PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sedation and analgesia from prolonged pain and stress during mechanical ventilation in preterm infants: Is dexmedetomidine an alternative to current practice?
AUTHORS	Ojha, Shalini Abramson, Janine Dorling, Jon

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Keliana O'Mara Institution and Country: Duke University Medical Center United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	08-Apr-2022

GENERAL COMMENTS	Overall a nice review of dexmedetomidine use in neonates. The tables compiling the various studies are helpful. It would be helpful if the authors included some additional information regarding safety outcomes with opioids/benzos to help better underscore the concern NICU providers have with opioids and why the long-term follow-up studies of dexmedetomidine are needed. Some to potentially include would be: McPherson C et al. Annals of Pharmacotherapy 2015; 49(12): 1291-1297. Duerden EG et al. Ann Neurol 2016; 79(4):548-559. I just have some minor editing suggestions: -Page 8 line 27: Would delete the word "however" given this is a bulleted list -Page 9 line 25: may consider changing "potentially painful" to "likely painful" as there are published studies specifically evaluating pain scores in mechanically ventilated neonates. -Page 12 line 55: I would perhaps mention that there are limited data regarding serum concentrations, but the clinical applicability of these data are unknown. With medications that have a surrogate marker of efficacy (i.e. pain/sedation scores), serum concentrations likely do not have much bedside clinical utility (i.e. if a patient is on a fentanyl drip and pain scores reflect need for a higher dose, we would not limit the dose because of a presumed therapeutic window. Instead, we would titrate to effect). -Page 13 line 5: the standard concentration is 4 mcg/mL and the bolus dose is generally 0.5-1 mcg/kg.

REVIEWER	Reviewer name: Dr. Nadir Yalcin Institution and Country: Hacettepe University, Faculty of Pharmacy, Ankara Turkey Competing interests: None
REVIEW RETURNED	29-Mar-2022

GENERAL COMMENTS	General comments - I was very interested to read this study entitled 'Sedation and analgesia from prolonged pain and stress during mechanical ventilation in preterm infants: Is dexmedetomidine an alternative to

	current practice?'. The authors aimed to evaluate the sedative and analgesic effect of dexmedetomidine despite the limited number of clinical studies in mechanical ventilated preterm infants. Dexmedetomidine is not currently labeled for use in infants there remains, a lack of robust safety and efficacy data for infants exposed to dexmedetomidine, particularly those with ELBW. Besides, according to the Stark et al study, dexmedetomidine, a medication previously not on the list of the top 100 medications used from 2005 to 2010, ranked as the medication with the greatest relative increase (9th greatest absolute increase) and the 90th most common medication used in the NICU from 2010 to 2018. I suggest that this trend be mentioned in the review (Stark A, Smith PB, Hornik CP, Zimmerman KO, Hornik CD, Pradeep S, Clark RH, Benjamin DK Jr, Laughon M, Greenberg RG. Medication Use in the Neonatal Intensive Care Unit and Changes from 2010 to 2018. J Pediatr. 2022 Jan;240:66-71.e4). - I suggest you mention that it has potential drug-drug interactions risk (bradycardia and hypotension) with some drugs such as beta-blockers, barbiturates, diazoxide, pentoxifylline, terlipressin, which are frequently used in the NICUs, where polypharmacy is common (Lexicomp-UpToDate Drug Interaction Database, accessed: 29 March 2022). - I suggest you mention that distribution (2.7 L/kg vs. 3.9 l/kg), half-life (7.6 hours vs. 3.2 hours), and clearance (0.3 L/hour/kg vs. 0.9 L/hour/kg) differ in preterm and term neonates. Therefore popPK studies are needed in the current literature. - Lastly, the authors can discuss the use of dexmedetomidine before invasive (eg, PICC line placement, peritoneal dialysis) and non-invasive (eg, EEG, MRI, PET scan, chest physiotherapy) procedures. Specific comments Page 11 Line 46: I could not see the 1600:1: α2: α1 specificity in ref 14. It should be as 'ratios of α2:α1 activity, 1620:1' (Gertler, R., Brown, H. C., Mitchell, D. H., & Silvius, E. N. (2001). Dexmedetomidine: a novel sedative-analgesic agent. Proceedings (Baylor University. Medical Center), 14(1), 13–21) Page 12 Line 19: In another rat model, dexmedetomidine postconditioning reduces hypoxia-ischaemia-induced brain injury in neonatal rats. This effect may be mediated by α-2 adrenergic receptor activation that inhibits inflammation in the ischemic brain tissues (Ren X, Ma H, Zuo Z. Dexmedetomidine Postconditioning Reduces Brain Injury after Brain Hypoxia-Ischemia in Neonatal Rats. J Neuroimmune Pharmacol. 2016 Jun;11(2):238-47.). Page 15 Line 8: I suggest adding ADR incidences in general population as well (bradycardia (5% to 42%), hypotension (24% to 56%)) (Lexicomp-UpToDate Dexmedetomidine: Pediatric drug information, accessed: 29 March, 2022). Page 21 Line 28: Please edit 'dexmed' to 'dexmedetomidine'. Page 23 Line 17: Please add to reference.

