BMJ Paediatrics Open

Sedation and analgesia from prolonged pain and stress during mechanical ventilation in preterm infants: is dexmedetomidine an alternative to current practice?

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To cite: Ojha S, Abramson J, Dorling J. Sedation and analgesia from prolonged pain and stress during mechanical ventilation in preterm infants: is dexmedetomidine an alternative to current practice? *BMJ Paediatrics Open* 2022;**6**:e001460. doi:10.1136/bmjpo-2022-001460

Received 25 March 2022
Accepted 22 April 2022

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ABSTRACT

Mechanical ventilation is an uncomfortable and potentially painful intervention. Opioids, such as morphine and fentanyl, are used for analgesia and sedation but there is uncertainty whether they reduce pain in mechanically ventilated infants. Moreover, there may be short-term and long-term adverse consequences such as respiratory depression leading to prolonged mechanical ventilation and detrimental long-term neurodevelopmental effects. Despite this, opioids are widely used, possibly due to a lack of alternatives.

Dexmedetomidine, a highly selective alpha-2-adrenergic agonist with analgesic and sedative effects, currently approved for adults, has come into use in newborn infants. It provides analgesia and simulates natural sleep with maintenance of spontaneous breathing and upper airway tone. Although data on pharmacokinetics–pharmacodynamics in preterm infants are scant, observational studies report that using dexmedetomidine in conjunction with opioids/benzodiazepines or on its own can reduce the cumulative exposure to opioids/benzodiazepines. As it does not cause respiratory depression, dexmedetomidine could enable quicker weaning and extubation. Dexmedetomidine has also been suggested as an adjunct to therapeutic hypothermia in hypoxic ischaemic encephalopathy and others have used it during painful procedures and surgery. Dexmedetomidine infusion can cause bradycardia and hypotension although most report clinically insignificant effects.

The increasing number of publications of observational studies and clinical use demonstrates that dexmedetomidine is being used in newborn infants but data on safety and efficacy are scant and not of high quality. Importantly, there are no data on long-term neurodevelopmental impact on preterm or term-born infants. The acceptance of dexmedetomidine in routine clinical practice must be preceded by clinical evidence. We need adequately powered and well-designed randomised controlled trials investigating whether dexmedetomidine alone or with opioids/benzodiazepines in infants on mechanical ventilation reduces the need for opioids/benzodiazepine and improves neurodevelopment at 24 months and later as compared with the use of opioids/benzodiazepines alone.

Key messages

⇒ Mechanical ventilation is a potentially painful intervention. Opioids and benzodiazepines are widely used to provide analgesia and sedation in mechanically ventilated infants.
⇒ Evidence suggests that opioids may be ineffective analgesics and there may be adverse consequences such as respiratory depression and detrimental long-term neurodevelopmental effects.
⇒ Dexmedetomidine, a highly selective alpha-2-adrenergic agonist, provides analgesia and simulates natural sleep with maintenance of spontaneous breathing and upper airway tone.
⇒ Emerging observational studies suggest that dexmedetomidine use in mechanically ventilated infants may reduce exposure to opioids/benzodiazepines and enable quicker weaning and extubation.
⇒ Data on safety and efficacy are scant. Adequately powered randomised controlled trials investigating use of dexmedetomidine in preterm infants are required.

INTRODUCTION

Mechanical ventilation via a tracheal tube is widely used for respiratory support in preterm infants. In England and Wales, despite the increase in use of non-invasive respiratory support, 57% of very preterm infants were mechanically ventilated on the day of birth and many others require ventilatory support later in the course of their care.[1] This included 91% of extremely preterm infants and the increasing survival of those born at these gestations could lead to further increases in the use of mechanical ventilation in neonatal care.

It is now well accepted that preterm infants perceive pain. Mechanical ventilation is an uncomfortable and painful intervention. Ventilated infants are, often, also subjected to multiple painful procedures and experience

pain caused by underlying diseases such as necrotising enterocolitis (NEC).[2 3] Pain and stress cause cardiorespiratory instability including interference with the ventilator synchronising with the infant's breathing efforts that lead to suboptimal ventilation, fluctuations in heart rate (HR), respiratory rate, blood pressure (BP) and oxygen saturation with complications such as intraventricular haemorrhages (IVH) and metabolic instability.[4]

