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Bubble CPAP for Preterm Infants with Respiratory Distress: A Meta-analysis

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Abstract ***Objective:*** A meta-analysis evaluated bubble continuous positive airway pressure (bCPAP) for respiratory distress and investigated the effectiveness and safety of bCPAP in the management of preterm infants via the rate of continuous positive airway pressure (CPAP) failure, the duration of CPAP, the duration of hospital stay and complications. ***Methods:*** Randomised controlled trials which compared bCPAP with continuous flow CPAP or variable flow CPAP on preterm infants were searched in electronic literature databases PubMed®, Embase®, Web of Science and Cochrane Library. The CPAP failure rate and incidence of complications was measured by the Risk Ratio (RR) with 95% confidence intervals (CI). The duration of CPAP (hr) and hospital stay (d) was measured by the mean difference (MD) with 95% CI. ***Results:*** A total of 196 studies were identified, and 7 citations (involving 566 participants) were included finally. The 5 studies on CPAP failure rate had a pooled RR of 0.61 (95% CI: 0.39, 0.96). Four studies on duration of hospital stay showed a MD of -3.95(95%CI: -4.49, -3.41). Four studies on nasal trauma showed a RR of 2.69 (95% CI: 1.36, 5.33). Other complications were comparable in both groups. ***Conclusion:*** Bubble CPAP is as effective as the other forms of CPAP in preterm infants with respiratory distress. It reduced the CPAP failure rate and the length of hospital stay; however, it was at higher risk of nasal trauma.

Key words Bubble CPAP; Meta-analysis; Preterm infants; Respiratory distress

Introduction

Despite the sufficient respiratory support in the intensive care units, the mortality rate is still high, and it is clear that, noninvasive ventilatory support continuous positive airway pressure (CPAP) is one of the most important ways of respiratory support for preterm infants. Traditionally, CPAP often use mechanical ventilator to deliver positive airway pressure with variable or continuous flow.[1-3] Variable flow CPAP mainly consists of the infant flow driver CPAP (IFD CPAP) and Medijet system CPAP. Continuous flow CPAP mainly consists of conventional CPAP (cCPAP) and bCPAP. Bubble continuous positive airway pressure is the early constant flow CPAP system. In recent years, it has been an increasing enthusiasm choice in preterm neonates with mild to moderate respiratory distress.[4,5] It achieves the positive pressure by simply immersing the distal expiratory tubing in an underwater seal to a desired depth considered equal to the desired end expiratory pressure. Lee et al showed that it was superior to cCPAP in some way through generating vibrations simulated the waveforms produced by high-frequency ventilation (HFV).[6] The waveforms were adjusted by the amount of gas flow and the mean CPAP pressure was adjusted by varying the depth of tubing in the water seal. Some studies observed that it may reduce the need for mechanical ventilation and decrease the incidence of chronic

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lung disease (CLD).[7-11] Nevertheless, other studies showed that bCPAP had the same benefits as the use of the other forms of CPAP and may have more incidences of nasal septal injury and longer hospital stay.[12-14] The efficacy and safety of bCPAP for preterm infants who were suffering from respiratory distress remains controversial, thus, we conducted a meta-analysis of randomised controlled trials in order to assess the effect of bCPAP in preterm infants with respiratory distress, and evaluate whether bCPAP can reduce the rate of complications.

Materials and Methods

Study Selection

Eligible studies published up to 30 April 2015 were identified from the electronic literature databases PubMed®, Embase®, Web of Science and Cochrane Library using the following keywords: 'bubble CPAP', 'B-CPAP', 'bCPAP', 'constant flow', 'preterm' and 'respiratory distress'. We also searched the references list of the relevant articles to identify additional relevant papers. Primary outcome was the rate of CPAP failure. Failure was defined when preterm infants were intubated and mechanically ventilated. Secondary outcomes were duration of hospital stay (d), duration of CPAP (hr) and common complications, which included CLD (chronic lung disease), IVH (intraventricular haemorrhage), NEC (necrotising enterocolitis), nasal trauma and abdominal distension.

