Pediatric Anesthesia and Critical Care Journal 2019;7(1):22-30
doi:10.14587/paccj.2019.4

PACCJ

Is dexmedetomidine a potential neuroprotective agent for term neonates with hypoxic-ischemic encephalopathy?

D. Surkov

Department of NICU, Regional Children's Hospital, Dnipr. Ukraine

Corresponding author: D. Surkov, Department of Anesthesia, Regional Children's Hospital, Dnipr. Ukraine.
Email: densurkov@hotmail.com

Keypoints

The objective is to determine the impact of dexmedetomidine and other sedatives on the cerebral blood flow and outcomes of hypoxic-ischemic encephalopathy in term neonates.

Abstract

Introduction

The negative impacts of standard pharmacologic sedative agents suggest that alternative agents should be investigated. Dexmedetomidine could be the new option for sedation in newborns with hypoxic-ischemic encephalopathy requiring mechanical ventilation. The objective is to determine the impact of dexmedetomidine and other sedatives on the cerebral blood flow and outcomes of hypoxic-ischemic encephalopathy in term neonates.

Material and methods

Data of 205 term infants with hypoxic-ischemic encephalopathy Sarnat stage II-III was collected during ≤72 hours of life. All the infants were divided using a simple open randomization by pharmacological sedative agents for mechanical ventilation synchronizing into groups by dexmedetomidine (n=46) and the control group (n=159), which included morphine, sodium oxybutyrate, and diazepam in standard recommended doses. A comparative analysis of the effect of dexmedetomidine and other drugs on cerebral perfusion and outcomes of hypoxic-ischemic encephalopathy was performed.

Results

A significant difference between groups in days of trachea extubation (p=0.022) was found; the chance for babies to be extubated before 7 days of treatment was significantly higher in the dexmedetomidine group 68% versus 33% in the control group (p=0.018) with HR 0.48 (95% CI 0.27-0.86, p=0.011). Also, the NIRS index $rScO_2$ differed significantly between the studied and control groups on the 1st day of treatment (65% versus 79%, p=0.012) and on the 2nd day of treatment (74% versus 81%, p=0.035). Mean arterial pressure was higher in the dexmedetomidine group compared to the control group (58 [51-65] mm Hg versus 53 [46-60] mm Hg, p<0.001), with a lower dose of dobutamine (EV -1.87, 95% CI from -3.25 to -0.48, p=0.009). In the dexmedetomidine group, the rate of seizures was significantly lower on the 1st day of observation (4.3% versus 48.3%, p <0.001); the incidence of unfavorable outcome as cerebral leukomalacia was also 7 times lower in the dexmedetomidine group compared to the control group (2.2% versus 15.1%, p = 0.018).

Conclusions

Dexmedetomidine is a safe sedative agent with a stable hemodynamics profile, no adverse cerebral influence and possible neuroprotective effects in term infants with HIE, additional to standard therapeutic hypothermia.

Keywords

Hypoxia, ischemia, encephalopathy, dexmedetomidine, neonates, mechanical ventilation.

Introduction

Hypoxic-ischemic encephalopathy (HIE), despite significant advances in diagnostics and understanding of the fetal and neonatal pathologies, remains one of the most frequent reasons for cerebral palsy and other types of severe neurodevelopmental impairment in children [3, 36]. In the United States and most technologically developed countries in the world the frequency of HIE according to different authors varies from 1.5-4 to 1-8 cases per 1,000 childbirths [4, 19, 35]. HIE morbidity is much higher in resource-limited settings and can reach as many as 26 cases per 1,000 newborns [1, 24].

In total it is associated with at least a quarter of all newborn deaths, however in the low-resources countries it could share amounts to 96% of all 1.15 million cases of HIE revealed in the world [20, 28, 34].

Sedation of neonates with HIE requiring mechanical ventilation is one of the debatable issues in neonatal intensive care. Conventionally, opiates or benzodiazepines are the pharmacologic agents most often used for treatment [6]. Questions remain regarding the efficacy, safety, and neurodevelopmental impact of these therapies. They possess certain advantages and disadvantages over each other, consequently, no ideal sedative agent for neonates has been established so far [7, 22].

Such pharmacological agent should provide mild to moderate depth of sedation with retaining a spontaneous breathing pattern, not having serious negative effect on the systematic hemodynamics as well as on blood, coagulation, metabolism, liver function, kidneys, etc. It may cause no long-term addiction in case of withdrawal and no neurodevelopmental retardation.