PAIN IN PRETERM INFANTS

Preterm infants have enhanced hormonal and physiological responses to pain. Anand *et al* showed that preterm infants undergoing patent ductus arteriosus surgery who did not receive fentanyl had a significantly higher hormonal stress response compared with those who received fentanyl.[5] More recently, MRI studies identified that exposure to pain and stress in neonatal care alters corticospinal tract, and subcortical white matter development with further evidence of reduced volume of the somatosensory thalamus and changes in the cortex, limbic system and basal ganglia, and the white matter that persist into school age.[6]

Management of pain and agitation is fundamental to good intensive care, yet neonatal pain is inconsistently assessed and inadequately managed.[3] A prospective cohort study of 243 European neonatal intensive care units (NICUs), the European Pain Audit in Neonates (EUROPAIN), reported 34% of admissions, including 82% of those who were mechanically ventilated, received some sedation or analgesia.[7] A retrospective cohort study from 348 Pediatrix Medical Group NICUs in the USA found that infants received a sedative, analgesic or paralytic only on 33% of days that they were mechanically ventilated.[8]

Although optimal management of pain and sedation during mechanical ventilation is as yet undiscovered, selective use of continuous infusion of opioids is recommended for infants who are mechanically ventilated for prolonged periods.[3 9] These recommendations stand despite the 2021 update of the Cochrane review that concluded that there is uncertainty whether opioids have any effect on reducing pain in mechanically ventilated infants.[2] In addition, there may be short-term and long-term adverse consequences of morphine infusion in preterm infants such as respiratory depression leading to prolonged duration of mechanical ventilation and detrimental long-term neurodevelopmental effects. The Cochrane systematic review[2] includes one trial that reported neurodevelopment at 18–24 months[10]: (RR 2.00, 95% CI 0.39 to 10.29; 78 participants); and one study that reported neurodevelopment outcomes at 5–6 years of age[11]: (RR 1.60, 95% CI 0.56 to 4.56; 95 participants) and concluded the evidence was uncertain. Puia-Dumitrescu *et al*[12] performed a post hoc analysis of infants who participated in the Preterm Erythropoietin Neuroprotection Trial to investigate the effect of exposure to opioids and benzodiazepines on development at 22–26 months' corrected age. Of the 936 extremely preterm infants 481 (51%) received opioids; 297 (32%) received both opioids and benzodiazepines; and 20 (2%) received benzodiazepines only. Infants exposed to both groups of drugs had more comorbidities compared with those exposed to only one or none with higher adjusted odds of IVH, NEC, severe bronchopulmonary dysplasia, and retinopathy of prematurity, and longer length of hospital stay. Outcomes at 2 years were negatively associated with the combined use of opioids and benzodiazepines even after adjusting for potential confounders. The lowest scores were noted among the infants who received the drugs for more than 7 days (median (IQR) score of 85 (73–97)) compared with 97 (91–107) in infants with no exposure. However, this was not a randomised allocation and the higher prevalence of multiple comorbidities in the group that received drugs makes it difficult to interpret the results.

Despite these uncertainties, opioids are the most popular choice for management of pain and sedation in mechanically ventilated infants. Of the 2142 mechanically ventilated infants included in the EUROPAIN audit, morphine and fentanyl were given to 923 (43%) and 639 (29%) infants, respectively, while 536 (25%) received midazolam.[7] Zimmerman *et al* similarly reported that in 433 587 ventilated-days, fentanyl (17%), midazolam (14%) and morphine (9%) were the most frequently administered drugs.[8] They also reported increase in administration of opioids during mechanical ventilation from 5% of ventilated days in 1997 to 32% in 2012. In the UK, the percentage of very preterm infants who receive intravenous morphine increased from 32% in 2010 to 37% in 2017.[13]

DEXMEDETOMIDINE: AN ALTERNATIVE AGENT FOR PAIN AND SEDATION IN NEWBORN INFANTS

This high use of opioids despite the uncertainty about benefit and harm is possibly due to a lack of alternative agents that could provide adequate and safe sedation and analgesia in newborn infants. Recently, dexmedetomidine, a highly selective alpha-2-adrenergic agonist (1620:1::α2:α1 specificity) with sedative and analgesic effects, has come into use in newborn infants receiving mechanical ventilation.[14] Several recent studies have explored the off-label use of dexmedetomidine in newborn infants for sedation and analgesia in NICU settings. A summary of the studies is given in tables 1–4.

