A Randomized Clinical Trial Evaluating Nasal Continuous Positive Airway Pressure for Acute Respiratory Distress in a Developing Country

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Objective Invasive mechanical ventilation is often not an option for children with acute respiratory infections in developing countries. An alternative is continuous positive airway pressure (CPAP). The authors evaluated the effectiveness of CPAP in children presenting with acute respiratory distress in a developing country.

Study design A randomized, controlled trial was conducted in 4 rural hospitals in Ghana. Children, 3 months to 5 years of age, presenting with tachypnea and intercostal or subcostal retractions or nasal flaring were randomly assigned to receive CPAP immediately or 1 hour after presentation. CPAP was applied by locally trained nurses. The primary outcome measure was change in respiratory rate at 1 hour.

Results The study was stopped after the enrollment of 70 subjects because of a predetermined stop value of $P < .001$. Mean respiratory rate of children who received immediate CPAP fell by 16 breaths/min (95% CI 10-21) in the first hour compared with no change in children who had CPAP delayed by 1 hour (95% CI −2 to +5). Thirty-five of the patients had a positive malaria blood smear. There were 3 deaths as a result of severe malaria. No major complications of CPAP use were noted.

Conclusions CPAP decreases respiratory rate in children with respiratory distress compared with children not receiving CPAP. The technology was successfully used by local nurses. No complications were associated with its use. CPAP is a relatively low-cost, low-technology that is a safe method to decrease respiratory rate in children with nonspecific respiratory distress. *(J Pediatr 2013;162:988-92)*.

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Acute respiratory infections remain a leading cause of mortality in children throughout the world, with ~2 million deaths per year in the under-5 age group.[1] In developing countries with limited resources, the use of invasive mechanical ventilation for respiratory distress or insufficiency is often not an option. One alternative to support children with reversible conditions during their acute respiratory distress stage is nasal continuous positive airway pressure (CPAP). The use of CPAP may increase lung volume and improve ventilation-perfusion matching and pulmonary compliance, resulting in improved oxygenation and decreased work of breathing.[2-4]

Several randomized controlled trials in developed countries support the use of CPAP in adults with acute pulmonary edema,[4-6] and others have shown significant early improvements in oxygenation and respiratory rate with CPAP in adult patients with acute respiratory insufficiency.[7,8] In developing countries, CPAP has been used in neonates with respiratory distress syndrome. These studies show the technology is much less expensive, has lower complication rates, and requires less technical skill than mechanical ventilation, making it an attractive option in resource-limited countries.[9-11]

We conducted a randomized controlled trial to determine whether CPAP, applied by locally trained nurses, decreases respiratory rate in children presenting with undifferentiated respiratory insufficiency in 4 Ghanaian district hospital emergency wards.

Methods

The study was approved by the Columbia University Institutional Review Board and the Committee on Human Research Publication and Ethics at the Kwame Nkrumah University of Science and Technology in Kumasi, Ghana.

Nasal bubble CPAP was introduced to local nurses through an intensive 4-hour didactic and hands-on training session led by 2 experienced neonatal intensive care unit nurses and a pediatric critical care physician from Columbia University, New York, NY. Emergency ward nurses received CPAP training: 4 in Kintampo, 4

CPAP	Continuous positive airway pressure
Sa_{O_2}	Arterial oxygen saturation

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in Mampong, 4 in Nkoranza, and 5 in Wenchi. Two of the nurses had been exposed to CPAP during their training in Ghana before the start of this study. In the following month, the physician spent 1 day a week at each site providing the nurses with in-service training and reviewing how to properly apply CPAP, obtain vital signs according to the standard method, and accurately complete datasheets. All nurses were observed successfully placing CPAP on at least 1 pediatric patient before the start of the study. One nurse at each site was selected as the site coordinator and received additional in-depth training on informed consent, study protocol, CPAP trouble-shooting, adverse events, and data entry.

A randomized controlled parallel-study design was used to test the hypothesis that CPAP reduces respiratory rate in children 3 months to 5 years of age presenting with tachypnea and retractions or nasal flaring. A computer-generated randomization scheme was used, with blocks of 24. Study assignments were kept at each site, in sequentially numbered, sealed opaque envelopes.

