Is noninvasive pressure support ventilation as effective and safe as continuous positive airway pressure in cardiogenic pulmonary oedema?

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ABSTRACT

Introduction: Noninvasive ventilation (NIV) with continuous positive airway pressure (CPAP) has been shown to decrease endotracheal intubation and mortality in patients with acute cardiogenic pulmonary oedema (ACPE). The Three Interventions in Cardiogenic Pulmonary Oedema showed no advantage of NIV over standard medical therapy. This meta-analysis is an update on the efficacy and safety of two different forms of NIV (noninvasive pressure support ventilation [NIPSV] vs. CPAP) in patients with ACPE.

Methods: We searched the MEDLINE and EMBASE databases for randomised clinical trials published from 1980 to 2008 that have compared NIPSV and CPAP in patients with ACPE. We calculated the odds ratio (OR) with 95 percent confidence intervals (CI) and pooled the results using three different statistical models (fixed effects, random effects and exact method).

Results: Ten studies (577 and 576 in the CPAP and NIPSV groups, respectively) met our inclusion criteria. NIPSV performed similar to CPAP in decreasing the intubation rates (OR 0.8; 95 percent CI 0.43–1.49), hospital mortality (OR 1.08; 95 percent CI 0.76–1.54) and the occurrence of myocardial infarction (OR 0.8; 95 percent CI 0.36–1.76). The results were similar when pooling the data with any of the three statistical methods and stratifying for the type of pressure therapy (fixed vs. variable) except for myocardial infarction, which was more frequent in the fixed pressure NIPSV arm (OR 5.06; 95 percent CI 1.66–15.44).

Conclusion: NIPSV appears to be as safe and efficacious as CPAP, if titrated rather than fixed pressures are employed.

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Keywords: acute cardiogenic pulmonary oedema, continuous positive airway pressure, intratracheal intubation, noninvasive pressure support ventilation, noninvasive ventilation, pulmonary oedema, positive-pressure respiration, respiratory insufficiency

Singapore Med J 2009; 50(6): 595-603

INTRODUCTION

Noninvasive ventilation (NIV) has revolutionised the management of patients with acute respiratory failure.[1] It has decreased the need for endotracheal intubation and its attendant complications like nosocomial pneumonia and other intensive care unit-acquired infections.[2,3] In selected situations like chronic obstructive pulmonary disease and pulmonary oedema, it has also been shown to decrease mortality.[4,5] Acute cardiogenic pulmonary oedema (ACPE) is a common medical emergency and NIV, in addition to conventional medical treatment, is beneficial for patients with ACPE.[5,6] Positive pressure therapy acts by augmenting the inspiratory flow, and thus the tidal volume and alveolar ventilation, re-expands flooded alveoli, and counteracts intrinsic positive end-expiratory pressure (PEEP).[7,8] During cardiac systole, the increase in intrathoracic pressure decreases the right and left ventricular preload by reducing the venous return. In diastole, NIV increases pericardial pressure, reduces transmural pressure and decreases the afterload.[9,10] NIV increases the cardiac index in patients with ACPE, and leads to a significant decrease in the heart rate by causing pulmonary hyperinflation.[8,11,12]

Positive pressure therapy can be delivered noninvasively either by bi-level noninvasive pressure support ventilation (NIPSV) or continuous positive airway pressure (CPAP). In NIPSV, the ventilator supports the patient's inspiration combining inspiratory pressure support and PEEP, whereas CPAP maintains a positive airway pressure throughout the respiratory cycle. Theoretically, NIPSV may confer an advantage in the treatment of ACPE by reducing the work of breathing during inspiration. Recent meta-analyses have shown that the use of CPAP

