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Non-invasive ventilation with bubble CPAP is feasible and improves respiratory physiology in hospitalised Malawian children with acute respiratory failure

J. Walk^{1,2}, P. Dinga², C. Banda², T. Msiska², E. Chitsamba², N. Chiwayula², N. Lufesi³, R. Mlotha-Mitole², A. Costello⁴, A. Phiri², T. Colbourn⁴, E. D. McCollum^{2,4,5}, and H. J. Lang²

¹University Medical Centre Utrecht, Utrecht, The Netherlands ²Department of Paediatrics, Kamuzu Central Hospital, Malawi ³Ministry of Health, Community Health Sciences Unit, Lilongwe, Malawi ⁴University College London Institute for Global Health, London, UK ⁵Department of Pediatrics, Division of Pulmonology, Johns Hopkins School of Medicine, Baltimore, USA

Abstract

Background—In low-income countries and those with a high prevalence of HIV, respiratory failure is a common cause of death in children. However, the role of non-invasive ventilation with bubble continuous positive airway pressure (bCPAP) in these patients is not well established.

Methods—A prospective observational study of bCPAP was undertaken between July and September 2012 in 77 Malawian children aged 1 week to 14 years with progressive acute respiratory failure despite oxygen and antimicrobial therapy.

Results—Forty-one (53%) patients survived following bCPAP treatment, and an HIV-uninfected single-organ disease subgroup demonstrated bCPAP success in 14 of 17 (82%). Compared with children aged < 60 months, infants of 0–2 months had a 93% lower odds of bCPAP failure (odds ratio 0.07, 95% confidence interval 0.004–1.02, $P = 0.05$). Following commencement of bCPAP, respiratory physiology improved, the average respiratory rate decreased from 61 to 49 breaths/minute ($P = 0.0006$), and mean oxygen saturation increased from 92.1% to 96.1% ($P = 0.02$).

Conclusions—bCPAP was well accepted by caregivers and patients and can be feasibly implemented into a tertiary African hospital with high-risk patients and limited resources.

Keywords

Respiratory failure; Bubble continuous airway pressure (bCPAP); HIV; Pneumonia; Respiratory disorders

Correspondence to: H-J Lang, Department of Paediatrics, Kamuzu Central Hospital, Private Bag B397, Lilongwe 3, Malawi. Hajoel23@yahoo.es.

Contributors JW, EDM and HJL conceived the study. JW, PD, CB, TM, EC, NC, and HJL were involved in data collection. RMM, AP and HJL supervised the clinical work. TC conducted the analysis with input from JW, AC, NL, TC, EDM and HJL. JW wrote the first draft which was revised with input from HJL, TC and EDM. All authors contributed intellectual content and read and approved the final manuscript.

Conflicts of interest The authors declare no conflicts of interest.

Disclaimer statements

Ethics approval The study was approved by the Malawi National Health Sciences Research Committee, protocol no. 941.

Introduction

Worldwide, pneumonia kills nearly 1.5 million children under 5 years of age annually and is the leading cause of child mortality in sub-Saharan Africa.¹ In patients with pneumonia, late presentation, malnutrition and HIV-infection increase the likelihood of respiratory failure and death.² Acute respiratory failure also complicates other common conditions such as malaria, sepsis and gastro-enteritis.³ In Malawi, which has a high prevalence of malnutrition and HIV infection, respiratory failure is a major cause of paediatric mortality.⁴ Mechanical ventilation is generally indicated for severe acute respiratory failure, but in resource-constrained countries such as Malawi its availability is severely limited. Non-invasive ventilation, already routinely used in industrialised countries, may provide an advanced treatment solution for certain patient populations.^{5,6}

Bubble continuous positive airway pressure (bCPAP) ventilation is non-invasive and is widely used for preterm neonatal respiratory failure in industrialised countries.^{7,8} Along with a flow generator, bCPAP uses a water column to deliver continuous positive pressure to a spontaneously breathing child.⁹ bCPAP is inexpensive and requires little technical expertise compared with mechanical ventilation,^{7,10} but there is limited experience of bCPAP in resource-poor settings. Recently, small studies have explored its use in preterm neonates in Malawi.¹⁰ However, few studies have described its use in older infants and children.^{11–13}

To examine the feasibility and outcomes of ventilation assisted with bCPAP in a resource-constrained country with a high HIV prevalence, a prospective observational study was undertaken in hospitalised children with acute respiratory failure managed with bCPAP during routine programme conditions.

