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Review Article

The Use of Bubble CPAP and Humidified High Flow Nasal Cannula Oxygen Therapy in Children with Severe Pneumonia and Hypoxemia: A Systematic Review of the Evidence

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Abstract

Background: *Among children with severe pneumonia hypoxemia is the commonest complication leading to death. Some children will have both type I (hypoxemic) and type II (hypercarbic) respiratory failure. Together this accounts for high case-fatality rates in most populations with severe pneumonia. Standard oxygen supplementation by nasal prongs (low flow) can be lifesaving, but is not always sufficient to manage respiratory failure. In recent years continuous positive airway pressure (CPAP) has been used to relieve hypoxemia and reduce the work of breathing. There are several ways to give positive airway pressure; one is bubble CPAP (BCPAP), another is high flow nasal cannula (HFNC) oxygen therapy.*

Objective: *To review the evidence for using BCPAP, and HFNC therapy in children with severe pneumonia and hypoxemia, particularly the experience of these therapies in developing countries.*

Methods: *Two of our study investigators independently conducted searches of the existing literature in PUBMED in October 2014 to identify reports focusing on the use of BCPAP or HFNC therapy in children with severe pneumonia and hypoxemia, as defined by the World Health Organization.*

Results: *13 relevant studies were identified. Ten evaluated the efficacy of BCPAP among 3164 children, and three described the same for HFNC in 255 children. In all studies the entry criteria was severe respiratory distress. The study methodologies, the outcomes recorded and results were heterogeneous. The age range of the children in the studies was from the immediate newborn period on day 1 of life up to the age of 12 years. However, we evaluated the outcome of our review in two aged categories and found: children 0-28 days for 8 studies and > 28 days for 2 studies. In 3 studies of children aged 0-28 days and 2 studies of older children had clinical features consistent with severe pneumonia and those who among them were treated with immediate BCPAP therapy had better outcome ($p<0.01$ or CI < 1) compared to those who were treated with delayed BCPAP, or historical control one each, or standard flow flow (LF) oxygen therapy (in two studies). Primary outcomes were comparable between BCPAP and ventilator driven CPAP in three studies and between BCPAP and low flow oxygen or variable flow nasal CPAP in two studies (95% CI contain 1) of children aged 0-28 days. Children treated with HFNC compared to those who did not receive HFNC in three relevant studies, all of them in older children had better outcome ($p<0.05$).*

Conclusion: *Studies of BCPAP and HFNC are heterogeneous with different populations, comparators, outcome measures and results. However limited studies suggest that BCPAP may be effective in managing respiratory distress and hypoxemia in developing countries, although evidence is not overwhelming. Studies of the use of HFNC therapy are more limited and do not allow firm conclusions to be made. Most studies of BCPAP and HFNC have been done in neonates with respiratory distress, and studies outside this age group, where the predominant pathologies are bacterial pneumonia, sepsis and viral bronchiolitis are needed.*

KEY WORDS: *Bubble CPAP, bronchiolitis, children, developing country, high flow nasal cannula, hypoxemia, neonates, severe pneumonia.*

Introduction

Pneumonia and hypoxemia: Hypoxemia is a common and

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serious complication in children with pneumonia. Hypoxemia is defined by WHO as a reduction of less than 90% arterial oxygen saturation measured by pulse oximetry [1]. Hypoxemia is estimated to occur in 13% of all cases of pneumonia presenting to health facilities [2], and is the major risk factors for death in pneumonia [2-4]. Among the estimated 7.6 million global deaths in children under five in 2010, pneumonia accounted for 18% of the deaths [5]. In the same year there were an estimated 180,000 deaths in children under 5 years of age in Bangladesh, 14% of these deaths were due to pneumonia [6].

Different modes of respiratory support for children with hypoxemia

Standard oxygen therapy, Bubble CPAP (BCPAP) and high flow nasal cannula (HFNC): Respiratory support for pneumonia can be achieved by various oxygen delivery methods. Low flow oxygen administration (0.5 to 2 L/min) is the conventional method [7]. When this fails the next level of respiratory support is often continuous positive airway pressure (CPAP). CPAP can be delivered in several ways: non-invasive or invasive continuous positive airway pressure or positive pressure ventilation (PPV). Among the non-invasive continuous positive airway pressure, BCPAP or HFNC therapy are now most commonly used in managing neonatal respiratory failure. BCPAP can be administered using a number of patient interfaces, including a tight-fitting face mask, nasal prongs, nasopharyngeal tube or endotracheal tube using a conventional ventilator or CPAP driver. HFNC therapy can also be administered using tight-fitting face mask, nasal prongs, blender machine, or CPAP driver.

