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Effectiveness of bubble continuous positive airway pressure for treatment of children aged 1–59 months with severe pneumonia and hypoxaemia in Ethiopia: a pragmatic cluster-randomised controlled trial

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Contributors

All authors conceptualised the study and developed its design. All authors collected data. Data curation was done by MFK, TB, MG, KH, MTF, MK, MSh, BS, and MJC. Data validation was done by MFK, TB, and MSh. MFK, MG, KH, JDC, and MJC analysed the data. MG, MJC, KH, MTF, MK, and JDC wrote the first draft of the manuscript. All authors critically reviewed the manuscript. MG, MJC, and MFK directly accessed and verified the underlying data reported in the manuscript. Funding acquisition was done by JDC, MJC, TA, TTB, and AA. JDC, TD, TA, and MJC supervised the overall study activities, data analysis, and drafting and finalising of the manuscript. All authors contributed to the writing of the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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Summary

Background—The safety and efficacy of bubble continuous positive airway pressure (bCPAP) for treatment of childhood severe pneumonia outside tertiary care hospitals is uncertain. We did a cluster-randomised effectiveness trial of locally made bCPAP compared with WHO-recommended low-flow oxygen therapy in children with severe pneumonia and hypoxaemia in general hospitals in Ethiopia.

Methods—This open, cluster-randomised trial was done in 12 general (secondary) hospitals in Ethiopia. We randomly assigned six hospitals to bCPAP as first-line respiratory support for children aged 1–59 months who presented with severe pneumonia and hypoxaemia and six hospitals to standard low-flow oxygen therapy. Cluster (hospital) randomisation was stratified by availability of mechanical ventilation. All children received treatment in paediatric wards (in a dedicated corner in front of a nursing station) with a similar level of facilities (equipment for oxygen therapy and medications) and staffing (overall, one nurse per six patients and one general practitioner per 18 patients) in all hospitals. All children received additional care according to WHO guidelines, supervised by paediatricians and general practitioners. The primary outcome was treatment failure (defined as any of the following: peripheral oxygen saturation <85% at any time after at least 1 h of intervention plus signs of respiratory distress; indication for mechanical ventilation; death during hospital stay or within 72 h of leaving hospital against medical advice; or leaving hospital against medical advice during intervention). The analysis included all children enrolled in the trial. We performed both unadjusted and adjusted analyses of the primary outcome, with the latter adjusted for the stratification variable and for the design effect of cluster randomisation, as well as selected potentially confounding variables, including age. We calculated effectiveness as the relative risk (RR) of the outcomes in the bCPAP group versus low-flow oxygen group. This trial is registered with ClinicalTrial.gov, NCT03870243, and is completed.

Findings—From June 8, 2021, to July 27, 2022, 1240 children were enrolled (620 in hospitals allocated to bCPAP and 620 in hospitals allocated to low-flow oxygen). Cluster sizes ranged from 103 to 104 children. Five (0·8%) of 620 children in the bCPAP group had treatment failure compared with 21 (3·4%) of 620 children in the low-flow oxygen group (unadjusted RR 0·24, 95% CI 0·09–0·63, p=0·0015; adjusted RR 0·24, 0·07–0·87, p=0·030). Six children died during hospital stay, all of whom were in the low-flow oxygen group (p=0·031). No serious adverse events were attributable to bCPAP.

Interpretation—In Ethiopian general hospitals, introduction of locally made bCPAP, supervised by general practitioners and paediatricians, was associated with reduced risk of treatment failure and in-hospital mortality in children with severe pneumonia and hypoxaemia compared with use of standard low-flow oxygen therapy. Implementation research is required in higher mortality settings to consolidate our findings.

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Introduction

Pneumonia is the leading infectious cause of death in children younger than 5 years, estimated to have caused 740 000 deaths worldwide in 2019.[1] Most deaths from pneumonia occurred in sub-Saharan Africa and southeast Asia.[2] In Ethiopia, pneumonia accounts for 18% of all deaths in children younger than 5 years.[3] Hypoxaemia is the major risk factor for death from pneumonia,[4] increasing the risk up to five times that of children without hypoxaemia.[2] However, hypoxaemia is often poorly managed in resource-limited settings,[5] and many hospitals have high case fatality rates despite availability of WHO-recommended oxygen therapy—ie, oxygen therapy through binasal cannula at 1–2 L/min for infants, and to a maximum of 4 L/min for older children (low flow).[6]

A systematic review of ten studies showed that use of bubble continuous positive airway pressure (bCPAP) for treatment of neonates with severe pneumonia was beneficial and recommended an efficacy trial with bCPAP in children with severe pneumonia and hypoxaemia beyond the neonatal period.[7] In children with pneumonia, bCPAP can increase functional residual lung capacity above alveolar closing capacity, thereby recruiting collapsed alveoli and reducing ventilation–perfusion mismatch, thereby reducing hypoxaemia and the work of breathing and supporting respiration.[8] On the basis of the knowledge gap identified by that systematic review, a trial was done in children beyond the neonatal age (up to 5 years) in a tertiary hospital in Bangladesh, which showed that bCPAP, when supervised by physicians, was safe and associated with improved outcomes compared with standard low-flow or high-flow oxygen therapy.[8,9] In addition to severe pneumonia and hypoxaemia, the children in that study had the comorbidities of severe acute malnutrition, severe sepsis, or diarrhoea. The locally made bCPAP used in the trial was evaluated by a locally qualified bioengineer and was found to generate continuous positive end-expiratory pressure (PEEP) and the depth of the tubing in the bottle was almost consistent with the PEEP generated to the patient (unpublished).

In a subsequent trial in children aged 1 month to 5 years with undifferentiated respiratory distress in two non-tertiary hospitals in Ghana, the primary analysis showed no difference in mortality between children assigned to a validated commercial bCPAP versus children in the control group (relative risk [RR] 0·67, 95% CI 0·42–1·08; p=0·11); however a post-hoc analysis in children younger than 1 year showed fewer deaths in the bCPAP group than in the control group (RR 0·42, 95% CI 0·19–0·82; p=0·01).[10] The children in the study were supervised by physicians and had malaria, pneumonia, or sepsis.