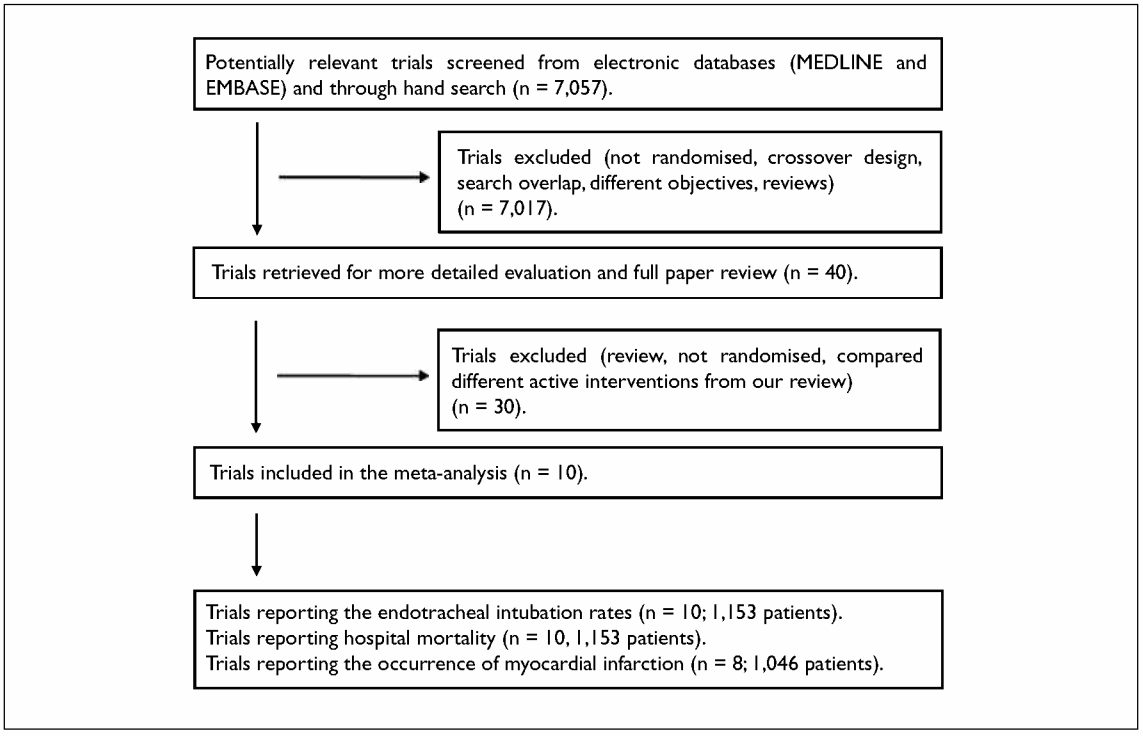

Fig. 1 Flow diagram shows the trial selection process for this systematic review.

(plus optimal medical therapy) is superior to conventional medical therapy alone in decreasing the intubation rates and mortality in patients with ACPE; however, there was only a trend towards improvement with the use of NIPSV.[13,14] No advantage of NIPSV over CPAP was registered in one meta-analysis, which compared the use of NIPSV directly with CPAP.[15] Recently, a large trial has been published, the Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial which showed no advantage of NIV over standard medical therapy.[16] This study is a meta-analytic update on the efficacy and safety of NIPSV vs. CPAP in patients with ACPE. In this study, in addition to the conventional techniques of pooling data in meta-analysis (fixed and random effects), we have also used the exact method of meta-analysis to increase the validity of the results.

METHODS

The MEDLINE and EMBASE databases from 1980 to 2008 were searched for fully published articles, limiting the search to human, adults (aged ≥ 19 years), randomised controlled trials and clinical trials (no language restrictions), using the following keywords: noninvasive ventilation, non-invasive ventilation, noninvasive positive pressure ventilation, nasal ventilation, nippv, bipap, cpap, bilevel positive airway pressure, continuous positive airway pressure, pulmonary edema and heart failure. The reference lists of all identified studies and reviews were reviewed and our personal files were manually searched. The following criteria were used to select the articles: (a) the study design was a randomised controlled trial; (b) the study population included patients with ACPE; (c) the intervention was an application of NIPSV vs. CPAP; and (d) the study reported the outcomes of endotracheal intubation, myocardial infarction and the hospital mortality.

Independently and in duplicate, two of the authors (RA, ANA) abstracted data from these trials. Differences in opinion were settled by consensus or after consultation with a third author (DG). The methodological quality of each trial was evaluated using a five-point Likert scale (0 = worst and 5 = best) as described by Jadad et al.[17] This instrument assessed the adequacy of randomisation, blinding and the handling of withdrawals and dropouts with a score of one point for each "yes" or zero points for each "no" answer. The studies were said to be of low quality if the Jadad score was ≤ 2, and high quality if the score was ≥ 3.[17,18]

Statistical analysis was performed using the statistical packages - Review Manager (RevMan for MS Windows, version 5.0, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008) and StatsDirect (StatsDirect version 2.7.2 for MS Windows, StatsDirect Ltd, England, 2005). The odds ratio (OR) with 95% confidence intervals (CI) for the individual studies were calculated.[19] The results from individual studies were then pooled using the fixed effects model of Mantel-Haenszel,[20] the random effects model of DerSimonian and Laird[21] and the exact

Table I. Trials employing noninvasive ventilation (NIV) in cardiogenic pulmonary oedema.

