JPPT | Single Health System Retrospective Study

The Use of Dexmedetomidine in Preterm Infants: A Single Academic Center Experience

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OBJECTIVE Preterm newborns (PTNBs) often require sedation and analgesia. Dexmedetomidine (DEX) is used to provide sedation in extremely PTNBs, even though information on such use is limited. The objective of this research is to describe the use of DEX in these patients in a single academic center.

METHODS This is a retrospective study of PTNBs receiving DEX from January 1, 2010, through December 31, 2018, at the Cleveland Clinic Children's Hospital, a tertiary academic center operating 2 Level III and 1 Level IV neonatal intensive care units (NICUs). Inclusion criteria were gestational age (GA) <36 weeks and receipt of DEX for >2 days. Adequacy of clinical response was based on achieving Neonatal Pain, Agitation and Sedation Scale (N-PASS) scores <3. Hypotension, bradycardia, and respiratory depression were recorded as the incidence as adverse events.

RESULTS A total of 105 patients were included. The birth weight median was 870 g (IQR, 615–1507); the GA median was 26 weeks (IQR, 24–31). The duration of DEX infusion averaged 7 days. The DEX dose averaged 0.4 mcg/kg (IQR, 0.3–0.45). Bradycardia was observed in 35 patients (57%) weighting <1 kg and in 7 patients (18%) >1 kg ($p < 0.01$). There was no difference in the incidence of other adverse events between these groups. However, infants <1 kg required more pharmacologic interventions to maintain N-PASS score <3.

CONCLUSIONS DEX was well tolerated overall and provided adequate sedation to PTNBs in this cohort. From this study, we recommend a starting dose of 0.2 to 0.4 mcg/kg/hr and titrating up hourly until adequate sedation is achieved.

ABBREVIATIONS BZDs, benzodiazepines; DEX, dexmedetomidine; EMR, electronic medical record; GA, gestational age; NICU, neonatal intensive care unit; N-PASS, Neonatal Pain, Agitation, and Sedation Scale; OPs, opioids; PTNBs, preterm newborns; WAT-1, Withdrawal Assessment Tool-1

KEYWORDS analgesia; dexmedetomidine; pain; preterm infants; sedation

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Introduction

Dexmedetomidine (DEX; Precedex, Hospira Inc, Lake Forest, IL)[1] is widely used in sedation and pain management protocols for adult and pediatric patients[2] and now in neonatal intensive care units (NICUs). DEX has been used for surgical purposes in the NICU since 2010.[3,4] DEX is primarily used as a sedative; emerging literature shows that it may be analgesic sparing without affecting the respiratory drive, making it an even more attractive option than benzodiazepines (BZDs) and opioids (OPs).[5]

Adequate sedation and pain management are imperative for an excellent neurodevelopmental outcome for preterm or term infants.[2,5] Older literature commonly recommends a combination of OPs and BZDs for comfort management in NICU infants. These drugs provide pain relief and sedation, but they also induce adverse effects such as cardiorespiratory depression, tolerance, and withdrawal.[2,5] Evidence in animal studies showing neuroapoptosis with OPs and BZDs raises concern for using these agents in the developing brain.[6–9] The mechanism of this effect is not known for BZDs. In contrast, the dose and duration of use appear to be related to neuroapoptosis associated with OPs.[8,9]

DEX was introduced in 2010 as a therapy for agitation and as procedural sedation in these NICUs after published reports showing promising results. Gradually, the use of BZD was phased out as DEX increased over time. Opioid use was also reduced as DEX became the first-line agent in many patients.

Reports of DEX in preterm and term infants have shown results with a significant decrease of exposure to OPs while maintaining an adequate level of sedation and analgesia.[10] However, no previous data had confirmed a reduction in use or exposure to OPs in extremely low birth weight infants, especially for those weighing <1 kg. These infants represent many of the most challenging cases in the NICU owing to the comorbidities associated with this level of immaturity.

This study describes the clinical characteristics, pharmacologic responses, and adverse effects of DEX use in a cohort of extremely preterm infants.