Selection Criteria

We used eligibility criteria as follows: (i) Participants: preterm infants (Gestation <37 weeks) with respiratory distress, who used CPAP after birth; (ii) Intervention: comparison of bCPAP and other forms of CPAP (included the conventional CPAP and variable flow CPAP); (iii) Outcome measures: CPAP failure rate (mechanical ventilation was considered for failure of CPAP); (iv) Methodological criteria: prospective, randomised, controlled trials. Unpublished studies and those with original data not available were excluded.

Data Extraction and Quality of Studies

Data were extracted from the included studies independently and in duplicate by two reviewers (T.W. and D.D.). The following data were extracted from each study: name of first author; year of publication; sample size in each group; type of CPAP; the rate of CPAP failure; duration of hospital stay (d); duration of CPAP (hr); common complications. All studies were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.[15]

Quality Assessment

Quality of the included studies was assessed by two investigators (T.W. and D.D.) independently and in duplicate, using predefined criteria based on Jadad Scale criteria.[16] The Jadad criteria are based on three aspects: (i) randomisation (0-2); (ii) double-blinding (0-2); (iii) dropouts and withdrawals (0-1). Total Jadad scores range from 0 (lowest) to 5 (highest). According to the Jadad scores, the included studies were classified as low quality (0-2) or high quality (3-5). Discrepancies regarding Jadad scores were resolved by discussion and consultation with an additional reviewer (J.L.).

Data Synthesis and Analysis

For the meta-analysis, the RevMan analytical software package (RevMan, version 5.3, Cochrane Collaboration, Oxford, UK) was used. The mean difference (MD) with 95% confidence intervals (CI) between the study groups was used for analysis of continuous outcomes. The Risk Ratio (RR) with 95% CI was used for analysis of dichotomous outcomes. Heterogeneity was evaluated using Cochran's Q-statistic ($P<0.05$ was regarded as statistically significant) and I^2 text (I^2 values ≥50% indicated substantial heterogeneity). Fixed-effects model was used when the studies had little variance; Random-effects model was presented when heterogeneity existed. One-way sensitivity analysis was performed to ensure the accuracy of the results. A funnel plot was used to assess possible publication bias.

Results

The study selection procedure is presented in Figure 1. The initial literature search identified 196 articles based on the title and keywords. One hundred and seventy-eight studies were excluded after reviewing the abstracts. After screening the full-text articles according to the inclusion criteria, the final meta-analysis included seven studies

(bCPAP, n=275; control group, n=291).[12-14,17-20] Each included study had been approved by an Ethics Committee, and details of the studies were qualitatively compared. The characteristics of the seven studies included in the meta-analysis are summarised in Table 1.

Five clinical randomised trials[12-14,18,20] with 394 participants showed the CPAP failure rate. In bCPAP group, twenty-five (13%) neonates led to failure. Forty-three (21%) neonates in other forms of CPAP were ventilated which considered failure of CPAP. The CPAP failure rate was higher in the control group than bCPAP group. The relative risk of CPAP failure rate was 0.61 (95% CI: 0.39, 0.96). The heterogeneity I^2 index was 26%. It indicates that the failure rate of CPAP was comparable in bCPAP vs. the other forms of CPAP. The results of the pooled statistical analyses are listed in Figure 2. A funnel plot of the studies of CPAP failure rate included in the meta-analysis is shown in Figure 3.

