Continuous positive airway pressure in children with severe pneumonia: a meta-analysis

Zhi-Li Wang¹ · Yu He¹ · Zheng-Xiu Luo¹

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Pneumonia is the leading cause of death among children aged 1–59 months worldwide [1]. WHO recommends providing low flow oxygen by nasal cannula in pediatric patients with oxygen saturation < 90% [2]. With the provision of oxygen supplementation, some children still require further respiratory support such as mechanical ventilation due to the failure to maintain oxygen saturation and severe respiratory distress [3, 4]. However, mechanical ventilation may result in ventilator-induced lung injury [5]. As a simple and minimally invasive technique, continuous positive airway pressure (CPAP) has been used in children with severe pneumonia [6, 7], but its effect and safety are uncertain. Therefore, we performed a meta-analysis that compared CPAP with standard therapy or low-flow oxygen to figure out the effects and safety of CPAP.

This meta-analysis was performed according to the PRISMA guidelines [8]. The present meta-analysis was registered at PROSPERO (CRD42020136450).

The literature search was carried out in Pubmed, Cochrane Library, Embase, and Web of Science from inception until February 12, 2020 and the search was restricted to articles published in English. The search terms and keywords were provided in Table S1 in the supplement.

Inclusion criteria: (1) randomized controlled trials (RCTs) and crossover studies; (2) having a comparison group

(standard therapy or low-flow oxygen); and (3) involving inpatients with severe pneumonia defined by WHO younger than 18 years. Case reports, observational studies, reviews, comments, conference abstracts were excluded.

The primary outcomes were the intubation rate and mortality. Secondary outcomes included the change in respiratory rate (RR), heart rate (HR), duration of hospital stay, and adverse events.

Data extraction was performed independently by two reviewers. Data extracted included: study design, participants and settings, interventions, outcomes, and adverse effects. Disagreements were solved by consensus.

We summarized the intervention effects by calculating risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes; we also calculated 95% confidence interval for each outcome. Fixed-effects model or random-effects model were used to perform meta-analysis depending on the heterogeneity across studies. I^2 statistic were used for the assessment of heterogeneity, with $I^2 > 50\%$ indicating significant heterogeneity [9]. To explore the potential causes of significant heterogeneity, we performed subgroup analyses for primary outcomes if data were sufficient. The factors including age, sample size, settings, and high-risk conditions were prespecified for subgroup analyses. Sensitivity analysis was conducted by removing crossover trails and those studies without the supervision of physicians respectively. P value < 0.05 was considered statistically significant.

Four studies (three RCTs [10–12], one randomized crossover trial [13]) with a total of 3040 patients satisfied the inclusion criteria and were included in the analysis. Descriptive data for each study are presented in Table 1.

Three studies [11–13] ($n = 2971$) investigated the mortality. The pooled data suggested that mortality was not significantly reduced in CPAP group with significant heterogeneity (RR: 0.75, 95%CI = 0.33, 1.73; $P = 0.50$, $I^2 = 83\%$) (Fig. 1a). The probability of intubation was reported in only one RCT [11] ($n = 146$), in which a trend towards reduction in intubation was found in the CPAP group, but the

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✉ Zheng-Xiu Luo
luozhengxiu816@163.com

¹ Chongqing Key Laboratory of Pediatrics, Department of Respiratory, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders (Chongqing), China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing 400014, China

Table 1 Characteristics of the researches included in the study

Studies	Design	Age	n	High-risk conditions	Treatment group		Control group		Main outcomes	
					Name	Device	PEEP	Name	Device	Flow
Wilson et al. [10] Ghana, rural ED	RCT	3 mon–5 y	69	Hypoxemia (0%) Severe malnutrition (NR) HIV infection (NA) HIV exposure (NA)	bCPAP	Nasal cannula	5 cm H ₂ O	Standard care (1st h) bCPAP (2nd h)	NR	NR
Chisti et al. [11] Bangladesh, urban ICU	RCT	<5 y	146	Hypoxemia (100%) Severe malnutrition (49%) HIV infection (NA) HIV exposure (NA)	bCPAP	Nasal prongs	5–10 cmH ₂ O	Low-flow oxygen	Nasal cannula	0.5–2 L/min for <2 y and 2–4 L/min for >2 y
McCollum et al. [12] Malawi, rural General ward	RCT	1–59 mon	644	Hypoxemia (89%) Severe malnutrition (69%) HIV infection (12%) HIV exposure (30%)	bCPAP	Nasal masks or nasal prongs	7–8 cmH ₂ O	Low-flow oxygen	Nasal prongs	0.5 L/min for 30–59 d and 2 L/min for 2–59 mon
Wilson et al. [13] Ghana, rural ED	Crossover trial	1 mon–5 y	2181	Hypoxemia (0%) Severe malnutrition (NR) HIV infection (NA) HIV exposure (NA)	bCPAP	Nasal prongs	5 cmH ₂ O	Standard medical therapy	NR	NR

