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Safety of 6% hydroxyethylstarch 130/0.42 in term neonates with severe HIE

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Keypoints

The load of fluids to increase intravascular volume is the method of choice in infants because unlike adults the cerebral blood flow in neonates depends mainly on the cardiac output than blood pressure but the choice of fluid is debatable. The objective of our study is to determine the safety of 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution in term neonates with severe hypoxic-ischemic encephalopathy.

Abstract

Background

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

Methods

Single-center, prospective, simple, randomized controlled study was performed in 65 full-term infants with hypoxic-ischemic encephalopathy grade II and grade III by Sarnat score (in Hill A., Volpe J.J. modification, 1994) were treated in NICU of Dnepropetrovsk Regional Children's Hospital (Ukraine) in the period of 2012-2014. Depending on fluids for volume resuscitation, all infants divided into three groups: two studied and one control group. Group 1: full-term infants (n=14) with hypoxic-ischemic encephalopathy treated with normal saline at a dose of 20 ml/kg as the loading volume. Group 2: full-term infants (n=19) with hypoxic-ischemic encephalopathy treated with 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution at a dose of 10 ml/kg. The control group included 32 full-term infants with hypoxic-ischemic encephalopathy undergoing routine intensive care with no need to administer additional fluids as volume resuscitation. 28-day and 90-day mortality were determined as well as the possible kidneys complications basing on the pRIFLE score (Akcan-Arikan A, 2007).

Results

At the 28th and 90th days of observation there was no deaths occurred in all groups of patients. All the infants survived and discharged for outpatient care. There were no statistically significant differences between the study and control groups regarding the possible kidney complications basing on pRIFLE score.

Conclusion

Using of 6% HES 130/0.42 at the dose of 10 ml/kg of body weight in term newborns with severe hypoxic-ischemic encephalopathy is safe comparing with normal saline. Moderate doses of 6% HES 130/0.42 can be used in full-term newborns with hypoxic-ischemic encephalopathy when the loading volume of crystalloids was not hemodynamically effective, but additional data needs to

be collected before any further conclusions can be drawn.

Keywords: neonates, hypoxia, encephalopathy, colloids, crystalloids, mortality, kidneys

Introduction

Severe perinatal hypoxia-ischemia is a leading cause of brain damage in term infants in Ukraine. Ischemic perinatal brain injuries lead to a high percentage of deaths and/or gross neurological deficits with severe disabilities in children of 1st year of life due to developing hypoxic-ischemic encephalopathy (HIE) (Raju T. et al ., 2003; Zanelli S. et al., 2015) [13, 20]. The main topics of intensive care include: targeted temperature control of 33-35˚C for 72 hours; positive pressure ventilation; volume resuscitation; blood pressure and cardiac output support; glucose control; anticonvulsant therapy (Ivanov D., 2011, Kapustina O., 2013, Surkov D., 2013, Zanelli S. et al., 2015) [8, 10, 18, 20]. The vast majority of treatment efforts should be aimed at supporting of ventilation and hemodynamic to ensure adequate cerebral perfusion pressure (CPP) (Figure 1).

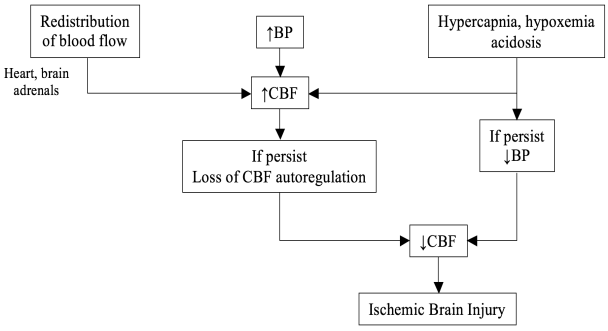

Figure 1. Pathophysiology of hypoxic-ischemic encephalopathy in neonates. (Zanelli S. et al., 2015). [20]. Fetal response to asphyxia illustrating the initial redistribution of blood flow to vital organs. With prolonged asphyxia insult and failure of compensatory mechanisms, cerebral blood flow falls, leading to ischemic brain injury.

The load of fluids to increase intravascular volume is the method of choice in infants because unlike adults the cerebral blood flow in neonates depends mainly on the cardiac output than blood pressure (Victor S. et al., 2006) [19] but the choice of fluid is debatable. Benefitsof restrictive volume resuscitation from one hand, short term of crystalloids circulating in the bloodstream from another - come upon searching for alternative fluids with a higher volume effect. Traditionally, 10-20% human albumin is using in neonatal intensive care as colloid fluid of choice (Namasivayam Ambalavanan, 2014) [12], but its ability to penetrate through the damaged blood-brain barrier and retain water restricts its applying in severe hypoxic-ischemic encephalopathy. So one of possible alternative ways to use colloids in neonatal HIE is the administration of 6% hydroxyethyl starch. 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution approved for use in the neonatal period, but there is limited data on its safety and evaluation related benefit/risk ratio in hypoxic-ischemic encephalopathy of newborns. Recently published data from several large multicenter studies using 6% HES 130/0.4-0.42 in adult patients reached the conclusion to use hydroxyethyl starches in patients with compromised renal function and/or coagulation with cautious. However, these studies are concerned, first, mostly patients with sepsis. Second, patients included in the sample were adult not young, and some results of these investigations proved disputable (Crystalloid versus Hydroxyethyl Starch Trial (CHEST), 2012; Estrada C.A., Murugan R., 2013, CRISTAL trial, 2013) [3, 5, 11]. Systematic reviews regarding use of starches in children have shown that there are not enough evidences as to influence on the risk of death using crystalloid vs colloid in pediatric intensive care (Sumpelmann R. et al., 2009-2011) [16, 17]. The objective of our study is to determine the safety of 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution in term neonates with severe hypoxic-ischemic encephalopathy.