Dexmedetomidine, first approved by the USA Food and Drug Administration in 1999, is similarly authorised by the European Medicine Agency[15] for use for sedation in adult intensive care unit patients requiring sedation level no deeper than arousal in response to verbal stimulation and for sedation of non-intubated patients before and/or during diagnostic or surgical procedures requiring sedation. It provides analgesia via inhibition of substance P release from the dorsal horns of the spinal cord while the anxiolysis and sedation are believed to be

Table 1 Summary of clinical studies of dexmedetomidine in newborn infants: studies with a comparator group that did not receive any dexmedetomidine

Reference Setting	Study design	Inclusion criteria	Dexmedetomidine group	Comparator	Outcomes Notes
Randomised controlled trials or quasi-randomised controlled trials—none					
Observational studies with comparator with no dexmedetomidine					
O'Mara 2012[28] USA Single centre	Retrospective case–control January 2005–May 2010	<36 weeks' GA at birth, <2 weeks of life at study entry and receiving mechanical ventilation	N=24 GA: 25.5.±0.1.7 BW: 832.±0.204.2 g	Fentanyl N=24 GA: 24.9.±0.1.6 BW: 675.±0.164.2	Dexmedetomidine group had ► Shorter duration of treatment (12.5 vs 20 days) ► Similar no of sedative boluses per day (1.7 vs 3) but in total less total additional sedation ► More no of days free of additional sedation ► Reduction in no of days on mechanical ventilation (14.4 (7.3) vs 28.4 (9.9)) ► Better GI function in including earlier establishment of full feeds ► Less late onset sepsis
Sellas 2019[32] USA Single centre	Retrospective cohort study with matched controls January 2010 to August 2015	Invasive surgical procedure Required at least 6 hours of continuous sedation and/or analgesia	Received dexmedetomidine in addition to opioids N=39 GA: 37 (29–39) PMA at surgery:39 (29–59) weeks	Opioids only (morphine or fentanyl) N=39 GA: 37 (27–38) PMA at surgery: 37 (27–41)	28/39 (72%) of those who received dexmedetomidine also received opioids Dexmedetomidine group had ► More episodes of bradycardia (12.8% vs 5.1%; p=0.01) ► No difference in episodes of hypotension or respiratory depression. ► Lower cumulative dose of opioids (1155 µg/kg vs 1841 µg/kg; p=0.01) ► No difference in the no of supplemental doses of opioids
Morton 2021[39] USA Single centre	QI initiative to reduce benzodiazepine exposure during Pre-QI: January 2015 to February 2018 Post-QI March 2018: to December 2019	At least 35 weeks' PMA <14 days of sedation Sedation needed for mechanical ventilation	Guideline and QI initiative to promote use of escalating dose of dexmedetomidine	Midazolam and no specific guideline for dexmedetomidine use	Proportion of infants receiving any dexmedetomidine increased from 18% to 49% Infants receiving only dexmedetomidine increased from 3% to 33% Infants receiving any midazolam decreased from 95% to 65% Infants who received dexmedetomidine received less daily midazolam (1.3 mg/kg/day vs 2.2 mg/kg/day) Increase in midazolam-free days No difference in mean duration of sedation episodes

BW, birth weight; GA, gestational age; PMA, postmenstrual ages; QI, quality improvement.

due to the reduction in sympathetic outflow from the locus coeruleus.[16] It stimulates the natural sleep pathways and induces activity similar to non-rapid eye movement sleep in adults and children.[17] The effects on respiration and airway also mimic natural sleep and therefore maintain spontaneous breathing and upper airway tone.[17]

Although there are no data to examine the early exposure to dexmedetomidine and long-term neurocognitive function in children, animal studies suggest that dexmedetomidine may have some neuroprotective effects including cell-protective effects under ischaemic conditions and after traumatic brain injury.[18] In rodents, cortical and white matter loss after hypoxic ischaemic injury may be prevented by dexmedetomidine.[19] In another rat model, brain tissue and cell loss induced by hypoxia-ischaemia were attenuated by dexmedetomidine post-conditioning, an effect that was inhibited by α2-adrenergic antagonists suggesting that the protective

Table 2 Summary of clinical studies of dexmedetomidine in newborn infants: studies without a comparator group that did not receive any dexmedetomidine