The negative impacts of standard pharmacologic agents suggest that alternative agents should be investigated. So, recently great attention has been paid to such sedative drugs as clonidine [27] and its derivate dexmedetomidine [21, 26].

Dexmedetomidine is an α2-adrenoceptor agonist, clonidine derivate, with sedative, anxiolytic, sympatholytic, and analgesic-sparing effects, and minimal depression of respiratory function. Compared with clonidine, α_2-agonist that has been used for several decades, dexmedetomidine has a greater selectivity for α_2-receptors. As central α1-adrenoceptor activation counteracts the sedative α_2 effects, dexmedetomidine is a more potent sedative than clonidine.

Dexmedetomidine exerts its hypnotic action through activation of central pre- and postsynaptic α_2-receptors in the locus coeruleus, thereby inducting a state of unconsciousness similar to natural sleep, with the unique aspect that patients remain at mild sedation level. This aspect, combined with the minimal influence on respiration, makes dexmedetomidine an interesting alternative sedative in long-term ventilated patients.

The impact on the cardiovascular system depends on the dose; in case of lower rates of infusion the central action prevails, which leads to the decrease in heart rate and arterial pressure. At higher doses peripheral vessel-constricting effects prevail, it leads to the increase in the systemic vessel resistance and arterial pressure whilst the bradycardic effect becomes manifested [40].

The evidences of the efficacy and safety of using of dexmedetomidine in adults has been obtained in some multicenter controlled studies [39]. The data on newborns (28-44 weeks of gestation) have been limited so far and administration of dexmedetomidine is considered mainly in low doses (≤0.5 mcg/kg/h) [32, 33].

No significant pharmacokinetic difference depending on the gender and age of patients was revealed. Newborn babies can be more sensitive to bradycardic effects of dexmedetomidine at therapeutic hypothermia and in clinical conditions when the heart rate depends on the cardiac output [16, 41]. However according to the data of the clinical observations, the episodes of bradycardia were registered in neonates more seldom compared to the pediatric population, but the children required higher doses of dexmedetomidine, therefore bradycardic side effect is dose-dependent [11].

To date there are no age-based contraindications to the administration of dexmedetomidine, and the experience

of it using demonstrate the dexmedetomidine to be the safe and effective sedation agent of both term and preterm neonates, it is well endured and possesses no severe side effects [8].

Moreover in recent years, additional experimental information on relatively neuro-protective features of dexmedetomidine has been accumulated in researches on animals, including at the expense of slowing apoptosis of neurons [10, 25, 38, 42, 44].

The objective is to determine the impact of dexmedetomidine and other sedatives on the cerebral blood flow and outcomes of hypoxic-ischemic encephalopathy in term neonates.

Material and Methods

Single-center, prospective, randomized controlled study was performed in 205 full-term infants with HIE treated in neonatal intensive care unit (NICU) level III of Dnipro Regional Children's Hospital (Ukraine) in the period of 2012-2017.

Inclusion criteria: gestational age 37 to 42 weeks, term infants with the present at admission signs and symptoms of moderate to severe HIE by Sarnat score (in Hill A., Volpe J.J. modification, 1994) during the first 72 hours of life.

Exclusion criteria: gestational age less than 37 weeks, infants aged over 72 hours of life, birth trauma, congenital malformations, early onset neonatal sepsis.

All the babies were treated by mild therapeutic hypothermia 33-35 °C for 72 hours, assisted positive-pressure ventilation under routine control of acid-base balance, monitoring of SpO_2 and $etCO_2$, control of systemic hemodynamics (heart rate, mean blood pressure (MBP), cardiac output). Cerebral hemodynamic evaluated by non-invasive method based on conventional ultrasound Doppler transfontanel measurement of blood flow in the front cerebral artery with estimation of systolic (Vs), diastolic (Vd), mean velocity (Vm) and calculation of Pourcelot Resistive Index (RI) and Gosling Pulsatility Index (PI) using ultrasound SonoSite Titan (USA) with microconvex probe 5-8 MHz [31]. RI – resistance index of brain arteries by Pourcelot (Pourcelot Resistive Index) [17, 43] according to the equation:

$RI = (Vs - Vd) / Vs$

PI – pulsation index of blood flow by Gosling (Gosling Pulsatility Index) [12] according to the equation:

$PI = (Vs - Vd) / Vm,$

$Vm = (Vs + 2 \cdot Vd) / 3$

Cerebral regional tissue oxygenation index ($rScO_2$) by INVOS™ 5100C Cerebral Oximeter (Somanetics, Medtronic, USA) was monitored during all the 72 hours period of therapeutic hypothermia [2]. The targeted reference range of rScO2 was considered within 60-80% [29].

