Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery

[Le remplissage vasculaire avec de l'HEA 130/0,4 peut réduire la réaction inflammatoire chez des patients en chirurgie abdominale majeure]

Katrin Lang MD,* Stefan Suttner MD,* Joachim Boldt PhD,* Bernhard Kumle MD,* Dietmar Nagel MD†

Purpose: To investigate the effects of intravascular volume replacement therapy on the inflammatory response during major surgery.

Methods: Thirty-six patients scheduled for elective abdominal surgery were randomized to receive either 6% hydroxyethylstarch (130,000 Dalton mean molecular weight, degree of substitution 0.4; $n = 18$, HES-group) or lactated Ringer's solution (RL-group; $n = 18$) for intravascular volume replacement. Fluid therapy was given perioperatively and continued for 48 hr in the intensive care unit. Volume replacement was guided by physiological parameters. Serum concentrations of interleukin (IL)-6, IL-8 and IL-10 and soluble adhesion molecules (sELAM-1 and sICAM-1) were measured after induction of anesthesia, four hours after the end of surgery, as well as 24 hr and 48 hr postoperatively.

Results: Biometric and perioperative data, hemodynamics and oxygenation were similar between groups. On average, 4470 ± 340 mL of HES 130/0.4 per patient were administered in the HES-group compared to 14310 ± 750 mL of RL in the RL-group during the study period. Release of pro-inflammatory cytokines IL-6 and IL-8 was significantly lower in the HES-group [(peak values) 47.8 ± 12.1 pg·dL^{-1} of IL-6 and 35.8 ± 11.2 pg·mL^{-1} of IL-8 (HES-group) *vs* 61.2 ± 11.2 pg·dL^{-1} of IL-6 and 57.9 ± 9.7 pg·mL^{-1} of IL-8 (RL-group); $P < 0.05$]. Serum concentrations of sICAM-1 were significantly higher in the RL-group [(peak values) 1007 ± 152 ng·mL^{-1} (RL-group) *vs* 687 ± 122 ng·mL^{-1}, (HES group); $P < 0.05$)]. Values of sELAM-1 were similar in both groups.

Conclusion: Intravascular volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major surgery compared to a crystalloid-based volume therapy. We hypothesize that this is most likely due to an improved microcirculation with reduced endothelial activation and less endothelial damage.

Objectif : *Vérifier les effets du remplissage intravasculaire sur la réaction inflammatoire pendant une intervention chirurgicale majeure.*

Méthode : *Trente-six patients devant subir une intervention abdominale réglée ont été répartis au hasard et ont reçu soit de l'hydroxyéthylamidon à 6 % (poids moléculaire moyen de 130 000 Dalton, degré de substitution de 0,4 ; n =18, groupe HEA), soit une solution de Ringer-lactate (groupe RL ; n =18) comme remplissage intravasculaire. Les liquides ont été administrés avant l'opération et, pendant 48 h à l'unité des soins intensifs. Le remplissage vasculaire dépendait de paramètres physiologiques. Les concentrations sériques d'interleukine (IL-6, IL-8 et IL-10 et molécules d'adhésion solubles (sELAM-1 et sICAM-1) ont été mesurées après l'induction de l'anesthésie, quatre heures après la fin de l'opération, de même que 24 h et 48 h après l'opération.*

Résultats : *Les données biométriques et périopératoires, l'hémodynamique et l'oxygénation ont été similaires chez les patients des deux groupes. Une moyenne de 4470 ± 340 mL de HEA 130/0,4 par patient ont été administrés dans le groupe HEA et de 14310 ± 750 mL de RL par patient du groupe RL pendant l'expérimentation. La libération de cytokines pro-inflammatoires IL-6 et IL-8 a été significativement plus faible dans le groupe HEA [(valeurs maximales) 47,8 ± 12,1 pg·dL^{-1} de IL-6 et 35,8 ± 11,2 pg·mL^{-1} de IL-8 (groupe HEA) vs 61,2 ± 11,2 pg·dL^{-1} de IL-6 et 57,9 ± 9,7 pg·mL^{-1} de IL-8 (groupe RL); P < 0,05]. Les concentrations sériques de sICAM-1 ont été significativement plus élevées dans le groupe RL [(valeurs maximales) 1007 ± 152 ng·mL^{-1} (groupe RL) vs 687 ± 122 ng·mL^{-1}, (groupe HEA); P < 0,05)]. Les valeurs de sELAM-1 ont été similaires dans les deux groupes.*