Materials and Methods

This single-institution, multisite retrospective cohort study included preterm infants born at less than 36 weeks' gestation, treated with DEX for pain, sedation, and agitation. These infants were admitted between January 2010 and December 2018 at any NICU in the Cleveland Clinic Children's Hospital system, an urban tertiary academic center. The system includes 2 Level III and 1 Level IV NICUs at different locations in Cleveland, Ohio, for a total of 88 beds. The same neonatology group covers all 3 units and follows the same guidelines and policies. DEX was introduced in Cleveland Clinic Hospital NICU at the end of 2010 to treat babies who were irritable and not responding well to traditional OPs and BZDs. As use expanded, it was noted that the doses of BZD and OPs could be markedly reduced or avoided altogether. However, the clinical effect of DEX on this patient population has not been well studied. We collected data to report the clinical response to DEX, based on the Neonatal Pain, Agitation, and Sedation Score (N-PASS), and the most significant adverse events.

The N-PASS score is an easy to use tool for assessing pain management and sedation in critically ill neonates and premature infants. N-PASS scoring is required to be performed at least once every 12 hours, depending on the procedure or desired level of pain control and sedation though it is usually performed every 3 hours with hands-on care by the bedside nurse, but this interval may change with care times. The N-PASS comprises 2 measurements; the 5 criteria assessed are crying or irritable, behavioral state, facial expression, extremity tone, and vital signs. The sedation score is typically assessed for patients receiving sedating medications and requires stimulation, with a score range of 0 to −10, with points of −2 to 0 assigned for each criterion.[11,12] The pain and agitation score is assessed through observation without intervention, with a score range of 0 to 10, with 0 to 2 points for each criterion. Treatment or intervention is recommended for scores of more than 3. The recommendation for good pain control is to keep the N-PASS score between 0 and 2.[11,12]

Data collected from the electronic medical record (EMR) included demographics such as gestational age (GA), birth weight, sex, and race. We also recorded Apgar scores at 1, 5, and 10 minutes, the presence of intraventricular hemorrhage, the use of mechanical ventilation, blood pressure and heart rate, and N-PASS. The use of antenatal steroids, surfactant, antibiotics, inotropic medications, OPs, BZDs, and clonidine was also noted. Data on these medications were collected owing to their possible association with the infant's clinical condition and their potential interaction with the N-PASS score. These represent the most common interventions in critically ill PTNBs.

Data gathered on the use of DEX in these infants included the day of life the drug was started, the length of therapy, and the maximum daily dose. Documentation of any symptoms of DEX withdrawal was also collected. Although there is not a defined withdrawal syndrome for DEX, nonspecific measures such as hypertension and tachycardia or an elevated Withdrawal Assessment Tool (WAT-1) score were used.[13–15] The WAT-1 is a tool developed for evaluating critically ill pediatric patients who may be experiencing the effects of abstinence or iatrogenic withdrawal.[15] It is an 11-item tool performed at least twice daily in the clinical setting by the bedside nurse. The sum of the 11 items is 0 to 12. A score of 3 or more is considered significant for withdrawal symptoms, and intervention is required.

Cardiovascular and respiratory events were obtained from the EMR to evaluate for adverse events of DEX. The incidence of bradycardia and hypotension was used as a measure of cardiovascular adverse events. Every incident of low blood pressure, heart rate, respiratory rate, and interventions listed in the EMR was recorded. Only events deemed to be clinically relevant were included in this analysis: bradycardia events with a sustained heart rate <80 beats per minute for at least 1 minute; systemic arterial hypotension, with mean arterial pressure less than the GA for at least 30 consecutive minutes; and interventions documented as use of inotropic support or volume expansion during these events. Respiratory depression was defined as less than 20 breaths per minute or apnea (respiratory pause for more than 20 seconds). Events were not included for analysis if they did not meet the above criteria.

Patient comfort was assessed by the N-PASS score tool to evaluate the clinical response and determine the level of sedation and analgesia. The N-PASS was evaluated throughout the infusion of DEX as mandated by NICU protocol. According to provider discretion, infants with a score of 3 or more received additional interventions, either by increasing the DEX infusion, or administering adjunct OPs or BZDs. Other data points collected included the concurrent use of OPs, maximum opioid dose in milligrams per kilogram of morphine equivalents, and supplemental sedative doses. NICU length of stay and survival to discharge were also documented.