Continuous monitoring of amplitude integrated electroencephalography (aEEG) had been carried out for 72 hours with the application of the diagnostics complex Neuron-Spectrum, “Neurosoft” (Russia).

In addition to the routine lab studies and monitoring the serum concentrations of biomarkers neuron-specific enolase (NSE) and protein S-100 were obtained at Day 1 and Day 3 of intensive care. Serum levels of the neuron-specific enolase (NSE) and protein S-100 were determined by the immune-chemical method with electrochemical luminescent detection (ECLIA, Synevo Laboratory, GCLP 2011, ISO 9001:2000).

The referent range according to the standards of the laboratory was considered for NSE up to 16.3 ng/ml, for protein S-100 up to 0.105 mcg/l. According to Simon-Pimmel J. et al. (2017), in neonates and infants up to 1 month old the upper limit of protein S-100 is <0.51 mcg/l, although according to Abbasoglu A. et al. (2015) the normal value of NSE concentration in term healthy neonates is 18.06±12.83 ng/ml (95% CI 13.94-22.19 ng/ml) [5, 9].

Using simple open randomization all the babies were divided into group of dexmedetomidine (DEX group, n=46) and the control group of standard sedation (n=159). Infants of DEX group received dexmedetomidine in dose of 0.5 mcg/kg/hour via continuous infusion. Neonates of control group received morphine (n=71) in loading dose 50 mcg/kg over 30 min infusion continuing by maintain dose 10-40 mcg/kg/hour, and sodium

oxybutiras (n=78) in dose of 50-100 mg/kg or/and diazepam (n=29) dosing 0.05-0.1 mg/kg every 4-6 hours if needed, or their combinations.

The end-points included: total days of the respiratory support including invasive and non-invasive ventilation; total days in NICU, and the rate of unfavorable outcome as cerebral leukomalacia.

The diagnosis of cerebral leukomalacia was based on the routine daily neurosonography screening; in case of ultrasound signs of leukomalacia the diagnosis was confirmed by CT/MRI scanning.

The statistics analysis of the study data was done using software JASP 0.9.0.1 (Amsterdam, The Netherlands, 2018) in accordance with the generally accepted standards of the mathematical statistics. Before the statistical analysis all the data had been examined for normal distribution using Shapiro-Wilk W-test.

For nonparametric data the initial statistical analysis included the calculation of the median M, 25% and 75% percentiles. For the statistical comparison of the values in the studied groups Mann-Whitney U-test was performed. Confidential interval (CI), hazard ratio (HR) and expected value (EV) were also calculated in appropriated manner. The p-value <0.05 was accepted as significant in all tests.

Results

The results of treatment of 205 term neonates was analyzed, the average gestation age in weeks was 39.6±1.4 (37-42); birth weight in grams was 3583±554 (2440-5300). By gender: 128 neonates (62.4%) were boys, and 77 (37.6%) were girls.

All the infants were transferred to the NICU from tertiary hospitals level II. 56 babies (27.4%) were admitted to the NICU in 0-6 hours after delivery, in 6-24 hours – 144 (70.2%), 24-72 hours – 5 (2.4%). 28-day mortality was 3 of 205 babies (1.46%).

First delivery occurred in 82 cases (40%), and 123 (60%) were subsequent. The rate of caesarean sections was 42 of 205 infants (20.5%). From 42 neonates born with Caesarean section 17 (40.5%) were first born and 25 (59.5%) with subsequent deliveries (p=0.994). The Apgar score at 1st minute was 4.04±2.27 points; at 5th minute 5.88±1.82 points; at 20th minute (estimated only in 56 babies) 6.29±1.19 points. Serum lactate level at admission was 7.93±5.44 [0.9-25.1] mmol/l (normal range 0.9-2.7 mmol/l).

Demographic data of the dexmedetomidine group and the control group at the baseline is presented in Table 1.

