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IMPACT OF 6% HYDROXYETHYLSTARCH 130/0.42 ON BRAIN PERFUSION IN TERM NEONATES WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Резюме

Intiduction. *Perinatal hypoxic ischemic encephalopathy (HIE) is associated with approximately one-quarter of global neonatal deaths. Dysregulated cerebral blood flow may be a key component for secondary neurologic injury in HIE. The load of fluids to increase intravascular volume is the point of care in infants because the cerebral blood flow in neonatal period depends mainly on the cardiac output but the choice of fluids is still debatable.*

Objective. *To determine the impact of 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution on brain perfusion in term neonates with severe hypoxic-ischemic encephalopathy.*

Materials and methods. *Single-center, prospective, simple, randomized controlled study was performed in 205 full-term infants with hypoxic-ischemic encephalopathy grade II and grade III by Sarnat score in the period of 2012-2016. Depending on fluids for volume resuscitation, all infants were randomly divided into HES and control groups. In HES group 45 term infants with moderate to severe hypoxic-ischemic encephalopathy were treated at the 1st DOL with 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution at a dose of 10 ml/kg. The control group included 160 term neonates with hypoxic-ischemic encephalopathy undergoing routine intensive care with normal saline at a dose of 20 ml/kg as the loading volume if needed. To assess the impact of 6% HES on systemic and cerebral hemodynamics, such criteria as mean blood pressure (MBP) and transfontanel Doppler indices RI, PI and CPP were obtained at the 1st, 2nd and 3rd DOL.*

Results. *Using of 6% HES 130/0.42 at the dose of 10 ml/kg of body weight for volume replacement in neonates with moderate to severe HIE at the 1st DOL led to increasing of Resistive Index (RI) in front cerebral artery 2nd DOL ($p = 0.025$) and 3rd DOL ($p = 0.023$).*

Conclusion. *Administration of 6% HES 130/0.42 in a balanced crystalloid solution in term newborns with severe hypoxic-ischemic encephalopathy for volume resuscitation results in significant improvement of cerebral blood flow, specifically increasing of Doppler Resistive Index in front cerebral arteries.*

Keywords: *neonates; hypoxia; encephalopathy; colloids; crystalloids; hemodynamics.*

Introduction

Perinatal hypoxic ischemic encephalopathy (HIE) is associated with approximately one-quarter of global neonatal deaths. In 2010, there were an estimated 1.15 million cases of neonatal encephalopathy, of which 96% of were from low- and middle-income countries [23]. More than a million children who survive birth asphyxia develop problems such as cerebral palsy, mental retardation, learning difficulties, and other disabilities [25]. The main strategies of intensive care remain: mild therapeutic hypothermia of 33-35˚C for 72 hours; positive pressure ventilation; volume resuscitation; cardiac output support; glucose control; anticonvulsant therapy [26].

Dysregulated cerebral blood flow may be a key component for secondary neurologic injury in HIE. Cerebrovascular autoregulation maintains relatively constant cerebral blood flow across changes in perfusion pressure. Cerebral vasoreactivity describes the vasodilatory and vasoconstrictive responses to changes in blood pressure that mediate cerebral blood flow autoregulation [2, 3]. The load of fluids to increase intravascular volume is the point of carein infants becauseunlike adults the cerebral blood flow in neonates depends mainly on the cardiac output than blood pressure [11] but the choice of fluids is still debatable.However, the safety of HES 6% in newborns seems quite proven [16, 22], its efficacy as a fluid for volume replacement in the acute period of severe hypoxic-ischemic encephalopathy remains discussible.

Objective

The objective of the study was to determine the impact of 6% hydroxyethylstarch (HES) 130/0.42 in a balanced crystalloid solution on brain perfusion in term neonates with severe hypoxic-ischemic encephalopathy.

Materials and methods

Single-center, prospective, simple, randomized controlled study was performed in 205 full-term infants with hypoxic-ischemic encephalopathy treated in NICU of Dnipro Regional Children's Hospital (Ukraine) in the period of 2012-2016.

Inclusion criteria: gestational age 37 to 42 weeks, term infants with the present at admission signs and symptoms of hypoxic-ischemic encephalopathy grade II and grade III by Sarnat score during the first 72 hours of life [9, 15].

