Annals of Case Reports
Shlomai NO, et al. Ann Case Rep: 8: 1309
www.doi.org/10.29011/2574-7754.101309
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research Article

Intranasal Dexmedetomidine May be a Worthy Alternative for Sedation in Preterm Infants: A Retrospective Single Center Study

Noa Ofek Shlomai[1*], Matan Gross[2], Smadar Eventov Friedman[1]

[1]Department of Neonatology, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel

[2]Department of Pediatrics, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel

***Corresponding author**: Noa Ofek Shlomai, Department of Neonatology, Hadassah and Hebrew University Medical Center, Jerusalem, Israel

Citation: Shlomai NO, Gross M, Friedman SE (2023) Intranasal Dexmedetomidine May be a Worthy Alternative for Sedation in Preterm Infants: A Retrospective Single Center Study. Ann Case Report. 8: 1309. DOI:10.29011/2574-7754.101309

Received: 12 May 2023, **Accepted:** 16 May 2023, **Published:** 18 May 2023

Abstract

Introduction: Neonatal intensive care units are a highly stressful environment exposing immature infants to pain and non-pain related stress. Our aim was to assess intranasal dexmedetomidine as sedation during stressful and painful episodes in VLBW infants.

Methods: Data were retrospectively collected from medical charts of infants before and after routine use of dexmedetomidine for sedation in a single centre. Primary outcomes were N-PASS scores after sedation and respiratory support parameters. Secondary outcomes included hemodynamic and respiratory adverse effects, length of hospital stay, days to full feeding, and neonatal morbidities. A multivariate logistic regression model was used to assess the effect of several variables on a dependent variable, and the association with intranasal dexmedetomidine administration.

Results: Sixty-three preterm very low birth weight infants were included. Birth weight and gestational were comparable between the groups. (28.3 vs 29.2, and 1076 vs 1218gr respectively). Infants were treated by intravenous fentanyl or midazolam, and intranasal dexmedetomidine. N-Pass scores were comparable before and after sedation between the groups. (2.72 and 2.54 before and 2.24 and 2.45 after). Rates of adverse effects and major neonatal morbidities were comparable between groups. There was statistically significant, although mild reduced use of adjunctive midazolam in infants treated with intranasal dexmedetomidine.

Conclusions: Our data indicate that in our cohort, intranasal dexmedetomidine served as a worthy option for sedation of preterm VLBW infants.

Keywords: NICU; Preterm Infants; Dexmedetomidine; Sedation

Abbreviations: BW: Birth Weight; BPD: Bronchopulmonary Dysplasia, GA: Gestational Age; IV: Intravenous, IVH: Intraventricular Haemorrhage; NEC: Necrotizing Enterocolitis; NICU: Neonatal Intensive Care Unit; PVL: Periventricular Leukomalacia; ROP: Retinopathy Of Prematurity; VLBW: Very Low Birth Weight

Introduction

Neonatal Intensive Care Units (NICU's) are a highly stressful environment for immature infants. Preterm infants are exposed to pain and non-pain related distress, including

