come. *J. Pediatr. (Rio J.).* 2017. Vol. 93, N 5. P. 439-441. DOI: https://doi.org/10.1016/j.jped.2017.03.002

43. Wang Y., Han R., Zuo Z. Dexmedetomidine-induced neuroprotection: is it translational? Transl. *Perioper. Pain Med.* 2016. Vol. 1, N 4. P. 15-19. PMID: 28217717, PMCID: PMC5310645.

44. Wenhao W. Model-based evaluation of dose regimens in preterm and term neonates for dexmedetomidine and vancomycin. *Digitala Vetenskapliga Arkivet*. 2017. URL: http://www.diva-portal.org/smash/record.jsf?pid=-diva2%3A1140628&dswid=1932.

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MANAGEMENT OF PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS

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Ключові слова: *відкрита артеріальна протока, рестриктивна інфузійна терапія, інгибітори ЦОГ, недоношені новонароджені*
Ключевые слова: *открытый артериальный проток, рестриктивная инфузионная терапия, ингибиторы ЦОГ, недоношенные новорожденные*

Abstract. Management of patent ductus arteriosus in premature infants. Obolonskyi A., Snisar V., Surkov D., Obolonska O., Kapustina O., Dereza K. *Closure of hemodynamically significant patent ductus arterios (HSPDA) is one of the most important questions in modern neonatal intensive care, especially for preterm babies. Long-term functioning of the hemodynamically significant arterial duct leads to a large number of complications in premature babies, such as: bronchopulmonary dysplasia, periventricular leucomalacia, intraventricular hemorrhage, retinopathy of the premature. To prevent all these complications, the PDA should be closed pharmacologically or surgically as soon as possible without any hesitation. COX inhibitors are commonly used nowa days. Ibuprofen and indomethacin show the equal efficacy and no significant adverse events. But some patients still need surgical treatment. The aim of the study was to determine the feasibility, effectiveness and safety of using various volumes of infusion in combination*

with COX inhibitors and to determine its effect on the timing of the closure of PDA. 91 premature infants with a gestational age of 26-31 weeks with manifestations of respiratory distress syndrome and HSPDA were studied retrospectively. Premies were divided into 2 groups. Research groups were representative as to gestational age, gender, and weight (1205.0±435.0 g). Therapy for PDA closure included the use of various volumes of restrictive or liberal infusion therapy (from 50 to 100 ml/kg/day) and COX inhibitors (indomethacin, ibuprofen). The volume of infusion therapy was limited in the first group. Preemies received 53.5±6.4 ml/kg/day on DOL1 and 2. From the third day urine excretion increased and the volume of infusion therapy also raised to 63.6±5.6 ml/kg/day, and on day 5 – to 89.7±6.8 ml/kg/day. In the second group there was no strict limitation of the volume of infusion therapy (especially in the first 5 days). Delayed period of PDA closure (on average from 14.55±0.56 DOL) was associated with absence of limitation of the infusion volume. In the first group, volume of infusion therapy was restricted in the first 5 days, and the closure of the ductus arteriosus occurred extremely early (on 2.35±0.48 DOL). COX inhibitors were prescribed according to the standard scheme: in the first 3 days indomethacin was administered orally in doses of 0.2/0.1/0.1 mg/kg/day. If the premature baby had symptoms of intestinal paresis (this restricted oral administration of indomethacin), ibuprofen was prescribed in a three-day course in doses of 10/5/5 mg/kg/day intravenously or 20/10/10 mg/kg/day in rectal form. In all groups, standard PDA closure therapy was used. In the more remote periods (14 and 28 days), there was no fundamental difference in the volume of infusion in all groups. For early PDA closure limitation of infusion therapy in the first 3-5 days in combination with COX is principle.

