Official Journal of the Society for Academic Emergency Medicine

PROGRESSIVE CLINICAL PRACTICE

Prehospital Noninvasive Ventilation for Acute Respiratory Failure: Systematic Review, Network Meta-analysis, and Individual Patient Data Meta-analysis

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Abstract

Objectives: This meta-analysis aimed to determine the effectiveness of prehospital continuous positive airway pressure (CPAP) or bilevel inspiratory positive airway pressure (BiPAP) in acute respiratory failure.

Methods: Fourteen electronic databases and research registers were searched from inception to August 2013. Randomized or quasi-randomized controlled trials that reported mortality or intubation rate for prehospital CPAP or BiPAP were selected and compared to a relevant comparator in patients with acute respiratory failure. An aggregate data network meta-analysis was used to jointly estimate intervention effects relative to standard care. A network meta-analysis using a mixture of individual patient-level data and aggregate data was carried out to assess potential treatment effect modifiers.

Results: Eight randomized and two quasi-randomized controlled trials (six CPAP, four BiPAP, sample sizes 23 to 207) were identified. The aggregate data network meta-analysis suggested that CPAP was the most effective treatment in terms of mortality (probability = 0.989) and intubation rate (probability = 0.639) and reduced both mortality (odds ratio [OR] = 0.41; 95% credible interval [CrI] = 0.20 to 0.77) and intubation rate (OR = 0.32; 95% CrI = 0.17 to 0.62), compared to standard care. The effect of BiPAP on mortality (OR = 1.94; 95% CrI = 0.65 to 6.14) and intubation rate (OR = 0.40; 95% CrI = 0.14 to 1.16) was uncertain. The network meta-analysis using individual patient-level data and aggregate data suggested that sex was a modifier of the effect of treatment on mortality.

Conclusions: Prehospital CPAP can reduce mortality and intubation rates compared to standard care, while the effectiveness of prehospital BiPAP is uncertain.

ACADEMIC EMERGENCY MEDICINE 2014;21:960–970 © 2014 Crown copyright. Academic Emergency Medicine Published by Wiley Periodicals, Inc.

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Received February 23, 2014; revision received May 8, 2014; accepted May 13, 2014.

This study was funded by the United Kingdom National Institute for Health Research Health Technology Assessment Programme (project number 11/36/09). The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors. The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. The authors have no relevant conflicts of interest to declare.

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ISSN 1069-6563
PII ISSN 1069-6563583

doi: 10.1111/acem.12466

Acute respiratory failure is a common but life-threatening medical emergency, especially in elderly patients with respiratory and cardiac diseases.[1–3] It is caused by a number of common cardiac or respiratory conditions, including heart failure, pneumonia, and exacerbation of chronic obstructive pulmonary disease. The definitive treatment of acute respiratory failure depends on the underlying cause, but patients often require prehospital treatment. At this point it is difficult to accurately determine the underlying cause, so prehospital treatment of acute respiratory failure often follows a common pathway, rather than being specific to the underlying cause.

Noninvasive ventilation (NIV) can be used to treat acute respiratory failure.[4–6] It involves providing respiratory support through a tight-fitting mask that is usually applied around the patient's mouth and nose and may take the form of continuous positive airway pressure (CPAP) or bilevel inspiratory positive airway pressure (BiPAP), including noninvasive pressure support ventilation. It is normally used in the hospital, but it may be more effective if treatment is commenced prior to arrival.[7] Prehospital NIV is considered in some guidelines,[8,9] but widespread use is limited by the need for additional training and equipment and may be informed by robust evidence of clinical effectiveness and cost-effectiveness.

Prehospital NIV has been evaluated in a number of studies, which have been summarized in systematic reviews[10–12] and meta-analysis.[13,14] These suggest that prehospital NIV, and specifically prehospital CPAP, can improve outcomes. Existing systematic reviews have been limited by failure to undertake meta-analyses,[10–12] inclusion of nonrandomized studies in the meta-analyses,[13] failure to include studies only published in abstract form,[14] analysis of CPAP and BiPAP together,[14] lack of a network meta-analysis to compare CPAP and BiPAP,[13,14] and lack of individual patient data meta-regression to explore potential causes of heterogeneity.[13,14] We aimed to address these limitations by undertaking a systematic review, aggregate data network meta–analysis, and individual patient data meta-analysis of randomized and quasi-randomized controlled trials to determine the effect of prehospital CPAP and BiPAP on mortality (primary outcome) and endotracheal intubation (secondary outcome), in patients with acute respiratory failure.

METHODS

We undertook a systematic review in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15] and the checklist for the review of evidence synthesis for decision-making.[16] The review was registered on the PROSPERO international prospective register of systematic reviews (CRD42012002933), and the protocol is available at http://www.nets.nihr.ac.uk/projects/hta/113609.

Eligibility Criteria

We included randomized or quasi-randomized controlled trials that compared prehospital CPAP or BiPAP to a relevant comparator treatment in patients with acute respiratory failure.

Information Sources

The following electronic databases and research registers were searched from inception to August 2013: MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Database of Abstracts of Review of Effects, BIOSIS Previews, Science Citation Index Expanded, Conference Proceedings Index-Science, UK Clinical Research Network Portfolio Database, National Research Register Archive, Current Controlled Trials, and ClinicalTrials.gov. Searches were supplemented by hand-searching the reference lists and performing a citation search of relevant articles, contacting key experts in the field, and undertaking systematic keyword searches of the internet using the Google search engine. No language or date restrictions were used on any database. Details of the search strategies are provided in Data Supplement S1 (available as supporting information in the online version of this paper).

