ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Is the Use of Dexmedetomidine during Extubation is Safer and More Effective than Midazolam for in Pediatric Patients?

Ganime Ayar[1]* and Serhat Emeksiz[2]

[1]*Department of Pediatric Intensive Care Unit, Ministry of Health, Ankara City Hospital, Bilkent, Ankara, Turkey*

[2]*Pediatric Intensive Care Specialist, Department of Pediatric Intensive Care Unit, Ministry of Health, Ankara City Hospital, Bilkent, Ankara, Turkey*

***Corresponding Author:** Ganime Ayar, Department of Pediatric Intensive Care Unit, Ministry of Health, Ankara City Hospital, Bilkent, Ankara, Turkey.

Received: April 14, 2020; **Published:** August 08, 2020

Abstract

Purpose: This study aims to evaluate how dexmedetomidine impacts extubation success as well as its adverse effects in comparison with midazolam among pediatric patients.

Methods: Children between 1 and 18 years following the intubation in the PICU and who had undergone either dexmedetomidine (dex) or midazolam (mid) infusion after extubation were included to the study. Dex or mid infusion was started after extubation for all of these patients. Patients' data was retrospectively obtained from patient files.

Results: A total of 218 patients were included in our analysis: 126 patients in the dexmedetomidine group (DEXg) and 92 patients in the midazolam group (MIDg). The rate of failed extubation was 15% in DEXg compared to 38% in MIDg, which is statistically significant ($p < 0.05$).

Conclusion: Leaving from ventilation rates were more significantly in patients who received dex after extubation. So, during the weaning period immediately after the extubation, the use dex instead of mid increases the success of extubation due to a lack of respiratory depression and its side effects.

Keywords: *Dexmedetomidine; Mechanical Ventilation; Weaning; Children; Pediatric Intensive Care Unit*

Introduction

Sedative agents such as opioid and/or benzodiazepine are commonly used for patients to whom mechanical ventilation is applied due to a need for respiratory support until extubation in order to prevent pain and/or agitation, and thus to ventilate lungs more efficiently as well as prevent accidental extubations [1]. The sedation of patients over a long time period can cause failed to extubation, reintubation, or prolonged mechanical ventilation duration even if the sedative drugs are stopped [1,2]. There are many challenges, especially for pediatric patients, such as agitation, delirium, and withdrawal due to the stopping of sedatives during preparation of the patients for extubation, thus preventing the weaning of patients needing to be re-sedated due to an increase in tachycardia and tachypnea [3,4]. This causes prolonged duration of dependence on ventilators, extended stay at intensive care units, and an increase in mortality and morbidity [5,6]. This leads to need for a sedative drug that is safe in terms of its adverse effects, and that does not suppress respiration during preparation

for extubation. Dexmedetomidine (dex) is a selective alpha-2 receptor agonist with a broad range of pharmacological qualities. Alpha-2 receptor agonists provide analgesia, reduce anxiety, and provide sedation without respiratory depression [7-9]. Over the past 10 years, dex has emerged as a usable option for sedation of critically ill children. Even though its use is limited in many North American Pediatric Intensive Care Units, dex is attractive because of its favorable hemodynamics and lack of respiratory depression [10]. Potential adverse events during sedation with dex include hypotension, hypertension, nausea, bradycardia, and atrial fibrillation [11].

Midazolam (mid) and lorazepam are the benzodiazepines that are optimal for sedation in the PICU because they can be implemented by either intermittent or continuous infusion and have a relatively short duration of effect. Benzodiazepines bind to specific receptors in the gamma aminobutyric acid (GABA) receptor complex, which raises the binding of this inhibitory neurotransmitter [12]. Anxiolysis is reached at low doses. Higher doses are associated with sedation, muscle relaxation, anterograde amnesia, anticonvulsant effects, and both respiratory and cardiovascular depression [13].

Benzodiazepines are used for sedation of patients who are agitated after extubation at our hospital's Pediatric Intensive Care Unit (PICU), however, the use of dex has also increased in recent years.