Conclusion : *Le remplissage vasculaire avec de l'HEA 130/0,4, comparé à la thérapie liquidienne à base de solutés cristalloïdes, peut réduire la réaction inflammatoire chez des patients qui subissent une*

From the Departments of Anesthesiology and Intensive Care Medicine,* and Clinical Chemistry,† Klinikum der Stadt Ludwigshafen, Akademisches Lehrkrankenhaus der Universität Mainz, Ludwigshafen, Germany.

Address correspondence to: Dr. Katrin Lang, Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Bremserstr. 79, D-67063 Ludwigshafen, Germany. Fax: +49-621-503–3024; E-mail: Lang.Katrin@gmx.de

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opération majeure. Nous pensons que cette situation relève d'une microcirculation meilleure accompagnée d'une activation endothéliale réduite et d'une lésion endothéliale moindre.

NUMEROUS stimuli such as trauma, infection, burns and major surgery may alter the physiologic immune balance and initiate systemic inflammatory processes.[1] This pathophysiological event is characterized by the release of potent inflammatory mediators into the circulation. Among these, pro- and anti-inflammatory cytokines such as interleukin-6 (IL-6), IL-8 or IL-10 play a dominant role as local or systemic regulators in the acute inflammatory response. Increased levels of these mediators are also thought to be responsible for the development of severe postoperative complications such as multiple organ dysfunction syndrome or adult respiratory distress syndrome.[2] The pathogenesis of inflammatory processes during major surgery has become of increasing interest. Kuntz *et al.*[3] could demonstrate that the release of IL-6 correlated with the severity and type of surgical procedure. Together with cytokines, cell adhesion molecules such as E-selectin (endothelial leukocyte adhesion molecule-1, ELAM-1) or the intercellular adhesion molecule-1 (ICAM-1) regulate the complex interaction of immune cells with each other, the endothelium and the extracellular matrix. Soluble subforms of some of these adhesion molecules have been detected in the circulating blood. They are supposed to be early indicators of an activated immune response and tissue damage.[4,5] Tremendous increases of such circulating adhesion molecules were found in patients with severe sepsis.[6]

The surgical patient is at risk of experiencing hypovolemia and subsequently tissue malperfusion and organ dysfunction.[7] Sufficient intravascular volume replacement is fundamental in the treatment of patients undergoing major surgery. The primary goal of volume therapy is to maintain hemodynamic stability and to diminish the risk of developing hypovolemia and tissue malperfusion.

A number of different colloid and crystalloid solutions are used worldwide for volume therapy. However, only limited information is available about the effects of different volume replacement regimens on the immunologic response during elective surgical procedures.

Recently a new 6% hydroxyethylstarch (HES) with an intermediate molecular weight (MW, 130,000 Dalton) and a very low degree of substitution (Ds 0.4) has been developed (HES 130/0.4; Voluven®, Fresenius AG, Bad Homburg, Germany). This HES specification has already been approved in several countries for routine volume replacement. HES 130/0.4 has been reported to have pharmacokinetic and pharmacodynamic advantages such as decreased tissue storage, rapid plasma elimination and low impact on coagulation.[8,9]

It was the goal of this prospective study to investigate the effects of intravascular volume replacement with HES 130/0.4 *vs* a colloid-free volume therapy on pro- and anti-inflammatory cytokines and soluble adhesion molecules in patients undergoing elective major abdominal surgery.

