Doctor of Philosophy

Efficacy, and safety of 6% hydroxyethyl starch 130/0.4 to albumin in post-operative patients following pancreaticoduodenectomy

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Efficacy, and safety of 6% hydroxyethyl starch 130/0.4 to albumin in post-operative patients following pancreaticoduodenectomy

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Abstract

Objective: This study was the efficacy, and safety of administering hydroxyethyl starch 6% 130/0.4 versus 5% albumin in patients undergoing pancreaticoduodenectomy.

Background: Hypovolemia often occurs in patients undergoing extensive abdominal surgery. We hypothesized that 6% hydroxyethyl Starch (HES) 130/0.4 is equally efficacious and safe, compared to albumin and has added advantages such as low cost, disease-free transmission, and ready availability.

Methods: Eligible adult patients were assigned following their surgery into either the HES 130/0.4 or the albumin group (n = 25 in each group). Crystalloids for hydration and colloid therapy for volume support were administered. The primary endpoint of the study was the hemodynamics. Secondary endpoints were efficacy and safety assessed by physical and laboratory examination, adverse events, and hospital courses.

Results: The HES group had a lower average heart rate (83.7 beats/min vs. 89.5 beats/min; $p = 0.017$) and showed no differences in MAP compared to the albumin group. In addition, the HES group maintained higher hematocrit (30.9% vs. 27.6%; $p = 0.02$), whereas the albumin group showed prolonged activated partial thromboplastin time during the first 24 h following surgery (38.6 s vs. 42.9 s; $p = 0.017$). Other laboratory values and hospital courses were comparable in the two groups. However, the mean cost of the colloids was significantly lower in the HES group than in the albumin group (462,176 Won vs. 106,459 Won; $p < 0.001$).

Conclusions: This study showed that 6% HES 130/0.4 is a more appropriate fluid strategy in post-operative patients following extensive abdominal surgery without sepsis.

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INTRODUCTION

Hypovolemia often occurs in patients undergoing extensive abdominal surgery. Possible reasons for the volume deficits include perspiration through the surgical wound, loss to the third space, and blood loss and exudation. [1, 2] Hypovolemia can lead to poor tissue perfusion and thus adversely affect the clinical outcome. [3, 4] The goal of volume replacement therapy is to maintain circulating blood volume and stable hemodynamics following surgery. Adequate volume therapy is therefore essential to improve tissue perfusion and to avoid organ dysfunction in hypovolemia.

Current evidence suggests that colloid resuscitation may reduce tissue edema and improve recovery compared to post-operative crystalloid resuscitation. [4, 5] Large amount of Lactate Ringer's solution is insufficient to maintain intravascular volume. [6] In intensive care units, the combination of crystalloids, colloids and blood products are used to help the treatment of septic shock. [6, 7] Albumin was the first colloid used in the clinical setting and remains widely used during perioperative periods. [8-10] Because of the lower cost, disease-free transmission, and ready availability of synthetic colloids, synthetic colloids are considered a possible substitute for albumin. However, the adverse effects of synthetic colloids, such as coagulopathy and nephrotoxicity, present a limitation to their use. [11, 12] In addition, fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 in patients with severe sepsis. [13, 14] But, several recent randomized controlled trials found no evidence for nephrotoxicity of artificial colloids when used in a perioperative setting in noncritically ill patients. [15-20] Also, the long-term mortality rates did not differ in patients with severe sepsis assigned to HES 130/0.42 versus Ringer's acetate. [21, 22]

Hydroxyethyl starch (HES) is a high polymeric glucose compound synthesized by hydrolysis and subsequent hydroxyethylation of maize or potato starch amylopectin. HES is characterized by its molecular properties, expressed as mean molecular weight/degree of substitution. HES 130/0.4, which is rapidly degradable, does not accumulate in the body,

even after repeated doses. The plasma expanding effects of 6% HES and 5% albumin were similar to 100% of the infused volume, lasting 3–4 h, and showed similar initial volume effects. [13] HES 130/0.4 is therefore believed to be at least as effective and have less adverse effects on hemostasis and nephrotoxicity compared to albumin. [10]

The purpose of this prospective, randomized clinical trial was that we investigated the efficacy and safety of 6% HES 130/0.4 administration, compared to 5% albumin in patients without septic shock, who undergo pancreaticoduodenectomy (extensive abdominal surgery) and perioperatively require fluid resuscitation.