interchanging caregivers, and multiple disturbing visual and auditory stimuli [1]. Pathways mediating nociception develop between 20 and 24 weeks of gestation, while descending inhibitory pathways mature much later, beyond term [2]. Preterm infants therefore, have poor localization and discrimination of sensory input, leading to increased responses to painful stimuli [3,4]. These negatively interfere with individual self-regulation and co-regulation processes, which are fundamental for adaptive behaviour throughout development [5,6]. Painful, and non-painful stress in ventilated infants and neonates, are treated nowadays with a variety of mostly intravenously administered sedatives, mainly opioids and benzodiazepines. In addition, non-pharmacological strategies such as swaddling are practiced to reduce pain and stress [7]. Traditionally, management of pain and stress consists of opioids, often morphine or fentanyl [8]. Morphine improves ventilator synchrony in ventilated neonates [9], and is associated with lower pain scores [10]. Side effects including hypotension, respiratory depression, and delay of enteral feeding were reported following sedation with morphine [11]. Furthermore, experimental data from animal studies show chronic morphine exposure in early life may result in reduced brain volume, decreased neuronal packing density and less dendritic growth and branching, which may be associated with learning and motor disabilities later in life [12]. Moreover, Postnatal studies in preterm infants exposed to opioids, demonstrate an association with decreased cerebellar volume and poorer 18-month motor and cognitive scores [13,14]. Benzodiazepines, most commonly midazolam, inhibit Gamma Aminobutyric Acid A receptors [15], and have a sedative but not an analgesic effect. Midazolam may induce respiratory depression and hypotension. A systematic review found insufficient evidence to recommend midazolam for sedation in preterm infants, and raised safety concerns, particularly regarding neurotoxicity [16]. Dexmedetomidine is a highly selective α2- adrenergic receptor agonist that provides analgesia, anxiolysis, and sedation via reduction in sympathetic outflow from the locus coeruleus and release of substance-P from the dorsal horn of the spinal cord, without compromising respiratory function [17]. Although safety and efficacy of dexmedetomidine have been established in the adult population [18], its use in infants and newborns, particularly in preterm infants, is still off-label. Chrysostomou et al. reported a phase II/III trial designed to investigate the safety, efficacy, and pharmacokinetic profile of IV dexmedetomidine in preterm and full-term neonates ≥28 to ≤44 weeks gestational age. They found that IV dexmedetomidine was effective for sedating preterm and full-term neonates and was well tolerated without significant adverse effects [19]. Several studies showed that intranasal dexmedetomidine may be a satisfied alternative for short sedation in the pediatric and neonatal population [19-23]. The aim of this study is to examine the possibility that intranasal dexmedetomidine is an alternative for sedation of preterm infants in the NICU during pain and non-pain related stress. We aimed at assessing adverse effects, and short and long- term outcomes, in comparison to fentanyl and adjunctive midazolam, which are used routinely in our unit for infants requiring sedation.

Methods

This is a retrospective single centre before/after study.

Study population

Study population included VLBW (birth weight < 1,500 gr) preterm infants born prior to 32 weeks' gestation in a single centre. Data were extracted from medical records of infants born prior to the use of dexmedetomidine in our unit between 2014-2016, and from medical records of infants born during 2017-2019 when intranasal dexmedetomidine was used routinely in our unit for sedation. Data were extracted from records of VLBW born consecutively during the analysed period. Infants with major congenital anomalies, and those who did not survive 72 hours were excluded from this study.

Sedation protocol

Sedation drugs were administered according to the unit's protocol, which includes the administration of sedation PRN (pro re nata) to infants assessed as experiencing pain related, or non-pain related stress. This practice was not changed between the two study periods. IV fentanyl was administered at a dose of 1-2 mcg/kg, and IV midazolam at a dose of 0.05-0.1 mg/kg. Dexmedetomidine was diluted (100mcg with 10ml 0.9% NaCl) and administered intranasal via a 1 ml syringe at 1-2 mcg/kg, administered to both nares. Intravenous fentanyl was administered PRN to infants during the pre and post dexmedetomidine period, as per the nurses' discretion. During the post dexmedetomidine period, when dexmedetomidine became our first line of sedation, fentanyl was administered as second line in ventilated infants. Respiratory and nutritional management has remained unchanged in the two study periods.

Assessing of pain and/or agitation

Pain/ agitation were assessed using the Neonatal Pain, Agitation and Sedation Scale (N-PASS). Five indicators were included, crying/irritability, behaviour/state, facial expression, extremities/tone and vital signs. Scores range from -10 in heavily sedated infants to +11, with scores of over 3 suggesting need for intervention [24]. In our unit VLBW infants are rarely heavily sedated, therefore the actual NPASS score range is most commonly 0-13. Pain/stress evaluation was performed 30 minutes and 1 hour after administration of any sedative agent (dexmedetomidine, fentanyl or midazolam). In infants who did not require sedation pain/stress evaluation was performed every 3 hours.

Outcomes

Primary outcomes were defined as N-PASS scores after sedation and respiratory support parameters. Secondary outcomes included hemodynamic and respiratory adverse effects (hypotension, apneas), length of hospital stay, days to full feeding, and neonatal morbidities including necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) defined by the need for oxygen or any respiratory support at 36 weeks corrected age, late onset sepsis occurring beyond the seventh day of life, high grade (grades 3-4) intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP).