Materials and methods

The study protocol was approved by the Ethic Study Board of the hospital. After obtaining written informed consent, 36 consecutive patients undergoing elective major abdominal surgery were included in this prospectively designed study. Defined exclusion criteria were: myocardial failure (> New York Heart Association grade II), renal insufficiency (serum creatinine > 132 $\mu mol \cdot L^{-1}$), severe pulmonary disease (chronic obstructive lung disease, paO_2 < 70 mmHg when breathing room air), liver dysfunction [aspartate aminotransferase (AST) > 40 $U \cdot L^{-1}$, alanine aminotransferase (ALT) > 40 $U \cdot L^{-1}$], diabetes mellitus, steroid therapy, and pre-existing signs of bacterial (white cell count > $9 \cdot nL^{-1}$, body temperature > 38.0°C) or viral infection (hepatitis B or C, human immunodeficiency virus, cytomegalovirus). Patients with known allergic reactions to starch preparations were also excluded from the study.

By using a closed envelope system, the patients were randomly allocated to one of two volume groups: in Group I (n = 18) 6% HES 130/0.4 was given for intravascular volume replacement; additional crystalloid solutions were supplied to equalize insensible fluid loss or as a solvent for drugs (e.g., antibiotics); in Group II (control group; n = 18): lactated Ringer's (RL) solution was used exclusively for volume replacement. Volume replacement was started immediately after induction of anesthesia (after baseline data had been obtained) and continued for 48 hr until the morning of the second postoperative day. The specific solutions were administered to maintain central venous pressure (CVP) between 5 and 9 mmHg throughout the study period. In the case of hypovolemia with hemodynamic instability, patients in both groups were treated with additional volume. When mean arterial blood pressure (MAP) was < 60 mmHg despite sufficient intravascular volume, dopamine (3–9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was given. Epinephrine

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(0.01–0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was added when volume therapy and dopamine were not successful in keeping MAP > 60 mmHg. Packed red blood cells (not older than 14 days) were administered to the patients when their hemoglobin (Hb) concentration was < 8 $g \cdot dL^{-1}$.

General anesthesia was induced with thiopental (3–5 $mg \cdot kg^{-1}$), fentanyl (2–3 $\mu g \cdot kg^{-1}$) and rocuronium (0.5 $mg \cdot kg^{-1}$). Balanced anesthesia was continued with desflurane, fentanyl and rocuronium adapted to the patient's physiological reaction to surgical stimuli. After intubation of the trachea, the lungs were ventilated with 50% O_2 in air using a semi-closed circle system. Ventilation was controlled with a tidal volume of 8 to 10 $mL \cdot kg^{-1}$, and the ventilatory rate was adjusted to maintain an arterial partial pressure of carbon dioxide ($paCO_2$) of 32 to 42 mmHg and arterial pH between 7.35 and 7.45. During the peri- and postoperative period standard monitoring for all patients included central venous catheterization and arterial cannulation. MAP, heart rate, CVP and body temperature were measured continuously and documented after induction of anesthesia (baseline), 120 min thereafter, four hours after the end of surgery (4 hr postOP) and in the mornings of the first and second postoperative day (1st POD, 2nd POD) in the intensive care unit (ICU). MAP was kept between 60 and 80 mmHg by adding the specific volume replacement. Hb and blood gas variables including lactate concentrations were measured from arterial blood samples. To avoid hypothermia during the operative period, the patients were covered with a warming blanket and received prewarmed fluids. Mechanical ventilation was maintained until the patient showed stable hemodynamics and adequate ventilation. Perioperative and postoperative treatment in the ICU was performed by anesthesiologists and physicians who were blinded to the study. If necessary, patients received piritramide boli (3.75–7.5 mg) for postoperative pain treatment. Non-steroid anti-inflammatory drugs were not administered throughout the investigation period. All patients received cefuroxime and metronidazole as antibiotic prophylaxis after induction of anesthesia.

