CLINICAL INVESTIGATION

Dexmedetomidine Versus Standard Therapy with Fentanyl for Sedation in Mechanically Ventilated Premature Neonates

Keliana O'Mara, PharmD,¹ Peter Gal, PharmD,^{2,3,4} John Wimmer, MD,^{2,5} J. Laurence Ransom, MD,^{2,5} Rita Q. Carlos, MD,^{2,5} Mary Ann V.T. Dimaguila, MD,^{2,5} Christie C. Davanzo, MD,^{2,5} and McCrae Smith, MD^{2,5}

¹Duke University Medical Center, Durham, North Carolina, ²Women's Hospital of Greensboro, Cone Health, Greensboro, North Carolina, ³Greensboro Area Health Education Center, Greensboro, North Carolina, ⁴University of North Carolina, Eschelman School of Pharmacy, Chapel Hill, North Carolina, and ⁵Piedmont Neonatology, PC, Greensboro, North Carolina

OBJECTIVE To compare the efficacy and safety of dexmedetomidine and fentanyl for sedation in mechanically ventilated premature neonates.

METHODS This was a retrospective, observational case-control study in a level III neonatal intensive care unit. Forty-eight premature neonates requiring mechanical ventilation were included. Patients received fentanyl (n=24) or dexmedetomidine (n=24) for pain or sedation. Each group also received fentanyl and lorazepam boluses as needed for agitation. The primary outcomes were efficacy and frequency of acute adverse events associated with each drug. Days on mechanical ventilation, stooling patterns, feeding tolerance, and neurologic outcomes were also evaluated.

RESULTS There were no significant differences in baseline demographics between the dexmedetomidine and fentanyl patients. Patients in the dexmedetomidine group required less adjunctive sedation and had more days free of additional sedation in comparison to fentanyl (54.1% vs. 16.5%, $p<0.0001$). There were no differences in hemodynamic parameters between the 2 groups. Duration of mechanical ventilation was shorter in the dexmedetomidine group (14.4 vs. 28.4 days, $p<0.001$). Meconium passage (7.5 vs. 22.4 days, $p<0.0002$) and time from initiation to achievement of full enteral feeds (26.8 vs. 50.8 days, $p<0.0001$) were shorter in the dexmedetomidine group. Incidence of culture-positive sepsis was lower in the dexmedetomidine group (48% vs. 88%). The incidence of either severe intraventricular hemorrhage or periventricular leukomalacia was not statistically significantly reduced (2% vs. 7%).

CONCLUSIONS Dexmedetomidine was safe and effective for sedation in the premature neonates included in this study. Prospective randomized-controlled trials are needed before routine use of dexmedetomidine can be recommended.

INDEX TERMS dexmedetomidine, fentanyl, mechanical ventilation, neonate, sedation

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INTRODUCTION

Sedation in mechanically ventilated neonates presents a unique therapeutic dilemma in which the provider must balance patient comfort with the potentially negative consequences of drug exposure to the developing brain. Standard therapy for sedation in these patients generally involves a combination of a narcotic and a benzodiazepine.¹ Common adverse effects include respiratory depression, gastrointestinal complications, and neurologic dysfunction, all of which can lead to additional morbidity in the premature infant.^{2,3}

Respiratory depression may lengthen the duration of mechanical ventilation, increasing the risk of chronic lung disease.⁴ Decreased gastrointestinal motility can lead to the development of abnormal stooling patterns, meconium plug syndrome, and delayed introduction or advancement of enteral feeds.^{2,5} In the hemodynamically unstable neonate, narcotic use has been linked to increased risk of intraventricular hemorrhage (IVH).⁶ Narcotic- and benzodiazepine-mediated neuronal apoptosis has been implicated as a potential cause of long-term neurologic complications in premature neonates.^{7,8}

