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REVIEW ARTICLE

The Use of Dexmedetomidine to Provide Sedation and Analgesia in Newborns with Hypoxia-Ischemia Encephalopathy Undergoing Therapeutic Hypothermia: Developement of a Protocol

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Hypothermia, induced, Dexmedetomidine, Infant, newborn, Diseases, Hypoxia-ischemia, Brain.

Abstract

The aim of this study was reporting the use of dexmedetomidine to provide sedation and analgesia in newborns with hypoxia-ischemia encephalopathy undergoing therapeutic hypothermia. This is a narrative review of literature obtained from PubMed/MEDLINE database, covering articles between 2001 and 2024. The use of dexmedetomidine was highlighted in the evaluated articles, especially when compared with opioids, due to its safety profile, ability to promote adequate sedation at low doses, minimal respiratory and gastrointestinal impact, as well as the possibility of neuroprotection. Based on the aspects described in this review, a protocol was developed to be implemented in our service for the use of dexmedetomidine as a first-line medication for newborns with hypoxia-ischemia encephalopathy undergoing therapeutic hypothermia.

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INTRODUCTION

Therapeutic hypothermia is the treatment of choice for term or near-term newborns with moderate or severe hypoxic–ischemic encephalopathy (HIE)[1]. Randomized controlled trials have shown that this therapy significantly reduces mortality and disability and improves neurological development in these patients[1–5].

It is recommended that neonates undergoing therapeutic hypothermia receive adequate sedation and analgesia to optimize comfort and reduce stress during the procedure[6–8]. Studies in animal models suggest that the use of sedation may potentiate the effects of therapeutic hypothermia[9].

Opioids are the most commonly used and studied agents for sedation and analgesia in this context[10–13]. However, they are associated with potential adverse effects such as respiratory depression, hypotension, and reduced gastrointestinal motility[6,11,14–18].

A study conducted between 2008 and 2015 evaluated 2,425 neonates with HIE undergoing therapeutic hypothermia and concluded that newborns who received opioids were more likely to require ventilatory support, nitric oxide use, and inotropic support when compared with unexposed neonates[12].

Given the adverse effects associated with opioids, dexmedetomidine hydrochloride may represent an alternative for sedation and analgesia in this group of patients, as described in studies reporting its use with efficacy[6,14–16,18–20].

Dexmedetomidine hydrochloride is an alpha-2 adrenergic agonist with sedative, anxiolytic, and analgesic effects, with minimal impact on respiratory function and gastrointestinal motility. It may also play a role in preventing shivering[6,16]. In addition, preclinical studies have demonstrated a possible neuroprotective effect, and it may represent an option in patients with neurological injury[21–24].

The aim of this study is to describe the use of dexmedetomidine hydrochloride in newborns with HIE undergoing therapeutic hypothermia and their outcomes, through a review of the available evidence. Based on this analysis, the intention is to develop a protocol to be implemented in our service for the use of this medication in this group of patients.

CASE REPORT

This is a narrative literature review conducted in the PubMed/MEDLINE database, with the aim of identifying articles related to the use of dexmedetomidine hydrochloride for sedation and analgesia in newborns with HIE undergoing therapeutic hypothermia, published in English or Portuguese between 2001 and 2024. The following descriptors were used in the search: “dexmedetomidine”, “therapeutic hypothermia” or “induced hypothermia”, and “newborns”. The references of the selected articles were reviewed to identify additional studies not retrieved in the initial search.

Articles addressing sedation and analgesia in neonates, with an emphasis on the use of dexmedetomidine in the context of therapeutic hypothermia, and containing at least one of the descriptors used, were included. Studies were excluded if the population included patients older than one month, preterm infants with gestational age <35 weeks, as well as those that did not describe the use of sedation and analgesia during therapeutic hypothermia; articles published before 2001 or written in languages other than English or Portuguese; and studies that did not include at least one of the defined descriptors.

Based on the analysis of the selected articles, an algorithm was developed to be implemented in our service for the use of dexmedetomidine hydrochloride as a first-line agent for sedation and analgesia in patients with HIE undergoing therapeutic hypothermia.