Study Selection

All titles were examined for inclusion by one reviewer (EP) and any citations that clearly did not meet the inclusion criteria (e.g., nonhuman, unrelated to acute respiratory failure) were excluded. All abstracts and full text articles were then examined independently by two reviewers (EP, AP). Any disagreements in the selection process were resolved through discussion.

Data Collection Process

Data abstraction was performed by one reviewer (EP) onto a standardized data extraction form and independently checked for accuracy by a second (AP). Discrepancies were resolved by discussion between the two reviewers, and if agreement could not be reached, a third reviewer (SG) was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Data Items

The following information was extracted for all studies when reported: study characteristics (author, year of publication, country, study design, setting, duration of follow-up, funding), participant details (age, sex, diagnosis, comorbidities, baseline physiology), intervention (system used, pressure(s) used, duration of treatment, practitioners providing intervention), comparator (any use of NIV, supplemental oxygen), details including information on any specified cotreatments, and outcomes (including definitions). The authors of all included studies were contacted to clarify details, obtain missing data, and request individual patient data for meta-analysis.

Assessment of Risk of Bias in Individual Studies

The methodologic quality of each included study was assessed by one reviewer (EP) and independently

checked by another (AP) to ensure consistency. In cases of disagreement a third reviewer (SG) was consulted. The study quality characteristics were assessed according to adapted criteria based on those proposed by Verhagen et al.[17] for randomized clinical trials.

Summary Measures

Results of the network meta-analysis are presented as odds ratios (OR) and 95% credible intervals (CrIs) relative to the baseline intervention (i.e., standard care). The 95% CrIs represent the 95% probability that the true underlying effect lies in the interval specified. The between-study standard deviations (SDs) together with their 95% CrIs are also presented.

Planned Methods of Analysis

A random-effects network meta-analysis of aggregate data of the number of events (i.e., mortality and intubation) was conducted using Markov chain Monte Carlo simulation to jointly estimate the intervention effects relative to standard care.[18] Separate one-stage random effects network meta-regressions using a mixture of individual patient data and aggregate data (where individual patient data were not available) were carried out to assess whether study characteristics (i.e., age, sex, provider, primary diagnosis, and severity of acute respiratory failure) were treatment effect modifiers. Any missing covariates in the individual patient data were assumed missing completely at random and were imputed using multiple imputation.

Sensitivity analyses were planned to explore the potential sources of heterogeneity, in particular whether CPAP or BiPAP was used and whether prehospital providers were paramedics or physicians. In the event, these issues were explored in the network meta-analysis and meta-regression. A post hoc sensitivity analysis was undertaken excluding quasi-randomized trials from the network meta-analysis of aggregate data.

We performed separate analyses of the aggregate data using different prior distribution for the between-study SDs (i.e., a vague Uniform(0,2)) prior distribution and two weakly informative prior distributions (i.e., Half-Normal(0,0.32^2) and Half-Normal(0,0.40^2)). A Uniform(0,2) prior distribution for a between-study SD implies that we believe a priori that extreme heterogeneity is plausible and as likely as mild heterogeneity. The conclusions and point estimates were consistent across the three analyses and, as we would expect, the CrIs for the ORs were slightly narrower when weakly informative prior distributions were used. A vague prior distribution for a between-study SD is not noninformative when there are relatively few studies, as we have in this case, so results of the aggregate and individual patient data meta-analyses are based on using Half-Normal(0,0.40^2) prior distributions for the between-study SDs.

Convergence of the Markov chains to their stationary distributions was assessed using the Gelman-Rubin statistic.[19] The Markov chains in each aggregate data network meta-analysis converged quickly and we used a burn-in of 10,000 iterations. The Markov chains in the mixed individual patient data and aggregate data network meta-analyses took longer to converge and we used a burn-in of 50,000 iterations. Parameters were estimated based on 10,000 iterations of the Markov chains after thinning them by retaining every fifth iteration. Goodness of fit of the aggregate data models was assessed using total residual deviance. The total residual deviance is the mean of the deviance under the current model minus the deviance for the saturated model, so that each data point should contribute about one to the deviance. The effect of the covariates in the mixed individual patient data and aggregate data meta-regression was assessed using the deviance information criteria.

The aggregate data network meta-analysis was implemented using WinBUGS 1.4.3[20] and the individual patient data network meta-analysis was implemented using OpenBUGS (http://www.openbugs.net/). Code is available on request.

RESULTS

Study Selection

The literature searches identified 2,284 citations. Eight randomized[21–28] and two quasi-randomized controlled trials[29,30] satisfied the inclusion criteria (participant numbers ranging from 23 to 207). The authors of seven of these 10 studies[22–26,28,30] provided data from 650 patients for individual patient data meta-analysis. The process is described in a PRISMA flow diagram (Figure 1).