Table 1. Baseline Demographics

Characteristics	FENT (n=24)	DMDT (n=24)	p Value
Gestational age (wk)*	24.9 ± 1.6	25.5 ± 1.7	0.095
Birth weight (g)*	675 ± 164.2	832 ± 204.2	0.051
Male/female	15/9	13/11	0.55
Antenatal corticosteroids (%)	79.2	87.5	0.438
5-min APGAR*	6.3 ± 1.5	6.4 ± 1.7	0.78
Number of surfactant doses per patient*	3.1 ± 1.1	2.9 ± 0.8	0.148
CRIB-II score*	11 ± 2	10 ± 2.4	0.167
Patients with patent ductus arteriosus (%)	75	79	0.73
Patients with hypotension requiring vasopressors at study entry (%)	62.5	54	0.56

DMDT, dexmedetomidine; FENT, fentanyl

*mean ± standard deviation

Dexmedetomidine is a centrally acting α_2 receptor agonist that has both sedative and analgesic properties.⁹ In contrast to a narcotic, dexmedetomidine does not have an appreciable effect on respiratory drive or gastric motility. Animal models suggest a potentially neuroprotective effect of dexmedetomidine, especially in the hypoxic-ischemic environment.¹⁰ There is also some evidence to suggest that dexmedetomidine diminishes inflammatory processes, particularly in sepsis and the mechanically ventilated lung.^{11,12} While it is not approved by the U.S. Food and Drug Administration for use in children or neonates, the adult and pediatric literature has been mostly in favor of its use for mechanically ventilated patients. In these populations, dexmedetomidine infusion is associated with decreases in the duration of mechanical ventilation, decreased use of narcotics/adjunctive sedation, and reduced incidence of intensive care unit (ICU) delirium/organic brain dysfunction and sepsis.^{13–21} Published literature describing the use of dexmedetomidine infusion in premature neonates is lacking. We detailed our initial experience with dexmedetomidine in a premature infant in a previously published case report.²² The patient was a 23-week gestational age infant in whom adequate sedation was not obtained with fentanyl infusion, scheduled lorazepam and phenobarbital, and as-needed boluses of lorazepam, midazolam, and fentanyl. After dexmedetomidine was initiated, the patient showed a dramatic response to therapy, allowing for ventilator synchrony and overall improved respiratory status. The impressive response in that case and the relative benefits with dexmedetomidine in other study populations compelled us to implement dexmedetomidine as

our first-line sedative in many of our neonates. We subsequently decided to compare our clinical outcomes with those experienced when we used more traditional sedation approaches as a means of assuring quality improvement with this approach. This study describes our use of dexmedetomidine in mechanically-ventilated premature infants in a neonatal intensive care unit (NICU), and compares them to matching cases treated with fentanyl infusion as the primary sedative. Since this reflected retrospective case review only, the study was exempted from informed consent by our institutional review board.

MATERIALS AND METHODS

This retrospective historical case control study includes premature neonates born at Women's Hospital of Greensboro between January 2005 and May 2010. Infants were eligible for study inclusion if they were <36 weeks gestation at birth, less than 2 weeks of life at study entry, and receiving mechanical ventilation. The fentanyl historical control patients were selected from the NICU database when sufficiently matched to a dexmedetomidine-treated neonate based on baseline demographics described in Table 1. Particular focus for matching cohort pairs was on gestational ages being within one week of each other since many of the long-term patient outcomes in the neonatal population are gestational age-dependent. Fentanyl patients were eligible for inclusion if they received fentanyl via continuous infusion or scheduled intravenous (IV) boluses for sedation within the first 48 hours of life and were born between January 2005 and May 2010. Patients in the dexmedetomidine group

were born between September 2008 and May 2010. These date ranges were chosen to minimize risk of practice variability in the NICU between the two groups. Dexmedetomidine was initiated within 48 hours of life, either empirically or in those who met predefined criteria for continuous infusion sedation (patients who required at least 5 doses of fentanyl 1 mcg/kg, lorazepam 0.1 mg/kg, or any combination of the 2 agents in a 24-hour period). Infants were excluded from either group if they had major congenital anomalies considered incompatible with life.