Study	Patient characteristics*		Inclusion criteria	Exclusion criteria	Intubation criteria
	CPAP	NIPSV			
Mehta et al[29]	13 patients Age: 77 ± 12 years APACHE II: 19 ± 3 $PaCO_2$: 56 ± 15 mmHg Pressure: 10 cmH_2O fixed Machine: Portable ventilator (BiPAP® S/T, Respironics)	14 patients Age: 76 ± 7 years APACHE II: 18 ± 4 $PaCO_2$: 52 ± 11 mmHg Pressure: 15/5 cmH_2O fixed Machine: Portable ventilator (BiPAP® S/T, Respironics)	RR > 30/min, use of accessory respiratory muscles, paradoxical abdominal motion, HR > 100/min, LVS3, bilateral rales, CXR-ACPE	Respiratory or cardiac arrest, unstable cardiac rhythm, SBP < 90 mmHg; unresponsive, agitated or uncooperative patient, any condition that precluded the application of a face mask.	Inability to tolerate mask, increasing RR or HR, significant haemodynamic compromise. Inability to maintain PaO_2 > 60 mmHg despite oxygen, $PaCO_2$ in creased by > 5 mmHg from baseline with clinical worsening.
Park et al[30]	9 patients Age and APACHE II: NA $PaCO_2$: 41 ± 11 mmHg Pressure: 5–12.5 cmH_2O to maintain SpO_2 > 90% Machine: CPAP valve in circuit (Vital SignsTM)	7 patients Age and APACHE II: NA; $PaCO_2$: 39 ± 15 mmHg Pressure: 8/3 increased by 2/2 to maintain SpO_2 > 90% Machine: Portable ventilator (BiPAP® S/T, Respironics)	Acute onset dyspnoea RR > 25/min, bilateral rales, CXR-ACPE	SBP < 90mmHg, cardiac arrhythmias, altered sensorium, bradypnoea, lack of cooperation or agitation, repetitive vomiting, UGI bleed, facial deformities, decompensated respiratory disease.	Clinical: determined by the physician responsible for the patient.
Cross et al[31]	36 patients Age: 73 ± 9 years $PaCO_2$ and APACHE II: NA Pressure: 5–20 cmH_2O Machine: NA	35 patients Age: 75 ± 10 years $PaCO_2$ and APACHE II: NA Pressure: 10–25/5 cmH_2O Machine: NA	SaO_2 < 90% on air, SaO_2 < 93% on 6 L O_2/min, inability to speak in sentences or R < 25/min	Mental obtundation, pneumonia, pneumothorax, endotracheal intubation, decision to withhold treatment by the patient/relative.	Respiratory arrest, apnoea, loss of consciousness, psychomotor agitation, HR < 50/min with loss of alertness, SBP < 70 mmHg, condition not improving satisfactorily or worsening.
Bellone et al[32]	22 patients Age: 77 ± 7 years APACHE II: 18 ± 3 $PaCO_2$: 53 ± 17 mmHg Pressure: 10 cmH_2O fixed Machine:Ventilator (Vela,Viasys)	24 patients Age: 77 ± 7 years APACHE II: 19 ± 5 $PaCO_2$: 55 ± 16 mmHg Pressure: 15/5 cmH_2O to maintain Vt of 400 ml Machine:Ventilator (Vela,Viasys)	SpO_2 < 90% with > 5 L/min O_2, severe dyspnoea, RR > 30/min, accessory respiratory muscles use, paradoxical abdominal motion, LVS3, HR > 100/min, bilateral rales, CXR- ACPE	Respiratory or cardiac arrest, ACS, SBP < 90 mmHg, unresponsive, agitated or uncooperative, ny condition that a precluded the application of a face mask.	Respiratory arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation, HR < 50 bpm with loss of alertness, haemodynamic instability with SBP < 70 mmHg.
Crane et al[33]	20 patients Age: 75 ± 12 years APACHE II: NA $PaCO_2$: 69 ± 19 mmHg Pressure: 10 cmH_2O fixed Machine: Portable ventilator (VPAP II, ResMed)	20 patients Age: 76 (8) years APACHE II: NA $PaCO_2$: NA Pressure: (17 ± 2)/(11 ± 2) cmH_2O variable Machine: Portable ventilator (VPAP II, ResMed)	RR > 23/min, CXR-ACPE, pH < 7.35	SBP < 90 mmHg, fever > 38°C, thrombolysis for ACS, dialysis for renal impairment, patients not responding to pain and patients with dementia.	RR > 40 bpm or < 10 bpm, reducing consciousness level, falling arterial pH (< baseline & < 7.2).
Park et al[34]	27 patients Age: 61 ± 17 years APACHE II: 19 ± 6 $PaCO_2$: NA Pressure: 11 (2) cmH_2O variable	27 patients Age: 66 ± 14 years APACHE II: 20 (2) $PaCO_2$: NA Pressure: (17 ± 2)/(11 ± 2) cmH_2O variable	Age >16 years, acute onset respiratory distress, RR > 25/min, tachycardia and diaphoresis, bilateral rales, CXR-ACPE	Altered sensorium, intractable vomiting, ACS, SBP < 90 mmHg, pulmonary embolism, COPD, pneumonia or pneumothorax.	Glasgow coma scale < 13 persistent respiratory distress, PaO_2 < 60 mmHg, SpO_2 < 90% despite maximal therapy, increase in $PaCO_2$ > 5 mmHg from the baseline.
Bellone et al[35]	18 patients Age: 77 ± 7 years APACHE II: 17 ± 3 $PaCO_2$: 61 ± 14 mmHg Pressure: 10 cmH_2O fixed Machine: Portable ventilator (BiPAP Vision, Respironics)	18 patients Age: 77 ± 7 years APACHE II: 19 ± 5 $PaCO_2$: 66 ± 14) mmHg Pressure: 15/5 cmH_2O to maintain Vt of 400 ml Machine: Portable ventilator (BiPAP Vision, Respironics)	SpO_2 < 90% with more than 5 L/min O_2 via face mask, RR > 30/min, accessory respiratory muscles, paradoxical abdominal motion, HR > 100/min, LVS3, bilateral rales, CXR-ACPE	$PaCO_2$ < 45 mmHg. respiratory or cardiac arrest, SBP < 90 mmHg, serum creatinine concentration > 2.5 mg/dL, COPD; unresponsive, agitated, or uncooperative, any condition that precluded the application of a face mask.	Respiratory arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation, HR < 50 bpm with loss of alertness, haemodynamic instability with SBP < 70 mmHg.