Characteristics of Included Studies

Table 1 shows the study characteristics. The studies were undertaken in Australia,[21] France,[22,23,25] Germany,[26,27,30] Spain,[24] Canada,[28] and the United States[29] and were published between 2000 and 2012. Six studies[21–23,25,29,30] were limited to patients with acute cardiogenic pulmonary edema and one[27] to patients with exacerbation of chronic obstructive pulmonary disease. Six studies[21–23,25,27,28] evaluated CPAP, and four[24,26,29,30] evaluated BiPAP. One study[25] compared early CPAP to delayed CPAP, while use of in-hospital NIV in the control arm was allowed in three[23,26,28] of the other studies, prohibited in one,[22] and not recorded in five.[21,24,27,29,30] The results of the individual trials are presented in Figures 2 and 3 for mortality and intubation rates, respectively.

Risk of Bias Within Studies

Data Supplements S2 and S3 (available as supporting information in the online version of this paper) present the methodologic quality of the included studies. Six studies[22–26,28] achieved positive assessments in at least six of the nine methodologic quality items. The potential sources of bias most frequently identified in studies concerned lack of blinding of outcome assessment and lack of adequate power to detect differences in the primary outcome. Two studies[29,30] were quasi-randomized studies: randomization in Weitz et al.[30] was based on date of birth; Craven et al.[29] did not provide details on the method of randomization, although 10 emergency service units were divided into five matched pairs with one unit from each pair equipped with a BiPAP ventilation system and one without.

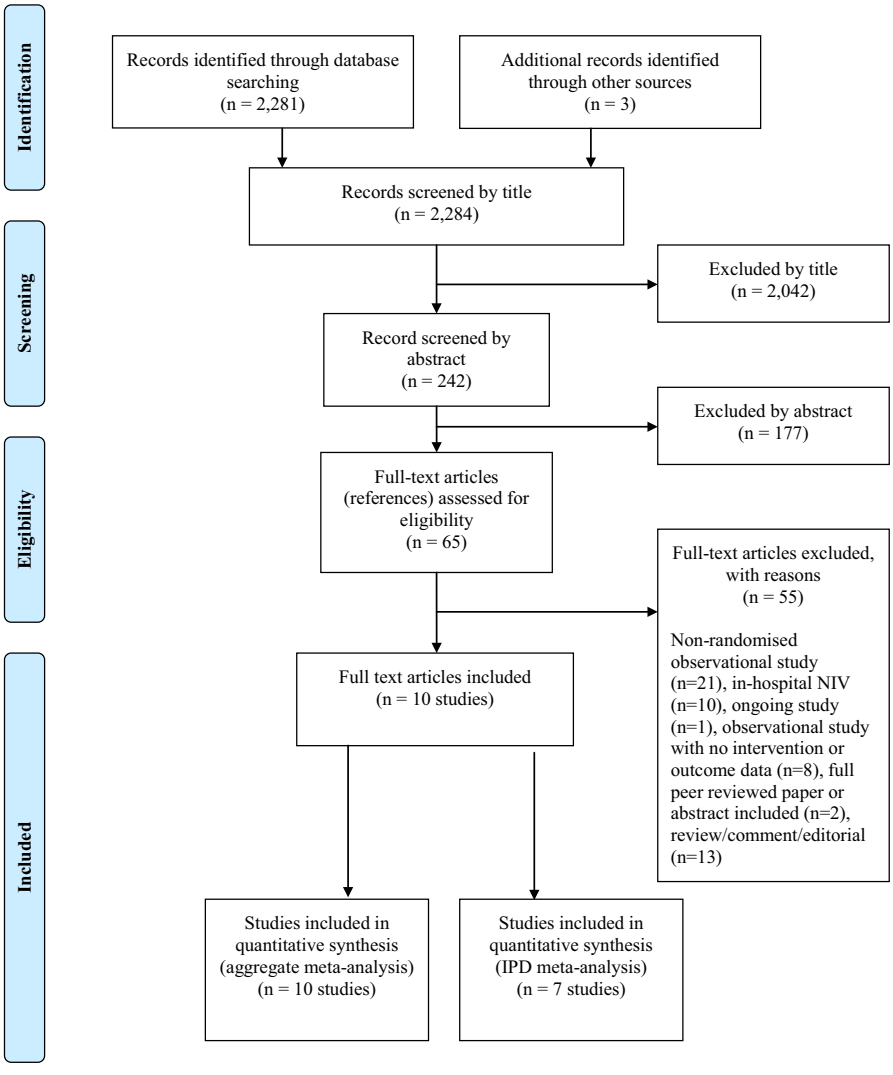

Figure 1. Study flow chart. IPD = individual patient data; NIV = noninvasive ventilation.

Data Analysis Issues

There were no deaths in the study by Schmidbauer et al.[27] Although the study is included in the analysis for completeness, the sample data provide no information about the effect of treatment on mortality. The study-specific ORs that are presented in Figures 2 and 3 are sample estimates and the pooled estimates are from the random-effects models. There are no feedback loops in the evidence network so there is not a mixture of direct and indirect evidence about treatment effects. Consequently, there are no potential inconsistencies in the evidence about treatment effects.