However, in another trial in Malawi in non-tertiary hospitals without supervision of physicians, use of validated commercial bCPAP was associated with increased mortality in high-risk children with severe pneumonia compared with low-flow oxygen therapy.[11] In that study, children not only had severe pneumonia, but also had the comorbidities of severe acute malnutrition, HIV infection or HIV exposure, or hypoxaemia. A systematic review and meta-analysis that exclusively included these three trials showed that the data for the use of bCPAP have overall low certainty for a mortality benefit, and hospitals introducing CPAP need to have a facilitated location of continuous monitoring by adequately trained staff in CPAP use with daily supervision of physicians and quality of care.[12]

In low-income and middle-income countries such as Ethiopia, there is a need for simple and cost-effective methods for the management of hypoxaemia outside of tertiary hospitals, where most children with severe pneumonia are treated. We first showed the feasibility and acceptability of bCPAP in the care of children with severe pneumonia and hypoxaemia in a study in two tertiary and two general hospitals in Ethiopia.[13] In the study, the clinicians and mothers invariably expressed that bCPAP was simple to handle, there were no adverse events, children had rapid recovery, and there was reduced bed occupancy; thus, bCPAP has the potential to be cost-effective. We therefore did a multihospital effectiveness trial to assess the effect of bCPAP in children aged 1–59 months with severe pneumonia and hypoxaemia under the supervision of general practitioners and paediatricians in general hospitals in Ethiopia.

Methods

Study design

This was an open, pragmatic, cluster-randomised controlled trial in children with severe pneumonia and hypoxaemia. Because our previous efficacy trial in Bangladesh included children in a head-to-head design,[8] to align with ethical considerations, this trial was done with a cluster design. The trial was approved by the Ethical Review Committees of the International Centre for Diarrhoeal Disease Research, Bangladesh, and the Armauer Hansen Research Institute Ethics Review Committee (protocol PO/32/17), the National Research Ethics Review Committee of Ethiopia, and the Ethiopian Food and Drug Authority. The trial was monitored by an external data safety and monitoring board and a clinical monitor. The trial protocol has been published elsewhere.[14]

Study setting

The trial was done in secondary (general) public hospitals (clusters) located in Amhara, Oromia, and South regions and Dire Dawa and Addis Ababa city administrations in Ethiopia. Children in all the selected hospitals are treated by general practitioners supervised by paediatricians. The children in the study were managed in a section of the paediatric ward in front of the nursing station. Hospitals in both bCPAP and low-flow oxygen groups delivered care in the same context with the same staffing levels and equal oxygen supply and equipment maintenance at all hospitals. Overall, the nurse-to-patient ratio was one nurse per six patients, and the general practitioner-to-patient ratio was one general practitioner per 18 patients. Other characteristics of the hospitals were similar and described elsewhere.[14] Treatment of children with severe pneumonia and hypoxaemia, including intravenous antibiotics and other supportive care, in all hospitals followed WHO guidelines.[15] Supportive care included feeding through a nasogastric tube and airway suctioning for those who had airway secretion or nasal blockage. Staff coverage during weekends was similar across all study hospitals (one nurse per nine patients; one general practitioner per 18 patients). Daily monitoring of vital signs of the paediatric patients was done by nurses (8 h shift duties) and general practitioners (morning and night) with direct supervisory clinical rounds by paediatricians in the paediatric wards. All patients apart from children with severe acute malnutrition were charged for the cost of the treatment, which is the typical situation across general hospitals in Ethiopia.

Low-flow oxygen therapy via nasal prongs was the primary method of oxygen delivery in all the hospitals before the study. Six of the general hospitals had intensive care units (ICUs) and mechanical ventilators in the ICU. Mechanical ventilation was considered only for patients with treatment failure and patients who did not respond to escalated treatment, following standard treatment protocols of the hospitals.[14] Nurses and doctors in hospitals with availability of mechanical ventilation were trained in ICU care. In general hospitals without mechanical ventilation, children who required increased respiratory support beyond low-flow oxygen therapy were referred to nearby tertiary hospitals that had ICUs. The referral was done using public transport and the proximity of tertiary hospitals to hospitals without mechanical ventilation varied from 50 km to 100 km.

Participants

Children aged 1–59 months were potentially eligible if they presented with severe pneumonia and hypoxaemia, defined according to 2013 WHO criteria.[15] Patients were enrolled any time during the study period after informed consent was obtained. Severe pneumonia was defined as cough or difficulty in breathing and any of the following danger signs: hypoxaemia or central cyanosis, grunting respiration, inability to breastfeed or drink, lethargy or reduced level of consciousness, or convulsions. Hypoxaemia was defined as oxygen saturation less than 90% at room air measured by pulse oximeter (NT1D Vital Signs Monitor, Solaris Medical, San Francisco, CA, USA) using a paediatric sensor (Pediatric SpO_2 Finger Sensor-160108, Solaris Medical). Pulse oximetry was used as a spot check for oxygen saturation measurement and removed from participants between measurements, then replaced again for spot checks at 4-h intervals for the first 24 h and 8-h intervals for the rest of the follow-up period. Additionally, other vital signs including respiratory rate, pulse rate, and temperature were checked manually during the same intervals. All the sites included in our study were located at an altitude of less than 2500 m, which justifies the definition of hypoxaemia requiring supplemental oxygen for our trial. Chest radiograph was not done routinely because all children were treated on the basis of clinical diagnosis. However, chest radiograph was done if any danger sign did not improve within 24 h of the intervention (bCPAP or low-flow oxygen), or if there was any suspicion of complication such as pleural effusion. Interpretation of chest radiograph was done by a radiologist of the study hospitals. We excluded children who had any one of the following: congenital heart disease, asthma, upper airway obstruction, tracheostomy, pneumothorax, or requirement for mechanical ventilation at admission as decided by the clinician. The indication for mechanical ventilation followed in all study hospitals is provided in the appendix (pp 2–3). Written informed consent was obtained from the child's parent or carer. Before enrolling patients in the study, we did a run-in period in which two patients were enrolled from each hospital to further familiarise the staff with the study procedures; these patients were not included in the analysis of the trial. Before the run-in period, hands-on training of paediatricians, general practitioners, and nurses was provided on screening, consent, enrolment, and management of severe pneumonia and hypoxaemia using bCPAP and low-flow oxygen therapy.

Quality control in adherence to the protocol was strictly maintained. The investigators made regular monitoring visits every 1–2 months to the sites. During these visits, they assessed the clinical signs of enrolled patients, checked for appropriate recording in the case report form, and checked for adherence to the protocol. During the visits, the investigators provided additional onsite training to nurses and doctors in knowledge and skills in areas requiring improvement. Moreover, there was a study clinical monitor from the Armauer Hansen Research Institute (Addis Ababa, Ethiopia) who made monthly visits to all hospitals to assess adherence to the protocol. All these measures helped to ensure the standardisation of identification of clinical signs by physicians and paediatricians. Physicians and paediatricians were given hands-on training in identification of clinical signs including respiratory distress, and a run-in period was done to certify that staff at the study sites had adequate clinical skills before study onset.