Statistical analysis

To test the association between two categorical variables, either the Chi-square test or the Fisher's exact test was applied. The comparison of a quantitative variable between two independent groups was carried out using the two-sample t-test. The paired t-test was used for testing change within group, for a quantitative variable, including NPASS score, which included multiple observations of the same infant. A multivariate logistic regression and ANCOVA models were used to assess the effect of several variables on a dependent variable, and the with intranasal dexmedetomidine administration. All statistical tests applied were two-tailed, and a p-value of 0.05 or less was considered statistically significant.

Results

The study population included a total of 63 preterm very low birth weight (VLBW) infants: 33 in the conventional sedation group (cohort 1), of infants who were not treated with intranasal dexmedetomidine, and 30 in the dexmedetomidine group (cohort 2). Infants receiving PRN dexmedetomidine were administered a mean of 5 doses per day during the first 2 weeks of life. The two cohorts were comparable in demographic characteristics including birth weight, gestational age, and sex. There were more infants with a 1-minute Apgar score under 7 in cohort 1, but the 5-minute Apgar score was comparable between the cohorts (Table 1). NPASS score after sedation, respiratory support parameters including oxygen days, and length of invasive ventilation were found comparable between infants treated with intranasal dexmedetomidine and those who were not, as well as the frequency of hypotension and apnea episodes. Multivariate regression analysis showed GA and BW were statistically significantly associated with neonatal morbidities and outcomes including BPD, days to extubation, oxygen days, days to full enteral diet, days to full oral diet, and hospital stay. There was no difference between the dexmedetomidine and no dexmedetomidine groups for these outcomes. We also found that BW and GA were not different between the dexmedetomidine and no dexmedetomidine groups. We found a statistically significant reduced use of adjunctive midazolam in infants treated with intranasal dexmedetomidine when compared to infants who were not. This difference was not affected by BW, GA or gender (Table 2). Multivariate analysis demonstrated neonatal morbidities were associated as expected with gestational age and birth weight, but not with the use dexmedetomidine (Table 3). ANCOVA analysis demonstrated the use of adjunctive midazolam was decreased in infants treated with intranasal dexmedetomidine when compared to infants who were not, but not associated with gender, birth weight or gestational age (Table 4).

Variable	Dexmedetomidine (N=30)	No Dexmedetomidine (N=32)	p value
Birth weight (gr)	1076±286	1218±454	0.15
Gestational age (week)	28.3±2.5	29.2±2.5	0.14
Sex (%males)	16 (53.3%)	19 (57.6%)	0.735
Apgar <7 1 min	5 (16.7%)	15 (45.5%)	0.014
Apgar <7 5 min	1 (3.3%)	3 (9.1%)	0.614
Cesarean section (%)	90%	91%	
Prenatal steroids (%)	93%	88%	
Intubated at delivery (%)	33%	42%	
Surfactant treatment (%)	60%	60%	

Table 1: Patient characteristics.

Variable		Dexmedetomidine (N=30)	No Dexmedetomidine (N=33)	p value
Supplemental Oxygen duration (days)		29.6±30.8	26.7±25.3	0.68
Days to extubation		5.9±9	4±5	0.334
Days to full feeds		9±4	9.8±7.5	0.593
Total apneas during the first 2 weeks of life		25.8±27.8	18.55±23.9	0.266
Total hypotension during the first 2 weeks of life		1.9±2	1.6±4	0.729
NPASS score before sedation		2.72±0.67	2.54±0.66	0.295
NPASS score after sedation		2.24±0.62	2.45±0.45	0.065
Use of adjunctive Midazolam (# of doses)		0.25±0.07	0.88±1.85	**0.018**
BPD*				
	None	15 (50%)	16 (48.5%)	0.175
	Mild	11 (36.7%)	8 (24.2%	
	Moderate	1 (3.3%)	7 (21.2%)	
	Severe	3 (10%)	2 (6.1%)	
High grade IVH	None–grade 2	26 (86.7%)	30 (90%)	0.9
	Grade 3	0 (0%)	1(3.3%)	
	Grade 4	3 (10%)	2 (6.1)	
PVL		4	1	0.183
Surgical NEC		1 (3.3%)	0 (0%)	0.476
ROP	None	5 (16.7%)	6 (18.2%)	0.955
	Stage 1	13 (43.3%)	13 (43.3%)	
	Stage 2	11 (36.7%)	13 (39.4%)	
	Stage 3	1 (3.3%)	1 (3%)	
Late onset sepsis		1 (3.3%)	4 (12.4%)	0.357