Effects of Interventions

Aggregate Data Network Meta-analysis. Continuous positive airway pressure is the most effective treatment on mortality (probability = 0.989), with OR of 0.41 (95% CrI = 0.20 to 0.77) compared to standard care. There was considerable uncertainty associated with the effect of BiPAP relative to standard care (OR = 1.94; 95% CrI = 0.65 to 6.14). The between-study SD of ±0.29 (95% CrI = 0.02 to 0.85) is indicative of mild heterogeneity between studies but with considerable uncertainty. Sensitivity analysis excluding two quasi-randomized trials and one study comparing early prehospital CPAP to late prehospital CPAP produced similar results, with CPAP more effective than standard care (OR = 0.45; 95% CrI = 0.21 to 0.93), while the effect of BiPAP relative to standard care remained uncertain (OR = 1.95; 95% CrI = 0.43 to 9.46).

CPAP was estimated to be the most effective treatment on intubation rate (probability = 0.639), with an OR of 0.32 (95% CrI = 0.17 to 0.62) compared to standard care. There was uncertainty associated with the effect of BiPAP relative to standard care (OR = 0.40; 95% CrI = 0.14 to 1.16). The between-study SD of ±0.21 (95% CrI = 0.01 to 0.73) is indicative of mild heterogeneity between studies but with considerable uncertainty. Sensitivity analysis excluding one quasi-randomized trial[29] (the other[30] did not report intubation rate) and one study comparing early prehospital CPAP to late prehospital CPAP[25] produced similar results, with CPAP more effective than standard care (OR = 0.34; 95% CrI = 0.15 to 0.77), while the effect of BiPAP relative to standard care remained uncertain (OR = 0.53; 95% CrI = 0.11 to 2.28).

Table 1
Summary of Study Design Characteristics

Author, Year, Country	Design (*n*)	Population	Intervention	Comparator	Primary Outcomes	Duration of Follow-up
Austin and Wills 2012[21]; Australia (abstract)	RCT (*n* = 50)	Adults with presumed ACPO experiencing severe respiratory distress with insufficient respiratory effort	CPAP (no details provided) (*n* = 24) Provider: NR	CMT including oxygen (*n* = 26) In-hospital NIV use: NR	Mortality (prehospital or in-hospital)	NR
Ducros et al. 2011[22]; France	RCT (*n* = 207)	Adults with presumed ACPO (orthopnea, diffuse crackles [Killip score > III], RR > 25 breaths/min, SpO_2 < 90%)	CPAP; 7.5 to 10 cm H_2O, FiO_2 0.3 to 1.0 by face mask (*n* = 107) Provider: physician	CMT including oxygen at 15 L/min (*n* = 100) In-hospital NIV use: prohibited	Composite endpoint of death, need for intubation, persistence of all symptoms or circulatory failure	Until time of hospital discharge or death
Frontin et al. 2011[23]; France	RCT (*n* = 122)*	Adults with presumed ACPO (orthopnea, diffuse crackles without signs of pulmonary aspiration or infection, RR > 25 breaths/min, SpO_2 < 90%)	CPAP; 10 cm H_2O by face mask for 1 hour (*n* = 60) Provider: physician	CMT including oxygen at 15 L/min (*n* = 62) In-hospital NIV use: allowed	Treatment success†	30 days
Plaisance et al. 2007[25]; France	RCT (*n* = 124)	Adults with presumed ACPO (orthopnea, diffuse crackles without signs of pulmonary aspiration or infection, $SpO_2 \leq 90\%$)	Early CPAP: the first 30 minutes at 7.5 cm H_2O, FiO_2 0.33 to 0.37 by face mask (*n* = 63) Provider: physician	Late CPAP included CMT with oxygen for the initial 15 minutes, followed by CPAP [7.5 cm H_2O] for another 15 minutes (*n* = 61) In-hospital NIV use: mandated	Effect of early CPAP on dyspnea score‡ and arterial blood gases	Until time of hospital discharge death
Schmidbauer et al. 2010[27]; Germany	RCT (*n* = 36)	Adults presenting with acute exacerbated COPD (acute dyspnea, RR > 25 breaths/ min, SpO_2 < 90%)	CPAP; 5 to 30 cm H_2O, FiO_2 0.5 to 1.0 by face mask (*n* = 18) Provider: physician	SOT delivered by face mask (flow rate NR) (*n* = 18) In-hospital NIV use: NR	Intubation rate	Until time of hospital discharge or death
Thompson et al. 2008[28]; Canada	RCT (*n* = 71)	Adults presenting with severe respiratory distress (failing respiratory effort, accessory muscle use, RR > 25 breaths/ min, hypoxia)	CPAP; 10 cm H_2O by face mask (*n* = 36) Provider: paramedic	CMT with oxygen by face mask (*n* = 35) In-hospital NIV use: allowed (*n* = 4)	Intubation rate	Until time of hospital discharge death
Mas et al. 2002[24]; Spain (abstract)	RCT (*n* = 56)	Adults presenting with ARF (RR > 28 breaths/min, SpO_2 < 92% or SpO_2 < 90% at any RR)	BiPAP; EPAP, 7 cm H_2O, IPAP, 19 cm H_2O (*n* = 28) Provider: paramedic and physician	Standard therapy, not specified (*n* = 28) In-hospital NIV use: NR	Intubation rate	Until time of hospital discharge or death
Roessler et al. 2011[26]; Germany	RCT (*n* = 49)§	Adults presenting with ARF due to presumed ACPO, COPD, or pneumonia with signs of hypoxemia (SpO_2 < 90%) or ventilator failure (SpO_2 < 90% with RR > 20 breaths/min, at rest)	BiPAP;‖ 5 to 20 cm H_2O, PEEP 5 to 15 cm H_2O, FiO_2 1.0 by face mask (*n* = 24) Provider: physician	CMT including supplementary oxygen (*n* = 25) In-hospital NIV use: allowed (*n* = 4)	Treatment success¶	30 days

Table 1
Continued.