All study hospitals routinely screen the HIV status of children younger than 5 years (HIV infection and HIV exposure) in accordance with the Ethiopian National Guidelines for Comprehensive HIV Prevention, Care and Treatment,[16] and none of the enrolled patients had documentation of HIV infection or exposure. Malaria was screened for according to the Ethiopia Malaria Elimination Strategic Plan: 2021–2025.[17]

Randomisation and masking

The 12 hospitals, each a cluster, were stratified by the availability of mechanical ventilation in the ICU. Within each stratum, hospitals were allocated in blocks of two to either bCPAP or low-flow oxygen therapy by an independent statistician using a table of random numbers. Accordingly, three hospitals in the bCPAP group and three hospitals in the low-flow oxygen group had mechanical ventilators. Each eligible, enrolled child received the mode of oxygen support assigned to the hospital. Because of the nature of the intervention, masking of participants and investigators was not possible. Data analysts were masked to allocation group.

Procedures

In hospitals assigned to bCPAP, the bCPAP was assembled on site using standard nasal oxygen prongs (Ventlab, Mocksville, NC, USA), plastic tubing normally used for administration of intravenous fluids (Opso Saline, Dhaka, Bangladesh), and a transparent plastic bottle filled with water to the 10 cm mark. Inspiratory gas flow was provided by oxygen concentrators (230 V, 50 Hz, 3·2 A; DeVilbiss Healthcare, Port Washington, NY, USA), with backup oxygen cylinders in the event of malfunction of the oxygen concentrators or interruption of electricity.[7]

For all enrolled children in the bCPAP group, bCPAP was initiated at a depth of 5 cm below the water level inside the plastic bottle into which the expiratory tubing was inserted and with 5 L/min of oxygen delivered from the oxygen source. If a peripheral oxygen saturation (SpO_2) of 90% or more was not achieved within 5 min, both the depth of the expiratory tubing and oxygen flow were titrated every 5 min (at 1 cm and 1 L/min each time up to a maximum of 10 cm and 10 L/min oxygen flow) to achieve SpO_2 of 90% or more.

A bioengineer from the Bangladesh University of Engineering and Technology (Dhaka, Bangladesh) tested the PEEP of our locally made bCPAP on five healthy volunteers and found it to have effective PEEP (using digital manometer, model 82 152, AZ Instrument Corp, Taichung City, Taiwan; 15 pounds per square inch with a mean pressure that was overall within 12% of target pressure; unpublished data).

In the low-flow oxygen group, flow was started at 1 L/min and increased every 5 min up to a maximum of 2 L/min for children 1 month to 2 years and 4 L/min for children older than 2 years to achieve SpO_2 of 90% or more. Reassessment was done at 1 h and 4 h after initiation, then, for patients who responded, every 4 h during the first 24 h, followed by every 8 h. During each follow-up, children in both treatment groups received normal saline drops in their nostrils to keep the nostril mucosa moist, because neither of the study interventions included heated humidification. A colour-coded paediatric monitoring and

response chart was introduced in all study hospitals to enable early identification of patients who were deteriorating.

For participants who had SpO_2 85–89%, systematic actions included checks for oxygen flow, any leakage in the circuit, nasal prong fitting, and nasal congestion in both groups, and for presence of bubbling in the water bottle in the bCPAP group. If any problems were detected, relevant corrective measures were taken. If such problems were not evident, PEEP of the bCPAP was increased from 5 cm to 6 cm water pressure with simultaneous increase of oxygen flow from 5 L/min to 6 L/min up to a maximum of 10 cm PEEP and 10 L/min oxygen flow. Low-flow oxygen was also gradually escalated to a maximum of 2 L/min for children younger than 2 years and 4 L/min for children 2 years or older. Each titration was observed by physician or nurse for 5 min in both study groups. However, if there was still no improvement in SpO_2, we started nasal suctioning if there was airway secretion or nasal blockage, salbutamol nebulisation if there was prolonged expiratory rhonchi, and fluid bolus if there were features of shock (cold periphery; rapid, thready, or absent pulse; or delayed capillary refilling time). In both groups, for children with treatment failure, the same procedure was followed before declaring the treatment failure. Children with treatment failure were put on either high-flow oxygen (5–10 L/min) with face mask, bCPAP oxygen therapy, or mechanical ventilation according to the judgement of the paediatrician of the hospital, and availability of equipment. Additionally, antibiotics were changed in all children with treatment failure.

Feeding was offered during the assessment; if unable to take food, the child was categorised as unable to feed and put on nasogastric tube feeding until they were able to take oral feed.

For both treatment groups, during the routine assessment of vital signs, if the patient's SpO_2 was 90% or more and they had no respiratory difficulty for more than 15 min without intervention (bCPAP or low-flow oxygen), the intervention was discontinued.

Outcomes

The original primary outcome of the trial was death. However, after analysis of the findings from the feasibility and acceptability study[13] by the regulatory authority in Ethiopia, initiation of the cluster-randomised controlled trial was only approved in the hospitals staffed by paediatricians. Thus, the intended number of study hospitals was reduced from 20 to 12. Before the commencement of the cluster-randomised controlled trial, the case fatality rate recorded over a 12-month period in the 12 study hospitals was low (37 [0·8%] deaths in 4890 admissions).[14] The primary outcome was changed from death to treatment failure to attain adequate power for the study.[14] The definition of treatment failure during calculation of the revised sample size and during the randomised controlled trial remained the same. These changes were made after discussion with the data and safety monitoring board of the study.

The composite primary outcome of treatment failure was defined as any of the following: (1) presence of severe hypoxaemia (SpO_2 <85%)[8] at any time after at least 1 h of intervention (bCPAP or low-flow oxygen) plus signs of respiratory distress such as age-specific fast breathing,[15] nasal flaring, chest-wall indrawing, head nodding, cyanosis,

grunting respiration, or apnoea; (2) development of an indication for mechanical ventilation; (3) death during hospital stay or within 72 h of leaving hospital against medical advice; or (4) leaving hospital against medical advice while still on study intervention (bCPAP or low-flow oxygen). Indication for mechanical ventilation included clinical worsening (increased work of breathing and severe hypoxaemia, SpO_2 <85%) while on bCPAP or low-flow oxygen therapy (after at least 1 h); respiratory failure (apnoea or respiratory arrest); inadequate ventilation or inadequate oxygenation; cardiac insufficiency or shock; or neurological dysfunction (central hypoventilation or frequent apnoea, Glasgow Coma Scale <8, and inability to protect airway).

All participants who left hospital against medical advice with their parents or carers were contacted by site study staff via telephone or home visit to identify the final outcome of each child and to provide treatment and support where possible.