* BPD definitions: mild: oxygen requirement at 28 days, moderate: oxygen requirement up to 30% FiO2 at 36 weeks corrected age, severe: oxygen requirement of > 30% FiO2 or positive pressure at 36 weeks corrected age

Table 2: Univariate analysis of outcome of preterm infants treated with and without intranasal Dexmedetomidine.

Outcome variable	Dexmedetomidine		Gestational age		Birth weight		gender	
	P value	aOR[*1](CI)[*2]	P value	aOR(CI)	P value	aOR(CI)	P value	aOR(CI)
BPD[*3]	0.23	0.451(0.123-1.656)	0.243	0.77(0.5-1.18)	0.054	0.99(0.99-1)	0.717	0.78(0.21-2.8)

High grade IVH[*4]	0.751	0.743(0.118-4.6)	0.068	0.5(0.24-1.05)	0.29	1(0.99-1)	0.857	0.84(0.12-5.6)
PVL[*5]	0.129	6.159 (0.59-64.2)	0.56	1.16(0.69-1.9)	0.857	1(0.99-1)	0.218	0.22(0.02-2.4)
LOS[*6]	0.153	0.176(0.016-1.9)	0.89	0.95(0.5-1.8)	0.31	0.99(0.99-1)	0.29	0.29(0.02-2.9)

*1 adjusted odds ratio; *2confidence interval; *3bronchopulmonary dysplasia; *4intraventricular hemorrhage; *5periventricular leukomalacia; *6late onset sepsis

Table 3: Logistic regression of outcome variables in preterm infants and treatment with intranasal dexmedetomidine.

Variables	Dexmedetomidine	GA	BW
Days to extubation	0.334	<0.001	0.02
Oxygen days	0.68	<0.001	<0.001
Days to Full enteral diet	0.593	0.044	0.016
Days to Full oral diet	0.470	<0.001	<0.001
Hospital stay	0.268	<0.001	<0.001
Total midazolam	0.018	0.09	0.325

Table 4: Association between preterm infants' short-term outcomes and treatment with intranasal dexmedetomidine, gestational age, and birth weight.

Discussion

This study aimed to examine the feasibility of using intranasal dexmedetomidine as an alternative for sedation of VLBW infants in the NICU. Our data demonstrated that compared to standard sedation consisting of intravenous fentanyl with adjunctive midazolam as required, intranasal dexmedetomidine was as effective, and did not negatively affect the infant's short to moderate term outcome. In addition, our data revealed that infants treated with intranasal dexmedetomidine have required significantly less adjunctive midazolam for sedation. This is particularly important in view of a recent Cochrane review raising concerns regarding the safety of midazolam in neonates [16], with data suggesting higher rates of adverse neurological outcomes, longer NICU stay and more. In this aspect, intranasal dexmedetomidine seems a promising alternative for sedation in preterm infants, a population in whom anti pain and sedative medication arsenal is overall limited. In a retrospective study of 48 preterm infants, intravenous dexmedetomidine was found a safe and effective sedation for ventilated infants [20]. Furthermore, a study of dexmedetomidine in neonatal anaesthesia, revealed stability of heart rate and hemodynamic when used as an adjuvant to sevoflurane [25]. In a case-control retrospective study of 50 neonates, O'Mara et al compared neonates receiving intravenous fentanyl to those receiving sedation by intravenous dexmedetomidine. Patients in the dexmedetomidine group required less adjunctive sedation, had reduced days of respiratory support, less sepsis, and reduced time to full enteral feeding, compared to patients in the fentanyl group [20]. Several studies showed that intranasal dexmedetomidine might be a satisfied alternative for short sedation in the pediatric population. In a double blind randomized controlled study Reynolds et al. reported intranasal dexmedetomidine is an effective alternative to oral chloral hydrate sedation for ABR testing, with the advantages of a higher incidence of testing completion with a single dose, shorter time to desired sedation level, and significantly more patients reported to return to baseline activity on the same day [21]. A similar outcome was reported in another retrospective study of intranasal dexmedetomidine for ABR in the pediatric population [22]. In a double blind, randomized controlled trial of 40 patients 1-5 years old with lacerations requiring suture repair patients received either intranasal dexmedetomidine or intranasal midazolam. Intranasal dexmedetomidine was found as a non-inferior alternative anxiolytic medication to intranasal midazolam for pediatric laceration repairs, performing similarly, except that patients who received dexmedetomidine had less anxiety at the time of positioning for procedure [23]. Intranasal dexmedetomidine was found to be a safe and effective sedation in multiple studies and Meta analyses of pediatric procedural sedation [26-29]. To the