Author, Year, Country	Design (*n*)	Population	Intervention	Comparator	Primary Outcomes	Duration of Follow-up
Craven et al. 2000[29]; United States	Quasi-RCT (*n* = 62)**	Adults experiencing CHF with presumed ACPO (dyspnea with increased RR, HR, sweating, peripheral edema)	BiPAP; by face mask (pressure level NR) (*n* = 37) Provider: paramedic††	CMT with oxygen (no further details provided) (*n* = 25) In-hospital NIV use: NR	NR	NR
Weitz et al. 2007[30]; Germany	Quasi-RCT (*n* = 23)	Adults with presumed ACPO (severe dyspnea; SpO_2 < 90%)	BiPAP; 12 cm H_2O, PEEP 5 cm H_2O, FiO_2 0.6 by face mask (*n* = 10) Provider: physician‡‡	CMT with oxygen at 8 L/min by face mask (*n* = 13) In-hospital NIV use: NR	Oxygen saturation	Until time of hospital discharge or death

ACPO = acute cardiopulmonary edema; ARF = acute respiratory failure; BiPAP = bilevel inspiratory positive airway pressure; BNP = B-type natriuretic peptide; CMT = conventional medical treatment; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; FiO_2 = fractional inspired oxygen; HR = heart rate; IPAP = inspiratory positive airway pressure; NIMV = noninvasive mechanical ventilation; NIPSV = noninvasive pressure support ventilation; NIV = noninvasive ventilation; NR = not reported; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; RR = respiratory rate, SOT = standard oxygen therapy; SpO_2 = oxygen saturation.
*Of the 124 patients randomized in the study, two patients in the CPAP group refused full consent and were excluded from analysis.
†Treatment success was defined as a respiratory rate < 25 breaths/min with SpO_2 > 90% after an hour of study inclusion.
‡Dyspnea clinical score consisted of four items yielding a total score of 10. Dyspnea: auscultation rates intensity and accessory muscle use were rated 0 (absent) to 3 (severe/important). The remaining criterion was based on the presence of cyanosis, rated as 0 (no) or 1 (yes).
§Of the 51 patients included in the study, two patients were excluded from the analysis because they were previously dependent on home oxygen.
‖NIV was initially started with FiO_2 and CPAP; however, this was quickly changed to BiPAP, if CPAP was tolerated (22 of 24 patients in the intervention group).
¶Treatment was considered to be inefficient if the following occurred while on NIV or CMT: If SpO_2 < 85% or dropped to ≤85% and/or if the respiratory rate was ≤30 or had increased to 30 breaths/min or more.
**Of the 71 patients enrolled in the study, 62 patients completed the study.
††Medical responders were emergency medical technicians (certified at cardiac technician or paramedic level) trained in advanced life support.
‡‡The emergency team was made up of one physician and two paramedics.

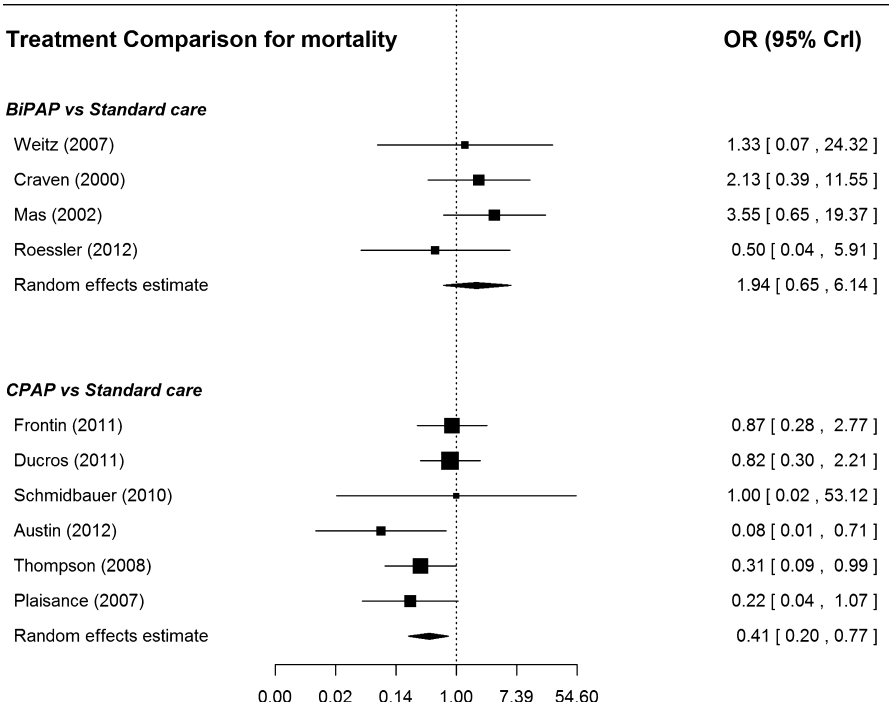

Figure 2. Comparison of mortality for interventions versus standard care from the primary trials. BiPAP = bilevel inspiratory positive airway pressure; CPAP = continuous positive airway pressure; CrI = credible interval.