The purpose of BCPAP/HFNC is to avoid airway collapse even during the expiration phase to improve oxygenation [8]. BCPAP or HFNC therapy can help to avoid the airway collapse by maintaining positive pressure in the alveoli which improves alveolar ventilation and oxygenation by increasing functional residual capacity, decreasing pulmonary edema, and minimizing expiratory bronchiolar collapse. The continuous flow of gas given throughout the respiratory cycle also assists in reducing the patient's work of breathing [9, 10].

Objective

The primary objective of this review was to evaluate the evidence for using BCPAP and HFNC oxygen therapy in children with severe pneumonia and hypoxemia particularly the experience of these therapies in developing countries.

Methods

We conducted a search of the existing literature to identify reports focusing on pneumonia, hypoxemia, BCPAP, and HFNC. We searched PubMed with no limitations. The search strategies and outcomes are summarized in Table 1. The initial searches were conducted in June 2013 and further searches in October 2014. All abstracts retrieved by the individual searches were reviewed. Full-text articles were retrieved and evaluated if the abstract suggested potential relevance. Some full-text articles were readily available in PubMed and those were not available in PubMed, retrieved though online "discovery search" from the library of the University of Melbourne. Inclusion criteria were studies investigating the role of BCPAP or HFNC therapy in children having the clinical features of severe pneumonia and hypoxemia as defined by WHO. Excluded were reports that included animal models or respiratory distress syndrome (RDS) or used surfactant, or used CPAP or HFNC therapy only for post extubation support.

Table 1. Search strategy used to identify relevant publications and outcome for this review (for bubble CPAP and humidified high flow nasal cannula therapy)

Database	Strategy and keywords used	Total number of matches	Publications relevant for review	Year of publications
Medline	{(bubble cpap) OR (bubble continuous positive airway pressure)) AND ((child*) OR (paediatric) OR (Pediatric) OR (infant*) OR (neonate*)}	71	10	1991-2014
Medline	((high flow nasal cannula) OR (humidified high flow nasal cannula)) AND (neonate OR Child*)	91	3	1985-2014

*plural number

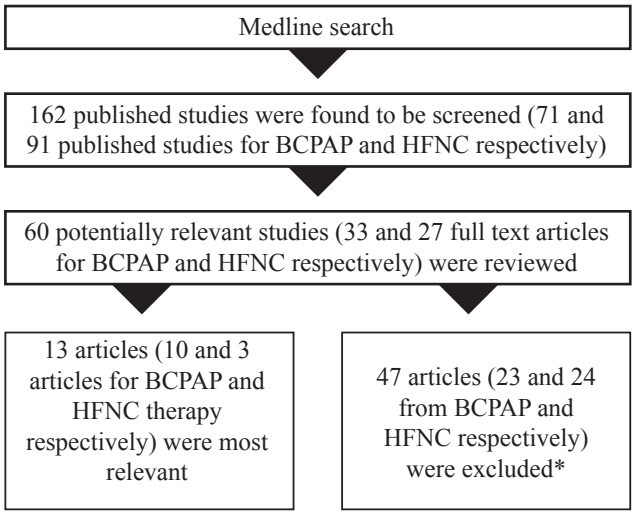
One of our study investigators helped me by performing independent searches in PubMed using the same search strategies. The outcome of both searches was the same and we did not have any dispute in finalizing the articles in our review.

Risk of bias in individual studies: Study quality was assessed using the Cochrane Collaboration risk of bias tool [11]. Two authors independently rated these criteria and were of the same agreement.

Results

The search retrieved 71 and 91 published studies for BCPAP and HFNC respectively in PubMed/Medline. Of these, 33 studies of BCPAP and 27 studies of HFNC were potentially relevant. The full texts of these studies were sought. Of the 59 articles retrieved, 40 were excluded: 23 on BCPAP [12-34] and 24 on HFNC [35-58] (Figure 1). Eventually 13 studies (10 for BCPAP) [59-68] and 3 for HFNC [69-71]) from 8 countries fulfilled the criteria for the review (Table 2).