Реферат. Терапія відкритої артеріальної протоки в недоношених новонароджених. Оболонський О.І., Снісар В.І., Сурков Д.М., Оболонська О.Ю., Капустіна О.Г., Дереза К.О. *Тривале функціонування гемодинамічно значущої відкритої артеріальної протоки (ГЗВАП) призводить до великої кількості ускладнень у недоношених дітей, таких як: бронхолегенева дисплазія, перивентрикулярна лейкомаляція, внутрішньошлуночкові крововиливи, ретинопатія новонародженого. Щоб запобігти всім цим ускладненням, ГЗВАП необхідно закрити фармакологічно або хірургічно протягом перших трьох днів, якщо це можливо. Закриття гемодинамічно значущої відкритої артеріальної протоки є одним з найважливіших питань інтенсивної терапії новонароджених, особливо для недоношених дітей. Інгібітори ЦОГ зазвичай використовуються на цей час для медикаментозного закриття протоки. Ібупрофен й індометацин показують рівну ефективність, менше побічних ефектів при використанні ібупрофену. Метою дослідження було визначити доцільність, ефективність і безпеку використання різних обсягів інфузії в комбінації з інгібіторами ЦОГ і визначити вплив на терміни закриття ГЗВАП. Ретроспективно було вивчено 91 недоношену дитину з гестаційним віком 26-31 тижнів, прояви респіраторного дистрес-синдрому, ГЗВАП, які лікувалися в реанімаційному відділенні. Дослідницькі групи були репрезентативними щодо гестаційного віку, статі та ваги (1205,0±435,0 г). Терапія для закриття КПК включала застосування різних обсягів рестриктивної або ліберальної інфузійної терапії (від 50 до 100 мл/кг/добу) та інгібіторів ЦОГ (індометацин, ібупрофен). Обсяг інфузійної терапії був обмежений у першій групі. Недоношені новонароджені отримали 53,5±6,4 мл/кг/день на 1 та 2 добу. З третього дня екскреція сечі збільшувалася, збільшувався об'єм інфузійної терапії до 63,6±5,6 мл/кг/день, а на 5 день збільшено до 89,7±6,8 мл/кг/добу. У другій групі, де застосовувалась ліберальна інфузійна терапія та не спостерігалося суворого дотримання обмеження обсягу інфузійної терапії (особливо в перші 5 днів), спостерігався відстрочений термін закриття ГЗВАП (у середньому з 14,55±0,56 доби). У першій групі, де обмеження обсягу інфузійної терапії дотримувалися більш чітко в перші 5 днів, закриття артеріальної протоки відбувалося рано (при 2,35±0,48 доби). Інгібітори ЦОГ призначались за стандартною схемою: в перші 3 дні індометацин вводять перорально в дозах 0,2/0,1/0,1 мг/кг/добу. Якщо в недоношеної дитини з'являлися симптоми парезу кишківника (це перешкоджало пероральному введенню індометацину), тоді ібупрофен призначався в триденному курсі в дозах 10/5/5 мг/кг/добу внутрішньовенно або 20/10/10 мг/кг/добу в ректальній формі. У всіх означених групах застосовували стандартну терапію закриття ГЗВАП. У більш віддалені періоди (14 і 28 днів) не було принципової різниці в обсязі інфузії у всіх групах, що говорить про те, що принцип раннього закриття КПК полягав у обмеженні інфузійної терапії в перші 3-5 днів на тлі стандартної терапії інгібіторами ЦОГ.*

One of the actual issues of modern neonatal medicine is the reduction of the negative influence of the patent ductus arteriosus (PDA) on morbidity and mortality in preterm infants. The hemodynamically significant PDA (HSPDA) has a great value on the development of periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), sepsis, retinopathy of prematurity (ROP), which leads to disability in preemies [6].

According to many authors, the time of PDA closure is also an independent factor affecting morbidity and mortality in preterm infants. In a number of publications, we substantiated and proved that delayed PDA closure (after day 3 of life), significantly increases the percentage of complications such as BPD, PVL, IVH, NEC, ROP [4].

As we have mentioned earlier [5], among the different ways of PDA management cyclooxygenase (COX) inhibitors, modes of infusion therapy,

diuretics play major role. Also it is important to reduce the negative impact of respiratory support (balanced approach to intubation, early extubation, the use of noninvasive ventilation).

