Original Article

Comparing the Efficacy of 6% Hydroxyethyl Starch 130/0.4 and Human Albumin for Intravenous Fluid Replacement in Pediatric Open-Heart Surgery

Mojgan Rahimi[1], MD; Saida Eshraqi[2], MD; Behrang Nooralishahi[*3], MD

ABSTRACT

Background: Providing and maintaining normovolemic condition during major surgeries is a major challenge, especially in children. In this respect, third-generation hydroxyethyl starches seem to be more cost-effective than human albumin. However, the efficacy of 6% hydroxyethyl starch (HES) 130/0.4 compared to other alternatives such as human albumin 5% remains uncertain in children.

The present study aimed to assess the efficacy and safety of replacing human albumin 5% with 6% HES 130/0.4 for volume replacement therapy in children undergoing selective open cardiac surgery.

Method: This randomized double-blinded clinical trial was performed on 59 children aged less than 2 years and ASA I-III who were candidated for selective open-heart surgery and referred to a children medical center in 2014. The patients were randomly assigned via the block randomization method to the case group (n = 30) receiving a solution of 6% HES 130/0.4 and the control group (n = 29) receiving 5% human albumin.

There were no between-group differences in hemodynamic parameters—including pulse rate, systolic and diastolic blood pressures, and mean blood pressure—at the time points of before anesthesia induction, before and after pump insertion, and 24 hours after surgery.

Results: Comparisons of the laboratory indices indicated no differences between the 2 groups at the different time points. The volume of packed cell and colloid fluids infused in the case and control group was also similar.

Conclusions: Compared to human albumin 5%, 6% HES 130/0.4 is a safe alternative to fluid supply during cardiac surgery among children. ***(Iranian Heart Journal 2018; 19(1):37-43)***

KEYWORDS: Hydroxyethyl, Human albumin, Pediatric open-heart surgery

[1] Department of Anesthesiology. Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, IR Iran.
[2] Tehran University of Medical Sciences, Tehran, IR Iran.
[3] Department of Anesthesiology. Children's Medical Center, Tehran University of Medical Sciences, Tehran, IR Iran.

***Corresponding Author:** Behrang Nooralishahi, MD; Children's Medical Center, Tehran University of Medical Sciences, IR Iran.
Email: Rcrdc.Nooralishahi@gmail.com **Tel:** 0912 225 8135

Received: September 23, 2017 **Accepted:** December 10, 2017

Providing and maintaining normovolemic condition during major surgeries is a major challenge, not least in children. It has been well shown that any fluid volume disturbance within surgery can lead to high intraoperative and postoperative mortality and morbidity. [1, 2] Because of the loss of a notable volume of fluid and blood during some major surgeries such as cardiac surgeries, compensating high volumes of suitable fluids is necessary with the aim of compensating for the cardiac output and hemodynamic stability. [3] Moreover, appropriate fluid replacement is essential for ensuring safety and reducing morbidity and mortality in the perioperative period. [4] This issue assumes even more significance in children who undergo major surgeries because of more susceptibility to hemodynamic instability following blood and fluid loss. [5] In children candidated for cardiac surgeries on cardiopulmonary bypass, the use of human albumin and crystalloid fluids have remained the first choice for volume replacement. Compared to crystalloids, the administration of human albumin can stabilize the oncotic pressure as well as decrease the intraoperative positive balance. [7-9] Nevertheless, its high cost compels physicians to discover other alternatives with lower expenses.

Third-generation hydroxyethyl starches seem to be more cost-effective than human albumin. According to a recent survey, 6% hydroxyethyl starch (HES) 130/0.4 can offer fluid volume expansion similar to that of older starches, but its effectiveness in hemostasis seems to be less marked. [10] In some recent investigations, administrating 6% HES 130/0.4 increased the need for renal replacement therapy and even increased the risk of early postoperative mortality. [11, 12] In total, the efficacy of 6% HES 130/0.4 compared to other alternatives such as human albumin 5% remains uncertain in children. The present study aimed to assess the efficacy and safety of replacing human albumin 5% with 6% HES 130/0.4 for volume replacement therapy in children undergoing selective open cardiac surgery.

