JPPT | Single Center Retrospective Study

Effectiveness and Safety of Dexmedetomidine in Neonates With Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia

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OBJECTIVE The objective of this study was to evaluate and compare the effectiveness and safety of dexmedetomidine as monotherapy between neonates with mild hypoxic ischemic encephalopathy (HIE) and moderate to severe HIE treated with therapeutic hypothermia (TH).

METHODS This retrospective study included neonates of gestational age ≥36 weeks with a diagnosis of HIE and undergoing TH between January 2014 and December 2021. Patients were included if they received at least 6 hours of continuous sedation with dexmedetomidine. Baseline characteristics, dose and duration of medication, adverse events, liver and kidney function tests, and hospital course were reviewed.

RESULTS Of the 97 neonates included, 46 had mild, 42 had moderate, and 9 had severe HIE. Dexmedetomidine was initiated at a median 5 hours of life, and the median infusion duration was 77 (46–87) hours. Fifty-two (53.6%) required at least 1 breakthrough opioid or sedative during the first 24 hours of dexmedetomidine infusion. Overall, 40 patients (41.2%) had at least 1 bradycardia episode with heart rate <80 beats/min and 14 patients (14.4%) had heart rate <70 beats/min. Hypotension was experienced by 7 patients (7.2%). Fifty-two patients (53.6%) were intubated in the delivery room and 33/52 (63.5%) were extubated on day of life 1 during dexmedetomidine infusion.

CONCLUSIONS Dexmedetomidine as monotherapy was effective and safe sedation for infants with HIE undergoing hypothermia. The most common side effect of dexmedetomidine was bradycardia. Dexmedetomidine may be considered as first and single agent for neonates with HIE undergoing TH.

ABBREVIATIONS ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; HIE, hypoxic ischemic encephalopathy; NICHD, National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; N-PASS, neonatal pain, agitation, and sedation scale; TH, therapeutic hypothermia

KEYWORDS dexmedetomidine; hypoxic ischemic encephalopathy; neonates; sedation; therapeutic hypothermia

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Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) is one of the most common causes of neonatal morbidity and mortality with an incidence of 1 to 3 in 1000 live births in developed countries and approximately 10 times higher in resource-limited countries.[1–4] Therapeutic hypothermia (TH) is currently the only effective treatment but produces physiologic stress, elevating circulating cortisol and norepinephrine concentrations after asphyxia when compared with normothermia.[5,6] Preclinical models have suggested that inadequate sedation may reduce the benefits of cooling.[7,8] In adults, sedation/analgesia medications during TH are associated with earlier attainment and better maintenance of target temperatures.[9] Opioid administration is a common practice during TH in neonates with HIE. Opioid use for sedation and analgesia during HIE has increased in the United States from 38% in 2007 to 68% in 2015.[10] Opioids have been associated with significant side effects, including tolerance, physical dependency, paradoxical agitation, withdrawal, inconsistent sedation, respiratory depression, and gastrointestinal dysmotility.[10–13] Moreover, opioids, especially morphine, accumulate substantially after hypoxia-ischemia and during hypothermia, and require dosing adjustments during TH.[14] Dexmedetomidine is a centrally acting alpha-2 adrenergic receptor agonist that may offer an alternative to opioids. Dexmedetomidine provides sedation, anxiolysis, and analgesia, but does not suppress ventilation or cause gastric dysmotility.[15–18] Following the latent phase of hypoxic-ischemic insult, blockade of

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noradrenaline-mediated alpha-2 adrenergic receptors results in loss of suppression and exacerbates neuronal loss.[19,20] Alpha-2 adrenergic receptor stimulation increases expression of enzymes responsible for neuronal survival and synaptic plasticity and suppresses inflammatory cytokines.[21,22] Animal neonatal models of HIE suggest that the alpha agonist dexmedetomidine protects against brain matter loss and improves neurologic functional deficit induced by hypoxic-ischemic insult.[21,23,24]

In our institution, we have been using dexmedetomidine since 2014 as single, continuous sedation during TH in neonates with HIE undergoing TH. The aim of this study was to evaluate and compare the effectiveness and safety of dexmedetomidine in infants with mild and moderate to severe HIE treated with TH.