At baseline, 4 hr postOP, 1st POD (24 hr after beginning of surgery in the ICU) and 2nd POD (48 hr after beginning of surgery in the ICU), blood samples were drawn into sodium citrate-containing tubes and centrifuged at 4000 g for eight minutes. Serum was removed, placed in pyrogen-free Eppendorf tubes and stored at -70°C until assayed (within one month). Serum levels of IL-6, IL-8 and IL-10 were measured by using commercially available enzyme-linked immunometric assays: 1) IL-6: Immulite®IL-6, EURO/DPC Llanberis, Gwynedd, United Kingdom; analytical sensitivity 5 $pg \cdot mL^{-1}$; normal range from nondetectable to 9.7 $pg \cdot mL^{-1}$. 2) IL-8: Immulite®IL-8, EURO/DPC Llanberis, Gwynedd, United Kingdom; analytical sensitivity 2 $pg \cdot mL^{-1}$; normal range from nondetectable to 62 $pg \cdot mL^{-1}$. 3) IL-10: Milenia®IL-10, DPC Biermann, Bad Nauheim, Germany; analytical sensitivity 3 $pg \cdot mL^{-1}$; normal range from 2 $pg \cdot mL^{-1}$ to 24 $pg \cdot mL^{-1}$. Serum levels of soluble ELAM-1 (sELAM-1), and soluble ICAM-1 (sICAM-1), were also measured by using enzyme-linked immunoassay kits: 1) sELAM-1: ELISA Test Kit, Diagnostic International, Karlsdorf, Germany; analytical sensitivity 50 $pg \cdot mL^{-1}$; normal range from 30 to 60 $ng \cdot mL^{-1}$. 2) sICAM-1: ELISA Test Kit, Hycult Biotechnology, Uden, Netherlands; analytical sensitivity 100 $pg \cdot mL^{-1}$; normal range from 200 to 300 $ng \cdot mL^{-1}$.

All data from enzyme assays are shown as the mean of duplicate measurements.

TABLE I Patient characteristics and perioperative data

	HES 130/0.4 (n = 18)	*RL (n = 18)*
Age (yr)	65 ± 14	62 ± 9
Sex (f/m)	9/8	11/6
Weight (kg)	69.7 ± 12.1	74.1 ± 9.7
Height (cm)	168 ± 9.6	169 ± 10.2
ASA (II/III)	11/7	10/8
Duration of surgery (min)	195 ± 46	185 ± 51
Duration of anesthesia (min)	235 ± 37	249 ± 21
Type of surgical procedure		
Gastrectomy	4	3
Esophageal surgery	2	1
Whipple operation	3	4
Hemicolectomy (right or left)	4	4
Rectal resection/exstirpation	5	6
Survivors		
Study period	All	All
Hospital	All	All

f = female; m= male; HES 130/0.4 = patients received hydroxyethylstarch 130/0.4; RL = patients received lactated Ringer's solution. Values are means (± standard deviation) or number of patients. No difference between groups.

Statistics

All statistical analyses were conducted using a PC-based statistical program (Systat™ 7.0 win). Data are presented as mean ± standard deviation (SD). The mean ± SD was calculated for all variables at every data point. The Kolmogorov-Smirnov test was used to examine the assumption of normality; continuous, normally distributed data were compared using paired and unpaired Student's t test or analysis of variance (ANOVA) for repeated measures. For multiple comparisons the

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TABLE II Hemodynamic and laboratory variables

	Baseline	*120 min*	*4 hr postOP*	*1st POD*	*2nd POD*
MAP (mmHg)					
HES 130/0.4	68.2 ± 6.9	70.5 ± 5.8	71.7 ± 6.5	71.8 ± 4.1	72.6 ± 6.1
RL	67.4 ± 6.5	69.3 ± 4.3	71.3 ± 7.2	69.4 ± 5.4	71.1 ± 4.8
HR (min^{-1})					
HES 130/0.4	72 ± 8	76 ± 8	71 ± 9	69 ± 12	85 ± 8+
RL	69 ± 9	71 ± 10	73 ± 8	71 ± 11	80 ± 11+
CVP (mmHg)					
HES 130/0.4	5.6 ± 0.4	7.3 ± 1.5 +	7.5 ± 1.2+	7.4 ± 1.5+	6.9 ± 1.8+
RL	5.5 ± 0.3	7.4 ± 1.6+	7.4 ± 1.3+	7.3 ± 1.6+	6.8 ± 1.9+
Hb ($g \cdot dL^{-1}$)					
HES 130/0.4	12.9 ± 1.5	10.4 ± 1.3+	10.1 ± 1.4+	9.7 ± 1.6+	9.7 ± 1.2+
RL	13 ± 1.2	10.7 ± 1.2+	10.2 ± 0.8+	9.9 ± 1.5+	10.3 ± 0.9+
PaO_2/FIO_2 (mmHg)					
HES 130/0.4	240 ± 79	207 ± 46	198 ± 48	189 ± 75	112 ± 30+
RL	227 ± 75	199 ± 55	188 ± 48	184 ± 70	107 ± 33+
$PaCO_2$ (kPa)					
HES 130/0.4	4.5 ± 0.3	4.7 ± 0.5	4.5 ± 0.8	4.8 ± 0.5	5.2 ± 0.5+
RL	4.7 ± 0.4	4.7 ± 0.4	4.8 ± 0.7	4.9 ± 0.4	5.5 ± 0.4+
Temperature (°C)					
HES 130/0.4	35.6 ± 0.4	35.2 ± 0.3+	34.9 ± 0.5+	36.6 ± 0.3+	36.7 ± 0.6+
RL	35.6 ± 0.3	34.9 ± 0.6+	34.7 ± 0.4+	36.4 ± 0.5+	36.5 ± 0.8+