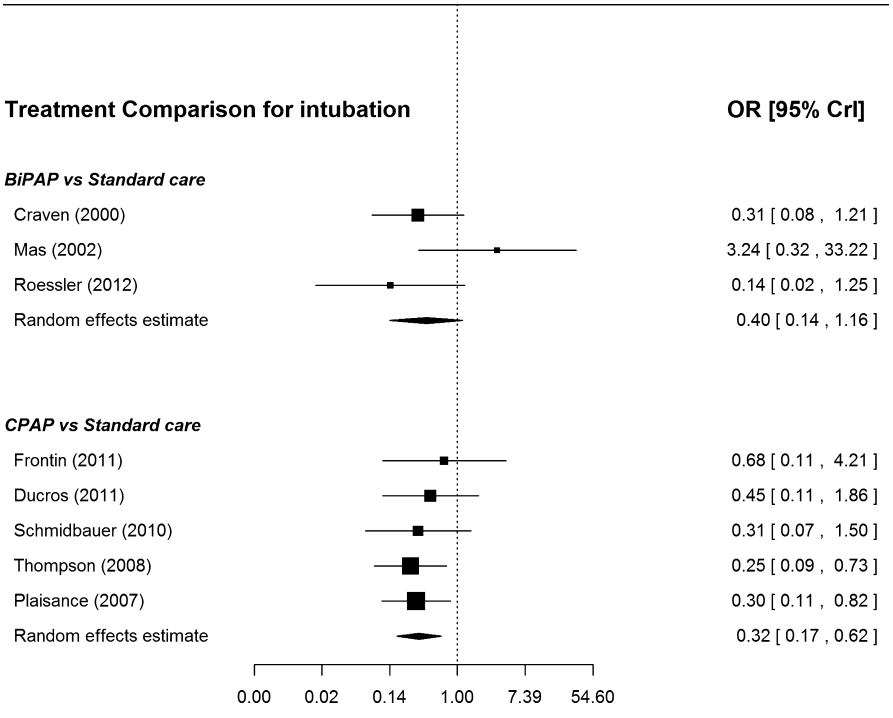

Figure 3. Comparison of intubation for interventions versus standard care from the primary trials. BiPAP = bilevel inspiratory positive airway pressure; CPAP = continuous positive airway pressure; CrI = credible interval.

Mixed Individual Patient Data and Aggregate Data Network Meta-analysis. Potential treatment effect modifiers were identified from separate analyses of each study adjusting treatment effect for age, sex, primary diagnosis, provider, and various measures of severity of acute respiratory failure. Age, sex, primary diagnosis, and respiratory rate were identified as potential modifiers of the effect of treatment on mortality and sex, respiratory rate, SpO_2, PaO_2, and $PaCO_2$ as potential modifiers of the effect of treatment on intubation rate to be included in the network meta-regression. Data on prehospital time delay were not well defined or

Table 2
Mortality in Prehospital NIV Patients With Acute Respiratory Failure With Continuous Treatment Effect Modifiers:* Posterior Results for the Odds of Death Relative to Standard Care (Random Effects)

	Potential Treatment Effect Modifier	
Variable	Age	Respiratory Rate
Data source		
Individual patient data	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler,[26] Thompson,[28] Mas,[24] Weitz[30]	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler,[26] Thompson,[27] Mas,[24] Weitz[30]
Aggregate	Austin and Wills,[21] Craven[29]	—
Coefficient of treatment effect modifier, OR (95% CrI)		
BiPAP	1.04 (0.92-1.18)	0.88 (0.70-1.04)
CPAP	1.02 (0.97-1.08)	0.95 (0.88-1.03)
Treatment effect at the mean value of the treatment effect modifier, OR (95% CrI)		
BiPAP	2.44 (0.76-8.71)	2.66 (0.59-15.19)
CPAP	0.40 (0.19-0.77)	0.62 (0.28-1.29)
Between-study SD (95% CrI)	0.31 (0.02-0.87)	0.30 (0.01-0.89)
Deviance information criterion (model with treatment effect modifier vs. model without treatment effect modifier)	481.80 vs. 470.54	455.99 vs. 451.62

BiPAP = bi-level inspiratory positive airway pressure; CPAP = continuous positive airway pressure; CrI = credible interval; NIV = noninvasive ventilation.
*Each potential treatment effect modifier was analyzed separately in the model.