Indomethacin and ibuprofen have been traditionally used as COX inhibitors. The possibility of using paracetamol for PDA closure is periodically being discussed [5, 9], but this way has not been widely accepted as for now. Comparative effectiveness of different COX inhibitors has been described in our resent publications [13]. The therapeutic value of COX inhibitors has no doubts, opposed to the restrictive infusion therapy in the maintance of the pharmacological PDA closure.

However, according to the Cohrane review, there is the so-called conservative therapy for the PDA closure, against which only the restriction of infusion therapy without COX inhibitors using is included [1, 6, 12]. Regarding the recommended volume of restrictive infusion therapy, the data vary significantly: from 100-130 ml/kg/day to 60-80 ml/kg/day in the first 3 DOL. The effectiveness of conservative therapy for the closure of hemodynamically significant PDA is 40-45% and therefore it is not accepted widely according to a number of authors [14]. Some authors believe that only the early surgical clumping of the duct is essential, but not the choice of COX inhibitor for PDA closure. The reduction of the infusion is often left unadressed [1, 3, 6, 7, 8, 10, 11]. Obviously, restrictive infusion therapy for treatment HPDA should be used in combination with COX inhibitors and is recommended by most authors and editions [1, 3, 6, 7, 8, 10, 11].

There also exists a theory that at present time there is a clear connection with the volume of infusion and the term of PDA closure. Taking into account the above, we have done a comprehensive research. We studied the impact of the termination of the PDA on morbidity and mortality in preterm infants and analyzed the effectiveness of various treatment options for PDA closure.

MATERIALS AND METHODS OF RESEARCH

Goal – the main purpose of the study was to establish the expediency, efficiency and safety of using different volumes of infusion in combination with COX inhibitors and to determine their effect on the timing of the HPDA closure.

Retrospective study of 91 preterm infants who received treatment in the intensive care unit of the Regional Children's Clinical Hospital in Dnipropetrovsk in 2012-2017 was carried out. Research groups were representative as for gestational age, gender and weight.

Criteria

Inclusion criteria: gestational age 26-31 weeks, manifestations of respiratory distress syndrome (RDS), HPDA.

Exclusion criteria: IVH grade 3-4, congenital malformation, early onset of neonatal sepsis.

Premature infants were admitted to the NICU on DOL 1-2. The doplerographic echocardiography has been performed during the first day of staying at the NICU. 100% of preemies had an open ductus arteriosus. All examined preterm infants in all groups had manifestations of acute respiratory distress syndrome and they were given artificial ventilation of lungs with different settings. After extubation, noninvasive respiratory support was used to complete the transition to spontaneous respiration.

Methods

Systemic and cerebral hemodynamics were assessed with ultrasound examination methods (doplerographic echocardiography, cranial ultrasound with doplerography) and clinically. All preterm infants included in the study were examined in seven stages. The first stage: observation immediately after admission to the NICU of the Regional Children's Clinical Hospital in Dnipropetrovsk. The second stage: a 3 day course of the therapy. Subsequent stages were in dynamics on day 5, 7, 14 and 28 of therapy respectively.

There were 54 (59.3%) boys, 37 (40.6%) girls. Weight at birth was 1205.0±435.0 grams on average. The all preterm infants who were admitted to the NICU were in severe condition. The main problems were respiratory distress syndrome, patent ductus arteriosus, which conditioned the need for respiratory and inotropic support.

All preterm infants received restrictive infusion therapy of varying degrees, along with COX inhibitors for the PDA closure. It has been noted that the arterial duct is closed at different times.

Depending on the term of PDA closure, preemies were retrospectively divided into two groups:

The first study group – an early closure of the arterial duct (in the first 3 days) – 40 preemies (67%). The preterm infants had gestational age of 29.0±1.5weeks, weight – 1222.2±356.0 grams in average. In the first group there were 27 (67.5%) boys, 13 (32.5%) girls.

The diameter of the PDA was 2.8±0.7 mm on the first examination in the NICU.