Study ID Setting	Study design	Inclusion criteria	Intervention	Outcomes
Chrysostomou 2014 USA eleven centres[29]	Phase II/III, open-label, multicentre safety, efficacy, and PK trial	intubated and mechanically ventilated neonates GA ≥28 to ≤44 weeks anticipated to require a minimum of 6 hours of continuous IV sedation excluded <1 kg infants	Dosing: 3 phases level 1: loading dose (LD), 0.05 mg/kg; maintenance dose (MD), 0.05 mg/kg/hour level 2: LD, 0.1 mg/kg; MD, 0.1 mg/kg/hour level 3: LD, 0.2 mg/kg; MD, 0.2 mg/kg/hour. N=42 (18 preterm; 24 term) N-PASS tool for need of sedation and analgesia	Need for additional sedation: no preterms; 4 term (midazolam) Need for additional analgesia: 17 (40%) – 3 preterms (fentanyl); 14 term (fentanyl and/or morphine) N-PASS scores: 5%>+3 in pain; 77% between −5 and +3 (adequate) and 18% ≤−6 deep sedation HR decreased by an average of 12%±9% at 7.7±7.3 hour, and systolic BP decreased by 14%±12% at 6.5±7 hour Other adverse effects: 26 (62%) patients (11 preterm and 15 term) – diastolic hypotension, hypertension, agitation, respiratory acidosis. No discontinuation, no significant lab or ECG abnormalities
Estkowski 2015 USA PICU Single centre[26]	Retrospective chart review October 2007 to Aug 2012	At least 37 weeks PMA	Compared neonates (up to 28 days of CGA) to infants (28d CGA to 1 year) Neonates: N=28 (13 born preterm) Infants: N=99	Neonates as compared with infants had: ► Similar minimum infusion rates ► Lower median maximum dosage: 0.4 µg/kg/hour (IQR, 0.26–0.6) vs 0.6 µg/kg/hour (IQR, 0.4–0.8) (p<0.01) ► Similar duration of use: 41 (17-76) hr ► Fewer had any episode of bradycardia: 2/28 (7%] vs 55/99 (56%) (p<0.01) ► Similar incidence of hypotension: 4/28 (14%) vs 30/99 (30%) (p=0.15) In neonates: 3/28 (11%) received a fluid bolus 4/28 (14%) dexmedetomidine discontinued due to cardiovascular adverse effects In infants: 3/99 discontinued infusion due to bradycardia 75/99 (76%) had additional sedative agents
Dersch-Mills 2019 Canada Single centre (out-born NICU)[33]	Retrospective observational study December 2014 to December 2016	Received dexmedetomidine for ≥3 hours	N=38 (30 for surgery) GA: 37.1 (30.7–38.3) 17 preterms; 41 (6–74) days old) BW: 2605 (1721–3212) used for mean (range): 11.1 (0.13–58) days most (36/38) received concomitant opioid infusion, mostly fentanyl	32/38, at least one adverse effect ► 15, hypotension ► 25 bradycardia (drop of ≥20 bpm from baseline) ► 7 severe bradycardia (drop of ≥40 bpm from baseline) ► No dose adjustment or discontinuation for any adverse effect Withdrawal: 22/38 had tachycardia and increase NAS scores

BP, blood pressure; CGA, corrected gestational age; GA, gestational age; IV, inverse variance; NAS, Neonatal Abstinene Syndrome; NICU, neonatal intensive care unit; N-PASS, Neonatal Pain and Sedation Scale; PICU, paediatric intensive care unit; PK, pharmacokinetics; PMA, postmenstrual ages.

Table 3 Summary of case reports of dexmedetomidine in newborn infants

Reference setting	Case description	outcomes Notes
Finkel 2007 USA[31]	2 days old, 3 kg female Repair of bladder exstrophy Received dexmedetomidine infusion	Hypothermia and bradycardia—at 0.4 µg/kg/hour dose reduced and maintained on 0.2 µg/kg/hour without further adverse events
O'Mara 2009 USA[16]	24 weeks GA, 9 days old infant on high frequency oscillatory ventilation. Was on fentanyl and lorazepam Started at 0.5 µg/kg over 10 min followed by 0.25 µg/kg/hour increased by 0.05–0.1 µg/kg/hour every 12 hours if needed. Max rate of 0.7 µg/kg/hour for 19 days.	Calmed and remained sedated Allowed weaning of ventilation and extubation
Kubota 2012 Japan[44]	Term infant—ventilated	EEG confirmed seizures, stopped 12 hours after discontinuation of dexmedetomidine infusion without any antiepileptic medication Normal development