Ferrari et al[36]	27 patients Age: 77 ± 9 years SAPS II: 45 (7) $PaCO_2$: 61 ± 18 mmHg Pressure: 9 ± 2 cmH_2O variable Machine: Flow generator (WhisperFlow, Caradyne) able to deliver high-flow and spring-loaded expiratory pressure valve (PEEP valve, GaleMed)	25 patients Age: 74 ± 10 years SAPS II: 47 ± 8 $PaCO_2$: 57 ± 18 mmHg Pressure: (15 ± 3)/7 ± 1) cmH_2O variable Machine: Ventilator (LTV 1000, Pulmonetics)	Rapid onset of symptoms, severe dyspnoea, RR < 30/min, use of accessory respiratory muscles, SpO_2 < 90% with FiO_2 60% via Venturi mask, CXR- ACPE	ACS, SBP < 90 mmHg on vasopressors, arrhythmias, immediate endotracheal intubation, inability to protect the airways, impaired sensorium, recent gastric/ oesophageal surgery, UGI bleed, facial deformities, Cancer with ECOGPS ≥ 2, long-term oxygen therapy, AECOPD, pulmonary embolism, refusal of intubation, pneumonia, pneumothorax.	Cardiac arrest or gasping for air, PaO_2/FiO_2 < 100, inability to improve respiratory distress and arterial blood gases within 60 min, coma, psychomotor agitation, haemodynamic instability, life-threatening arrhythmias.
Moritz et al[37]	59 patients Age: 78 ± 9 years APACHE II: NA $PaCO_2$: NA Pressure: 8 (2) cmH_2O variable Machine: Virtual CPAP valve (Boussignac, Vygon)	50 patients Age: 78 ± 9 years APACHE II: NA $PaCO_2$: NA Pressure: (12 ± 3)/(5 ± 1) cmH_2O variable Machine: Bi-level device details NA	Sudden dyspnoea; bilateral rales, RR > 30 /min; SpO_2 < 90%, with O_2 > 5 L/min through facemask, use of accessory muscles, CXR- ACPE	Out-of-hospital use of NIV, Fever > 39°C, Altered mental state, COPD, CRF, pneumonia, ACS, SBP < 90 mmHg, cardiac or respiratory arrest, SpO_2 < 85% with 100% FIO_2, decreased alertness, major agitation, active contraction of the respiratory accessory muscles with paradoxical abdominal or thoracic motion.	NA
Gray et al[16]	346 patients Age: 78 ± 10 years APACHE II: NA $PaCO_2$: 56 ± 14 Pressure: 10 ± 4 cmH_2O variable Machine: Respironics Synchrony ventilator	356 patients Age: 77 ± 10 years APACHE II: NA $PaCO_2$: 58 ± 19 Pressure: (14 ± 5)/(7 ± 3) cmH_2O variable Machine: Respironics Synchrony ventilator	Age > 16 years, clinical diagnosis of acute CPE, CXR suggestive of CPE, RR > 20/min, pH < 7.35	Requirement for an emergency intervention, such as primary percutaneous coronary intervention; inability to provide consent; or previous recruitment into the trial.	NA

*expressed as mean ± SD, where applicable.
ACPE: acute cardiogenic pulmonary oedema; APACHE: acute physiology and chronic health evaluation; bpm: beats per minute; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CRF: chronic respiratory failure; CXR: chest radiograph; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: heart rate; LVS3: cardiac gallop; NA: not available; NIPPV: noninvasive positive pressure ventilation; NIPSV: noninvasive pressure support ventilation; RR: respiratory rate; SAPS: simplified acute physiology score; SBP: systolic blood pressure; UGI: upper gastrointestinal; Vt: tidal volume

Table II. Quality of the trials as assessed by the Jadad score.

Study	Randomised nature	Blinding	Description of withdrawals and dropouts
Mehta et al, 1997[29]	2	2	1
Park et al, 2001[30]	1	0	1
Cross et al, 2003[31]	1	0	1
Bellone et al, 2004[32]	2	0	1
Crane et al, 2004[33]	2	0	1
Park et al, 2004[34]	2	0	1
Bellone et al, 2005[35]	2	0	1
Ferrari et al, 2007[36]	2	0	1
Moritz et al, 2007[37]	2	0	1
Gray et al, 2008[16]	2	0	1

method of Martin and Austin,[22] where appropriate.

The impact of heterogeneity on the pooled estimates of the individual outcomes of the meta-analysis was assessed using the I^2 test and the Cochran Q statistic. The I^2 test measures the extent of inconsistency among the results of the studies, which were interpreted as the approximate proportion of total variation in study estimates that was due to heterogeneity rather than sampling error. An I^2 value of more than 50% indicated significant heterogeneity.[23] The Cochran Q test calculated the weighted sum of squared