The second study group – 20 preterm infants (33%). Preemies had gestational age of 28.6±2.2 weeks, and weight – 1218.5±356.0 grams on average. In the second group there were 9 (45%) boys and 11 (55%) girls. The diameter of the PDA was 3.0±0.3 mm on the first examination in the NICU. In the second group arterial duct was closed in a delayed time (more than 4 days) pharmacologically or by surgical clumping.

There was no significant difference in sex between the groups. There was no principal difference between the groups in patient's weight.

The statistical processing of the research materials was carried out using the biostatistics methods implemented in the STATISTICA v.6.1 software package (StatsoftInc., USA) (license number AJAR909E415822FA).

The hypothesis about the normal law of distribution of indicators was verified according to the Kolmogorov-Smirnov criterion. Comparison of statistical characteristics in different groups and observation in dynamics was carried out using parametric and nonparametric criteria (taking into account the distribution law): verification of the equality of dispersions - according to the criteria of Fisher (F) and Leuven (LeveneTest); Estimation of probability of mean differences for unrelated samples – according to Student (t) and Mann-Whitney (U) criteria, for bound - according to Student (t) and Wilcoxon criteria (T); The probability of differences in relative indices is based on the criterion of the Hex-squared of Pearson (2). For the correlation between the signs, a correlation analysis was performed with the calculation of the Spirman rank correlation coefficients (r). The critical significance level of the statistical significance (p) was taken at ≤5% (p≤0.05).

The Therapy of PDA

The therapy of PDA closure included the use of different volumes of restrictive infusion therapy (from 50 to 100 ml/kg/day) in combination with COX inhibitors. Also dobutamine was prescribed in doses of 7.5-10 μg/kg/min intravenously. COX inhibitors were prescribed according to standard regimens: in the first 3 days - indomethacin orally in doses 0.2/0.1/0.1 mg/kg/day. If the preterm infant had symptoms of intestinal paresis (this prevented the oral administration of indomethacin), Ibuprofen was administered in a three-day course in doses of 10/5/5 mg/kg/day intravenously or in a rectal form at a dose of 20/10/10 mg/kg/day.

Thus, in all groups of preterm babies standard therapy was used for PDA closure.

RESULTS AND DISCUSSION

Volume of Infusion Therapy

The volume of infusion therapy was restricted in the first group. Preemies received 53.5±6.4 ml/kg/day on DOL1 and 2. From the third day urinary excretion increased, there was an increase in the amount of infusion therapy up to 63.6±5.6 ml/kg/day, and on day 5 it was raised to 89.7±6.8 ml/kg/day.

It should be noted that precisely with the application of this given limited amount of infusion therapy, we observed an early closure of the arterial duct in this group.

Comparing the first and second groups, it should be noted that in the second group there was no strict adherence to the restriction of the volume of infusion therapy (especially in the first 5 days), and we associated the delayed term for the PDA closure of arterial duct with that fact. In the first group the limit of the volume of infusion therapy was observed more clearly in the first 5 days, and we have the closure of the arterial duct exceptionally early. With regard to the volume of infusion therapy in a more distant terms (14 and 28 days), there were no fundamental differences in the volume of infusion in all groups, which suggests that the principle was the restriction of the infusion therapy in the first 5 days only (Fig. 1).