Baseline = after induction of anesthesia; 120 min = 120 min after start of surgery; 4 hr postOP = four hours after end of surgery; 1st POD = morning of the first postoperative day; 2nd POD = second postoperative day; MAP = mean arterial blood pressure; HES 130/0.4 (n = 18) = patients received hydroxyethylstarch 130/0.4; RL (n = 18) = patients received lactated Ringer's solution; HR = heart rate; CVP = central venous pressure; Hb = hemoglobin. Values are expressed as means (± standard deviation). +$P < 0.05$ *vs* baseline.

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Bonferroni correction was applied. Continuous, non-normally distributed data were compared using the Wilcoxon test. Binominal data were compared using Chi square analysis and Fisher's exact test, respectively. P-values < 0.05 were considered statistically significant.

Results

There were no significant differences between the two groups with respect to biometric profile, type of surgical procedure, duration of anesthesia/surgery and survival rate (Table I).

Hemodynamic data, body temperature and Hb concentrations were similar in both groups and comparable at any time. (Table II). PaO_2/FIO_2 and $paCO_2$ values were also similar (Table II). No changes in arterial lactate concentrations were observed in any group throughout the whole study period. Inotropic support was not necessary in any patient at any time of the study period.

In the HES group, 4470 ± 340 mL of HES 130/0.4 and 4140 ± 310 mL of RL were infused until the end of the study period (Table III). In the RL group a total of 14310 ± 750 mL of RL was administered (Table III). There were no significant differences in blood loss and use of allogeneic blood products between the two groups. In the RL group, urine output was significantly higher than in the HES group (Table III).

IL-6, IL-8 and IL-10 values significantly increased from baseline in both groups during the study period [(peak values) 47.8 ± 12.1 $pg \cdot dL^{-1}$ of IL-6; 35.8 ± 11.2 $pg \cdot mL^{-1}$ of IL-8, 30.6 ± 12.2 $pg \cdot dL^{-1}$ of IL-10 in the HES group and 61.2 ± 11.2 $pg \cdot dL^{-1}$ of IL-6, 57.9 ± 9.7 $pg \cdot mL^{-1}$ of IL-8 and 29.2 ± 7.3 $pg \cdot mL^{-1}$ of IL-10 in the RL group; Figure 1]. The release of IL-6 and IL-8 was significantly lower in the HES 130 treated patients on the first POD ($P < 0.05$; Figure 1).

Serum concentrations of sICAM-1 increased in both groups with a significantly higher increase in the RL treated patients [(peak values) 1007 ± 152 $ng \cdot mL^{-1}$ in the RL group and 687 ± 122 $ng \cdot mL^{-1}$ in the HES group). Concentrations of sELAM-1 were not different between groups [(peak values) 21.8 ± 4.2 $ng \cdot mL^{-1}$ in the HES group and 24.6 ± 3.9 $ng \cdot mL^{-1}$ in the RL group; Figure 2].

