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Continuous clonidine infusion: an alternative for children on mechanical ventilation

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SUMMARY

OBJECTIVE: This study aimed to assess the clonidine infusion rate in the first 6 h, as maintenance dose (first 24 h), and in the pre-extubation period (last 24 h), as well as the cumulative dose of other sedatives and the hemodynamic response.

METHODS: This is a retrospective cohort study.

RESULTS: Children up to the age of 2 years who were admitted to the pediatric intensive care unit of a tertiary referral hospital in the south region of Brazil, between January 2017 and December 2018, were submitted to mechanical ventilation, and received continuous clonidine infusions were included in the study. The initial, maintenance, and pre-extubation doses of clonidine; the vasoactive-inotropic score; heart rate; and systolic and diastolic blood pressure of the study participants were assessed. A total of 66 patients with a median age of 4 months who were receiving clonidine infusions were included. The main indications for mechanical ventilation were acute viral bronchiolitis (56%) and pneumonia associated with acute respiratory distress syndrome (15%). The median of clonidine infusion in the first 6 h (66 patients) was 0.53 μg/kg/h (IQR 0.49–0.88), followed by 0.85 μg/kg/h (IQR 0.53–1.03) during maintenance (57 patients) and 0.63 μg/kg/h (IQR 0.54–1.01) during extubation period (42 patients) (p=0.03). No differences were observed in the doses regarding the indication for mechanical ventilation. Clonidine infusion was not associated with hemodynamic changes and showed no differences when associated with adjuvants.

CONCLUSION: Clonidine demonstrated to be a well-tolerated sedation option in pediatric patients submitted to mechanical ventilation, without relevant influence in hemodynamic variables.

KEYWORDS: Clonidine. Pediatric intensive care unit. Artificial respiration. Sedation, conscious. Analgesia.

INTRODUCTION

Several factors negatively contribute to the physical and emotional status of critically ill children, including the absence of relatives, the high level of noise in pediatric intensive care unit (PICU), and the need of invasive procedures[1-4]. PICU patients often require ventilatory support and are submitted to procedures that can lead to pain; therefore, drugs are used to control anxiety, pain, and discomfort[1,5-7].

Sedation and analgesia goals must be tailored individually. For example, a patient who are submitted to mechanical ventilation (MV) during the acute phase may need sedation and muscle relaxation; however, the same patient during weaning may need comfort and lighter sedation levels to allow spontaneous breathing[1,6,8,9].

Studies suggest that the use of clonidine for long-term sedation is safe, despite the associated occurrence of bradycardia and hypotension[10-12]. In children, such negative hemodynamic effects have not led to an increase in inotropic support[13-16]. In the neonatal population, the use of clonidine continuous infusion was associated with adequate analgesia and sedation, with no discernible risks in the short term[4,16,17].

The primary aim of this study was to describe the clonidine continuous infusion doses, as well as the cumulative doses of adjuvants in three different time periods: (1) initial (hour 6 of clonidine continuous infusion), (2) maintenance (hour 24 of infusion), and (3) pre-extubation (24 h before extubation). The secondary aim was to evaluate the correlation between clonidine dose and the vasoactive-inotropic score (VIS)[18], heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) during the three time periods.

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METHODS

We conducted a retrospective cohort study including all MV children £2 years old who received continuous infusion of clonidine, between January 2017 and December 2018, at the PICU of Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Exclusion criteria included the presence of complex congenital heart disease, use of £2 anticonvulsants or antipsychotics, patients submitted to hemodialysis, use of non-invasive ventilation, patients who progressed to extubation in <6 h, patients with complex chronic diseases hospitalized for >100 days, and patients readmitted to the PICU. This study was approved by the HCPA Research Ethics Board (project 95105718.2.0000.5327).

The HCPA is a university-affiliated hospital in southern Brazil, reference for complex diseases (e.g., genetic disorders), major surgeries, and bone marrow and liver transplant. Its tertiary PICU has 13 beds, with an average of 600 annual admissions; 60% of PICU patients require MV, with a mortality rate close to 7%.

The sedation and analgesia goals for the next 24 h for each patient are decided during the PICU morning round. Sedation targets vary according to individual patient needs and therapeutic goals, and potential contraindications for drugs. Throughout the day, sedation and analgesia doses are monitored by the nursing and medical team and adjusted according to the desired purposes. Two previously trained researchers (CCN and VIF) collected data from medical charts. Study variables included age, weight, sex, hospital and PICU admission date, intubation and extubation date, PICU and hospital discharge date, and hospital mortality. Data on HR, mean arterial pressure (MAP), DBP, and SBP were collected in three time periods: at hour 6 of clonidine infusion, at hour 24 of clonidine infusion, and at 24 h before extubation. Data on the hourly continuous infusion doses of clonidine and other sedatives (continuous infusion and bolus) were collected during the first 24 h of sedation and the 24 h before extubation.