PEEP positive end expiratory pressure, RCT randomized controlled trial, bCPAP bubble continuous positive airway pressure, NR nor reported, RR respiratory rate, HR heart rate, NA not applicable, ED emergency department, ICU intensive care unit, LOS length of hospital stay

Fig. 1 Efficacy of CPAP vs. control on **a** mortality rate and **b** intubation rate

difference was not statistically significant between CPAP and control groups ($RR = 0.39$, 95%CI 0.14, 1.05, $P = 0.06$) (Fig. 1b). We conducted subgroup analyses to investigate whether effects of CPAP on mortality and intubation differed according to different age. In the subgroup analysis, no significant differences regarding mortality were found between CPAP and control groups in different age groups (children age < 1 year: $RR = 0.66$, 95%CI 0.20, 2.15, $P = 0.49$, $I^2 = 84\%$; children age 1–5 years: $RR = 0.95$, 95%CI 0.53, 1.72, $P = 0.88$, $I^2 = 34\%$) (see Fig. S1a in supplement). Similarly, there was no difference in intubation rate in CPAP group compared with control group (children age < 1 year: $RR = 0.41$, 95%CI 0.11, 1.44, $P = 0.16$; children age 1–5 years: $RR = 0.32$, 95%CI 0.06, 1.73, $P = 0.19$) (see Fig. S1b in supplement). We did not conduct subgroup analyses based on different settings, sample size, and high-risk conditions because of the limited number of studies. Note that sensitivity analysis by removing the crossover trial or the study without the supervision of physicians separately did not change the result of mortality (see Fig. S2a, Fig. S2b in supplement).

Data for change in RR were available from only one RCT [10] ($n = 69$). The RR was remarkably decreased in the CPAP group after 1 h ($MD = -15.00$ 95%CI -21.52 , -8.48 , $P < 0.00001$) (Fig. 2a). HR was observed with no significant change in the same trial [10]; nonetheless, the lack of original data prevented us from a meta-analysis. The pooled data from one RCT [11] ($n = 146$) suggested there was no significant reduction in the length of hospital stay in CPAP group ($MD = 0.29$, 95%CI -0.37 , 0.96 , $P = 0.39$) (Fig. 2b). Two studies [12, 13] ($n = 2825$) reported the incidence of adverse events and most of the adverse events were not serious. Only one child was reported to be

suffering from probable pneumothorax and four probable aspiration episodes happened in CPAP group in one study [12]. The pooled data suggested there was no significant difference in adverse events between CPAP and control groups ($RR = 3.06$, 95%CI 0.38, 24.98, $P = 0.30$, $I^2 = 76\%$) (Fig. 2c).

The pooled data are contradictory regarding mortality. One crossover trial [13] found no significant difference in mortality between groups, but the study population was relatively low-risk; few children had hypoxemia or were severely malnourished. Another RCT [11] that recruited children with severe pneumonia and hypoxemia showed significantly lower mortality in CPAP group, but the study was done in an intensive care unit, which means higher nurse-to-patient ratios and better medical supervision. Differently, the latest and largest RCT [12] which was done in the general ward without daily physician supervision showed an increase in mortality with the use of CPAP among high-risk (such as HIV, malnutrition, or hypoxemia) children with severe pneumonia. The differences mentioned above may contribute to the inconsistent results. Notably, WHO-defined severe pneumonia is a clinical diagnosis that does not require chest radiographs to confirm the presence of lower respiratory disease. The nonspecific signs and symptoms can be found in children without primary respiratory disorders such as circulatory failure [12, 14], which may cause the recruited participants not to be wholly homogenous in different studies. Due to heterogeneity between the studies and the conflicting results, it is difficult to conclude the effect and safety of CPAP.

Limited evidence indicated that CPAP decreased the respiratory rate. There was no significant difference in intubation rate, length of hospital stay, and adverse events between the CPAP and control groups.

Fig. 2 Efficacy of CPAP vs. control on **a** respiratory rate, **b** duration of hospital stay, and **c** incidence of adverse events

In conclusion, data regarding safety is contradictory for the use of CPAP among children with severe pneumonia. Limited evidence suggests CPAP may reduce respiratory rate. Still, there is a lack of evidence to show significant benefit for the use of CPAP for other outcomes. More well-designed RCTs are needed to evaluate which specific patient populations could benefit from CPAP in various settings. Case reports, observational studies, reviews, comments, conference abstracts were excluded.

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