Discussion

Adequate volume replacement is paramount in the treatment of surgical patients and the controversy surrounding the kind of volume therapy best suited for

TABLE III Fluid input and output (cumulative)

	HES 130/0.4 (n = 18)	*RL (n = 18)*
Infused crystalloid solution (mL)		
4 hr postOP	2480 ± 520	6740 ± 210*
1st POD	3360 ± 340	12280 ± 1550*
2nd POD	4140 ± 310	14310 ± 750*
Infused colloidal solution (mL)		
4 hr postOP	2230 ± 410	None
1st POD	3090 ± 380	None
2nd POD	4470 ± 340	
PRBC (units·group^{-1})		
4 hr postOP	6	5
1st POD	8	7
2nd POD	8	8
FFP (units·group^{-1})		
4 hr postOP	4	4
1st POD	6	7
2nd POD	6	7
Urine (mL)		
4 hr postOP	940 ± 190	2230 ± 210*
1st POD	2340 ± 330	5330 ± 250*
2nd POD	3140 ± 220	6230 ± 210*
Drainage blood loss (mL)		
1st POD	820 ± 230	920 ± 190
2nd POD	910 ± 110	950 ± 80

HES 130/0.4 = patients received hydroxyethylstarch 130/0.4; RL = patients received lactated Ringer's solution; 4 hr postOP = four hours after end of surgery; 1st POD = morning of the first postoperative day; 2nd POD = second postoperative day; PRBC = packed red blood cells; FFP = fresh frozen plasma. Blood products were required in only two patients in each group. Values are means (± standard deviation). *$P < 0.05$ *vs* other group.

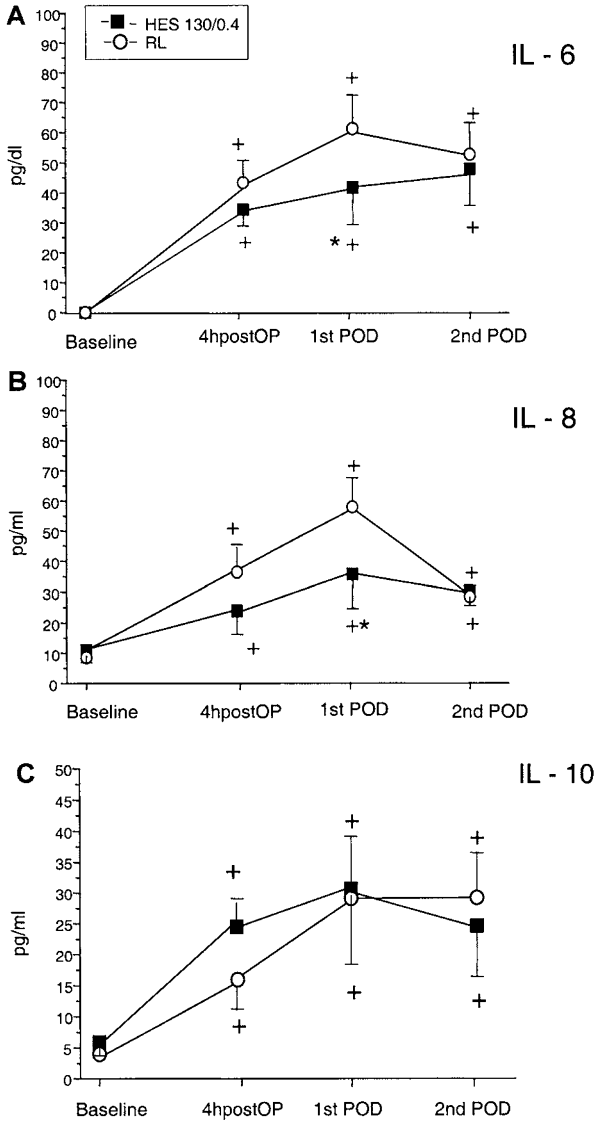

FIGURE 1 Changes in serum concentrations of: A) interleukin (IL)-6; B) IL-8; C) IL-10. Baseline = after induction of anesthesia; 4 hr postOP = four hours after end of surgery; 1st POD = 24 hr after beginning of surgery, first postoperative day; 2nd POD = 48 hr after beginning of surgery, second postoperative day. Values are expressed as mean ± standard deviation. +$P < 0.05$ *vs* baseline; *$P < 0.05$ *vs* other group.

