RESEARCH PAPER

Prolonged Infusion of Dexmedetomidine in Critically-ill Children

*#CINARA ANDREOLIO, JEFFERSON PEDRO PIVA, ELISA BALDASSO, ROBERTA FERLINI AND RAFAELA PICCOLI

From Pediatric Intensive Care Unit at Hospital de Clinicas de Porto Alegre and Pediatric Emergency and Intensive Care Department - Medical School – UFRGS University, Brazil.

Correspondence to:
Cinara Andreolio – Rua Ramiro Barcelos, 2350 – Zip Code 90035003.
cinarandreolio@hotmail.com
Received: June 30, 2015; Initial review: December 19, 2015; Accepted: September 09, 2016.

Objective: To describe main indications, doses, length of infusion and side effects related to dexmedetomidine infusion.

Methods: Observational and retrospective study evaluating dexmedetomidine use in pediatric intensive care unit.

Results: 77 children received dexmedetomidine infusion longer than 6 hours for mechanical ventilation weaning (32.5%), post- neurosurgery and post-upper airway surgery (24.7%), non-invasive ventilation (13%), refractory tachycardia (6.5%) and other causes (23.3%). After 6 hours of infusion, significant decrease in mean arterial pressure and heart rate was observed in all groups. Six children (8%) required withdrawal of drug because of possible side effects: hypotension, bradycardia and somnolence.

Conclusion: Dexmedetomidine may be used as sedative in critically ill children without much side effects.

Keywords: *Bradycardia, Hypotension, Intensive care, Sedation*.

Dexmedetomidine (DEX) is an α2-adrenergic agonist with 8 times more affinity to the receptors than clonidine, promoting "conscious sedation" without or minimal respiratory depression [1-3]. The onset of action is observed in 15 minutes. There is increasing evidence that DEX achieves anoxic-ischemic protection [3-6].

Use of DEX has been proposed in several pediatric clinical and surgical conditions, such as: to facilitate the weaning process after long period of mechanical ventilation, to prevent and treat delirium and abstinence syndrome, in the post-surgery period (cardiac, upper airway and neurosurgery surgery), and to facilitate non-invasive ventilation [3-8]. DEX is metabolized in the liver with 95% of the inactive metabolites excreted in urine [3,6].

We evaluated the main indications, initial and maximal doses, length of infusion and side effects related to prolonged DEX infusion in children and adolescent treated in a pediatric intensive care unit (PICU).

METHODS

Observational and retrospective study involving children (age 2 months to 18 years) who received DEX infusion (>6 hours) in a referral Brazilian Pediatric Intensive Care Unit (PICU) between November 2011 and June 2014. The local Ethical and Research Committee approved the study.

We used DEX infusion starting at 0.3 µg/kg/hr and increasing up to 0.7 µg/kg/hr, at the discretion of the medical assistant, depending on clinical goals and child response. Two researchers collected the data in the medical chart. Demographic data, the main indications, the initial and maximal dose, length of use, the side effects related to DEX infusion, as well as the Heart Rate, systolic, diastolic and the mean arterial pressure (MAP) were evaluated at onset, 6 and 24 hours of continuous DEX infusion.

RESULTS

Prolonged DEX infusion was administered to 77 children with median (IQR) age of 15 [4, 84] months, weight of 10 [5.7, 20] kg and length of PICU stay of 8 [5,14] days (***Table* I**). The median (IQR) PIM score was 0.82 [0.3, 4], with a mortality rate of 9% (7 children).

Five groups were identified as the main indications for prolonged DEX infusion: mechanical ventilation weaning (32.5%), postoperative period of neurosurgery and upper airway surgery (24.7%), non-invasive mechanical ventilation (13%), refractory tachycardia (6.5%) and others (23.3%). There were no differences between the five groups (P=0.443) regarding the mean

TABLE I CHARACTERISTICS OF CHILDREN RECEIVING DEXMEDETOMIDINE INFUSION IN THE PEDIATRIC INTENSIVE CARE UNIT (*N*=77)

Variable	*Median (IQR)*
Age (mo)	15 (4-84)
Weight (kg)	10 (7-20)
Length of PICU stay (d)	8 (5-14)
PIM Score (%)	0.82 (0.29-4)
Length of infusion (h)	48 (24-96)
Mortality, *n* (%)	7 (9)
Diagnosis, n(%)	
Respiratory disease	36 (46,8)
Post-surgical Sepsis/Shock	33 (42.8) 6 (7.8)
Others	2 (2.6)

PICU: *Pediatric intensive care unit; PIM*:*Pediatric Index of Mortality*.

initial dose of DEX infusion, maximal dose, and mean length of DEX infusion (***Table* II**).

The heart rate and the MAP decreased significantly (*P*=0.01) after 6 hours of DEX infusion when compared to the pre-infusion levels. However, when comparing the means values of heart rate and MAP over the 3 time periods (pre-infusion, 6 h and 24 h of infusion), there were no differences (*P*=0.80 and 0.38, respectively).

Opioids, midazolam and/or ketamine were concomitantly administered with DEX in 28 children (36.3%). In six children (8%), DEX was withdrawn in view of possible side effects: hypotension (4), bradycardia (1) and somnolence (1).

