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Influence of low-molecular-weight hydroxyethyl starch on microvascular permeability in patients undergoing abdominal surgery: comparison with crystalloid

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Abstract
Purpose. Adequate volume therapy is essential for stable hemodynamics and sufficient urinary output perioperatively. Hydroxyethyl starch (HES) has been reported to attenuate the microvascular hyperpermeability which occasionally occurs in surgical patients. This study was carried out to evaluate the effect of low-molecular-weight HES on the urinary microalbumin/creatinine ratio (MACR), a marker of microvascular permeability, in surgical patients.
Methods. In a prospective, controlled, and randomized clinical trial, 21 patients undergoing abdominal surgery were divided into two groups. Group HES ($n = 10$) received HES at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during surgery and at 1 $ml \cdot kg^{-1} \cdot h^{-1}$ after surgery, and additionally they received acetated Ringer's solution (AR) at a rate to keep central venous pressure (CVP) at 3–5 mmHg. Group AR ($n = 11$) received AR at a rate to keep CVP at 3–5 mmHg. MACR, soluble intercellular adhesion molecule-1 (sICAM-1), and urinary output were measured intermittently in the perioperative period.
Results. MACR was significantly increased during surgery in both groups. There was no significant difference in MACR between the two groups throughout the study period. The serum concentration of sICAM-1 decreased during surgery in both groups, and that in group HES was significantly lower than that in group AR at the end of surgery. Postoperative urinary output in group HES was greater than that in group AR. The intensive care unit (ICU) stay in group HES was shorter than that in group AR.
Conclusion. Although low-molecular-weight HES does not improve microvascular hyperpermeability, the expansion of the intravascular volume by HES results in higher urinary output in the postoperative period than that seen with crystalloid solution. The lower concentration of sICAM-1 after surgery may be due to hemodilution.

Key words Hydroxyethyl starch · Microvascular permeability · Microalbuminuria · Intravascular volume · Urinary output

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Introduction

The systemic inflammatory response following surgery causes complement activation and the release of inflammatory mediators; this results in endothelial activation, endothelial damage [1,2], and microvascular hyperpermeability [3]. The movement of fluid from the intravascular space to the interstitial compartment due to microvascular hyperpermeability results in hypovolemia [4]. These factors may contribute to organ damage during the perioperative period [1,2]. Thus, attenuating these responses and keeping an adequate intravascular volume might reduce perioperative complications in surgical patients.

A number of different colloid and crystalloid solutions are used for perioperative volume replacement therapy. Some recent reports have shown that intravascular volume replacement with medium-molecular-weight hydroxyethyl starch (HES; molecular weight [MW], 130–200 kD) attenuated endothelial activation and injury (determined by measuring adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) [5–7]) and also attenuated microvascular hyperpermeability (determined by measuring microalbuminuria [7,8]) compared with crystalloid solution. However, it is unclear whether low-molecular-weight HES (MW, 70 kD) has the same effects as medium-molecular-weight HES on ICAM-1 and microalbuminuria during the perioperative period.

Although agreement is not universal [9], microalbuminuria is generally accepted as a nonspecific marker of inflammation and as a marker of widespread vascular endothelial damage, implicating increased microvascular permeability of the systemic microcirculation [10], in surgical patients and critically ill patients (including those with sepsis [11], subarachnoid hemorrhage [12], intracerebral hemorrhage [13], and burns [14,15]).

This study was carried out to determine whether intravascular volume replacement with low-molecular-

weight HES had beneficial effects on microalbuminuria, perioperative complications, and the durations of intensive care uit (ICU) stay and hospital stay in patients undergoing abdominal surgery.

Patients and methods

After the approval of the Institutional Research Committee (No. 02004) was obtained, written informed consent was obtained from each patient. Twenty-one patients undergoing elective abdominal surgery were included in this prospective, controlled, and randomized clinical trial. Elderly patients (>80 years old), patients who had renal dysfunction (serum creatinine [sCr] >1.2 $mg \cdot dl^{-1}$), proteinuria (urinary albumin/creatinine ratio >300 $mg \cdot g^{-1}$), heart disorders of New York Heart Association grade II–IV, and/or severe pulmonary disease, as well as patients who received packed red cells due to anemia during the study period were excluded.

