Case Series

Dexmedetomidine for the Difficult to Sedate PICU Patient: A Case Series

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Abstract

Background: In the PICU many patients require prolonged sedation with opioids and benzodiazepines. Tolerance to those agents is often problematic. Many of these patients also require adjunct paralysis. Dexmedetomidine is a new sedative agent that may prove useful for these patients.

Objective: Evaluate the effectiveness of Dexmedetomidine on our difficult to sedate PICU patients.

Methods: We performed a retrospective chart review on patients that had received Dexmedetomidine in our PICU. We evaluated the effects of sedative dosing for those patients and any changes in doses that occured. Side effects were also evaluated.

Results: We found a decreased sedative dose requirement, and less use of muscle relaxants. Also noted was a decreased methadone requirement in those patients that received Dexmedetomidine. Side effects were minimal.

Conclusion: The use of dexmedetomidine seemed to be helpful in managing patients in our PICU that were difficult to sedate. Further analysis of Dexmedetomidine use in other patients, as well as cost analysis would be useful.

INTRODUCTION

In the Pediatric Intensive Care Unit (PICU), some patients require the need for prolonged sedation. Due to both the development of opiate and benzodiazepine tolerance [1], this may become difficult to achieve satisfactorily and often requires adjunct paralysis. Other sedative agents have been tried, propofol use is limited due to the risk of developing propofol infusion syndrome [2]. Ketamine has raised concerns about psychiatric manifestations post infusion [3]. Inhalational anesthetic agents, although effective sedation agents, require specialist delivery equipment and are usually outside the realm of practice of most pediatric intensivists [4]. Dexmedetomidine, an alpha2 receptor agonist, is a newer sedative agent providing another alternative regimen in terms of sedation [5]. It has been shown to be an effective sedation agent for either moderate [6], or deep procedural sedation [7]. It may be effective even in those patients that have become tolerant to the more commonly used sedative options. In fact, clonidine, a less potent alpha2 agonist, has been used for treating opiate withdrawal syndrome [8]. Dexmedetomidine may have several advantages when used for ICU sedation [9], such as a lower incidence of delirium, a safe side effect profile, and the ability to rouse patients if necessary. Although there are limited large scale randomized studies involving dexmedetomidine in pediatric patients, reviews have suggested that it has the potential to provide significant benefits over standard sedation regimens used presently [10,11]. However, Dexmedetomidine is not FDA approved for pediatric ICU sedation. Over the past few years, we have used dexmedetomidine in our PICU under the direction of our pharmaceutical and therapeutics committee to evaluate its clinical use for the difficult to sedate PICU patient.

In the PICU, critically ill children require sedation, usually deep in nature, when intubated to prevent accidental extubation or loss of central or arterial line access. Due to tolerance development [12], the dosing requirement tends to escalate over time. This can result after several weeks of receiving high dosing in sedation and still requiring the concomitant use of paralysis. The aim of this retrospective study was to review the use of dexmedetomidine sedation in our PICU in difficult to sedate patients.

METHODS

After IRB approval, we identified all patients who had received dexmedetomidine in the PICU. The indication for dexmedetomidine use in our PICU during this period was

difficult to sedate patients with high dose opiates (> 10 mcg/kg/hour fentanyl equivalents) plus benzodiazepine or paralysis. The use of dexmedetomidine was considered if this high dose combination regimen sedation was proving clinically ineffective and or weaning to extubation was desired in a paralyzed patient in whom stopping paralysis would usually require a significant increase in sedation dosing to continue with a patient safe sedation plan. A retrospective medical chart and PICU quality assurance (QA) database review was performed to evaluate all the sedative dosing: prior to, during, and after dexmedetomidine infusion, as well as the use of muscle relaxants. Any cardiovascular changes during and after the dexmedetomidine infusion were recorded. We also collected patient demographics, PICU length of stay mortality, and evaluated the chart for any side effects.

RESULTS

Over a 30 month period, we identified 31 patients who had received dexmedetomidine in our PICU. Of these patients, 28 were receiving high dose opiates for sedation prior to starting the dexmedetomidine infusion. Patient demographics for these 28 children are shown in Table 1. The mean patient age was 4 years old, and all patients had extensive ICU stays.