best of our knowledge there are no studies describing intranasal dexmedetomidine use in preterm infants. In addition to its' sedative effects, dexmedetomidine was found to have anti-inflammatory effects, by reducing inflammatory cytokine (such as TNF-α and IL-6). This effect was demonstrated in vitro, in vivo, and in clinical experiments [30,31]. Furthermore, research has demonstrated an anti-apoptotic effect of dexmedetomidine, through various signalling pathways and the activation of mitochondrial ATP-sensitive K+ channels [32-34]. Animal studies have demonstrated a protective effect of dexmedetomidine on the nervous system, including inhibition of sympathetic nerve excitability, and therefore catecholamine release, regulating central glutamate and anti-inflammatory cytokine release, inhibiting apoptosis and reducing antioxidant stress [30]. Furthermore, studies in rodents demonstrated a dexmedetomidine has additional protective effects, that include the gastrointestinal and the pulmonary systems [35,36]. This effect may be significant in perinatal ischemic-hypoxic encephalopathy, necrotizing enterocolitis, PVL and bronchopulmonary dysplasia, which are beyond the scope of our study [37-39]. Extensive research in animal models has shown protective effects of dexmedetomidine in additional systems including the heart, the kidneys, the liver, and more [40-42]. Clearly, these findings should be further studied clinically. Our study has several limitations. Firstly, our relatively small sample size does not allow true appreciation of the effects on low incidence morbidities. Secondly, this is an observational retrospective study, with its' inherent limitations. However, the study has several strengths. These include that to the best of our knowledge, this is the first report of intranasal dexmedetomidine as routine sedation for preterm infants in the NICU, including VLBW infants who do not have intravenous access. This may allow use even in the delivery room during resuscitation necessitating intubation. The data were collected from infants' charts in a single centre, with unity of treatment protocols and pain scores reporting systems. Significant correlations were demonstrated in both study groups between GA / BW and leading neonatal outcomes, suggesting high population reliability.

Conclusion

Our data suggests that intranasal dexmedetomidine may be worthy alternative for sedation of preterm VLBW infants in the NICU. Intranasal administration poses an advantage in preterm infants who often require long term sedative treatment, as it does not require venous assess, and is available even in infants who are not fed enterally. Additional larger scale, preferably randomized studies are needed to assess these outcomes.

Funding source: This research was not funded.

Conflict of interest: The authors declare there is no conflict of interest to disclose.

Data sharing: The data are part of the Hadassah NICU database, and available for sharing.

Ethics: This study was approved by the Hebrew University ethics committee, approval number HMO-002820.

Contributor's statement: Dr Ofek Shlomai and Prof Eventov Friedman conceptualized and designed the study, drafted the initial manuscript, critically reviewed the manuscript for important intellectual content. And revised the manuscript. Dr Gross designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest: The authors have no conflict of interest to declare.