Materials and Methods

This was a retrospective cohort study with a review of charts of neonates admitted with a diagnosis of HIE and treated with TH, between January 2014 and December 2021, at Cleveland Clinic Children's Main Hospital.

Patient Selection and Unit Protocol. The need to initiate TH was determined by the clinician and based on an adaptation of standard criteria previously described by Shankaran and colleagues.[25] Entry criteria for TH include a gestational age of 36 weeks or more, birth weight of 1.8 kg or greater, and age of 6 hours or less. All neonates included had evidence of HIE defined by a pH of 7.0 or less and/or a base deficit greater than 16 mmol/L, or a pH between 7.01 and 7.15 and/or a base deficit between 10 and 15.9 mmol/L in umbilical cord blood or any blood during the first hour after birth, Apgar score of 5 or less at 10 minutes of life, or prolonged resuscitation at birth defined as chest compressions and/or intubation or mask ventilation at 10 minutes of life. All patients were classified by a neonatal intensive care unit physician, using modified Sarnat staging (level of consciousness, spontaneous activity, posture, muscle tone, primitive reflexes, and autonomic function), as having mild, moderate, or severe encephalopathy. An infant's condition was scored as mild if they had at least 1 domain consistent with mild, but did not meet criteria for moderate or severe HIE; as moderate if they had 3 or more domains consistent with moderate or severe HIE, but more domains were moderate than severe; and as severe if they had 3 or more domains consistent with moderate or severe HIE, but more domains were severe than moderate.[26,27] Babies born with lethal congenital malformations, chromosomal anomalies, or receiving another continuous sedation were excluded. Infants with severe coagulopathy or birth/head trauma were assessed individually by the clinician for TH. Whole body cooling to 33.5°C was performed for 72 hours, followed by slow warming over at least 6 hours at a rate of 0.5°C per hour until esophageal temperature reached the desired temperature of 36.5°C.[25]

Patients were included in the study if they required at least 6 hours of continuous sedation with dexmedetomidine within 12 hours after birth. They received dexmedetomidine, which was initiated at 0.2 mcg/kg/hr and increased by 0.1 mcg/kg/hr, based on N-PASS (neonatal pain, agitation, and sedation scale) scores and breakthrough opioid or sedation dose requirements. N-PASS is the first neonatal-specific sedation assessment tool studied and validated as an assessment tool both for pain and sedation. Based on N-PASS tool, sedation is scored from −2 → +2 for each criterion, including crying/irritability, behavior state, facial expressions, extremities tone, and vital signs (heart rate, respiration rate, blood pressure, oxygen saturation). The score ranges from −10 to +10 and, the goal score is −2 to +2.[28,29]

In our institution, N-PASS scoring is performed by a registered nurse with hands on care at every 2 to 3 hours and as needed. An N-PASS score of ≥+3 was the prompt to give a bolus of opioid or sedative. If patients required breakthrough opioid or sedative for ≥3 consecutive doses or for >4 to 5 doses/24 hr, this prompted an increase in dexmedetomidine dose. Dexmedetomidine was decreased by 0.1 mcg/kg/hr for bradycardia, or appearance of oversedation, and reevaluated every 1 to 2 hours before another dose adjustment. Oversedation is defined as no response to any stimuli. Dexmedetomidine was paused if bradycardia was not responsive to decreased dosage until bradycardia was resolved. After rewarming and once normothermia was reestablished, dexmedetomidine was discontinued without weaning the dose unless clinical status warranted continued sedation or pain medication. Bradycardia was defined as a sustained heart rate of <80 beats per minute (bpm) for at least 3 consecutive readings in a 1- to 2-hour period.

Dexmedetomidine dose was not influenced by blood pressure changes. Systemic hypotension was identified by the need for volume expansion or inotropic support after starting dexmedetomidine infusion. Systemic hypertension was identified as systolic pressure or mean arterial pressure at ≥95th percentile for gestational age for at least 3 consecutive readings in a 1- to 2-hour period.

Outcomes. The primary outcome was to determine if dexmedetomidine was an effective monotherapy for sedation and analgesia with reduction of N-PASS scores and need for additional bolus medications in infants with HIE undergoing TH. The secondary outcome was to categorize and compare incidence of side effects of dexmedetomidine, including bradycardia, hypotension, and hypertension, between patients with mild and moderate to severe HIE. The third outcome was to determine and compare clinical outcomes between patients with mild and moderate to severe HIE who received dexmedetomidine during TH.