METHODS

Study design

This was a prospective, randomized, active-controlled, open-label phase IV, parallel group study to compare the hemodynamic effects and clinical outcomes of HES 130/0.4 and 5% albumin during operation and post-operative 1 day in patients undergoing pancreaticoduodenectomy. Due to the apparent differences in the packaging of the study drugs, this was not a blinded trial. This study was approved by the Institutional Review Board of the ASAN Medical Center, Seoul, South Korea and was monitored in accordance with applicable local regulations, standard operating protocols (SOPs), and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all patients. This study protocol was registered in the clinical trial protocol registration system (ClinicalTrials.gov: NCT01758172).

Fifty consecutive patients undergoing elective pancreaticoduodenectomy were included in this study. Patients with a history of known hypersensitivity to 6% HES 130/0.4 (Voluven®; Fresenius Kabi, Bad Homburg, Germany) or 5% albumin, renal dysfunction (serum creatinine > 1.5 mg/dL), severe cardiac disease (New York Heart Association classes III and IV), severe respiratory disease (PaO_2 / FiO_2 < 200), preoperative coagulopathy (platelet count

< 100,000 / mm^3, activated partial thromboplastin time < 70 s, or prothrombin time INR > 2.5, were excluded from enrollment. In addition, pregnant women or lactating patients and those enrolled in other clinical trials within 3 months of this study period were excluded.

Pancreaticoduodenectomy or pylorus preserving pancreaticoduodenectomy was performed according to the decision by the individual surgeons. Combined wedge or segmental resection of major vessels was performed when the mass was inseparable or tumor invasion was suspected.

After surgery, the enrolled patients were randomly assigned at a ratio of 1:1 into two groups: patients in the study group received HES infusion and those of the control group received albumin. The patients were then transferred to the surgical intensive care unit (ICU). The study was conducted during the first 24 h post-surgery.

Protocol

Prior to surgery, each patient was screened through their medical history and physical examination to determine their clinical status. Baseline hemodynamic and laboratory tests were also performed. All patients were sent to the ICU after pancreaticoduodenectomy and received close hemodynamic monitoring consisting of five-lead electrocardiogram, pulse oxymetry, noninvasive blood pressure, arterial and central venous lines, and urinary catheter for 24 h.

Intravenous fluid therapy administered during the first 24 h post-surgery consisted of a) crystalloid therapy using Lactated Ringer's solution (RL), and b) colloid therapy with either 5% human albumin in a 250-mL pack (n = 25) or 6% HES 130/0.4 in a 500-mL pack (n = 25).

Fluid replacement therapy (crystalloids and colloids) was given in the following manner. Crystalloids were administered as a maintenance fluid to compensate for fluid lost by sweating, drains, gastrointestinal tract, and urine output in a dose according to standard

protocol. Colloid therapy consisting of either 6% HES 130/0.4 or 5% albumin was administered to keep the central venous pressure (CVP) up to 7 mmHg. Concomitant fluid therapy with drugs other than those prescribed for the treatment group was prohibited. After the study period (post-operative 24 h), fluid therapy was administered per the standard management techniques used following surgery.

All patients underwent the standard procedures indicated for extensive abdominal surgery including general anesthesia, pain medication, antibiotic therapy and management of infectious complications. Predefined standardized policies, as per our hospital protocol, were used for providing ventilator support, if needed, starting enteral nutrition support, and discharging from the ICU and hospital. Blood/plasma products were administered by the following policies: packed red blood cells (RBCs) were transfused if the patient's hemoglobin was below 8 g/dL, and fresh frozen plasma (FFP) and platelet concentrates were transfused as per the American Society of Anesthesiologists (ASA) practice guidelines for blood component therapy.

Hemodynamics, efficacy, and safety measurement

Mean arterial pressure (MAP), heart rate, and urine output were recorded every hour during the first 24 h following surgery. Routine hematology and biochemistry, including serum albumin, blood coagulation tests, and renal function parameters, were assessed at the end of the operation and on the first and second post-operative days (POD). The volume of crystalloids and colloids infused during the study period was recorded, and the cost of the fluids was estimated. The blood products administered, the length of the hospital and ICU stays, and the time at which enteral nutrition was started were also recorded. In addition, post-operative bleeding, the need for hemodialysis, mechanical ventilation, and re-exploration, and in-hospital mortality were documented. The primary end point of this study is hemodynamic parameters for fluid therapy and secondary end point is laboratory result

such as platelet counts (10^3μL), PT (%), aPTT (s) and Creatinine (mg/dL).