References

1. Anand KJ (1998) Clinical importance of pain and stress in preterm neonates. Biol Neonate. 73: 1-9.
2. Anand KJ, Hickey PR (1987) Pain and its effects in the human neonate and fetus. N Engl J Med. 317: 1321-1329.
3. Fitzgerald M, Shaw A, MacIntosh N (1988) Postnatal development of the cutaneous flexor reflex: comparative study of preterm infants and newborn rat pups. Dev Med Child Neurol. 30: 520-526.
4. McPherson C, Miller SP, El-Dib M, Massaro AN, Inder TE (2020) The influence of pain, agitation, and their management on the immature brain. Pediatr Res. 88: 168-175.
5. Sameroff A (2010) A unified theory of development: a dialectic integration of nature and nurture. Child development. 81: 6-22.
6. Gorzilio DM, Garrido E, Gaspardo CM, Martinez FE, Linhares MB (2015) Neurobehavioral development prior to term-age of preterm infants and acute stressful events during neonatal hospitalization. Early human development. 91: 769-775.
7. Bucsea O, Pillai Riddell R (2019) Non-pharmacological pain management in the neonatal intensive care unit: Managing neonatal pain without drugs. Semin Fetal Neonatal Med. 24: 101017.
8. Hall RW, Anand KJ (2014) Pain management in newborns. Clin Perinatol. 41: 895-924.
9. Quinn MW, Vokes A (2000) Effect of morphine on respiratory drive in trigger ventilated pre-term infants. Early Hum Dev. 59: 27-35.
10. Bellù R, de Waal K, Zanini R (2010) Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 95: F241-51.
11. Hall RW, Kronsberg SS, Barton BA, Kaiser JR, Anand KJ (2005) Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial. Pediatrics. 115: 1351-1359.
12. Durrmeyer X, Vutskits L, Anand KJ, Rimensberger PC (2010) Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data. Pediatr Res. 67: 117-127.

13. Zwicker JG, Miller SP, Grunau RE, Chau V, Brant R, et al (2016) Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine. J Pediatr. 172: 81-7. e2.

14. Squillaro A, Mahdi EM, Tran N, Lakshmanan A, Kim E, et al (2019) Managing Procedural Pain in the Neonate Using an Opioid-sparing Approach. Clin Ther. 41: 1701-1713.

15. Lorman WJ (2017) Pharmacology Update: Benzodiazepines. J Addict Nurs. 28: 96-97.

16. Ng E, Taddio A, Ohlsson A (2012) Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database Syst Rev. 2012: Cd002052.

17. Yuen VM, Hui TW, Irwin MG, Yuen MK (2008) A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesth Analg. 106: 1715-1721.

18. Barends CR, Absalom A, van Minnen B, Vissink A, Visser A (2017) Dexmedetomidine versus Midazolam in Procedural Sedation. A Systematic Review of Efficacy and Safety. PLoS One. 12: e0169525.

19. Chrysostomou C, Schulman SR, Herrera Castellanos M, Cofer BE, Mitra S, et al (2014) A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. J Pediatr. 164: 276-82 e1-3.

20. O'Mara K, Gal P, Wimmer J, Ransom JL, Carlos RQ, et al (2012) Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature neonates. J Pediatr Pharmacol Ther. 17: 252-262.

21. Reynolds J, Rogers A, Medellin E, Guzman JA, Watcha MF (2016) A prospective, randomized, double-blind trial of intranasal dexmedetomidine and oral chloral hydrate for sedated auditory brainstem response (ABR) testing. Paediatric anaesthesia. 26: 286-293.

22. Reynolds J, Rogers A, Capehart S, Manyang P, Watcha MF (2016) Retrospective Comparison of Intranasal Dexmedetomidine and Oral Chloral Hydrate for Sedated Auditory Brainstem Response Exams. Hospital pediatrics. 6: 166-171.

23. Neville DN, Hayes KR, Ivan Y, McDowell ER, Pitetti RD (2016) Double-blind Randomized Controlled Trial of Intranasal Dexmedetomidine Versus Intranasal Midazolam as Anxiolysis Prior to Pediatric Laceration Repair in the Emergency Department. Acad Emerg Med. 23: 910-917.

24. Hillman BA, Tabrizi MN, Gauda EB, Carson KA, Aucott SW (2015) The Neonatal Pain, Agitation and Sedation Scale and the bedside nurse's assessment of neonates. J Perinatol. 35: 128-131.

25. Dilek O, Yasemin G, Atci M (2011) Preliminary experience with dexmedetomidine in neonatal anesthesia. J Anaesthesiol Clin Pharmacol. 27: 17-22.