Their sedation dosing requirements are shown in Table 2. All patients were on high opiate doses (many requiring sufentanil). All the opiate doses were converted to fentanyl equivalents to allow for easy comparison. The conversion factors used (Table 2) are those we use in our PICU when converting from one opiate to another depending on the clinical indications for each patient.

Most commonly, we convert fentanyl at a dose of 20 mcg/kg/hr to sufentanil for fluid balance reasons. Many of the children were also receiving high dose midazolam infusions (mean high dose 0.4 mg/kg/hr) and most were paralyzed (cis-atracurium).

The dexmedetomidine infusion was started about 2 weeks into their PICU stay. The dexmedetomidine infusion data is shown in Table 3. A bolus dose was used in half of the patients. The dose requirement for dexmedetomidine doubled over its average infusion of 4 days. In 13 patients, the infusion was continued into the post-extubation period for up to 72 hours.

During the dexmedetomidine infusion, we were able to reduce the opiate and benzodiazepine doses significantly (†$p <$ 0.05) in most of the patients. Changes in sedation dosing related to dexmedetomidine use are shown in Table 4. All patients were on high dose opiates when the infusion was started (> 20 mcg/kg/hr fentanyl equivalents). The opiate dose was reduced on average by 60% and opiates were successfully discontinued in over 75% of the patients. The results for midazolam were very similar.

The use of paralysis was discontinued in all but 2 patients. One patient was very difficult to sedate and eventually died; proper comfort measures were taken. The other patient's sedation quality improved dramatically both by bispectral index monitoring and bedside assessment. In the patients weaned off paralysis, all were successfully extubated within 5 days of starting the dexmedetomidine.

Table 1: Patient Demographics (High Dose Opiate Patients Only).

n =28	Gender	Age (years)	Weight (kg)	Mortality (%)	LOS (days)
Mean	13 M / 15 F	4.0	17.5	3.6	23.7
SD	X	6.0	18.7	X	16.8

LOS: length of PICU stay

Table 2: Sedation / Paralysis Requirements (opiates as fentanyl equivalent doses).

	High Fentanyl Dose (mcg/kg/hr)	High Sufentanil Dose (mcg/kg/hr)	High Midazolam Dose (mg/kg/hr)	High Cis-Atracurium Dose (mg/kg/hr)
	n = 27	n = 15	n = 27	n = 15
Mean	14.1	39.0	0.42	0.50
SD	4.3	27.0	0.50	0.21

All opiates doses were converted to fentanyl equivalents.
1 mcg/kg/hr sufentanil = 5 mcg/kg/hr fentanyl

Table 3: Dexmedetomidine Dosing.

	Mean	SD
Start day (PICU duration)	13.8	8.3
Duration infusion (days)	4.3	1.8
Bolus dose (n = 13) (mcg/kg over 10 mins)	0.39	0.16
Starting infusion dose (mcg/kg/hr)	0.40	0.15
Highest infusion dose (mcg/kg/hr)	0.77	0.37
Starting post extubation dose	?	?
Duration of Post extubation infusion (n= 13) (hrs)	31.2	19.3

The use of methadone in these patients who received dexmedetomidine is shown in Table 5. The majority of these patients received methadone on extubation due to the high doses of opiates that had been used with the subsequent high risk of withdrawal. In our PICU the methadone dose used is based upon the recent highest dose of opiate used prior to extubation [12]. As shown in Table 5, the daily dose of methadone used for all patients was high (1.7mg/kg/day) as the fentanyl dose used to calculate this was also high (23.3 mcg/kg/hr). This predicts a methadone dose of: 23.3 * 24 hrs * 3 doses = 1.7mg/kg day. When patients were extubated on dexmedetomidine, a lower dose of methadone was used, which was also significantly less than that predicted from their opiate infusion dose (p < 0.05).

With respect to complications, one patient required 2 transient pauses in the dexmedetomidine infusion for bradycardia; this may be related, in part, to the recent use of a loading dose of dexmedetomidine. No treatment was required for the bradycardia. Otherwise, there appeared to be little change overall in the HR and BP during and after the dexmedetomidine infusion (Table 6).

We also used dexmedetomidine in 3 other patients (Table 7). These were patients who required sedation and either did not respond to low doses of IV benzodiazepines, or had significant airway concerns. In all of these patients, 2 days of successful sedation was provided without any complications. In the latter 2 patients with airway concerns, we felt that we had avoided the need for intubation.

