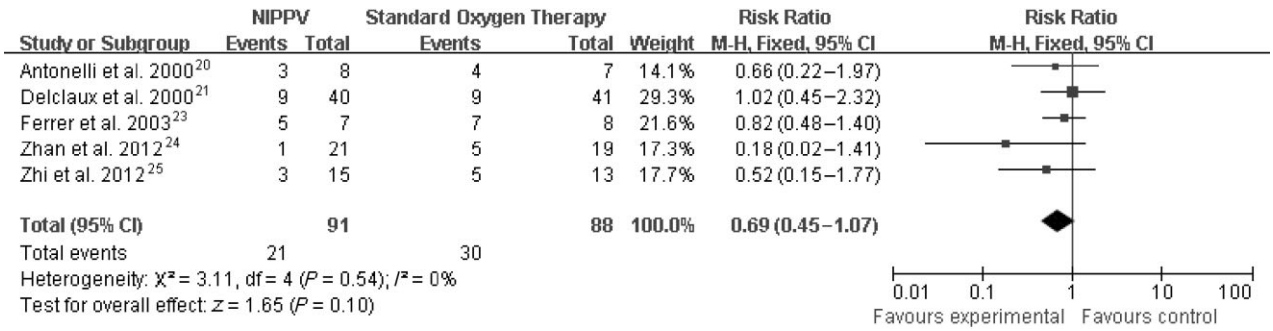

Figure 3 ICU mortality rate: NIPPV versus standard oxygen therapy. CI, confidence interval; ICU, intensive care unit; M.-H., Mantel-Haenszel; NIPPV, non-invasive positive pressure ventilation.

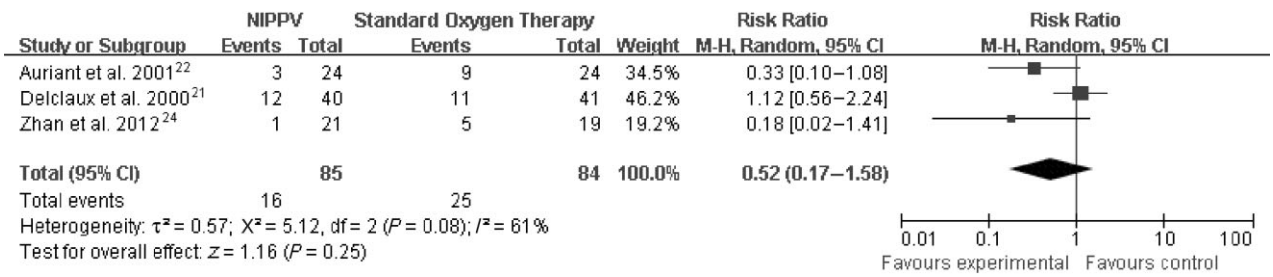

Figure 4 Hospital mortality rate: NIPPV versus standard oxygen therapy. CI, confidence interval; M.-H., Mantel-Haenszel; NIPPV, non-invasive positive pressure ventilation.

statistical heterogeneity was found in hospital mortality rate (I^2 = 61%, χ^2 = 5.12, P = 0.08) (Fig. 4). No statistical heterogeneity (I^2 = 0%, χ^2 = 0.31, P = 0.58) was found in NIPPV patients with ALI/ARDS of either pulmonary or extra-pulmonary aetiology (Fig. 5).

Outcomes

The pooled RR of endotracheal intubation rate, ICU mortality rate and hospital mortality rate in all ALI/ARDS patients was 0.59 (95% CI: 0.44–0.80) (Fig. 2), 0.69 (95% CI: 0.45–1.07) (Fig. 3) and 0.52 (95% CI: 0.17–1.58) (Fig. 4), respectively. Data analysis showed significant differences between NIPPV and standard oxygen therapy in endotracheal intubation rate (z = 3.44, P = 0.0006) (Fig. 2), but no differences in ICU mortality (z = 1.65, P = 0.10) (Fig. 3) and hospital mortality (z =1.16, P = 0.25) (Fig. 4). Nevertheless, in NIPPV patients with ALI/ARDS of either pulmonary or extra-pulmonary aetiology, the pooled RR of endotracheal intubation rate was 1.77 (95% CI: 0.35–9.08), but the differences were not significant (z = 0.69, P = 0.49) (Fig. 5).