Data Collection. Data were collected from patients with HIE, including patient demographics, modified

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Sarnat score, medication information (time of initiation, duration, cumulative dose), adverse events (bradycardia, hypotension and hypertension episodes), laboratory assessments (liver and kidney function tests), and hospital course (length of hospital stay, duration in reaching full enteral and oral feeds, tube feeding at discharge, noninvasive and mechanical ventilation need and duration).

Statistical Analysis. Continuous variables were described by using medians and IQRs; categorical variables were described by using counts and percentages. Demographic and clinical characteristics were compared between patients with mild and moderate/severe HIE by using Wilcoxon rank sum test for continuous/ordinal characteristics and Pearson chi-square test or Fisher exact test for categorical characteristics, as appropriate. All analyses were performed on a complete-case basis; subjects with missing data for certain variables were excluded only for analyses in which those variables were used. SAS 9.4 software (SAS Institute, Cary, NC) was used for all analyses. Statistical significance was defined as a p value of less than 0.05.

Results

Between January 2014 and December 2021, a total of 124 patients were admitted to the neonatal intensive care unit (NICU) of Cleveland Clinic Children's Main Hospital for TH. Twenty-seven patients were excluded for the following reasons: 8 received dexmedetomidine infusion for less than 6 hours, 8 received both morphine and dexmedetomidine infusions, 5 received only morphine infusion, 3 received only intermittent sedation, and 3 had lethal congenital or chromosomal anomalies. Of the 97 neonates included, 46 met criteria for mild HIE, 42 infants were categorized as having moderate HIE, and the remaining 9 infants experienced severe HIE. Owing to low patient numbers for the severe group, moderate to severe groups were combined for statistical analysis. Patients with moderate to severe HIE had lower 10-minute Apgar scores; had a higher base deficit in cord arterial blood gases; had lower pH, bicarbonate, a higher base deficit, and lactate in 1-hour of life blood gases; and were more likely to have seizures than those with mild HIE ($p < 0.05$) (Table 1).

Table 1. Baseline Characteristics of Patients*

	Total Patients With HIE (N = 97)	Mild HIE (N = 46)	Moderate and Severe HIE (N = 51)	p value
Sex				0.74†
Female	46 (47.4)	21 (45.7)	25 (49.0)	
Male	51 (52.6)	25 (54.3)	26 (51.0)	
Gestational age, wk	39.5 [38.3–40.4]	39.6 [38.3–40.5]	39.5 [38.1–40.4]	0.84‡
Birth weight, kg	3.3 [3.1–3.7]	3.4 [3.2–3.6]	3.2 [2.9–3.8]	0.40‡
Delivery type				0.12†
SVD	29 (29.9)	11 (23.9)	18 (35.3)	
Vaginal assisted	13 (13.4)	4 (8.7)	9 (17.6)	
Cesarean delivery	55 (56.7)	31 (67.4)	24 (47.1)	
Apgar scores				
1 min	2.0 [1.0–2.0]	2.0 [1.0–2.0]	1.0 [1.0–2.0]	0.13‡
5 min	4.0 [3.0–5.0]	4.0 [3.0–5.0]	4.0 [2.0–5.0]	0.31‡
10 min	5.0 [4.0–7.0]	6.0 [5.0–7.0]	5.0 [4.0–6.0]	**0.003**‡
Cord arterial				
pH	7.0 [6.8–7.1]	7.0 [6.9–7.1]	6.9 [6.8–7.1]	0.41‡
Bicarbonate	18.0 [14.0–20.0]	17.0 [14.0–20.0]	18.0 [15.0–20.0]	0.77‡
Base deficit	14.0 [10.0–19.6]	12.0 [9.0–16.1]	17.0 [12.8–22.0]	**0.005**‡
< 1 hr of life blood gas				
pH	7.2 [7.1–7.2]	7.2 [7.2–7.3]	7.1 [7.0–7.2]	**<0.001**‡
Bicarbonate	13.0 [10.0–16.0]	14.0 [13.0–18.0]	13.0 [9.0–15.0]	**0.020**‡
Base deficit	15.0 [12.0–18.0]	13.0 [10.0–16.0]	18.0 [14.5–21.0]	**0.002**‡
Lactate	12.6 [8.2–15.0]	10.2 [6.9–14.0]	13.2 [11.1–17.9]	**0.014**‡
Seizures	21 (21.6)	2 (4.3)	19 (37.3)	**<0.001**†
Timing of first seizure, hr	14.0 [11.0–20.0]	4.5 [9.0–20.0]	14.0 [11.0–24.0]	0.95‡