Meta-analysis for the duration of CPAP (hr) of bCPAP

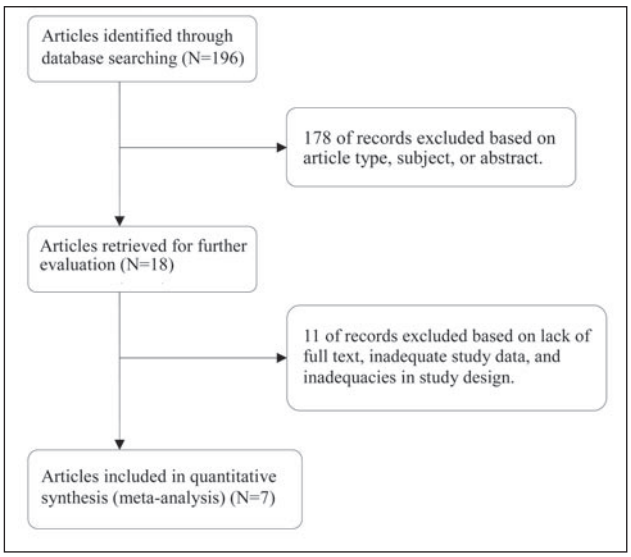

Figure 1 Flow diagram of the study selection process in a meta-analysis undertaken to evaluate the effectiveness and safety of bCPAP compared with the other forms of CPAP.

Table 1 Study characteristics

First author	Year	N	CPAP type		Jadad score
			bCPAP	Control group	
Gupta, S.	2009	140 (71/69)	Fisher&Paykel	Infant Flow Driver	5
Tagare, A.	2010	30 (15/15)	Fisher&Paykel	cCPAP	4
Bahman-Bijari, B.	2011	50 (25/25)	Fisher&Paykel	cCPAP	3
Yagui, A. C.	2011	39 (20/19)	Fisher&Paykel	Infant Flow Driver	5
Hosseini, M. B.	2012	161 (71/90)	Fisher&Paykel	Medijet system	4
Yadav, S.	2012	32 (16/16)	Fisher&Paykel	cCPAP	5
Tagare, A.	2013	114 (57/57)	Fisher&Paykel	cCPAP	4

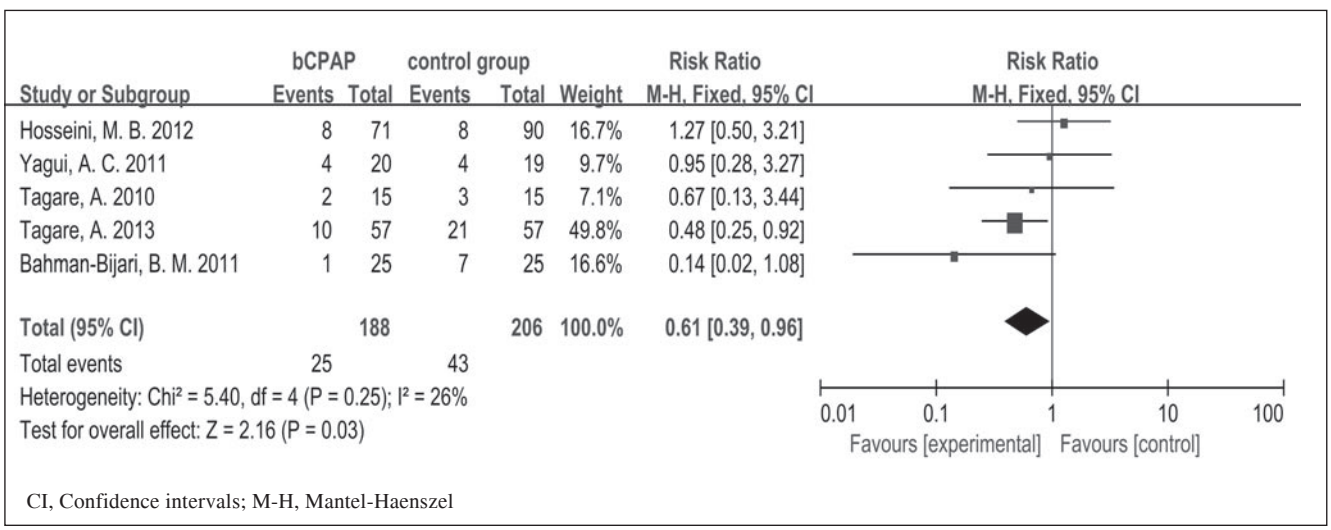

Figure 2 Statistical pooling of 5 studies (394 patients) revealed that there was significant reduction in CPAP failure rate with the use of bCPAP as compared with control group.

