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RESEARCH ARTICLE

Intravenous Clonidine: A Useful and Safety Sedation for Critically Ill Children

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Abstract

Aim: To determine usefulness and safety of intravenous infusion of clonidine in critically-ill children.

Methods: Prospective, single-centre observational study from January 2013 to December 2014. PICU of Hospital Sant Joan Déu.

Results: 73 patients were enrolled. Median age 7.9 months. Reasons for admission: Respiratory failure (42.5%) and post-cardiac surgery (30.1%). Median PICU length of stay: 14 days. 72 patients were intubated. The median days of clonidine use was 4. Reason for choosing clonidine: To improve prior sedation. We found no major adverse effects but some asymptomatic bradycardia.

Conclusions: Clonidine seems to be a good alternative for sedation in critically-ill children.

Keywords

Clonidine, Sedation, Critically-ill child

Introduction

Critically ill children who are admitted to Pediatric Intensive Care Unit (PICU) often receive analgesia and sedation for pain, comfort and safety. Moreover the new objectives of sedation include maintenance of the functioning of the neuromuscular system early upon ventilatory support, synchronization of the patient to the ventilator and minimizing circulatory side effects while balancing the patient's comfort and cognitive abilities [1].

Opioids and benzodiazepines are the most frequently administered, but long-term use of these drugs is associated with tolerance and withdrawal, suppression of respiratory drive with prolonged ventilation, constipation, and delayed enteric feeding [2,3].

Clonidine is a mixed alpha-1 and alpha-2 adrenoceptor agonist with a predominant alpha-2 action [4]. It has a sedative effect mediated by binding to post-synaptic alpha-2 receptors in the pontine locus ceruleus, reducing noradrenergic output and thereby facilitating the firing of inhibitory neurones, mainly, the gamma-aminobutyric acid system. Clonidine has an analgesic action through binding to alpha-2 receptors in the dorsal horn and supra-spinal sites and thereby reduce the release of P substance [1,5,6]. It also causes peripheral vasodilatation and a decrease in systolic blood pressure, heart rate and cardiac output by decreasing sympathetic nervous system activity. Clonidine has varying degrees of affinity for other cellular components called Nonadrenergic Imidazoline Binding Sites (NAIBS). It seems that the hypotensive effect of clonidine would owe more to their affinity for one type of NAIBS, called I1 receptors [7].

As clonidine is lipid soluble, it penetrates the blood-brain barrier to reach the hypothalamus and medulla [5]. It does not require transformation in to another substance prior to its action and about 20-40% is bound to protein. 50% of the drug is metabolized in the liver to inactive metabolites which are excreted in the urine

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with a half-life of 8-18 hours [4].

Clonidine can provide dose-dependent sedation with cardiovascular stability and a noticeable lack of drug tolerance and withdrawal. These attributes suggest that clonidine might be a useful continuous intravenous sedative in the Critically-ill child [5].

The use of clonidine in pediatrics has grown over the last 10-15 years [8]. Several studies describe the beneficial effects of clonidine for premedication in pediatric anesthesia, prevention of emergence agitation, prolongation of postoperative analgesia as a supplement to regional anesthesia, reduction of the incidence of post-operative vomiting, and treatment of emergence delirium [6,9-13]. Clonidine can also be used in opiate withdrawal treatment, attention deficit/hyperactivity disorder, Tourette's syndrome, schizophrenia and Korsakoff syndrome [1].

However, reports of its use as an intravenous sedative and analgesic in infants and in PICU have not been sufficiently investigated [8,14].

The first aim of this study was to describe the use of the intravenous clonidine infusion all together with other sedative agents. Side effects of clonidine were also registered in our study, which was the second aim.

Materials and Methods

This is a single-centre, prospective, observational study to investigate the efficacy and safety of the intravenous infusion of clonidine in critically ill patients.

The study was conducted from January 2013 to December 2014 in the Paediatric Intensive Care Unit from a tertiary care hospital (Hospital Sant Joan de Déu) in Barcelona (Spain).