METHOD

This randomized double-blinded clinical trial was performed on 59 children aged less than 2 years and ASA I-III who were candidated for selective open-heart surgery and referred to a children medical center in 2014. The exclusion criteria were requiring blood transfusion before pumping, underlying hepatic or coagulation disorders, history of cardiac interventions, preoperative unconsciousness, present anemia or cerebral hemorrhage, hypo- or hypernatremia, heart failure or respiratory distress, serum platelet count lower than 100 000, and any renal disturbances leading to oliguria or anuria.

The study was registered by the Ethics Committee of Tehran University of Medical Sciences (No. 1394.650). The day before surgery, the patients were all visited by the anesthesiologist, and the procedures were explained to the parents in detail. On the day of surgery and before transferring the patients to the operating room, written consent was obtained from the parents. After intravenous catheterization and rubbing the EMLA ointment, the syrup of midazolam (0.5 mg/kg) was administered to the children younger than 2 months and the children were transferred to the operating room. The patients were randomly assigned via the block randomization method to the case group (n = 30) receiving a solution of 6% HES 130/0.4 and the control group (n = 29) receiving 5% human albumin. All the patients were monitored at the operating room regarding hemodynamic parameters—including ECG, pulse oximetry, blood pressure, cerebral oximetry, and renal oximetry. Anesthesia was induced using sevoflurane (2.5 mac) along with oxygenation using masks and the Bain circuit system. Thereafter, a peripheral intravenous line was taken using 24-F or 26-F catheters and then dextrose water 5% was infused as

maintenance until cardiopulmonary bypass pump insertion. Subsequently, the anesthesia protocol was changed to fentanyl (50 µg/kg/h) plus midazolam (100 µg/kg/h) and sevoflurane (1.5 mac) with atracurium if required repeated at an interval of 40 minutes. The solutions of HES and albumin were maintained and used for the patients with the maximum dosages of 50 mL/kg. If blood transfusion was required, packed cells were ordered to achieve a hemoglobin level higher than 12 g/dL. The total volume of the infused fluids, arterial and central venous blood pressures, total volume of the blood transfused intraoperatively or within 24 hours after surgery, urinary output, percentage of oxygenation, plasma cell count, need for inotrope agents, and length of ICU stay were assessed in the 2 groups. The baseline characteristics of the patients—including demographics and medical history—were collected by reviewing the hospital recorded files.

For the statistical analyses, the results are presented as means ± standard deviations (SDs) for the quantitative variables and summarized by absolute frequencies and percentages for the categorical variables. The normality of the data was analyzed using the Kolmogorov–Smirnov test. The categorical variables were compared using the χ^2 test or the Fisher exact test when more than 20% of cells with an expected count of fewer than 5 were observed. The quantitative variables were also compared using the *t*-test or the Mann–Whitney U test. For the statistical analyses, the statistical software SPSS, version 16.0 for Windows (SPSS Inc, Chicago, IL), was used. A *P* value of 0.05 or less was considered statistically significant.

RESULTS

The comparison of the baseline characteristics (Table 1) showed no differences in terms of gender, mean age, mean weight, and history of cyanotic diseases between the case and control groups. There were no between-group differences in regard to the hemodynamic parameters—including pulse rate, systolic and diastolic blood pressures, and mean blood pressure—at the time points of before anesthesia induction, before and after pump insertion, and 24 hours after surgery (Table 2).

Table 1. Baseline characteristics of the 2 study groups, who received 6% HES 130/0.4 and 5% human albumin

Characteristics	HES Group	Albumin Group	*P*
Age **(y)**	8.06 ± 7.80	5.93 ± 5.23	0.224
Male gender **(%)**	19 (65.5)	14 (48.3)	0.185
Mean weight **(kg)**	6.06 ± 2.80	5.69 ± 2.60	0.571
Cyanotic disease **(%)**	17 (56.7)	16 (55.2)	0.558

HES, Hydroxyethyl starch

Table 2. Hemodynamic parameters of the 2 study groups, who received 6% HES 130/0.4 and 5% human albumin at different time points

