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**USING OF DEXMEDETO MIDINE IN TERM NEONATES WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY**

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**Ключові слова:** гіпоксія, ішемія, енцефалопатія, дексмедетомідин, новонароджені, искусственная вентиляция легких

**Abstract.** Using of dexmedetomidine in term neonates with hypoxic-ischemic encephalopathy. Surkov D. 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 aim – to determine the impact of dexmedetomidine and other sedatives on the cerebral blood flow and outcomes of hypoxic-ischemic encephalopathy in term neonates. Data of 205 term infants with hypoxic-ischemic encephalopathy by Sarnat scale stage II-III were collected during ≤72 hours of life. The infants were divided using a simple open randomization by pharmacological sedative agents during mechanical ventilation into dexmedetomidine group (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. A significant difference between groups in days of trachea extubation (p=0.022) was found; the chance for babies to be extubated before the 7th day 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 rScO2 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 such 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). Dexmedetomidine is a safe sedative agent with a stable hemodynamic profile, without adverse influence on cerebral perfusion and possible neuroprotective effects in term infants with HIE, as addition to standard therapeutic hypothermia.

**Résumé.** Utilisation de la dexmedétomidine en néonatologie hypoxico-ischémique. Surkov D. L’impact négatif des agents de séduction standard en pharmacologie suggère qu’il est nécessaire d’investiguer d’autres agents. La dexmedétomidine pourrait être une nouvelle option pour la séduction des nouveau-nés hypoxico-ischémiques nécessitant une ventilation mécanique. L’objectif de cette étude est de déterminer l’impact de la dexmedétomidine et d’autres agents de séduction sur le flux sanguin cérébral et les résultats de l’encephalopathie hypoxico-ischémique en néonatologie. Les données de 205 nouveau-nés de terme avec une encephalopathie hypoxico-ischémique selon l’échelle de Sarnat II-III ont été recueillies dans les 72 premières heures de vie. Les nouveau-nés ont été répartis selon un simple tirage au sort en utilisant des agents de séduction pharmacologiques durant la ventilation mécanique entre le groupe dexmedétomidine (n=46) et le groupe contrôle (n=159), qui incluaient de la morphine, de l’oxybuteurate de sodium et du diazépam dans des doses recommandées. Une analyse comparative a été effectuée de l’effet de la dexmedétomidine et d’autres agents sur le flux sanguin cérébral et les résultats de l’encephalopathie hypoxico-ischémique. On a démontré une différence significative entre les groupes en termes de temps de déstraction trachéale (p=0.022); les chances pour les nouveau-nés de ne pas être déstrachés avant le 7e jour de traitement étaient significativement plus élevées dans le groupe dexmedétomidine à 68% versus 33% dans le groupe contrôle (p=0.018) avec un rapport de risque (HR) de 0.48 (CI 95% 0.27-0.86, p=0.011). De plus, l’indice NIRS rScO2 a différencié significativement entre les groupes sur la 1ère journée de traitement (65% versus 79%, p=0.012) et sur la 2ème journée de traitement (74% versus 81%, p=0.035). La pression artérielle moyenne était plus élevée dans le groupe dexmedétomidine comparée au groupe contrôle – (58 [51-65] mm Hg versus 53 [46-60] mm Hg, p<0.001), avec une dose plus basse de dobutamine (EV -1.87, CI 95% de -3.25 à -0.48, p=0.009). Dans le groupe dexmedétomidine, le taux de crises était significativement plus bas sur la 1ère journée d’observation (4.3% versus 48.3%, p <0.001); l’incidence de résultats défavorables tels que la leukomalacie cérébrale était aussi 7 fois plus basse dans le groupe dexmedétomidine comparée au groupe contrôle (2.2% versus 15.1%, p=0.018). La dexmedétomidine est un agent de séduction sûr avec un profil hémodynamique stable, sans influence adverse sur le flux sanguin cérébral et des effets neuroprotecteurs possibles en nouveau-nés avec HIE, en plus de la thérapie standard hypothermique.
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 [6, 41]. In the United States and most technologically developed countries of the world the frequency of HIE according to different authors varies from 1.5-4 to 1-8 cases per 1,000 childbirths [8, 18, 19]. HIE morbidity is much higher in resource-limited settings and can reach as many as 26 cases per 1,000 newborns [1, 29]. 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 [15, 24, 31].

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 [23]. Questions regarding the efficacy, safety, and neurodevelopmental impact of these therapies remain. They possess certain advantages and disadvantages over each other, consequently, no ideal sedative agent for neonates has been established so far [13, 22]. Such pharmacological agent should provide mild to moderate depth of sedation with retaining a spontaneous breathing pattern, without serious negative effect on the systematic hemodynamics as well as on blood, coagulation, metabolism, liver function, kidneys, etc. It may cause neither long-term addiction in case of withdrawal nor 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 [37] and its derivate dexmedetomidine [21, 32].

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, an α2-agonist that has been used for several decades, dexmedetomidine has a greater selectivity for α2-receptors. As activation of central α1-adrenoceptors reduces sedative effects of α2 -receptors, dexmedetomidine is a more potent sedative than clonidine. Dexmedetomidine exerts its hypnotic action through activation of central pre- and postsynaptic α2-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 [7].

The evidences of the efficacy and safety of dexmedetomidine in adults have been obtained in some multi-center controlled studies [2]. 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) [10, 40]. 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 [17, 44]. 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 [12].

To date there are no age-based contraindications to the administration of dexmedetomidine, and the experience of its using shows dexmedetomidine to be a safe and effective sedation agent for both term...
and preterm neonates, it is well tolerated and possesses no severe side effects [3].

Moreover in recent years, additional experimental information on relatively neuro-protective features of dexmedetomidine has been accumulated in researches on animals, at the expense of apoptosis slowing down, including neurons [25, 26, 27, 30, 43].