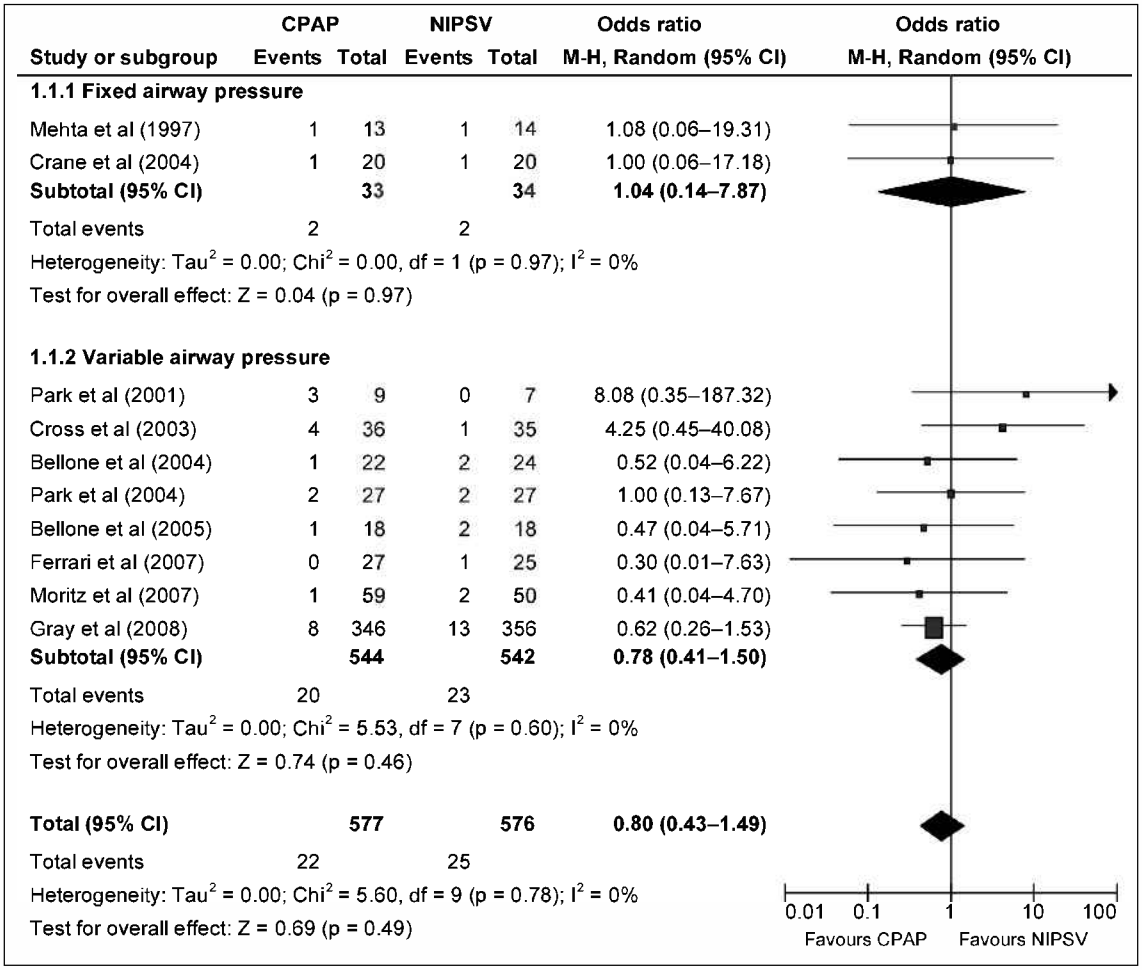

Fig. 2 Forest plots show that noninvasive pressure support ventilation (NIPSV) is similar in efficacy to continuous positive airway pressure (CPAP) in decreasing the intubation rates in patients with cardiogenic pulmonary oedema (odds ratio [OR], 95% confidence intervals [CI]; random effects model).

differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. The p-value level at which heterogeneity should be diagnosed was unclear, given that the Q statistic had a low power, and Fleiss had recommended a value of at least 0.1.[24]

The presence of publication bias were checked using the Begg's funnel plot.[25] The funnel plot is a measure of the log of the OR (in the x-axis, a measure of diagnostic accuracy) against the standard error of the log of the OR (in the y-axis, an indicator of sample size). Each open circle represented each study in the meta-analysis. The line in the centre indicated the summary OR and the other two lines indicated the 95% CI. In the absence of a publication bias, the OR estimated from smaller studies were expected to be scattered above and below the summary estimate, producing a triangular or funnel shape.

We also checked for publication bias using three statistical tests: (a) Egger test, which was a test for asymmetry of the funnel plot. This was a test for the y intercept = 0 from a linear regression of normalised effect estimate (estimate divided by its standard error) against precision (reciprocal of the standard error of the estimate);[26] (b) Harbord's test, which was similar to the Egger test but used a modified linear regression method to reduce the false positive rate, which was a problem with the Egger test when there were large treatment effects, few events per trial or when all trials were of similar sizes;[27] and (c) Begg and Mazumdar's test, which tested the interdependence of variance and effect size using the rank correlation method.[28] The institutional review board's clearance was not required for this manuscript as this was a meta-analysis of published studies.

RESULTS

Our initial electronic and manual searches yielded 7,057 references (Fig. 1). After screening titles and abstracts, we excluded 7,017 clearly irrelevant references and retrieved 40 references, all written in English, for further assessment. 30 trials were excluded because they were either reviews or had a crossover design, were not randomised studies or did not evaluate CPAP vs. NIPSV (Fig. 1). Ten trials finally