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

All the babies were treated using 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), the estimation of consciousness by modified GCS [10], cerebral hemodynamic evaluation by non-invasive method based on conventional ultrasound Doppler transfontanel measurement of blood flow in the front cerebral artery (Arteria Cerebri Anterior, ACA) with estimation of systolic (Vs), diastolic (Vd), mean velocity (Vm) and calculation of Pourcelot

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Resistive Index (RI), Gosling Pulsatility Index (PI) and cerebral perfusion pressure (CPP) by the formula of Aaslid R. (1986) [1].

Basing on cerebral perfusion Doppler indices and systemic circulation the hemodynamic support included volume resuscitation and control of blood pressure and cardiac output with the following inotropic and vasopressor administration if needed. Dobutamine and/or dopamine were administered in routinely recommended dosage. The intensive therapy was focused on normovolemia, support of mean blood pressure above 35-40 mm Hg and adequate cardiac output [26].

Depending on fluids for volume resuscitation, all infants were randomly divided into HES and control groups. In HES group 45 term infants with moderate to severe hypoxic-ischemic encephalopathy were treated at the 1st DOL with 6% hydroxyethylstarch (HES) 130/0.42 in a balanced crystalloid solution at a dose of 10 ml/kg. The control group included 160term neonates with hypoxic-ischemic encephalopathy undergoing routine intensive care with normal saline at a dose of 20 ml/kg as the loading volume if needed.The issues of safety of HES 6% 130/0.42 in newborns we considered in a previous publication [22]. To assess the efficacy of 6% HES we selected such criteria as mean blood pressure (MBP) and transfontanel Doppler indices RI, PI and CPP [1].

Statistical analysis was performed with JASP 0.9.0.1 software (Amsterdam, The Netherlands, 2018) in accordance with generally accepted standards for mathematical statistics. Before the statistical processing, all data were checked for normal distribution using the Shapiro-Wilk's W-test. For non-parametric data primary statistical analysis included the calculation of the median, 25thand 75thpercentiles. The Mann-Whitney U-test was used for statistical comparison of the studied groups. Kendall's Tau and Spearman's rank correlation coefficient used to measure the strength of the relationship between variables. The unidirectional analysis of variance (ANOVA test) performed to determine the significant influence of each factor on subject effects in the dynamics. A p-value less than 0.05 was considered as significant in all of the tests.

Results and discussion

Analysis of the data for 205 term newborns has conducted. The average gestational age was 39.6±1.4 (37-42) weeks, the birth weight was 3573±549 (2440-5300) grams. 128 babies (62.4%) were males and 77 (37.6%) were females. 47 babies (22.9%) were admitted to the NICU in the first 6 hours of life, 136 (66.3%) in the 6-24 hours of life, 19 (9.3%) in 24-72 hours of life and 3 infants (1.5%) were admitted over 72 hours of life. Mortality ratio was 3 of 205 babies (1.46%) at the 28thday of treatment.

At the first step, we figured out benchmarks for the HES 6% efficacy evaluation. Depending on short-term end-point as cerebral leukomalacia rate,we conducted acomparative analysis between central and cerebral hemodynamics indices and leukomalacia diagnosed by US/MRI criteria (Tab. 1).

Table 1

Comparative analysis of central and cerebral hemodynamics on Day 1 and Day 3 of the study in infants with cerebral leukomalacia / no leukomalacia as short-term follow up

Variables		No leukomalacia group (n=180)	Leukomalacia group (n=25)	p-value
		Median (25%-75%)		
Day 1	MBP, mm Hg	55 (47-60)	53 (42-63)	0.842
	ACA Vs, cm/s	21 (16-28)	21(17.4-28.2)	0.671
	ACA Vm, cm/s	11.6 (8.1-15.6)	13 (10-17.5)	0.244
	RI	0.68 (0.59-0.75)	0.62 (0.55-0.69)	0.037
	PI	1.2(0.99-1.5)	1.0 (0.84-1.22)	0.006
	CPP Aaslid	7.8 (4.2-11.5)	8,9 (5.75-13.85)	0.232
Day 3	MBP, mm Hg	60 (52-69.3)	54 (50-58.8)	0.053
	ACA Vs, cm/s	26 (20.1-33)	26 (18.8-34.5)	0.854
	ACA Vm, cm/s	14 (11-18)	16.5 (10.8-19.8)	0.336
	RI	0.67 (0.61-0.73)	0.6 (0.5-0.76)	0.033
	PI	1.2 (1.0-1.4)	1.0 (0.75-1.5)	0.042
	CPP Aaslid	10.4 (6.7-15.2)	12.5 (6.6-16.8)	0.418