Aim of the Study

This study aims to compare dex and mid in terms of their success rate of when it comes to extubation and drug safety for pediatric patients needing sedation after extubation.

Methods

Participants

This study was conducted on patients admitted to the PICU between September 2016 and August 2018. The requirement for written, informed consent was waived due to the nature of the study. However, in order to follow our institution's policy, informed parental consent was obtained from patients verbally over the phone. Our research was conducted in accordance with the Declaration of Helsinki and was approved by the Local Research Ethics Committee. Children between 1 and 18 years of age following the intubation in PICU and who had undergone dex or mid infusion after extubation were included in the study. Patient exclusion criteria were as follows:

1. Patients age < 1 month or > 18 years,
2. Patients using a combination of opioids/benzodiazepines for sedation analgesia after extubation,
3. Patients with muscle blockage,
4. Patients with congenital airway abnormalities,
5. Patients on extended ventilation (more than seven days) and
6. Patients with incomplete file records.

The following data was obtained from patient files:

- Demographics (age, gender, primary diagnosis),
- Information about mechanical ventilation (i.e. indications of intubation, ventilation mode, duration of intubation, ventilator settings before extubation, extubation time, after extubation; reintubation, need for non-invasive mechanical ventilation (NIV-MV)),
- High flow oxygen therapy (HFOT),
- Type of treatment used for sedation and analgesia, initial dose and total dose,
- Duration of the infusion,
- Whether there is any side effect related to sedation,

- Requirement for additional sedation and inotropic support,
- Length of stay at PICU and
- Mortality status.

Measures

In order evaluate the safety of the drug, we collected hemodynamic parameters including heart rate, mean arterial pressure, and saturation of oxygen. Vital findings (i.e. heart rate, saturations of oxygen) of all the patients in PICU are routinely monitored through monitors connected to a central screen, whereupon non-invasive blood pressure is measured every hour and monitored from the same screen. The mean arterial pressure (MAP) and heart rate (HR) at different time points (two (B2h) and one hour before extubation (B1h), as well as one (A1h), two (A2h), four (A4h), eight (A8h), and twenty-four hours after extubation (A24h)) were obtained from nurse observation records. The period of time from intubating the patient to weaning was defined as the intubation duration time. Given that institutional protocol, midazolam and/or fentanyl infusion is used for sedation and analgesia of intubated patients, the use of MV is thus monitored at our clinic. We stop sedatives and analgesics before extubation, and we wait for patient to wake up. The decision regarding extubation readiness is based on several observations following criteria:

- Whether the patient was alert and awake or not,
- Hemodynamic stability,
- Oxygen saturation > 90%,
- Positive inspiratory pressure < 20,
- Positive end expiratory pressure < 7 cm H_2O,
- Normal blood gas results and
- Stable ventilation and oxygenation.

Patients identified for extubation typically have normal lung function and hemodynamics. Signs of withdrawal were defined according to a Withdrawal Assessment Tool-Version 1 (WAT-1) score > 3 [14].

Patients were divided into 2 groups: those receiving dex infusion after extubation; dexmedetomidine group (DEXg) and those receiving midazolam infusion; midazolam group (MIDg). Each group was evaluated in terms of side effects, drug dose, drug infusion time, the need for non-invasive mechanical ventilation, the need for reintubation, length of stay at PICU and mortality status.

Statistical analysis

The Shapiro-Wilk test was used to check to see whether the continuous variables in the study were normally distributed. Descriptive statistics were expressed in terms of numbers and percentages for categorical variables as well as in terms a mean, standard deviation, and median (Interquartile Range: IQR) for numerical variables. Normally distributed variables were expressed in terms of mean ± standard deviation (M ± SD), whereas non-normally distributed variables were expressed in terms of median and IQR or (25 - 75th percentile). The Mann-Whitney U test was employed for two group comparisons of the non-normally distributed numerical variables. The changes in Mean Arterial Pressure (MAP) and heart rate values were compared using the Wilcoxon signed rank test. A logistic regression analysis was used for evaluate the factors that effect on extubation success. Statistical significance was considered in terms of p values < 0.05. IBM SPSS for Windows 21.0 (IBM Corp. Released 2012, Armonk, NY) was used for analyses and calculations.