Data were collected in RedCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN) and transferred to Stata 16.1 (StataCorp LP, 2019) and SAS (SAS Institute, STAT 15.2) for all the statistical analyses. Descriptive statistics, including mean, median, SD, range, IQR, and minimum and maximum values, were used for analyzing continuous measures, including weight, GA, Apgar scores, and the duration of treatment with DEX. In addition, the Student *t* test was

Table 1. Dexmedetomidine Group Demographics

DEX Group 105 (100)		<1 kg 62 (59)	≥1 kg 43 (41)	p Value
Birth weight, median (Q1–Q3), g	870 (615–1507)	650 (560–740)	1800 (1320–2390)	<0.01
Gestational age, median (Q1–Q3), wk	26 (24–31)	24 (24–25)	32 (29–35)	<0.01
Sex, n (%)	M: 65 (62)	M: 34 (55)	M: 31 (72)	NS
Race, n (%)	African American: 37 (35) White: 56 (53) Hispanic: 2 (2) Asian: 1 (1) Multiracial: 7 (7) Declined: 2 (2)	African American: 29 (47) White: 28 (45) Hispanic: 2 (3) Asian: 0 (0) Multiracial: 2 (3) Declined: 1 (2)	African American: 8 (19) White: 25 (65) Hispanic: 0 (0) Asian: 1 (2) Multiracial: 5 (12) Declined: 1 (2)	<0.01 NS NS NS NS
Apgar 1 min, mean ± SD	4 ± 2	3 ± 2	5 ± 3	<0.01
Apgar 5 min, mean ± SD	5 ± 3	5 ± 3	6 ± 3	<0.01
Apgar 10 min, mean ± SD	7 ± 2	7 ± 2	7 ± 2	NS
NICU length of stay, mean ± SD, days	94 ± 59	122 ± 58	57 ± 39	<0.01
Antenatal steroids, n (%)	66 (63)	59 (95)	20 (46)	<0.01
Intubation, n (%)	98 (93)	61 (98)	37 (88)	0.04
Surfactant, n (%)	87 (83)	62 (100)	25 (58)	<0.01
Mechanical ventilation, median (Q1–Q3), days	19 (0–100)	34 (2–100)	4 (0–55)	<0.01
Intraventricular hemorrhage grade III/VI, n (%)	19 (18)	12 (19)	7 (16)	NS
Survival, n (%)	93 (89)	57 (92)	36 (84)	NS

DEX, dexmedetomidine; NICU, neonatal intensive care unit; NS, No statistical significance

used for comparing means between groups, and the Wilcoxon rank sum test was used for nonparametric data. Finally, categorical variables such as race, outcome, antenatal steroid use, intubation, OPs, BZDs, surfactant, hypotension, bradycardia, and interventions were compared between weight cohorts, using the chi-square test for independence or Fisher exact test, as applicable. A p value ≤0.05 was considered statistically significant.

Results

The EMRs of 381 patients were evaluated; 276 were excluded (see Supplemental Figure), leaving 105 included in the study. The median GA for the cohort receiving DEX was 26 weeks (IQR, 24–31), and the median birth weight was 870 g (IQR, 605–1507). The baseline demographics for this cohort are described in Table 1, and DEX treatment in this cohort is described in Table 2. The most common reason for admission to the NICU was extreme prematurity requiring mechanical ventilation (Table 3). The median infusion rate of DEX for the entire cohort was 0.4 mcg/kg (IQR, 0.3–0.45). Infants weighting less than 1 kg had a minimum dose rate of 0.2 mcg/kg/hr and a maximum of 1.2 mcg/kg, while infants weighing 1 kg or more had a minimum dose rate of 0.2 mcg/kg and a maximum dose of 0.6 mcg/kg. When compared with infants weighing less than 1 kg, the larger infants required smaller doses ($p < 0.01$) to maintain adequate scores. The median duration of therapy was 7 days (IQR, 3–14), with a minimum of 2 days (per inclusion criteria) and a maximum of 81 days.