The main secondary outcome was death during hospital stay. Other secondary outcomes were death within 72 h of leaving hospital against medical advice; pneumothorax; aspiration pneumonia; incidence of nasal trauma, abdominal distension, septic shock, or air leaks; duration of bCPAP and low-flow oxygen therapy; length of hospital stay; and time from decision to start bCPAP to time of start of bCPAP.

Statistical analysis

Sample size estimation was based on the following assumptions. First, the 12 hospitals would enrol approximately the same number of eligible patients and six hospitals would be allocated to each group. Second, on the basis of earlier data from the hospitals, the risk of treatment failure in children in the low-flow oxygen group would be 10%. Third, there would be a 50% reduction in risk of treatment failure in children in the bCPAP group compared with the low-flow oxygen group. We aimed to explore this difference with 80% power at p<0·05, two-tailed, and we adjusted for an intracluster correlation coefficient of 0·003. With these assumptions, 620 participants were required in each treatment group. To enrol the same number of patients (n=620) in each group, we decided to stop enrolment in each hospital after enrolment of 104 children for the initial two hospitals started on protocol, followed by 103 children for the remaining hospitals in each group.

We analysed the data with Stata version 15. Baseline categorical variables were compared between groups using χ^2 test, or Fisher's exact test when assumptions for the χ^2 test were not fulfilled. Comparisons of continuous variables were analysed with the independent sample *t* test, or the Mann–Whitney test when parametric assumptions were not met. In crude (unadjusted) analysis, we estimated RR of the primary and secondary outcomes in the bCPAP versus low-flow oxygen groups and estimated p values and their 95% CIs using test-based methods. Log-linear binomial regression was applied to assess RRs for the association between treatment group and primary and secondary outcomes after adjusting for potential confounders. The potential confounders were those that were significantly associated with treatment failure using bivariate unadjusted analysis and other biologically plausible clinical parameters such as male sex, age, immunisation as per Ethiopian National Expanded Programme on Immunisation schedule, severe acute malnutrition, severe hypoxaemia, severe sepsis, respiratory rate, and temperature. The variable used to stratify randomisation of the

hospitals (ie, availability of mechanical ventilation) was included as an independent variable in all models. The inclusion of mechanical ventilation in models for assessing interventional impact derives from the statistical necessity for including all stratification variables in models when stratified randomisation is used in trials.[18] The models were also adjusted for the design effect of cluster randomisation using a robust sandwich variance estimator. To avoid overfitting the models, we limited the number of independent variables to the number of outcomes divided by ten, and for outcomes with fewer than ten events, we did unadjusted analysis only.[19] As a result, in each model we included a total of three independent variables that included randomly assigned treatment, availability of mechanical ventilation, and one potential confounder. $p<0·05$ (two-sided) was taken as the threshold of statistical significance. This study is registered with ClinicalTrials.gov, number NCT03870243.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 8, 2021, and July 27, 2022, 1974 children aged 1–59 months admitted to hospital with severe pneumonia and hypoxaemia were assessed for eligibility. 682 (34·5%) children did not meet the study inclusion criteria and parents or carers of 52 (2·6%) children did not give consent to participate (figure). The reasons for exclusion are provided in the appendix (p 5). Of the 1240 (62·8%) children who met the inclusion criteria and whose parents or carers provided informed consent, 620 children were in hospitals allocated to receive bCPAP for provision of oxygen therapy and 620 were in hospitals allocated to low-flow oxygen therapy (range of participants per hospital 103–104). All allocated children completed the interventions at least up to the assessment of the study outcomes. All enrolled children were included in the final analyses (figure).

Children in the treatment groups were similar at baseline with respect to their distributions by age, sex, mean temperature, mean respiratory rate, immunisation status, and proportion of children with severe acute malnutrition (weight-for-length or weight-for-height Z score <−3·0, mid-upper arm circumference less than 11·5 cm for children 6–59 months, or nutritional oedema), features of severe sepsis, or malaria (table 1). Compared with the low-flow oxygen group, the bCPAP group had a higher proportion of children with some features indicative of more severe illness (inability to feed, dehydration, lethargy or unconscious, lower oxygen saturation [SpO_2 (%) measured by pulse oximeter in room air], cyanosis, abnormal chest radiograph, and general danger signs [inability to feed, lethargy or unconscious, or convulsion]), and a lower proportion of children with other severity features (chest-wall indrawing, lower weight, grunting respiration, a history of convulsions, and respiratory distress [severe lower chest-wall indrawing, head nodding, tracheal tugging, grunting, or apnoea]). None of the study participants had HIV infection or HIV exposure.

Five (0·8%) of 620 children in the bCPAP group had treatment failure compared with 21 (3·4%) of 620 children in the low-flow oxygen group (unadjusted RR 0·24, 95% CI 0·09–0·63, p=0·0015; table 2). In the multivariable models, we adjusted the base model for all the

covariates individually, irrespective of having imbalance in the baseline analysis; significant reduction in treatment failure was seen in each of the models (table 3). Our base model includes outcome (treatment failure) and intervention (bCPAP *vs* low-flow oxygen) adjusted for the availability of mechanical ventilation. Six children died during hospital stay, all of whom were in the low-flow oxygen group (p=0·031; table 2). Four deaths were in hospitals with availability of mechanical ventilation and two were in hospitals without availability of mechanical ventilation. Eight children still receiving their assigned intervention left hospital against medical advice with their parents or carers (three in the bCPAP group and five in the low-flow oxygen group). Of these, the outcome of two children in the bCPAP group and three children in the low-flow oxygen group was not known because of loss to follow-up. Of those with known outcome, one child in each group died within 72 h after leaving hospital against medical advice (RR for death during hospital stay or known death within 72 h of leaving hospital against medical advice 0·14, 95% CI 0·02–1·16, p=0·069; table 4).

All children with treatment failure (apart from eight children who left hospital against medical advice and two children in the bCPAP group) discontinued the intervention (16 in the low-flow oxygen group). Of these, two were put on bCPAP and 14 on high-flow oxygen 10 L/min by face mask using an oxygen cylinder; ten children improved, and five children died. One child in the low-flow oxygen group was put on mechanical ventilation after no improvement with escalated oxygen using bCPAP but died. No other child with initial treatment failure could be placed on mechanical ventilation because the mechanical ventilators were occupied by other patients. Because of unavailability of mechanical ventilators, treatment with bCPAP was continued (with a PEEP of 10 cm water pressure and 10 L/min oxygen) in two children after declaration of treatment failure in the bCPAP group; SpO_2 gradually improved and both children survived.