Results

1,950 patients were admitted to the PICU between September 2016 an August 2018. The medical records of 493 patients requiring intubation among the patients were examined, whereby 275 of them were excluded. 211 patients were excluded for not meeting the in-

clusion criteria, and 64 patients were excluded due to incomplete medical records (Figure 1). A total of 218 patients were included in our analysis: 126 patients in the dexmedetomidine group (DEXg) and 92 patients in the midazolam group (MIDg). There was no difference in terms of age, gender, or follow-up diagnosis. Patient characteristics and demographics are presented in table 1. Dex was infused at a dose between 0.1 and 0.4 μg/kg/h, with the median initial dose being 0.27 μg/kg/h. The median initial dose of mid was 0.07 mg/kg/h and the maximum dose was increased up to 0.55 mg/kg/h. No loading dose was administered to any of the patients. The rate of ailed extubation was 15% in DEXg, compared to 38% in MIDg, which in turn is statistically significant ($p < 0.05$). Additionally, the duration of stay in the PICU was significantly longer in MIDg ($p < 0.05$) (Table 2). Multivariable analysis revealed that precedex was a significant factor upon it being adjusted for the children's age and type of disease.

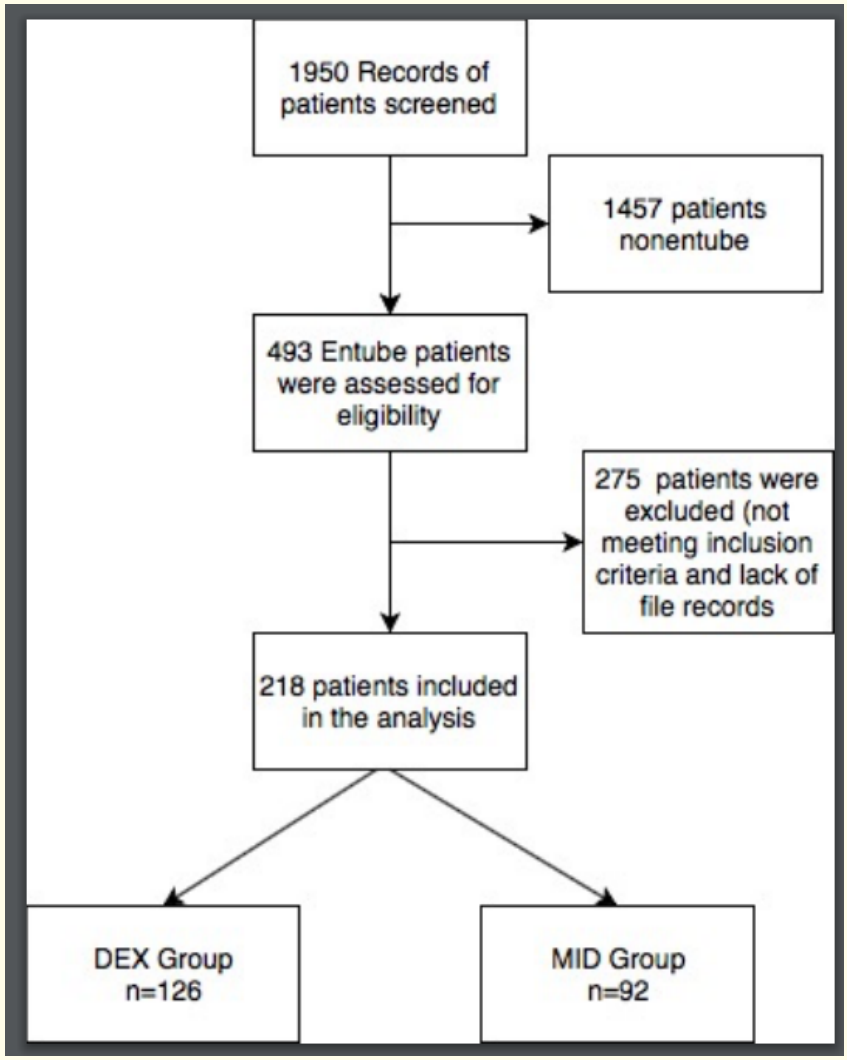

Figure 1: *Patient enrollment flow.*

Group	DEX Group	MID Group	P value
Age, months, median (IQR)	33.0 (15.0 - 72.0)	43.0 (22.3 - 78.0)	NS
Sex (male/female), n	64/62	47/45	NS
Diagnosis, n, %			
Sepsis	19 (15)	18 (20)	NS
Trauma	21 (17)	15 (16)	NS
Postop	16 (13)	13 (14)	NS
Pneumonia	15 (12)	11 (12)	NS
Bronchiolitis	10 (8)	9 (10)	NS
Metabolic disease	12 (10)	8 (9)	NS
Encephalitis	4 (3)	2 (2)	NS
Meningitis	3 (2)	2 (2)	NS
Acute encephalopathy	4 (3)	2 (2)	NS
Asthma	5 (4)	4 (4)	NS
Other	16 (13)	8 (90)	NS
Dose of Drug infusion median, (IQR)			
İnitial dose (mc/kg/h)	0.27 (0.30 - 0.50)	0.07 (0.05 - 0.10)	
Max Total dose (mc/kg/h)	0.30 (0.30 - 0.50)	0.16 (0.05 - 0.55)	
Infusion duration (after MV), hours, median, (IQR)	48 (33.8 - 72)	29 (20.5 - 48)	< 0.001

Table 1: *Demographic profile.*

IQR: Interquartile Range; N: Number; mc/kg/h: Microgram Per Kilogram Per Hour; MV: Mechanical Ventilation; NS: Nonsignificant.