Statistical analysis

Statistical analysis was performed using SAS software (version 9.1). The study sample size was calculated to evaluate the non-inferiority of 6% HES 130/0.3 compared to 5% albumin. Based on the assumption of a standard deviation for MAP of 9% as significantly difference (power, 0.8; a significance threshold, 0.025; drop out rate, 20%), the total number of patients required for this study was 48. Secondary endpoints, including laboratory parameters and clinical results between patient groups, were compared using two-sided tests at a 5% significant level and using the T-test, repeated measure ANOVA, and chi-square test as applicable.

RESULTS

Study participants

A total of 66 adult patients were assessed for eligibility. From these, 16 subjects were found to be ineligible due to changes in the nature of their operation (8); non-admittance to the ICU (7); refusal of consent (1). The remaining 50 patients admitted to the ICU after pancreaticoduodenectomy were randomized into the study treatment groups, 25 in each of the HES 130/0.4 and albumin groups (Figure 1). The demographic characteristics of the patients, including sex, age, height, and weight, laboratory and histopathologic findings were comparable in the two groups. The baseline characteristics of the patients are summarized in (Table 1.) The baseline hemodynamics of MAP (89.8 mmHg vs. 89.7 mmHg; $p = 0.989$) and heart rate (66.7 beats/min vs. 71.3 beats/min; $p = 0.119$) showed similar values in both groups. Laboratory tests including hematology, coagulation tests, biochemical tests and urinalysis data demonstrated no differences between the HES and albumin groups. In addition, histopathologic findings of disease showed no differences between both groups (*p*

= 0.874).

Fluid input and output

The average time of operation for patients administered HES and albumin were similar (387 min vs. 417 min; $p = 0.989$). Surgical technique performed was evenly distributed for both groups of patients ($p = 0.612$).Intraoperative colloid and crystalloid administration did not differ between the two groups (Table 2). An equal amount of crystalloid (4,100 ml vs. 4,400 ml; $p = 0.318$) and colloid (1,000 ml vs. 975 ml; $p = 0.377$) was given to patients receiving either HES or albumin during surgery.

Although the infused crystalloid volume (2,625 ml vs. 2,445 ml; $p = 0.427$) was the same, patients in the HES group received a significantly greater volume of HES than those in the albumin group (3,725 ml vs. 2,250 ml; $p = 0.0002$) during the first 24 h after surgery. (Table 3)

Hemodynamics

Hemodynamic data, including mean arterial pressure, heart rate, and CVP, were analogous at baseline between both groups. At the primary end point, the difference in the lowest MAP between the HES (78.0 mmHg) and albumin (79.6 mmHg) group was significantly smaller than the inferiority margin of 9 % (8.228 mmHg). This demonstrates that HES 130/0.4 is not inferior to albumin in terms of its hemodynamics. In addition, a higher mean heart rate was observed in the albumin group than in the HES group patients during the first 24 h post-surgery (83.7 beats/min vs. 89.5 beats/min; $p = 0.017$). The HES group showed greater hemodynamic stability compared to the albumin group.

Efficacy and safety

Routine hematology parameters were maintained in normal ranges during the entire study period. Patients in the HES group had significantly higher hematocrit levels compared to

those in the albumin group (30.9% vs. 27.6%; $p = 0.02$) under the same amount of RBCs were transfused, whereas patients in the albumin group showed more prolonged activated partial thromboplastin time (aPTT) (38.6 s vs. 42.9 s; $p = 0.017$) during the first 24 h following

Figure 1. Flow diagram showing enrollment, randomization, and follow-up of the study population