Characteristics	HES Group	Albumin Group	*P*
Heart rate (beats/min)			
Before induction	124.13	122.45	0.692
Before pumping	126.57	123.59	0.438
After pumping	128.87	124.38	0.240
24% after surgery	126.47	127.17	0.484
Systolic blood pressure (mm Hg)			
Before induction	78.37	76.41	0.631
Before pumping	73.60	73.93	0.923
After pumping	75.00	77.69	0.506
24% after surgery	80.97	79.90	0.800
Diastolic blood pressure (mm Hg)			
Before induction	46.10	41.90	0.224
Before pumping	43.63	39.86	0.250
After pumping	42.53	41.31	0.674
24% after surgery	48.77	48.77	0.234
Mean blood pressure (mm Hg)			
Before induction	56.53	53.00	0.311
Before pumping	53.10	50.72	0.456
After pumping	53.10	52.66	0.888
24% after surgery	59.13	55.72	0.301

HES, Hydroxyethyl starch

These insignificant differences were also revealed separately in both cyanotic and non-cyanotic subgroups. The comparison of the laboratory indices between the case and control groups indicated that in both groups, arterial O_2 saturation and O_2 pressure were increased after pump insertion and also 24 hours after surgery as compared to before the pump, but the condition of the other indices—including PH,

PCO_2, HCO_3, and serum hemoglobin level—remained partially unchanged before and after pump in both groups. Overall, no differences were revealed in the blood gas parameters, serum lactate level, serum hemoglobin level, and brain oximetry between the case and control groups (Table 3).

Table 3. Laboratory parameters of the 2 study groups, who received 6% HES 130/0.4 and 5% human albumin at different time points

Characteristics	HES Group	Albumin Group	*P*
Arterial O_2 saturation (%)			
Before induction	84.17	82.52	0.780
Before pumping	87.03	83.72	0.450
After pumping	97.00	97.10	0.876
24% after surgery	96.27	97.48	0.133
Brain oximetry (%)			
Before induction	72.64	65.00	0.069
Before pumping	58.80	57.03	0.668
After pumping	69.87	68.00	0.451
24% after surgery	68.09	64.44	0.436
O_2 pressure			
Before pumping	107.60	152.31	0.166
After pumping	152.73	190.72	0.212
24% after surgery	165.28	166.32	0.971
HCO_3 level (meq/L)			
Before pumping	23.46	22.63	0.520
After pumping	23.14	23.10	0.973
24% after surgery	22.98	24.46	0.343
PCO_2 (mm Hg)			
Before pumping	39.20	40.62	0.614
After pumping	37.07	35.93	0.572
24% after surgery	35.69	39.07	0.166
Arterial PH			
Before pumping	7.39	7.36	0.307
After pumping	7.40	7.41	0.885
24% after surgery	7.42	7.40	0.599
Arterial lactate level (meq/L)			
Before pumping	2.25	1.74	0.385
After pumping	3.56	2.82	0.248
24% after surgery	3.59	3.68	0.910
Serum hemoglobin level (g/dL)			
Before pumping	12.81	11.82	0.250
After pumping	11.43	10.64	0.262
24% after surgery	11.58	11.16	0.330

HES, Hydroxyethyl starch

Similar findings were observed in both cyanotic and non-cyanotic subgroups. The comparison of the other parameters such as serum platelet counts, need for inotrope use, volume of bleeding, urine output, and total ICU stay showed no between-group differences (Table 4). Similarly, the volume of packed cells infused in the case and control groups was 17.97 and 15.82 mL/kg (P = 0.676), the volume of colloid fluid infused was 37.30 and 34.62 mL/kg (P = 0.264), and the volume of prime fluid plus packed cell was 36.57 and 34.23 mL/kg (P = 0.662), respectively, with no difference between the groups.

Table 4. Volume of bleeding, urine output, inotrope use, and ICU stay of the 2 study groups, who received 6% HES 130/0.4 and 5% human albumin at different time points

Characteristics	HES Group	Albumin Group	*P*
Volume of platelet (unit)	1.71	1.83	0.598
Inotrope use after pump (µg /kg/min)	0.04	0.05	0.068
Total bleeding (mL/kg)	19.01	15.90	0.436
Urine output (cc/kg/h)	37.03	34.62	0.840
Total ICU stay (d)	4.10	4.48	0.739

