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Fluid resuscitation with colloids of different molecular weight in septic shock

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Abstract *Objective:* The aim of this study was to investigate the short-term effect of fluid resuscitation with 4% modified fluid gelatine (GEL) versus 6% hydroxyethyl starch (HES) on haemodynamics and oxygenation in patients with septic shock and acute lung injury (ALI). *Design:* Prospective randomised clinical trial. *Setting:* Twenty-bed intensive care unit in a university hospital. *Patients:* Thirty hypovolemic patients (intrathoracic blood volume index, ITBVI <850 ml/m^2) in septic shock with ALI were randomised into HES (mean molecular weight: 200,000 Dalton, degree of substitution 0.6) and GEL (mean molecular weight: 30,000 Dalton) groups (15 patients each). *Interventions:* For fluid resuscitation 250 ml/15 min boluses (max. 1,000 ml) were given until the end point of ITBVI >900 ml/m^2 was reached. Repeated haemodynamic measurements were done at baseline (t_b), at the end point (t_{ep}) then at 30 min and 60 min after the end point was reached (t_{30}, t_{60}). Cardiac output, stroke volume, extravascular lung water (EVLW), and oxygen delivery was determined at each assessment point. For statistical analysis two-way ANOVA was used. *Measurements and results:* ITBVI, cardiac index, and oxygen delivery index increased significantly at t_{ep} and remained elevated for t_{30} and t_{60}, but there was no significant difference between the two groups. The increase in the ITBVI by 100 ml of infusion was similar in both groups (HES: 26±19 ml/m^2 vs GEL: 30±19 ml/m^2). EVLW, remained unchanged, and there was no significant difference between the groups (HES, t_b: 8±6, t_{60}: 8±6; GEL, t_b: 8±3, t_{60}: 8±3 ml/kg). The PaO_2/FiO_2 did not change significantly over time or between groups (HES, t_b: 207±114, t_{60}: 189±78; GEL, t_b: 182±85, t_{60}: 182±85 mmHg). *Conclusion:* The results of this study indicate that both HES and GEL infusions caused similar short-term change in ITBVI in septic shock, without increasing EVLW or worsening oxygenation.

Keywords Septic shock · Acute lung injury · Fluid resuscitation · Colloid · Extravascular lung water

Introduction

Hypovolemia is a common clinical occurrence in severe sepsis, and changes in cardiorespiratory physiology play a key role in outcome. Whilst adequate volume replacement therapy appears to be essential in this situation to maintain tissue perfusion and prevent multiple system organ failure (MSOF), it may also lead to interstitial fluid accumulation due to increased endothelial permeability [1, 2]. Excessive volume loading or increased capillary leakage may result in pulmonary oedema often referred to as extravascular lung water (EVLW). It seems reasonable that fluid man-

agement based on EVLW measurements may be beneficial to the critically ill [3]. Indeed, it has been shown that fluid restriction, and keeping a low EVLW or low pulmonary arterial occlusion pressure (PAOP) improves oxygenation, reduces length of mechanical ventilation, and may also improve survival [4, 5, 6]. On the other hand, in a recent prospective clinical trial early goal-directed fluid challenge also improved survival in patients with sepsis, indicating that fluid resuscitation still remains one of the most important interventions in septic shock [7].

However, it is still uncertain which solution is most suitable for fluid resuscitation in patients with sepsis with impaired oxygenation requiring mechanical ventilation. One of the options may be the administration of artificial colloids especially those with a higher molecular weight than that of albumin. There is some evidence that hydroxyethyl starches (HES) reduce interstitial oedema, by sealing the endothelium [8, 9]. Despite the theoretical advantages of high molecular weight colloids similar haemodynamic effects were found following fluid resuscitation with the smaller size modified fluid gelatine (GEL), with conflicting results regarding oxygenation [10, 11, 12]. However, none of the studies were designed to answer this specific problem of the pulmonary effects of different molecular weight colloids on oxygenation and EVLW in mechanically ventilated patients with sepsis.

The aim of our study was to investigate the short-term cardio-respiratory effects of fluid resuscitation with 4% GEL (mean molecular weight: 30,000 Dalton) versus HES (mean molecular weight: 200,000 Dalton, degree of substitution 0.6) in patients with septic shock and acute lung injury (ALI) [13].