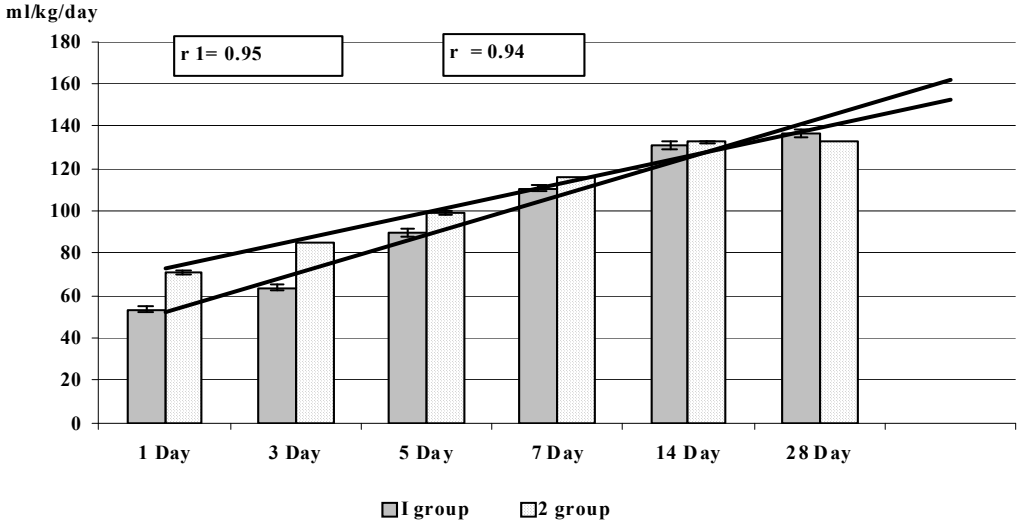

Fig. 1. The volume of infusion therapy in 1 and 2 groups at different times

According to our data, we can conclude that the term of PDA closure in preterm infants as much as possible depends on the restriction of infusion therapy on DOL 1 to DOL 5. The recommended volume of infusion on the first and second day of life can be considered 53.5±6.4 ml/kg/day, and for third day of life it 63.6±5.6 ml/kg/day.

The Rate of Diuresis

We analyzed the rate of diuresis. It was normal: 2.2±1.2 ml/kg/hour in the first group on DOL 1. Diuresis increased significantly on DOL 3 up to 3.6±1.6 ml/kg/hour. The maximal rate of urination 6.1±1.4 ml/kg/hour was on DOL 5.

Despite the fact that most literary sources describe a significant decrease in diuresis up to oligoanuria which is associated with the COX inhibitors using, we did not observe this in our own experience. Diuresis, despite a significant limitation of infusion therapy, was in the normal range for the patient's age in all groups and in all stages of the study (Fig. 2). In our opinion, the temporal diuresis did not affect the term of arterial duct closure in the subjects.

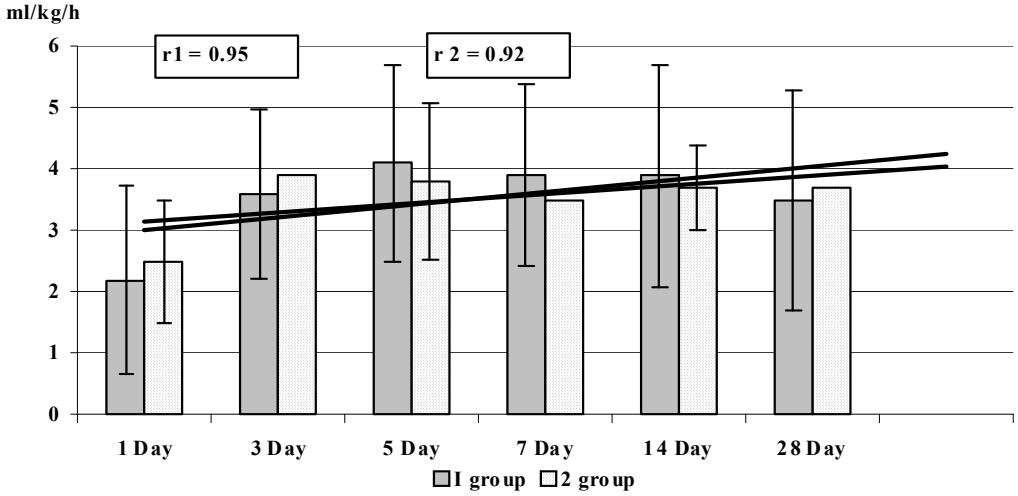

Fig. 2. The rate of diuresis in 1 and 2 groups

Body Weight Dynamics

Regarding the dynamics of body weight, there is a physiological weight loss in the completely healthy newborns in the first 3-4 days. In our subjects, we used restrictive infusion therapy (50-80 ml/kg/day) for PDA closure and the patient's weight loss was planned and even desirable. Weight loss observed in the first group was (-7.1%±4.6) up to the third day of life (Fig. 3).