HIE, hypoxic ischemic encephalopathy; N, number of patients; SVD, spontaneous vaginal delivery

* Statistics presented as median [IQR], N (column %). Bold p values are statistically significant.
† Pearson chi-square test.
‡ Wilcoxon rank sum test.

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Dexmedetomidine was initiated at a median 5 hours of life, with median initial dose of 0.2 (IQR, 0.2–0.2) mcg/kg/hr and median maximum dose of 0.3 (IQR, 0.2–0.4) mcg/kg/hr for all patients with HIE. The median infusion duration was 77 hours, with a median cumulative dose of 16.6 mcg/kg. Fifty-five patients (56.7%) required at least 1 bolus of opioids during TH with 47 of the 55 (85.5%) occurring in the first 24 hours of dexmedetomidine initiation. Seven patients (7.2%) required at least 1 bolus of sedatives (midazolam or lorazepam) during TH with 5 (71.4%) occurring in the first 24 hours. There was no significant difference for dosing and adverse events of dexmedetomidine between mild and moderate to severe HIE cases. (Table 2). There were no clinically significant differences in pain scores any time points, and median pain score was zero.

Forty patients (41.2%) had at least 1 episode of bradycardia (heart rate (HR) <80 bpm). There was no difference in bradycardia rates between mild and moderate to severe HIE. More than half of the patients with bradycardia had the drug dose decreased (52.5%) or discontinued (57.5%). Among those with HR <80 bpm and dose decreased, 8 patients (6/10 with mild, 2/11 with moderate to severe HIE) were able to continue dexmedetomidine therapy. Only 14 patients (14.4%) had low HR (<70 bpm), and approximately three-quarters

Table 2. Medication and Adverse Events*

	Total Patients With HIE (N = 97)	Mild HIE (N = 46)	Moderate and Severe HIE (N = 51)	p value
Dexmedetomidine				
Initiation, hours of life	5.0 [4.5–8.0]	5.5 [5.0–9.0]	5.0 [4.0–6.0]	0.054†
Duration, hr	77.0 [46.0–87.0]	77.0 [49.0–86.0]	75.0 [30.0–90.0]	0.77†
Cumulative dose, mcg/kg	16.6 [9.9–22.7]	16.3 [10.2–21.0]	17.0 [9.2–23.8]	0.56†
Breakthrough opioid use	55 (56.7)	29 (63.0)	26 (51.0)	0.23‡
Doses, first 24 hours	2.0 [1.0–2.0]	2.0 [1.0–2.0]	[1.0–2.0]	0.18†
0	8 (14.5)	2 (6.9)	6 (23.1)	
1	19 (34.5)	10 (34.5)	9 (34.6)	
2+	28 (50.9)	17 (58.6)	11 (42.3)	
Doses, first 80 hours	4.0 [2.0–5.0]	[2.0–6.0]	3.0 [2.0–4.0]	0.15†
Breakthrough sedative use	7 (7.2)	3 (6.5)	4 (7.8)	>.99§
Doses, first 24 hours	1.0 [0–2.0]	1.0 [0–1.0]	1.5 [0.50–2.0]	0.48†
0	2 (28.6)	1 (33.3)	1 (25.0)	
1	3 (42.9)	2 (66.7)	1 (25.0)	
2+	2 (28.6)	0 (0)	2 (50.0)	
Doses, first 80 hours	1.0 [1.0–2.0]	1.0 [1.0–2.0]	1.5 [1.0–4.0]	0.71†
Bradycardia <80 bpm	40 (41.2)	21 (45.7)	19 (37.3)	0.40‡
1–2 episodes	29 (29.8)	15 (32.6)	14 (27.5)	
3–4 episodes	8 (8.3)	4 (8.7)	4 (7.8)	
>4 episodes	3 (3.1)	2 (4.3)	1 (2)	
Intervention for bradycardia				
No changes	14 (35.0)	5 (23.8)	9 (47.4)	0.12‡
Dose decreased	21 (52.5)	10 (47.6)	11 (57.9)	0.52‡
Able to continue till end	8 (38.1)	6 (60)	2 (18.2)	
Discontinued	23 (57.5)	11 (52.4)	12 (63.2)	0.49‡
Bradycardia <70 bpm	14 (14.4)	5 (10.9)	9 (17.6)	0.34‡
Intervention for bradycardia				
No changes	3 (21.4)	0 (0)	3 (33.3)	0.26‡
Dose decreased	10 (71.4)	3 (60.0)	7 (77.8)	0.58‡
Able to continue till end	3 (30.0)	2 (66.7)	1 (14.3)	
Discontinued	11 (78.6)	3 (60.0)	8 (88.9)	0.51‡
Hypotension	7 (7.2)	2 (4.3)	5 (9.8)	0.44‡