***Note. HES** – Hydroxyethyl starch, MBP – Mean Blood Pressure, RI – Resistive Index, PI – Pulsatile Index, CPP – Cerebral Perfusion Pressure*

The data presented in Table 1 shows that newborns, who subsequently were diagnosed with cerebral leukomalacia, had statistically lower RI and PI rates on the 1st and 3rd days of intensive care. The correlation between these variables is also confirmed by the correlation analysis of Kendall-Tau. The RI value on Day 1 negatively correlated with the development of leukomalacia (r = -0.12; p = 0.018), as well as RI on Day 3 (p = -0.13; p = 0.016). The weakness of the described correlation could be explained by the unpredictable state of autoregulation of cerebral blood flow in newborns with HIE during therapeutic hypothermia and the presence of ante-/intranatal factors that influence the development of leukomalacia.

Understanding that hemodynamics and cerebral Doppler indices on Day 1 are mostly baseline characteristics, we used mean blood pressure, Pourcelot Resistive Index (RI) and Gosling Pulsatility Index (PI) on Day 3 as benchmarks for the HES 6% efficacy evaluation. Exactly the same, Day 3 RI predictable value coincides with data by Elstad M. et al. (2011) and Gerner G.J. et al. (2016) [5, 7].

Next step we conducted the comparative analysis between central and cerebral hemodynamics indices on Day 2 and Day 3 in neonates with HES 6% administration / no HES 6% on Day 1 (Tab. 2).

Table 2

Comparative analysis of central and cerebral hemodynamics on Day 2 and Day 3 of the study in infants with HES 6% administration / no HES 6% on Day 1

Variables		No HES 6% group (n=160)	HES 6% group (n=45)	p-value
		Median (25%-75%)		
Day 2	MBP, mm Hg	56 (48-65)	55 (49-65)	0.007
	RI	0.69 (0.64-0.76)	0.71 (0.59-0.79)	0.649
	PI	1.29 (1.12-1.55)	1.35 (0.98-1.76)	0.395
Day 3	MBP, mm Hg	57 (50-68)	61 (53-71)	0.115
	RI	0.66 (0.60-0.71)	0.68 (0.59-0.76)	0.879
	PI	1.2 (0.99-1.37)	1.24 (0.96-1.52)	0.667

***Note. HES** – Hydroxyethyl starch, MBP – Mean Blood Pressure, RI – Resistive Index, PI – Pulsatile Index*

Evaluating data from Table 2, no statistically significant differences in RI and PI values on Days 2 and 3 between two groups found excepting slight but significant distinction in mean blood pressure (MBP).

Considering of the above, we provided the ANOVA test to decisively figure out if the administration of HES 6% 130/0.42 fluid on Day 1 for volume resuscitation affects cerebral blood flow patterns the nearest days after. Impact of HES 6% administration at Day 1 on RI dynamics on Day 1 and Day 2 presented in Table 3 and Figure 1.

Table 3

Effect of HES 6% administration at Day 1 on RI dynamics on Day 1 and Day 2

Variables	Sum of Squares	df	Mean Square	F	p-value
Within-Subjects Effects					
RI dynamics	0.069	1	0.069	5.568	0.020
RI dynamics • Day 1 HES 6% (0-no, 1-yes)	0.008	1	0.008	0.659	0.418
Residual	1.839	148	0.012		
Between-Subjects Effects					
Day 1 HES 6% (0-no, 1-yes)	0.077	1	0.077	5.129	0.025
Residual	2.209	148	0.015		

***Note. HES** – Hydroxyethyl starch, RI – Resistive Index*

The results from ANOVA test in the Table 4 show, that there is a significant difference between RI measured on the Day 1 and Day 2 (p=0.020) inside the groups of patients who received and did not receive HES 6% at Day 1. However, administration of HES 6% at Day 1 resulted in similar changes in RI level on both Day 1 and Day 2 of treatment (p=0.418),exactly RI increased in both days. RI level was significantly higher in patients who received HES 6% comparing to no-HES 6% group (p=0.025).

The graph on Figure 1 represents the dynamics confirming that administration of HES 6% resulted in significant improvement of RI level on Day 1 and Day 2 (p=0.025).