EEG, electroencephalogram; GA, gestational age; HIE, hypoxic ischaemic encephalopathy; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

effect was mediated by α2-adrenergic receptor activation.[20] However, when combined with hypothermia, Ezzati *et al* found that dexmedetomidine was associated with adverse cardiovascular events and was neurotoxic following hypoxia-ischaemia.[21] In a model comparing the effect of ketamine to that of dexmedetomidine on brain cell degeneration and apoptosis in postnatal day-7 rats, dexmedetomidine produced significant damage in the primary sensory regions which was different to the limbic injury induced by ketamine.[22] In 10 mechanically ventilated very low birth weight infants born at 25–30 weeks' gestational age (GA) who received dexmedetomidine infusion (2–30 days of postnatal age), Cortes-Ledesma *et al* found that after 6 hours of dexmedetomidine infusion (0.1–0.4 µg/kg/min), brain regional oxygen saturation decreased and fractional oxygen tissue extraction increased without any change in HR, mean BP, oxygen saturation or haemoglobin while amplitude integrated electroencaphalogram (EEG) showed a prolongation of interburst interval.[23] As the decrease in brain oxygen saturation could not be related to increased brain activity, it suggested a vasoconstrictor effect on cerebral vessels.[23] Currently used sedative and analgesics also adversely impact brain development, for example, exposure to midazolam is associated with macrostructural and microstructural alterations in hippocampal development and lower cognitive scores[24] while opioid use is linked to reduced cerebellar volume, poorer cognitive and motor outcomes and behavioural problems in infancy.[6] No clinical studies have investigated the impact of dexmedetomidine on neurological outcomes or neurodevelopment in preterm or term-born infants.

PHARMACOLOGICAL STUDIES ON DEXMEDETOMIDINE IN NEWBORN INFANTS

The evaluation of pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of drugs in vulnerable newborn infants is challenging.[24] Dexmedetomidine is metabolised via glucuronidation, hydroxylation (via CYP2A6) and N-methylation and primarily eliminated via the urine.[25] As these pathways, particularly glucuronidation, are immature in the first year after birth, dexmedetomidine clearance may be decreased but there is a lack of PK-PD studies in preterm infants.[17]

The therapeutic window for dexmedetomidine in older children is 0.4–0.8 µg/L (optimum level around 0.6 µg/L)[26] with a safety measure of maintaining plasma concentrations below 1 µg/L and is assumed to be the same in neonatal studies.[24] The clinical applicability of these serum concentrations is not yet determined and surrogate markers of efficacy such as pain and sedation scores are used to determine clinical utility and titrate dosing,[27] The drug is available as dexmedetomidine hydrochloride (100 µg/mL or 4 µg/mL),[28] usually delivered in a concentration of 0.5–1 µg/mL as a loading dose (LD) over 10–20 min and maintenance dose (MD) as continuous infusion using rate-controlled syringe pumps. In a phase II/III open-label, safety, efficacy and PK trial including 11 centres, Chrysostomou *et al* investigated three escalating dose regimens (LD followed by MD) of dexmedetomidine mechanically ventilated 28–44 weeks' GA infants.[29] In 42 infants (18 preterm and 24 term-born), they found that additional sedation (midazolam) was required only in 4 infants (all term-born) while additional analgesia (fentanyl or morphine) was required in 17 infants (3 preterms and 14 term-born). Using the Neonatal Pain and Sedation Scale (N-PASS), they found that at all three dose levels, infants had signs of pain or agitation (N-PASS score >3) at 5% time points only. Preterm infants, as compared with term infants, had lower weight-adjusted plasma clearance (0.3 vs 0.9 L/hour/kg) and increased elimination half-life (7.6 vs 3.2 hours). Van Dijkman *et al* performed a dose-finding study of dexmedetomidine in mechanically ventilated newborn infants who received dexmedetomidine infusion over 24 hours.

Table 4 Clinical studies of use of dexmedetomidine in infants undergoing therapeutic hypothermia for HIE

Study ID setting	Study design	Inclusion criteria	Dexmedetomidine group	Comparator	Outcomes notes
O'Mara 2018 USA Single centre[35]	Retrospective cohort study July 2013 to October 2016	HIE requiring TH Received dexmedetomidine for 48 hours	N=19 2, dexmedetomidine only; 17, combination with fentanyl	No comparator	Fentanyl weaned down in 13/17 after starting dexmedetomidine 10 infants required inotropes. Initiation of dexmedetomidine did not affect HR, or BP. One infant had bradycardia – resolved with discontinuation of fentanyl Clinical outcomes: 1 died; 8 had seizures
Cosnahan 2021 USA single centre[19]	Retrospective cohort study January 2018 to April 2020	HIE requiring TH (NICHD criteria)	March 2019-April 2020 N=34 Continuous dexmedetomidine 0.3 µg/kg/hour with increments of 0.1 µg/kg/hour based on pain scores and breakthrough morphine dose requirements Maximum: 2 µg/kg/hour	January 2018-March 2019 N=36 Intermittent morphine 0.1 mg/kg every 4 hours	No difference in N-PASS scores Dexmedetomidine group had: ► Higher breakthrough morphine requirement: 0.13 (0.13) vs 0.04 (0.09) mg/kg, p=0.001 ► Lower total morphine requirement: 0.13 (0.13) vs 1.79 (0.23) mg/kg, p<0.0001 ► Reduced respiratory support requirement ► Similar outcomes for feeding, EEG and MRI scan All HR measurement in normal range ► morphine group had higher HR and BP at some timepoints
Elliot 2022 abstract only USA Single centre[34]	Retrospective cohort 2011–2019	Dexmedetomidine and/or fentanyl	Dexmededetomidine=46 (14 monotherapy; 32 in combination)	Fentanyl=120	Dexmedetomidine group had lower HR: 91±9 vs 103±11 bpm Dexmedetomidine was reduced or discontinued in 22 (48%) due to inadequate sedation with low HR