bpm, beats per minute; HIE, hypoxic ischemic encephalopathy; N, number of patients

* Statistics presented as median [IQR], N (column %).
† Wilcoxon rank sum test.
‡ Pearson chi-square test.
§ Fisher exact test.

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Table 3. Serum Laboratory Assessment*

	Overall (N = 97)	Mild HIE (N = 46)	Moderate and Severe HIE (N = 51)	p value
ALT, U/L				
DEX initiation	30.0 [17.0–70.0]	22.5 [16.0–35.0]	44.0 [24.0–107.0]	**<0.001**†
TH	40.0 [20.5–116.5]	30.0 [19.0–68.0]	53.0 [28.0–185.0]	**0.013**†
Rewarming	39.0 [24.0–104.0]	29.0 [21.0–82.0]	46.0 [27.0–121.0]	0.069†
Post TH	40.0 [21.0–102.0]	30.0 [20.0–52.0]	52.0 [26.0–126.0]	**0.032**†
AST, U/L				
DEX initiation	83.0 [62.0–169.0]	73.5 [58.0–106.0]	129.0 [72.0–235.0]	**<0.001**†
TH	101.5 [70.5–191.5]	95.0 [57.0–132.0]	116.0 [76.0–229.0]	**0.020**†
Rewarming	66.0 [50.0–90.0]	59.0 [43.0–80.0]	76.0 [51.0–102.0]	**0.021**†
Post TH	52.5 [39.0–78.5]	45.0 [37.5–67.5]	59.0 [44.0–90.5]	**0.032**†
Conjugated bilirubin, mg/dL				
DEX initiation	0.30 [0.20–0.40]	0.30 [0.20–0.30]	0.30 [0.20–0.40]	0.17†
TH	0.30 [0.20–0.30]	0.30 [0.20–0.30]	0.30 [0.20–0.30]	0.90†
Rewarming	0.30 [0.30–0.40]	0.30 [0.20–0.40]	0.30 [0.30–0.50]	0.15†
Post TH	0.30 [0.20–0.40]	0.25 [0.20–0.40]	0.40 [0.30–0.50]	**0.006**†
BUN, mg/dL				
DEX initiation	10.0 [8.0–12.0]	10.0 [8.0–12.0]	10.0 [8.0–12.0]	0.59†
TH	10.0 [8.0–14.0]	10.0 [8.0–12.0]	12.0 [8.0–15.0]	0.28†
Rewarming	13.0 [8.0–19.0]	13.0 [8.0–19.0]	13.0 [9.0–21.0]	0.56†
Post TH	12.0 [8.0–17.0]	11.0 [7.0–16.0]	14.0 [10.0–17.5]	0.093†
Creatinine, mg/dL				
DEX initiation	0.89 [0.72–1.1]	0.84 [0.70–1.0]	0.90 [0.75–1.1]	0.46†
TH	0.68 [0.56–0.86]	0.62 [0.52–0.78]	0.78 [0.63–0.95]	**0.001**†
Rewarming	0.41 [0.34–0.55]	0.38 [0.34–0.42]	0.45 [0.35–0.62]	**0.003**†
Post TH	0.41 [0.32–0.48]	0.38 [0.29–0.42]	0.45 [0.36–0.51]	**0.003**†

ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urine nitrogen; HIE, hypoxic ischemic encephalopathy; N, number of patients; TH; therapeutic hypothermia

* Statistics presented as median [IQR]. Bold p values are statistically significant.
† Wilcoxon rank sum test.

had medication dose decreased (71.4%) or discontinued (78.6%). Among patients with HR <70 bpm and dose decreased, 3 (2/5 with mild, 1/9 with moderate to severe HIE) were able to continue dexmedetomidine therapy. Patients with hypotension in need of treatment were rare (n = 7): 4.3% in the mild and 9.8% in the moderate to severe group. None of our patients had hypertension (Table 2).

In mild HIE, median alanine transaminase (ALT) concentrations were within normal range (10–54 U/L) at 4 time points (at dexmedetomidine initiation, TH, rewarming, and post TH); aspartate aminotransferase (AST) concentrations (normal: 14–40 U/L) were elevated at initiation of dexmedetomidine but were almost normalized post TH (see Table 3). In moderate to severe HIE, median ALT concentrations were within normal range at 4 time points, but AST concentrations were significantly elevated ($p < 0.001$) at initiation of dexmedetomidine, gradually decreasing but remaining elevated post TH. ALT concentrations were higher at all time points, except at rewarming, and AST concentrations were consistently higher at 4 time points in moderate to severe HIE, compared with those in mild HIE ($p < 0.05$). Median conjugated bilirubin concentrations were elevated (normal: <0.2 mg/dL) at dexmedetomidine initiation in both mild and moderate to severe HIE (see Table 3). Conjugated bilirubin concentrations started trending down in mild HIE and trending up in moderate to severe HIE post TH. Conjugated bilirubin concentrations were higher in moderate to severe HIE than in mild HIE post TH ($p < 0.05$).

Blood urea nitrogen median concentrations were within normal range (4–19 mg/dL) at 4 time points in both mild and moderate to severe HIE. Creatine concentrations were within normal range (0.31–0.88 mg/dL) at 4 time points in mild HIE. In moderate to severe HIE, creatine concentrations were elevated at initiation of dexmedetomidine, and normalized at rewarming. Creatinine concentrations were higher at all time points, except at dexmedetomidine initiation in moderate to severe HIE, compared with those in mild HIE ($p < 0.05$) (Table 3).

Patients with moderate to severe HIE had a longer NICU length of stay (11 vs 9 days, $p < 0.05$), were more likely to be intubated on admission (64.7% vs 41.3%), had longer duration of intubation (median [IQR], 1 [1–3]

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Table 4. Hospital Course*

	Overall (N = 97)	Mild (N = 46)	Moderate and Severe (N = 51)	p value
NICU LOS, days	10.0 [8.0–14.0]	9.0 [7.0–12.0]	11.0 [8.0–18.0]	**0.010**†
Reaching full enteral feeds NG/OG tube, day of life	5.0 [5.0–7.0]	6.0 [5.0–7.0]	6.0 [5.0–8.0]	0.29†
Reaching full oral feeds, day of life	6.0 [5.0–10.0]	6.0 [5.0–8.0]	7.0 [6.0–12.0]	0.12†
Home with tube feeding				**0.029**‡
No	90 (92.8)	46 (100.0)	44 (86.3)	
NG	4 (4.1)	0 (0)	4 (7.8)	
G-tube	3 (3.1)	0 (0)	3 (5.9)	
Mechanical ventilation	52 (53.6)	19 (41.3)	33 (64.7)	**0.021**§
Duration, days	1.0 [1.0–2.0]	1.0 [1.0–1.0]	1.0 [1.0–3.0]	**0.023**†
Noninvasive ventilation	21 (21.6)	6 (13.0)	15 (29.4)	0.051§
Duration, days	4.0 [2.0–7.0]	1.5 [1.0–3.0]	4.0 [3.0–11.0]	**0.020**†

G-tube, gastric tube; LOS, length of stay; NG, nasogastric; NICU, neonatal intensive care unit; OG, orogastric

* Statistics presented as median [IQR], N (column %). Bold p values are statistically significant.
† Wilcoxon rank sum test.
‡ Fisher exact test.
§ Pearson chi-square test.