	Control group, n=159	DEX group, n=46	P
Gestation, weeks (M±SD [min-max])	39.6±1.5 [36-42]	39.6±1.2 [36-42]	0.852
Birth weight, kg (M±SD [min-max])	3.5±0.5 [2.4-5.3]	3.7±0.6 [2.8-4.8]	0.097
Boys, n (%)	95 (59.8%)	34 (73.9%)	0.080
Girls, n (%)	64 (40.2%)	12 (26.1%)	0.080
Admission 0-6 hours, n (%)	41 (25.8%)	15 (32.6%)	0.360
Admission 6-24 hours, n (%)	113 (71.1%)	31 (67.4%)	0.631
Admission 24-72 hours, n (%)	5 (3.1%)	0	N/A
1st delivery, n (%)	67 (42.1%)	24 (52.2%)	0.228
>1 delivery, n (%)	92 (57.9%)	22 (47.8%)	0.228
C-section, n (%)	32 (20.1%)	9 (19.6%)	0.933
C-section, 1st delivery, n (%)	12 (17.9)	6 (25)	0.454
C-section, >1st delivery, n (%)	20 (21.7)	3 (13.6)	0.395
Apgar, 1st min. (M±SD [min-max])	3.9±2.3 [0-9]	4.5±2.1 [1-8]	0.125
Apgar, 5th min. (M±SD [min-max])	5.8±1.9 [1-9]	6.3±1.7 [2-8]	0.107
Apgar, 20th min (M±SD [min-max])	6.2±1.1 [5-8]	6.5±1.1 [5-8]	0.614
Lactate, mmol/l (M±SD [min-max])	8.5±5.6 [0.9-25.1]	5.2±3.7 [1.0-15.6]	0.019
pH (M±SD [min-max])	7.38±0.1 [7.14-7.69]	7.42±0.1 [7.23-7.73]	0.035

Table 1. Demographic data of studied groups at the baseline.

Basing on data of Table 1, there was no statistically significant differences between groups in birth weight, sex, and time of admission, proportion of 1st delivery, caesarian section rate and Apgar score at birth. pH was significantly but slightly differ between the groups (7.38±0.1 vs. 7.42±0.1, p=0.035). The serum lactate level was significantly lower in the DEX group (8.5±5.6 vs. 5.2±3.7, p=0.019), but it was noticeably higher over normal range in both groups. The comparative statistics of the dexmedetomidine group and the control group is presented in Table 2. There was no significant difference between the studied groups in indices RI and PI on the 1st day

(p=0.944 and p=0.671 respectively) and on the 3rd day of treatment (p=0.923 and p=0.385 respectively).

	Control group, n=159	DEX group, n=46	P
	Median [25%-75%]		
$rScO_2$ on Day 1, %	79 [68-85]	65 [50-73]	0.012
$rScO_2$ on Day 2, %	81 [73-93]	74 [67-86]	0.035
MBP, mmHg	53 [46-60]	58 [51-65]	<0.001
Seizures on Day 1, n (%)	77 (48.3%)	2 (4.3%)	<0.001
Extubation (days)	5 [4-8]	5 [4-6]	0.022
Cerebral leukomalacia, n (%)	24 (15.1%)	1 (2.2%)	0.018

Table 2. Comparison of the intermediate characteristics and short term outcomes of treatment for term neonates with HIE using of dexmedetomidine versus the control group of sedative agents. *n - number of neonates in each group; in [] - interquartile range; p - statistical significance of a result; $rScO_2$ – regional mixed cerebral oxygen saturation; MBP – mean blood pressure.*

Similarly, as to NSE and S-100 level there were no difference on the Day 1 (p=0.524 and p=0.572 respectively) and Day 3 (p=0.384 and p=0.353 respectively). It confirms that the severity of the brain damage and the preservation of autoregulation for cerebral blood flow were comparable in both groups, and newborns from two groups were comparable by the degree of hypoxic-ischemic encephalopathy.