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

VERSION 1 – AUTHOR RESPONSE

Associate Editor Comments to the Author: (There are no comments.) Thank you for reviewing our manuscript. In addition to the changes made as per the reviewers' suggestions (detailed below), we have updated the manuscript with addition of two recent references discussing the impact of dexmedetomidine on the preterm brain (ref 23) and a view on its increasing use in neonatal practice (ref 44). Reviewer 1 General comments - I was very interested to read this study entitled 'Sedation and analgesia from prolonged pain and stress during mechanical ventilation in preterm infants: Is dexmedetomidine an alternative to current practice?'. The authors aimed to evaluate the sedative and analgesic effect of dexmedetomidine despite the limited number of clinical studies in mechanical ventilated preterm infants. Dexmedetomidine is not currently labeled for use in infants there remains, a lack of robust safety and efficacy data for infants exposed to dexmedetomidine, particularly those with ELBW. Besides, according to the Stark et al study, dexmedetomidine, a medication previously not on the list of the top 100 medications used from 2005 to 2010, ranked as the medication with the greatest relative increase (9th greatest absolute increase) and the 90th most common medication used in the NICU from 2010 to 2018. I suggest that this trend be mentioned in the review (Stark A, Smith PB, Hornik CP, Zimmerman KO, Hornik CD, Pradeep S, Clark RH, Benjamin DK Jr, Laughon M, Greenberg RG. Medication Use in the Neonatal Intensive Care Unit and Changes from 2010 to 2018. J Pediatr. 2022 Jan;240:66-71.e4). Thank you. We have added this information to the review: "In an update of medication prescribing patterns in the US neonatal intensive care units, 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 [3] although its use was not reported, at least until 2017, in neonatal care in the UK." I suggest you mention that it has potential drug-drug interactions risk (bradycardia and hypotension) with some drugs such as beta-blockers, barbiturates, diazoxide, pentoxifylline, terlipressin, which are frequently used in the NICUs, where We have added this. "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 polypharmacy is common (LexicompUpToDate Drug Interaction Database, accessed: 29 March 2022). can, potentially interact with other frequently used drugs such as phenobarbitone, with additional central nervous system depression and with others such as, beta-blockers and diazoxide, with worsening of bradycardia and hypotension." I suggest you mention that distribution (2.7 L/kg vs. 3.9 l/kg), half-life (7.6 hours vs. 3.2 hours), and clearance (0.3 L/hour/kg vs. 0.9 L/hour/kg) differ in preterm and term neonates. Therefore popPK studies are needed in the current literature. We have added this information "Preterm infants, as compared to term infants, had lower weight-adjusted plasma clearance (0.3 vs. 0.9 L/h/Kg) and increased elimination half-life (7.6 vs. 3.2 h)." And added the following to the conclusion section: "The initial results demonstrating pharmacokinetic differences between term and preterm infants suggest that further population PK-PD studies are required." Lastly, the authors can discuss the use of dexmedetomidine before invasive (eg, PICC line placement, peritoneal dialysis) and non-invasive (eg, EEG, MRI, PET scan, chest physiotherapy) procedures. The focus of this review is to explore the use of dexmedetomidine during mechanical ventilation and therefore we have, purposefully, stayed away from its shortterm use as for procedures. We have added this briefly as below but not expanded further to keep the review within its remit. "It is also used sedation during procedures such as MRI scan" Page 11 Line 46: I could not see the 1600:1: α2: α1 specificity in ref 14. It should be as 'ratios of α2:α1 activity,