vs 1 [1–1] day; $p < 0.05$), although 19/33 (57%) were extubated after day of life 1. Patients with moderate to severe HIE were more likely to be discharged with tube feeding at home (nasogastric [n = 4] or gastric tube [n = 3]: 13.7% vs 0%; $p < 0.05$). Only 21.6% of all patients required noninvasive ventilation: time transitioned to room air was longer in moderate to severe HIE than in mild HIE (4.0 vs 1.5 days, $p < 0.05$). None of the neonates spontaneously breathing or undergoing noninvasive ventilation at dexmedetomidine initiation required intubation. The median time for reaching full enteral feeds and oral feeds was 6 days for both, which was not significantly different between HIE severity groups (Table 4).

One patient in the moderate to severe HIE group died during hospitalization.

Discussion

Use of opioids for sedation in neonates with HIE during TH is a common practice, but these drugs have been associated with significant side effects. Dexmedetomidine provides sedation but does not suppress ventilation, does not cause gastric dysmotility, and has neuroprotective effects.[18,21,23,24,30,31] In our retrospective study we described our experience with dexmedetomidine as a single, continuous sedative used in infants with HIE undergoing TH. To the best of our knowledge, this study is the largest study in infants with HIE who received dexmedetomidine during TH.

Efficacy of Dexmedetomidine. We used N-PASS scores to assess efficacy of dexmedetomidine and need for additional opioid/sedative doses. Average N-PASS score was zero at all time points. About half of the patients required at least 1 breakthrough opioid/sedative during TH, which most received in the first 24 hours of initiation of dexmedetomidine. Other studies in similar patient populations also reported decreased breakthrough opioid requirement or decreased cumulative dose of opioids in the dexmedetomidine group compared with the morphine or fentanyl group.[32-35] McAdams and colleagues[36] suggested a loading dose of dexmedetomidine may be needed to achieve effective plasma concentrations owing to a longer elimination half-life in newborns with HIE. Loading doses may decrease breakthrough opioid/sedative doses in the first 24 hours.

Adverse Events. Dexmedetomidine has potential adverse effects including bradycardia, hypotension, and hypertension.[32–35,37] Dexmedetomidine is a centrally acting α-2 adrenergic receptor agonist; adverse effects of bradycardia and hypotension might be caused by a reduction in norepinephrine, leading to sympatholytic effect from activation of central presynaptic α-2A receptors in the medullary vasomotor center.[38] The limited published data on dexmedetomidine use for sedation in neonates report bradycardia is the most common side effect.[33,38–40] We have been using dexmedetomidine as a single, continuous medication sedation since 2014. Our initial dose is 0.2 mcg/kg/hr, and titration is based on level of sedation and heart rate. In our unit, bradycardia is defined as ≤80 bpm for interventions during TH. In our study, 41% of the patients had at least 1 episode of bradycardia (HR <80 bpm), and more than half had the drug dose decreased or discontinued. Elliott and colleagues[40]

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compared heart rate trends in 3 groups of neonates with HIE undergoing TH: dexmedetomidine (n = 14), fentanyl (n = 120), and both (n = 32). Their dosing practices were like those of our practice; however, heart rate alarm limit was set at 90 bpm. Nearly half of the neonates required dosage decrease or discontinuation owing to low heart rate. However, only 14 of 166 neonates received dexmedetomidine monotherapy.[40] In our population, 14.4% of patients had a HR <70 bpm; of those, approximately three-quarters had a medication dose decrease or discontinuation. Therapeutic hypothermia itself decreases basal metabolism and causes lower heart rates.[6] It is currently unknown at what heart rate we should adjust dexmedetomidine dose without compromising cardiac output in infants with HIE undergoing TH. After this study we changed our heart rate limit, set at 70 bpm for interventions during TH.

Previous pediatric studies have shown clinically significant hypotension associated with the use of dexmedetomidine.[37,41] In our patient population approximately 5% of patients in the mild and 10% in the moderate to severe group had systemic hypotension and needed treatment. Most of these infants (5/7 [71%]) had systemic hypotension before the initiation of dexmedetomidine. Dexmedetomidine may cause systemic hypertension,[32,37] but none of our patients had systemic hypertension.