After a thoracic epidural catheter was inserted at Th9-Th10 or Th10-Th11, general anesthesia was induced with propofol (1–1.5 $mg \cdot kg^{-1}$), fentanyl (100 μg), and vecuronium (0.1 $mg \cdot kg^{-1}$). Balanced anesthesia was maintained with sevoflurane, fentanyl, thoracic epidural anesthesia, and vecuronium titrated according to the patient's requirement. Thoracic epidural anesthesia was maintained with continuous administration of 1% mepivacaine at 4 $ml \cdot h^{-1}$ during surgery and 0.2% ropivacaine at 4 $ml \cdot h^{-1}$ after surgery. After tracheal intubation, mechanical ventilation was performed in all patients, with 40% oxygen in air, to keep peripheral oxygen saturation (Sp_{O_2}) at more than 95% and end-expiratory CO_2 between 35 and 40 mmHg. After surgery, all patients were extubated and transferred to the ICU. Patients were transferred to a ward when they met the following criteria: stable respiratory function with less than 4 $l \cdot min^{-1}$ of oxygen, and stable hemodynamics with less than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine.

Baseline data were obtained before the induction of general anesthesia. Volume replacement was started immediately after the induction of general anesthesia. The patients were randomly divided into two groups. Group HES (n = 10) received low-molecular-weight HES (MW, 70 kD, degree of substitution [DS], 0.50–0.55; HESPANDER; Kyorin, Tokyo, Japan) at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ during surgery and at 1 $ml \cdot kg^{-1} \cdot h^{-1}$ after surgery, and additionally they received acetated Ringer's solution (AR) at a rate to keep central venous pressure (CVP) at 3–5 mmHg during the study period. Group AR (n = 11) received AR alone at a rate to keep CVP at 3–5 mmHg. When mean arterial blood pressure (MAP) was lower than 60 mmHg in spite of CVP being 4 mmHg or greater, dopamine was given. When urinary output was less than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ in spite of CVP being 4 mmHg or greater, 10 mg furosemide was given intravenously.

Hemodynamic parameters, including MAP, heart rate (HR), and CVP were recorded at baseline (T0), at the end of surgery (T1), 5 h after surgery (T2) and 17 h after surgery (T3). The cumulative volumes of infusion from the beginning of anesthesia, as well as the urinary output, were measured at T1, T2, and T3, and urine samples were collected at the same time points to measure urinary microalbumin. To exclude the influence of urinary flow, we calculated the microalbumin/creatinine ratio (MACR). Urinary albumin was measured by an immunonephelometric method (N-antiserum albumin; Dade Behring, Liederbach, Germany), and urine creatinine was measured quantitatively by an enzymatic colorimetric test. The sensitivity limit for urinary albumin was 2.3 $mg \cdot l^{-1}$; for statistical analysis, values below this limit were considered to be 0 $mg \cdot l^{-1}$. Both the interassay and intraassay coefficients of variation (CV) were within 5%. Clinically relevant proteinuria is defined as an MACR of 300 $mg \cdot g^{-1}$ or more. MACR values between 30 and 299 $mg \cdot g^{-1}$ were defined as the presence of microalbuminuria, and values of less than 30 $mg \cdot g^{-1}$ were considered to be normal. Arterial blood samples were collected at T0, T1, and T3 to analyze arterial blood gas and to measure hemoglobin concentration (Hgb) and the serum concentration of soluble ICAM-1 (sICAM-1). The sICAM-1 level was measured using an enzyme-linked immunosorbent assay (ELISA; Funakoshi, Tokyo, Japan). sICAM-1 values between 200 and 300 $ng \cdot ml^{-1}$ were defined as normal. The levels of serum creatinine were also measured and the glomerular filtration rate (GFR) was calculated at T0, at T3, and just before discharge.

Statistical analysis

Data distributions for the quantitative variables were expressed as medians (interquartile ranges; IQRs). Intergroup comparisons of age, height, weight, duration of surgery, sCr, glomerular filtration rate (GFR), MAP, HR, CVP, Hgb level, the Pa_{O_2}/fractional inspired oxygen ($F_{I_{O_2}}$) ratio, body temperature, operative blood loss, total amount of infusion, the durations of ICU stay and hospital stay, MACR, sICAM-1, and urinary output were made with Mann-Whitney U-tests. Innergroup comparisons of MACR and sICAM-1 were made with the Friedman test and Wilcoxon's signed rank test. Dichotomous variables, including sex, American Society of Anesthesiologists (ASA) physical status classification, and the incidence of perioperative complications were analyzed using Fisher's exact probability test. $P < 0.05$ was considered to be statistically significant.