Impact of HES 6% administration at Day 1 on RI dynamics on Day 2 and Day 3 presented in Table 4 and Figure 2.

The results from ANOVA test in the Table 4 show, that there is a significant difference between RI measured on the Day 2 and Day 3 (p=0.019) inside the groups of patients received and did not receive HES 6% at Day 1. However, administration of HES 6% on Day 1 resulted in similar changes in RI values on both Day 2 and Day 3 of treatment (p=0.330),

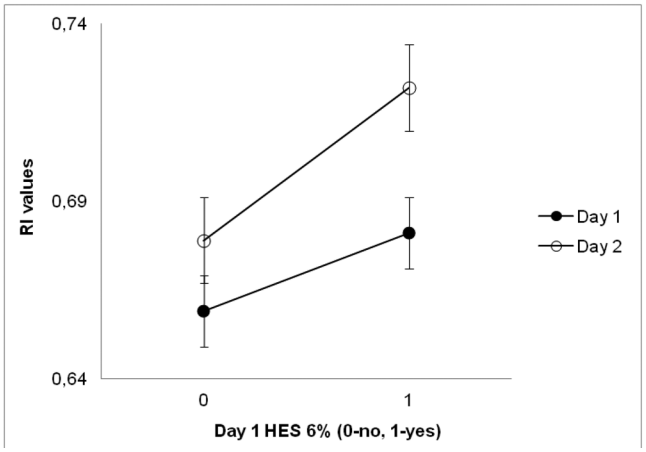

Figure 1. The descriptive plot for effect of HES 6% administration at Day 1 on RI dynamics on Day 1 and Day 2. HES – Hydroxyethyl starch, RI – Resistive Index

exactly RI increased in both days. RI level was significantly higher in infants who received HES 6% comparing to no-HES 6% group (p=0.023).

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Table 4

Effect of HES 6% administration at Day 1 on RI dynamics on Day 2 and Day 3

Variables	Sum of Squares	df	Mean Square	F	p-value
Within-Subjects Effects					
RI dynamics	0.056	1	0.056	5.645	0.019
RI dynamics • Day 1 HES 6% (0-no, 1-yes)	0.009	1	0.009	0.953	0.330
Residual	1.441	146	0.010		
Between-Subjects Effects					
Day 1 HES 6% (0-no, 1-yes)	0.071	1	0.071	5.281	0.023
Residual	1.960	146	0.013		

***Note. HES** – Hydroxyethyl starch, RI – Resistive Index*

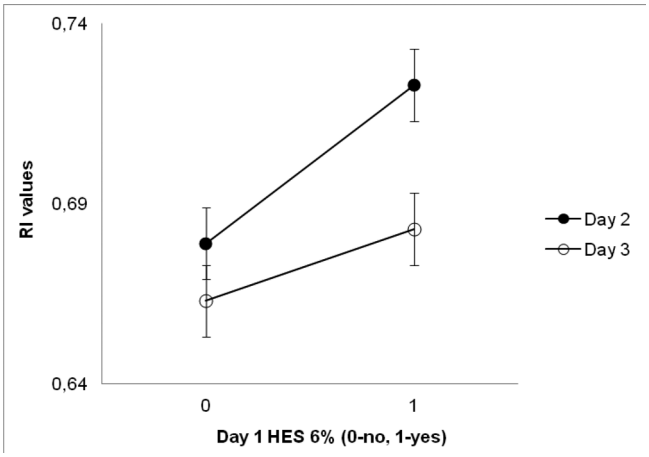

Figure 2. The descriptive plot for effect of HES 6% administration at Day 1 on RI dynamics on Day 2 and Day 3. HES – Hydroxyethyl starch, RI – Resistive Index

The graph on Figure 2 represents the dynamics confirming that administration of HES 6% resulted in significant improvement of RI level on Day 2 and Day 3 (p=0.023).

The ideal fluid for neonates should have a composition as similar as possible to the extracellular fluid, to support cellular metabolism and avoid organ dysfunction, and should increase intravascular volume and persist over time, to optimize cardiac output. Unfortunately, no ideal fluid exists, and the available fluid options are roughly divided in three groups: crystalloids, colloids, and blood products. Crystalloid and colloid solutions are discussed, emphasizing advantages and disadvantages of each [18].

