

**THE ASSESSMENT SAFETY OF HYDROXYETHYLSTARCH 130/0.4 TO RENAL
FUNCTION IN PEDIATRIC CARDIAC SURGERY**
Zokirov N.K.¹, Sharipov A.M.², Mamatkulov B.B.³, Shoikramov Sh.Sh.⁴, Abdullaev K.G.⁵
Email: Zokirov663@scientifictext.ru

¹Zokirov Nodirzhon Komilzhon o'g'li - Student of master degree;
²Sharipov Alisher Mirkhamidovich - Doctor of Medical Sciences, Professor, Head of Department;
³Mamatkulov Bahrom Bosimovich - Teaching Assistant;
⁴Shoikramov Shoiles Shorasulovich - Teaching Assistant;
⁵Abdullaev Komilzhon Gafurzhanovich - Teaching Assistant,
DEPARTMENT OF THE DEPARTMENT OF EMERGENCY PEDIATRICS. DISASTER MEDICINE,
TASHKENT PEDIATRIC MEDICAL INSTITUTE,
TASHKENT, REPUBLIC OF UZBEKISTAN

Abstract: the use of cardiopulmonary bypass has an enormous effect on the body's water metabolism. This trial was conducted to evaluate the safety of hydroxyethylstrach (HES) 130/0.4 to kidney function in pediatric cardiac surgery. Aim of the study was to evaluate the effects of HES (130/0.4) usage, as a fluid replacement, on the renal functions in pediatric patients undergoing open heart surgery.

Keywords: children, cardiac surgery, fluid replacement, HES (130/0.4), renal dysfunction, creatinine clearance.

**ОЦЕНКА БЕЗОПАСНОСТИ ГИДРОКСИЭТИЛКРАХМАЛА 130/0,4 ДЛЯ ФУНКЦИИ
ПОЧЕК В ПЕДИАТРИЧЕСКОЙ КАРДИОХИРУРГИИ**
Зокиров Н.К.¹, Шарипов А.М.², Маматкулов Б.Б.³, Шоикрамов Ш.Ш.⁴, Абдуллаев К.Г.⁵

¹Зокиров Нодиржон Комилжонович – магистр;
²Шарипов Алишер Мирхамидович - доктор медицинских наук, профессор, заведующий кафедрой;
³Маматкулов Бахром Босимович – ассистент;
⁴Шоикрамов Шоилес Шорасулович – ассистент;
⁵Абдуллаев Комилжон Гафуржанович – ассистент,
кафедра неотложной педиатрии. Медицины катастроф,
Ташкентский педиатрический медицинский институт
г. Ташкент, Республика Узбекистан

Аннотация: использование искусственного кровообращения оказывает огромное влияние на водный обмен в организме. Это исследование было проведено для оценки безопасности гидроксиптилкрахмала (ГЭК) 130 / 0,4 для функции почек в детской кардиохирургии.

Целью исследования было оценить влияние использования ГЭК (130 / 0,4) в качестве заменителя жидкости и его влияние на функции почек у детей, перенесших операцию на открытом сердце.

Ключевые слова: дети, кардиохирургия, замещение жидкости, ГЭК (130 / 0,4), почечная дисфункция, клиренс креатинина.

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Actuality: Hydroxyethyl starches (HES) have been used as standard solutions for volume replacement therapy for decades. Molecular weight and molar substitution have continuously been adapted to minimize adverse effects such as impairment of blood coagulation or renal function [1]. In 2013, in three reviews and/or meta-analyses, authors have evaluated the effect of HES in different surgical settings. In the first, the authors analysed the safety of tetrastarches for mortality, renal function and clinical effects on coagulation in cardiac and non-cardiac surgical patient populations and found no adverse effects. In the second, the authors specifically evaluated renal safety for cardiac and non-cardiac surgical patients and found no adverse effects of HES compared to other fluids [2-3]. In the third one [4], the authors also did not identify any differences in the incidence of death or acute kidney injury (AKI) in surgical patients. Nevertheless, analysis of a more homogeneous patient population might provide more detailed insights and improve the sensitivity of such analyses. Especially surgical patients with relatively high perioperative blood loss, such as in cardiovascular surgery, might reveal additional safety information. In patients who underwent surgery with CPB, panendothelial damage related to systemic inflammatory response is observed frequently. As a consequence, protein loss, increased endothelial permeability, and interstitial edema can emerge. Fluid loss from intravascular area to interstitial area leads to hypovolemia. During CPB, renal blood flow and vascular resistance decrease by 30% [5]. In children, elevated perfusion rates are required due to increased metabolic requirements, which also show destructive effects on the structural blood components. Although the CPB technology is advancing, CPB circuits are too large for pediatric population, and these circuits lead to critical decrease in the structural components of blood, coagulation factors, and other plasma proteins. In newborns and children, oligouric renal failure after CPB is very common [6]. The purpose of colloid usage during CPB is to sustain osmotic pressure to avoid fluid loss from tissues and decrease fluid