Sample size was determined on the basis of a previous work [8], which indicated that, with ten patients in each group, there was a power of 75% to detect a 120% difference in MACR between the two groups at a significance level of 5%.

Results

There were no significant differences in patients' characteristics or in the durations of surgery between the two groups (Table 1). Hemodynamic data, body temperature, Hgb level, and the Pa_{O_2}/FI_{O_2} ratio were similar in the two groups throughout the study period (Table 2).

In group HES, 1386 ml (IQR, 993–1530 ml) of HES and 2979 ml (IQR, 1954–3748 ml) of AR were administered by T3. In group AR, 4152 ml (IQR, 3534–4599 ml) of AR was administered. There were no significant differences in the total amount of infusion or in the operative blood loss between the two groups (Table 3).

Urinary MACR was significantly increased at T1 compared with that at T0 in both groups, although there was no significant difference in MACR between the groups throughout the study period (Fig. 1). Urinary output in group HES was significantly greater than that in group AR at T2 and T3 (Fig. 2). On the other hand, the serum concentration of sICAM-1 was significantly decreased at T1 compared with that at T0 in both groups, and, additionally, that in group HES was significantly lower than that in group AR at T1 (Fig. 3). In the

Table 1. Patients' characteristics and perioperative data

Variables	HES ($n = 10$)	AR ($n = 11$)
Age (years)	67 (60, 70)	70 (60, 77)
Sex (M/F)	6/4	6/5
Height (cm)	161 (149, 166)	158 (149, 166)
Weight (kg)	62 (58, 65)	62 (56, 64)
ASA (1/2)	4/6	5/6
Duration of surgery (min)	190 (175, 225)	160 (140, 229)
Type of surgical procedure		
Distal gastrectomy	4	6
Total gastrectomy	3	1
Sigmoidectomy	2	1
Right hemicolectomy	0	1
Ileocecal resection	0	1
High anterior resection	0	1
Transverse resection	1	0

Values are expressed as medians (interquartile ranges)
HES, Patients who received hydroxyethyl starch; AR, patients who received acetated Ringer's solution; ASA, American Society of Anesthesiologists physical status

Table 2. Hemodynamic data and laboratory variables

	Baseline (T0)	End of surgery (T1)	5 h After surgery (T2)	17 h After surgery (T3)	Discharge
MAP (mmHg)					
HES ($n = 10$)	75 (70, 85)	82 (71, 91)	98 (92, 103)	99 (88, 103)	—
AR ($n = 11$)	78 (70, 86)	91 (78, 99)	91 (86, 106)	101 (86, 107)	—
HR (bpm)					
HES ($n = 10$)	62 (55, 69)	61 (58, 64)	82 (75, 100)	77 (73, 80)	—
AR ($n = 11$)	65 (57, 72)	65 (57, 72)	77 (68, 94)	79 (65, 86)	—
CVP (mmHg)					
HES ($n = 10$)	4.0 (2.0, 6.0)	5.0 (4.0, 8.0)	5.5 (4.0, 7.0)	7.5 (6.0, 8.0)	—
AR ($n = 11$)	4.0 (2.3, 5.5)	5.0 (4.0, 7.0)	5.0 (4.0, 6.0)	6.0 (4.3, 7.0)	—
Hgb ($g \cdot dl^{-1}$)					
HES ($n = 10$)	13.0 (10.5, 13.4)	11.6 (9.5, 12.6)	—	11.6 (9.8, 13.2)	—
AR ($n = 11$)	12.3 (9.8, 12.7)	11.9 (9.1, 12.6)	—	11.8 (9.6, 12.6)	—
Pa_{O_2}/FI_{O_2} ratio (mmHg)					
HES ($n = 10$)	457 (423, 535)	454 (380, 506)	—	309 (285, 351)	—
AR ($n = 11$)	487 (400, 513)	384 (329, 470)	—	343 (309, 355)	—
Temperature (°C)					
HES ($n = 10$)	36.7 (36.3, 37.0)	36.4 (36.3, 36.8)	37.5 (37.2, 37.8)	37.1 (36.8, 37.5)	—
AR ($n = 11$)	36.6 (36.4, 37.0)	36.6 (36.2, 36.9)	37.2 (37.1, 37.5)	37.3 (36.9, 37.5)	—
sCr ($mg \cdot dl^{-1}$)					
HES ($n = 10$)	0.63 (0.50, 0.85)	—	—	0.57 (0.48, 0.83)	0.71 (0.49, 0.86)
AR ($n = 11$)	0.79 (0.57, 0.88)	—	—	0.74 (0.50, 0.88)	0.65 (0.55, 0.83)
GFR ($ml \cdot min^{-1} \cdot 1.73\ m^2$)					
HES ($n = 10$)	75 (72, 106.)	—	—	91 (70, 120)	78 (73, 104)
AR ($n = 11$)	65 (63, 91)	—	—	85 (63, 96)	78 (68, 95)