DISCUSSION

This retrospective review of dexmedetomidine use in our PICU demonstrated several benefits in a select population of sedated patients. Dexmedetomidine is a new drug that has not yet been approved by the FDA for pediatric use. We chose to evaluate its use in the PICU under the guidance of our pharmacy and therapeutics committee (P&T). In our hospital, the P&T committee is responsible for determining the drug formulary. When new drugs come onto the market, they have to be approved by the P&T committee in order for them to be added to the formulary. We have previously evaluated dexmedetomidine, under guidance of the P&T committee in our institution, for deep sedation provided for MRI procedures in children by anesthesia [13].

As with most new drugs, dexmedetomidine is expensive and the current sedation regimens we use in most of our patients based upon fentanyl and midazolam are significantly cheaper. Sedation with dexmedetomidine costs 11.7 times more than fentanyl and 6.3 times more than midazolam [14]. We decided to use dexmedetomidine as an adjunct in a select group of PICU patients who were difficult to sedate. Dexmedetomidine often performs better as an adjunct [13], than as a sole sedation agent, where high doses may be required.

We found the use of dexmedetomidine to be helpful in effectively sedating these difficult patients. An added benefit was the ability to reduce both the opiate and benzodiazepine doses significantly during this period. This, along with the ability to stop paralysis, allowed us to start ventilation weaning (to successful extubation) without the usual requirement for more post-paralysis opiates or benzodiazepines.

Dexmedetomidine appears to provide sedation similar to natural sleep and it has an opiate sparing, as well as a sympatholytic effect [10]. Both of these are useful during weaning from a previous high dose opiate sedation regimen. Also, the

Table 4: Change in Sedation/Paralysis Dosing During Dexmedetomidine Infusion.

	Starting Opiate (mcg/kg/hr)	Lowest Opiate (mcg/kg/hr)	Starting BDZ (mg/kg/hr)	Lowest BDZ (mg/kg/hr)	Starting Cis-Atra (mg/kg/hr)	Lowest Cis-Atra (mg/kg/hr)
Mean	21.89	8.07	0.43	0.07	0.50	0.05
SD	14.22	15.10	0.51	0.12	0.21	0.14
% Patients Drug discontinued	x	61	x	61	x	87
% Dose Reduction	x	76.1	x	75.90	x	90.18

BDZ: Benzodiazepine; Cis-Atra: Cis-atracurium

Table 5: Methadone Use (Mean ± SD) and Extubation.

(n=27 : survivors)	All Patients	Extubated on Dexmedetomidine	Extubated off Dexmedetomidine
Day PICU methadone started	16.5 ± 9.9	17.2 ± 11.4	15.5 ± 7.9
Starting Methadone Dose (mg/kg/day)	1.2 ± 1.8	1.7 ± 2.3	0.6 ± 0.2
Last Opiate dose (mcg/kg/hr)	23.3 ± 24.2	27.5 ± 31.1	17.7 ± 9.3
Predicted Methadone Dose (mg/kg/day)	1.7 ± 1.7	2.0 ± 2.2	1.3 ± 0.7
% Predicted dose	71.6 ± 30.7	84.9 ± 26.4*	59.7 ± 33.3*
Dexmedetomidine dose post extubation (mcg/kg/hr)	X	X	0.47 ± 0.17

Predicted methadone dose = Total daily fentanyl dose in mcg (or fentanyl equivalents) given as methadone IV every eight hours, weaned as appropriate.
* p < 0.05

Table 6: Hemodynamic Changes on Dexmedetomidine Infusion (Compared to Pre Dexmedetomidine Day).

	On Dexmedetomidine	Post Dexmedetomidine
% Change Daily High Systolic BP	-2.7	-4.3
% Change Daily Low Systolic BP	-6.1	-16.5
% Change Daily High Heart rate	-3.4	-1.5
% Change Daily Low Heart rate	5.3	-3.1

Table 7: Other Patients in the PICU who received Dexmedetomidine.

Diagnosis	Age	Reason for Use	Duration	Lo / Hi Dose
S/P Pulm Stenosis repair	5	Would not settle on midazolam	2	0.5 / 0.5
Stridor (not intubated)	3 month	When agitated, resp. distress / avoid intubation	3	0.5 / 0.6
RSV (not intubated)	1 year	When agitated, resp. distress / avoid intubation	2	0.3 / 0.7

reduced risk of respiratory depression makes it a useful agent during the peri-extubation period.