Methods

Study setting

Kamuzu Central Hospital (KCH) in Lilongwe is an urban, government-run referral hospital with more than 20,000 paediatric admissions a year.¹⁴ This operational study was conducted from July to September 2012 on two wards, the six-bedded paediatric high-dependency unit with a nurse-to-patient ratio of 1:6, and the emergency ward which had between 40 and 70 patients at any one time staffed by one or two nurses. A clinical officer, medical intern or qualified doctor also staffed the ward. Patients were reviewed at least twice daily.

Participants

Patients with hypoxaemia, defined by the World Health Organization (WHO) as a peripheral oxygen saturation (SpO_2) $<90\%$,¹⁵ received oxygen from an oxygen concentrator through nasal prongs. As laboratory diagnostics and chest radiographs were limited, the child's illness was diagnosed clinically and treated according to WHO guidelines.¹⁵

HIV testing was performed on children after their caregivers gave verbal consent. Being HIV-infected was defined as a child older than 12 months who was HIV antibody- or HIV

DNA PCR-positive, or a child younger than 12 months who was PCR-positive. Being HIV-exposed was defined as a child younger than 12 months who was HIV antibody-positive (from an HIV-infected mother) if PCR was unavailable. A child confirmed to be HIV-infected or who was HIV-exposed was defined as HIV-affected.

All patients with acute respiratory failure who were deteriorating on standard treatment with antibiotics and oxygen were eligible for bCPAP. Patients' carers gave verbal consent for bCPAP. Pressure for bCPAP was commenced at 5–6 cm of water and increased if necessary, depending upon SpO₂, respiratory rate and respiratory effort. A nasogastric tube for feeding and stomach decompression was placed in all patients. bCPAP failure was defined as a patient who either died receiving bCPAP or required endotracheal intubation with manual ventilation. (Paediatric mechanical ventilation was not available.) Baseline data including SpO₂ and respiratory rate were recorded at initiation of bCPAP. Follow-up data were collected once daily while the patient was on bCPAP and during the first 48 hours after cessation of bCPAP, consistent with routine care.

Nasal bCPAP

Because of a lack of resources, an improvised bCPAP set-up was used (Fig. 1). Flow was generated by an oxygen concentrator, a device that filters nitrogen from atmospheric air to deliver up to 5 or 10 litres/minute of a fractional inspired oxygen concentration (FiO₂) of 90–95% under optimum conditions. The oxygen concentrators did not allow for regulation of FiO₂ or humidification of inspired air.¹⁶ A water bottle was used to control the pressure delivered to the child's respiratory system. The pressure was determined by the depth of the pressure control tube below the water surface, which functions as a pressure relief device. Binasal prongs or a nasopharyngeal tube, in the case of older children for whom well fitting binasal prongs were unavailable, delivered the pressure-regulated oxygen flow to the patient's nostrils or nasopharynx.

Statistical analysis

Patient records were summarised in Microsoft Excel and analysed by Stata 13.1 for Mac. Socio-demographic and clinical characteristics were described for all participants. Univariable logistic regressions were used to quantify differences in the odds ratio (OR) of bCPAP failure between covariates of interest and a reference in several separate categories. The small sample size precluded multivariable logistic regression analyses. Mean oxygen saturation and respiratory rates before and after bCPAP treatment were compared via paired *t*-tests.

Ethical approval

The study was approved by the Malawi National Health Sciences Research Committee, protocol no. 941. Individual informed consent was not required as this was an observational study during routine care.

Results

Table 1 presents patient characteristics and hospital outcomes of 77 children treated with bCPAP. The median (range) age of bCPAP recipients was 5 months (1 week to 14 years) and 43% were male. Patients received bCPAP treatment for a median of 3 days. Two children aged 11 and 14 years received bCPAP via a nasopharyngeal tube; all others received bCPAP via binasal prongs. Of 44 patients for whom HIV status was known, 17 (22%) were HIV-affected, 86% of all patients met the WHO criteria for 'very severe pneumonia',¹⁵ and 30% had additional diagnoses including meningitis, convulsions, severe malaria or gastro-enteritis. Twenty-four per cent of bCPAP recipients also had signs of circulatory failure sufficiently severe to require at least one fluid bolus. Patients aged 0–2 months were found to have 93% lower odds of bCPAP failure than patients over 60 months of age (OR 0.07, 95% confidence interval (CI) 0.004–1.02, Table 1), and children who were HIV-affected had high odds of failing bCPAP compared with HIV-uninfected patients (OR 4.35, 95% CI 1.19–15.87). Compared with patients with uncomplicated very severe pneumonia (no additional co-morbidity or multi-organ failure), children with pneumonia and an additional co-morbidity (OR 3.52, CI 1.07–11.67) or multi-organ failure (OR 12.67, CI 2.77–57.83) had higher odds of bCPAP failure.

