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Clonidine in the sedation of mechanically ventilated children: A pilot randomized trial☆,☆☆

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ABSTRACT

Purpose: Clonidine is often used as a sedative in critically ill children, but its effectiveness has not been evaluated in a large, rigorous randomized controlled trial. Our objectives in this pilot trial were to assess the feasibility of a larger trial with respect to (1) effective screening, (2) recruitment, (3) timely drug administration, and (4) protocol adherence.

Materials and methods: This is a randomized, blinded, placebo-controlled pilot trial. Mechanically ventilated children received enteral clonidine 5 μg/kg or placebo every 6 hours; additional sedatives were at the discretion of attending physicians.

Results: We enrolled 50 children. The median interquartile range (IQR) age was 2.5 (0.7-5.2) years, and Pediatric Risk of Mortality score on pediatric intensive care unit admission was 12 (8-15). In terms of feasibility outcomes, 90 (87%) of 104 eligible patients were approached for consent, and on average, 1.7 children were enrolled per month. Thirty-five (70%) were enrolled within 1 day of becoming eligible (mean, 1.2 days). Thereafter, 94% of doses were administered by protocol. Clinical outcomes and adverse effects were not significantly different between the groups.

Conclusions: This pilot trial demonstrated feasibility of a larger randomized controlled trial. Some important challenges emerged, allowing refinement of the study protocol and enrolment estimates. We recommend that future trials capitalize on the experience gained and use these results to design a larger trial focusing on clinically important outcomes.

Critically ill children who are mechanically ventilated usually receive analgesia and sedation for comfort and safety. Opioids and benzodiazepines are the most frequently administered [1,2]. Current approaches are often inadequate, as sedation-related adverse events are common. In observational studies, 22% of preventable adverse events in critically ill children are related to sedation[3], and 54% of mechanically ventilated children experience at least 1 sedation-related adverse event (1.9 events on average) such as uncontrolled pain, delirium, severe agitation, oversedation, or unplanned extubation during their pediatric intensive care unit (PICU) stay [4]. High levels of sedation in the first 24 hours of weaning from mechanical ventilation are associated with a longer duration of weaning and with unsuccessful extubation of children [5]. Sedatives and analgesics may also cause adverse events when they are stopped. Among mechanically ventilated children, 17% to 57% experience withdrawal [6,7]. Children who receive higher doses and longer durations of opioids and benzodiazepines (particularly 5 days or longer) are at higher risk of withdrawal [8,9].

Clonidine is an attractive treatment option in this setting. Enterally administered, it is an inexpensive and readily available medication with minimal respiratory depression. Clonidine is widely used in critically ill children, both as a sedative and to treat and prevent withdrawal from opioids and benzodiazepines [1,2,10]. We hypothesize that it may reduce the need for opioids and benzodiazepines. Despite its common use, it has not been rigorously investigated as a primary or adjunctive sedative for critically ill children [11]. An adequately powered trial focusing on outcomes important to clinicians, critically ill children, and their families is warranted to evaluate the effects of adjunctive clonidine for sedation. Such a trial poses significant challenges, primarily related to the need for a large, multicenter collaboration and to the willingness of clinicians to randomize patients into a trial investigating a drug that is readily

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available outside the trial and commonly used in some centers. Before embarking on such a trial, our objective was to conduct a pilot randomized trial of adjunctive clonidine for sedation in critically ill children specifically assessing screening and enrolment, recruitment, timely drug administration, and protocol adherence.

1. Materials and methods

1.1. Study design

This randomized, double-blind, placebo-controlled, pilot trial was conducted in the PICUs of 2 tertiary academic pediatric centers in Ontario, Canada (McMaster Children's Hospital, Hamilton and Children's Hospital, London Health Sciences Centre, London) between January 2010 and September 2012. Combined, the 2 units have 20 beds and approximately 1100 admissions per year. This trial was registered with ClinicalTrials.gov (NCT00959062).

1.2. Participants

We enrolled children aged 1 month to 18 years who were expected to require mechanical ventilation for at least 2 more days, were receiving a continuous infusion of an opioid or benzodiazepine or had received more than 3 intermittent doses of these medications in the previous 12 hours, and had a feeding tube in place. Exclusion criteria were hemodynamic instability (receiving dopamine, dobutamine, norepinephrine, epinephrine, phenylephrine, vasopressin, or active fluid resuscitation in the past 4 hours), chronic use of antihypertensive medications, traumatic brain injury with increased intracranial pressure, status epilepticus, nonstudy clonidine use, enrolment in a potentially confounding trial, known pregnancy, consideration for organ procurement, or a contraindication to clonidine use due to allergy, drug interaction, or the ketogenic diet. This trial was approved by the research ethics board at both centers. Parents or guardians of all participants provided written informed consent.