BP, blood pressure; HIE, hypoxic ischaemic encephalopathy; HR, heart rate; N-PASS, Neonatal Pain and Sedation Scale; TH, therapeutic hypothermia.

Initial dosing (0.3 µg/kg/hour) was determined by extrapolation of previously published PK of dexmedetomidine in older children and was subsequently increased to 0.4 µg/kg/hour in the follow-up phase due to higher clearance of the drug. Additional sedation was required in 83% of the participants as indicated by Comfort-neo scores. In seven term infants with hypoxic ischaemic encephalopathy (HIE) and therapeutic hypothermia (TH), McAdams *et al* found that dexmedetomidine clearance was either comparable or lower but volume of distribution was larger compared with estimates in normothermic infants.[30] They recommended doses up to 0.4 µg/kg/hour and that a LD may be needed to achieve therapeutic concentration without a lag. Dose regimens used in published clinical studies of preterm infants and available neonatal formularies are given in table 5.

CLINICAL REPORTS OF THE USE OF DEXMEDETOMIDINE IN PRETERM INFANTS

Case reports of dexmedetomidine use to sedate a difficult to ventilate 24 weeks' GA infant[16] and others reporting adverse effects[30 31] were followed by larger single-centre studies. Use has been reported in extremely preterm

Table 5 Dose of dexmedetomidine in newborn infants

Study ID		Bolus at start of infusion	Infusion			
			Starting dose	Increments	Range/maximum	Weaning
O'Mara 2012[28]		0.5 µg/kg	0.3 µg/kg/hour	0.1 µg/kg/hour twice daily if need for >3 doses of adjunct sedation	0.3–1.2 µg/kg/hour	0.1 µg/kg/hour every 12–24 hours
Morton 2021[39]		–	0.5 µg/kg	0.1–0.2 µg/kg/hour not more frequently than every 30 min	Two µg/kg/hour	No specific regimen given
Estkowski 2015[26]		–				
Dersch-Mills 2019[33]		–	0.2–0.3 µg/kg/hour	0.1 µg/kg/hour based on pain and sedation scores	0.5 µg/kg/hour	No regimen specified—weaned over median of 79 hours (IQR, 35–175). 10 infants needed clonidine (nine had dexmedetomidine for >10 days)
Australasian Neonatal Medicines Formulary[45]	<37 weeks' GA	0.2 µg/kg	0.2 µg/kg/hour	0.1–0.2 µg/kg/hour every 30 min	One µg/kg/hour	0.1 µg/kg/hour every 30 min OR 0.2 µg/kg/hour every 8 hours
	Term infant ≤14 days	0.35 µg/kg	0.3 µg/kg/hour		1.2 µg/kg/hour	
	Term infant >14 days	0.5 µg/kg	0.5 to 0.75 µg/kg/hour		1.5 µg/kg/hour	
Neonatal Drug Dosing Guideline, Izaak Walton Killam Health Centre (personal communication)		0.5–1 µg/kg 'not usually required'	0.1 to 0.3 µg/kg/h	0.1 µg/kg/hour every 1–2 hours	One µg/kg/hour	0.1 µg/kg/hour every 12–24 hours as tolerated

infants in the first weeks after birth,[16 27] in preterm infants at later postmenstrual ages (PMA) and term-born infants, after surgical procedures,[32 33] and in infants undergoing TH for hypoxic ischaemic encephalopathy (HIE).[19 34 35] It is also used for sedation during procedures such as MRI.[36 37] In an update of medication prescribing patterns in the US NICUs, Stark *et al* reported that between 2010 and 2018, dexmedetomidine was ninth in the list of drugs that had the greatest relative increase in use and had become the 90th most frequently prescribed medication[38] although its use was not reported, at least until 2017, in neonatal care in the UK.[13]