Table 2. Dexmedetomidine Use in Preterm Infants

DEX Group N = 105 (100)		<1 kg n = 62 (59)	≥1 kg n = 43 (41)	p Value
Day of life DEX started, median (Q1–Q3), days	5 (1–14)	10 (2–20)	2 (0–5)	<0.01
DEX length of therapy, median (Q1–Q3), days	7 (3–14)	9 (5–17)	4 (3–11)	<0.01
DEX max dose, median (Q1–Q3), mg/kg/hr	0.4 (0.3–0.45)	0.4 (0.3–0.6)	0.4 (0.3–0.4)	<0.01
OP exposure, n (%)*	100 (95)	59 (95)	41 (95)	NS
Morphine equivalent dose, median (Q1–Q3), mg/kg	1.47 (0.32–5)	2.8 (0.53–7.43)	0.91 (0.15–1.8)	NS
BZDs, n (%)†	35 (34)	22 (35)	13 (30)	NS
Hypotension, n (%)‡	34 (31)	23 (37)	11 (26)	NS
Bradycardia, n (%)§	42 (40)	35 (57)	7 (18)	<0.01
Inotropes, n (%)¶	29 (28)	17 (28)	12 (27)	NS
Clonidine, n (%)	9 (9%)	5 (8%)	4 (9%)	NS

BZDs, benzodiazepines; DEX, dexmedetomidine; NS, No statistical significance; OP, opioid.

*Morphine or fentanyl.
†Midazolam.
‡Hypotension: a mean arterial pressure less than the gestational age for at least 30 consecutive minutes.
§Bradycardia: a sustained heart rate <80 for at least 1 minute.
¶Dopamine or epinephrine.

Table 3. Etiology for NICU Admission and Dexmedetomidine Use

DEX Group, 105 (100)		<1 kg 62 (59)	≥1 kg 43 (41)	p Value
Agitation/sedation, n (%)	**62 (59)**	**43 (69)**	**19 (44)**	0.02
Mechanical ventilation–related agitation	58 (55)	41 (66)	17 (40)	
Pulmonary hemorrhage	4 (4)	2 (3)	2 (5)	
Procedural pain/sedation, n (%)	**14 (13)**	**7 (11)**	**7 (16)**	NS
Pneumothorax	10 (10)	6 (10)	4 (9)	
Pericardiocentesis	1 (1)	1 (2)	0 (0)	
Therapeutic hypothermia	2 (2)	0 (0)	2 (5)	
Thoracentesis	1 (1)	0 (0)	1 (2)	
Postoperative pain, n (%)	**29 (28)**	**12 (19)**	**17 (40)**	0.03
Necrotizing enterocolitis	5 (5)	4 (6)	1 (2)	
Intestinal atresia/obstruction	9 (9)	1 (2)	8 (19)	
Myelomeningocele	2 (2)	1 (2)	1 (2)	
Spontaneous perforation	6 (6)	4 (6)	2 (5)	
Tracheoesophageal fistula	2 (2)	2 (3)	0 (0)	
Gastroschisis	2 (2)	0 (0)	2 (5)	
Congenital diaphragmatic hernia	1 (1)	0 (0)	1 (2)	

DEX, dexmedetomidine; NICU, neonatal intensive care unit; NS, No statistical significance

Thirty-five infants (57%) with a birth weight <1 kg experienced episodic bradycardia compared with 7 infants (18%) of 1 kg or more while receiving a DEX infusion. A similar number of infants in both groups required interventions such as repositioning, stimulation, or medication adjustment. There was no significant difference between the groups in the incidence of hypotension or inotropic intervention. No infant required discontinuation of DEX owing to hypotension or bradycardia.

DEX was used for sedation during invasive mechanical ventilation in 98 infants (93%) in this cohort. Additionally, 7 patients (7%) received DEX during noninvasive mechanical ventilation, and 30 patients (29%) continued DEX after extubation for a median of 2.5 days (IQR, 1–4.5). No infant required discontinuation of DEX for respiratory depression.

Thirty-three infants (53%) weighing <1 kg and 14 infants (36%) weighing >1 kg required subsequent intervention, implying inadequate pain control. Patients either had their DEX infusion rate increased or received adjunct therapy for an N-PASS score >3 at least once in 72 hours. One hundred infants (95%) receiving DEX also received simultaneous OPs. Thirty-five infants (33%) received a BZD infusion or intermittent doses of BZDs. Five patients (5%) received DEX as first-line therapy and maintained an adequate level of pain and sedation (N-PASS score <3). Nine infants (9%) in the cohort treated with DEX for more than 14 days received a clonidine taper to lessen the possible effects of a DEX withdrawal.