Figure 1: Flow chart showing retrieval strategy and reasons for study exclusion



*22 from BCPAP therapy (5 with respiratory distress syndrome, 5 post-extubated neonates, 4 neonates who used surfactant, 2 editorials, 2 case reports, and 5 review articles) and 24 from HFNC therapy (9 post-extubated neonates, 7 review articles, 2 case series, 2 articles involving surgical cases, 1 neonate who used surfactant, 1 had nebulised 3% NaCl as comparison group, 1 article with ARDS cases, and 1 had no comparison group)

Description of the included studies

BCPAP

Among the 10 relevant publications for children treated with BCPAP, the age range of the study children was 4 hours to 12 years and the gestational age of newborns ranged from 26 weeks onwards (Table 2). Among these 10 studies 8 were found to have children aged 0-28 days and rest 2 had children 0-12 years (Table 2). Four publications included data from developed countries such as two from United States of America (USA) [61, 66], one each from United Kingdom (UK) [67] and Australia [64] while six other publications from developing countries such as three from India [60, 65, 68], one each from Fiji [63], Brazil [62], and 4 rural hospitals from Ghana (RCT) [59] (Table 2).

All the ten studies were prospective and five among 0-28 days group[61, 62, 64-66] and one among >28 days group[59] were RCTs. These 10 studies evaluated the efficacy of BCPAP involving 3164 children: 3059 in children aged 0-28 days and 105 children >28 days old. The study methodologies, the outcomes recorded and results were heterogeneous, although severe respiratory distress (severe dyspnea, or grunting or severe chest retraction and/or hypoxemia) was the common components of all these prospective studies. There were differences in the methods of analysis. Five studies in 0–28 days old[62-65, 67] reported the relative risk of main outcome variable and their 95% confidence intervals. Three studies, two in children >28 days [59, 60] and one in children 0-28 days[68] reported only p values between groups and other two [61, 66] reported as "not significant" (Table 2). Children treated with BCPAP therapy compared to other forms of oxygen therapy (head box oxygen, historical control, delayed BCPAP, or conventional oxygen therapy) in four of these studies (2 in children 0-28 days[63, 64] and other in children >28 days[59, 60]) had better outcomes (Table 2). Primary outcomes were comparable between BCPAP and ventilator driven CPAP in three RCTs in children 0-28 days old[61, 62, 65]. The primary outcomes of rest of the two studies treated with BCPAP oxygen therapy compared to low flow.

Table 2. Role of bubble CPAP in children with clinical signs of severe pneumonia

Reference	Country	Age commencing BCPAP	Gestational age (weeks)	Patient`s number (Total)	Type of BCPAP/patient`s number	Comparison group (patient`s number)	Main outcome variable	RR (95% CI) or P value
In children aged 0-28 days								
Daga S et al. (2014)	India	<7 days	≥ 32	140	Nasal prong (84)	Standard flow oxygen (56)	Deaths [6 (11%) vs. 2 (2%)]	0.04
Heuvel et al. (2011)	UK	4-40 hours	27-40	25	Nasal prong (5)	Conventional oxygen (20)	Death [2 (40%) vs. 14 (70%)]	0.6 (0.02-3.0)
Yagui et al (2011)	Brazil	>24 hours	32-39	39	Nasal prong (20)	VCPAP (19)	CPAP failure [4 (20%) vs. 4 (21%)]	1.0 (0.3-3.3)
Courtney et al. (2011)	USA	4-28 days	26-33	18	Nasal prong (13)	VCPAP (5)	WOB	NS
Tagare et al. (2010)	India	-	<37	30	BCPAP (15)	VCPAP (15)	Success of BCPCP	1.1 (0.8-1.5)
Buckmaster et al. (2007)	Australia	<24 hours	> 30	300	Hudson binasal prong (151)	Headbox Oxygen (149)	Treatment failure [35 (23%) vs. 60 (40%)]	0.6 (0.4-0.8)
Koyamaibole et al. (2006)	Fiji	<28 days	34-40	2488	Nasal prong (1382)	Historical control (1106)	Need for MV [70 (5%) vs. 113 (10%)]	0.5 (0.4-0.7)
Liptsen et al (2005)	USA	<28 days	<30 weeks	18	BCPAP (9)	Variable flow NCPAP (9)	WOB	NS

Reference	Country	Age commencing BCPAP	Gestational age (weeks)	Patient`s number (Total)	Type of BCPAP/patient`s number	Comparison group (patient`s number)	Main outcome variable	RR (95% CI) or P value
In children aged >28 days								
Wilson PT et al. (2013)	Ghana	3-60 months	-	69	Hudson BCPAP nasal cannula imediately (31)	Hudson BCPAP nasal cannula delayed (38)	Change in respiratory rate at 1 hour of enrolment	<0.001
Kinikar et al. (2011)	India	0-12 years	-	36	BCPAP (36)	Before received BCPAP (36)	Improvement of vital signs	<0.001

BCPAP = bubble CPAP; VCPAP = Ventilator derived CPAP ; WOB = work of breathing; MV = mechanical ventilation; NS = not significant

oxygen or variable flow nasal CPAP therapy in children aged 0-28 days were also comparable [66, 67] (Table 2).