RESULTS

We summarized our results using means (standard deviation [SD]) or medians (interquartile ranges [IQRs]) for continuous variables. Categorical variables were described in absolute and relative frequency (proportions). To assess the continuous variables, we applied the Student's t-test and ANOVA. We compared the median clonidine infusion dose at the three predetermined time points (hour 6 and hour 24 of continuous infusion, and 24 h before extubation) using the Mann-Whitney U test. We applied the Kruskal-Wallis test to compare the clonidine doses used for different patient subgroups and evaluated the correlation between clonidine dose and VIS by applying the Spearman's test. Data were analyzed using Stata Statistics version 13.0.

During the study period, we identified 170 patients who had received clonidine infusion, and 66 of whom fulfilled the inclusion criteria (Figure 1).

The median age was 4 months (IQR 2–10), with 67% (44 patients) being male. The main indications for MV were acute viral bronchiolitis (56%) and pneumonia associated with acute respiratory distress syndrome (ARDS) (15%). The median duration of MV was 6 days (IQR 4–9 days). The medians of length of PICU and hospital stay were 10 days (IQR 8–13 days) and 20 days (IQR 16–42 days), respectively (Table 1). No patient died during the study observation period.

No patient received a bolus dose of clonidine before starting the continuous infusion. The median dose of clonidine infusion at hour 6 was 0.54 µg/kg/h, reaching a median dose infusion of 0.85 µg/kg/h at hour 24 (Figure 2). In the

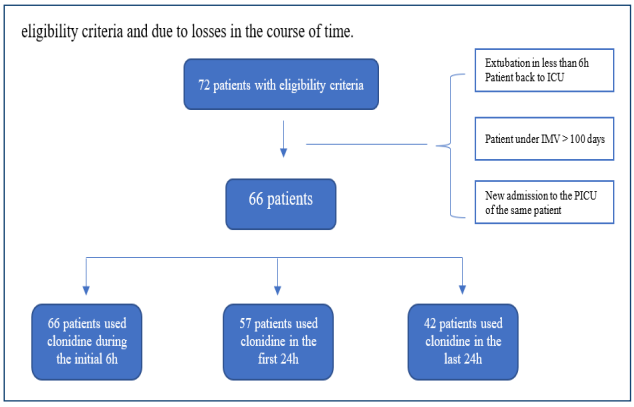

Figure 1. Flowchart of study population.

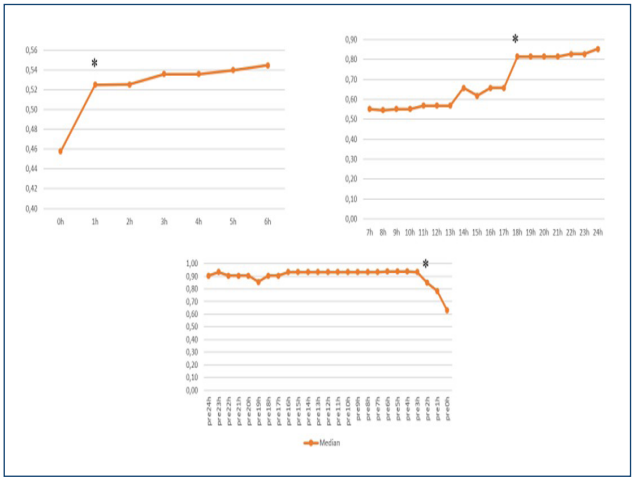

Figure 2. Median of continuous clonidine infusion doses (A: over the first 6 h of mechanical ventilation; B: over the hours 7 and 24; C: over the last 24 h pre-extubation). (*p<0.001).

Table 1. Demographic data and characteristics of 66 patients submitted to mechanical ventilation and using continuous clonidine infusion as an alternative.

Age, n (%)	
Median (IQR), months	4 (2–10)
< 6	38 (58)
6–12	13 (20)
12–24	15 (23)
Sex, n (%)	
Male	44 (67)
Indications for PICU, n (%)	
Bronchiolitis	37 (56)
Pneumonia/ARDS	10 (15)
Postoperative	9 (14)
Others	10 (15)
Duration of MV, median ($IQ_{25-75\%}$), days	6 (4–9)
PICU length of stay, median ($IQ_{25-75\%}$), days	10 (8–13)
Hospital length of stay, median ($IQ_{25-75\%}$), days	20 (16–42)

IQR: interquartile ranger; PICU: pediatric intensive care unit; ARDS: acute respiratory distress syndrome; MV: mechanical ventilation.

pre-extubation period, 24 patients were still receiving clonidine with a median dose of 0.63 µg/kg/h. We did not observe any difference regarding the median dose between the three time points (p>0.4).