Children who were HIV-uninfected and had only single-organ failure (such as uncomplicated pneumonia or respiratory depression) had a high bCPAP success rate at 82% (14 of 17 survived, 95% CI 57–96%, Table 2).

Table 3 demonstrates that following initiation of bCPAP mean respiratory rate was reduced from 61 to 49 breaths/minute in the 22 patients for whom data were available. Additionally, mean oxygen saturation increased from 92.1% to 96.1% in 34 children with complete data and progressive respiratory failure despite oxygen supplementation.

Complications owing to bCPAP were recorded in 16.9% of cases. In all children, bCPAP caused drying of upper airway mucosa, requiring frequent saline nasal drops, and in two cases (2.6%) dried secretions caused partial upper airway obstruction which required suctioning. Nosebleeds were the most frequently recorded complication, occurring in 11.7% of cases (9 of 77). Both children who received a nasopharyngeal tube complained of discomfort, but this was not severe enough to require discontinuation of treatment. Three (3.9%) patients receiving bCPAP via nasal prongs suffered nasal septum damage. Overall, the use of bCPAP was well accepted as no bCPAP patients absconded during this time.

Discussion

In resource-rich settings, the benefits of non-invasive ventilation of premature neonates⁶ and older children with respiratory failure have been extensively described.^{17–19} In low-resource settings, the role of non-invasive ventilation is less clear. bCPAP, a low-cost CPAP device for the care of premature neonates, has been studied in Malawi,¹⁰ but little is known about its effectiveness in older children with acute respiratory failure, especially in HIV-endemic regions. In this observational study, 77 children aged between 1 week and 14 years in acute respiratory failure despite oxygen and antimicrobials received bCPAP. Respiratory

physiology improved after initiation of bCPAP and its use may be more effective in younger than in older children. bCPAP is potentially less effective in HIV-infected or -exposed patients in whom it is known to be associated with a poorer outcome than in HIV-uninfected children. Similarly, it may be less therapeutic in children with complicated (additional co-morbidity or multi-organ failure) very severe pneumonia, which carries a much higher risk of mortality than uncomplicated, very severe pneumonia. The study demonstrates that bCPAP use is feasible in a tertiary African hospital with limited resources and high-risk patients.

Overall, bCPAP treatment was accepted by carers and patients and was feasible to administer. The finding that it was acceptable to carers is similar to an observational study of older infants in India in which the authors also concluded that bCPAP is feasible to administer with locally trained nursing staff.²⁰ Although in general bCPAP treatment was found to be achievable in a busy, high acuity but low-resource hospital, there were some notable challenges. Firstly, bCPAP nasal prongs required frequent adjustment to maintain an adequate nasal seal on children owing to dislodgement or mucous occlusion of the prongs. This increased the nursing workload and limited the number of bCPAP set-ups which could be managed at any one time. Secondly, nosebleeds occurred in 11% of patients, probably because of the inability to humidify the air oxygen gas. Thirdly, nasal septum damage owing to pressure by the prongs occurred in three patients who received bCPAP for prolonged periods. This could be corrected by a higher nurse-to-patient ratio, allowing for continual adjustment and thus better placement of the nasal prongs; however, this is a challenge in severely resource-constrained settings such as Malawi. One alternative solution could be to train patient carers to assist nurses with simple but frequently required respiratory support tasks such as maintaining an adequate nasal prong seal.

In the absence of controlled studies demonstrating mortality reduction after bCPAP, the improvement of physiological parameters such as hypoxaemia, a predictor of mortality in children with pneumonia,^{21,22} can serve as a proxy indicator for bCPAP effectiveness. In this study there were physiological benefits from bCPAP in a group of children with acute respiratory failure and a high prevalence of HIV: respiratory rates, oxygen saturation and respiratory effort all improved in the hours following initiation of bCPAP. These findings confirm and extend the results in non-HIV-affected cohorts of Indian and Ghanaian children who also had lower respiratory rates and increased oxygen saturations after bCPAP administration.^{13,20} Controlled studies in HIV-endemic settings may be needed to confirm these findings, including studies adequately powered to assess children's physiological response to bCPAP when stratified by HIV status.