Dexmedetomidine use is associated with a higher drug cost. Studies have shown that the use of a dexmedetomidine sedation regimen in the ICU can shorten the time to extubation and as such reduce the ICU component cost of care [15]. In our described PICU population, patients were sedated, often not to the desired clinical level, on extremely high doses of opiates, benzodiazepines, and many were paralyzed. Getting these patients to a successful extubation platform can be very difficult .We used dexmedetomidine as an adjunct to facilitate weaning to extubation, with our ICU costs offset related both by: the reduced use of other sedatives and paralytics, as well as a shortened ICU stay due to earlier successful extubation in most cases. The cost savings are especially notable with the ability to stop cis-atracurium as it costs about 5 times less to replace the cis-atracurium with dexmedetomidine [16].

A small loading dose was used initially, however we decided to stop the load due to the episode of bradycardia noted in one patient immediately after the dexmedetomidine bolus had completed. The absence of a load was not clinically apparent and no further bradycardia noted. Bradycardia has been reported when dexmedetomidine is used in the PICU. There is also the potential for a drug interaction predisposing to bradycardia such as with digoxin [17]. Hypotension and hypertension have also been reported, especially in high doses (> 1.5 mg/kg/hr). However, in a comparison of dexmedetomidine with propofol for deep sedation [18], the blood pressure was maintained in the dexmedetomidine compared to the hypotension experienced with propofol. Some tolerance to dexmedetomidine was experienced over the period of the infusion. This may also have reflected, and increased, need due to the significant reduction in the doses of the other sedative agents. Tolerance to dexmedetomidine, as with most other sedative agents, is to be expected.

For longer-term infusions, it may be prudent to continue the dexmedetomidine post-extubation and gradually wean the dose over the next 24 -36 hours. Abrupt withdrawal of dexmedetomidine after long-term infusion may cause tachycardia and hypertension [19], which may also cause some confusion with the diagnosis of opiate withdrawal. An adult study [20], demonstrated mild withdrawal symptoms in about 15% of patients who had received dexmedetomidine infusion for greater than 24 hours. In pediatric patients, withdrawal like phenomena has been reported in up to 30% after long term infusion [21]. Post-extubation dexmedetomidine weaned over 24 - 48 hours may also prove useful in preventing any withdrawal of agitation post-extubation and ensure the child is more comfortable. Dexmedetomidine has less respiratory depressant effects than most other sedatives and post extubation may reduce the need for other boluses of adjunct sedative agents. The use of clonidine has also been reported for the hypertension / tachycardia that may occur after ceasing dexmedetomidine infusion [21].

We routinely use methadone in all patients who have been on long-term opiate infusions (to good effect). The methadone requirements were much less in those extubated on dexmedetomidine. This is not unexpected as there are case reports of its use to prevent or treat opiate withdrawal [22]. This lower starting methadone dose may reduce the time spent weaning off the methadone.

The use of dexmedetomidine for non intubated patients in the PICU may also be a useful indication. The three children we reported all did very well, as well as the 13 children who were extubated on the dexmedetomidine. The child with respiratory distress who is not yet intubated but becoming more agitated is a difficult sedative scenario. There are many reasons for the agitation: respiratory distress, unfamiliar surroundings, young age, pain, drug therapy (continuous nebulized albuterol) and medical interventions. The agitation may eventually push the child towards intubation especially those with stridor, which gets worse with the child's distress. This non-intubated use has also been reported in adults receiving non-invasive positive pressure ventilation [20]. We believe that dexmedetomidine may be a useful choice in this scenario along with its effects of slowing the heart rate and being cardiovascularly stable with minimal risk or respiratory depression.

CONCLUSION

After following the recommendations of our P&T committee in the evaluation of the new and relatively expensive dexmedetomidine in our PICU, we found that dexmedetomidine

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was useful in sedating these difficult to sedate children in the PICU. The bridge to weaning and extubation with the ability to stop paralysis, wean opiates and benzodiazepines, and extubate within 5 days is very helpful. The use in non intubated children with respiratory distress was another successful arena for its use.

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