Table 1. Patient Baseline Data

	HES Group (n = 25)	Alb Group (n = 25)	*p*-value
Age (years)	58.7 ± 10.8	57.3 ± 11.2	0.645
Male sex, no. (%)	16 (64)	14 (56)	0.564
Weight (Kg)	62.5 ± 7.7	61.7 ± 9.7	0.765
Height (cm)	163.7 ± 9.0	161.4 ± 7.6	0.319
Hemodynamics			
Mean arterial pressure (mmHg)	89.8 ± 11.7	89.7 ± 9.9	0.989
Heart rate (beats/minute)	66.7 ± 10.9	71.3 ± 9.6	0.119
Laboratory findings			
Hematocrit (%)	37.85 ± 3.35	36.56 ± 4.18	0.234
Platelet (10^3/μL)	226.20 ± 54.12	279.40 ± 145.12	0.295
PT (%)	96.23 ± 12.82	93.48 ± 11.67	0.431
aPTT (s)	27.91 ± 2.34	28.34 ± 2.66	0.554
Creatinine (mg/dL)	0.76 ± 0.20	0.68 ± 0.16	0.122
Albumin	3.68 ± 0.31	3.67 ± 0.32	0.893
Cystic GFR	131.16 ± 23.99	129.72 ± 27.01	0.843
Histopathologic findings			0.874
Pancreas head carcinoma	12	16	
Ampullary carcinoma	6	5	
Distal common bile duct carcinoma	1	2	
IPMT	4	1	
Endocrine tumor	1	0	
Pseudopapillary neoplasm	1	0	
Chronic pancreatitis	0	1	

Values are represented as means ± standard deviations.

HES group, 6% hydroxyethyl starch 130/0.4 group; Alb group, 5% albumin group; PT, prothrombin time; aPTT, activated partial thromboplastine time; GFR, Glomerular filtration rate; IPMT, intrapapillary mucin producing tumor.

Table 2. Intraoperative findings

	HES Group (n = 25)	Alb Group (n = 25)	*p*-value
Time of operation (minutes)	387 (309,428)	417 (319,490)	0.989
Intraoperative fluid administration			
RBC transfused (mL)	800 (800,1520)	800 (720,1520)	1.000
Crystalloid (mL)	4100 (3400,5500)	4400 (3100,7450)	0.318
Colloid (mL)	1,000(1000,1200)	975 (700,1200)	0.377
Surgical technique			0.612
PD	7	9	
PD with PVR	3	3	
PD with PVR, HAR	1	0	
PPPD	11	10	
PPPD , PVR	2	0	
PPPD, PVR, SMAR	0	3	
PPPD, HAR	1	0	

Values are represented as medians (interquartile range) or means ± standard deviations.

HES group, 6% hydroxyethyl starch 130/0.4 group; Alb group, 5% albumin group; RBC, red blood cell; PD, pancreaticoduodenectomy, PVR, portal vein resection; HAR, hepatic artery resection; PPPD, pylorous preserving pancreaticoduodenectomy; SMAR, superior mesenteric artery resection.

Table 3. Fluid input and output at post-operative 24 hours

	HES Group (n = 25)	Alb Group (n = 25)	*p*-value
RBC transfused (mL)	800 (800-1,520)	800 (720-1,520)	1.000
Crystalloid (mL)	2,625 (2,270-2,865)	2,445 (2,300-2,735)	0.427
Colloid (mL)	3,575 (2,500-4,250)	2,250 (1,250-2,500)	0.0002
Urine (mL)	4,826 ± 1,767	4,163 ± 1,479	0.157

Values are represented as medians (interquartile range) or means ± standard deviations.

HES group, 6% hydroxyethyl starch 130/0.4 group; Alb group, 5% albumin group; RBC, red blood cell.

surgery (Table 4). Other laboratory values, including renal function parameters and C reactive protein (CRP) levels, were comparable and maintained similar throughout the study. No significant abnormalities were observed in either the HES or albumin group patients. In addition, the levels of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), were not different between groups (data not shown).

A similar serum albumin level was observed in the two groups at baseline (Table 1). Following surgery the serum albumin level was maintained only in the albumin group, whereas HES group patients showed a decline from preoperative values, with a significantly lower albumin level 24 h following surgery compared to albumin group patients (2.0 g/dL vs. 3.9 g/dL; $p = 0.001$).

Clinical outcomes

from after surgery until 24 h post-surgery, was 4-fold more in the albumin group than in the HES group (462,176 Won (approximately 415 USD) vs. 106,459 Won (approximately 95 USD); $p < 0.001$).