Data collection included patient demographics and indices of treatment efficacy and toxicity. Mean daily doses/infusion rates of either fentanyl or dexmedetomidine were obtained for each patient. The treatment period for the primary outcome began when the patient was started on the study drug and ended after the study drug was discontinued, either because there was no continuing need for sedation or on account of hospital transfer/death. Data were collected for several secondary outcomes beyond the actual infusion period to better assess the safety outcomes. The primary efficacy outcome was the need for adjunctive analgesia or sedation during the treatment period. Adjunctive sedation was defined as any bolus dose(s) of fentanyl (1 mcg/kg) or lorazepam (0.1 mg/kg) given in addition to the continuous infusion or scheduled boluses of the treatment drug. Total fentanyl and lorazepam requirements were collected for each patient. The percent of time during which the infant required no additional sedation and the mean number of doses per day of adjunctive sedation during the study period were calculated. Since dexmedetomidine is thought to have minimal inhibitory effects on respiratory drive and gastrointestinal function, several variables were collected to evaluate these endpoints and compare them to infants treated with fentanyl, including duration of mechanical ventilation, stool pattern, and feeding tolerance. Respiratory function was evaluated by recording the duration of mechanical ventilation from birth to sustained extubation (at least 48 hours without requiring reintubation). The mean number of chest x-rays in each group was also calculated. Gastrointestinal function was measured using multiple markers. Time to first meconium stool and duration of meconium passage (determined by days until transitional stools) were used as

markers of gastric motility. Feeding tolerance was explored by determining time to start enteral feeds and time to achieve full enteral feeds (150 mL/kg/day).

Since little published literature exists describing how to use dexmedetomidine in premature neonates, a comparison of dosing strategies was included in the study. Loading dose, mean effective dose, and duration of drug infusion were evaluated.

Weaning of fentanyl and dexmedetomidine was done cautiously to prevent withdrawal. Fentanyl was weaned by 1 mcg/kg/day as tolerated. Weaning was to be halted if any infant displayed signs of withdrawal. Dexmedetomidine weaning was similar, except infusion rates were decreased by 0.1 mcg/kg every 12 to 24 hours as tolerated.

To assess drug toxicity, hemodynamic parameters (heart rate and systolic, diastolic, and mean arterial blood pressures) were recorded hourly for both groups. Dosage adjustments were to be held for any patient who showed >20% change in baseline heart rate or blood pressure or required a volume bolus to maintain blood pressure goals. Cranial ultrasound results (at 7-10 days and at 30 days) to evaluate IVH and periventricular leukomalacia (PVL) and rates of culture-positive sepsis were included as available. Data are presented as means $\pm$ standard deviations or percentages. Median data are presented in the instance of significantly skewed data. Student's *t*-test and chi-square test were used as appropriate for statistical analysis of selected demographic data and outcomes. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 48 patients were included in the analysis. The baseline demographics of each group are described in Table 1. None of the demographic data represented statistically significant differences, although the difference in mean birth weight was 157 grams. The mean gestational age was 25 weeks, the mean age at study entry was 27 hours, and the severity of illness in fentanyl and dexmedetomidine groups, as measured by CRIB-II scores, was similar. The primary underlying diagnoses at study entry were respiratory distress syndrome, respiratory failure secondary to prematurity (all patients were intubated immediately following delivery), sepsis, and

Table 2. Sedation requirements

Treatment Group	Adjunctive Fentanyl (Mean No. Doses/Day)*		Adjunctive Lorazepam (Mean No. Doses/Day)*		% of Treatment Days Requiring No Adjunctive Sedation
	Prior to Study Entry	During Study Period	Prior to Study Entry	During Study Period	
Fentanyl	4.8 ± 1.6	1.4 ± 0.68	3.5 ± 1.6	1.6 ± 0.69	16.5†
Dexmedetomidine	3.5 ± 2.8	1 ± 0.91	3.0 ± 3	0.73 ± 0.62	54.1

* mean ± standard deviation

† $p < 0.05$

hypotension. Echocardiogram-confirmed patent ductus arteriosus was present in approximately 80% of the patients in each group. All patients who had a patent ductus arteriosus were treated with indomethacin. The primary indication for the use of fentanyl or dexmedetomidine was as part of a sedation treatment regimen for mechanical ventilation.