HES, Hydroxyethyl starch

DISCUSSION

Open cardiac surgery is generally accompanied by high bleeding rates and thus with need for blood transfusion. [13, 14] In such operations, supplying fluids is of vital importance for stabilizing hemodynamic status. Because of instability after being weaned from the pump, this fluid compensation is necessary to achieve appropriate postoperative outcomes. In other words, the lack of fluid management can lead to systemic tissue hypoperfusion and acidosis. Additionally, the pump itself can induce inflammatory reactions, resulting in endothelial dysfunction and thus interstitial edema. [15-17] Although crystalloid fluids are available and cost-effective, they should be administered in high volumes to maintain normal hemodynamic status. Moreover, these fluids may not provide enough intravascular volume loads and thus may not be the first and only choice for major surgeries. [18-20] In this regard, 6% HES 130/0.4, which is a colloid fluid, is deemed a good alternative for the supply of fluids in such

clinical conditions—particularly in children subgroups. [21] Nonetheless, its efficiency has hitherto remained unclear. According to our findings, the total efficacy of 6% HES 130/0.4 was completely similar to that of 5% human albumin as an acceptable standard fluid replacement regarding all hemodynamic parameters and laboratory indices both before and after pump insertion. This finding indicates the high efficacy of 6% HES 130/0.4 in providing appropriate hydration condition in cardiac surgeries in children. Van der Linden et al [22] (2015) succeeded in showing that the intraoperative use of HES was associated with a low positive fluid balance compared to human albumin. Likewise, perioperative blood loss, volumes of red blood cells and fresh frozen plasma administered, and number of children who received transfusions were also significantly lower in the HES group, but we observed no difference regarding the incidence of postoperative renal failure requiring renal replacement therapy or of morbidity and mortality. Similarly, Hanart et al [23] (2009) indicated that the volume of colloid used intraoperatively was similar in both groups, who received 6% HES 130/0.4 and 5% human albumin, correspondingly. The measured and calculated blood losses were not different between the groups, but a higher number of the children in the albumin group required allogeneic blood transfusion. Moreover, intraoperative fluid balance was lower in the HES group. In their study, in total, the postoperative outcome was not different between the groups. Morioka et al [24] (2013) reported that all their pediatric patients were hemodynamically stable at different time points of surgery. The changes observed in the assessed laboratory parameters—including hematological and coagulation parameters—or in any other safety parameter determined did not reveal any safety concern related to the administration of 6% HES 130/0.4 up to doses of 50 mL/kg body weight. In a study by Standl et al [25] (2008), comparable volumes of 6% HES 130/0.4 and 5% human albumin were infused in 82 small infants (< 2 y) undergoing non-cardiac surgery to restore or maintain hemodynamic stabilization. It can be concluded that receiving similar volumes of 6% HES 130/0.4 and 5% human albumin for intraoperative volume requirements in patients undergoing cardiac surgery was associated with no differences in transfusion requirements or blood loss. The study results finally indicated that 6% HES 130/0.4 had a reliable volume effect, contributed to significant human albumin savings, and was safe in pediatric patients undergoing major cardiac surgeries. However, when interpreting the results of the current study, some limitations should be taken into account such as the low patient number and the missing control group. Thus, the data can only be considered as explorative with respect to volume effects and human albumin savings, and safety conclusions are limited.

CONCLUSIONS

Our study showed no difference in hemodynamic parameters, laboratory indices, inflammatory condition, and bleeding load within cardiac surgeries following the infusion of 6% HES 130/0.4 and 5% human albumin and thus the former fluid can be a safe alternative for fluid replacement in children undergoing major surgeries.

Acknowledgments
The authors wish to thank the Clinical Research Development Center of Rasoul-e-Akram Hospital, Iran University of Medical sciences, for the technical support of the current project.

REFERENCES

1. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. Ann Intensive Care. 2012;2:S1.

2. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. PediatrCrit Care Med. 2014; 15:131–8.

3. Stein A, de Souza LV, Belettini CR, Menegazzo WR, Viégas JR, Costa Pereira EM, et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study.Crit Care. 2012; 16:R99.

4. Peng et al.. Effects of colloid pre-loading on thromboelastography during elective intracranial tumor surgery in pediatric patients: hydroxyethyl starch 130/0.4 versus 5% human albumin. Anesthesiology (2017) 17:62.

5. Hazle MA, Gajarski RJ, Yu S, Donohue J, Blatt NB. Fluid overload in infants following congenital heart surgery.PediatrCrit Care Med. 2013;14:44–9.

6. Bailey AG, McNaull PP, Jooste E, Tuchman JB. Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? AnesthAnalg. 2010; 110:375–90.