DISCUSSION

Importance of sedation and analgesia during therapeutic hypothermia and the use of dexmedetomidine

Newborns with HIE undergoing therapeutic hypothermia require intensive care, including procedures such as blood sampling, venipuncture, and mechanical ventilation, which can cause pain and stress, potentially exacerbated by hypothermia itself[7,13]. In addition, studies in animal models suggest that the benefits of therapeutic hypothermia may be reduced if patients do not receive adequate sedation and analgesia[9]. For this reason, it is essential to ensure effective control of pain and stress in this group of patients[7,13,16,25].

There is no established standardized practice regarding the management of pain and stress in neonates with hypoxic–ischemic encephalopathy undergoing therapeutic hypothermia[7,8,10,25]. The available studies are heterogeneous, with different settings, comparators, and outcomes assessed[8,10,25]. A systematic review did not identify randomized controlled trials on the topic[7]. There is only one ongoing randomized safety trial comparing dexmedetomidine with morphine during therapeutic hypothermia[11].

Among the studies analyzed, the use of dexmedetomidine stands out due to its safety profile, lower respiratory depression, opioid-sparing effect, greater thermal stability, shivering control, and possible neuroprotective effect[6,8,10,11,16,17]. In the studies assessed, dexmedetomidine was considered safe, well tolerated, and able to provide adequate sedation at low doses[6,14–16,18–20]. In general, the initial dose used was 0.2–0.3 mcg/kg/h, with titration up to a maximum dose of 1–2 mcg/kg/h, as shown in Table 1.

Opioid-sparing effect of dexmedetomidine

Because of adverse effects commonly associated with opioid use, such as respiratory depression, hypotension, and reduced gastrointestinal motility, some studies have been

Table 1. Doses of dexmedetomidine used for sedation in neonates with hypoxic–ischemic encephalopathy during therapeutic hypothermia in the studies assessed.

Study	Dexmedetomidine dose
Elliot *et al*[6]	Starting dose 0.3 mcg/kg/h with titration of 0.1 mcg/kg/h up to a maximum dose of 1 mcg/kg/h.
Elliot *et al*[15]	Starting dose 0.2 mcg/kg/h with titration of 0.1 mcg/kg/h up to a maximum dose of 1 mcg/kg/h.
Naveed *et al*[14]	Starting dose 0.16 ± 0.06 mcg/kg/h, with a maximum of 0.27 ± 0.12 mcg/kg/h.
Cosnahan *et al*[16]	Starting dose 0.3 mcg/kg/h with titration of 0.1 mcg/kg/h up to a maximum dose of 2 mcg/kg/h.
McAdams *et al*[19]	Starting dose 0.2 mcg/kg/h with titration up to 0.4 mcg/kg/h.
Surkov *et al*[20]	Starting and maximum dose of 0.5 mcg/kg/h.
O'Mara *et al*[18]	Starting dose 0.3 mcg/kg/h with titration of 0.1–0.2 mcg/kg/h as needed.
Baserga *et al*[11]	Loading dose of 1 mcg/kg followed by doses ranging from 0.1 to 0.5 mcg/kg/h.

conducted to minimize the use of these medications by introducing dexmedetomidine as an alternative for sedation and analgesia in patients with HIE undergoing therapeutic hypothermia[6,14–16,18].

One of these studies, conducted at two centers, aimed to reduce cumulative opioid exposure in these patients through the implementation of a protocol that established dexmedetomidine as the first-line agent for sedation and analgesia, compared with fentanyl or morphine[6]. After a two-year observation period, cumulative fentanyl exposure decreased from 30 mcg/kg to 1.7 mcg/kg, and morphine exposure decreased from 648 mcg/kg to 85 mcg/kg, corresponding to reductions of 94% and 87%, respectively. In addition, no patient required continuous infusion of another sedative in association with dexmedetomidine[6]. A reduction in length of stay was also observed, from 18 to 14 days, when comparing the groups that received fentanyl or morphine with the group that received dexmedetomidine, respectively[6].