We included all patients treated with continuous infusion of clonidine admitted to PICU. We do not have any exclusion criteria.

The data collected included sex, age, Pediatric Risk of Mortality (PRISM), reason for admission, length of stay at PICU, days of mechanical ventilation and inotropes, clonidine maximum and minimum dose, reason for choice, reason for withdrawal and concomitant sedation.

According to our protocol, we start intravenous clonidine as an adjunct to sedation after 7 days of intubation with the aim of weaning other sedatives and as prevention of withdrawal. It is also used in hemodynamically unstable patients (defined as blood pressure less than 10th percentile) as a first option instead of midazolam or when our patients have been unstable after midazolam was started.

This study was approved by the local ethics committee. Written informed consent was obtained from all the parents.

Table 1: Demographic characteristics of the sample.

Variable	Result
Sex (males) n (%)	48 (65.8%)
Age (months) median (IQR)	7.9 (3.4-23.8)
PRISM score (points) median (IQR)	6 (4-11)
Length of stay in PICU (days) median (IQR)	14 (9-24.5)
Intubated patients n (%)	72 (98.6%)
Inotropic therapy n (%)	54 (74%)

IQR: Interquartile Range; PRISM: Pediatric Risk of Mortality; PICU: Pediatric Intensive Care Unit.

Statistics

Categorical variables were expressed as percentages and continuous variables as medians with 25-75 interquartile ranges. We used Student's t test or Wilcoxon test to compare the medians, depending on the distribution. Statistical significance was defined at $p < 0.05$. Statistical analysis was performed using SPSS v. 17 (SPSS Inc, Chicago, IL).

Results

We included in this study 73 patients with an intravenous infusion of clonidine. Forty eight were males (65.8%). Their median age was 7.9 months (IQR 3.4-23.8 months), with a median PRISM value of 6 points (IQR 4-11 points) (Table 1).

The reasons for admission were: 31 due to respiratory failure (42.5%), 22 after cardiac surgery (30.1%), 12 polytraumatized patients (16.4%), 6 due to sepsis (8.2%) and 2 due to neurological injuries (2.7%).

Median length of stay at PICU was 14 days (IQR 9-24.5 days). Seventy two patients (98.6%) required intubation with a median duration of mechanical ventilation of 9 days (IQR 6-16 days). Fifty four patients (74%) required inotropic therapy (median duration of 5 days, IQR 3.8-7.3 days) (Table 1).

The median days of the use of clonidine was 4 (IQR 3-9 days), with a maximum dose of 3 mcg/Kg/h and minimum dose of 0.3 mcg/kg/h (median dose 2 mcg/Kg/h; IQR 1-2 mcg/Kg/h). The reasons for choosing clonidine were: As first course on sedation in 6 cases (8.2%), to improve prior sedation in 59 (80.8%) and as prevention of withdrawal in 8 (11%).

Patients received the following concomitant sedation: Opiates in 72 cases (98.6%), benzodiazepines in 53 (72.6%), neuroleptics in 27 (36.9%), propofol in 18 (24.7%) and chloral hydrate in 11 (15.1%). Table 2 shows the doses 12 hours before and 12 hours after the introduction of clonidine and their variation.

Table 2: Sedative doses before and after the introduction of clonidine.

Sedative agent	Pre-clonidine dose Median (IQR)	Post-clonidine dose Median (IQR)	p
Fentanyl (mcg/Kg/hour)	2 (1.96-2.22)	1.84 (1-2.01)	0.001
Morphic chloride (mcg/Kg/hour)	40 (28.4-45)	30 (29.2-31)	0.18
Remifentanil (mcg/Kg/minute)	0.12 (0.1-0.15)	0.12 (0.1-0.14)	1
Midazolam (mg/Kg/hour)	0.18 (0.1-0.2)	0.1 (0.0-0.16)	0.001
Propofol (mg/Kg/hour)	1.5 (1-2.07)	1.1 (0.0-1.7)	0.007
Levomepromazine (mg/Kg/day)	3.15 (2.22-3.65)	2 (0.42-3.37)	0.028
Chlorpromazine (mg/Kg/day)	1.86 (1.7-2.3)	1.7 (1.0-2.79)	0.674
Chloral hydrate (mg/Kg/day)	35 (23.25-40)	34.5 (0.0-41)	0.401

IQR: Interquartile Range.