retention. Hydroxyethyl starch (HES) solution is widely used as intravascular volume dilator and priming solution in CPB in adult patients [7]. It has

been required that AKI risk is increased during hypovolemia treatment with HES. Therefore, the effects of HES on kidney functions are still controversial and investigations under this issue are still being continued [8]. Although low molecular- weight HES (130/0.4) solution does not affect kidneys, its influences on children are yet to be checked.

Aim of the study is to evaluate the effects of HES (130/0.4) usage, as a fluid replacement, on the renal functions in pediatric patients undergoing open heart surgery.

Materials and methods. Our research was conducted in clinical hospital of Tashkent Pediatric Medical Institute and Republican Research Centre for Emergency Medicine. 20 children between 2-6 years age included to study with congenital heart defects. 10 of them were operated due to Tetralogy of Fallot and rest 10 was operated with atrial (4) and ventricular (6) septal defects. Patients who were operated in emergency conditions were not included in the study. During cardiopulmonary bypass (CPB), all children received HES 130/0.4 as a volume replaced solution. . Serum creatinine, blood urea nitrogen (BUN), urinary albumin and creatinine, serum and urine electrolytes were analyzed during CPB (P1), after CPB (P2), at the end of the operation (P3), on 24th hour (P4), and on 48th hour postoperatively (P5). Fractional sodium excretion (FENa), urinary albumin/creatinine ratio, and creatinine clearance were measured. CPB was performed using modified «Jostra» (Sweden-Germany) pump, membrane oxygenator (Dideco membrane D-901 or D-902), nonpulsatile blood flow (2.5 mL/m²), and moderate hypothermia (27–30 C) and average perfusion pressure was kept between 45 and 50 mmHg during CPB. Hematocrit level was kept above 25% for patients with weight >10 kg and 32% for patients with <10 kg. All the patients were administered to Cardiac Intensive Care Unit (ICU) after the operation. Hemodynamic parameters including systolic arterial pressure, diastolic arterial pressure , mean arterial pressure , heart rate and CVP were recorded at the same time except the CPB. In the urine samples collected from the patients, the following urine electrolytes were monitored: Na, K, Cl, albumin, and creatinine. Fractional sodium excretion (FENa) value was determined by using the formula: (urine Na x plasma creatinine x100) / (urine creatinine x plasma Na). Creatinine clearance was determined according to the following formula: Cr. Clearance (mL/min) = [(140 – age) x (body weight)]/[serum creatinine (mg/dL) x 72]. The first stage of AKI was defined by at least one of the following criteria: an increase in serum creatinine of at least 50% above baseline, an absolute increase in serum creatinine of at least 0.3 mg/dL, and/or a urine output <0.5 mL/kg/h for at least 6 hours.

Results. All patients included in the study. During CPB (P1 period) serum creatinine was average 0.4-0.5 mg/dL in 12 children and 0.5-0.7 mg/dL in rest 8 children . In P2 period of trial serum creatinine showed average 0.6- 0.7 mg/dL in all children and this result stayed till the P4 period. In the final (P5) stage of investigation, serum creatinine was mean 0.3-0.4 mg/dL in all pediatric patients. The BUN was mean 8-12 mg/dL in P1 and P2 periods of trial , showed 16-18 mg/dL in the P3 stage of study and again dropped to 7-10 mg/dL at the end period of investigation. In terms of creatinine clearance examination, the results were between 80-88 ml/min in the initial stages of trial (P1-P3) , little enhanced to 90-100 ml/min in the P4 stage and showed mean 86-90 ml/min result in the end of the investigation period. Urine albumin/creatinine ratio was increased to mean 158.4±225.6 µg/mg after CPB (in the P2-P3 periods) and decreased to average 64.3±91.5 µg/mg in end stage of trial . The data of FENa was 0.6-0.8 % in the beginning stage of trial (P1-P2), decreased to 0.4% in the middle period of the study (P3) and again showed the results of initial stage investigation (0.6-0.8%) . Urinary albumin and creatinine, serum and urine electrolytes were in normal records in all children during the whole investigation periods. Urine output was mean 1376.2 ±672.1 ml during the trial periods. Diuretic (furosemide) was administered to 7 patients and inotropic support (dopamine) was required for 5 patients. As the fluid replacement , average 414.8 ± 80.6 ml HES 130/0.4 was administered during our trial. It was not observed any kidney dysfunction (an increase in serum creatinine of at least 50% above baseline, an absolute increase in serum creatinine of at least 0.8 mg/ dL, and/or a urine output <0.5 mL/kg/h for at least 6 hours).