Another study assessed the efficacy and safety of modifying the sedation protocol by replacing intermittent morphine with dexmedetomidine[16]. Patients who received dexmedetomidine required higher amounts of rescue morphine (0.13 mg/kg versus 0.04 mg/kg; p = 0.001), but had lower cumulative opioid exposure (0.13 mg/kg versus 1.79 mg/kg; p < 0.0001)[16].

The study by Naveed et al. compared dexmedetomidine and fentanyl, demonstrating similar control of pain and agitation during therapeutic hypothermia. The dexmedetomidine group required fewer rescue sedation doses and had a shorter time to discontinuation of sedation after rewarming (1 versus 5 days; p = 0.001)[14]. Another study, which evaluated neonates undergoing therapeutic hypothermia receiving dexmedetomidine—most often in combination with fentanyl—showed a reduction in the need for fentanyl in 76% of patients who received both medications, allowing fentanyl discontinuation in most cases[18]. In addition, no patient required additional sedation doses after initiation of dexmedetomidine[18].

Pharmacokinetics of dexmedetomidine

The pharmacokinetics of dexmedetomidine hydrochloride in newborns with HIE undergoing therapeutic hypothermia were evaluated in the study by McAdams et al.[19]. Based on the analysis of 94 blood samples, a gradual increase in plasma concentrations was observed, reaching near-plateau levels (300 to 900 pg/mL) between 12 and 24 hours after initiation of the infusion, that is, more than 10 hours after the infusion rate reached 0.4 mcg/kg/h. After discontinuation of the medication, performed 6 hours after rewarming, plasma concentrations decreased exponentially and remained detectable for up to 43 hours[19].

Although the difference was not statistically significant, clearance in normothermic neonates without HIE (0.91 ± 0.5 L/h/kg) was faster than in neonates undergoing hypothermia (0.761 ± 0.155 L/h/kg) of similar gestational ages[19]. During hypothermia, the elimination half-life was longer (7 hours in patients with HIE and 3 hours in normothermic patients without encephalopathy)[19]. Thus, steady state is not achieved before approximately 28 hours (four half-lives) after initiation or an increase in the infusion rate in neonates undergoing therapeutic hypothermia, compared with about 13 hours in normothermic neonates.

In addition, medication loss due to adsorption to the infusion tubing may further delay achievement of steady state, resulting in an effective infusion rate up to 30% lower than the programmed rate during the first 6 hours of infusion, with a mean cumulative loss of 5% of the administered dose over 55 to 75 hours of infusion[19].

These pharmacokinetic findings are consistent with the studies by Elliot et al. and Cosnahan et al., in which sedation requirements and opioid rescue doses were higher in the early phase of hypothermia and during the dexmedetomidine titration period, with the possibility of gradual dose reduction and reduction in rescue medications over the course of treatment until completion of therapeutic hypothermia[6,16].

Based on these results, administration of a loading dose or faster initial titration of dexmedetomidine may be considered in cases in which sedation or shivering prevention is insufficient due to the delay in achieving adequate serum concentrations. However, this strategy may be associated with a higher risk of adverse effects[10,19].

Hemodynamic characteristics

Studies reinforce the safety of dexmedetomidine during therapeutic hypothermia, with bradycardia being the most frequently reported adverse effect[6,15,16,18].

A single-center retrospective study compared heart rate in neonates undergoing therapeutic hypothermia who received dexmedetomidine, fentanyl, or a combination of both[15]. Although it was not associated with significant hemodynamic instability, dexmedetomidine was related to a reduction in heart rate, with a nadir between 12 and 36 hours of life, when compared with fentanyl monotherapy (91 ± 9 bpm versus 103 ± 11 bpm; $p < 0.002$)[15]. A multicenter study evaluating the use of dexmedetomidine in neonates demonstrated a similar impact on heart rate, with bradycardia occurring in up to 12% of patients, without hemodynamic repercussions and without the need to discontinue the medication[26].