The reasons for stopping clonidine were: prior to extubation in 12 patients (16.4%), slowly decrease of doses and change to oral administration in 52 (71.2%), and the death of the patient by other causes in 5 (6.8%). In 4 patients (5.5%) clonidine was stopped due to sinus bradycardia (cardiac rate less than 10th percentile) that resolved after discontinuing the treatment. These patients do not have other reasons for suffering bradycardia.

There was no severe adverse effect of clonidine on the cardiac rhythm. Clonidine did not cause low blood pressure resulting in additional inotropic need to reach the target blood pressure.

Discussion

As far as we have reviewed, the present study is one of the largest prospective surveys of intravenous clonidine administration focused on critically ill children. However, in recent years an increase of studies about the use of alpha-agonists has been seen, as shown in the systematic review published in the literature recently [15]. The data are very heterogeneous, which prevents getting good conclusions.

In our experience, we used intravenous clonidine to a large number of paediatric patients with a wide range of age and pathology; however the two main causes of admission were respiratory failure and post-cardiac surgery.

Clonidine is used regularly as an analgesic and sedative in UK PICU [16]. Consensus guidelines on sedation and analgesia in critically ill children recommend a dose of intravenous clonidine of 0.1-2 mcg/kg/h [17]. In our study we used a dose range up to 3 mcg/Kg/h. While we did not identify significant adverse events at the higher doses we used, our small sample size prevents us from drawing conclusions about safety at the highest doses.

The main reason of using clonidine was to improve prior sedation (80.8%), as it was described in critical care setting [1]. Clonidine has a multifaceted profile: sedation combined with arousability and preservation of respiratory drive allowing the use of modern ventilatory techniques with reduced intrathoracic pressure and, therefore, better weaning from mechanical ventilation. Pichot, et al. also describes a reduction of oxygen consumption, preservation of renal function, reduction of protein metabolism, decrease of arterial impedance, improvement of left ventricular performance, preservation of vascular reactivity to exogenous amines, preservation of cardiac baroreflex reactivity, preservation of vasomotor baroreflex activity combined with a lowered pressure set point, and improvement of tissue perfusion [1].

We also used intravenous clonidine as prevention of withdrawal (11%). In some studies was found to be an effective analgesic, and sedative and it ensured haemodynamic stability by decreasing withdrawal symptoms like hypertension, tachycardia and fever following cardiovascular surgery in infants treated with midazolam and fentanyl, aged 0-24 months [14].

The most important studies were published in 2014 by Wolf, et al. and Hunseler, et al., which concluded that clonidine as intravenous continuous infusion is a good alternative combined with other sedatives [2,18]. Our patients received other sedatives associated to clonidine as opiates or benzodiazepines, allowing to decrease significantly the dose of these drugs.

The decrease in sedation following the association of intravenous clonidine was especially significant in opiates, benzodiazepines, propofol and levomepromazine, drugs which could have important side effects. This fact is especially relevant because it allows us to improve the global safety profile in our patients.

In the first study carried out by Wolf, et al. [8], they treated 61 patients with clonidine compared to 59 patients treated with midazolam in a randomised, double-blind study. They conclude that clonidine is likely to be a cost-effective sedative agent in the PICU in comparison with midazolam. Rebound hypertension did not appear to be a significant problem but, owing to its effects on heart rate, specific cardiovascular attention needs to be taken during the loading and early infusion phase.

In the second study, conducted by Hünseler [2], they enrolled 212 newborns and infants younger than 2 years in a randomized and double-blind study. Patients received clonidine (100) or placebo (112) on day 4 after intubation, and fentanyl and midazolam were adjusted to achieve a defined level of analgesia and sedation. Authors conclude that a continuous infusion of clonidine (1 mcg/kg/h) in ventilated newborns reduced fentanyl and midazolam demand with deeper levels of analgesia and sedation without substantial side effects. According to these studies, clonidine seems to be a good alternative in order to decrease the dose of sedatives, as we observed in our study.