Dexmedetomidine Dosing

Nearly half of the dexmedetomidine patients received a 0.5-mcg/kg bolus at the start of therapy. Every patient was started at a maintenance infusion rate of 0.3 mcg/kg/hr. Increases in infusion rate by 0.1 mcg/kg/hr were made up to twice daily based on patient response (i.e., elevated sedation scores with a need for >3 doses of adjunctive sedation during a 12-hour nursing shift). Hemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate) were monitored hourly to assess toxicity.

Dexmedetomidine was infused via peripheral or central venous access on a syringe pump to allow for the smaller infusion rates required in the extremely low birth weight population. The standard manufacturer-recommended 4-mcg/mL dilution was used (reconstituted in normal saline). For infants whose calculated initial bolus was less than 0.1 mL (the smallest allowable bolus volume to be infused on the syringe pump), 0.1 mL was given over an extended infusion period to prevent hypotension or fluctuations in blood pressure. A visual compatibility test was done to assess the compatibility of dexmedetomidine with total parenteral nutrition. We found it to display no visible particles, so dexmedetomidine was infused with total parenteral nutrition when intravenous access was limited.

The mean dexmedetomidine infusion rate was 0.6 mcg/kg/hr (range, 0.3-1.2 mcg/kg/hr) and the mean duration was 12 days. Dexmedetomi-

dine was weaned by decreasing the infusion by 0.1 mcg/kg/hr every 12 to 24 hours, as tolerated. No patients displayed signs of withdrawal (hypertension, tachycardia, increased agitation) during dexmedetomidine weaning. It was not felt that any patient developed tolerance over the course of therapy, since the highest effective dose was maintained for several days without need for up-titration secondary to decreased response. If an infant was on extended infusions, the drip was weight-adjusted as appropriate.

Sedation/Efficacy Outcomes

Sedation use in each group is summarized in Table 2. The mean treatment durations for fentanyl and dexmedetomidine were 20 and 12.4 days, respectively. Dexmedetomidine patients had similar requirements to fentanyl patients prior to the start of dexmedetomidine infusion. Mean number of sedative boluses per day during the treatment period was similar as well (combined fentanyl + lorazepam boluses in fentanyl group = 3.0, vs. 1.73 in dexmedetomidine group). However, dexmedetomidine patients had a greater percentage of treatment days requiring no additional sedation compared to fentanyl patients (54.1% and 16.5%, respectively). The mean total fentanyl and lorazepam exposures in the dexmedetomidine group were 20.6 mcg/kg and 2.7 mg/kg, respectively. Fentanyl patients received 398 mcg/kg of fentanyl and 6.8 mg/kg of lorazepam.

Hemodynamic Outcomes

In the fentanyl group, there were no significant changes from baseline hemodynamic parameters (Table 3). No patients required intervention for hypotension as defined earlier. A primary short-term safety concern with dexmedetomidine use is its effect on hemodynamic parameters such as blood pressure and heart rate. While hypertension, hypotension, and bradycardia are

Table 3. Hemodynamic profile associated with fentanyl

Parameter	Baseline	Treatment	Post-treatment
SBP (mmHg)*	51 ± 8	44 ± 8	57 ± 11
DBP (mmHg)*	30 ± 6	26 ± 7	34 ± 11
MAP (mmHg)*	38 ± 6	32 ± 6	42 ± 11
HR (bpm)*	149 ± 15	153 ± 11	158 ± 13

BPM, beats per minute; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial blood pressure; SBP systolic blood pressure

* mean ± standard deviation

potential adverse effects associated with dexmedetomidine, no patient in the dexmedetomidine group experienced any appreciable effect on either blood pressure or heart rate per the hourly measurements obtained (Table 4). Dexmedetomidine titration was done slowly and in small increments to minimize potential fluctuations in hemodynamic parameters. Likewise, weaning was completed slowly to allow the patients to acclimate before discontinuation of the drug.