Values are expressed as medians (interquartile ranges)
HES, Patients who received hydroxyethyl starch; AR, patients who received acetated Ringer's solution; MAP, mean arterial blood pressure; HR, heart rate; CVP, central venous pressure; Hgb, hemoglobin concentration; sCr, serum creatinine; GFR, glomerular filtration rate

Table 3. Amount of blood loss and amount of infusion

Variables	HES (n = 10)	AR (n = 11)
Operative blood loss (ml)	115 (90, 200)	110 (93, 193)
Total amount of infusion (ml)	3953 (3208, 5093)	4152 (3533, 4599)
Infused colloid volume (ml)	1386 (993, 1530)	0

Values are expressed as medians (interquartile ranges)
HES, Patients who received hydroxyethyl starch; AR, patients who received acetated Ringer's solution

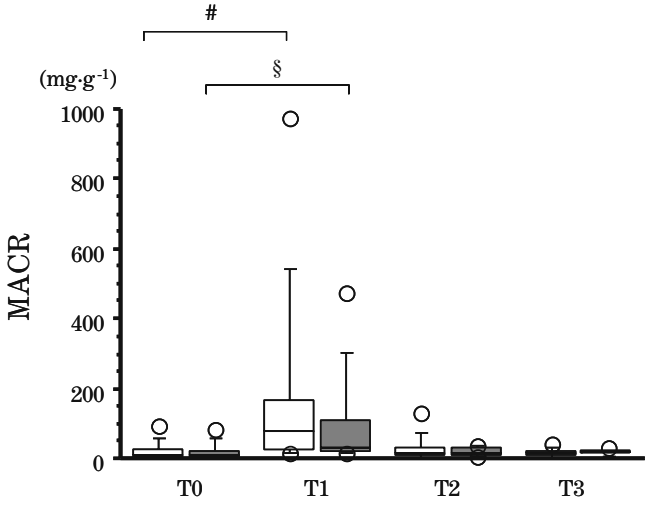

Fig. 1. Time course of the urinary microalubumin/creatinine ratio (*MACR*). Values are expressed as medians (*middle lines in the boxes*) with 25th–75th percentiles. *Whisker lines* indicate 10th–90th percentiles. *Open circles* indicate values over 90th percentiles or 10th percentiles. $^{\#}P < 0.05$ vs baseline data. $^{\S}P < 0.01$ vs baseline data. Group AR (*white boxes*) received acetated Ringer's solution. Group HES (*gray boxes*) received hydroxyethyl starch. *T0*, Before anesthesia; *T1*, at the end of surgery; *T2*, 5 h after surgery; *T3*, 17 h after surgery

Table 4. Durations of ICU and hospital stays and incidence of perioperative complications

Variables	HES (n = 10)	AR (n = 11)
ICU stay (h)	20 (18, 20)*	22 (20, 23)
Hospital stay (days)	24 (21, 25)	31 (23, 37)
Complications		
Incidence (%)	60	36
Hypoxemia	2	0
Ileus, subileus	1	2
Syncope	1	0
Arrythmia	1	1
Surgical site infection	0	1
Anastomotic leakage	1	0

* $P = 0.02$ versus group AR
Values are expressed as medians (interquartile ranges)
HES, Patients who received hydroxyethyl starch; AR, patients who received acetated Ringer's solution