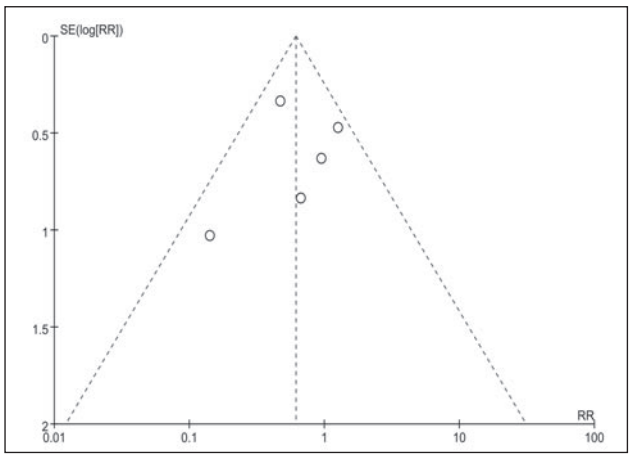

Figure 3 Funnel plots of studies included in a meta-analysis of bCPAP on the rate of CPAP failure.

and control group are shown in Figure 4. Five studies[12-14,18,20] recorded the duration of CPAP (hr) had a heterogeneity I^2 index of 0%. There were no significant effects of the length of CPAP time (RR1.18 (95% CI -1.93, 4.29)).

Within the 4 studies,[13,17,18,20] we identified a total of 282 participants (132 infants with bCPAP vs. 150 with control group) in the analysis of duration of hospital stay (d). The heterogeneity I^2 index was 21%. The pooled RR was -3.95 (95%CI: -4.49, -3.41). Significant effects were observed from the pooled analysis of studies ($p<0.05$) (Figure 5). It indicated that the duration of hospital stay was reduced significantly with bCPAP compared with control group. Sensitivity analysis showed that this outcome was reliable (data not shown).

The major complications included in this meta-analysis

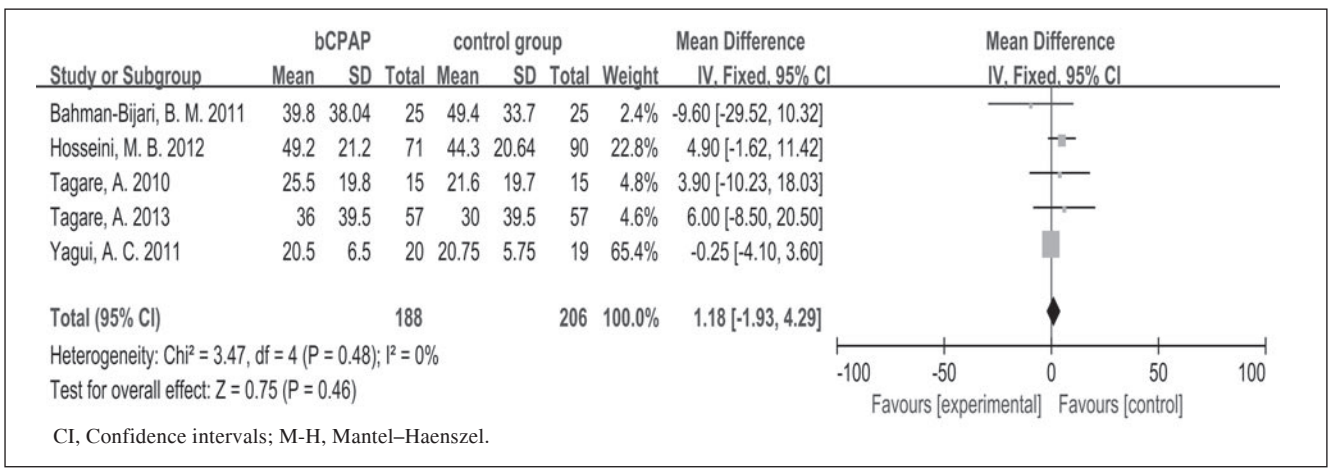

Figure 4 Statistical pooling of 5 studies (394 patients) revealed that there was no significant reduction in duration of CPAP (hr) (p=0.46) with the use of bCPAP as compared with control group.