Dexmedetomidine is used for sedation and analgesia on its own or in combination with other agents with the aim of reducing cumulative exposure to opioids and benzodiazepines. Comparing 48 infants with a mean GA of 25 weeks who received either fentanyl or dexmedetomidine, O'Mara *et al* found that the dexmedetomidine group required less adjunctive sedation.[28] Comparing 39 infants who received dexmedetomidine, (including 28 who concomitantly received opioid infusion) with 39 matched controls who only received opioids, Sellas *et al* found that there was no difference in the duration of use or the number of doses of opioids but the total dose of opioids received was lower in the group that received dexmedetomidine.[32] With an aim to reduce benzodiazepine exposure in infants who were at least 35 weeks' PMA and needed sedation for mechanical ventilation, Morton *et al* implemented a quality improvement project with a sedation guideline recommending the use of dexmedetomidine as initial agent or in addition to midazolam. They demonstrated reduction in use of midazolam with fewer infants receiving midazolam, increased midazolam-free days and lower daily midazolam doses in those who received additional dexmedetomidine without any increase in the mean duration of sedation episodes.[39] In 38 infants at a median PMA of 38.8 weeks, of whom 30 were postsurgical, Dersch-Mills *et al* found that the opioid infusion was reduced within 24 hours of initiation of dexmedetomidine in 12 of the 18 infants who were on concomitant opioids.[33]

As dexmedetomidine does not cause respiratory depression, it is postulated that its use with no or reduced doses of opioids should enable quicker weaning off mechanical ventilation and support extubation. O'Mara *et al* found a significantly shorter duration of mechanical ventilation in those who received dexmedetomidine compared with those on fentanyl only (mean±SD: 14.4±7.3 vs 28.4±9.9; p<0.0001). They also reported that clinicians extubated 19 of 28 infants who received dexmedetomidine while receiving infusion of the drug at the time of extubation. Due to the early extubation, fewer infants received dexamethasone (4 vs 11) and there were fewer chest X-rays performed (mean±SD: 28±8.8 vs 49±13.8) in the dexmedetomidine group compared with those who received fentanyl.

The main concerns with dexmedetomidine use are bradycardia and hypotension. In the general adult population, bradycardia is reported in 5%–42% and hypotension in 24%–56% of those who receive dexmedetomidine.[40] Chrysostomou *et al* found, in 42 neonates, that the HR decreased by an average of 12%±9% and systolic BP decreased by 14%±12% at 6–7 hours of starting the dexmedetomidine infusion.[29] Although mostly reported to be not of clinical significance, dexmedetomidine can induce reduction in HR and BP. Dersch-Mills *et al* analysed adverse effects in 38 infants, 36 of whom were also receiving opioid infusion and found that 25 had at least one episode of bradycardia (drop of >20 bpm from baseline lasting for >2 hours) including 7 who had a drop of >40 bpm. Hypotension occurred in 15 infants. Dopamine was used concurrently in 17 infants of which 5 were started on dopamine after the initiation of dexmedetomidine. No infants had dexmedetomidine infusion discontinued due to adverse effects.[33] Similarly, Sellas *et al* found that 5 of 39 infants who received dexmedetomidine experienced episodes of bradycardia as compared with 2 of 39 in the no-dexmedetomidine group although all episodes were self-limiting and did not require any intervention.[32] O'Mara *et al* measured BP and HR hourly and did not see any appreciable effect on either in those on dexmedetomidine compared with the infants on fentanyl[28] and Morton *et al* reported that following their initiative to increase use of dexmedetomidine in mechanically ventilated infants, one infant had dexmedetomidine discontinued due to bradycardia without haemodynamic compromise however discontinuing the drug did not resolve the bradycardia.[39] Estkowski *et al* compared neonates in a paediatric intensive care unit with older infants and found that among the 28 neonates, 4 experienced hypotension and 2 had bradycardia as compared with 30 and 55 of 99 infants who had hypotension and bradycardia, respectively. Three neonates required fluid bolus, one had dopamine infusion started after dexmedetomidine and four had dexmedetomidine discontinued due to adverse events.[26]

There are no reports of additional adverse events due to dexmedetomidine interacting with other drugs when used in neonatal care, however, polypharmacy is common in neonatal practice and dexmedetomidine can, potentially interact with other frequently used drugs such as phenobarbitone (additional central nervous system depression) and others such as, beta-blockers and diazoxide (worsening of bradycardia and hypotension).[41]