Respiratory Outcomes

Patients in the dexmedetomidine group had a significantly shorter duration of mechanical ventilation (14.4 days) than patients in the fentanyl group (28.4 days; Table 5). Since dexmedetomidine has minimal appreciable effect on respiratory drive, extubation while receiving the drug, regardless of the infusion rate, is permissible. Clinicians are often reluctant to extubate patients who are still receiving narcotic infusions. Eighty-three percent of the patients in the dexmedetomidine group were receiving dexmedetomidine when they were extubated, most at rates above 0.3 mcg/kg/hr (Figure). This allowed the provider to extubate the patient when appropriate from a respiratory standpoint, rather than waiting until the sedation was light enough to prevent respiratory compromise. None of the patients in the fentanyl group were receiving continuous infusion of fentanyl at the time of extubation. Significantly fewer dexmedetomidine patients required dexamethasone for facilitation of extu-

bation compared to fentanyl patients (18.2% vs. 45.8%, respectively; Table 5). At our institution, eligibility for dexamethasone use is limited to infants requiring mechanical ventilation for >3 weeks, who are unable to tolerate ventilator weaning to settings compatible with extubation, and who exhibit radiographic changes consistent with severe lung disease. Since the mean age at the time of extubation in the dexmedetomidine group was 14 days, few of these patients required dexamethasone to facilitate extubation. Dexmedetomidine patients underwent an average of 28 chest x-rays during their hospital stay versus 49 chest x-rays in the fentanyl population (Table 5). This allows for less radiation exposure to the infant, as well as cost containment, and is most likely a result of fewer ventilator days and fewer sepsis evaluations.

Gastrointestinal Outcomes

Since dexmedetomidine does not impact gastrointestinal motility as strongly as opioids, we examined possible clinical benefits to this pharmacologic difference. There were statistically significant differences favoring dexmedetomidine in outcomes reflecting gastrointestinal function. This includes considerable differences in stooling and feeding. The main outcomes describing gastrointestinal function are outlined in Table 6 and show numerous statistically significant benefits to dexmedetomidine. Time to first meconium stool was shorter in dexmedetomidine patients than in fentanyl patients (7.6 vs. 12.4

Table 4. Hemodynamic profile associated with Dexmedetomidine

Parameter	Baseline	Start of Infusion	Highest Infusion Rate	Post-infusion
SBP (mmHg)*	46 ± 11	47 ± 8	60 ± 10	62 ± 9
DBP (mmHg)*	26 ± 8	24 ± 4	36 ± 9	36 ± 8
MAP (mmHg)*	33 ± 9	32 ± 5	44 ± 9	45 ± 7
HR (bpm)*	152 ± 14	147 ± 15	152 ± 12	162 ± 13

BPM, beats per minute; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial blood pressure; SBP systolic blood pressure

* mean ± standard deviation

Table 5. Respiratory outcomes

Outcome	FENT (n=24)	DMDT (n=24)	p Value
Days on mechanical ventilation*	28.4 ± 9.9	14.4 ± 7.3	<0.0001
% of patients requiring dexamethasone for ventilator weaning	45.8	18.2	<0.02
Number of chest x-rays during hospitalization*	49 ± 13.8	28 ± 8.8	<0.0001

DMDT, dexmedetomidine; FENT, fentanyl

*mean ± standard deviation

days, respectively). The duration of meconium passage was also reduced in the dexmedetomidine group compared to the fentanyl group (7.5 vs. 22.4 days, respectively). The dexmedetomidine patients started to have transitional stools around day 15 of life, compared to day 33 of life in the fentanyl patients. There was not a statistically significant difference in the incidence of meconium plug syndrome between dexmedetomidine and fentanyl patients (4% vs. 21%, respectively), although the only patient in the dexmedetomidine group who experienced a meconium plug had received a large quantity of narcotic boluses in the days preceding the initiation of dexmedetomidine. In conjunction with delayed stooling, fentanyl patients took longer to initiate and achieve full enteral feeds compared to dexmedetomidine patients. Dexmedetomidine patients were started on trophic enteral feeds approximately 2 days earlier than fentanyl patients. Feeding tolerance was improved in dexmedetomidine patients, who, on average, were maintained on full enteral feeds 24 days earlier than the fentanyl patients. No patient in the dexmedetomidine group was diagnosed with confirmed necrotizing enterocolitis (NEC) during the study period, compared to 9% of patients in the fentanyl group.