Crystalloids are the fluids most commonly used in neonates as well as in pediatric and adult population [6]. Comparing to colloids crystalloids are low-cost, thenoted side effect such as tissue edema can develop when large volumes are used.However, the volume-replacement ratio for crystalloids is quite low and crystalloids only have a short-lived effect on the systemic perfusion. According to Starling's "Three-compartment model", four-times more crystalloids have the same volume effect as colloids [12].

Colloids are composed of large molecules designed to remain in the intravascular space for several hours, increasing plasma osmotic pressure and reducing the need for further fluids. The use of albumin is associated with improved mean arterial pressure and cardiac output with an infusion of a lower volume, but the increased blood–brain barrier permeability restricts it's using in neonates with severe HIE because of the relative risk of brain edema [4].

Systematic reviews regarding use of starches in children have shown that there are not enough evidence as to influence on the risk of death using crystalloid vs colloid in pediatric intensive care [20, 21]. Applying of 6% hydroxyethylstarch (HES) 130/0.42 in a balanced crystalloid solution approved for use in the neonatal period, but there is limited data on its benefit/risk ratio in hypoxic-ischemic encephalopathyof newborns [8].

Unlike adult population [13, 14], there are no strict evidences in neonatal patients regarding serious adverse events as coagulopathy or renal impairment related to administration of HES 6% 130/0.42 in routine dosage 10 ml/kg IV [8, 17, 19] as well as in children [24]. Considering that fluid restriction is typically recommended for infants with HIE [26], 6% HES 130/0.42could be used for volume replacement in this group of patients in standard dosage not exceeding 10-15 ml/kg of body weight to avoid potential side effects.

Conclusion

Administration of 6% HES 130/0.42 in a balanced crystalloid solution at the dose of 10 ml/kg of body weight in term newborns with severe hypoxic-ischemic encephalopathy isan effective tool for volume resuscitation resulting in improvement of cerebral blood flow, specifically increasing of Doppler Resistive Index in front cerebral arteries. Having regard toits influence on central and cerebral hemodynamics, preventing of secondary post-ischemic brain injury is quite feasible, but additional data needs to be collected before any further conclusions can be drawn.

The perspectives of future studies

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.

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ВПЛИВ 6% РОЗЧИНУ ГІДРОКСИЕТИЛКРОХМАЛЮ НА СТАН МОЗКОВОЇ ПЕРФУЗІЇ У ДОНОШЕНИХ НОВОНАРОДЖЕНИХ З ВАЖКОЮ ГІПОКСИЧНО-ІШЕМІЧНОЮ ЕНЦЕФАЛОПАТІЄЮ

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Резюме

Вступ. Перинатальну гіпоксично-ішемічну енцефалопатію (ГІЕ) пов'язують приблизно з ¼ усіх випадків неонатальної смертності у світі. Порушення регуляції церебрального кровотоку може бути ключовим моментом щодо розвитку вторинного пошкодження головного мозку при ГІЕ. Волемічне навантаження для забезпечення адекватного внутрішньосудинного об'єму крові розглядається як терапія вибору у немовлят, оскільки мозкова перфузія протягом неонатального періоду залежить в основному від серцевого викиду, але вибір розчинів для інфузії залишається дискусійним.

Мета дослідження. З'ясувати вплив 6% гідроксиетилкрохмалю (ГЕК) 130/0,42 у збалансованому кристалоїдному розчині на стан мозкової перфузії у доношених новонароджених з важкою ГІЕ.

Матеріали і методи дослідження. Одноцентрове, проспективне, просте, рандомізоване контрольоване дослідження було проведене у 205 доношених новонароджених з ГІЕ II та III ступеня за шкалою Sarnat протягом 2012-2016 років. В залежності від обраного розчину для полемічної ресусцитації всі немовлята були рандомізовано розподілені на групу із застосуванням ГЕК та контрольну групу. У групі ГЕК 45 малюків із середньою або важкою ГІЕ лікувалися із застосуванням у 1й день 6% розчину гідроксиетилкрохмалю (ГЕК) 130/0,42 у збалансованому кристалоїдному розчині в дозі 10 мл/кг. Контрольну групу включали 160 доношених новонароджених з ГІЕ, яким під час проведення рутинної інтенсивної терапії за необхідності застосовувався для об'ємного навантаження фізіологічний розчин у дозі 20 мл/кг. Для оцінки впливу 6% ГЕК на системну та церебральну гемодинаміку були вивчені такі показники, як середній артеріальний тиск (САТ) та допплерівські індекси мозкового кровотоку: індекс резистентності (RI), пульсаційний індекс (PI) та церебральний перфузійний тиск (ЦПТ) на 1й, 2й та 3й дні дослідження.