Materials and methods

Single-center, prospective, simple, randomized controlled study was performed in 65 full-term infants with hypoxic-ischemic encephalopathy were treated in NICU

of Dnepropetrovsk Regional Children's Hospital (Ukraine) in the period of 2012-2014.

Inclusion criteria: gestational age 37 to 42 weeks, term infants with present at admission signs and symptoms of hypoxic-ischemic encephalopathy grade II and grade III by Sarnat score (in Hill A., Volpe J.J. modification, 1994) during the first 24 hours of life. Exclusion criteria: gestational age less than 37 weeks, infants aged over 24 hours of life, trauma at birth, congenital malformations, early onset neonatal sepsis.

To assess the severity of HIE at admission the evaluation of Sarnat score in in Hill A., Volpe J.J. modification (1994) and neonatal score NTISS (Neonatal Therapeutic Intervention Scoring System, 1992) [6, 7] were obtained. Dynamic assessment of conscious level conducted basing on the modified Glasgow Coma Scale (GCS) for infants and children Glasgow - St Petersburg Coma Scale, Jova A. et al., 2005). [9].

The middle gestation age (GA) of all the neonates included in the study was 39.6±0.1 weeks with birth weight 3453.0±49.7 grams and birth height 52.73±0.52 cm. The leading symptoms included neurological disorders and the need for respiratory and inotropic support.

In all the babies there were performed assisted positive-pressure ventilation, routine control of acid-base balance, monitoring of SpO_2 and $etCO_2$, control of systemic hemodynamics (heart rate, blood pressure, cardiac output), the estimation of consciousness by modified GCS (Glasgow - St Petersburg Coma Scale, Jova A. et al., 2005) [9], control of tissue perfusion by serum lactate level, cerebral hemodynamic evaluation by non-invasive method based on conventional ultrasound Doppler transfontanel measurement of blood flow in the front cerebral artery (arteria celiaca anterior, ACA) with estimation of systolic (Vs), diastolic (Vd), mean velocity (Vm) and calculation of resistance index (RI), pulsating index (PI) and cerebral perfusion pressure (cerebral perfusion pressure, CPP) by the formula of Aaslid R. (1986) [1].

Basing on cerebral perfusion Doppler indexes 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, dopamine and/or norepinephrine were administered in routinely recommended dosage. The intensive therapy was focused to achieve normovolemia, normotension and adequate cardiac output.

Depending on fluids for volume resuscitation, all infants divided into three groups: two studied and one control group. Group 1: full-term infants (n=14) with hypoxic-ischemic encephalopathy treated with normal saline at a dose of 20 ml/kg as the loading volume. Group 2: full-term infants (n=19) with hypoxic-ischemic encephalopathy treated with 6% hydroxyethyl starch (HES) 130/0.42 in a balanced crystalloid solution at a dose of 10 ml/kg. Infants were divided in two studied groups by simple randomization. The control group included 32 full-term infants with hypoxic-ischemic encephalopathy undergoing routine intensive care with no need to administer additional fluids as volume resuscitation.

To assess the safety of 6% HES 130/0.42 we selected such criteria as the 28-day and 90-day survival as well as possible renal complications (kidney injury, the development of acute renal failure, the need for renal replacement therapy) which were determined basing on pRIFLE score (Akcan-Arikan A., 2007) [2] and the glomerular filtration rate (GFR) formula by Schwartz-Gauthier (1985) [15].

Results and discussion

Children from the control group who did not need the resuscitating volume load were the majority of research (49.23%). These infants from the admission and during all the period of observation took routine intensive care according to international reliable protocols.

Infants of two studied groups and the control group were initially at the same conditions and had the similar NTISS score. According to the NTISS, all newborns be-

longed to Class 3: infants of Group 1 had middle score 23.68±0.76 points, respectively, in Group 2 middle score was 24.92±0.94 points (p=0.175 between groups by the χ^2 criteria). This shows that all the babies were in a severe condition at admission.

Neurological disorders were observed in all infants of studied groups. Neonates of Group 1 had GCS 8.26±0.76 points, the consciousness level in patients of Group 2 was 8.63±0.34 points by GCS (p=0.184 between groups by the χ^2 criteria).

To clarify the question of the presence of acute kidney damage in newborns after perinatal hypoxia-ischemia, we estimated the GFR using Schwarz-Gauthier formula (1985). During all the research period, we did not receive any data as to reduced GFR in all the observed neonates and no significant differences between studied groups were found. Therefore, the data showed no kidney damage in infants of Group 1 (GFR 33.98±3.67 ml/min/1.73 m^2) as well as in Group 2 (GFR 30.44±3.99 ml/min/1.73 m^2; p=0.151 between groups by the χ^2 criteria).

Exploring the urine output we also did not reveal significant differences in either 1st group (1.65±0.26 ml/kg/h), or in the 2nd study group (1.52±0.22 ml/kg/h; p=0.207 between groups by the χ^2 criteria).

Analyzing the data of both study groups and control group, we have not received significant differences in GFR (p=1.0), urine output (p=0.17), or creatinine serum level (p=1.0).

At 28th and 90th days of observation in our study, there were no deaths in studied groups nor in the control group. All the babies survived and were discharged to outpatient care.

Conclusion

Using of 6% HES 130/0.42 at the dose of 10 ml/kg of body weight in term newborns with severe hypoxic-ischemic encephalopathy is safe comparing with normal saline. Moderate doses of 6% HES 130/0.42 can be used in full-term newborns with hypoxic-ischemic encephalopathy when the loading volume of crystalloids was not hemodynamically effective, but additional data needs to be collected before any further conclusions can be drawn.

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