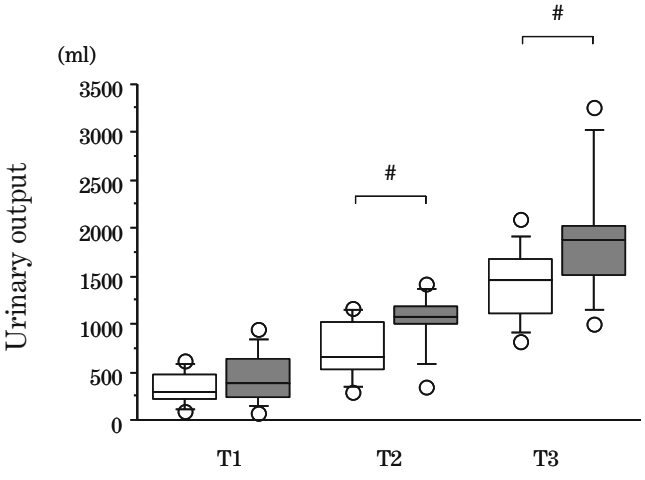

Fig. 2. Time course of cumulative urinary output from the beginning of anesthesia. Values are expressed as medians (*middle lines in the boxes*) with 25th–75th percentiles. *Whisker lines* indicate 10th–90th percentiles. *Open circles* indicate values over 90th percentiles or 10th percentiles. $^{\#}P < 0.05$ vs the other group. Group AR (*white boxes*) received acetated Ringer's solution. Group HES (*gray boxes*) received hydroxyethyl starch. *T1*, At the end of surgery; *T2*, 5 h after surgery; *T3*, 17 h after surgery

postoperative period, there were no significant differences in sCr, or in GFR ($ml \cdot min^{-1} \cdot 1.73m^2$; Table 2), or in the incidence of complications (Table 4). The duration of the ICU stay in group HES was significantly shorter than that in group AR.

Discussion

Our results showed that MACR increased during surgery in both groups undergoing elective abdominal surgery, and that low-molecular-weight HES did not decrease MACR, compared with crystalloid. Postoperative urinary output in the patients who received HES was greater than that in the patients who received crystalloid in spite of the similar amounts of infusion. Although there was no difference in the incidence of perioperative complications between the groups, the duration of the ICU stay in group HES was significantly shorter than that in group AR.

Adequate volume replacement is important to prevent hypovolemia and keep hemodynamics stable in

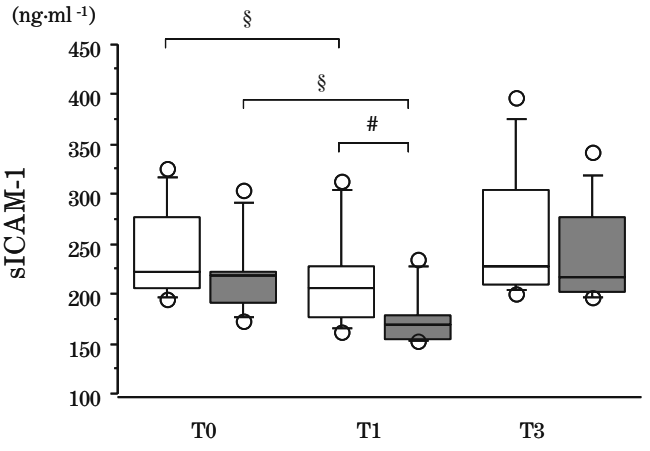

Fig. 3. Time course of soluble intercellular adhesion molecule-1 (*sICAM-1*). Values are expressed as medians (*middle lines in the boxes*) with 25th–75th percentiles. *Whisker lines* indicate 10th–90th percentiles. *Open circles* indicate values over 90th percentiles or 10th percentiles. $^{\#}P < 0.05$ vs the other group. $^{\S}P < 0.01$ vs baseline data. Group AR received acetated Ringer's solution. Group HES received hydroxyethyl starch. *T0*, Before anesthesia; *T1*, at the end of surgery; *T3*, 17 h after surgery

order to supply sufficient blood flow to organs in the perioperative period. Some reports have shown that HES is not only useful as a volume expander but that it also has beneficial effects against endothelial activation, endothelial injury [5–7], and microvascular hyperpermeability [7,8]. In the previous studies which investigated the influence of continuous infusion of HES on inflammatory markers, the rates of HES administration were decided according to perioperative hemodynamics such as CVP, HR, MAP, or urinary output [5–8]. We set the rate of HES administration noted in the "Methods" section in accordance with the maximum dose of low-molecular-weight HES (HESPANDER; Kyorin) per day being 20 ml·kg^{-1} body weight.