DISCUSSION

This prospective, randomized study investigated the hemodynamics, efficacy, and safety of 6% HES 130/0.4 compared to 5% albumin in patients undergoing extensive abdominal

surgery. The primary goal of this study was to demonstrate that 6% HES 130/0.4 is at least as effective as albumin and may be safely used as an alternative to albumin. Hemodynamic parameters for fluid therapy were selected as the primary endpoints. Clinical outcomes, including laboratory parameters and adverse events, were recorded to compare the efficacy and safety of both colloids.

Good hemodynamics were maintained post-operatively in all study subjects receiving either

Table 4. Hemodynamics and laboratory findings at post-operative 24 hours

	HES Group (n = 25)	Alb Group (n = 25)	*p*-value
Hemodynamics			
Mean arterial pressure (mmHg)	78.0 (67.1-89.3)	79.6 (70-87.5)	0.254
Heart rate (beats/minute)	83.7 (77.3-88.3)	89.5 (82.7-102.0)	0.017
Central venous pressure (mmHg)	7 (6-8)	8 (7-9)	0.128
Laboratory findings			
Hematocrit (%)	30.9 ± 3.9	27.6 ± 3.3	0.002
Platelet (10^3μL)	168 ± 42	170 ± 95	0.244
PT (%)	62.9 ± 12.3	59.0 ± 11.8	0.252
aPTT (s)	38.6 ± 11.5	42.9 ± 8.5	0.017
Creatinine (mg/dL)	0.7 ± 0.2	0.6 ± 0.2	0.104
Albumin	2.0 ± 0.4	3.9 ± 0.5	0.0001
Cystatic GFR	178.7 ± 46.9	160.6 ± 31.7	0.121
CRP (mg/dL)	10.6 ± 3.9	11.6 ± 3.6	0.320
Clinical outcomes			
ICU stay (days)	1 (1-1)	1 (1-1)	0.695
Soft diet start (days)	7 (7-8)	7 (7-8)	0.536
Hospital stay (days)	24 (17-30)	22 (20-33)	0.613
Total cost of fluid therapy (Won)	111,387 (80,439-127,809)	483,462 (270,674-536,839)	<0.0001

Values are represented as medians (interquartile range) or means ± standard deviations.

HES group, 6% hydroxyethyl starch 130/0.4 group; Alb group, 5% albumin group; PT, prothrombin time; aPTT, activated partial thromboplastine time; GFR, Glomerular filtration rate; CRP, C reactive protein; ICU, intensive care unit.

HES 130/0.4 or albumin. In fact, improved heart rate was observed in the HES group compared to that in the albumin group, with no disparity in MAP and CVP between the two groups. No patient used any vasopressor agent during this study. Taken together, our data show that HES is as an effective therapy not inferior to albumin for maintaining the hemodynamics of patients immediately following extensive abdominal surgery. [15, 17)]

HES solutions have been previously shown to have beneficial effects on hemodynamics, and colloids are superior to crystalloids for achieving optimal hemodynamics. [4, 5)] HES 130/0.4, but not albumin, had a beneficial effect on post cardiac surgery patient recovery because of improved tissue perfusion at the microcirculatory level as well as enhanced tissue oxygen supply with no alterations in the acid-base equilibrium. [23, 24)] Conversely, negative base excess was observed after albumin infusion and, in addition, albumin's effect on cardiac output during the early post-operative phase was inferior to that of HES following adult cardiac surgery. [23)] In this study, there were also no statistically significant or clinically relevant differences observed in the treatment groups for other hemodynamics parameters.

From similar baseline values in the HES and albumin groups, serum albumin levels decreased significantly in the HES group post-operatively. However, as expected, because of the infusion of albumin, serum albumin levels were not decreased and were significantly higher in the albumin group than in the HES group. Despite the differences in serum albumin levels, the nature and frequency of post-operative complications and adverse events during the study period were similar between the two groups. Despite hypoalbuminemia is well known as an independent risk factor for the development of surgical site infection and prolonged inpatient stay, albumin supplement after surgery does not alter the post-surgical outcome. [24-26)] Even in critically ill patients who admitted to the ICU, no beneficial effects of albumin on fluid resuscitation were shown in the SAFE study. [27)] Albumin supplementation to nearly double normal serum concentrations in profoundly hypo-albuminemic septic patients had no clinically significant effect in reducing microvascular permeability. [28)]