Other Outcomes

No patient in the dexmedetomidine group showed signs of withdrawal during the weaning period. Approximately half the patients in the fentanyl group required slower weaning of the fentanyl drip because of signs of withdrawal. No adjunctive medications were started to treat withdrawal in the fentanyl group; instead, the frequency of weaning was decreased to every 48 hours. Patients in the dexmedetomidine group experienced an insignificant decrease in the combined outcomes of severe IVH (grades III-IV) and PVL compared to the fentanyl patients (2% vs. 7%, respectively). There was a lower incidence of culture-positive sepsis in the dexmedetomidine group (combined blood, sputum, and urine), as

well as sepsis and NEC workups, during their hospital stay. There was no difference between the 2 groups in the incidence of catheter-associated bloodstream infections. These results are summarized in Table 7.

DISCUSSION

Meta-analyses of narcotic and benzodiazepine use in mechanically ventilated neonates show increased time to achieve full enteral feeds, prolonged duration of mechanical ventilation, higher incidence of adverse neurologic events (death, severe IVH, PVL), and increased length of hospitalization.¹⁻³ Failure to provide sedation in premature neonates has negative consequences as well, including acute physiologic and behavioral responses to painful stimuli that create a catabolic state, which can also lead to increased risk of IVH and PVL.²³ Additional consequences related to untreated pain in the neonate include ventilator dyssynchrony leading to periods of hypoxemia, blood pressure fluctuations, and hyperalgesia. The neonatal provider is thus forced to choose between the negative impacts of unaddressed pain/agitation in the neonate and

Figure. Dexmedetomidine infusion rates upon patient extubation.

Table 6. Gastrointestinal and Infection outcomes

Outcome	FENT (n=24)	DMDT (n=24)	p Value
Meconium stool (day of life)*	12.4 ± 7.7	7.6 ± 6.4	<0.03
Time from meconium to transitional stool (days)*	22.4 ± 13.2	7.5 ± 5.2	<0.0002
Transitional stool (day of life)*	33.6 ± 13.8	15.2 ± 8.8	<0.0001
Start of enteral feeds (day of life)*	11.3 ± 5.5	8.5 ± 3.4	0.0574
Time from start of feeds to full feeds (days)*	50.8 ± 18.1	26.8 ± 10.8	<0.0001
Meconium plug syndrome (%)*	5 ± 21	1 ± 4	0.08
Percent of patients with NEC workups*	15 ± 63	4 ± 17	<0.001
Incidence of NEC (%)*	9 ± 37.5	0	<0.001
Mean number of septic workups per patient	5	2.9	<0.01
Culture-positive sepsis (%)*	22 ± 88	11 ± 48	<0.0006
Catheter-associated bloodstream infection (%)*	6 ± 24	6 ± 26	1

DMDT, dexmedetomidine; FENT, fentanyl

*mean ± standard deviation

the negative adverse effects of the drugs currently used to treat it.

Dexmedetomidine presents a novel option for the management of pain and sedation in premature neonates. This study demonstrated the achievement of adequate sedation without the development of hemodynamic instability when neonates were given a continuous infusion of dexmedetomidine. Patients in the dexmedetomidine group required less adjunctive analgesic and sedation medications, suggesting that dexmedetomidine effectively provides both antinociception and hypnosis in premature infants. Animal models suggest that the hypnotic effect of dexmedetomidine may actually be stronger in the premature patient, while its analgesic effect is consistent across developmental ages.²⁴

An absence of appreciable respiratory suppression with dexmedetomidine was demonstrated in the premature neonate population in this study. Despite having similar baseline respiratory disease, as evidenced by the number of surfactant doses and CRIB-II scores, patients in the dexmedetomidine group were extubated approximately 2 weeks earlier than patients in the fentanyl group. This outcome is most likely not entirely the result of decreased respiratory drive suppression with dexmedetomidine. Interleukin (IL)-1 β and cyclooxygenase-2/prostaglandin E2 released in response to pulmonary inflammation are important mediators of ventilator-induced lung injury.¹¹ Dexmedetomidine-induced reductions in IL-1 β and cyclooxygenase-2 in rat models of ventilator-induced lung injury have mitigated pulmonary inflammatory responses and led to reduction in lung tissue damage. The role of