7. Riegger LQ, Voepel-Lewis T, Kulik TJ, Malviya S, Tait AR, Mosca RS, et al. Albumin versus crystalloid prime solution for cardiopulmonary bypass in young children. Crit Care Med. 2002;30:2649–54.

8. Van der Linden et al. Efficacy and safety of 6% hydroxyethyl starch 130/0.4 (Voluven) for perioperative volume replacement in children undergoing cardiac surgery: a propensity-matched analysis. Critical Care. 2015, 19 (1): 87.

9. Golab HD, Scohy TV, de Jong PL, Kissler J, Takkenberg JJ, Bogers AJ. Relevance of colloid oncotic pressure regulation during neonatal and infant cardiopulmonary bypass: a prospective randomized study. Eur J Cardiothorac Surg. 2011; 39:886–91.

10. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H. Hydroxyethyl starches: different products, different effects. Anesthesiology. 2009;111:187 202.

11. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012; 367:1901–11.

12. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012; 367:124–34.

13. Wong JC, Torella F, Haynes SL ,Dalrymple K, Mortimer AJ, McCollum CN, et al. Autologous versus allogeneic transfusion in aortic surgery: a multicenter randomized clinical trial. Annals of surgery. 2002; 235(1):145-51.

14. Atlee JL. Complications in anesthesia: Elsevier Health Sciences. 2006.

15. Hosseinzadeh Maleki M et al. Comparing the Effects of 5% Albumin and 6% Hydroxyethyl Starch 130/0.4 (Voluven) on Renal Function as Priming Solutions for Cardiopulmonary Bypass: A Randomized Double Blind Clinical Trial. Anesth Pain Med. 2016;6(1).

16. Toraman F, Evrenkaya S, Yuce M, Aksoy N, Karabulut H, Bozkulak Y, et al., editors. Lactic acidosis after cardiac surgery is associated with adverse outcome. The heart surgery forum; 2003.

17. Boldt J, Brosch C, Röhm K, Papsdorf M, Mengistu A. Comparison of the effects of gelatin and a modern hydroxyethyl starch solution on renal function and inflammatory response in elderly cardiac surgery patients. BJA: The British Journal of Anaesthesia. 2008;100(4).

18. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013; 2(2).

19. Rout C, Akoojee S, Rocke D, Gouws E. Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective caesarean section. British Journal of Anaesthesia. 1992; 68(4):394-7.

20. Kammerer et al. Comparison of 6 % hydroxyethyl starch and 5 % albumin for

volume replacement therapy in patients undergoing cystectomy (CHART): study protocol for a randomized controlled trial. Trials (2015) 16:384

21. Witt L, Osthaus WA, Juettner B, Heimbucher C, Suempelmann R. Alteration of anion gap and strong ion difference caused by hydroxyethyl starch 6%(130/0.42) and gelatin 4% in children. Pediatric Anesthesia. 2008;18(10):934-9.

22. Van der Linden P, De Villé A, Hofer A, Heschl M, Gombotz H. Six percent hydroxyethyl starch 130/0.4 (Voluven®) versus 5% human serum albumin for volume replacement therapy during elective open-heart surgery in pediatric patients. The Journal of the American Society of Anesthesiologists. 2013;119(6):1296-309.

23. Hanart C, Khalife M, De Ville A, Otte F, De Hert S, Van der Linden P. Perioperative volume replacement in children undergoing cardiac surgery: albumin versus hydroxyethyl starch 130/0.4. Critical care medicine. 2009; 37(2):696.

24. Nobutada Morioka, Makoto Ozaki, Michiaki Yamakage, Hiroshi Morimatsu: The Volume Effect and Safety of 6% Hydroxyethyl Starch 130/0.4 in Patients Undergoing Major Elective Surgery: An Uncontrolled, Open-Labeled, Multi-Center Study. The Open Anesthesiology Journal.2013; 03:326-337.

25. T. Standl, H. Lochbuehler, C. Galli, A. Reich, G. Dietrich and H. Hagemann, "HES 130/0.4 (Voluven) or Human Albumin in Children Younger than 2 yr Undergoing Non- Cardiac Surgery. A Prospective, Randomized, Open Label, Multicentre Trial," European Journal of Anaesthesiology, Vol. 25, No. 6, 2008, pp. 437-445.