this purpose persists. A large variety of natural and synthetic colloid preparations are used world-wide. Among the synthetic colloids, HES was reported to have the lowest rate of anaphylactic complications.[10,11]

The primary goal of the present study was to compare the effects of volume replacement with a novel HES solution (HES 130/0.4) to a crystalloid-based volume replacement strategy on the release of inflammatory markers in patients undergoing elective abdominal surgery. In both groups all cytokines increased from baseline during the study period. In the HES group the increase of the pro-inflammatory cytokines IL-6 and IL-8 was significantly lower than in the RL treated patients. In addition, we found significantly lower serum concentrations of sICAM-1 in the HES treated patients.

There may be several reasons for this attenuated inflammatory response in HES treated patients. Tissue trauma and hemorrhage *per se* may produce depression of immune function. By using peritoneal lavage, Stephan *et al.*[12] investigated the effects of midline laparotomy on antigen presentation and IL-1 activity in anesthetized mice. Their main result was a significantly reduced induction of T helper cell proliferation and a depressed membrane IL-1 activity in operated mice. The authors concluded that immunodepression enhanced the susceptibility to intra-abdominal sepsis.

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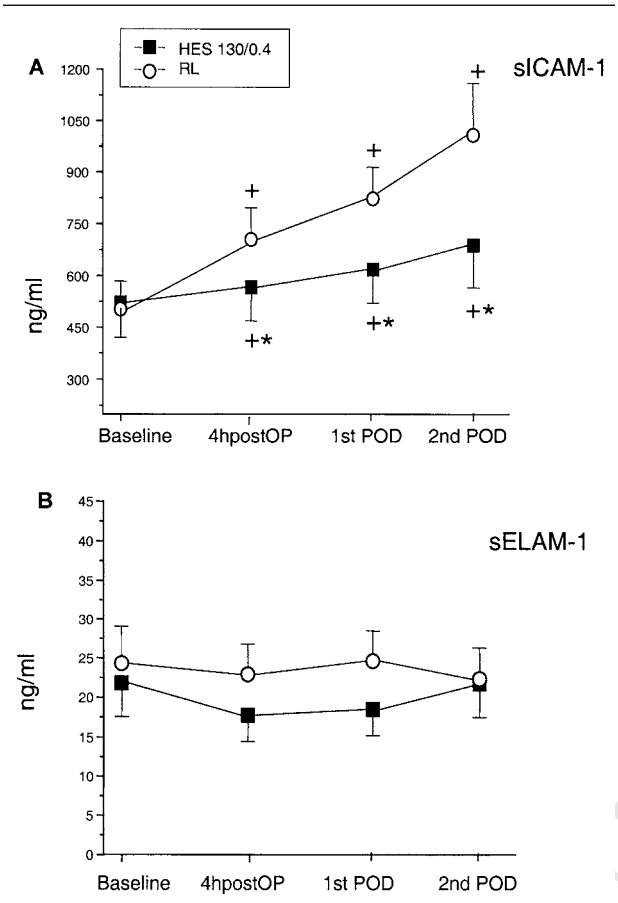

FIGURE 2 Changes in serum concentrations of: A) soluble intercellular adhesion molecule-1 (sICAM-1); B) soluble endothelial leucocyte adhesion molecule (sELAM-1). Baseline = after induction of anesthesia; 4 hr postOP = four hours after end of surgery; 1st POD = 24 hr after beginning of surgery, first postoperative day; 2nd POD = 48 hr after beginning of surgery, second postoperative day. Values are expressed as mean ± standard deviation. $+P < 0.05$ *vs* baseline; $*P < 0.05$ *vs* other group.

These results were supported in another experimental setting using hemorrhage without tissue trauma.[13] In our study, the surgical procedures (all patients had a laparotomy) were comparable in both groups. Furthermore, there were no significant differences with regard to biometric data, hemodynamics, duration of anesthesia or surgery and blood loss. One could argue that the use of allogeneic blood products might have influenced the release of inflammatory markers. The use of blood products and natural colloids may lead to an increased incidence of inflammatory complications.[14] However, blood loss or transfusion requirements in this study were similar between groups.