Table 3
Mortality in Prehospital NIV Patients With Acute Respiratory Failure With Binary Treatment Effect Modifiers:* Posterior Results for the Odds of Death Relative to Standard Care (Random Effects)

	Potential Treatment Effect Modifier			
Variable	Sex	ACPO†	COPD†	Provider
Data source				
Individual patient data	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler,[26] Weitz[30]	Roessler,[26] Mas[24]	Roessler,[26] Thompson,[28] Mas[24]	—
Aggregate	Thompson,[28] Austin,[21] Craven[29]	Ducros,[22] Frontin,[23] Plaisance,[25] Thompson,[28] Austin,[21] Craven[29]	Ducros,[22] Frontin,[23] Plaisance,[25] Austin,[21] Craven[29]	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler,[26] Thompson,[28] Mas,[24] Weitz,[30] Austin,[21] Craven[29]
Coefficient of treatment effect modifier, OR (95% CrI)				
BiPAP	0.19 (0.01-2.44)	1.45 (0.25-9.44)	0.19 (0.01-1.70)	0.57 (0.06-3.59)
CPAP	0.18 (0.04-0.74)	1.30 (0.25-7.13)	0.27 (0.03-1.92)	1.43 (0.32-6.36)
Treatment effect at the mean value of the treatment effect modifier, OR (95% CrI)				
BiPAP	Males: 0.55 (0.08-3.40) Females: 2.92 (0.44-21.82)	Patients with ACPO: 2.07 (0.59-8.11) Patients without ACPO: 1.41 (0.28-7.65)	Patients with COPD: 0.50 (0.04-4.34) Patients without COPD: 2.58 (0.82-9.51)	Physicians: 1.29 (0.19-7.45) Paramedics: 2.31 (0.72-8.83)
CPAP	Males: 0.16 (0.05-0.44) Females: 0.88 (0.34-2.20)	Patients with ACPO: 0.42 (0.20-0.81) Patients without ACPO: 0.32 (0.06-1.60)	Patients with COPD: 0.12 (0.01-0.83) Patients without COPD: 0.45 (0.22-0.87)	Physicians: 0.55 (0.24-1.19) Paramedics: 0.38 (0.10-1.41)
Between-study SD (95% CrI)	0.32 (0.01-0.89)	0.31 (0.02-0.87)	0.30 (0.01-0.86)	0.25 (0.01-0.80)
Deviance information criterion (model with treatment effect modifier vs. model without treatment effect modifier)	353.39 vs. 358.43	210.65 vs. 208.36	207.89 vs. 208.46	77.95 vs. 76.32

ACPO = acute cardiopulmonary edema; BiPAP = bi-level inspiratory positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CrI = credible interval.
*Each potential treatment effect modifier was analyzed separately in the model.
†Primary diagnosis.

Table 4
Intubation Rates in Prehospital NIV Patients With Acute Respiratory Failure With Continuous Treatment Effect Modifiers:* Posterior Results for the Odds of Intubation Relative to Standard Care (Random Effects)

	Potential Treatment Effect Modifier			
Variable	RR	SpO_2	PaO_2	$PaCO_2$
Data source				
Individual patient data	Ducros,[21] Frontin,[23] Plaisance,[25] Roessler,[26] Mas[24]	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler,[26] Mas[24]	Ducros,[22] Frontin,[23] Plaisance[25]	Ducros,[22] Frontin,[23] Plaisance[25]
Aggregate	Thompson[29]	Thompson[29]	—	—
Coefficient of treatment effect modifier, OR (95% CrI)				
BiPAP	0.94 (0.77-1.12)	1.02 (0.92-1.14)	—	—
CPAP	0.99 (0.90-1.10)	1.02 (0.95-1.11)	1.0 (0.99-1.02)	1.03 (0.96-1.10)
Treatment effect at the average value of the treatment effect modifier, OR (95% CrI)				
BiPAP	0.50 (0.10,2.33)	0.57 (0.08-3.28)		
CPAP	0.35 (0.15-0.83)	0.34 (0.15-0.74)	0.38 (0.14-0.97)	0.32 (0.11-0.82)
Between study SD (95% CrI)	0.29 (0.01-0.91)	0.26 (0.01-0.87)	0.24 (0.01-0.81)	0.24 (0.01-0.81)
Deviance information criterion (model with treatment effect modifier vs. model without treatment effect modifier)	320.76 vs. 318.67	325.83 vs. 318.67	241.17 vs. 234.69	228.30 vs. 234.69

— = analysis not possible; BiPAP = bilevel inspiratory positive airway pressure; CPAP = continuous positive airway pressure; CrI = credible interval; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; RR = respiratory rate; SpO_2 = oxygen saturation.
*Each potential treatment effect modifier was analyzed separately in the model.

Table 5
Intubation Rates in Prehospital NIV Patients With Acute Respiratory Failure With Binary Treatment Effect Modifiers:* Posterior Results for the Odds of Intubation Relative to Standard Care (Standard Oxygen Therapy) (Random Effects)

	Potential Treatment Effect Modifier	
Variable	Sex	Provider
Data source		
Individual patient data	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler[26]	—
Aggregate	Thompson,[28] Craven[29]	Ducros,[22] Frontin,[23] Plaisance,[25] Roessler,[26] Thompson,[28] Mas,[24] Weitz,[30] Austin,[21] Craven[29]
Coefficient of treatment effect modifier, OR (95% CrI)		
BiPAP	3.42 (0.26-43.80)	0.46 (0.04-2.81)
CPAP	3.61 (0.78-19.11)	1.12 (0.26-4.59)
Treatment effect at the mean value of the treatment effect modifier, OR (95% CrI)		
BiPAP	Males: 0.37 (0.06-1.98) Females: 0.11 (0.02-0.63)	Physicians: 0.23 (0.02-1.21) Paramedics: 0.51 (0.15-1.70)
CPAP	Males: 0.55 (0.21-1.43) Females: 0.16 (0.04-0.49)	Physicians: 0.33 (0.15-0.70) Paramedics: 0.30 (0.09-1.00)
Between-study SD (95% CrI)	0.21 (0.01-0.74)	0.23 (0.01-0.80)
Deviance information criterion (model with treatment effect modifier vs. model without treatment effect modifier)	298.76 vs. 293.92	80.229 vs. 76.318

BiPAP = bilevel inspiratory positive airway pressure; CPAP = continuous positive airway pressure; CrI = credible interval.
*Each potential treatment effect modifier was analyzed separately in the model.

reported so this was not explored as a potential treatment effect modifier.