DISCUSSION

This meta-analysis included six RCT with 227 ALI/ARDS patients, and data analysis showed

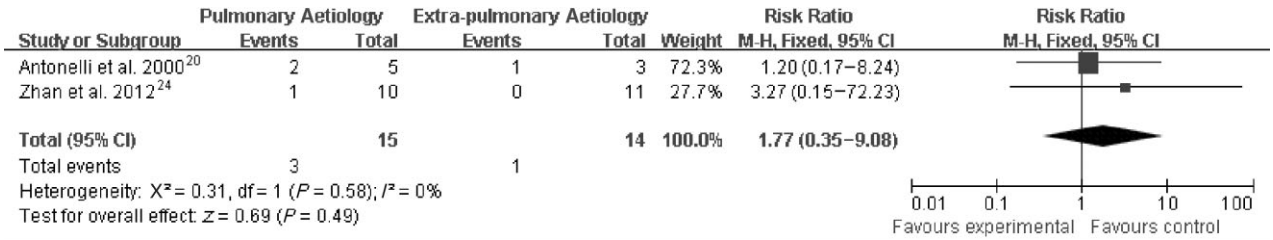

Figure 5 Endotracheal intubation rate of NIPPV in ALI/ARDS: Pulmonary aetiology versus extra-pulmonary aetiology. ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; NIPPV, non-invasive positive pressure ventilation; M.-H., Mantel-Haenszel.

NIPPV reduced endotracheal intubation rate compared with standard oxygen therapy, and pulmonary or extra-pulmonary aetiology did not change NIPPV effects. However, NIPPV did not improve ICU or hospital mortality.

The clinical hallmarks of ALI/ARDS are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance.[1,18] In 2012, a new ARDS Berlin definition was created by ARDS Definition Task Force.[1] By this definition, PEEP was first included as a diagnosis standard because it can reduce ventilator-induced lung injury by reducing the proportion of non-aerated lung,[26–29] markedly affect PaO_2/FiO_2,[30,31] and allow arterial-oxygenation goals to be met with the use of a lower fraction of inspired oxygen and thus reduce the adverse pulmonary effects of oxygen.[32] Therefore, it is possible that NIPPV provides a similar PEEP, which opens the lungs, decreases oedema in alveoli and improves lung compliance and finally reduces the need for endotracheal intubation in ALI/ARDS patients.

Although our meta-analysis concluded that early use of NIPPV can decrease the endotracheal intubation rate in patients with ALI/ARDS but did not change the mortality rate, NIPPV may still be useful in that invasive mechanical ventilation is associated with an important incidence of complications and mortality and may lead to increased medical cost and social economic burden.[7–10,33–36] However, different types of ventilator or interface, ventilation mode and ventilation pressure may affect the clinical outcome of ARDS. For example, in terms of non-invasive mechanical ventilation mode, Keenan *et al.* recommended CPAP not to be used because of higher complications and greater patients intolerance compared with oxygen therapy.[21,37] Moreover, treatment of ARDS is diverse including antibiotics, and fluid conservation, in addition to mechanical ventilation. This means that endotracheal intubation is not the only determinant of ARDS mortality. Future studies may focus more on the effect of different non-invasive ventilation modes on the prognosis of ARDS.

We hypothesized that different causes of ALI/ARDS may result in varied effectiveness of NIPPV, because lung damage is probably more severe in pulmonary aetiology than in extra-pulmonary aetiology. In addition to the pathophysiological change of ALI/ARDS, diffuse alveolar damage (i.e. oedema, inflammation, hyaline membrane or haemorrhage) may cause refractory hypoxemia and bilateral radiographic opacities associated with increased venous admixture, increased physiological dead space and decreased lung compliance.[1,38] There may be direct damage to the lung parenchyma and the interstitium in the pulmonary aetiology group, so it is more difficult to improve oxygenation. Therefore, to further investigate whether different aetiologies would influence the effectiveness of NIPPV, we divided patients with ALI/ARDS into two groups, that is, pulmonary aetiology and extra-pulmonary aetiology. We found that pulmonary aetiology itself did not change the effects of NIPPV on endotracheal intubation. However, it is difficult to draw definite conclusions because the number of patients in each group was very small.

Statistical heterogeneity is known as a consequence of clinical or methodological diversity, or both.[19] In the six included trials, different types of ventilators or interfaces, ventilation modes and ventilation pressure were used, and the causes of ALI/ARDS also varied, which may have resulted in statistical heterogeneity. In addition, endotracheal mechanical ventilation-related complications, such as tracheobronchial bacterial contamination, bronchopleural fistula and pyothorax, may also cause significant statistical heterogeneity in hospital mortality between NIPPV and standard oxygen therapy in all ALI/ARDS patients.[39,40]

Our meta-analysis still has three major limitations. First, the total number of studies and patients enrolled was relatively small. Second, the definition of ARDS has inherent limitations, due to the variability in chest radiograph interpretation, difficulty in excluding left atrial hypertension, absence of the definition of acute onset and the sensitivity of PaO_2/FiO_2 to different ventilator settings. Finally, the baseline characteristics of patients were not completely described and provided, which may lead to selection biases.

In conclusion, the early use of NIPPV can decrease the endotracheal intubation rate in patients with ALI/ARDS, but does not change the mortality of these patients. More large RCTs are needed, particularly in patients with ARDS according to the latest Berlin definition of ARDS, to further determine the role of NIPPV, including the best modes and pressures to use as well as the most appropriate time to commence therapy.

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