For children who were discharged, the median duration of initial respiratory support was 24 h (IQR 20–32) in the bCPAP group, and 32 h (24–48) in the low-flow oxygen group (p<0·0001). The median length of hospital stay was 53·0 h (IQR 44·9–76·0) in the bCPAP group and 62·2 h (IQR 44·5–96·0) in the low-flow oxygen group (p=0·024; table 4).

24 children (two in each hospital, thus, 12 in each group) were enrolled during the run-in period. One child in the bCPAP group and two children in the low-flow oxygen group had treatment failure, of whom one died in each group. Median duration of intervention was significantly lower in the bCPAP group compared with the low-flow oxygen group (39 h [IQR 22–59] *vs* 75 h [46–109], p=0·019).

In the bCPAP group, one child developed abdominal distension, and another child developed heart failure. In the low-flow oxygen group, two children had nasal obstruction, one had nasal trauma, and one had heart failure. No nasal bleeding, aspiration pneumonia, or pneumothorax was observed in either group (appendix p 4). No serious adverse events were attributed to bCPAP.

Discussion

This cluster-randomised trial found that in hospitals where children received low-cost bCPAP run by oxygen concentrators, there was a significantly lower probability of treatment failure and death (during hospital stay) than in hospitals where children received standard low-flow oxygen as the primary therapy for severe pneumonia and hypoxaemia. Additionally, the proportion of children who died during hospital stay or within 72 h of leaving hospital against medical advice was 0·2% in the bCPAP group compared with 1·1% in the low-flow oxygen group; however, the difference between groups was not significant. In settings with paediatricians and general practitioners to supervise care, bCPAP oxygen therapy was not associated with clinically significant adverse effects.

Several non-randomised studies[20,21] have reported that bCPAP has a positive effect on outcomes of severe pneumonia in low-income and middle-income countries. To date, only three randomised trials have been reported.[8,10,11] The results of our trial, which showed a reduction in treatment failure in the bCPAP group compared with the low-flow oxygen group (RR 0·24, 95% CI 0·09–0·63) and an RR for mortality during hospital stay or within 72 h of leaving hospital against medical advice of 0·14 (95% CI 0·02–1·16), are consistent with randomised trials of oxygen therapy for pneumonia in Bangladesh and Ghana,[8,10] both of which were done in well equipped hospital settings with highly trained physicians and nurses, supervised by paediatricians. In the Bangladesh trial that was done in a tertiary care hospital, mortality and treatment failure were reduced in the bCPAP group compared with the low-flow oxygen group (mortality RR 0·25, 95% CI 0·07–0·89; treatment failure RR 0·27, 99·7% CI 0·07–0·99).[8] In the Ghana trial that was done in two non-tertiary care hospitals, a subgroup analysis in infants younger than 1 year showed a reduced risk of mortality in those who received bCPAP compared with those who received low-flow oxygen therapy (RR 0·40, 95% CI 0·19–0·82). By contrast, another trial in Malawi reported no mortality benefit of bCPAP. The trial in Malawi was done in settings where clinical care was overseen by trained nurses, with telephone consultation of paediatricians. Our findings extend those of the Bangladesh and Ghana trials by demonstrating the utility and impact of bCPAP even in non-tertiary, general care settings staffed by paediatricians. The simplicity of the method of giving CPAP in our trial compared with conventional commercial CPAP used in the trials in Malawi and Ghana could be important; in the method in our trial, the nasal interface is similar to standard oxygen prongs, and therefore familiar to healthcare workers, and children's tolerance of the interface and therapy might be better than with other CPAP interfaces, such as tight-fitting masks which often require sedation in older infants. Therefore, the safety and efficacy of CPAP in non-tertiary settings might be technique dependent, as well as requiring a high-quality level of monitoring and supportive care administered by trained nurses and general practitioners, supervised by paediatricians.

In addition to the locally made bCPAP being simple to handle, the cost of equipment (excluding oxygen source) required to make the device was less than US$2, whereas the cost of conventional commercial bCPAP ranges from $5000 to $18 000. Moreover, all the study hospitals received similar support with human resources, monitoring, and oxygen concentrators. Oxygen concentrators deliver the cheapest and most consistent source of oxygen in resource-limited settings where power supplies are reliable.[22] Furthermore,

children who received bCPAP required significantly shorter duration of intervention and hospital stay compared with those who received low-flow oxygen therapy, although children in the bCPAP group received higher flow of oxygen. Thus, the simplicity and low cost of the locally made bCPAP device, run by the cheapest oxygen source, requiring shorter duration of oxygen therapy as well as hospital stay, made it more accessible and affordable for hospitals in low-resource settings. However, a cost-effectiveness analysis of bCPAP oxygen therapy compared with low-flow oxygen therapy from this study will provide more comprehensive and definite results for the affordability and sustainability of bCPAP in these settings.

The overall mortality in this study was low: eight deaths in 1240 children with severe pneumonia and hypoxaemia (case fatality rate 0·6%), which is similar to the baseline case fatality rate recorded over a 12-month period in the 12 hospitals (37 [0·8%] deaths in 4890 admissions). The good quality of care with daily follow-up and monitoring both by nurses and general practitioners with the direct, daily supervision of paediatricians might be one of the reasons for overall low mortality. A very low prevalence of HIV (<1%)[23] and malaria,[24] and a low rate of malnutrition in children younger than 5 years might also be reasons for the overall low mortality in the study population. However, all the hospitals charge treatment cost to all patients apart from those who have severe acute malnutrition. Although this is common practice for all general hospitals in Ethiopia, it is still possible that the cost of treatment might have deterred some caregivers from bringing children to the study hospitals.

In settings with limited resources, WHO and UNICEF recommend one option of oxygen therapy to be from an oxygen concentrator, and that delivery from a single concentrator can occur by splitting the flow to as many as five children using a device with precise flow measures.[25] However, validated flow splitters are not available in Ethiopian hospitals, so the safety of splitting oxygen flow from a single source cannot be assured. Therefore, to maintain effective flow of oxygen in bCPAP as well as low-flow oxygen therapy, we used one oxygen concentrator for one patient for our study populations.

Oxygen security is a huge concern to running both the interventions included in this trial, especially in low-income and middle-income countries. However, during COVID-19, with the help of local government, most of the secondary hospitals in Ethiopia and other low-income and middle-income countries including Bangladesh substantially improved oxygen security.[26,27] The number of secondary hospitals with available paediatricians and oxygen security is increasing[28] because of greater political commitment. Thus, in the present scenario, with these trends in low-income and middle-income countries in Asia and sub-Saharan Africa, we believe that our findings are generalisable to many hospitals at present and will be generalisable to many more hospitals in the near future.