Extensive surgery can increase microvascular permeability, leading to transcapillary leak of serum protein, especially albumin. Therefore, albumin supplementation is believed to reduce microvascular permeability. In addition, albumin is regarded as related to its transport function for various drugs and endogenous substances. However, previous studies have provided no evidence that albumin administration can alter clinical outcome. [28)]

In this study, we assessed hematology and coagulation parameters to demonstrate the efficacy of HES compared to that of albumin. aPTT was significantly prolonged in the albumin group. In addition, despite the same amount of RBCs being transfused in both groups, a higher hematocrit value was found in the HES group than in the albumin group during the first 24 h post-surgery. Our data agree with those of several other studies. [29-34)] Even in children undergoing cardiac surgery, moderate administration of HES did not cause more bleeding or higher blood product exposure than albumin. [34)] In addition, HES 130/0.4 infusion did not lead to increased blood loss when given in high doses (e.g., 49 mL/kg) in cardiac surgery patients[33)] or when given in 70 mL/kg/day repetitive doses over several days to critically ill head trauma patients. [31)] Because of the combined increased renal clearance and improved pharmacokinetics following optimization of drug molecular weight leading to reduced effects on coagulation, a recent pooled analysis of 449 adults recommended HES 130/0.4 to reduce bleeding complications, blood loss, and transfusion requirements during major surgery. [32)]

Artificial starches with high molecular weight and high molar substitution are associated with negative effects on blood coagulation and may increase the tendency toward post-operative bleeding. [35)] Starch with a low degree of substitution is degraded rapidly and eliminated faster than starch with a higher degree of substitution. [35)] HES 130/0.4, a modern, third-generation hydroxyethyl starch, appears to be nearly free of negative effects compared to second-generation waxy maize starch HES 200/0.5. [33)] Similarly, improved hemodynamics and reduced complications occurred in patients receiving HES 130/0·4 compared to patients

receiving a more viscous starch solution HES 200/0·5. [24, 31-33, 36, 37)]

In our study, HES 130/0.4 had no negative effect on renal function. Colloids such as HES with a low degree substitution are rapidly degradable and have increased renal elimination without plasma accumulation, [38)] while hyperoncotic colloid solutions with prolonged plasma expansion effects have the potential to induce renal impairment. [36, 39-41)] HES, with its beneficial effects on hemodynamics, could play an important role in reducing renal arteriolar vasoconstrictor release or decreasing the size of the renal capillary leak. [40)] The HES 130/0.4 solution, despite repetitive large dosing, preserved comparable volume effects and resulted in a faster metabolism without macromolecule accumulation in plasma. Furthermore, it resulted in no renal complications compared to HES 200/0.5. [41)] Therefore, according to several studies, perioperative HES 130/0.4 causes no adverse impact on the renal function of patients. [37, 42)]

The immunological response of both patient groups was similar for all tests performed at all time points during the study period. In animal studies, HES 130/0.4 downregulate the inflammatory response, through inhibition of the TLRs/NF-kB signaling pathway. [43, 44)] HES has been proposed as a more appropriate plasma substitute in sepsis. Therefore, the effect of HES on immunologic function warrants further study.

Clinical outcomes, as evaluated by the time to commencement of enteral nutrition support, and the number of days in the ICU and hospital, were equivalent in both groups. However, the cost of the total amount of fluid administered from the end of surgery until the patient's discharge from the ICU was 4-fold higher in the albumin group (462,176 Won; approximately 415 USD) than in the HES group (106,459 Won; approximately 95 USD). Despite the higher amount of post-surgical colloid infusion in patients in the HES group, the cost was significantly lower in this group compared to that in the albumin group. [29, 31-34)] Literature studies are increasingly demonstrating the higher cost involved in the restoration of fluid volume by albumin. Perhaps it was because of its lower cost than 6% HES 130/0.4

was suggested as a valid alternative to albumin. [27] While we had only calculated the cost of the administered fluid, as shown in the study of Neff et al,[31] there are other factors which can influence the overall total cost, such as the reduced number of ventilation days, colloid treatment days, and ICU days with HES compared to albumin therapy.