No reliable difference was revealed between the DEX group and the control group in total days of the respiratory support (p=0.071) and total days in NICU (p=0.362). But the terms of extubation were significantly different (p=0.022). Prospective data hints that DEX patients were significantly more often extubated during 7 days comparing to control group (68% vs. 33% with log-rank p-value of 0.018). Retrospective dataset shows no difference. Pooled analysis reduces the difference slightly but the difference 68% vs. 42% was statistically significant (p=0.011), with hazard ratio of 0.48 which is interpreted that after DEX treatment neonates were 52% less likely to be still intubated at Day 7 (95% CI 0.27-0.86, Cox's regression 0.013). NIRS data of $rScO_2$ was reliably different between the groups on the 1st day (65% vs. 79%, p=0.012) and on the 2nd day of treatment (74% vs. 81%, p=0.035), but the same was not observed on the 3rd day of the study (p=0.600). The data analysis revealed significantly differ level of mean blood pressure between both groups. MBP was higher in the DEX group (p<0.001), at the same time infants from DEX group demanded lower doses of dobutamine (EV -1.87; 95% CI -3.25 to -0.48, p=0.009). A significantly lower rate of seizures was revealed in DEX group on Day 1 comparing to control group (p<0.001). And the most essential finding is that the rate of unfavorable outcome as cerebral leukomalacia was also lower in the DEX group in comparison with the control group (2.2% vs. 15.1%, p=0.018).

Discussion

Dexmedetomidine appeared to be well-tolerated in neonates with HIE requiring therapeutic hypothermia. No adverse effects of dexmedetomidine as hypotension or bradycardia were experienced during the study, its infusion rate was not changed during this time. The most probable explanation is the administration of dexmedetomidine in dose not exceeding 0.5 mcg/kg/hour, which matches the results of Estkowski L.M., et al. (2015), who registered the episodes of bradycardia in the range of doses over 0.6 mcg/kg/hour [11]. Because dexmedetomidine does not have significant effects on respiratory drive, it may present a good sedation option in babies requiring therapeutic hypothermia to preserve their spontaneous breathing pattern.

Considering earlier extubation of trachea, the advantage of dexmedetomidine over other sedative agents has been confirmed by the data of O'Mara K., Weiss M.D. (2018) [23].

Data of the NIRS monitoring for cerebral oximetry looks quite remarkable and demonstrated the reliably lower rScO2 indices in the dexmedetomidine group compared to the control group. However the interpretation of the data makes possible to state that in the DEX group $rScO_2$

index remained within the normal reference range of 60-80% [30], while in the control group this index insignificantly exceeded the upper limit of the conditionally normal values. It is important to notice that mixed blood saturation $rScO_2$ supposes the estimation of the balance between oxygen supply and consumption by the brain. If the decrease in $rScO_2$ <40% testifies to the condition of severe hypoxia-ischemia, then rather high value of $rScO_2$ >80% according to Sood B., et al. (2015), Hyttel-Sorensen S., et al. (2017), Garvey A., et al. (2018) and Herold F., et al. (2018) means the decrease in the consumption of oxygen and metabolic slowdown, and the value of $rScO_2$ >90% is the evidence of the deep metabolism inhibition, stop in oxygen consumption by the brain tissue. Although this interpretation cannot be absolutely fair for the period of therapeutic hypothermia, when the metabolism of the brain is slowed down on purpose and under control [13, 14, 15]. Therefore nowadays the cerebral oximetry in the near-infrared spectrum according to Van Meurs K. and Bonifaci S. (2017) becomes essential as a component of the required neuroresuscitation monitoring [37].

The reliability of the influence of dexmedetomidine on the rate of unfavorable outcome of HIE as cerebral leukomalacia, and the reliably of a smaller percent of neonates with seizures during the acute period of HIE in comparison with the control group, requires further investigations, but the results match with the data of the experimental works by Endesfelder S., et al. (2017) and Kurosawa A., et al. (2017) on neuroprotective features of dexmedetomidine [10, 18].

Conclusion

1. Dexmedetomidine is a safe sedative agent with a stable hemodynamics profile, no adverse cerebral influence and possible neuroprotective effects in term infants with HIE, additional to standard therapeutic hypothermia.
2. The determined peculiarities make possible to use dexmedetomidine in the daily practice of the neonatal intensive care, but additional data needs to be collected before any further conclusions can be drawn.

Compliance with Ethical Standards

The study was approved by Biomedical Ethical Commission of the Regional Children's Hospital, Dnipro, Ukraine. Protocol #5, 2011 Feb 21.

Disclosure

The author has no conflict of interest to declare.