CONCLUSIONS AND RECOMMENDATIONS

Emerging clinical data suggest that dexmedetomidine may be an alternative to opioids and benzodiazepines for managing pain and sedation in mechanically ventilated newborn infants. It may help reduce the exposure to these agents and as it does not cause respiratory depression, it may facilitate quicker extubation. The potential neuroprotective effect on the immature brain could ease the concerns about the impact of pain and stress and that of opioids and benzodiazepines on the developing

Table 6 Registered clinical trials

Study ID	Study design	Eligibility	Intervention	Comparator	Outcomes
Dexmedetomidine for LISA Procedure in preterm infants NCT04820101	Single group assignment Open label Sample size=40	Inclusion criteria: ► GA 26–36 weeks' ► Respiratory distress syndrome requiring surfactant therapy Exclusion criteria: ► Need for emergency intubation in the delivery room ► Major congenital malformations or chromosoal anomaly abnormalities ► Fetal hydrops ► Hypercapnia ► Pneumothorax ► Haemodynamic compromise	Dexmedetomidine one µg/kg slowly IV over 10 min	None	Change in Neonatal Infants Pain Scale score before, during and immediately after the procedure In 24 hours, ► No of apnoea ► No of severe apnoea ► Need for ventilation
Dexmedetomidine use in infants undergoing cooling due to neonatal encephalopathy Trial NCT04772222 [46]	Randomised controlled trial Parallel 1:1 allocation Open label Sample size=50	► ≥36 weeks' GA with HIE treated with TH. ► Requiring sedation and/or treatment to prevent shivering during TH as assessed by the Neonatal Pain, Agitation, and Sedation Scale scores and a modified Bedside Shivering Assessment Scale.	Dexmedetomidine ► Loading dose of 1 µg/kg followed by 0.1–0.5 µg/kg/hour continuous infusion	Morphine ► Intermittent dosing every 3–4 hours of 0.02–0.05 mg/kg/dose or continuous infusion of 0.005–0.01 mg/kg/hour	Safety – potential adverse events such as hypotension, hypertension, bradycardia, cardiac arrhythmias, hypothermia, acute renal failure, liver failure, seizures Shivering Days to full oral feeding Mother assessment at 7 days, 3–4 mo Neurological assessment at 3–4 months and 6–9 months

GA, gestational age; IV, inverse variance; TH, therapeutic hypothermia.

brain although other reports suggest that dexmedetomidine could also adversely impact the newborn brain. Despite the creeping acceptance of its use in this population, there are no robust data to demonstrate either the efficacy or the safety of this drug in preterm infants. The studies discussed above are observational and mostly retrospective chart reviews. It is encouraging to see robust PK-PD studies focussing on determining the optimal dose regimens.[25] The initial results demonstrating PK differences between term and preterm infants suggest that further population PK-PD studies are required. A Cochrane systematic review was registered in 2016[42] but there are no completed randomised controlled trials (RCTs) or systematic reviews of use of dexmedetomidine in preterm infants. The increasing number of publications of observational studies and use in clinical practice as seen by the availability of neonatal drug formularies for its use demonstrat evolving practice that dexmedetomidine is being used in newborn infants in neonatal units. The data on safety and efficacy are scant and not of high quality and there are no data on long-term neurodevelopmental impact on preterm or term-born infants. We found one registered pilot RCT[21] in term infants undergoing TH for HIE and one investigating the use of bolus dose for supporting less invasive surfactant administration in preterm infants (table 6).

The acceptance of dexmedetomidine in routine clinical practice must be preceded by clinical evidence. While there is a suggestion that dexmedetomidine may be the agent that could provide analgesia and sedation with minimal adverse impacts, the available data are not sufficient to ensure that it is safer than the alternatives used in current practice.[43] Although all currently used sedatives and analgesics have adverse impact on the preterm brain, new agents must be investigated thoroughly before being accepted as standard practice. We need adequately powered and well-designed RCTs investigating whether dexmedetomidine alone or in conjunction with opioids/benzodiazepines in preterm infants who require analgesia and sedation during mechanical ventilation reduces the need for opioids/benzodiazepine and improves neurodevelopment at 24 months and later as compared with the use of opioids/benzodiazepines alone.

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Contributors SO and JD conceived the piece. SO led the write up. JA conducted the literature search and completed the study summaries. SO, JD and JA revised and approved the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SO has received funds from the National Institute of Health Research, UK and the Medical Research Council, UK for other research. JD has received funds from the National Institute of Health Research, UK, Canadian Institute for Health Research, Canada, Nova Scotia Research, Canada and Action Medical Research, UK for other research

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

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