Volume therapy with HES in our patients was associated with decreased inflammatory markers. The reason for this disparity with RL-treated patients remains speculative for the moment. The use of HES may result in less endothelial cell damage and an improved microcirculation. The important role of the endothelium in the pathogenesis of inflammation has been described in several studies.[15] Aside from vasoconstrictive and vasodilating substances, the endothelium produces adhesion molecules which are expressed on the cell surface (membrane-bound ligands). They regulate the binding of neutrophils to the endothelium which results in neutrophil migration with subsequent tissue injury.[16] An increase of soluble isoforms of adhesion molecules may be the result either of an increased expression by the membrane-located ligands (due to cytokine stimulation) or caused by endothelial damage with subsequent release into the circulation.

The higher concentrations of the pro-inflammatory cytokines IL-6 and IL-8 in the RL-treated patients with a subsequent enhanced stimulation of the membrane-bound ligands may be one reason for the significant higher expression of sICAM-1 in this group. IL-6 (aside from IL-1 and tumour necrosis factor α) is one of the mediators of the acute phase response and has been shown to play a pivotal role in the upregulation of cell adhesion molecules.[17] IL-8 previously called the neutrophil activating protein is a potent chemoattractant for neutrophils and has been implicated in neutrophil-mediated endothelial damage.[18]

An improved microcirculation may be another reason for the lower concentration of sICAM-1 in the HES-treated patients. Different HES preparations have already been used to improve microcirculatory blood flow.[19,20] The hemorheologic effectiveness of HES preparations is determined by their high hemodilutional capacity in combination with their inherent specific effects on platelet function, plasma viscosity, and blood corpuscle-endothelial cell interactions.[21] In a recent clinical study, intravascular volume replacement with HES 130/0.4 improved tissue oxygenation in patients undergoing abdominal surgery.[20] In contrast, equivalent volumes of a crystalloid solution were associated with a marked decrease of tissue oxygen tensions. The latter finding was explained by the fact that crystalloids were mainly distributed in the interstitium, resulting in reduced interstitial colloid osmotic pressure and subsequently tissue and endothelial edema.[20] Moreover, low shear rates and microcirculatory alterations in the venules promote neutrophil

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adhesion and endothelial activation with subsequent increased levels of soluble adhesion molecules. This is supported by the results of an experimental study by Funk and Baldinger, who compared the effects of fluid therapy with Ringer's solution and artificial colloids on microcirculatory blood flow and tissue oxygenation with an *in vivo* microscopy technique.[22] The main result was an altered microcirculatory blood flow in the RL-treated animals despite similar hemodynamic conditions. The lower concentrations of soluble adhesion molecules in our HES patients may, thus, reflect the positive effects of HES on the microcirculation.

The influence of HES on immune function has been described in previous studies. In an experimental setting, Lawrence *et al.*[23] demonstrated that cell-mediated immunity was not affected after the administration of HES in mice. Another experimental study indicated no deleterious effects of volume replacement with HES on the reticuloendothelial function and host resistance to sepsis.[24] In a resuscitation model in mice Schmand *et al.*[25] investigated the effects of a starch preparation with a high MW and high Ds (Hespan, Dupont Pharmaceuticals, Wilmington, DE, USA) and RL solution on cell-mediated immunity after trauma-hemorrhagic shock. An immunodepressive effect was found in both groups. In contrast, HES restored peritoneal macrophage function and prevented the increase of circulating IL-6 concentrations. Although experimental findings cannot be extrapolated to clinical studies, our study supports these findings. Therefore we hypothesize that our results are most likely due to an improved microcirculation with subsequently decreased endothelial activation and less endothelial damage.

In summary, we found that volume replacement with HES 130/0.4 compared to volume replacement with crystalloid solutions may have the advantage of reducing the inflammatory response in patients undergoing elective major abdominal surgery. To draw definitive conclusions with regard to the influence of these findings on postoperative infectious complications or patient outcome, further controlled and adequately powered studies are warranted.

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