HFNC

Among the 3 relevant publications for children treated with HFNC therapy, none of the studies categorized the age limit as 0-28 days and these 3 studies aged 0-12 years and involved 255 children. One of the studies originated from New Zealand [69], one from USA [70], and another study originated from Australia [71].

Table 3. Role of humidified high flow nasal cannula in children with clinical signs of severe pneumonia

Reference	**Country**	**Age commencing HFNC**	**Gestational age (weeks)**	**Patient`s number**	**Type of HFNC/ patient`s number**	**Comparison group (patient`s number)**	**Main outcome variable**	**P value**
In children with signs of severe pneumonia without bronchiolitis								
Spentzas et al. (2009)	USA	0-12 years	-	46	Normal HFNC (46)	Standard low flow oxygen, before receiving HFNC (46)	Respiratory distress and hypoxemia	<0.05
In children with bronchiolitis								
Mayfield S et al. (2014)	Australia	<12 months	-	94	HFNC (61)	Standard low flow oxygen	Respiratory rate, heart rate and ICU admission from emergency department	<0.05
Mckiernan et al. (2010)	New Zealand	<24 months	-	115	HFNC-A (58)	Standard low flow oxygen due to HFNC-NA (57)	Rates of intubation (5 vs. 13)	<0.05

MCS = modified comfort score; HFNC-A = high flow nasal cannula-available; HFNC-NA = high flow nasal cannula-not available;

Studies from New Zealand and USA used chart analysis and evaluated the use of HFNC oxygen therapy compared to historical control of conventional low flow oxygen therapy in children with clinical features consistent with severe pneumonia and hypoxemia. The study from Australia was prospectively done and evaluated the efficacy of HFNC oxygen therapy compared to conventional low flow oxygen therapy in children with bronchiolitis. Children treated with HFNC therapy compared to those who did not receive HFNC therapy in both the studies had better outcome (Table 3).

Risk of bias within studies

Table 4: Risk of bias assessment within studies

Authors	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete data (attrition bias)	Selective reporting (reporting bias)
Daga S et al.	-	-	-	-	+	+
Heuvel et al.	-	-	-	-	+	+
Yagui et al	+	+	-	-	+	+
Courtney et al.	+	-	-	-	+	+
Tagare et al.	+	+	-	-	+	+
Buckmaster et al.	+	+	-	-	+	+
Koyamaibole et al.	-	-	-	-	+	+
Liptsen et al	+	+	-	-	+	+
Wilson PT et al.	+	+	-	-	+	+
Kinikar et al.	-	-	-	-	+	+
Spentzas et al.	-	-	-	-	+	+
Mayfield S et al.	-	-	-	-	+	+
Mckiernan et al.	-	-	-	-	+	+

Table 4 shows the risk of bias assessment. Among a total of thirteen included studies in this review, six were randomized trials. All presented adequate random sequence generation but only five reported adequate allocation concealment. Another seven studies were case-control without any random sequence with the risk of selection bias. None of the twelve studies under our review were blinded due to the nature of the interventions, thus there is always a risk of performance bias. Moreover, outcome assessment was also not blinded which might carry a risk of detection bias. None of the studies described any measures that have been taken against these potential biases. The table also shows that the attrition rates were reported and considered acceptable in all the studies. All studies used an intention-to-treat principle for statistical analyses.

Discussion

Bubble CPAP: The review provides some evidence that BCPAP is effective in improving severe respiratory distress, improving respiratory vital signs, and reducing the use of mechanical ventilation (MV) in children 0-28 days old [63, 64] as well as in older children [59, 60]. However, there were only two studies from developing countries involving older children which evaluated the effect of BCPAP [59, 60]. A recently conducted RCT in Ghana in older children [59] observed significant decrease in respiratory rate (primary outcome) in children with hypoxemia and respiratory distress receiving BCPAP immediately after admission compared to those not receiving BCPAP immediately after admission for one hour (comparison group received LF oxygen therapy for the initial one hour followed by BCPAP). This study involving 4 rural hospitals in Ghana was stopped after the enrolment of a total of only 69 patients in both the groups (Table 2) because of the achievement of the predetermined significance value ($p<0.001$). BCPAP used by the study was low cost and successfully handled by the local nurses. Another study done in India in older children, observed significant reduction of hypoxemia and respiratory rate among the children who received BCPAP compared to same patients who received conventional oxygen before receiving BCPAP, although the sample size was very small (Table 2). This study mainly involved children with influenza like illness with hypoxemia[60].