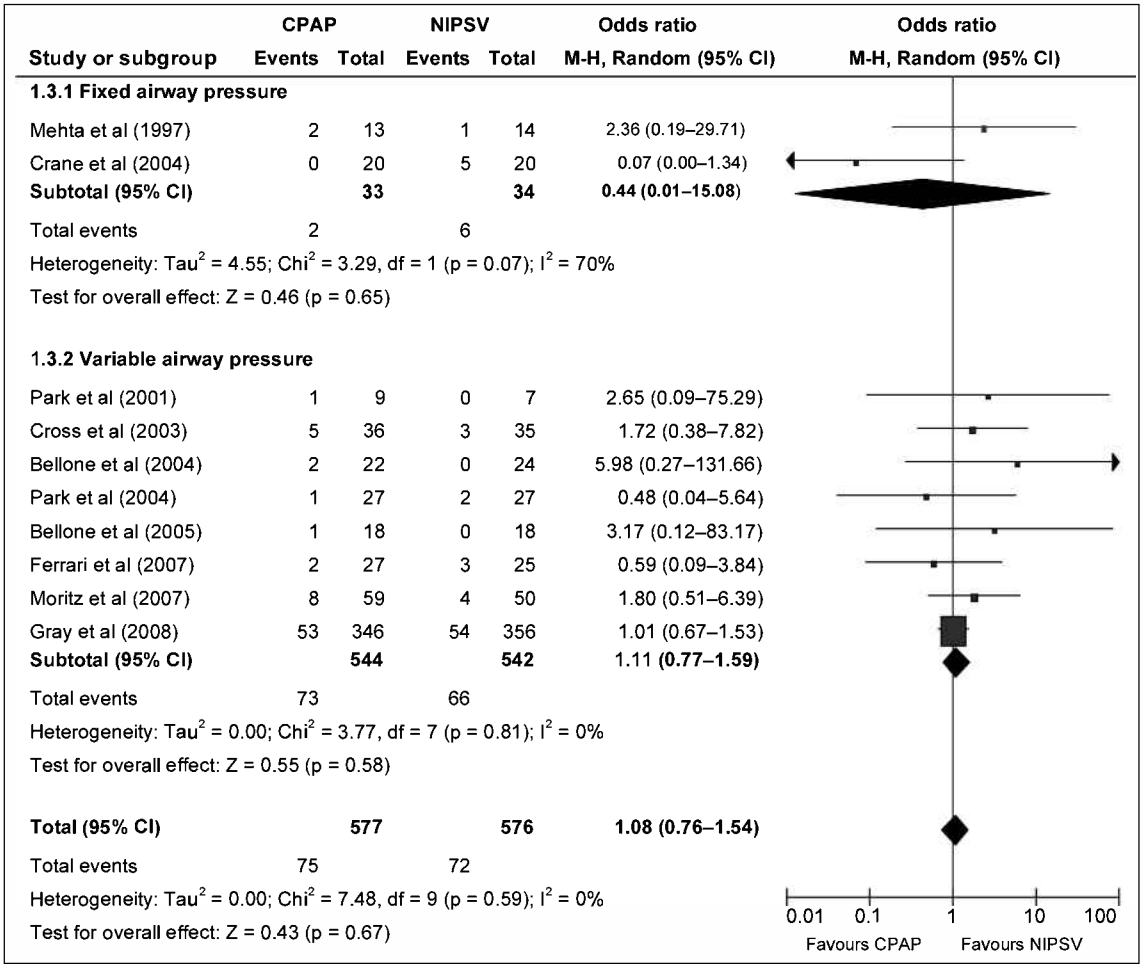

Fig. 3 Forest plots show that noninvasive pressure support ventilation (NIPSV) is similar in efficacy to continuous positive airway pressure (CPAP) in decreasing the hospital mortality in patients with cardiogenic pulmonary oedema (odds ratio [OR], 95% confidence intervals [CI]; random effects model).

met our inclusion criteria (Table I).[16,29-37] These trials were published from 1997 to 2008, and included 1,153 patients (577 in the CPAP group and 576 in the NIPSV group). All ten trials were randomised, and all but two had used concealed randomisation.[30,31] Only one trial, however, was blinded.[29] The median (range) Jadad score was 3 for all the studies,[2-5] indicating that the individual studies were of good quality (Table II).

The mean age of the trial participants ranged from 44 to 89 years, and the acute physiology and chronic health evaluation (APACHE) II scores ranged from 14 to 25 (Table I). Of the nine studies, two had used fixed levels of CPAP (10 cmH_2O) as well as NIPSV (15/5 cmH_2O),[29,33] two had used a fixed level of CPAP (10 cmH_2O) but titrated the NIPSV from 15/5 cmH_2O to achieve a tidal volume of 400 ml,[32,35] and six studies used variable levels of CPAP and NIPSV.[16,30,31,34,36,37] Three trials had used expiratory-hold devices to generate CPAP (Table I).[30,36,37] The mean partial pressure of carbon dioxide in arterial blood ($PaCO_2$) at entry was more than 45 mmHg in seven studies,[16,29,32,33,35-37] two studies recruited patients with a mean $PaCO_2$ of less than 45 mmHg[30,34] and one study did not provide details on $PaCO_2$ levels.[31]

Pooled analysis of the data showed no difference between NIPSV and CPAP in the intubation rates (OR 0.87, 95% CI 0.49–1.54 by the fixed effects; OR 0.80, 95% CI 0.43–1.49 by the random effects [Fig. 2]; OR 0.87, 95% CI 0.48–1.56 by the exact method); hospital mortality (OR 1.05, 95% CI 0.75–1.48 by fixed effects; OR 1.08, 95% CI 0.76–1.54 by random effects [Fig. 3]; OR 1.05, 95% CI 0.74–1.49 by the exact method); and the occurrence of myocardial infarction (OR 0.96, 95% CI 0.71–1.29 by fixed effects; OR 0.80, 95% CI 0.36–1.76 by random effects [Fig. 4]; OR 0.96, 95% CI 0.71–1.29 by the exact method). The results were no different when stratifying for the type of pressure therapy applied (fixed vs. variable) except for the occurrence of myocardial infarction, which was less in the CPAP group compared to the fixed pressure therapy group in the NIPSV arm (7/33 in the CPAP group vs. 19/34 in the NIPSV group; OR 0.2, 95% CI 0.06–0.6).