In the study by Elliot et al., 9.6% of patients had the medication discontinued due to sustained bradycardia, despite dose adjustments according to the algorithm implemented in the protocol[6]. None of these patients showed worsening perfusion or other adverse effects associated with bradycardia, which resolved after discontinuation of dexmedetomidine. In some cases, the medication was restarted without recurrence of the event. In that study, a heart rate of 70 bpm or higher was considered acceptable, provided there was hemodynamic stability[6]. The dexmedetomidine group had the lowest heart rate nadir (93 bpm), compared with newborns who received morphine (100 bpm) and fentanyl (97 bpm)[6].

In other studies, no significant differences in heart rate over follow-up were observed between groups that received dexmedetomidine or opioids. In addition, no patient developed bradycardia requiring discontinuation of dexmedetomidine[16,18].

Studies also showed no significant differences in mean arterial pressure, peripheral oxygen saturation, the occurrence of apnea episodes, the need for vasoactive drugs or hydrocortisone, or the need for intravenous volume replacement when comparing dexmedetomidine and opioids[6,14,16,18]. In the study by Surkov et al., dexmedetomidine was not associated with bradycardia, and the group that received this medication had a lower incidence of hypotension and a lower need for inotropes compared with other sedatives[20].

Respiratory characteristics

The study by Cosnahan et al. demonstrated an association between dexmedetomidine use and a shorter duration of mechanical ventilation[16]. All patients who received dexmedetomidine had reductions in ventilatory parameters during therapeutic hypothermia, whereas 31.58% of patients in the intermittent morphine group required increased respiratory support[16].

Another study reported a shorter time to orotracheal extubation (3 versus 11 days; $p = 0.004$) when comparing dexmedetomidine and fentanyl, respectively[14]. In the study by Surkov et al., dexmedetomidine use was associated with higher extubation rates around the seventh day of life compared with the control group (68% versus 33%; $p = 0.018$)[20].

In the study by O'Mara et al., patients on mechanical ventilation were extubated while receiving dexmedetomidine, with no recorded extubation failure. In addition, none of the patients who were not intubated required invasive mechanical ventilation while receiving the medication[18]. These findings suggest that dexmedetomidine does not compromise respiratory drive when compared with opioids and may be used in patients undergoing therapeutic hypothermia who do not require invasive mechanical ventilation[16,18,20].

Nutritional characteristics

A study comparing dexmedetomidine and fentanyl reported a shorter time to achieve full enteral feeding, defined as at least 120 mL/kg/day (9 versus 13 days; $p = 0.03$), in the dexmedetomidine group[14]. A similar result was observed in another study, in which full enteral feeding was achieved in a shorter time when compared with the period before the introduction of dexmedetomidine, during which opioids were used[18].

Other studies found no differences between opioid and dexmedetomidine use regarding the timing of feeding initiation or the time to achieve full enteral feeding[6,16].

Opioids may affect gastrointestinal motility[16]. In most of the studies evaluated, newborns did not receive feeding during therapeutic hypothermia, which limits the assessment of the impact of sedative medications on nutritional outcomes[14,16].

Neurological characteristics

Preclinical studies have reported a neuroprotective effect of dexmedetomidine through reduction of neuronal injury and improvement of functional outcomes across multiple experimental models, including hypoxia-induced injury, ischemia–reperfusion, traumatic brain injury,

intracerebral hemorrhage, epilepsy, neurodegeneration, and neuroinflammation[21–24]. The neuroprotective effect involves reductions in inflammation, cellular apoptosis, and autophagy; preservation of the blood–brain barrier; reduction of cerebral edema; and protection of cellular integrity[21,25].

In one study, neuronal injury was induced by oxygen and glucose deprivation in cultures of neurons and glial cells from the cortex of newborn mice[23]. Dexmedetomidine, administered at the onset of the induced injury, attenuated neuronal damage in a concentration-dependent manner. At the maximum dose, 80% neuronal protection was observed. In addition, the medication protected neurons exposed to pathological levels of glutamate, reducing cell death by apoptosis and necrosis. In the same study, mice treated with dexmedetomidine showed a significant improvement in functional performance when reassessed 30 and 40 days after the injury[23]. These findings are consistent with an earlier study demonstrating a dose-dependent reduction in neuronal death induced by exogenous N-methyl-D-aspartate in an in vitro model of perinatal neuronal injury[24].