Potential limitations require consideration. First, our trial was open, and entailed no masking of physicians or participants. This could have resulted in differential enrolment of patients in the different hospitals. However, the rates of refusal of participation were low and similar in both groups, and although there were some imbalances between the groups in baseline characteristics, bCPAP seemed to confer better outcomes across each of the objective criteria of our composite primary outcome even after adjusting for all the imbalances

observed in baseline characteristics, thus making it unlikely that subjective judgement made by unmasked physicians biased the study. Second, although this was conducted as an effectiveness trial, the study ensured adequate supply and maintenance of supplies and equipment for oxygen delivery, which might have exceeded the support available in routine public health practices in Ethiopia. Third, although this trial was designed to understand the overall effectiveness of bCPAP oxygen therapy compared with low-flow oxygen therapy, further study is required to identify the subset(s) of children likely to benefit most from bCPAP. Fourth, in Ethiopia, many patients treated for severe pneumonia and hypoxaemia are seen in front-line hospitals staffed only by general practitioners. Whether our study findings derived from hospitals where care was supervised by paediatricians will apply to all front-line hospitals with higher mortality settings, including settings with different rates of comorbidities, will require further study.

bCPAP oxygen therapy used in this trial is validated to generate adequate PEEP (unpublished data); however, it is unclear whether the observed clinical benefit was because of a PEEP effect or just higher flow rate of oxygen (children on bCPAP received 5–10 L/min, compared with 2 L/min up to a maximum of 4 L/min in the low-flow oxygen group), or because of a combination of both CPAP and higher flow of oxygen. Nevertheless, the growing evidence on the clinical benefit of bCPAP oxygen therapy from low-income and middle-income countries in Asia and sub-Saharan Africa suggests that bCPAP should be available for the care of severe childhood pneumonia and hypoxaemia in settings able to provide sufficient monitoring, staffing, and paediatrician supervision. A cost-effectiveness analysis of bCPAP oxygen therapy is the next key step to be done before the nationwide scale-up of bCPAP oxygen therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

After publication, de-identified data will be made available to interested researchers for secondary data analysis upon approval of a Data Licensing Application and Agreement by the icddr,b Data Centre Committee (Dhaka, Bangladesh), and Ethics Review Committee of the Armauer Hansen Research Institute (Addis Ababa, Ethiopia). The data request may be sent to Ms Shiblee Sayeed (shiblee_s@icddrb.org), Head, Research Administration. The study protocol, statistical analysis plan, and informed consent form are available with the published protocol (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9456562/pdf/jcm-11-04934.pdf).

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Research in context

Evidence before this study

We searched MEDLINE for articles published in any language up to April 30, 2022, with the terms (“bubble cpap” OR “bubble continuous positive airway pressure” OR “continuous positive airway pressure”) AND (“child*” OR “paediatric” OR “pediatric” OR “infant*” OR “neonate*”). Our search found that most of the evidence on the role of bubble continuous positive airway pressure (bCPAP) for treatment of severe childhood pneumonia and hypoxaemia published before the current study was from studies in neonates with respiratory distress syndrome. Our previous efficacy trial, published in *The Lancet* in 2015, was the first randomised clinical trial in children with severe pneumonia outside the neonatal period. That study was done in a tertiary hospital in a lower-middle-income country (Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh) between 2011 and 2013, and assessed the effect on mortality of oxygen therapy using locally made, low-cost bCPAP versus standard low-flow oxygen therapy and high-flow nasal cannula oxygen therapy. Two other relevant trials have also been published. One trial in Malawi showed that bCPAP was associated with increased mortality in high-risk children with severe pneumonia compared with standard-flow oxygen therapy. However, in that trial, the severely ill children were enrolled without direct monitoring by physicians. The primary analysis of another trial in Ghana with daily physician supervision and routine monitoring by nurses showed that commercial bCPAP was not superior to low-flow oxygen in reducing deaths in children aged 1 month to 5 years with undifferentiated respiratory distress. However, in a post-hoc analysis in children younger than 1 year, there were fewer deaths in the bCPAP group than in the control group. The study included children with malaria, pneumonia, and sepsis. This collective evidence showed that, with proper monitoring and other safeguards, bCPAP has the potential to be implemented in other hospitals in low-income and middle-income countries and reduce mortality from childhood pneumonia.

Added value of this study

The findings of this study show that implementation of oxygen therapy using bCPAP in general hospitals in Ethiopia, with a protocol for monitoring and follow-up by nurses supervised by general practitioners and paediatricians, was associated with reduced risk of treatment failure and mortality in children with severe pneumonia and hypoxaemia compared with standard low-flow oxygen therapy.

Implications of all the available evidence

Evolving evidence strongly suggests that if routine monitoring and follow-up of patients receiving bCPAP oxygen therapy with adherence to a protocol could be ensured by nurses overseen by qualified physicians and paediatricians, bCPAP can be implemented in general hospitals in low-income and middle-income countries, with a survival benefit in treating childhood severe pneumonia and hypoxaemia.

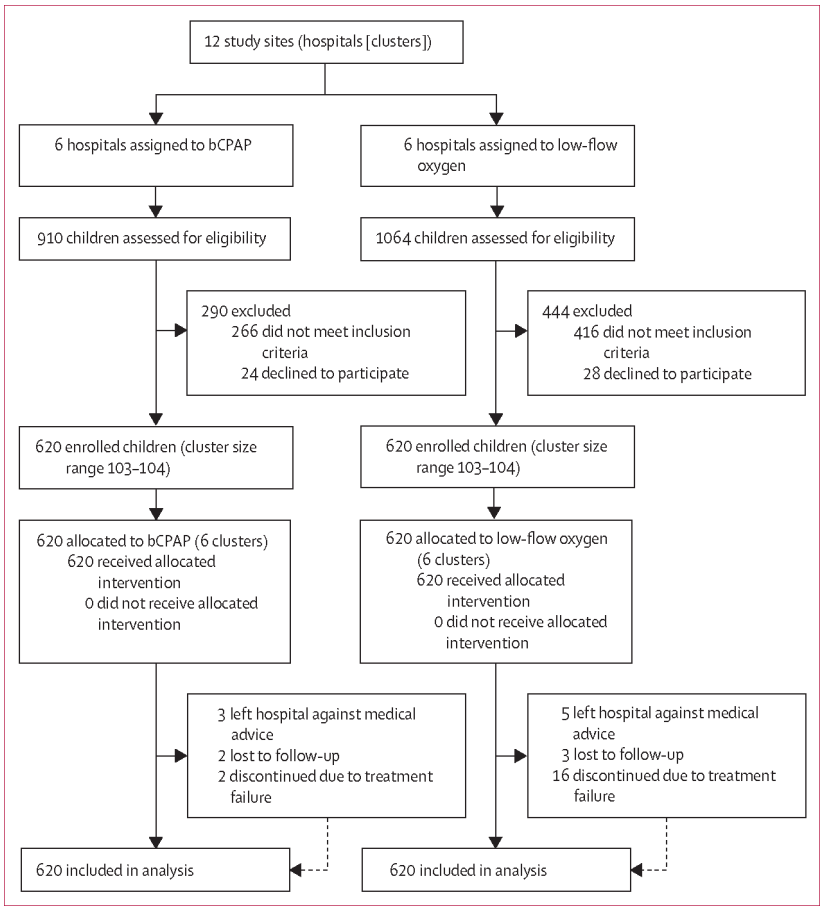

Figure: Trial profile

See appendix (p 5) for list of reasons for exclusion. bCPAP=bubble continuous positive airway pressure.