inflammation in the development of neonatal chronic lung disease is not well understood, but mechanical ventilation-induced trauma to the premature lung is a known risk factor.²⁵ It is possible that reduced pulmonary inflammatory mediators in the dexmedetomidine group contributed to less severe lung disease, allowing for earlier extubation. Finally, the reluctance of neonatologists to extubate from higher fentanyl infusion rates may also prolong intubation time, thus worsening ventilator-induced lung damage. As can be seen in the Figure, dexmedetomidine infusion rates at extubation could be fairly high, and no such reluctance to extubate neonates while still on dexmedetomidine infusion is necessary. Further studies are needed to better characterize the effect of dexmedetomidine on the premature lung.

The lower incidence of culture-positive sepsis seen in this study is consistent with the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) trial, which also showed a 50% lower rate of sepsis in the dexmedetomidine group.¹³ The SEDCOM trial evaluated the use of dexmedetomidine versus midazolam for sedation of critically ill adult patients, focusing particularly on those with expected duration of mechanical ventilation >24 hours and incidence of delirium. A lower incidence of sepsis was an incidental finding in the study. Where benzodiazepines inhibit macrophage function, alpha agonists such as dexmedetomidine are thought to promote macrophage activity and exhibit some independent antimicrobial effects.²⁶ Several animal models suggest that dexmedetomidine has protective immunomodulation effects in the en-

Table 7. Other outcomes

Outcome	FENT (n=24)	DMDT (n=24)	p Value
Grade III-IV IVH (%)	7 ± 30	2 ± 9.1	0.06
PVL (%)	2 ± 8	0 ± 0	0.14

DMDT, dexmedetomidine; FENT, fentanyl; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia

* mean ± standard deviation

vironment of sepsis, particularly with reduction in inflammatory mediators such as tissue necrosis factor- α (TNF- α), IL-1 β , and interleukin-6.^{12,26} Animal models of endotoxemia demonstrate that dexmedetomidine-treated subjects have lower mortality rates, lower inflammatory markers, and better overall outcomes.^{12,27-29} The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study evaluated the effect of sepsis on patients randomized to dexmedetomidine or lorazepam as an a priori sub-analysis and found shorter duration of mechanical ventilation, more coma-/delirium-free days, and a 70% reduction in 28-day mortality for patients who received dexmedetomidine.³⁰ The dexmedetomidine group in our study may have had a reduced incidence of culture-positive sepsis for a variety of reasons independent of the immunomodulatory effects dexmedetomidine, including shorter duration of mechanical ventilation, earlier enteral feeding, and fewer days with central intravenous access.

In a study comparing dexmedetomidine to propofol in 40 adult ICU patients with severe sepsis, the dexmedetomidine patients showed significant reductions in TNF- α , IL-1, IL-6, and intra-abdominal pressure (IAP).³¹ Although information is scarce characterizing the influence of IAP in neonatal sepsis, elevated IAP in children and adults is associated with development of abdominal compartment syndrome, which carries a mortality rate of 50%-60%.³² Some data suggest that elevated IAP in the setting of neonatal NEC is a predictor of mortality.³³ Dexmedetomidine may play a beneficial role in this population. Since the pathophysiology of NEC remains unclear, the authors are unsure as to what part dexmedetomidine may have played in the decreased incidence of NEC in the dexmedetomidine group.

Narcotic-induced gastrointestinal dysfunction is an important source of morbidity in the neonatal patient. Narcotics have been shown to delay enteral feeds and meconium passage.^{2,34} Delayed enteral nutrition is associated with increased

risk of infection, delayed intestinal maturation, slower growth, cholestasis, and adverse neurologic outcomes.³⁵ Feeding tolerance may be impacted by meconium passage. Some studies have shown that infants with earlier evacuation of meconium achieve full feeds more rapidly.^{36,37} Opioid exposure in premature neonates represents a significant risk factor for the development of meconium plug syndrome, which can lead to intestinal perforation and a need for surgical intervention.³⁸ Per the hospital feeding protocol, once infants were deemed eligible for feeds (normotensive/no use of vasopressors, no indomethacin within 48 hours), trophic enteral feeds at 20 mL/kg/day were initiated for 5 days and advanced as tolerated up to 150 mL/kg/day. If patients were designated as unable to take anything orally, it was at the discretion of the provider to determine at what rate to resume feeds when appropriate. Since dexmedetomidine does not alter gastrointestinal function like fentanyl, patients in the dexmedetomidine group were expected to achieve enteral feeds and meconium passage more quickly compared to the fentanyl group, and this was indeed the case.