Discussion

Standard therapy for sedation in the NICU in the past has generally been a combination of OPs and BZDs.[4] Common adverse effects of these medications include respiratory depression, gastrointestinal complications, and neurologic dysfunction, all of which can lead to additional morbidity in the premature infant.[4]

We describe the experience of 3 NICUs within a single academic hospital system with the increasing use of DEX in preterm infants. In 2010, we implemented the use of DEX to treat babies who were irritable and not responding well to traditional OPs and BZDs. As use expanded it was noted that the doses of BZD and OP could be markedly reduced or avoided altogether.

Inadequate sedation and analgesia in former PTNBs admitted to the NICU put this population at higher risk for developmental delay later in life.[7] All the infants in our cohort achieved a good pain control and sedation as indicated by N-PASS score. However, 78 (74%) had at least 1 documented N-PASS score >3 during their DEX infusion, and these patients required pharmacologic interventions with increases in DEX infusion rates, and/or the addition of OPs, or BZDs.

Infants <1 kg are often very challenging patients to manage in the NICU, especially the infants weighing less than 500 g. Prematurity plays a significant role in the clinical course of these infants, depending on their level of immaturity. For that reason, infants in our study were stratified into 2 cohorts: preterm neonates with a birth weight of <1 kg and those with a birth weight equal to 1 kg or more. The use of DEX in this cohort was at the discretion of the neonatal team.

The pediatric dosing recommendations for DEX are currently based on 2 prospective[2,3] and 3 retrospective[5,16,17] studies. Continuous infusion doses as large as 2 mcg/kg/hr of DEX have been documented in older infants.[2,18,19] The starting dose of DEX in this study was 0.2 to 0.4 mcg/kg. Even knowing that larger doses might be needed, the starting point remained the same. The infusion would then be titrated to achieve an N-PASS score between 0 and 2, which translates to adequate pain control. No loading doses were given in this study. The median dose for continuous infusion of DEX was 0.4 mcg/kg (IQR, 0.3–0.45). The infusion was started as early as 1 hour after birth. The treatment length was a median of 7 days (IQR, 3–14), with 1 infant receiving DEX for a total length of 81 days. If the DEX infusion was not adequate, concomitant administration of morphine or BZDs was used to maintain N-PASS scores within the target range.

The N-PASS score is an important tool in NICUs for assessing sedation in these patients. It is easy to use, noninvasive, and can be administered to all patients in the unit. The Cleveland Clinic system has trained all bedside NICU nurses to use the N-PASS score system and verified that consistent measures are provided among caregivers. Scoring is usually performed every 3 hours, but this interval may change with caregiving. N-PASS scoring is required at least once a shift, depending on the procedure or desired level of pain control and sedation.

The N-PASS comprises 2 measurements, pain and sedation, each assessing 5 criteria. Treatment or intervention is recommended for scores of more than 3. The recommendation for good pain control is to keep the N-PASS score between 0 and 2.[11,12]

DEX was usually well tolerated in this cohort. When present, systemic arterial hypotension was usually associated with the administration of other agents, such as OPs or BZDs with DEX. Bradycardia was observed in our group but rarely required intervention. The incidence of bradycardia was significantly higher in infants with a birth weight of less than 1 kg. However, no infant required discontinuation of DEX for bradycardia. The incidence of bradycardia may have been correlated with the infusion rate of DEX, because infants weighing less than 1 kg were exposed to larger doses deemed necessary to achieve an adequate level of comfort.

Our group has previously described our clinical experience with DEX use in managing postoperative pain in term infants.[20] From data collected on 32 preterm infants exposed to OPs alone, the calculated morphine equivalent dose (median, 19.7 mg/kg; IQR, 5.6–54.95)

was significantly higher than this cohort's morphine equivalent dose, (median, 1.47 mg/kg; IQR, 0.32–5; p < 0.01). However, this comparison to a historical control group is potentially confounded by prior use of fentanyl as a joint agent for sedation and analgesia in the NICU.