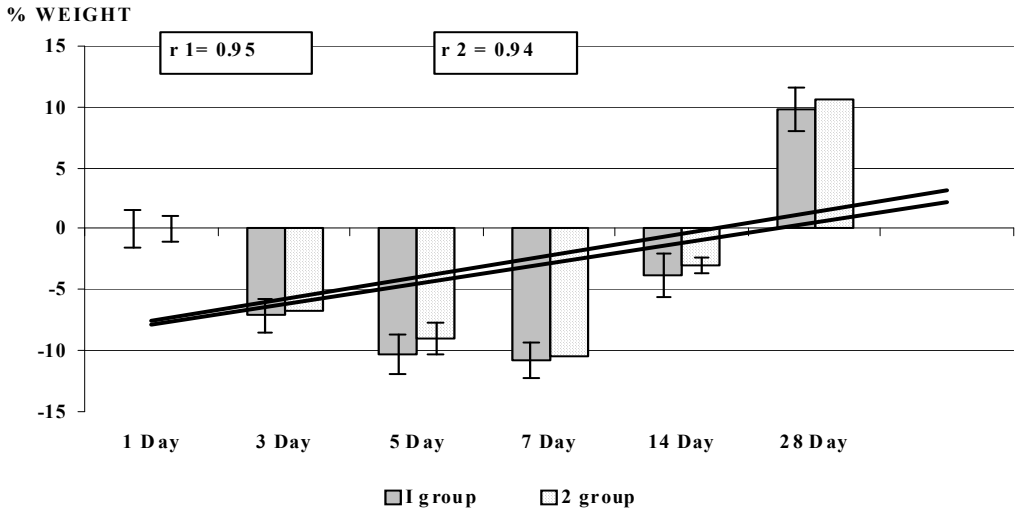

Fig. 3. Body weight dynamics

On DOL 5, more negative dynamics of body weight was maintained (-10.3%±4.3). The maximum of weight loss was observed on DOL 7 and it was (-10.8±5.6). With the onset of enteral nutrition and increasing in the volume of infusion after PDA closure, the body weight deficit reduced to (-3.8%±3.0) and on DOL 28 there was positive dynamics in patient's weight (+ 9.8%±2.6).

It should be noted that the degree of weight loss on DOL 3, 5, 7, 14 was closely related to the term of arterial duct closure. In the second group, the degree of weight loss at all stages was slightly higher than in the first group.

The arterial duct was closed in all groups in 100% of cases. Mortality in all groups was 0%. The pharmacological PDA closure was successful in 100% (40 preemies) of cases in the first group and in 70% (16 preemies) of the second grope (Table). In the second group the PDA closure occurred in a delayed period (more than 4 days) on DOL 14.55±0.56 on average. In the first group, the PDA closure occurred earlier on DOL 2.35±0.48 on average. 6 children (30%) of the second group had surgical clapping of the arterial duct in a delayed period (on average after 23 days). Recanalization of the arterial duct was found in 6 children (30%) after DOL 20.

Methods and terms of the PDA closure

Indicator	2 Group	1 Group
Diameter of PDA in DOL1	3,1±1,0 mm	2,8±0,5mm
Terms of PDA closure	14,55±0,56 DOL	2,35±0,48DOL
Pharmacological PDA closure	70%	100%
Surgical PDA closure	30%	0%
Recanalization of PDA	30%	0%
Indomethacin using as 1st course	84%	85%
Ibuprofen using as 1st course rectal form	16%	15%
Ibuprofen using as 2st course intravenous form	40%	0%

It should be noted that in the first group in all cases the arterial duct was closed pharmacologically and there was no PDA recanalization comparing to the second group.

Analyzing the data we can summarize the following: the mortality rate in all groups was 0% and the PDA was closed in 100% of cases. The PDA was in the second group with liberal infusion therapy in delayed period after DOL 4, on 14.55±0.56 DOL on average. In the first group with restrictive infusion therapy, the PDA closure occurred earlier on DOL 2.35±0.48. 6 children (30%) from the second group had surgical clapping of the PDA in a delayed period (on DOL 23 in average). In the first group, in contrast to the second group, there was no case of PDA recanalization, so there was no need for surgical treatment. Diuresis was in normal range for age in all groups during the study, despite a significant fluid limitation.

