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Intraoperative Use of Large Volume of Hydroxyethyl Starch 70/0.5 Affects Postoperative Serum Creatinine Level-A Retrospective Study

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Abstract

Background: A 6% hydroxyethyl starch (Hespander®, Fresenius-Kabi Japan; HES) solution is generally used for perioperative fluid optimization, though intraoperative use of large amounts is regulated because of possible renal failure or other complications. On the other hand, some studies found that HES70/0.5, with the lowest molecular weight and molar substitution rate, did not affect renal function. In this retrospective study, we investigated the effect of intraoperative use of a large volume of HES70/0.5 on postoperative renal function.

Methods: Hospital electronic medical records of adult patients who had undergone surgery with general anesthesia without blood transfusion were retrospectively reviewed. Those with an intraoperative administration of ≥ 2000 ml of HES were classified as the HES group, while patients who received <1000 ml were used as the control group. They were matched based on amount of estimated total blood loss and total fluid administration. The groups were compared for serum hemoglobin, albumin, and creatinine levels obtained in preoperative and postoperative examinations. We also investigated other postoperative complications.

Results: There were 109 patients in the HES group and 109 in the control group. No significant differences in amount of intraoperative urinary output and infused 5% albumin between the groups were found. In the control, crystalloids were given significantly more often ($p<0.05$). Although there was no significant difference in preoperative creatinine level, that was significantly higher in the HES group on postoperative day 1 (0.90 ± 0.26 mg/dl) as compared to the control (0.81 ± 0.33 mg/dl) ($p<0.05$). The number of patients postoperatively diagnosed with acute kidney injury or who required renal replacement therapy was not significantly different.

Conclusion: Our findings suggest that intraoperative use of a large volume of HES70/0.5 can increase serum creatinine in the postoperative period. However, it remains unclear whether HES at ≥ 2000 ml induces complications.

Keywords: Hydroxyethyl starch; Serum creatinine; Renal dysfunction

Introduction

A 6% hydroxyethyl starch (Hespander®, Fresenius-Kabi Japan; HES) solution is widely used in Japan for plasma volume expansion. Perioperative fluid optimization is a generally accepted procedure [1-6] and several studies have reported that intraoperative use of HES is advantageous to avoid excessive fluid administration [6-9]. However, it has also been shown that fluid resuscitation with HES is likely to require renal-replacement therapy or increase mortality [10-12], thus the Ministry of Health, Labour and Welfare of Japan has warned regarding compliance to HES administration standards.

In Japan, use of the HES product with the lowest molecular weight and molar substitution rate of all related products is mandated, namely, an average molecular weight of 70,000 and molar substitution rate of 0.5 (HES70/0.5). This is different from standard HES, which has been associated with increased risk of renal injury or other complications in previous reports [10-12], while other studies [8,9,13], have concluded that HES70/0.5 does not have an effect on renal function. In this retrospective study, we examined whether intraoperative use of a large volume of HES70/0.5 has effects to induce postoperative renal dysfunction.

Materials and Methods

This retrospective study was approved by the ethical review board of Hiroshima University Hospital. We reviewed the electronic medical records of adult patients who had undergone an operation with general anesthesia without a blood transfusion at our hospital between September 2008 and July 2013. Exclusion criteria were prior dental surgery or thoracotomy procedures. We also excluded those who received a blood transfusion during the perioperative period.

We recorded patient age, gender, intraoperative estimated blood loss, and urinary output, and administrations of crystalloids, colloids, HES, and 5% albumin, as well as postoperative complications by surveying the medical records. Patients with an intraoperative administration of ≥ 2000 ml of HES were classified as the HES group. The control group included patients given 1000 ml of HES intraoperatively, and were chosen at random after matching to the HES group for amount of estimated total blood loss and total fluid administration.

The groups were compared for serum hemoglobin (Hb) and albumin (Alb) levels during the preoperative period and on postoperative day (POD) 1, and daily for serum creatinine (Cre) level, amount of catecholamine used, and other complications on POD1-7. Preoperative data were retrieved within 30 days before the operation.

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We also investigated patients diagnosed with postoperative acute kidney injury (AKI) using the following criteria; increase in serum creatinine ≥ 0.3 mg/dl or ≥ 150% as compared with preoperative levels by POD7 [14]. Patients given a continuous administration of catecholamine or postoperative hemodialysis were also noted.

Statistical comparisons between the groups were conducted using a Mann-Whitney U test, while a χ^2 test was used for comparing the numbers of patients between the groups. We considered a p value <0.05 to be statistically significant.

Results

There were 109 patients in the HES group and 109 in the control group, who were matched for amount of total blood loss and total fluid administration. Demographic and intraoperative values for both groups are shown in Table 1. The surgical procedures employed are listed in Table 2.

The volume of HES administered was 2220 ± 348 ml (mean ± standard deviation) and ranged from 2000-3500 ml. There were no significant differences in amount of intraoperative urinary output or 5% albumin infused between the groups. In the control group, crystalloids were given significantly more often than in the HES group (*p<0.05).

Table 3 shows comparisons of preoperative and postoperative values between the groups. The levels of Hb and Alb were not statistically different between them during the preoperative period and on POD1. There was also no significant difference for preoperative Cre level, whereas that was significantly higher on POD1 in the HES group (0.90 ± 0.26 vs. 0.81 ± 0.33 mg/dl) (p<0.05).

The number of patients diagnosed with AKI by POD7 in HES group and control group was 21 and 13, respectively, which was not a significant difference (p=0.135), while 6 and 10 patients, respectively, received continuous catecholamine infusions during the postoperative period, which was also not significantly different (p=0.436). No patient in either group required renal replacement therapy during the postoperative period.