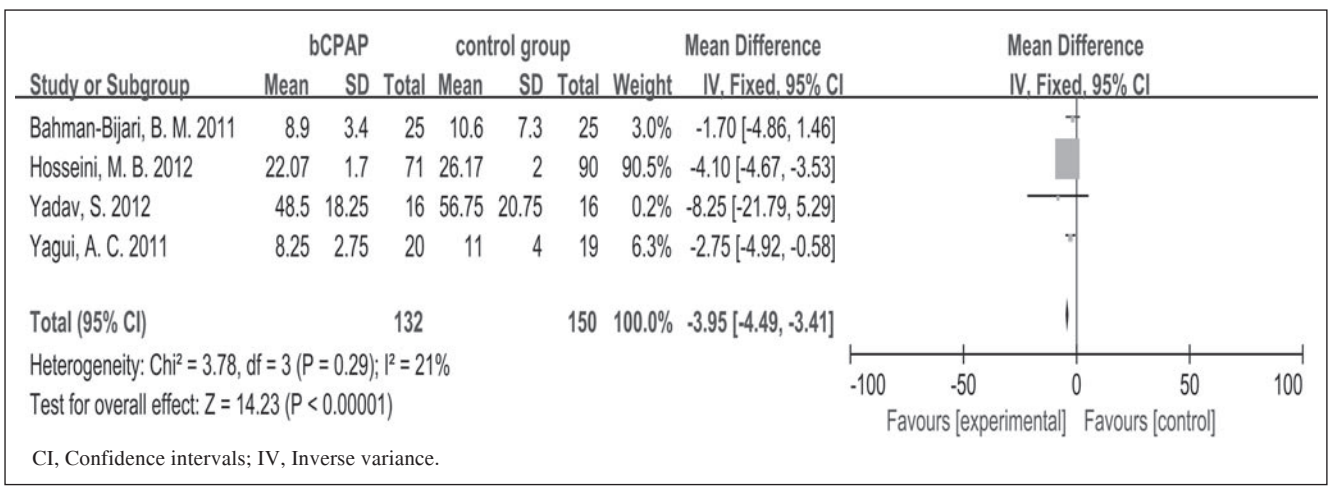

Figure 5 Statistical pooling of 4 studies (282 patients) revealed that bCPAP results in a significant reduction in duration of hospital stay (d) ($p<0.00001$) as compared with the other forms of CPAP.

were CLD (chronic lung disease), IVH (intraventricular haemorrhage), NEC (necrotising enterocolitis), nasal trauma and abdominal distension. The RR for each group was 0.77 (95% CI: 0.49, 1.24), 0.94 (95% CI: 0.50, 1.75), 0.72 (95% CI: 0.29, 1.79), 2.69 (95% CI: 1.36, 5.33) and 0.93 (95% CI: 0.63, 1.38), respectively, as showed in Table 2. The proportion of neonates with nasal trauma (included nasal septal injury, hyperemia of the nose and columella necrosis) was significantly higher in the bCPAP compared with the other forms of CPAP (p=0.004). The bCPAP group did not incur greater risks of CLD, IVH, NEC and abdominal distension from the pooled analysis of included studies.

Discussion

In this meta-analysis, we found that the CPAP failure rate in bCPAP group was lower than the control group. Furthermore, the incidence of CLD was reduced by ~5.8% in bCPAP group, but it was no significant (p=0.28). Nevertheless, the present meta-analysis presented an interesting phenomenon that the duration of hospital stay was reduced significantly in bCPAP group (p<0.05), which prompted that it could reduce hospitalisation expense simultaneously. Anyway, bCPAP may be a safe and effective way of respiratory support. Ho et al found that bCPAP could decrease the rates of extubation failure for premature infants with respiratory distress syndrome.[21] Courtney et al demonstrated that bCPAP could improve oxygenation.[22] Therefore, it is imperative to conduct further investigation.