Grant Acknowledgment

NSE and protein S-100 lab evaluation was granted by Orion Corporation

References

1. Tkachik SJ. [Forecasting and preventive maintenance perinatal pathologies at anomalies patrimonial activity]. Health of Woman 2016;4:168-170.
2. Abbasoglu A, Sarialioglu F, Yazici N, Bayraktar N, Haberal A, Erbay A. Serum neuron-specific enolase levels in preterm and term newborns and in infants 1-3 months of age. Pediatrics and Neonatology 2015;56:114-119.
3. Allanson E, Tunçalp Ö, Gardosi J, Pattinson RC, Erwich JJ, Flenady VJ, et al. Classifying the causes of perinatal death. Bull World Health Organ 2016;94:79–79A.
4. Arnaez J, García-Alix A, Arca G, Valverde E, Caserío S, Moral MT, et al; Grupo de Trabajo EHI-ESP. Incidence of hypoxic-ischaemic encephalopathy and use of therapeutic hypothermia in Spain. An Pediatr (Barc) 2018;89:12-23.
5. Baik N, Urlesberger B, Schwaberger B, Schmölzer GM, Mileder L, Avian A, Pichler G. Reference ranges for cerebral tissue oxygen saturation index in

term neonates during immediate neonatal transition after birth. Neonatology 2015;108:283-286.

6. Borenstein-Levin L, Synnes A, Grunau RE, Miller SP, Yoon EW, Shah PS. Narcotics and sedative use in preterm neonates. J Pediatr 2017;180:92-98.e1.
7. Carbajal R, Eriksson M, Courtois E, Boyle E, Avila-Alvarez A, Andersen RD, et al; EUROPAIN Survey Working Group. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. Lancet Respir Med 2015;3:796-812.
8. Chrysostomou C, Schulman SR, Herrera Castellanos M, Cofer BE, Mitra S, da Rocha MG, et al. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. J Pediatr 2014;164:276-282.e1-3.
9. Dix LM, van Bel F, Lemmers PM. Monitoring cerebral oxygenation in neonates: an update. Front Pediatr 2017;5:46.
10. Endesfelder S, Makki H, von Haefen C, Spies CD, Bührer C, Sifringer M. Neuroprotective effects of dexmedetomidine against hyperoxia-induced injury in the developing rat brain. PLoS One 2017;12:e0171498.
11. Estkowski LM, Morris JL, Sinclair EA. Characterization of dexmedetomidine dosing and safety in neonates and infants. J Pediatr Pharmacol Ther 2015;20:112-118.
12. Forster DE, Koumoundouros E, Saxton V, Fedai G, Holberton J. Cerebral blood flow velocities and cerebrovascular resistance in normal-term neonates in the first 72 hours. J Paediatr Child Health 2018;54:61-68.
13. Garvey AA, Kooi EM, Smith A, Dempsey EM. Interpretation of cerebral oxygenation changes in the preterm infant. Children (Basel) 2018;5. pii:E94.
14. Herold F, Wiegel P, Scholkmann F, Müller NG. Applications of functional near-infrared spectroscopy (fNIRS) neuroimaging in exercise-cognition science: a systematic, methodology-focused review. J Clin Med. 2018;7. pii:E466.
15. Hyttel-Sorensen S, Pellicer A, Alderliesten T, Austin T, van Bel F, Benders M, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. BMJ 2015;350:g7635.
16. Ibrahim M, Jones LJ, Lai N, Tan K. Dexmedetomidine for analgesia and sedation in newborn infants receiving mechanical ventilation (Protocol). Cochrane Database Syst Rev 2016;9:CD012361.
17. Kumar AS, Chandrasekaran A, Asokan R, Gopinathan K. Prognostic value of resistive index in neonates with hypoxic ischemic encephalopathy. Indian Pediatr 2016;53:1079-1082.
18. Kurosawa A, Sato Y, Sasakawa T, Kunisawa T, Iwasaki H. Dexmedetomidine inhibits epileptiform activity in rat hippocampal slices. Int J Clin Exp Med 2017;10:6704-6711.
19. Lee AC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatr Res 2013;74:50-72.
20. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-2013, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385:430-440.
21. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. BJA 2015;115:171-182.
22. Mayock DE, Gleason CA. Pain and sedation in the NICU. NeoReviews 2013;14;e22-e31.
23. O'Mara K, Weiss MD. Dexmedetomidine for sedation of neonates with HIE undergoing therapeutic hypothermia: a single-center experience. AJP Rep 2018;8:e168-e173.