When analyzing the temporal evolution of clonidine dose, we observed that the median dose increased in the first hour, from 0.46 to 0.52 µg/kg/h (p<0.001), and in hour 17 of infusion, from 0.66 to 0.82 µg/kg/h (p<0.001). Later, the median clonidine dose remained stable until the end of the 24 h (Figure 2). In the 24 h pre-extubation, continuous infusion dose was kept stable at 0.93 µg/kg/h until hour 3 of pre-extubation. From this period onward, clonidine dose was gradually decreased until it reached a median dose of 0.63 µg/kg/h during extubation (p<0.001) (Figure 2).

We did not find differences between the medians of clonidine doses at the three observed periods when stratified by MV indication.

While evaluating the necessity of adjuvants to the continuous clonidine infusion, we did not observe any differences related to it, except during pre-extubation period, due to the decreased number of associations. Only cases with a cumulative of ketamine were depicted (n=11), perceiving an increase in the rate of clonidine infusion with a median of 1.88 (0.72–2.07) µg/kg/h.

The correlation between clonidine and VIS, HR, SBP, and DBP was poor (r<0.4).

DISCUSSION

Clonidine has been used as a sedative for some time, but literature on it is still scarce[9,16]. Most studies demonstrate the restricted use of dexmedetomidine infusion in children, which were limited to specific populations and conducted in developing countries, where the reasons for MV are different compared to the ones observed in regions with limited resources[8,19].

Clonidine is a good alternative as it acts on the postsynaptic alpha-2-adrenergic receptors, leading to an attenuation of neuronal activation. It is also a partial agonist stimulating alpha-2 receptors in the brain, resulting in a reduction of sympathetic stimulus on the *locus coruleus* which leads to a sedative effect[6,20]. Clonidine also has an antihypertensive effect, possibly leading to hypotension and bradycardia depending on the doses[21]. Despite its potential side effects, studies show that clonidine may have a beneficial effect in critically ill patients by reducing afterload and consequently increasing cardiac output[10,13,22]. Such findings have been confirmed in patients, for whom VIS score remained stable[1,18,21].

In our study, clonidine was not associated with negative hemodynamic effects, neither during MV period nor during extubation. This finding corroborates with others suggesting that continuous infusion of clonidine does not necessarily induce significant negative hemodynamic response. Kleiber et al.[15] used clonidine (0.5–2 µg/kg/h, over 30 h of infusion) in 23 newborn babies submitted to cardiac surgery. Authors reported that, despite a statistically significant reduction in HR (p<0.0001) and DBP (p=0.018), no clinical repercussions were observed. In the Sleeps[16] study, clonidine use was compared to intravenous midazolam in 120 MV children who required sedation for more than 12 h. Authors showed that patients were adequately sedated (medians clonidine 73.8% vs. midazolam 72.8%).

As previously mentioned, the use of dexmedetomidine, an alpha-2 agonist that promotes a "conscious sedation" without respiratory depression, has been better documented in pediatric patients[3,23]. It is known for having greater selectivity for alpha-2-agonist receptors when compared to the clonidine's alpha-1-agonist receptors (1620:1 for dexmedetomidine and 220:1 for clonidine)[19,24]. Despite being a good sedative, dexmedetomidine is significantly more expensive. The cost of using dexmedetomidine can be four times higher than the cost of clonidine. Thus, having clonidine as a sedative option could have major therapeutic and financial implications in low- and middle-income countries.

Our study has limitations. The use of a retrospective design is associated with the absence of a predefined rigid protocol for titrating the doses of clonidine infusion and for reporting the

minor side effects related to the drug. Nevertheless, our results are consistent with similar ones already published[2,16,21]. In contrast, our study also has important strengths. We included a pragmatic sample size of patients and described the adjustment of clonidine continuous infusion doses in daily practice, and to the best of our knowledge, this is the first study to assess the use of clonidine continuous infusion during the extubation period.

CONCLUSION

In this regard, our data suggest that clonidine could be an option to be used during weaning of MV support up to the extubation moment. Another strong point is that our results emphasize the strategy of starting continuous clonidine infusion at a lower dose, without bolus attack, which is frequently associated with cardiovascular side effects. However, more studies are required to confirm and extrapolate these results in other pediatric populations.

AUTHORS' CONTRIBUTIONS

CCN: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **VIF**: Data curation, Investigation. **PSF**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **JPP**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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