Результати дослідження. Використання 6% ГЕК 130/0,42 у дозі 10 мл/кг маси тіла для відновлення об'єму циркулюючої крові у новонароджених з середньою або важкою ГІЕ на 1й день життя призводило до збільшення індексу резистентності (RI) у передній мозковій артерії на 2й день (p = 0,025) і на 3й день дослідження (p = 0,023).

Висновки. Застосування 6% ГЕК 130/0,42 у збалансованому кристалоїдному розчині у доношених новонароджених з важкою ГІЕ для волемічної ресусцитації призводить до значного покращення церебрального кровотоку, зокрема підвищення допплерівського індексу резистентності передніх мозкових артерій.

Ключові слова: новонароджені; гіпоксія; енцефалопатія; колоїди; кристалоїди; гемодинаміка.

ВЛИЯНИЕ 6% РАСТВОРА ГИДРОКСИЭТИЛКРАХМАЛА НА СОСТОЯНИЕ МОЗГОВОЙ ПЕРФУЗИИ У ДОНОШЕННЫХ НОВОРОЖДЁННЫХ С ТЯЖЕЛОЙ ГИПОКСИЧЕСКИ-ИШЕМИЧЕСКОЙ ЭНЦЕФАЛОПАТИЕЙ

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Summary

Вступление. Перинатальную гипоксически-ишемическую энцефалопатию (ГИЭ) связывают примерно с ¼ всех случаев неонатальной смертности в мире. Нарушение регуляции церебрального кровотока может быть ключевым моментом в развитии вторичного повреждения головного мозга при ГИЭ. Волемическая нагрузка для обеспечения адекватного внутрисосудистого объема крови рассматривается как терапия выбора у младенцев, поскольку мозговая перфузия в течение неонатального периода зависит в основном от сердечного выброса, однако выбор инфузионных растворов остается дискуссионным.

Цель исследования. Выяснить влияние 6% гидроксиэтилкрахмала (ГЭК) 130/0,42 в сбалансированном кристаллоидном растворе на состояние мозговой перфузии у доношенных новорождённых с тяжёлой ГИЭ.

Материалы и методы исследования. Одноцентровое, проспективное, простое, рандомизированное контролируемое исследование было проведено у 205 доношенных новорождённых с ГИЭ II и III степени по шкале Sarnat в течение 2012-2016 годов. В зависимости от выбранного раствора для волемической ресусцитации все дети были рандомизированно разделены на группу с применением ГЭК и контрольную группу. В группе ГЭК 45 младенцев со средней или тяжелой ГИЭ лечились с использованием в 1й день 6% раствора гидроксиэтилкрахмала (ГЭК) 130/0,42 в сбалансированном кристаллоидном растворов в дозе 10 мл/кг. Контрольную группу включали 160 доношенных новорождённых с ГИЭ, которым во время проведения рутинной интенсивной терапии при необходимости применялся для объемной нагрузки физиологический раствор в дозе 20 мл/кг. Для оценки влияния 6% ГЭК на системную и церебральную гемодинамику были изучены такие показатели, как среднее артериальное давление (САД) и допплеровские индексы мозгового кровотока: индекс резистентности (RI), пульсационный индекс (PI) и церебральное перфузионное давление (ЦПД) на 1й, 2й и 3й дни исследования.

Результаты исследования. Использование 6% ГЭК 130/0,42 в дозе 10 мл/кг массы тела для восполнения объема циркулирующей крови у новорожденных со средней или тяжелой ГИЭ в 1й день жизни приводило к увеличению индекса резистентности (RI) в передней мозговой артерии на 2й день (p = 0,025) и на 3й день исследования (p = 0,023).

Выводы. Применение 6% ГЭК 130/0,42 в сбалансированном кристаллоидном растворе у доношенных новорожденных с тяжелой ГИЭ для волемической ресусцитации приводит к значительному улучшению церебрального кровотока, в частности повышению допплеровского индекса резистентности передних мозговых артерий.

Ключевые слова: новорожденные; гипоксия; энцефалопатия; коллоиды; кристаллоиды; гемодинамика.

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