Table 1:

Baseline characteristics

	bCPAP (n=620)	Low-flow oxygen (n=620)	Total (n=1240)
Sex			
Female	263 (42·4%)	255 (41·1%)	518 (41·8%)
Male	357 (57·6%)	365 (58·9%)	722 (58·2%)
Age (months)	11·0 (5·2-19·6)	10·0 (5·7-18·2)	10·4 (5·5-18·8)
Weight (kg)	8·5 (6·8-10·5)	8·0 (6·8-10·0)	8·2 (6·8-10·0)
MUAC (cm)	13·0 (12·5-13·5)	13·5 (12·5-14·0)	13·0 (12·5-13·5)
Immunised as per EPI schedule *	558 (90·2%)	564 (91·1%)	1122 (90·6%)
Severe acute malnutrition †	90 (14·5%)	87 (14·0%)	177 (14·3%)
Severely underweight ‡	31 (5·0%)	53 (8·6%)	84 (6·8%)
Unable to feed	405 (65·3%)	297 (47·9%)	702 (56·6%)
Dehydration	79 (12·7%)	38 (6·1%)	117 (9·4%)
Chest-wall indrawing	561 (90·5%)	604 (97·4%)	1165 (94·0%)
Grunting respiration	432 (69·7%)	492 (79·4%)	924 (74·5%)
Cyanosis	47 (7·6%)	14 (2·3%)	61 (4·9%)
Oxygen saturation in room air (%)	82% (77·86)	83% (79·86)	83% (78·86)
Severe hypoxaemia (SpO_2 <85%)	409 (66·0%)	381 (61·5%)	790 (63·7%)
Adventitious sound on auscultation	499 (80·5%)	435 (70·2%)	934 (75·3%)
History of convulsion	3 (0·5%)	20 (3·2%)	23 (1·9%)
Malaria	5 (0·8%)	4 (0·7%)	9 (0·7%)
Severe sepsis	4 (0·7%)	7 (1·1%)	11 (0·9%)
Lethargy or unconscious	90 (14·5%)	48 (7·7%)	138 (11·1%)
Respiratory rate (breaths per min)	62·6 (12·0)	62·1 (11·2)	62·4 (11·6)
Temperature (°C)	37·6 (1·0)	37·6 (1·0)	37·6 (1·0)
Composite general danger sign §	414 (66·8%)	307 (49·5%)	721 (58·1%)
Composite respiratory distress ¶	598 (96·5%)	613 (98·9%)	1211 (97·7%)
Pneumonic consolidation on chest x-ray //	86 (56·6%)	60 (39·7%)	146 (48·2%)

Data are n (%), median (IQR), or mean (SD). No participants had HIV infection or HIV exposure. bCPAP=bubble continuous positive airway pressure. EPI=Ethiopian National Expanded Programme on Immunisation. MUAC=mid-upper arm circumference. SpO_2=peripheral oxygen saturation.

* bCPAP, n=619; low-flow oxygen, n=619; total, n=1238.

† Weight-for-length or weight-for-height Z score <–3·0, MUAC less than 11·5 cm for children 6–59 months, or nutritional oedema.

‡ Weight-for-age Z score <–3 following the WHO anthropometry.

§ Convulsion, feeding difficulty, or lethargy or unconscious.

¶ Severe lower chest-wall indrawing, head nodding, tracheal tugging, grunting, or apnoea.

// bCPAP, n=152; low-flow oxygen, n=151; total, n=303.

Table 2:

Primary outcomes

	bCPAP (n=620)	Low-flow oxygen (n=620)	Unadjusted RR (95% CI)*	p value*
Primary outcome criteria				
Severe hypoxaemia (SpO_2 <85%) plus respiratory difficulty after at least 1 h of intervention	2 (0·3%)	16 (2·6%)	··	··
Mechanical ventilation	0	1 (0·2%)	··	··
Death in the hospital	0	6 (1·0%)	··	··
Left hospital against medical advice while on intervention	3 (0·5%)	5 (0·8%)	··	··
Composite primary outcome†	5 (0·8%)	21 (3·4%)	0·24 (0·09-0·63)	0·0015

Data are n (%), unless otherwise stated. ··=not applicable. bCPAP=bubble continuous positive airway pressure. RR=relative risk. SpO_2=peripheral oxygen saturation.

*bCPAP versus low-flow oxygen.

†Totals exceed the sum of patients meeting individual primary outcome criteria because individual patients could have more than one primary criterion.

Table 3:

Regression results for assessing consistency of intervention effect in unadjusted and adjusted models incorporating statistical and clinical factors