It is worth noting that bCPAP decrease the duration of hospital stay significantly compared with the other forms of CPAP with no difference in the duration of CPAP (hr). This interesting finding may support the effectiveness of bCPAP. The bCPAP delivered mechanical oscillatory vibrations that simulate waveforms produced by high-frequency ventilation (HFV), which may improve gas exchange by the principle of facilitated diffusion. Although hospital stay is influenced more likely by factors like gestational age, birth weight, co-morbidities, hospital policy etc., the type of CPAP used may have a role in later respiratory function, feeding tolerance and weight gain. More studies should be conducted to confirm this speculation. Overall, this can provide an evidence for applying bCPAP effectively in developing countries when the varying stages of economic factor taken into account. The simple and effective method of providing respiratory support could substantially reduce the cost and attenuate the risk of illness during the hospital stay. It is likely an optimal alternative in the future among the underdeveloped countries or the relatively poor. As all the studies quoted in the meta-analysis used F&P system, whether it could be extended to other types of bubble systems is still being assessed.

Due to limited data, it was not possible to analyse each complication such as pneumothorax, pulmonary haemorrhage, sepsis, air leak, and retinopathy of prematurity. In this meta-analysis, CLD, IVH, nasal trauma, abdominal distension and NEC were the most common complications in the included studies, among which nasal trauma had the highest incidence in bCPAP group compared with the other forms of CPAP. The F&P Infant Interface consists of the FlexiTrunk Nasal Tubing, Nasal Prongs or Masks, and Infant Bonnet or Head Gear. The interface used in the bCPAP group was Nasal Prongs. Nasal trauma partly depends on the interface. Larger and heavier prong adapter size may contribute to the greater prevalence of nasal trauma. This indicates that neonates approved by bCPAP need better nursing care and should choose the suitable nasal prongs.

Through conducting this meta-analysis, several

Table 2 Results of statistical pooling

Complications	N	Relative risk (95% CI)	P-value	Heterogeneity	
				P-value	I^2 (%)
CLD	50	0.77 (0.49, 1.24)	0.28	0.3	17
IVH	36	0.94 (0.50, 1.75)	0.85	0.75	0
NEC	18	0.72 (0.29, 1.79)	0.47	0.32	13
Nasal trauma	36	2.69 (1.36, 5.33)	0.004*	0.49	0
Abdominal distension	75	0.93 (0.63, 1.38)	0.73	0.19	39

CI, Confidence intervals; CLD, Chronic lung disease; IVH, Intraventricular haemorrhage; NEC, Necrotising enterocolitis

*p<0.05: statistically significant

limitations were presented. Firstly, certain baseline demographics of the infants (including Apgar score, haemodynamic changes and antenatal steroids) were not unified across the studies and this may have affected the results. Secondly, the indication for giving non-invasive CPAP and the weight between different studies was different, especially the study by Gupta. It is on all cases of premature neonate regardless of mechanical ventilation before commencement of nCPAP. The included studies have patients with weight more than 1000 g while Gupta included those extremely premature from 600-1500 g. However, we found that the data of this study was only used in the comparison of morbidity (CLD, IVH, and NEC). One-way sensitivity analysis was performed. We excluded the study of Gupta, the RR for each group was 1.13 (95% CI: 0.52, 2.46), 0.70 (95% CI: 0.26, 1.85), 0.36 (95% CI: 0.09, 1.42), respectively, and there was also no statistical significance. Additionally, unpublished articles and abstracts were not included due to incomplete data. What's important is that the included studies are too little and easy to increase the chance of bias. Although each study population was well defined and had similar inclusion criteria, there may be unknown factors that could have influenced our results. Larger scale clinical trials are required to contribute to the screening and long-term effects of bCPAP on the preterm infants.

Conclusion

In conclusion, based on this meta-analysis of related published studies, the administration of bCPAP is as effective as the other forms of CPAP, and can reduce the CPAP failure rate and the length of hospital stay, which indicates that bCPAP could be an optimal alternative in developing country.

Contributors

H.W. conceived the study. The data were collected by T.W. and D.D. The research design was formulated by T.W., D.D., J.L., J.D. and H.W. The statistical analyses were undertaken by T.W. T.W. wrote the manuscript, which was edited by J.L. and J.D. All authors approved the final manuscript.

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Declaration of Interest

The authors declare that they have no conflict of interest.

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