1620:1' (Gertler, R., Brown, H. C., Mitchell, D. H., & Silvius, E. N. (2001). Dexmedetomidine: a novel sedative-analgesic agent. Proceedings (Baylor University. Medical Center), 14(1), 13–21) We have corrected this and added the reference (now ref 14). Page 12 Line 19: In another rat model, dexmedetomidine postconditioning reduces hypoxia-ischaemia-induced brain injury in neonatal rats. This effect may be mediated by α-2 adrenergic receptor activation that inhibits inflammation in the ischemic brain tissues (Ren X, Ma H, Zuo Z. Dexmedetomidine Postconditioning Reduces Brain Injury after Brain HypoxiaIschemia in Neonatal Rats. J Neuroimmune Pharmacol. 2016 Jun;11(2):238-47.). We have added this: "In another rat model brain tissue and cell loss induced by hypoxia-ischaemia were attenuated by dexmedetomidine postconditioning, an effect that was inhibited by α2-adrenergic antagonists suggesting that the protective effect was mediated by α2- adrenergic receptor activation." Page 15 Line 8: I suggest adding ADR incidences in general population as well (bradycardia (5% to 42%), hypotension We have added this: (24% to 56%)) (Lexicomp-UpToDate Dexmedetomidine: Pediatric drug information, accessed: 29 March, 2022). "In the general adult population, bradycardia is reported in 5 to 42% and hypotension in 24-56% of those who receive dexmedetomidine" Page 21 Line 28: Please edit 'dexmed' to 'dexmedetomidine'. We have corrected these. Page 23 Line 17: Please add to reference. Reviewer 2 Overall a nice review of dexmedetomidine use in neonates. The tables compiling the various studies are helpful. It would be helpful if the authors included some additional information regarding safety outcomes with opioids/benzos to help better underscore the concern NICU providers have with opioids and why the long-term follow-up studies of dexmedetomidine are needed. Some to potentially include would be: McPherson C et al. Annals of Pharmacotherapy 2015; 49(12): 1291-1297. Duerden EG et al. Ann Neurol 2016; 79(4):548-559. We have already described these in the initial section of the manuscript but on this suggestion, we have further emphasised the point by adding the following to the section discussing the impact of dexmedetomidine on the infant's brain: "Currently used sedative and analgesics also adversely impact brain development e.g., exposure to midazolam is associated with macro- and microstructural alterations in hippocampal development and lower cognitive scores [10] while opioid use is linked to reduced cerebellar volume, poorer cognitive and motor outcomes and behavioural problems in infancy." Page 8 line 27: Would delete the word "however" given this is a bulleted list We have deleted "however" Page 9 line 25: may consider changing "potentially painful" to "likely painful" as there are published studies specifically evaluating pain scores in mechanically ventilated neonates. We agree. We have deleted painful as mechanical ventilation is a painful procedure. Page 12 line 55: I would perhaps mention that there are limited data regarding serum concentrations, but the clinical applicability of these data are unknown. With medications that have a surrogate marker of efficacy (i.e. pain/sedation scores), serum concentrations likely do not have much bedside clinical utility (i.e. if a patient is on a fentanyl drip and pain scores reflect need for a higher dose, we would not limit the dose because of a presumed therapeutic window. Instead, we would titrate to effect). We have added this point. "The clinical applicability of these serum concentrations are not yet determined and surrogate markers of efficacy such as pain and sedation scores are used to determine clinical utility and titrate dosing" Page 13 line 5: the standard concentration is 4 mcg/mL and the bolus dose is generally 0.5-1 mcg/kg. We have added these figures

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

VERSION 2 – AUTHOR RESPONSE

VERSION 3 – REVIEW

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

VERSION 3 – AUTHOR RESPONSE