6% hydroxyethyl starch 130/0.4 is efficacious and safe expander in major abdominal operation. Because fluid management influences patient's outcome, there is important what kind of fluid is suitable for perioperative fluid resuscitation in major surgery. Inevitably, 4 reasons were identified that HES 130/0.4 is appropriate for volume resuscitation of open abdominal procedure like Wheaple's operation. First, 6% hydroxyethyl Starch (HES) 130/0.4, compared to albumin, has no differences in hemodynamic parameters and is very cheaper. Second, colloids included HES 130/0.4 are more suitable for volume resuscitation in acute hypovolemia than crystalloids to distribute freely between interstitial and intravascular space. [45] Third, low-molecular preparations like HES 130/0.4 seem not to be harm renal function and have only minimal effects on coagulation. [37] In addition, the Crystalloids Morbidity Associated with Severe Sepsis(CRYSTMAS) study, comparing the efficacy and safety of 6% HES 130/0.4 and NaCl 0.9% for hemodynamic stabilization in patients with severe sepsis, found no difference for adverse events in both groups, whereas a faster hemodynamic stabilization was achieved with HES. [46]

The limitation of this study was that it was conducted in non-blind manner for technical reasons. After surgery, a significantly greater amount of colloid infusion was recorded in HES group patients than in albumin group patients. The disparity of the infused volume between the two colloid groups was due to the difference between the available packages of the two fluids (500 mL of HES vs. 250 mL of albumin). Specifically, according to this study protocol, to maintain CVP up to 7 mmHg, a 500-mL infusion (one bag) of HES 130/0.4 was required, whereas only a 250-mL infusion (one bag) of albumin was used repetitively, thus caused the differences in total amount of colloid between both groups.

CONCLUSION

We conclude that the clinical outcome and safety of HES 130/0.4 is similar to that of albumin administration for volume restoration post-surgery. A more favorable safety profile for coagulation function was seen following HES-based fluid therapy. In addition, the total cost of colloid therapy with HES was 25% of that of albumin therapy. A recent study did not differ in patients with severe sepsis assigned to HES 130/0.42 versus Ringer's acetate [22], compared to a previous research about the significant coagulopathy and adverse kidney effects using HES to stabilize patients with sepsis. [13] The strength of our study is that we focused on the post-operative fluid management of patients who underwent extensive abdominal surgery, while most studies were performed during the operation, and these patients actually require much more fluid post-operatively than during surgery. Therefore, HES is considered to be a more appropriate fluid strategy in post-operative patients without sepsis undergoing extensive abdominal surgery.

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국문요약

이 연구는 췌, 십이지장 절제술을 받은 환자들에서 수술 전후 투여한 6% 하이드록실에틸 전분 130/0.4 이 알부민에 비해 혈역학적 비교, 효율성 및 안정성에 대한 전향적이고 무작위적인 비교연구이다. 규모 있는 복부 수술 후 종종 저혈량증을 경험하게 되는데, 이런 치료에 알부민과 6%하이드록실에틸 전분 130/0.4 이 동등한 효율을 보이며, 후자가 낮은 가격, 무전염 등 장점이 있다고 가정한다. 수술 후 적격의 성인 환자들에게 알부민을 투여한 그룹 (n=25) 과 하이드록실에틸 전분을 투여한 그룹 (n=25) 으로 나눈다. 수액보충에는 정질용액을 용량보충에는 교질용액을 투여한다. 일차 종점으로 혈역학적 변수로 하고, 이차종점으로는 혈액 검사, 부작용, 병원 재원 기간 등의 분석에 대한 효율성과 안정성으로 한다. 결과적으로, 6% 하이드록실 에틸 전분 그룹에서 좀더 낮은 맥박수 (83.7 회/분 : 89.5 회/분; p = 0.017) 를 보이지만, 평균 동맥압에서는 알부민 그룹과 차이가 없었다. 부가적으로, 하이드록실에틸 전분 그룹이 알부민에 비해 높은 혈색소수치 (30.9% : 27.6% ; p = 0.02)를 보이는 반면, 알부민 그룹에서 부분 프로트롬보플라스틴 검사가 더 지연되었다. (38.6 s vs. 42.9 s; p = 0.017). 다른 검사 수치와 재원 기간 등의 차이가 없지만 비용에서는 알부민 그룹보다 하이드록실에틸 전분 그룹이 의미 있게 낮다. (462,176 원 : 106,459 원 ; p < 0.001). 결론적으로 6% 하이드록실에틸 전분 130/0.4 는 패혈증을 보이지 않는 큰 복부 수술을 받은 환자들의 수술 후 사용하는 수액 치료에 좀더 적절하다고 보여진다.