Discussion. We evaluated HES (130/0.4) usage as a volume replacement on subclinical and clinical renal functions on pediatric patients undergoing cardiac surgery. Because of large volumes of priming solution and volume replacement, blood loss and transfusion requirements are especially relevant in cardiac surgery. A central safety aspect of starches is their effect on coagulation. Generations with a higher degree of molar substitution (0.5 or higher) have been shown to impair coagulation [9]. The results of several studies comparing tetrastarches with a molar substitution of 0.4 to other generations suggest a smaller effect on coagulation with tetrastarches [10]. Other safety parameters we analysed were overall mortality, the incidence of AKI and the need for reoperations, which might also indicate bleeding events. Firm conclusions could not be drawn for AKI and mortality, owing to a very low number of reported events. For AKI, there is an overall trend towards providing specific definitions only in the later studies, which mainly relied on creatinine values (for example, peak creatinine value at least 50% above baseline) and need for renal replacement therapy. In a recently published trial by Van der Linden *et al.* [11], tetrastarch was compared with albumin in paediatric cardiac surgery. They assessed safety parameters until 28 days after surgery and monitored highly sensitive markers of renal function, but they could not detect significant differences between groups. With regard to the need for reoperations, a pooled analysis of all starches showed no difference compared to other volume substitutes, which confirms the data about blood loss and transfusions. With regard to length of stay in the ICU or in the hospital, tetrastarches seem to be superior to crystalloids and gelatin. Albumin might offer advantages in terms of length of stay compared to tetrastarches. As length of stay in the hospital is a parameter that is especially prone to non-medical confounders, such as availability of secondary care or weekend discharges, the validity of this endpoint may be lower than that for other safety endpoints, given the low number of studies and patients available for this comparison. Generally, volume used for fluid therapy is a tricky parameter in assessment of the efficacy of therapy, as this need is

judged by physicians on the basis of different parameters, such as volumetric parameters or cardiac preload. Yet, it is the only parameter consistently reported in studies on volume therapy. In addition, combining study results might be more reliable than evaluating single studies, as individual deviations in judgement about the need for fluid therapy might regress towards the mean. The volume effect of colloids has been discussed extensively and also controversially [12]. In pediatric age group, acute renal failure (ARF) was the most commonly observed complication of CPB and showed poor prognosis.⁷ In a study conducted by Chesney and colleagues,⁸ among 248 infant patients, 20 patients developed ARF, 6 patients required dialysis, and 13 patients were lost. In another study conducted by Ridgen and colleagues,⁹ the risk factors that lead to ARF development after CPB were investigated in pediatric patients. The research team concluded that complexity of cardiac diseases, risky nature of cardiac surgery and long CPB period, chronic hypoxia and acidosis as the result of already existing diseases, and heart failure observed in early terms increased the incidence of postoperative ARF. The group reported a significant increase in ARF ratio, especially in newborn patients. It was also stated that in pediatric patients, already existing diseases and age were more crucial parameters for determining the postoperative renal failure than bypass time period alone. In our study, none of the patients developed renal failure or required dialysis. The studies in the literature that was based on HES 130/0.4 usage in CPB to understand its effects on renal functions were based on adult patients. In those trials, it was found that HES 130/0.4 usage as the primary solution was reliable. We used HES 130/0.4 solution as fluid replacement in pediatric CPB patients and tried to examine the effects on renal functions. In investigation, we did not detect any renal negative functional effect of HES 130/0.4.

Conclusion. To put it in a nutshell, HES 130/0.4 usage as the primary fluid replacement in pediatric patients who are undergoing cardiac surgery did not show any negative effects on kidney functions and it can be used safely as the CPB fluid replacement in pediatric patients undergoing cardiac surgery.

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