The I^2 and the Cochran Q test did not indicate the presence of statistical heterogeneity in any outcome;

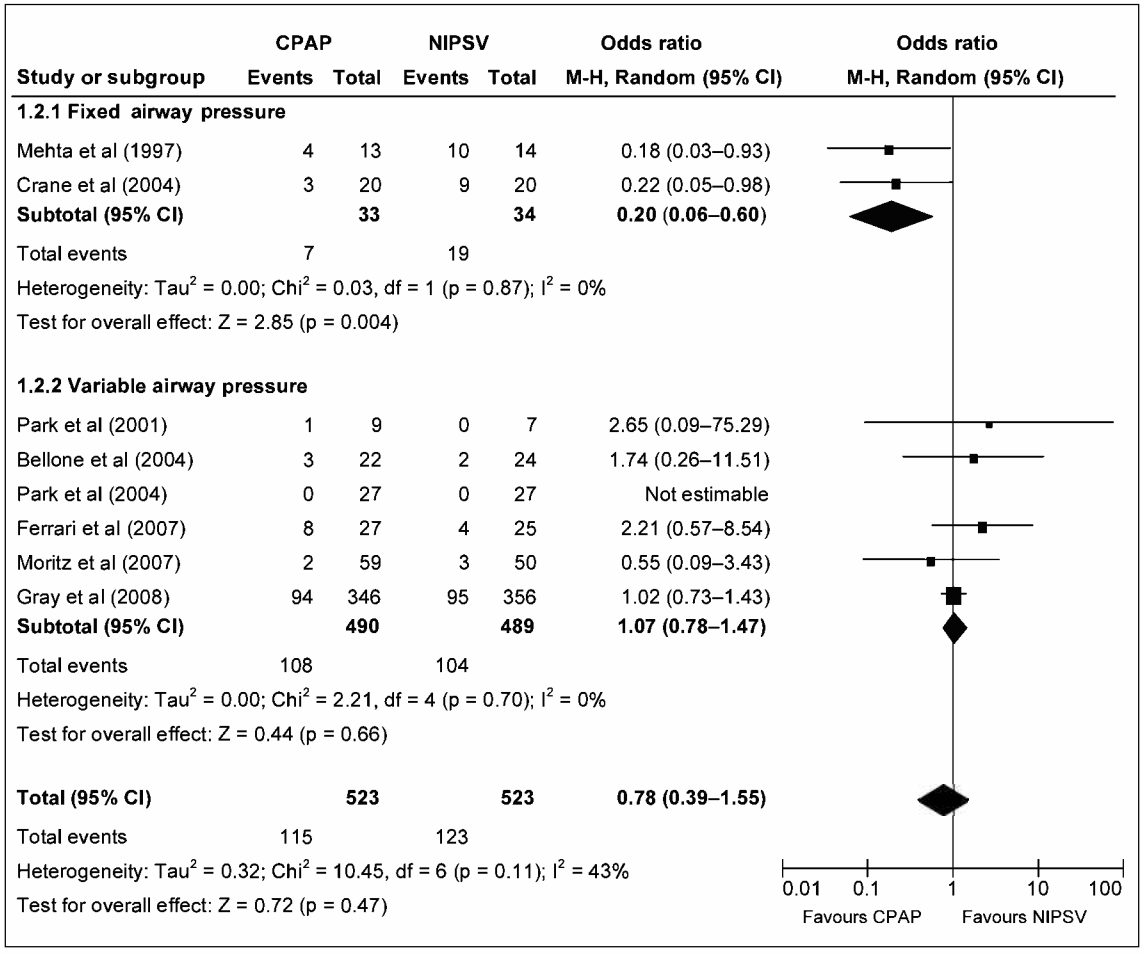

Fig. 4 Forest plots show that the myocardial infarction rates are similar overall in noninvasive pressure support ventilation (NIPSV) versus in continuous positive airway pressure (CPAP), in patients with cardiogenic pulmonary oedema. However, stratifying the results based on the type of positive pressure therapy (fixed vs. variable) shows that myocardial infarction rates are higher in patients with fixed pressure NIPSV (odds ratio [OR], 95% confidence intervals [CI]; random effects model).

however, there was significant methodological heterogeneity (Table I). The funnel plot showed no evidence of publication bias for the outcome of hospital mortality (Fig. 5), and was further confirmed by the statistical tests, which also showed no evidence of publication bias (Begg-Mazumdar: Kendall's tau = –0.022, p = 0.86; Egger: bias = 0.18 [95% CI –0.83 to 1.19], p = 0.69; Harbord-Egger: bias = 0.35, p = 0.56).

DISCUSSION

The results of this meta-analysis suggest that NIPSV is similar in efficacy to CPAP and offers no advantage over CPAP in terms of reducing intubation rates and hospital mortality. The occurrence of myocardial infarction was more in the fixed pressure NIPSV group, though only two studies (67 patients) fulfilled the criteria for inclusion in this group. There was no evidence of heterogeneity and publication bias. Thus, the results of this meta-analysis confidently suggest no advantage of NIPSV over CPAP in patients with ACPE.