In preterm neonates (0-28 days old), the observation of lack of difference in comparing main outcome variables between BCAP and MV in three RCTs [61, 62, 65], two of them done in developing countries, one each in Brazil [62] and India [65], underscore the importance of the use of BCPAP in newborn period in developing countries with limited resources. A difference in BCPAP compared to MV driven CPAP is that the BCPAP is highly flow dependent whereas MV driven CPAP is flow independent. However, considering the need for skilled manpower, training, costs, and invasive nature of MV driven CPAP, BCPAP is non-invasive, very cheap, more user

friendly, does not need special training and can be handled by nurses or health workers at hospitals in resource limited settings especially in the Thana or district level.

Among the two other studies in children 0-28 days with large sample who had better outcome with BCPAP, one RCT done in Australia involving newborn and receiving BCPAP had significantly lower treatment failure [64], and another from Fiji involved neonates as historical control and receiving BCPAP had the significant reduction of requirement of MV [63]. However, both the studies have been conducted in developed country set ups with high resources and the age of the children in both the studies was below 28 days and the evidence of affectivity of BCPAP in beyond this age group is yet to be proven.

Observation of failure to show better outcome of BCPAP in two other studies done in 0-28 days old children[66, 67] may question the overwhelming effectiveness of BCPAP even in neonates among the nine relevant studies in our review. This might be due to small sample in two groups. However, there might have other contributing factors especially in study done by Liptsen et al. [66] where study results had been obtained within short time span (5 to 10 minutes of stabilization period) and authors also raised the issue that it was not possible to draw conclusions about the long term clinical importance from statistically insignificant short term physiological studies. Study done by Heuvel at al. [67] had different primary outcome which was not relevant to our review but sub-analysis of their study, relevant to our review, revealed that death in both the groups were comparable. This might be also due to small sample size (Table 2) in the group of patient who received BCPAP compared to LF therapy [2/5 (40%) vs. 14/20 (70%); 95% CI=0.02-3.0).

Limitation of this review

Marked heterogeneity is one of the main limitations of this review. There was heterogeneity between study populations and methodologies, including differences in sample size, gestational age, variations in disease severity, variations of comparison groups (such as conventional low flow oxygen, head box oxygen, ventilator driven CPAP, variable flow nasal CPAP, historical control, and no CPAP), and primary outcomes (such as treatment or CPAP failure, success of BCPAP, need for mechanical ventilation, work of breathing, change in respiratory rate at one hour of enrolment, improvement of vital signs, hypoxemia and death). The review did not identify any study involving children specifically with severe pneumonia and hypoxemia comparing the efficacy of BCPAP therapy with LF therapy and/or HFNC.

HFNC: Three relevant studies involving mostly older children receiving HFNC had better outcome compared to those receiving LF therapy, however all these studies were conducted in developed countries. We did not identify any studies conducted in developing countries involving the children receiving HFNC therapy compared to LF therapy. One of these two studies done in the USA by Spentzas T et al. used modified comfort score (MCS) as the primary outcome which included the response to signs of respiratory distress in addition to a number of other physical parameters [70]. Primary outcome of the study also involved improvement in oxygen saturation. The study children receiving HFNC therapy observed to have significant improvement in signs of respiratory distress and oxygen saturation. Assessment of MCS in improving the signs of respiratory distress has already been observed in a number of previously conducted studies [72-74]. Another study among these two, conducted in New Zealand by McKiernan C et al. used the rates of intubation as the main outcome variable and observed significant reduction in the rate of intubation among the children receiving HFNC therapy [69]. On the other hand, significant reduction of ICU admission and reduction in respiratory rate were observed in the third relevant study in our review, prospectively conducted in a hospital emergency department in Australia by Mayfield et al. [71]. From these studies the authors concluded that HFNC oxygen therapy provides a well tolerated means of respiratory support in children with respiratory distress and improves different parameters of increased respiratory effort in order to prevent intubation and mechanical ventilation in developed countries. However retrospective nature of two of these three studies and lack of randomization are the main limitations. The lack of measurement of actual PEEP in HFNC therapy is another limitation of the studies.

Conclusions: There is evidence that BCPAP oxygen therapy is effective in managing neonates with respiratory distress and hypoxemia in developed countries, however, the evidence is limited in regard children beyond newborn especially in developing countries. Although, HFNC therapy may be effective in managing children with respiratory distress and hypoxemia in developed countries, studies of the use of HFNC therapy are also limited and do not allow firm conclusions to be made. However, none of the studies of BCPAP or HFNC therapy specifically included children with severe pneumonia and hypoxemia beyond the neonatal period, and evaluated treatment failure or mortality.

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