Tables 2 and 3 give the results for mortality. The individual patient data and aggregate data network meta-regression suggested that sex was a modifier of the effect of treatment with CPAP, compared to standard care on mortality (OR for males relative to females = 0.18; 95% CrI = 0.04 to 0.74). There was insufficient evidence that sex was a modifier of the effect of treatment with BiPAP compared to standard care on mortality.

Tables 4 and 5 give the results for intubation rate. The individual patient data and aggregate data network meta-regression suggested that none of the covariates were modifiers of treatment effect.

Safety and Adverse Events

Safety information was inconsistently recorded and reported. Three studies[25,26,30] reported that no adverse events were identified, one study[22] reported one case of vomiting that resolved spontaneously, and one study[23]

reported vomiting as the only adverse event in both intervention and comparator groups (two of 60 vs. three of 62, respectively).

Risk of Publication Bias

For completeness and descriptive purposes, funnel plots were drawn to explore publication bias. There was no obvious indication of asymmetry, although the number of studies available was small and less than recommended for statistical hypothesis testing[31] (Data Supplement S4, available as supporting information in the online version of this paper).

DISCUSSION

Prehospital CPAP appears to reduce mortality and intubation rate in acute respiratory failure. The effectiveness of prehospital BiPAP is uncertain, with estimates of the effect on mortality and intubation, including the possibility of either worthwhile benefit or potential harm. The network meta-analysis using a mixture of individual patient data and aggregate data suggested that male sex was a significant modifier of the effect of treatment effect on mortality, with CPAP being more effective in males. It could be postulated that muscle mass allows CPAP to have an enhanced effect in males, but given that this was one of a number of associations explored, it should be interpreted with caution. We found no such association in the analysis of intubation data.

Two previous meta-analyses of prehospital NIV have been published.[13,14] Williams et al.[13] only evaluated prehospital CPAP and included nonrandomized studies. They reported that CPAP was associated with lower mortality and fewer intubations, with similar ORs to ours. The inclusion of nonrandomized studies may be inappropriate, given their high risk of bias. Our decision to include quasi-randomized trials could be criticized for similar reasons, but sensitivity analysis showed similar results when these were excluded. Mal et al.[14] evaluated prehospital CPAP and BiPAP, but combined results from studies of these different modalities. They reported that NIV was associated with a reduction in mortality (relative risk = 0.58; 95% CI = 0.35 to 0.95) and need for invasive ventilation (relative risk = 0.37; 95% CI = 0.24 to 0.58). Our analysis showed that this finding is confirmed for prehospital CPAP but not for prehospital BiPAP.

LIMITATIONS

Although our review is the most comprehensive to date, it is possible that we may have missed studies that were neither registered nor published, resulting in publication bias. There were relatively few studies available for analysis, and the between-study variability was uncertain. The analysis of BiPAP in particular involved fewer studies and fewer patients (190 vs. 610 receiving CPAP). Patients eligible for prehospital NIV might be expected to receive in-hospital NIV if prehospital treatment were not available, but this was only clearly mandated in one study. Thus some of the studies may be more appropriately considered as evaluations of NIV per se, rather than evaluations of prehospital versus in-hospital NIV. Prehospital NIV was typically delivered by physicians or paramedics with online physician support in the studies, so findings may not be generalizable to prehospital systems based on paramedics working without physician support. Safety and adverse events were inconsistently reported so we are unable to draw reliable conclusions on these issues. Finally, we did not examine cost-effectiveness, so even if prehospital CPAP is considered clinically effective, it may not be cost-effective.

CONCLUSIONS

Prehospital continuous positive airway pressure can reduce mortality and intubation rates for patients with acute respiratory failure, although the available evidence may not be generalizable to some prehospital systems. In particular, existing studies have not all compared prehospital continuous positive airway pressure to in-hospital noninvasive ventilation and thus may not be generalizable to systems where in-hospital noninvasive ventilation is standard practice. The substantial cost of implementing prehospital continuous positive airway pressure means that evidence of cost-effectiveness is required before implementation can be recommended. The available evidence does not currently support the use of prehospital bilevel inspiratory positive airway pressure. Further research is required in the form of a large pragmatic study and economic analysis comparing prehospital continuous positive airway pressure to in-hospital noninvasive ventilation for patients with acute respiratory failure.

We thank Gavin Perkins, Matt Ward, and Jerry Penn-Ashman for providing expert clinical advice and Kathryn MacKellar for clerical assistance. We thank Rebecca Harvey for creating the forest plots and funnel plots.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Literature search strategies.

Data Supplement S2. Methodological quality graph: review authors' judgments about each methodological quality item as percentages across all included studies.

Data Supplement S3. Methodological quality summary: review authors judgements about each methodological quality item for each included study.

Data Supplement S4. Funnel plots of sample treatment effects.