Group	Group DEX	Group MID	P value
Failed extubation, n, %	19 (15)	35 (38)	< 0.001
Need of NIV, n, %	58 (46)	52 (56)	NS
NIV-MV	24 (19)	19 (20)	NS
HFOT	34 (27)	33 (36)	NS
Extubation duration time, (hour), median, IQR	52 (29.5 - 99.0)	47 (28.5 - 109.5)	NS
PICU Time, (day), median, IQR	4.0 (3.0 - 7.0)	5.5 (3.1 - 11.0)	=0.004

Table 2: *Comparison of failed extubation, need of NIV and PICU time between each group.*

NIV: Noninvasive Ventilation; MV: Mechanical Ventilation; HFOT: High Flow Oxygen Therapy; IQR; Interquartile Range; NS: Nonsignificant.

There also was a difference between two groups in terms of sedative drug infusion durations ($p < 0.001$).

here was no difference in MIDg when the median values of mean arterial pressures (MAP) were compared either before or after sedation; however, there was a slight difference in MAP both before and after the initiation of dex. There was no clinical hypotension considering the percentiles suitable for the age and height of the patient. Comparison of hemodynamic indexes between the MIDg and DEXg during before and after extubation was summarized in table 3. All patients with bradycardia fell in the DEXg, whereby the median age was 12 months, the initial dex infusion median dose was 0.3 (IQR = 1.75 - 0.3) µg/kg/h, and the lowest recorded heart rate was A1h and A2h (Table 4). The infusion of dex was stopped in two of the patients with bradycardia, whereupon they were continued with half a dose after pausing for 1 hour in three patients with bradycardia. There was no problem recorded in any of the patients during follow-up.

Time	B2h	B1h	A1h	A2h	A4h	A8h	A24h
HR (beats/minute), median, IQR							
Group DEX	111.0 (95.0 - 123.0)	105.0 (95 - 121.0)	100.0 (87.0 - 117.0)	100.0 (88.0 - 120.0)	108.0 (88.0 - 120.0)	105.0 (92.0 - 120.0)	110.0 (94.0 - 120.0)
Group MID	102 (98 - 112)	105 (96 - 117.3)	103.5 (95.5 - 115.8)	102.0 (92.5 - 116.5)	99.0 (90 - 115.8)	100.5 (94.3 - 117.8)	98.0 (90.3 - 112)
MAP (mm/Hg), median, IQR							
Group DEX	75.5 (71.8 - 85.0)	76.0 (71.8 - 85.0)	75.5 (71.0 - 85.0)	75.5 (71.0 - 85.0)	76.0 71.8 - 85.0)	76.0 (71.0 - 85.0)	75.5 (71.0 - 85.0)
Group MID	77.0 (69.3 - 86.0)	77.0 (70.0 - 85.8)	77.0 (69.0 - 85.8)	77.5 (69.3 - 86.0)	77.0 (70.0 - 85.8)	77.0 (70.0 - 85.8)	77.0 (69.0 - 85.8)