Conclusions

The combination of COX inhibitor with the strict adherence to the restriction of infusion in the first 5 days is considered to be a principle for the early closure of the arterial duct. The recommended volume of infusion for the successful PDA closure should be 50 ml/kg/day for DOL 1, and 60 ml/kg/day for DOL 3. The recommended weight loss for the successful PDA closure should be 7% for DOL 3 and up to 10% for DOL 5. The rate of diuresis did not affect the term of arterial duct closure in the subjects. Exact adherence to a combination of COX inhibitors and restrictive infusion therapy is more likely to contribute to the pharmacological closure of the ductus arteriosus and reduce the percentage of children who need surgical ligation of the ductus. The use of restrictive therapy and earlier closure of the arterial ductus reduces the percentage of such severe complications in premature babies as BPD, IVH, NEC, ROP, which decreases the risk of disability in these children. Early pharmacological PDA closure reduces length of hospitalization as well as the cost of treatment.

Perspectives

The open arterial duct should be pharmacologically closed at early stage with the help of COX inhibitors (indomethacin, ibuprofen) in combination

with restrictive infusion therapy. We are planning to study effects of rectal and intravenous forms of paracetamol as COX inhibitors for the pharmacological closure of PDA as the main or second course, but no more than 7 days.

List of Abbreviations

BPD - bronchopulmonary dysplasia
COX – cyclooxygenase
DOL – day of life
ELBW - extremely low birth weight
GA - gestational age
HPDA - hemodynamically significant patent ductus arteriosus
IVH - intraventricular hemorrhage
MV - mechanical ventilation
NEC - necrotizing enterocolitis
NICU – neonatal intensive care unit
NIV - non-invasive ventilation
NSAIDs - non-steroidal anti-inflammatory drugs
PDA - patent ductus arteriosus
PVL - periventricular leukomalacia
RDS - respiratory distress syndrome
ROP - retinopathy of prematurity
RI - Resistant Index, an index of resistance
VLBW - very low body weight

REFERENCES

1. Vanhaesebrouck S, Zonnenberg I, Vandervoort P, Bruneel E, Van Hoestenberghe MR, Theyskens C. Conservative treatment for patent ductus arteriosus in the preterm. Arch Dis Child Fetal Neonatal Ed. 2007;92(4):F244-F247. doi: https://doi.org/10.1136/adc.2006.104596
2. Dent CL, Schwartz SM. Postoperative care of the pediatric cardiac surgical patient. In: Cardiovascular Pediatric Critical Illness and Injury. London, United Kingdom, Springer. 2010;169-79.
3. Edward FB, Michael JA. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2014;CD000503.
4. Evans N. Patent ductus arteriosus in the neonate. Current Paediatrics. 2005;15(5):381-9. doi: https://doi.org/10.1016/j.cupe.2005.06.002
5. Hammerman C, Bin-Nun A, Markovitch E, et al. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011 Dec;128(6):e1618-21. Epub 2011 Nov 7. doi: https://doi.org/10.1542/peds.2011-0359.
6. Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials. Semin Neonatol. 2001;6:63-73. doi https://doi.org/10.1053/siny.2000.0036
7. Rahbari NN, Zimmermann JB, Schmidt T, et al. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. Br. J. Surg. 2011;96:331-41. doi: https://doi.org/10.1002/bjs.6552
8. Nankervis CA, Martin EM, Crane ML. Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes. Acta Paediatr. 2010;99:188-93. doi: https://doi.org/10.1111/j.1651-2227.2009.01563.x
9. Oncel MY, Yurttutan S, Degirmencioglu H, et al. Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. Division of Neonatology, Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey; 2009.
10. Tomas C, Julia E, Joy R, et al. Perioperative Fluid Management Strategies in Major Surgery: A Stratified Meta-Analysis. Society of Critical Care Anesthesiologists. 2012;640-61.
doi: https://doi.org/10.1213/ANE.0b013e318240d6eb
11. Soni N. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP). Cassandra's view. Anaesthesia. 2011;64:235-8. doi: https://doi.org/10.1111/j.1365-2044.2009.05886_1.x
12. Mandhan P, Brown S, Kukkady A, et al. Surgical closure of patent ductus arteriosus in preterm low birth weight infants. Congenit Heart Dis. 2011;4(1):34-37. doi: https://doi.org/10.1111/j.1747-0803.2008.00241.x
13. Surkov D, Obolonskiy A, Kapustina O, Volkov D. Use of rectal ibuprofen for PDA closure in preterm neonates. Pediatric Anesthesia and Critical Care Journal. 2014;2(1):11-16.
14. Tsai E. Withholding and withdrawing artificial nutrition and hydration. Paediatr. Child. Health. 2011;16(4):241-2.
doi: https://doi.org/10.1093/pch/16.4.241