Although bCPAP use was feasible, lowering elevated respiratory rates and normalising hypoxaemic oxygen saturation, nearly half of the patients died. When non-invasive ventilation fails in resource-rich settings, respiratory care is escalated to mechanical ventilation in 16.8–43% of paediatric patients with acute respiratory failure,^{18,23} with rates as high as 45.5% in immunocompromised children.²⁴ Risk factors for the failure of non-invasive ventilation include multi-organ failure,^{25,26} acidaemia,²⁵ high oxygen requirement and sepsis.^{27,28} The failure rate in our cohort may be explained by their high-risk profile. Almost all the children (86%) met the WHO criteria for 'very severe pneumonia', many

(22%) of those tested were HIV-affected, and a large proportion (24%) had evidence of perfusion abnormalities suggestive of multi-organ involvement, all of which are risk factors for treatment failure and mortality.^{29–31} Early use of bCPAP can play an important role in providing better care for critically ill children in low-resource settings.

In addition, late presentation was common in this cohort and earlier initiation of non-invasive ventilation has been associated with a higher chance of treatment success.³² Despite the high rate of bCPAP failure, its success rate in HIV-uninfected children with only single-organ failure was 82%. While this is encouraging, it needs to be confirmed in a larger sample. We also found bCPAP to be more effective in younger infants than in older children. This might be because it is easier to maintain an effective nasal seal and therefore deliver consistent pressure in younger infants who are unable to dislodge the nasal prongs with their hands or body movements. Further surveys need to be conducted with better equipment providing humidified air/oxygen flow and improved patient interfaces.

There were some limitations to the study. It was non-randomised and uncontrolled which limits the extent to which the results can be compared with current WHO recommendations for oxygen supplementation and antibiotics in older infants. Studies designed to use standard care as a control group and mortality as a primary outcome may be expensive and potentially difficult to design. This study also had a small sample size, limiting its power to detect associations between socio-demographic and clinical baseline variables with bCPAP failure, and to control for confounders. Another limitation was that the children were cared for on a busy, understaffed and resource-limited ward under routine programme conditions. The operational nature of this study was limiting for two reasons. First, it made accurate diagnoses difficult, including a definitive HIV status, but makes the results applicable to similar settings with little laboratory support which primarily rely on clinical diagnoses. It will be important for future studies in HIV-endemic countries to be adequately powered to differentiate outcomes by HIV status. Second, many patients lacked documented pre- and post-bCPAP oxygen saturation and respiratory rates despite the collection of these measurements by clinical staff. Comprehensive cost analyses of bCPAP will also be critical. These are the logical next steps in evaluating whether bCPAP is appropriate for widespread use in developing countries.

In conclusion, a low-cost bCPAP device can be used effectively in a resource-constrained setting with a high HIV prevalence and respiratory physiology improves after commencement even in high-risk children with acute respiratory failure. Further research is recommended, including cost-effectiveness analyses, to include non-neonates and HIV-affected populations to better inform treatment guidelines, policy development and potential scale-up of this technology in developing countries.

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Figure 1.

Diagram of bubble CPAP set-up used in this study. (A) A photograph representative of the standard set-up used during routine clinical care. (B) Flow was generated by an oxygen concentrator, a device that filters nitrogen from atmospheric air to deliver up to 5 litres/minute of a fractional inspired oxygen concentration (FiO_2) of 90–95% under optimum conditions. A water bottle was used to control the pressure delivered to the child's respiratory system. The pressure was determined by the depth of the pressure control tube below the water surface, which functions as a pressure relief device. Bi-nasal prongs

delivered the pressure- regulated oxygen flow to the patient's nostrils or nasopharynx. Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. The Union©. McCollum ED, Smith A, Golitko CL. Bubble continuous positive airway pressure in a human immunodeficiency virus-infected infant. *Int J Tuberc Lung Dis.* 2011;15:562–4.