A previous study that examined the safety of DEX found a statistically significant difference between the number of neonates (n = 2, 7%) as compared with infants (n = 55, 56%) experiencing bradycardia (p < 0.01).[5] However, there was no difference in the incidence of hypotension between neonates (n = 4, 14%) and infants (n = 30, 30%; p = 0.15). The present study found a significant difference in bradycardia events between the weight groups. Infants weighing less than 1 kg were more affected by bradycardia. No statistically significant difference was found in the incidence of hypotension between the groups. Other studies report a decrease in systolic blood pressure and heart rate in their patient population with the use of DEX, but no changes in clinical status that required discontinuation of DEX infusion.[21] DEX is also reported to have no appreciable effect on respiratory drive.[2,18] This study supports that observation, as 37 patients (35%) were treated with DEX without invasive respiratory support and did not require reintubation due to respiratory failure or apnea.

OP and BZD exposure have been found in animal studies to have potential neurologic consequences when used early in life. Studies performed on neonatal rats have found that OPs have neuroapoptotic properties through the activation of N-methyl-D-aspartate receptors.[6,17] In neonatal humans, early exposure to OPs has been associated with alterations in the cerebral structure and short-term neurobehavioral problems.[6,22] On the other hand there are data that suggest a neuroprotective effect of DEX mediated by activation of the central alpha-2 adrenergic receptor subtype protecting against hypoxic-ischemic injury, reducing both apoptotic and necrotic brain cell death.[23] Therefore, finding a safe, effective, and accessible analgesia agent for these patients is crucial. Improving our understanding of the pharmacokinetics and pharmacodynamics of DEX may help limit the number of additional agents required to achieve therapeutic goals and minimize untoward effects on the developing brain. New strategies have been reported with adequate level of sedation and pain control in postoperative pediatric patients with the combination of DEX and intravenous acetaminophen as a substitute for morphine.[20,21,24]

It has been suggested that prolonged infusions of DEX may be associated with rebound tachycardia, hypertension, and withdrawal symptoms after rapid discontinuation.[14] There was no report of rebound hypertension in this cohort, but owing to these possible withdrawal and rebound symptoms, a slow wean approach should be considered for a patient on long-term DEX therapy (more than 5 days). In this study, 9 infants (9%) received clonidine because they did not tolerate a rapid wean of the drip. Based on the present study it may be safe to stop DEX for infusion rates from 0.2 to 0.3 mcg/kg/hr for infants who have been exposed for less than 5 days. For infants receiving larger doses (infusion rates of >0.5 mcg/kg), weaning at 0.1 mcg/kg every 12 to 24 hours can be considered, based on assessing withdrawal symptoms. For infants treated with DEX for more than 14 days, clonidine may facilitate weaning or transition from intravenous to oral therapy.

There are limitations to the study based on its retrospective nature. Our determination of adverse events relied on the accuracy of information in the EMR. The doses used in this study were not standardized, and the infusion rates were at the discretion of attending physicians. Furthermore, there is a lack of pharmacokinetic data on DEX in preterm infants; therefore, our dosing was based on clinical responses. Finally, the concomitant use of OPs and BZDs with DEX made it challenging to establish whether one agent or combination of agents was responsible for adverse events.

Conclusions

For over a decade DEX has been adopted and is being used more commonly in many NICUs, providing good sedation and analgesia in preterm infants. This is a report of its use in extremely PTNBs, which was overall well tolerated with significant clinical effects. We recommend a starting dose of 0.2 to 0.4 mcg/kg, no loading dose, titrate as needed, until reaching N-PASS score of 0 to 2. For infants weighing less than 1 kg, the maximum dose was 1.2 mcg/kg. For infants on a DEX infusion for less than 5 days, on doses of 0.2 to 0.3 mcg/kg, weaning off the drip appears safe. For infants on larger doses of DEX, a possible weaning strategy is weaning by 0.1 mcg/kg every 12 to 24 hours. Further prospective studies are needed to evaluate the acute pharmacodynamic effects of DEX, and additional data are needed to demonstrate long-term neurodevelopmental outcomes of DEX use as an adjunct or substitute to other analgesic and sedative medications.

Article Information

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