The neuroprotective effects of dexmedetomidine have also been investigated in clinical studies. In the study by Cosnahan et al., which compared dexmedetomidine with intermittent morphine, no differences were observed in video-electroencephalogram patterns or in magnetic resonance imaging findings after therapeutic hypothermia[16]. Another study identified a reduction in the occurrence of new seizures, with an incidence of 41.2% in the fentanyl group and 13.6% in the dexmedetomidine group, without statistical significance[14].

In the study by Surkov et al., a lower incidence of seizures on the first day of follow-up was observed in the dexmedetomidine group compared with the control group (4.3% versus 48.3%; $p < 0.001$)[20]. The incidence of leukomalacia was also lower in the dexmedetomidine-treated group (2.2% versus 15.1%; $p = 0.018$)[20].

None of the selected studies evaluated long-term neurological outcomes related to dexmedetomidine exposure[10].

Nonpharmacological methods for pain control

Nonpharmacological methods can serve as adjuncts to analgesics and sedatives in the management of mild pain in newborns undergoing therapeutic hypothermia[6,10,11]. Some strategies can be used during potentially painful procedures, such as non-nutritive sucking and facilitated tucking, a technique in which the caregiver positions their hands at the newborn's head and lower limbs[8,10].

In clinically stable patients, parents may hold the newborn in their arms, even while using the cooling mattress during therapeutic hypothermia[6,8]. Other nonpharmacological measures include colostrum therapy or the provision of minimal enteral feeding, preferably with breast milk. In addition to promoting newborn comfort, these interventions are associated with improved structural and functional intestinal integrity, increased diversity of the gut microbiota, reduced systemic inflammation, and earlier achievement of full enteral feeding. They also promote greater maternal involvement in neonatal care[8].

Protocol for the use of dexmedetomidine during therapeutic hypothermia

Based on the analysis of the studies included in this review, a protocol is proposed for the use of dexmedetomidine as a first-line agent for sedation in neonates with hypoxic–ischemic encephalopathy undergoing therapeutic hypothermia, as shown in Figure 1. Guidance for dose titration and tapering was based on the Neonatal Pain, Agitation and Sedation Scale (N-PASS)[27,28].

The recommended initial dose of dexmedetomidine is 0.3 mcg/kg/h. In the presence of agitation and/or pain (N-PASS > +3), increasing the dose by 0.1 mcg/kg/h up to a maximum dose of 1 mcg/kg/h is recommended. Nonpharmacological measures should always be used in conjunction with pain control. In cases of deep sedation (N-PASS < −5), a dose reduction of 0.1 mcg/kg/h is indicated.

Criteria for discontinuation of the medication include a heart rate below 70 beats per minute sustained for 30 minutes or more, as well as hypotension or hypertension requiring therapeutic intervention. After discontinuation due to bradycardia, dexmedetomidine may be restarted if the heart rate stabilizes above 70 beats per minute and the neonate has blood pressure appropriate for gestational age.