Table 3: *Comparison of hemodynamic indexes between each group during, before, and after extubation.*
MAP: Mean Arterial Pressure; HR: Heart Rate; DEX: Dexmedetomidine; MID: Midazolam; IQR: Interquartile Range.

Group	DEX group
Age (months, median, IQR)	12.0 (6.5 - 18.0)
Sex (male/female), n	3/2
HR (beats/minute), median, IQR	
B2h	128.0 (117.5 - 131.0)
B1h	125.0 (116.0 - 131.5)
A1h	58.0 (51.5 - 78.0)
A2h	120.0 (53.5 - 120.0)
A4h	125.0 (99.0 - 129.0)
A8h	119.0 (106.0 - 127.5)
A24h	122.0 (110.5 - 128.5)
Dose of Drug infusion median, (IQR), İnitial dose (mc/kg/h)	0.30 (1.75 - 0.30)
Infusion duration (after MV), hours, median, (IQR)	72.0 (48.0 - 84.0)

Table 4: *Characteristics of patients with bradycardia.*
Heart rate (HR) at different time points (two (B2h) and one hour before extubation (B1h);
one (A1h), two (A2h), four (A4h), eight (A8h), and twenty - four hours after extubation (A24h); Interquartile Range.

Moreover, none of the patients were reported to have any drug withdrawal or any abnormalities such as hallucination or delirium. All of the patients included in our study survived.

Discussion

Sedation and ventilator weaning are closely linked [15]. There are some studies demonstrating the sedative effects of dex in pediatric patients [16-19]. However, most of these studies have been conducted on patients needing sedation after surgery and/or for a short term [16,19-21] and they also are not related to extubation success. The number of studies conducted on use of dex especially for weaning in pediatric patients at Medical PICUs is currently insufficient. Therefore, we evaluated the effect of dex on extubation and its adverse

effects in pediatric patients in this study. The need for reintubation among our patients was small, whereby the duration of stay in intensive care was apparently shorter in DEXg. Parallel to this study, Gupta., *et al*. conducted a study on 60 adult intubated patients in order to compare the efficacy of dex. They reported that those who were administered dex were extubated within a shorter time period, and that dex facilitated extubation [22]. They used dex right before extubation, while we used dex after extubation. Nevertheless, the important this was that dex did not cause respiratory depression while providing sedation. Intubation time was longer among our DEXg (which was not statistically significant), but however successful weaning was higher. Nunes., *et al*. compared dex with other sedative drugs, and found that although duration of ventilation in patients administered only dex was longer, their success at weaning success was compared to others [23]. Likewise, Lu., *et al*. reported in a study conducted on adults that the consecutive use of mid with dex increased quality of extubation, maintained respiratory, and circulatory parameters, and that it reduced negative reaction when compared to the exclusive use of midazolam [24]. Le., *et al*. conducted a study a group of pediatric patients in which 89 patients took dex after cardiac surgery. They found that dex did not have any significant impact in terms of early extubation, ventilation time, or duration of stay in intensive care in comparison to the standard regime (benzodiazepine-based practice) they used [21].