26. Tervonen M, Pokka T, Kallio M, Peltoniemi O (2020) Systematic review and meta-analysis found that intranasal dexmedetomidine was a safe and effective sedative drug during paediatric procedural sedation. Acta Paediatr. 109: 2008-2016.

27. Cozzi G, Norbedo S, Barbi E (2017) Intranasal Dexmedetomidine for Procedural Sedation in Children, a Suitable Alternative to Chloral Hydrate. Paediatr Drugs. 19: 107-111.

28. Jun JH, Kim KN, Kim JY, Song SM (2017) The effects of intranasal dexmedetomidine premedication in children: a systematic review and meta-analysis. Can J Anaesth. 64: 947-961.

29. Mondardini MC, Amigoni A, Cortellazzi P, Di Palma A, Navarra C, et al (2019) Intranasal dexmedetomidine in pediatrics: update of current knowledge. Minerva Anestesiol. 85: 1334-1345.

30. Bao N, Tang B (2020) Organ-Protective Effects and the Underlying Mechanism of Dexmedetomidine. Mediators Inflamm. 2020: 6136105.

31. Qiao H, Sanders RD, Ma D, Wu X, Maze M (2009) Sedation improves early outcome in severely septic Sprague Dawley rats. Crit Care. 13: R136.

32. Zhu YM, Wang CC, Chen L, Qian LB, Ma LL, et al (2013) Both PI3K/Akt and ERK1/2 pathways participate in the protection by dexmedetomidine against transient focal cerebral ischemia/reperfusion injury in rats. Brain Res. 1494: 1-8.

33. Chi X, Wei X, Gao W, Guan J, Yu X, et al (2015) Dexmedetomidine ameliorates acute lung injury following orthotopic autologous liver transplantation in rats probably by inhibiting Toll-like receptor 4-nuclear factor kappa B signaling. J Transl Med. 13: 190.

34. Wang Y, Wu S, Yu X, Zhou S, Ge M, et al (2016) Dexmedetomidine Protects Rat Liver against Ischemia-Reperfusion Injury Partly by the α2A-Adrenoceptor Subtype and the Mechanism Is Associated with the TLR4/NF-κB Pathway. Int J Mol Sci. 17.

35. Laudenbach V, Mantz J, Lagercrantz H, Desmonts JM, Evrard P, et al (2002) Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. Anesthesiology. 96: 134-141.

36. Paris A, Mantz J, Tonner PH, Hein L, Brede M, et al (2006) The effects of dexmedetomidine on perinatal excitotoxic brain injury are mediated by the alpha2A-adrenoceptor subtype. Anesthesia and analgesia. 102: 456-461.

37. Fu C, Dai X, Yang Y, Lin M, Cai Y, et al (2017) Dexmedetomidine attenuates lipopolysaccharide-induced acute lung injury by inhibiting oxidative stress, mitochondrial dysfunction and apoptosis in rats. Mol Med Rep. 15: 131-138.

38. Yang CL, Tsai PS, Huang CJ (2008) Effects of dexmedetomidine on regulating pulmonary inflammation in a rat model of ventilator-induced lung injury. Acta Anaesthesiol Taiwan. 46: 151-159.

39. Yeh YC, Sun WZ, Ko WJ, Chan WS, Fan SZ, et al (2012) Dexmedetomidine prevents alterations of intestinal microcirculation that are induced by surgical stress and pain in a novel rat model. Anesth Analg. 115: 46-53.

40. Sahin T, Begeç Z, Toprak H, Polat A, Vardi N, et al (2013) The effects of dexmedetomidine on liver ischemia-reperfusion injury in rats. J Surg Res. 183: 385-390.

41. Ibacache M, Sanchez G, Pedrozo Z, Galvez F, Humeres C, et al (2012) Dexmedetomidine preconditioning activates pro-survival kinases and attenuates regional ischemia/reperfusion injury in rat heart. Biochim Biophys Acta. 1822: 537-545.

42. Bao N, Tang B, Wang J (2020) Dexmedetomidine Preconditioning Protects Rats from Renal Ischemia-Reperfusion Injury Accompanied with Biphasic Changes of Nuclear Factor-Kappa B Signaling. J Immunol Res. 2020: 3230490.