Materials and methods

Inclusion criteria

All patients had to fulfil the following criteria of severe cardiovascular and respiratory system failure:

1. Septic shock. Septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference (i.e., signs of sepsis and prolonged systolic hypotension of <90 mmHg for >1 h, despite adequate fluid resuscitation without inotropic support) [14].
2. The criterion of severe respiratory failure was defined as the requirement of mechanical ventilation with a PaO_2/FiO_2 <225 mmHg (the limit was decided as determined by the respiratory organ dysfunction score $\geq$2 as monitored by the Multiple Organ Dysfunction Scoring system, MODS) [15].
3. Once patients fulfilled the above criteria invasive haemodynamic monitoring by arterial thermodilution (PiCCO) was commenced. Measurements were done six-hourly, or whenever it was required by a change in the patients' blood pressure, heart rate, cardiac index or hourly urine output. When hypovolaemia was diagnosed as intrathoracic blood volume 750–850 ml/kg (reference range by Pulsion Medical Systems, Munich, Germany) patients were recruited into the study.

Exclusion criteria

Patients with chronic cardiovascular system failure (New York Heart Association Class IV), chronic respiratory failure (chronic hypoxia, hypercapnia), chronic renal failure requiring renal replacement therapy, chronic liver failure (biopsy proven cirrhosis or portal hypertension), or those with diabetes mellitus or with known aortic aneurysm were excluded from the study.

Clinical parameters

Haemodynamic parameters were determined in each patient by single arterial thermodilution, for which a flexible catheter with an integrated thermistor (PiCCO, Pulsiocath 4F, PV 2024L, Pulsion Medical Systems, Munich, Germany) was introduced via the femoral artery. Intrathoracic blood volume (ITBV) and EVLW measurements were obtained by injections of a 20 ml bolus of 0.9% saline <10 °C via a central venous catheter. The mean value of three consecutive measurements was used for analysis. For inter-individual comparison, absolute values for ITBV and EVLW were normalised as indexed by body surface area (ITBVI, normal range: 850–1,000 ml/m^2) and body weight (EVLWI, normal range: 5–7 ml/kg). All injections were made manually and not synchronised with the respiratory cycle. Cardiac index (CI) and systemic vascular resistance index (SVRI) were also recorded.

The degree of subcutaneous peripheral oedema was assessed on study entry using the pitting-score as described by Diskin et al. [16]. Depth of "pit" was measured following a 10-s compression on the ankle and hand by one finger. Score: 1 = no oedema, 2 = pit: 1–2 mm, 3 = pit: 3–4 mm, 4 = pit: $\geq$4 mm.

Clinical management

Patients received routine intensive monitoring and therapy. Regarding respiratory support every patient received lung protective ventilation (V_T~6 ml/kg) applying the open-lung concept with a PEEP of 5–25 cmH_2O, which was adjusted individually according to blood gas values (mean PEEP values are shown in Table 1). The weaning strategy was to decrease FiO_2 first to at least 50% and the PEEP was only decreased afterwards (Servo 300, Siemens, Solana, Sweden). All patients received noradrenaline to maintain mean arterial pressure above 60 mmHg, and dobutamine was added to seven patients in each group for improving cardiac index above 2.5 $l \cdot min \cdot m^2$.

Biochemical investigations

Together with each haemodynamic measurement arterial blood samples were taken for blood gas analysis (ABL 700, Radiometer, Copenhagen, Denmark). Full blood count, serum bilirubin, creatinine, and albumin levels were determined by routine methods.

Study protocol

The Local Ethics Committee approved the study protocol and consent was obtained from the patients' next of kin. The study design was a randomised clinical trial. Patients were randomly allocated in a block-of-six fashion following the initial haemodynamic measurement to receive 6% HES (weight average molecular weight: 200,000 Daltons; number average molecular weight: 60,000; substitution ratio: 0.6; half life: 24 h; Haes-Steril 6%, Fresenius-Kabi, Budapest, Hungary) or 4% succinylated GEL (weight average molecular weight: 35,000 Daltons; number average molecular weight: 21,700; half life: 4 h; Gelofusin, B. Braun

Table 1 Demographic data of the patients in the GEL and HES group. Data are presented as mean±SD. SAPS II and diagnoses indicate the severity score and diagnosis on admission to ICU (*SAPS* II Simplified Acute Physiology Score II, *S* survivors, *NS* non-survivors)