In another study, conducted by Ambrose [5], intravenous clonidine in combination with midazolam provided dose-dependent sedation in ventilated critically ill children without adverse effects on cardiovascular performance and achieved satisfactory sedation scores. It is important because fifty four of our patients required inotropic therapy and ensuring haemodynamic stability is an important fact when deciding which sedative is appropriate for each patient. Although one of the effects of clonidine is hypotension, in our study we have not observed it. Probably the fact that many patients underwent inotropic treatment avoided this effect, despite not having to significantly increase the doses.

Duffet, et al. studied the effects of oral clonidine (5 mcg/kg) in mechanically ventilated children. They enrolled children aged 1 month to 18 years in a randomized, double-blind, placebo-controlled, pilot trial. They conclude that clonidine may be a good adjuvant to sedation in these patients [3]. Although there are different routes of administration, our study focused on intravenous infusion. The advantages and disadvantages appear to be similar.

Lowery, et al. has reported a long term use of about four and a half months in a critically ill newborn as an adjunct for sedation and pain management [8].

The appearance of atrioventricular block has been repeatedly described as a side-effect of Clonidine [19,20]. Clonidine leads to sinus slowing and depression of nodal conduction, which is of less importance than those observed following beta-blocker administration. Lengthening of the PR interval is more prominent when the baseline PR interval is long [1,21,22].

Dawson reported a case study of a 10-year-old boy with sinus dysrhythmia, bradycardia (rate 46 beats/minute), first-degree heart block and several nonconducted P waves. In 1994, Chandran described abnormal EKG findings in children taking relatively low doses of Clonidine [22]. However Kofoed, et al. [21] demonstrated the necessity of pre-treatment EKGs in assessing cardiac effects and the difficulty in separating drug-induced changes from variability unrelated to drug effects. In their study, they observed several abnormalities which might have been attributed to cardiac effects of clonidine in the absence of pre-treatment data, and some variation which was not due to drug effects but to variability of measurement of EKGs over time.

In our study, we did not experience any serious adverse effects of clonidine on cardiac rhythm, and although in four patients clonidine was stopped after sinus bradycardia, it was asymptomatic and resolved after discontinuing the treatment, which has also been described in the literatura [23]. These patients had the same age and received similar doses of clonidine than those who did not suffered bradycardia.

The respiratory depressant effect has been described in clonidine poisoning of children 19 and several case reports describing apnea in preterm infants, ex-preterm infants and neonates in connection with caudal Clonidine [24-26].

This study has some limitations. The first one is that our data are based on a single hospital study done with a relatively small sample size that lacked statistical power. We did not use sedation/withdrawal scores to evaluate the effectiveness of drugs at the time of the study, only the discretion of the physician. Currently the use of these scores has been standardized in our unit. Secondly, we did not compare clonidine with dexmedetomidine, because we did not have this drug in our hospital. There are no comparisons between clonidine and dexmedetomidine in the literature in terms of effectiveness or side effects, only comparisons of each drug separately with the rest of sedatives. It could be an interesting point to study. Finally, not being a randomized study, we have not compared the effectiveness of this drug over other sedatives.

Further prospective studies of clonidine as an adjunctive sedative are warranted, and should include strict regulation of concomitantly administered opioids and benzodiazepines to minimize the variables that can confound interpretation of the patient's responses.

Conclusion

Clonidine in continuous intravenous infusion is a good drug for use as a sedative or for the treatment of withdrawal syndrome. In addition, it significantly reduces other sedative drugs which could have important adverse effects. There is little experience in our environment, but it seems to be a safe drug.

Disclosures

Ethical approval: This study was approved by the local ethics committee. Written informed consent was obtained from all the parents.

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Conflict of interest: None declared.

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