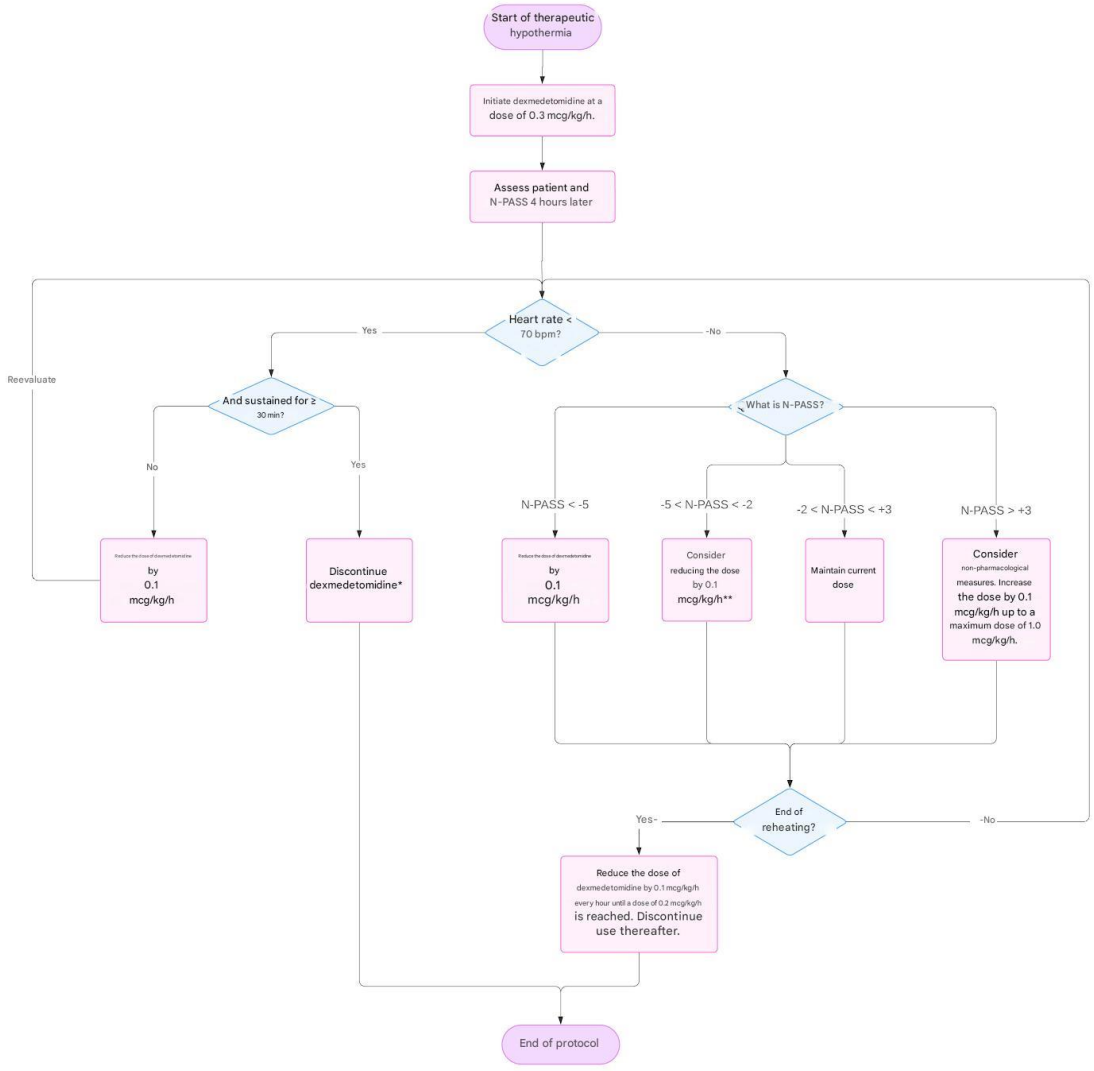
After completion of rewarming, a gradual reduction of dexmedetomidine by 0.1 mcg/kg/h every 1 hour is recommended until reaching a dose of 0.2 mcg/kg/h, at which point the medication may be discontinued.

CONCLUSION

Adequate sedation and analgesia during therapeutic hypothermia are fundamental components of the care of newborns with hypoxic–ischemic encephalopathy. Dexmedetomidine has stood out in this context as a safe alternative, with a potential neuroprotective effect and minimal respiratory and gastrointestinal impact when compared with opioids.

Based on the evidence analyzed, an institutional protocol was developed recommending its use as a first-line sedative for this group of patients.

Figure 1. Flowchart for the use of dexmedetomidine during therapeutic hypothermia.



Legend: **Discontinue dexmedetomidine also in cases of hypotension or hypertension requiring treatment. Consider restarting the medication later if the heart rate stabilizes above 70 beats per minute, with blood pressure appropriate for gestational age. ***Consider dose reduction if this is the goal, for example, during the rewarming period, ventilatory weaning, or extubation.*

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