The use of dex was approached with precaution due to concerns about its adverse effects on pediatric patients [7,25]. The adverse effects of dex infusion related to hypotension, hypertension, and bradycardia have been mentioned in several studies [17-20]. Hayden., *et al*. conducted a PICU-based study and found that while dex caused reduction of heart rate, it nevertheless had minimal effects on blood pressure [17]. Another study conducted on adult intubated patients comparing the adverse effects of dex concluded that there was an apparent decrease in heart rate and blood pressure among patients being administered dex. This, however, was deemed insignificant, and dex was deemed reliable and effective as a sedative. Another study conducted involving newborn and pediatric intensive care compared cardiovascular system adverse effects of dex. The study revealed that the bradycardia episodes were higher among infants, and that the decrease in the heart rate was thought to be associated with a higher dose of dex administered to infants [25]. A recent study reported that dex was tolerated well both in intubated and non-intubated newborn and infant patients. However, Banasch., *et al*.'s study conducted at a PICU investigating the adverse effects and tolerability of dex, had revealed that hypotension was observed in 27% of patients and that bradycardia was found in 21% of patents. It also found that both effects were observed in 7% of patients, but that these adverse effects were only observed in patients who were administered dex at an earlier age and for a longer time period [18].

In our study, patients with bradycardia were also younger (median 12 months). We observed bradycardia usually within the first 2 hours after starting infusion, whereupon we stopped the drug, and continuing with lower doses, which did not seem to cause any problems among patients. Bradycardia is seen as one adverse effect after the infusion of dex in studies conducted on pediatric patients whereby the rate was 14% and 21% [18,26]. The rate of bradycardia was not so high (5/126) in this study. That is, mild hypotension was observed especially in the first two hours after dex infusion, and minimal changes were recorded in tension arterial (TA) as long as the infusion continued. However, these values were deemed as normal upon considering the TA percentiles based on the age and height of the patient. The dex infusion initial dose in those who had bradycardia after dex infusion was higher when compared to the median values of our patients, (0.27 vs 0.30 µg/kg/min). Similarly, the duration of infusion was also longer in the bradycardia group (48 vs 72 hours) as well. Even though we detected a slight difference in MAP and heart rate in our study, hypotension among these adverse effects was not clinically significant whereby bradycardia was resolved rapidly upon stopping the drug. The rate of extubation failure was 15% in DEXg, whereas it was 38% in the MIDg. Likewise, the duration of stay in the PICU was longer in MIDg.

Limitation of the Study

Several limitations of the study should not be ignored. First, data was collected retrospectively, and so may be prone to selection and information bias. Second, some patients were excluded due to incomplete medical records, furthermore this was a single-center study with limited sample size, so the generalizability of the findings is unknown. Thirdly, our patients were all critically ill, making it difficult to ascertain whether the adverse events were related to the therapy or to the underlying critical illness. Additionally, there was a lack of

evaluation with other sedative agents because of the use of these drugs in our clinic. A randomized controlled trial with a larger sample size will be needed to confirm our findings.

Conclusion

In conclusion, we would like to state that dex is a reliable drug, and that both can be used in pediatric intensive care units, and that it increases the rate of extubation success during the weaning of pediatric patients when compared with midazolam. In conclusion, we might recommend that hospitals include dexmedetomidine in weaning protocols for pediatric patients.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Clinical research ethics committee.

Funding

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Disclosure of Interest

The authors declare that they have no competing interest.

Acknowledgements

We gratefully acknowledge the contribution of all participating children and their parents. In addition, we also give many thanks to our clinical nurses.

Bibliography

1. Motta E., *et al*. "Importance of the use of protocols for the management of analgesia and sedation in pediatric intensive care unit". *Revista da Associação Médica Brasileira* 62.6 (2016): 602-609.

2. Cocoros NM., *et al*. "Factors Associated With Pediatric Ventilator-Associated Conditions in Six U.S. Hospitals: A Nested Case-Control Study". *Pediatric Critical Care Medicine* 18.11 (2017): 536-545.

3. SRLF Trial Group. "Impact of oversedation prevention in ventilated critically ill patients: a randomized trial-the AWARE study". *Annals of Intensive Care* 8.1 (2018): 93.

4. Haenecour AS., *et al*. "Prolonged Dexmedetomidine Infusion and Drug Withdrawal In Critically Ill Children". *Journal of Pediatric Pharmacology and Therapeutics* 22.6 (2017): 453-460.