Discussion

In this study, we demonstrated that postoperative serum Cre level in the HES group was significantly higher as compared to the control group despite no significant difference in preoperative findings. However, the number of patients postoperatively diagnosed with acute kidney injury or who required renal replacement therapy was not significantly different between the groups.

	HES group	Control group
N	109	109
Age (years)	59 ± 14	59 ± 15
Gender (M/F)	92/17	75/34
Duration of operations (minutes)	429 ± 159	407 ± 156
Blood loss (ml)	964 ± 649	955 ± 626
Urine output (ml)	1175 ± 931	1057 ± 853
Amount of fluid administered (ml)	5197 ± 1469	5091 ± 1295
Amount of crystalloids administered (ml)	2724 ± 1311	3926 ± 1058*
Amount of HES administered (ml)	2220 ± 348	1000
Amount of 5% albumin administered (ml)	671 ± 273	705 ± 334

Data are expressed as the mean ± standard deviation. Mann-Whitney's U test was used to determine differences between the groups. *p<0.05

Table 1: Patient demographic and intraoperative data.

	HES group	Control group
Hepato-biliary-pancreatic surgery	29	29
Liver surgery	14	16
Living donor for liver transplantation	7	6
Living donor for renal transplantation	2	2
Upper gastrointestinal surgery	6	8
Lower gastrointestinal surgery	30	20
Urologic surgery	11	15
Gynecologic surgery	1	2
Orthopedic surgery	4	2
Neurosurgery	3	5
Others	2	4
Total	109	109

Table 2: Types of surgical procedures performed in each group.

		HES group	Control group	P
Hb (g/dl)	Pre	13.6 ± 1.8	13.1 ± 1.6	0.058
	Post (POD1)	10.8 ± 1.8	10.3 ± 1.7	0.060
Alb (g/dl)	Pre	4.1 ± 0.6	4.2 ± 0.5	0.315
	Post	2.7 ± 0.4	2.8 ± 0.4	0.060
Cre (mg/dl)	Pre	0.77 ± 0.18	0.77 ± 0.27	0.340
	Post	0.90 ± 0.26	0.81 ± 0.33	0.002*

Data are expressed as the mean ± standard deviation. Mann-Whitney's U test was used to determine differences between the groups. *p<0.05
Pre: Preoperative values, Post: Postoperative values, Hb: Hemoglobin, Alb: Albumin, Cre: Creatinine, POD1: Postoperative day 1

Table 3: Comparison of preoperative and postoperative values.

It has been reported that fluid overload may be related to severe complications or increase mortality. Optimization of perioperative fluid management is a widely accepted procedure [1-6], with HES shown useful in such cases with lower oncotic pressure [6-9]. However, administration of a large amount of HES may increase the risk of severe renal failure or require renal-replacement therapy, and might also increase mortality as compared with crystalloids in critically ill patients with conditions such as sepsis [10-12].

In those studies, patients received HES with a molecular weight of 130,000 or more for fluid resuscitation. Based on those findings, the allowed amount for use in Japan was strictly restricted under government control in October 2013 to that of HES70/0.5, as shown in the attached document. No relationship between HES70/0.5, with a lower molecular weight, and renal injury has been demonstrated [8,9,13], while several studies have concluded that use of HES in surgical patients is not associated with perioperative incidence of death or renal injury [15,16]. Furthermore, others have noted that perioperative use of HES should be distinguished from use in critically ill patients [17,18].

In the present HES group, the postoperative serum Cre level was significantly higher and there are reports of postoperative renal failure associated with HES administration [19-22]. Intraoperative administration of ≥ 2000 ml may have an effect to increase serum Cre,

as the preoperative Cre and intraoperative urinary output levels were not statistically different between the HES and control groups in our study.

According to the AKI classification [14], there are 2 criteria for determining stage 1 injury. First is serum Cre, for which the criteria state an increase by ≥ 0.3 mg/dl or to ≥ 150% from the baseline, and the second is urine output, <0.5 ml/kg per hour for more than 6 hours. In the present study, we used serum Cre level, because it was difficult to accurately determine postoperative urine output. There was no significant difference between the groups regarding the number of patients diagnosed with stage 1 AKI by POD7 using those criteria. There were 4 patients in the HES group with stage 2 injury, based on the criterion of an increase in serum Cre of 200-300% from baseline, while 1 patient in the control group was classified as stage 3, based on the criteria of increase in serum Cre to >300% from the baseline or serum Cre level ≥ 4.0 mg/dl with an acute increase of ≥ 0.5 mg/dl. We found no statistical difference for the incidence of postoperative AKI between the groups. Furthermore, the number of patients who received catecholamine infusion postoperatively was also not different.

Our findings have several limitations. First, this was a retrospective, observational study. Presently in Japan, it is considered ethically difficult to give HES at ≥ 1000 ml per day to patients, thus our investigation of larger amounts was only possible by using a retrospective protocol. Second, intraoperative data such as urinary output and amount of 5% albumin administered were not different between the groups, thus we could not carefully evaluate patient background or types of surgical procedure utilized. Third, we did not consider perioperative mean arterial pressure (MAP). Although it has been reported that low MAP is associated with AKI [23], information in regard to intraoperative MAP and the duration of low MAP was not available for our retrospective examination.

In conclusion, our findings suggest that intraoperative use of a large amount of HES70/0.5 can increase serum Cre during the postoperative period. However, it remains unclear whether ≥ 2000 ml of HES is associated with complications.

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