1.3. Trial procedures

Research staff screened children in the PICU for eligibility on weekdays and, when staff was available, on weekends. Pharmacy research staff at each site used a computer-generated randomization list, stratified by center, with undisclosed variable block sizes, to assign participants to receive clonidine suspension prepared from commercially available tablets or visually identical placebo suspension [12]. All patients, families, clinicians, and research staff remained blinded throughout the trial; only the pharmacy research staff was aware of group assignment.

Children initially received 5 μg/kg (maximum, 200 μg) of clonidine or placebo enterally every 6 hours. The study medication was continued regardless of feeding. Doses were held or reduced by 50% as needed by the treating clinicians for clinically important hypotension, bradycardia, or oversedation. All other sedation, analgesia, and monitoring were managed by the attending PICU team with the exception that nonstudy clonidine or dexmedetomidine was not permitted. We did not permit unblinding.

The study medication was continued until either (1) discontinuation of opioids and benzodiazepines (except those used for procedural sedation, seizures, or a single dose for bedtime sedation) for 24 hours; (2) no further decreases in sedatives or analgesics were planned (eg, treatment of chronic pain); or (3) hospital discharge or transfer to another hospital. The study medication was then weaned over 48 hours or discontinued (if the child received the study medication for 48 hours or less). We collected data daily for 48 hours after the study medication was discontinued to a maximum of 90 days; thereafter, we recorded the date of hospital discharge or death. Children still receiving the study medication at the time of hospital discharge completed the tapering course at home with telephone follow-up by the research team.

1.4. Outcomes

The primary objectives of this pilot trial were to evaluate feasibility, specifically: effective screening and enrolment: To approach a minimum of 90% of eligible patients for consent; recruitment rate: To randomize a mean of 4 patients per month; timely drug administration: To have 80% of participants receive their first dose of the assigned study drug within 1 day of becoming eligible; protocol adherence: To have greater than 80% of doses administered in accordance with the trial protocol.

The secondary objectives were to measure clinical outcomes, focusing on the level of sedation, medication use, duration of ventilation, PICU and hospital stay, and adverse effects (including withdrawal). We used the sedation scores documented by the PICU nursing staff, who use either the COMFORT [13] or the State Behavioral [14] scales (depending on the center) at least 4 times daily. We recorded all sedative and analgesic medications administered within the first 30 days after randomization, excluding local or epidural anesthetics, medications given in the operating room, procedural sedation, and anticonvulsants. To compare the amount of sedation given in the 2 groups, we converted benzodiazepines to midazolam equivalents and opioids to morphine equivalents and also used a summary sedative score based on the estimated hourly sedation in a child not previously exposed to opioids and benzodiazepines [5] (see Appendix E1: sedative equivalents and scoring).

Withdrawal was diagnosed, according to the usual practice in the PICUs, using either the attending clinicians' clinical impression or a Withdrawal Assessment Tool 1 (WAT-1) score of 3 or more [15]. We defined the end date of invasive mechanical ventilation as the last day of ventilation if it was not reinstituted within 2 days. If a child was discharged from the PICU while mechanically ventilated, we used the PICU discharge date as the end date for mechanical ventilation. We excluded children who were chronically ventilated (for greater than 30 days) before PICU admission from the analysis of the duration of mechanical ventilation. We recorded the duration of PICU and hospital stay among those children who survived their PICU stay. In the case of multiple PICU admissions during a single hospitalization, we recorded the duration of the first PICU stay after randomization only.

We recorded any adverse effects reported within 48 hours of receiving the study medication, specifically any episodes of hypotension or bradycardia that required intervention (including holding or discontinuing the study medication, which was at the discretion of the clinical team) or accidental removal of endotracheal tubes. We also recorded any other adverse events that the clinical or research teams suspected may have been directly related to participation in the study.

1.5. Statistical analysis

To estimate the sample size, we used 95% confidence intervals (CIs) to estimate the proportion of children who would meet the criteria for timely enrolment. For the lower boundary of the associated 95% CI (0.81-0.97) to be above the 80% prespecified criteria for success, 46 of 50 patients were required to meet the criteria.[16] We summarized continuous data as medians with interquartile range and binary data as proportions. We used a 2-group t test to compare continuous outcomes and a logistic model to compare dichotomous outcomes. All statistical tests were 2 sided, and the criterion for statistical significance was $P < .05$. All analyses were conducted using STATA 13.0 (College Station, TX). An independent data safety monitoring committee reviewed progress of the trial and reports of adverse effects (blinded to treatment allocation) when 50% of the children were enrolled. There was no interim analysis