5. Shehabi Y., *et al*. "Dexmedetomidine infusion for more than 24 hours in critically ill patients: Sedative and cardiovascular effects". *Intensive Care Medicine* 30 (2004): 2188-2196.

6. Saiphoklang N and Auttajaroon J. "Incidence and outcome of weaning from mechanical ventilation in medical wards at Thammasat University Hospital". *PLoS One* 13.10 (2018): e0205106.

7. Reel B and Maani CV. "Dexmedetomidine". StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2019-2018.

8. Chen K., *et al*. "Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients". *The Cochrane Database of Systematic Reviews* 1 (2015): CD010269.

9. Arain SR and Ebert TJ. "The efficacy, side effects and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation". *Anesthesia and Analgesia* 95 (2002): 461-466.

10. Saliski M and Kudchadkar SR. "Optimizing Sedation Management to Promote Early Mobilization for Critically Ill Children". *Journal of Pediatric Intensive Care* 4.4 (2015): 188-193.

11. Jakob SM., *et al*. "Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials". *The Journal of the American Medical Association* 307.11 (2012): 1151-1160.

12. Möhler H and Richards JG. "The benzodiazepine receptor: a pharmacological control element of brain function". *European Journal of Anaesthesiology* 2 (1988): 15.

13. Gupta R., *et al*. "Effect of Different Dosages of Intravenous Midazolam Premedication on Patients Undergoing Head and Neck Surgeries- A Double Blinded Randomized Controlled Study". *Journal of Clinical and Diagnostic Research* 11.8 (2017): UC01- UC04.

14. Franck LS., *et al*. "The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients". *Pediatric Critical Care Medicine* 9 (2008): 573-580.

15. Luetz A., *et al*. "Weaning from mechanical ventilation and sedation". *Current Opinion in Anesthesiology* 25.2 (2012): 164-169.

16. Chrysostomou C., *et al*. "Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants aftercardiac surgery?" *Pediatric Critical Care Medicine* 10.6 (2009): 654-660.

17. Hayden JC., *et al*. "Efficacy of α2-agonists for sedation in pediatric critical care: A systematic review". *Pediatric Critical Care Medicine* 17 (2016): 66-75.

18. Banasch HL., *et al*. "Dexmedetomidine Use in a Pediatric Intensive Care Unit: A Retrospective Cohort Study". *Annals of Pharmacotherapy* 52.2 (2018): 133-139.

19. Plambech MZ and Afshari A. "Dexmedetomidine in the pediatric population: a review". *Minerva Anestesiologica* 81.3 (2015): 320-332.

20. Li H., *et al*. "Impact of Dexmedetomidine on Pediatric Agitation in the Postanesthesia Care Unit". *Journal of PeriAnesthesia Nursing* 33.1 (2018): 53-57.

21. Le KN., *et al*. "Impact of dexmedetomidine on early extubation in pediatric cardiac surgical patients". *Intensive Care Medicine* 37.4 (2011): 686-690.

22. Gupta S., *et al*. "Role of dexmedetomidine in early extubation of the intensive care unit patients". *Journal of Anaesthesiology Clinical Pharmacology* 31.1 (2015): 92-98.

23. Nunes SL., *et al*. "Effect of Sedation Regimen on Weaning from Mechanical Ventilation in the Intensive Care Unit". *Clinical Drug Investigation* 38.6 (2018): 535-543.

24. Lu X., *et al*. "Clinical study of midazolam sequential with dexmedetomidine for agitated patients undergoing weaning to implement light sedation in intensive care unit". *Chinese Journal of Traumatology* 19.2 (2016): 94-96.

25. Estkowski LM., *et al*. "Characterization of dexmedetomidine dosing and safety in neonates and infants". *The Journal of Pediatric Pharmacology and Therapeutics* 20.2 (2015): 112-118.

26. Honey BL., *et al*. "Evaluation of Adverse Events Noted in Children Receiving Continuous Infusions of Dexmedetomidine in the Intensive Care Unit". *The Journal of Pediatric Pharmacology and Therapeutics* 15.1 (2010): 30-37.

Volume 9 Issue 9 September 2020