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

MATERIALS AND METHODS OF RESEARCH

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 signs and symptoms of moderate to severe HIE by Sarnat score (in Hill A., Volpe J.J. modification, 1994) at admission 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 of 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 SpO2 and etCO2, control of systemic hemodynamics (heart rate, mean blood pressure (MBP), cardiac output). Cerebral hemodynamic was 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 [39].

RI – resistance index of brain arteries by Pourcelot (Pourcelot Resistive Index) [20, 36] according to the equation:

$$RI = \frac{(Vs - Vd)}{Vs}$$

PI – pulsation index of blood flow by Gosling (Gosling Pulsatility Index) [4] according to the equation:

$$PI = \frac{(Vs - Vd)}{Vm}$$

$$Vm = \frac{(Vs + 2 \cdot Vd)}{3}$$

Cerebral regional tissue oxygenation index (rScO2) by INVOS™ 5100C Cerebral Oximeter (Somanetics, Medtronic, USA) was monitored during the whole 72 hours’ period of therapeutic hypothermia [33]. The targeted reference range of rScO2 was considered within 60-80% [35].

Continuous monitoring of amplitude integrated electroencephalography (aEEG) had been carried out in 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 neuron-specific enolase biomarkers (NSE) and protein S-100 were obtained on day 1 and day 3 of intensive care. Serum levels of the neuron-specific enolase (NSE) and protein S-100 were determined by the immunochemical method with electrochemical luminescent detection (ECLIA, Synevo Laboratory, GCLP 2011, ISO 9001:2000). The referent range according to the standards of the laboratory for NSE up to 16.3 ng/ml was considered, 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) [11, 34].

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 (n=71) received morphine infusion in loading dose of 50 mcg/kg not earlier than 30 min followed by maintaining dose of 10-40 mcg/kg/hour, in monotherapy or in combination with sodium oxybutyrates (n=78) in dose of 50-100 mg/kg or/and diazepam (n=29) in dose of 0.05-0.1 mg/kg every 4-6 hours if needed.

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 study was approved by Biomedical Ethical Commission of the Dnipropetrovsk Medical Academy, Ukraine. Protocol N 5, 2011 Feb 21.

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 appropriate manner. The p-value <0.05 was accepted as significant in all tests.

RESULTS AND DISCUSSION

The results of treatment of 205 term neonates were 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, during 6-24 hours – 144 (70.2%), in the first 24-72 hours – 5 (2.4%) babies. 28 days’ 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.

| Table 1  |
|---|---|---|
| Demographic data of studied groups at the baseline | 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 (7.9%) | 6 (25) | 0.454 |
| C-section, >1st delivery, n (%) | 20 (13.7) | 3 (13.6) | 0.395 |
| Apgar, 1st min. (M±SD [min-max]) | 5.9±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 |

Basing on data of Table 1, there were 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 different 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 than normal range in both groups.

The comparative statistics of the dexmedetomidine group and the control group is presented in Table 2.
Comparison of the intermediate characteristics and short term outcomes of treatment of term neonates with HIE while using dexmedetomidine versus standard sedative agents

|                         | Control group n=159 | DEX group n=46 | P       |
|-------------------------|---------------------|---------------|---------|
| **rScO₂ on Day 1, %**   | 79 [68-85]          | 65 [50-73]    | 0.012   |
| **rScO₂ 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   |

**Note**: n – number of neonates in each group; in [ ] – interquartile range; p – statistical significance of a result; rScO₂ – regional mixed cerebral oxygen saturation; MBP – mean blood pressure.

There was no significant difference between the studied groups in indices RI and PI on day 1 (p=0.944 and p=0.671 respectively) and on day 3 of treatment (p=0.923 and p=0.385 respectively). Similarly, as to NSE and S-100 level there was no difference on 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 show 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 demonstrated slightyless difference but the difference of 68% vs. 42% was statistically significant (p=0.011), with hazard ratio of 0.48 which is interpreted that after DEX treatment 52% neonates were still intubated by day 7 (95% CI 0.27-0.86, Cox’s regression 0.013). NIRS data of rScO₂ were reliably different between the groups on day 1 (65% vs. 79%, p=0.012) and on day 2 of treatment (74% vs. 81%, p=0.035), but the same was not observed on day 3 of the study (p=0.600).

The data analysis revealed significantly differend 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 such as cerebral leukomalacia was also lower in the DEX group in comparison with the control group (2.2% vs. 15.1%, p=0.018).

Dexmedetomidine appeared to be well-tolerated in neonates with HIE requiring therapeutic hypothermia. No adverse effects of dexmedetomidine such 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 more than 0.6 mcg/kg/hour [12]. 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) [28].

Data of the NIRS monitoring for cerebral oximetry look quite remarkable and demonstrate the reliably lower rScO₂ indices in the dexmedetomidine group compared to the control group. However the interpretation of the data makes it possible to state that in the DEX group rScO₂ index remained within the normal reference range of 60-80% [38], 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 rScO₂ supposes the estimation of the balance between oxygen supply and consumption by the
brain. If the decrease in rScO2 <40% testifies to the condition of severe hypoxia-ischemia, then rather high value of rScO2 >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 rScO2 >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 [5, 14, 16]. 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 [42].

The reliability of the influence of dexmedetomidine on the rate of unfavorable outcome of HIE such 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 [9, 25].

CONCLUSIONS

5. Dexmedetomidine is a safe sedative agent with a stable hemodynamic profile, without adverse cerebral influence and possible neuroprotective effects in term infants with HIE, additional to standard therapeutic hypothermia.

6. The determined peculiarities make it 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.

Conflicts of interest. Author has no conflict of interest to declare.

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