Laboratory Findings and Hospital Course. Dexmedetomidine is metabolized primarily by the liver and eliminated primarily through the urine after biotransformation via glucuronidation, hydroxylation, and N-methylation, and pharmacokinetics are altered by hypoxia-ischemia and TH. Dexmedetomidine exhibits 94% protein binding to serum albumin and to α-1 glycoprotein and may require dose reduction with hepatic dysfunction, although dexmedetomidine dose adjustment usually is not necessary in renal failure.[31,38,42] Our study reported liver and kidney function before, during, and after TH. The moderate to severe HIE group had higher ALT, AST, direct bilirubin, and creatinine concentrations than infants in the mild HIE group, as expected owing to severity of insult (see Table 3). Infants with mild HIE had mild elevation of hepatic and renal function markers, which normalized after TH. In patients with moderate to severe HIE, liver and kidney functions also gradually decreased during dexmedetomidine infusion, suggesting elevated liver and kidney function markers were the result of hypoxic injury.

One of the other advantages of dexmedetomidine compared with morphine is its not affecting respiratory drive negatively.[15,35] In a National Institute of Child Health and Human Development (NICHD) therapeutic hypothermia trial, the opioid group had longer duration of mechanical ventilation and supplemental oxygen than the control neonates (9 days vs 3 days, p < 0.0001).[43] Cosnahan and colleagues[33] reported increased fraction of inspired oxygen and ventilator support in the morphine group compared with the dexmedetomidine group in infants with HIE undergoing hypothermia. Similar findings were reported by Naveed and colleagues[34] with 19 patients in the fentanyl group and 26 patients in the dexmedetomidine group in neonates with HIE undergoing TH; the dexmedetomidine group had shorter time to extubation after birth at a median of 3 vs 11 days. In our study 53.6% of patients were intubated on admission and 63.5% were extubated on day of life 1. None of the neonates spontaneously breathing or undergoing noninvasive ventilation at dexmedetomidine initiation required intubation. Dexmedetomidine was not associated with any extubation failures and was continued after extubation in all patients.

Opioids also negatively affect gastrointestinal motility, whereas dexmedetomidine does not decrease gastrointestinal motility. In the NICHD therapeutic hypothermia trial, time to attain full oral feedings was longer for infants treated with opioids than for control neonates (13 days vs 8 days, p = 0.04).[43] In a recent study comparing dexmedetomidine with fentanyl in neonates with HIE undergoing TH, the dexmedetomidine group had earlier time to transition to full enteral feeds than the fentanyl group (8.5 vs 13 days).[34] The practice of keeping infants on nothing-by-mouth protocols during cooling is still common.[44] A recent study demonstrated that minimal enteral feeding during TH is safe and leads to a shorter time to full enteral feeding and higher rates of breast milk feeding at discharge.[45] We have recently started minimal enteral feeding (10–20 mL/kg/day) during TH. During the study period we were not feeding the patients with HIE, so could not assess their feeding tolerance during TH. Median time to reach full oral feeds was 6 days in mild and 7 days in moderate to severe HIE groups.

Opioids prolong the time to hospital discharge for neonates; in a retrospective analysis of sedation/analgesic exposure (including opioids, benzodiazepines, and barbiturates) in late preterm and term infants with HIE enrolled in a TH trial, a longer length of stay (14 vs 24 days, p = 0.08) was noted for treated neonates than for control neonates.[43] In our group, median length of hospital stay was 9 days in the mild and 11 days in the moderate to severe HIE group (Table 4).

Strengths and Limitations. Our study is the largest report of dexmedetomidine use for neonates with HIE during TH. This is also the only study to report liver and kidney function before, during, and after TH in infants with HIE undergoing TH who received dexmedetomidine.

There are several limitations to this study: it was a retrospective, monotherapy study, with no comparison with morphine or fentanyl. We were not able to account for all the potential confounding variables affecting the need for sedation dose arrangements. We also did not include all medications and interventions during TH that can affect heart rate and blood pressure.

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Conclusions

Dexmedetomidine was an effective and safe treatment in infants with HIE during hypothermia. The most common side effect was bradycardia. A randomized controlled trial of dexmedetomidine as an adjunct to TH is needed to assess full effectiveness, safety, and short- and long-term outcomes for infants with HIE.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. Given the nature of this retrospective study, informed consent was not required.

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