Eligible subjects were children 3 months to 5 years of age presenting to the participating emergency wards with tachypnea (respiratory rate >50 breaths/min in children 3 months to 1 year of age or >40 breaths/min in children 1-5 years of age) with the presence of at least one of the following: subcostal, intercostal, or supraclavicular retractions or nasal flaring. Children were excluded if they had skin breakdown around the nose or mouth, facial trauma, inability to protect their airway, uncontrollable emesis, poor respiratory effort requiring positive pressure ventilation or the need for invasive mechanical ventilation for respiratory failure, known or suspected cardiac disease, or known or suspected pneumothorax.

All children had vital signs measured on study entry and every 20 minutes for a period of 2 hours. Children who were assigned to immediate CPAP had CPAP initiated after baseline vital signs were measured. Those assigned to delayed CPAP were managed according to Ghana Health Service protocols for the first hour of the study. After the 1-hour vital signs were obtained, CPAP was initiated (**Figure 1**). The primary outcome measure was change in respiratory rate from the start of the study to the 1-hour time point. Both groups received supplemental oxygen if the arterial oxygen saturation (Sao_2) was <92% and were treated according to the Ghana Health Service's standards of care. After 2 hours, CPAP was continued at the discretion of the treating health care provider.

Baseline demographics (sex and date of birth) and physical examination (weight and vital signs) were obtained. All laboratory results requested by the Ghanaian health care provider were recorded. Respiratory rate was counted for 60 seconds, either continuously or in two 30-second blocks using a stopwatch or the second hand of a timepiece. GE Dinamap V100 (Fairfield, Connecticut) machines were used to measure Sao_2, heart rate, and temperature. Respiratory rate, heart rate, and Sao_2 were obtained every 20 minutes for a total of 2 hours. Dispositions of patients were categorized as death, intubation, transfer to other facility, admission to pediatric ward, or discharge home.

The device used in the study was the Hudson RCI CPAP nasal cannula (Durham, North Carolina). A DeVilbiss IntelliPAP CPAP machine (Somerset, Pennsylvania) was used to deliver a pressure of 5 cm H_2O in the inspiratory limb of the system, while the expiratory limb was placed 5 cm below the level of a 0.0025% acetate solution in water. Adequacy of seal was monitored by observing air bubbles in the water/acetate solution during expiration. Oxygen was administered as needed for Sao_2 levels <92%, via a nonrebreather face mask or through the CPAP circuit. All equipment provided for the study was left with the hospitals for clinical use after the study.

Statistical Analyses

The anticipated sample size was calculated to be 48 subjects per group, assuming a difference of 7 breaths/min (SD, 12 breaths/min) between the groups, with a 2-sided α of 0.05 and a power of 80%. A Data and Safety Monitoring Board composed of a Ghanaian physician, a Ghanaian biostatician, and a US physician performed planned interim analyses at 25% and 50% of anticipated enrollment for safety monitoring, and a predetermined stop value of $P < .001$ was used (Haybittle-Peto rule).[12] Normally distributed continuous variables were compared using the Student t test, nonnormally distributed data using the Mann-Whitney test, and categorical variables using χ^2 or Fisher exact tests.

Results

Between June 27 and November 22, 2011, the parents of 70 eligible children were approached for consent to participate in the study; all 70 provided written documentation of consent. Consent was sought by local investigators in the local language if the parents did not speak English. Thirty-one children were randomized to the immediate CPAP group, and 39 were randomized to the delayed CPAP group. Respiratory rates were not recorded at any time point for one subject in the delayed group, so that subject was not included in the analysis. That subject improved and was admitted to the pediatric ward. Baseline characteristics of the 2 groups are summarized in the **Table**.

CPAP was successfully initiated in all children assigned to the immediate CPAP group. In children assigned to immediate CPAP, the mean respiratory rate fell by 16 breaths/min (66-50, 24% decrease) over the first hour of the study (95% CI 10-21) compared with little change (61-60, 2% decrease) in the delayed CPAP group (95% CI −2 to +5) ($P < .001$ for a difference in magnitude of drop in respiratory rate; **Figure 2**). All subjects assigned to delayed CPAP had CPAP initiated at 1 hour. The mean respiratory rate of children in the delayed CPAP group decreased by 13 breaths/min (95% CI 8-19, $P < .01$) over the second hour of the study (**Figure 2**). Heart rates did not differ between the 2 groups.

Thirty-five of the patients had positive blood smears for malaria on light microscopy. There were 3 deaths as a result of severe malaria reported in the immediate CPAP group ($P = .09$); 1 patient was transferred to a higher-level facility