Patients in the dexmedetomidine group had an insignificantly lower incidence of severe IVH (grades III-IV) and PVL than the fentanyl group. Hypotension prior to starting narcotic infusion has been linked to development of severe IVH.²³ There was no statistically significant difference in baseline use of vasopressors for hypotension in the 2 groups. Other risk factors for IVH or PVL, such as antenatal corticosteroid use, early sepsis, maternal chorioamnionitis, and incidence of respiratory distress syndrome, were also not statistically significant.³⁹ Neonatal benzodiazepine use has been linked to increased mortality, severe IVH, and PVL.³ Overall benzodiazepine use was higher in the fentanyl group, but it is not known whether this played an important role in the neurologic outcomes in the study.

Animal neonatal models with dexmedetomidine have demonstrated significant neuropro-

tective effects with its use, particularly in the hypoxic-ischemic neonatal brain.⁴⁰⁻⁴² Several theories regarding alpha agonist-mediated neuroprotection abound, including anti-apoptosis in perinatal excitotoxic brain injury and reduced ischemic volume in cerebral ischemia. Neonatal rats exposed to dexmedetomidine prior to asphyxia demonstrated improved neurologic functional deficit and dose-dependent reduction of white matter loss compared to placebo. It is not known at this time what the long-term neurologic implications for premature neonates will be following dexmedetomidine infusion.

One of the primary limitations of this study is its retrospective case-control design. Although historical controls were used for the fentanyl patients, there was overlap in the dates of included patients with the dexmedetomidine group. Patients born before 2005 were not included in the study in an effort to ensure that there were no major changes in standards of care in the unit that would significantly impact outcomes in either group. Another weakness of the study is the small sample size. Larger numbers of patients will be needed to determine whether the findings in this study are consistent when evaluated prospectively with a greater number of participants. Also, the differences in birth weight cannot be ignored entirely. Although gestational ages were similar, the Ballard score used to estimate gestation is accurate to within 2 weeks, and it is possible that differences in maturity explain important parts of our results. However, we do not feel this is the case, given the similarities in severity of other diseases.

Another study weakness is that long-term neurologic outcomes in the patient groups are not available at this time. While the short-term safety of dexmedetomidine in premature neonates seems to be favorable based on our findings, long-term follow-up is warranted and needed before widespread use of dexmedetomidine can be supported.

Our impetus for changing to dexmedetomidine from routine narcotic infusions was a combination of negative outcomes routinely reported with the standard sedative approach of narcotics and benzodiazepines. It seemed unwise to continue to practice in such a knowingly harmful manner. Alternatively, the human and animal studies with dexmedetomidine seemed to point

to this agent as effective, relatively safe, and possibly neuroprotective. This study seems to support our approach in our institution. We now have a large population that we have treated with dexmedetomidine as our primary agent and we continue to have impressive results.

CONCLUSIONS

Dexmedetomidine demonstrated efficacy and short-term safety when used for sedation in the premature neonates included in this study. Potential benefits for dexmedetomidine use over fentanyl include shorter duration of mechanical ventilation, fewer days to achieve full enteral feeds, more rapid passage of meconium, and lower infection rates. While many of the outcomes were positive in this retrospective case-control study, it is reasonable for clinicians to await prospective randomized controlled trials before dexmedetomidine is used routinely in premature neonates.

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ABBREVIATIONS IAP, intra-abdominal pressure; ICU, intensive care unit; IL, interleukin; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia; TNF, tissue necrosis factor.

CORRESPONDENCE Keliana O'Mara, PharmD, BCPS, Duke University Medical Center, 2100 Erwin Rd., Durham, NC 27710, email: Keliana.omara@gmail.com

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