DISCUSSION

We demonstrated that DEX can be used in different circumstances in the PICU (*e.g,* facilitating non-invasive mechanical ventilation, to treat/prevent abstinence syndrome, as sedative in the post-operative period, adjunct treatment of symptomatic tachycardia). The average of initial and maximal dose of DEX infusion in our study was in the low range, demonstrating that even at a lower dose, the desired effects are achieved with only occasional side effects.

Bradycardia and hypotension induced by DEX are related to brain and spinal medulla receptor's inhibition of norepinephrine release [2,9,10]. Reduction on HR and MAP 6 hours after DEX onset, without difference in the following 24 hours, has also been observed with conventional sedatives and analgesics [3,6]. Hypotension induced by DEX has been more frequently associated with intravenous bolus than with constant infusion [3]. This could be the reason for the low number of patients in our study presenting relevant hypotension demanding DEX withdrawal.

Originally, DEX infusion was recommend for short periods. Several pediatric studies support its use over prolonged periods [11-13]. Walker, *et al*. [12] reported an average of DEX infusion of 11 (2 to 50) days, with a median dose of 0.5 µg/kg/h, without major side effects. Reiter, *et al*. [4] demonstrated prolonged DEX use in children (110 ± 83h) with initial dose of 0.36 (0.16) µg/kg/h and maximal dose of 0.65 (0.34) µg/kg/h, without significant side effects [4]. Even considering the possible limitations of our study (retrospective analysis of the medical chart), our findings are consistent with other similar studies, highlighting the potential, safety, and spectrum of DEX infusion in critically ill children.

Contributors: All authors participated in study design, data collection, data analysis, manuscript writing, and its final approval.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? J Intensive Care Med. 2012;27: 219-37.

TABLE II CHARACTERISTICS OF DEXMEDETOMIDINE INFUSION AS PER INDICATION FOR USE

	Initial Dose (µg/kg/h)	*Maximal Dose (µg/kg/h)*	*Length of infusion (h)*
MV weaning (*n*=25)	0.37 (0.06)	0.42 (0.09)	94.4 (101.3)
Post-opertive (*n*=19)	0.32 (0.08)	0.43 (0.13)	57.5 (38.4)
NiMV (*n*=10)	0.36 (0.05)	0.43 (0.11)	34.4 (29.2)
Refractory Tachycardia (*n*=5)	0.33 (0.08)	0.39 (0.14)	66.0 (63.6)
Others (*n*=18)	0.36 (0.10)	0.45 (0.11)	87.2 (74.5)
P value	0.443	0.903	0.716

*MV: Mechanical ventilation; NiMV: Non-invasive mechanical ventilation. *The initial and maximal doses were compared by the ANOVA one way while the Kruskall Wallis test was used to compare the length of DEX infusion between the groups.*

WHAT THIS STUDY ADDS?

• Dexmedetomidine infusion is effective with few side-effects when used in children.

2. Panzer O, Moitra V, Sladen RN. Pharmacology of sedative-analgesic agents: Dexmedetomidine, Remifentanil, Ketamine, volatile anesthetics, and the role of peripheral Mu antagonists. Crit Care Clin. 2009;25: 451-69.
3. Hsu CD, Cravero JP. Pharmacologic agents for pediatric procedural sedation outside of the operating room. UpTo Date. Available from: *www.uptodate.com/online*. Accessed July 6, 2014.
4. Reiter PD, Pietras M, Dobyns EL. Prolonged dexmedetomidine infusions in critically ill infants and children. Indian Pediatr. 2009;46:767-73.
5. Chrysostomou C, Schmitt CG. Dexmedetomedine: sedation, analgesia and beyond. Expert Opin Drug Metabo Toxicol. 2008;4:619-27.
6. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8:115-31.
7. Burbano NH, Otero AV, Berry DE, Orr RA, Munoz RA. Discontinuation of prolonged infusions of dexmedetomidine in critically ill children with heart disease. Intensive Care Med. 2012;38:300-7.
8. Zhang X, Zhao X, Wang Y. Dexmedetomedine: a review of applications for cardiac surgery during perioperative period. J Anesth. 2015;29:102-11.
9. Chrysostomou C, Beerman L, Shiderly D, Berry D, Morell VO, Munoz R. Dexmedetomidine: A novel drug for the treatment of atrial and junctional tachyarrhythmias during the perioperative period for congenital cardiac surgery: a preliminary study. Anesth Analg. 2008;107:1514-22.
10. Whalen LD, Di Gennaro JL, Irby GA, Yanay O, Zimmerman JJ. Long-term Dexmedetomidine use and safety profile among critically ill children and neonate. Pediatr Crit Care Med. 2014;15:706-14.
11. Su F, Nicolson SC, Zuppa AF. A dose-response study of dexmedetomidine administered as the primary sedative in infants following open heart surgery. Pediatr Crit Care Med. 2013;14:499-507.
12. Walker J, Maccallum M, Fischer C, Kopcha R, Saylors R, McCall J. Sedation using dexmedetomidine in pediatric burn patients. J Burn Care Res. 2006;27:206-10.
13. Prasad SR, Simha PP, Jagadeesh AM. Comparative study between dexmedetomidine and fentanyl for sedation during mechanical ventilation in post-operative paediatric cardiac surgical patients. Indian J Anaesth. 2012;56:547-52.