24. Parikh P, Juul SE. Neuroprotective strategies in neonatal brain injury. The Journal of Pediatrics 2018;192:22-32.
25. Perez-Zoghbi JF, Zhu W, Grafe MR, Brambrink AM. Dexmedetomidine-mediated neuroprotection against sevoflurane-induced neurotoxicity extends to several brain regions in neonatal rats. BJA 2017;119:506–516.
26. Pullen LC. Dexmedetomidine effective sedative for neonates [Internet]. 2013 [cited 2019 Feb 19]. Available from: https://www.medscape.com/viewarticle/818075.
27. Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for sedation and analgesia for neonates receiving mechanical ventilation. Cochrane Database Syst Rev 2017;5:CD012468.
28. Simiyu IN, Mchaile DN, Katsongeri K, Philemon RN, Msuya SE. Prevalence, severity and early outcomes of hypoxic ischemic encephalopathy among newborns at a tertiary hospital, in northern Tanzania. BMC Pediatr. 2017;17:131.
29. Simon-Pimmel J, Lorton F, Masson D, Bouvier D, Hanf M, Gras-Le Guen C. Reference ranges for serum S100B neuroprotein specific to infants under four months of age. Clinical Biochemistry 2017;50:1056-1060.
30. Sood BG, McLaughlin K, Cortez J. Near-infrared spectroscopy: applications in neonates. Semin Fetal Neonatal Med 2015;20:164-72.
31. Sorokan ST, Jefferies AL, Miller SP, Canadian Paediatric Society, Fetus and Newborn Committee. Imaging the term neonatal brain. Paediatr Child Health 2018;23:322–328.
32. Su F, Gastonguay MR, Nicolson SC, DiLiberto M, Ocampo-Pelland A, Zuppa AF. Dexmedetomidine pharmacology in neonates and infants after open heart surgery. Anesth Analg 2016;122:1556-1566.
33. Su F, Nicolson SC, Zuppa AF. A dose-response study of dexmedetomidine administered as the primary sedative in infants following open heart surgery. Pediatr Crit Care Med 2013;14:499-507.
34. Tagin M, Abdel-Hady H, Rahman S, Azzopardi DV, Gunn AJ. Neuroprotection for perinatal hypoxic ischemic encephalopathy in low- and middle-income countries. Journal of Pediatrics 2015;167:25–28.
35. Torbenson VE, Tolcher MC, Nesbitt KM, Colby CE, EL-Nashar SA, Gostout BS, et al. Intrapartum factors associated with neonatal hypoxic ischemic encephalopathy: a case-controlled study. BMC Pregnancy Childbirth 2017;17:415-422.
36. UNICEF. Neonatal mortality [Internet]. 2018 [cited 2019 Jan 31]. Available from: https://data.unicef.org/topic/child-survival/neonatal-mortality/
37. Van Meurs KP, Bonifacio SL. Brain-focused care in the neonatal intensive care unit: the time has come. J Pediatr 2017;93:439-441.
38. Wang Y, Han R, Zuo Z. Dexmedetomidine-induced neuroprotection: is it translational? Transl Perioper Pain Med 2016;1:15-19.
39. Weatherall M, Aantaa R, Conti G, Garratt C, Pohjanjousi P, Lewis MA, et al. A multinational, drug utilization study to investigate the use of dexmedetomidine (Dexdor®) in clinical practice in the EU. Br J Clin Pharmacol 2017;83:2066-2076.
40. Weerink MA, Struys MM, Hannivoort LN, Barends CR, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet 2017;56:893-913.
41. Wenhao W. Model-based evaluation of dose regimens in preterm and term neonates for dexmedetomidine and vancomycin. Digitala Vetenskapliga Arkivet [Internet], 2017 Available from: http://www.diva-portal.org/smash/record.jsf?pid=diva2%3A1140628&dswid=1932.
42. Wu J, Vogel T, Gao X, Lin B, Kulwin C, Chen J. Neuroprotective effect of dexmedetomidine in a murine model of traumatic brain injury. Scientific Reports 2018;8:4935.

43. Zamora CA, Oshmyansky A, Bembea M, Berkowitz I, Alqahtani E, Liu S, et al. Resistive index variability in anterior cerebral artery measurements during daily transcranial duplex sonography. J Ultrasound Med 2016;35:2459-2465.
44. Zhang MH, Zhou XM, Cui JZ, Wang KJ, Feng Y, Zhang HA. Neuroprotective effects of dexmedetomidine on traumatic brain injury: Involvement of neuronal apoptosis and HSP70 expression. Mol Med Rep 2018;17:8079-8086.