	Unadjusted results of individual variables		Adjusted results of effect of intervention (bCPAP *vs* low-flow oxygen)		Adjusted results of mechanical ventilation*		Adjusted results of individual variable	
	Unadjusted RR (95% CI)	p value	Adjusted RR (95% CI)	p value	Adjusted RR (95% CI)	p value	Adjusted RR (95% CI)	p value
Effect of bCPAP without any adjustment	0·24 (0·07-0·86)	0·029	..	..	..	..	..	..
Mechanical ventilation available	0·63 (0·22-1·76)	0·37	..	..	..	..	..	..
Base model (includes outcome and intervention adjusted for mechanical ventilation)†	..	..	0·24 (0·07-0·87)	0·030	0·62 (0·29-1·35)	0·23	..	..
Extended models (base model plus additional individual variable)‡								
Age	0·91 (0·85-0·98)	0·0078	0·24 (0·06-0·93)	0·040	0·60 (0·27-1·32)	0·20	0·91 (0·85-0·98)	0·017
Sex (male)	1·15 (0·77-1·72)	0·50	0·24 (0·06-0·87)	0·030	0·62 (0·28-1·36)	0·23	1·13 (0·75-1·71)	0·55
Weight	0·73 (0·58-0·91)	0·0064	0·25 (0·06-0·96)	0·043	0·62 (0·27-1·39)	0·25	0·73 (0·58-0·93)	0·011
MUAC	0·69 (0·40-1·21)	0·20	0·31 (0·08-1·21)	0·091	1·32 (0·45-3·89)	0·61	0·69 (0·43-1·12)	0·14
Immunisation	0·28 (0·18-0·45)	<0·0001	0·23 (0·06-0·91)	0·037	0·70 (0·30-1·65)	0·42	0·29 (0·18-0·45)	<0·0001
Severe acute malnutrition	1·80 (0·59-5·48)	0·30	0·24 (0·06-0·88)	0·032	0·61 (0·27-1·36)	0·23	1·91 (0·60-6·10)	0·28
Severely underweight	4·11 (2·27-7·43)	<0·0001	0·26 (0·07-0·91)	0·036	0·67 (0·30-1·47)	0·31	3·40 (1·92-6·03)	<0·0001
Unable to feed	1·05 (0·54-2·02)	0·90	0·22 (0·06-0·85)	0·028	0·57 (0·24-1·36)	0·20	1·48 (0·90-2·43)	0·12
Dehydration	2·29 (0·68-7·71)	0·18	0·21 (0·05-0·85)	0·029	0·56 (0·24-1·33)	0·19	3·40 (1·32-8·76)	0·011
Chest-wall indrawing	1·61 (0·23-11·23)	0·63	0·24 (0·06-0·93)	0·039	0·62 (0·28-1·37)	0·24	0·93 (0·12-7·48)	0·95
Grunting	1·88 (0·77-4·59)	0·17	0·25 (0·07-0·95)	0·042	0·62 (0·29-1·35)	0·23	1·59 (0·73-3·48)	0·24
Cyanosis	0·77 (0·09-6·63)	0·81	0·23 (0·06-0·90)	0·034	0·60 (0·28-1·31)	0·20	1·56 (0·27-8·83)	0·62
SpO_2	0·97 (0·93-1·02)	0·20	0·23 (0·06-0·85)	0·027	0·63 (0·29-1·40)	0·26	0·98 (0·95-1·01)	0·24
Severe hypoxaemia	1·28 (0·40-4·09)	0·68	0·24 (0·06-0·86)	0·029	0·63 (0·29-1·38)	0·25	1·34 (0·48-3·76)	0·58
Respiratory rate	1·02 (0·99-1·04)	0·20	0·24 (0·06-0·93)	0·039	0·60 (0·26-1·34)	0·21	1·02 (0·99-1·05)	0·13
Temperature	1·22 (0·88-1·69)	0·24	0·24 (0·06-0·89)	0·032	0·62 (0·28-1·35)	0·23	1·20 (0·92-1·58)	0·18
Auscultation	1·38 (0·66-2·88)	0·40	0·23 (0·06-0·85)	0·027	0·65 (0·29-1·46)	0·29	1·55 (0·67-3·59)	0·31
Convulsion	6·90 (3·48-13·69)	<0·0001	0·26 (0·07-0·97)	0·045	0·54 (0·21-1·38)	0·20	5·86 (3·19-10·75)	<0·0001

	Unadjusted results of individual variables		Adjusted results of effect of intervention (bCPAP *vs* low-flow oxygen)		Adjusted results of mechanical ventilation*		Adjusted results of individual variable	
	Unadjusted RR (95% CI)	**p value**	**Adjusted RR (95% CI)**	**p value**	**Adjusted RR (95% CI)**	**p value**	**Adjusted RR (95% CI)**	**p value**
Sepsis	14·60 (5·47-38·9)	<0·0001	0·25 (0·07-0·88)	0·031	0·62 (0·29-1·34)	0·22	11·85 (4·66-30·09)	<0·0001
Lethargy or unconscious	3·55 (1·54-8·17)	0·0030	0·20 (0·05-0·83)	0·027	0·56 (0·23-1·38)	0·21	4·86 (2·28-10·38)	<0·0001
Danger sign	1·62 (0·87-3·01)	0·13	0·20 (0·05-0·84)	0·028	0·52 (0·19-1·38)	0·19	2·37 (1·40-4·01)	0·0014

··=not applicable. MUAC=mid-upper arm circumference. RR=relative risk. SpO_2=peripheral oxygen saturation.

*Both intervention and availability of mechanical ventilation are included in all models to ensure a more accurate estimate of their effects on the outcome. When accounting for various factors, there was no statistically significant association between the outcome and the availability of mechanical ventilation.

†The base model includes outcome (treatment failure) and intervention (bCPAP vs low-flow oxygen) adjusted for mechanical ventilation (available vs not available) and for the design effect of cluster randomisation. For the base model, the results indicate that the intervention (bCPAP) is effective in significantly lowering mortality with RR of 0·24 (95% CI 0·07-0·87) and p value of 0·030. However, mechanical ventilation was not found to be significantly associated with mortality (RR 0·62, 95% CI 0·29-1·35, p=0·23).

‡Each of the extended models in the table comprises the outcome, intervention, mechanical ventilation, and an additional potential variable. As a worked example, for base model plus age, we extended the base model by including an additional covariate, age. In this expanded model, bCPAP continued to show a significant association with reduced mortality risk (RR 0·24, 95% CI 0·06-0·93, p=0·040), age was associated with lower mortality (RR 0·91, 95% CI 0·85-0·98, p=0·017), while mechanical ventilation remained non-significant (RR 0·60, 95% CI 0·27-1·32, p=0·20).

Table 4:

Secondary outcomes

	bCPAP (n=620)	Low-flow oxygen(n=620)	Unadjusted RR (95% CI)*	p value*
Death during hospital stay	0	6 (1·0%)	··	0·031
Death during hospital stay plus death within 72 h of leaving hospital against medical advice†	1 (0·2%)	7 (1·1%)	0·14 (0·02-1·16)	0·069
Length of hospital stay (excluding leaving hospital against medical advice, h)	53·0 (44·9-76·0)	62·2 (44·5-96·0)	··	0·024
Duration of intervention (excluding leaving hospital against medical advice, h)	24 (20·32)	32 (24·48)	··	0·0001
Nasal trauma	0	1 (0·2%)	··	1·00
Abdominal distension	1 (0·2%)	0	··	1·00
Pneumothorax	0	0	··	··
Aspiration pneumonia	0	0	··	··

Data are n (%) or median (IQR), unless otherwise stated. ··=not applicable. bCPAP=bubble continuous positive airway pressure. RR=relative risk.

*bCPAP versus low-flow oxygen.

†Of children who left hospital against medical advice, the outcome of two children in the bCPAP group and three children in the low-flow oxygen group was not known because of loss to follow-up, despite repeated attempts by study personnel of the respective site and investigators to communicate with them.