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Table 1

Baseline characteristics and bCPAP outcome

	All patients	Survived bCPAP <i>n</i> (%)	bCPAP failure ¹ <i>n</i> (%)	Odds ratio of failure ² (95% CI)
Total patients	77	41 (53)	36 (47)	
Demographics				
Gender, <i>n</i> (%)				
Male	33 (43)	21 (64)	12 (36)	0.49 (0.19–1.27)
Female	37 (49)	17 (46)	20 (54)	1.0
Unknown	7 (9)	3 (43)	4 (57)	1.13 (0.21–5.79)
Median age, mths (IQR)	5 (2–11)	5 (1.9–11)	7 (3–11)	
Age, mths, <i>n</i> (%)				
0–<2	11 (14)	10 (91)	1 (9)	0.07 (0.004–1.02)
3–5	25 (32)	12 (48)	13 (52)	0.72 (0.10–5.09)
6–11	19 (25)	8 (42)	11 (58)	0.92 (0.12–6.82)
12–23	8 (10)	5 (63)	3 (38)	0.40 (0.04–3.95)
24–59	5 (6)	3 (60)	2 (40)	0.44 (0.35–5.58)
60	5 (6)	2 (40)	3 (60)	1.0
Unknown	4 (5)	1 (25)	3 (75)	
HIV status, <i>n</i> (%)				
Affected	17 (22)	6 (35)	11 (65)	4.35 (1.19–15.87)*
Uninfected	27 (35)	19 (70)	8 (30)	1.0
Unknown	33 (42)	16 (50)	17 (52)	2.52 (0.86–7.37)
Diagnosis, <i>n</i> (%)				
Very severe pneumonia, uncomplicated ³	26 (34)	19 (73)	7 (27)	1.0
Very severe pneumonia with co-morbidity ⁴	23 (30)	10 (43)	13 (57)	3.52 (1.07–11.67) [†]
Very severe pneumonia with multi-organ failure ⁵	17 (22)	3 (18)	14 (82)	12.67 (2.77–57.83) [‡]
Respiratory depression ⁶	8 (10)	7 (88)	1 (12)	1.35 (0.11–17.42)
Congenital heart disease	3 (4)	2 (67)	1 (33)	0.39 (0.04–3.74)
Median duration of treatment, days (IQR)	3 (2–4)	3 (3–5)	2 (2–3)	

* $P = 0.03$;[†] $P = 0.04$;[‡] $P = 0.001$;

CI, confidence interval; IQR, interquartile range.

¹ 25 died while on bCPAP, 10 died while intubated, and one died within 48 hrs of coming off bCPAP.² From univariable logistic regressions of bCPAP failure. The reference category is indicated by an odds ratio of 1.0. and * indicates $P < 0.05$.³ 'Very severe pneumonia' with co-morbidity of one other organ system, e.g. gastro-intestinal symptoms, decreased consciousness, convulsions, meningitis, severe malaria, cardiac anomaly.⁴ 'Very severe pneumonia' with co-morbidity of at least two other organ systems or with circulatory failure.

⁵ Includes 4 status epilepticus, 2 lidocaine overdoses, one phenobarbital overdose and one tracheomalacia.

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Table 2

No. (%) of patients who survived or died by HIV status and diagnosis category

		Uncomplicated	Cardiac failure	Respiratory depression	Two-organ failure	Multi-organ failure	Total
HIV-uninfected	Survived	9 (75)	1 (100)	4 (100)	5 (56)	0	19 (70)
	Died	3 (25)	0	0	4 (44)	1 (100)	8 (30)
HIV-affected*	Survived	4 (57)	0	0	2 (33)	0	6 (35)
	Died	3 (43)	0	1 (100)	4 (67)	3 (100)	11 (65)
Unknown HIV status	Survived	6 (86)	1 (50)	3 (100)	3 (38)	3 (23)	16 (48)
	Died	1 (14)	1 (50)	0	5 (62)	10 (77)	17 (52)
Total	Survived	19 (73)	2 (67)	7 (88)	10 (43)	3 (18)	41 (53)
	Died	7 (27)	1 (33)	1 (12)	13 (57)	14 (82)	36 (47)

Uncomplicated pneumonia: 6 HIV-exposed (4 survived, 2 died) and 1 HIV-infected (died). Respiratory depression: 1 HIV-infected. Two-organ failure: 4 HIV-exposed (1 survived, 3 died) and 2 -infected (1 survived, 1 died). Multi-organ failure: 3 HIV-exposed.

Table 3

Short-term physiological benefit of bCPAP in 77 patients with recorded outcomes

	Before bCPAP Mean (SD)	1–6 hours after bCPAP commenced Mean (SD)	Difference Mean (95% CI)	P-value
SpO ₂ , <i>n</i> = 34 [*]	92.1 (7.8)	96.1 (10.6)	4.0 (0.7–7.2)	0.02
Respiratory rate, <i>n</i> = 22 [†]	61.0 (18.9)	49.5 (17.5)	–11.4 (–5.5–17.3)	0.0006

^{*} 43 patients did not have both pre- and post-SpO₂ measurements;

[†] 55 patients did not have both pre- and post-respiratory rate measurements.