СПИСОК ЛІТЕРАТУРИ

1. Conservative treatment for patent ductus arteriosus in the preterm / Vanhaesebrouck S. et al. *Arch Dis Child Fetal Neonatal Ed.* 2007. Vol. 92, N 4. P. 244-247. DOI: https://doi.org/10.1136/adc.2006.104596.
2. Dent C. L., Schwartz S. M. Postoperative care of the pediatric cardiac surgical patient. Cardiovascular Pediatric Critical Illness and Injury. London, United Kingdom: Springer, 2010. P. 169-179.
DOI: https://doi.org/10.1007/978-1-84800-923-3_16
3. Edward F. B., Michael J. A. Restricted versus liberal water intake for preventing morbidity and

mortality in preterm infants. *Cochrane Database Syst Rev*. 2014. CD000503.

4. Evans N. Patent ductus arteriosus in the neonate. *Current Paediatrics.* 2005; Vol. 15, N 5. P. 381-9. DOI: https://doi.org/10.1016/j.cupe.2005.06.002

5. Hammerman C., Bin-Nun A., Markovitch E. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics.* 2011 Vol. 128, N 6. P. 1618-21. Epub 2011 Nov 7. DOI: https://doi.org/10.1542/peds.2011-0359

6. Knight D. B. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials. *Semin Neonatol*. 2001. Vol. 6. P. 63-73. DOI: https://doi.org/10.1053/siny.2000.0036

7. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery / Rahbari N. N. et al. *Br. J. Surg.* 2011. Vol. 96. P. 331-341. DOI: https://doi.org/10.1002/bjs.6552

8. Nankervis C. A., Martin E. M., Crane M. L. Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes. *Acta Paediatr*. 2010. Vol. 99. P. 188-193.
DOI: https://doi.org/10.1111/j.1651-2227.2009.01563.x

9. Oncel M. Y., Yurttutan S., Degirmencioglu H. Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. *Division of Neonatology*. Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey, 2009. DOI: https://doi.org/10.1159/000345337

10. Perioperative Fluid Management Strategies in Major Surgery: A Stratified Meta-Analysis / Tomas C. et al. *Society of Critical Care Anesthesiologists*. 2012. P. 640-661.
DOI: https://doi.org/10.1213/ANE.0b013e318240d6eb

11. Soni N. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP). Cassandra's view. *Anaesthesia*. 2011. Vol. 64. P. 235-238.
DOI: https://doi.org/10.1111/j.1365-2044.2009.05886_1.x

12. Surgical closure of patent ductus arteriosus in preterm low birth weight infants / Mandhan P. et al. *Congenit Heart Dis*. 2011. Vol. 4, N 1. P. 34-37. DOI: https://doi.org/10.1111/j.1747-0803.2008.00241.x

13. Surkov D., Obolonskiy A., Kapustina O., Volkov D. Use of rectal ibuprofen for PDA closure in preterm neonates. *Pediatric Anesthesia and Critical Care Journal.* 2014. Vol.2, N 1. P. 11-16.

14. Tsai E. Withholding and withdrawing artificial nutrition and hydration. *Paediatr. Child. Health*. 2011. Vol. 16, N 4. P. 241-242.
DOI: https://doi.org/10.1093/pch/16.4.241

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