We measured urinary microalbumin, which is considered to be a marker of microvascular permeability [7,8], as well as an indicator of renal dysfunction, during the perioperative period. Urinary MACR at the end of surgery was significantly increased compared with that at the beginning of surgery in both groups, indicating that microvascular hyperpermeability occurred during surgery. The change in MACR was accordance with the findings of previous studies [7,8]. In previous studies, although medium-molecular-weight or high-molecular-weight HES attenuated these changes [7,8], low-molecular-weight HES did not improve microvascular hyperpermeability in the present study. Some possible explanations for this difference could be advanced, as follows:

(1) To explain the effect of HES on microvascular hyperpermeability, the term, "sealing the pores" has often been used [16]. To show this effect, colloids must have a certain MW and shape to seal leaky capillaries. The MW must not be too big or too small. The MW of low-molecular-weight HES may be too small to have this sealing effect. However, HES has a branched shape, which is more effective than a globular unbranched shape for exerting a sealing effect [16].
(2) The rate of their metabolism also greatly influences the sealing effect of colloids. This metabolic rate depends mainly on the degree of hydroxyethyl substitution and the C2/C6 ratio of hydroxyethylation. HES with a low DS or C2/C6 ratio is rapidly degradable into small molecules because the solution consists of polydisperse chains [17].

Thus, compared with medium-molecular-weight HES, the molecular size of low-molecular-weight HES may be too small, and low-molecular-weight HES may be too rapidly degradated to have a sealing effect on leaky capillaries.

In the present study, we also measured serum levels of sICAM-1 during the perioperative period. Cell adhesion molecules are cell-surface proteins which play a part in the binding of cells to each other, and in the binding of cells to the endothelium and to the extracellular matrix [18]. Soluble subforms of these adhesion molecules can be detected in the systemic circulation [5]. Inflammatory stimulation by agents such as cytokines, lipopolysaccharide, complement activation products, hypoxia, or oxygen-derived free radicals causes the activation of endothelial cells. Activated endothelial cells produce adhesion molecules which make neutrophils adhere to the endothelium. Neutrophils adherent to the endothelium release cytotoxic proteases and oxygen-derived free radicals, which may cause organ damage. Thus, increased serum levels of adhesion molecules are considered as one of the markers of endothelial activation [5]. We measured the serum concentration of sICAM-1 to clarify whether its serum concentration was related to microvascular hyperpermeability, because endothelial activation sometimes causes microvascular hyperpermeability. In both groups in our study, the serum concentration of sICAM-1 decreased during surgery. We could not detect any correlation between the serum concentration of sICAM-1 and microvascular hyperpermeability. The decrease in sICAM-1 may have been caused by blood dilution due to the volume replacement. Of interest, the serum concentration of sICAM-1 in the HES-treated group was significantly lower than that in the AR-treated group, and this may have resulted from the greater volume-expanding effect of low-molecular-weight HES compared with that of AR.

The influence of HES on renal function has been discussed in several studies. Some reports have shown

that HES has no adverse influence on renal function in surgical patients [19,20], while other reports have shown that HES may impair renal function in surgical patients [21,22]. A recent review suggested that HES may have adverse effects on renal function, regardless of its molecular weight, DS, or C2/C6 ratio [23]. In the present study, the postoperative urinary output in the HES-treated group was significantly greater than that in the AR-treated group, probably because of the volume-expanding effect of the HES. There were no significant differences between our two groups in either sCr or GFR from the beginning of this study until discharge. No adverse effects of low-molecular-weight HES on renal function were observed.

The duration of ICU stay in our HES-treated group was shorter than that in the AR-treated group, although there was no significant difference in the duration of hospital stay or in the incidence of complications between the two groups. Volume expansion by the low-molecular-weight HES may have contributed to the shortening of the ICU stay in the HES group.

The small sample size in our study would result in low statistical power and therefore a greater chance of making a type 2 error. The ICU stay in group HES was shorter than that in group AR. However, the median difference was only 2 h. With respect to the shortening of the ICU stay, the administration of low-molecular-weight HES does not seem to had a significant advantage.

In conclusion, low-molecular-weight HES does not improve microvascular permeability, in patients undergoing abdominal surgery, but it preserves urinary output, probably because of its volume-expanding effect.

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