NIPSV appears to be theoretically superior to CPAP as it provides inspiratory assistance over and above the end-expiratory pressure, and unloads the respiratory muscles. It has also been shown that the short-term use of NIPSV compared with CPAP causes a greater reduction in respiratory load but with similar improvements in cardiac performance in patients with ACPE.[12] Moreover, NIPSV unloads the respiratory muscles, reduces respiratory effort and increases tidal volume before any alterations in pulmonary mechanics in contrast to CPAP, which requires the pulmonary mechanics to change before any benefits of respiratory muscle unloading are observed.[12] If there are theoretical and experimental benefits, one would ask why these are not translated into clinical benefits? Could it be due to an inappropriate sample size? One reason may be the sample size of the study population, and it is possible that NIPSV may indeed be superior to CPAP, but the currently available studies are underpowered to detect these differences. This analysis involved almost 1,153 patients with ACPE, which is a sufficiently large study population. If we assume the mortality in the CPAP arm to be around 10% and hypothesise that NIPSV could decrease the

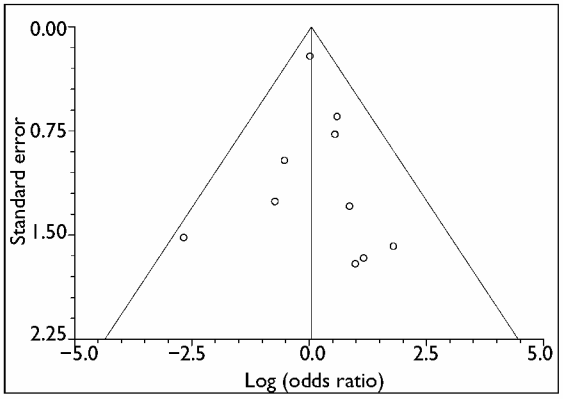

Fig. 5 Funnel plots comparing log odds ratio (OR) versus the standard error of log OR for the outcomes of hospital mortality.
Open circles represent trials included in the meta-analysis. The line in the centre indicates the summary log OR. The other lines represent the 95% confidence intervals. There was no evidence of publication bias.

mortality rate by another 5%, then we require 475 patients (confidence level [1 – α] 95%, power level [1 – β] 80%) each in the NIPSV and CPAP arms, and this analysis fulfils the sample size criteria.

Is it because of the wrong statistical modelling of the data? This again is unlikely as we have used three different statistical models for pooling the data and the results are consistent with any of the three models. Ideally, a meta-analysis should only be considered when a group of trials is sufficiently homogeneous in terms of participants, interventions and outcomes. However, the fixed effects model can be used if there is no significant statistical heterogeneity, and the random effects model used if there is significant statistical heterogeneity.[19] However, by examining the studies listed in Table II, the presence of *clinical heterogeneity*, which refers to variability in the participants, interventions and outcomes; and variability in the trial design and quality known as *methodological heterogeneity*, are observed.[19] Thus, heterogeneity is inevitable, and in fact, homogeneity of studies is unlikely to be encountered in clinical practice. It can even be argued that since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable whether or not the statistical tests can detect heterogeneity. Thus, the test for heterogeneity is probably irrelevant to the choice of analysis; heterogeneity will always exist whether or not we happen to be able to detect it using a statistical test.[38] Apart from the conventional techniques of fixed effects and random effects meta-analysis, we also used the exact method in this study.[22] This method employs the partial polynomial multiplication algorithm. Thus, a sparseness of individual studies and rare occurrence of outcome events, which was seen in this analysis, is not an issue. Hence, NIPSV seems to be equal in efficacy to CPAP.

One worrisome issue is the higher occurrence of myocardial infarction reported with NIPSV.[29] The results of our analysis showed that the occurrence of myocardial infarction is higher in the NIPSV group only with the fixed pressure group. In the variable pressure group, there is a trend towards a higher occurrence of myocardial infarction rates in the CPAP arm, although this is not statistically significant. It is probably the use of high airway pressures both with CPAP or NIPSV rather than the mode that has increased these complications. It is known that the use of high airway pressures with CPAP or NIPSV can decrease cardiac output,[12,39] which can potentially worsen the cardiac ischaemia. Of late, when NIPSV has been compared to conventional medical therapy in four randomised controlled trials, no significant difference was found in the occurrence of new-onset myocardial infarction.[30,40-42] Thus, it is likely that it is the higher pressure rather than the mode of NIV that is responsible for the higher occurrence of myocardial infarctions. In clinical practice and in further studies, NIV should be delivered using a variable pressure therapy protocol, where positive pressure therapy is started with lower pressures and titrated to specific end-points, either clinical (respiratory rate and heart rate), spirometric (tidal volume) or blood gases (pH, PaO_2, $PaCO_2$) rather than through the use of a pre-fixed pressure.

We have previously shown that CPAP is superior to standard medical therapy in preventing intubation and mortality rates.[5] However, the recently-published 3CPO trial showed no advantage of CPAP or NIPSV in preventing intubation or mortality.[16] Although the application of NIV provides earlier improvement and resolution of dyspnoea and respiratory distress, these effects do not result in improved rates of survival. Thus, the current place of NIV (CPAP or NIPSV) is as an adjunctive therapy in patients with ACPE and who have severe respiratory distress or whose condition does not improve with pharmacological therapy.

There are several limitations of this meta-analysis; the first is the studies were not blinded and this could lead to bias on the part of the physicians managing these patients. Another limitation is the rarity of outcome events, although an attempt was made to compensate for this factor by using the exact method of meta-analysis. Finally, there was the presence of clinical and methodological heterogeneity between the trials which, in most meta-analyses, is inevitable. In conclusion, based on the currently-available data, NIPSV does not appear to confer any significant advantage over CPAP in the management of patients with ACPE. There is a higher occurrence of myocardial infarction with the fixed pressure NIPSV. In clinical practice, NIV

should be used in a protocol where positive pressure therapy is titrated to specific clinical, blood gases and spirometric end-points rather than using fixed pressures.

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