	HES	GEL
	n=15	*n*=15
Age (years)	49±17	56±14
Sex (M/F)	4/11	4/11
SAPS II	34±21	34±14
ICU stay (days)	20±17	21±13
Days elapsed to study entry	5±3	4±3
Albumin (g/l) (on ICU admission)	19±4	16±4
Albumin(g/l) (on study entry)	18±4	17±4
Fluid balance (ml) (last 24 h)	837±1769	204±1695
Oedema score	3±1	3±1
PEEP (cmH_2O)	13±6	11±3
Lung Injury Score	2.5±1	2.33±1
Norepinephrine (μg/min)	10.5±8.5	15.7±11.4
Dobutamine (μg/kg/min)	6±5	7±5
Diagnoses		
Postop. ARDS	3	
Pneumonia		1
Pancreatitis	4	4
Polytrauma	3	2
Postop. Sepsis	5	5
Survival (S/NS)	3/12	5/10

Medical, Budapest, Hungary) 250 ml bolus during 15 min (maximum of 1,000 ml) until the desired end-point (ITBVI >900 ml/m^2) was not reached. After each 250 ml colloid bolus haemodynamic measurements were performed to assess the volemic status of the patients. When the end-point was reached, haemodynamic and arterial blood gas measurements were repeated 30 min and 60 min after the colloid infusion. During protocol no other maintenance infusions and no changes of ventilator settings or drug administration were allowed.

Statistical analysis

All data are presented as mean±SD. To test normal distribution the Kolgomorov-Smirnov test with the Lilliefors modification was used. Analysis of variance (ANOVA) was used for testing the significance levels between the different groups, and ANOVA for repeated measures was used for testing significance levels between the measurement stages. For statistical analysis the Statistical Program for Social Sciences (SPSS version 10.0) software for Windows was used. Statistical significance was considered at $P<0.05$. In a pilot study of the same design Ringer lactate was compared to Gelofusine with no significant difference regarding haemodynamic effects. Following 100 ml of infusion the rise in ITBVI in the whole study population was 25.6±18.6 ml/m^2. Therefore, the smallest difference between the means that we regarded as clinically acceptable and which could not to be overlooked was 15 ml/m^2 (i.e., mean 30 ml/m^2 for GEL and 45 ml/m^2 for HES). With type I alpha of 5% and type II (power) of 80% we calculated we would need about 13 patients per group.

Results

Between January 2002 and May 2003, 45 consecutive patients in septic shock were evaluated. Thirty-five patients met the inclusion criteria, but due to diabetes mellitus and chronic renal failure five patients were excluded from the study. The remaining 30 patients were randomised into GEL and HES groups (15 patients each). Patients' demographic data are summarized in Table 1. Changes in ITBVI showed a similar pattern in both groups (Table 2). Regarding the amount of fluid required to achieve the end-point in ITBVI there was no difference between the groups as indicated by the change in ITBVI when infusing 100 ml of the given colloid (Table 2). Cardiac index (CI) and DO_2I increased significantly in both groups, whilst EVLWI, although moderately elevated, remained unchanged, and there was no significant

Table 2 Cardiorespiratory variables. Data are presented as mean±SD. For statistical analysis two-way ANOVA was used

	t_b	t_{ep}	t_{30}	t_{60}
$ITBVI_{HES}$ (ml/m^2)	798±37	956±53*	904±70*	854±116*
$ITBVI_{GEL}$	791±52	967±71*	897±96*	905±92*
CI_{HES} (l·min·m^2)	3.84±0.96	5.06±1.19*	4.69±1.14*	4.04±1.09
CI_{GEL}	3.82±0.88	4.88±0.85*	4.69±0.77*	4.58±1.25
Hb_{HES} (g/l)	99±14	97±15	97±18	96±16
Hb_{GEL}	95±21	95±22	93±22	94±22
DO_2I_{HES} (ml·min·m^2)	477±99	630±183*	598±126*	527±109
DO_2I_{GEL}	457±101	615±186*	560±163*	550±178
$EVLW_{HES}$ (ml/kg)	8±6	8±6	9±7	8±6
$EVLW_{GEL}$	8±3	8±3	8±3	8±3
MAP_{HES} (mmHg)	76±14	83±9	84±11	83±10
MAP_{GEL}	73±10	81±13	76±13	78±13
CVP_{HES} (mmHg)	15±6	19±6	19±8	17±6
CVP_{GEL}	15±8	18±8	17±9	17±8
HR_{HES} (beats/min)	107±9	102±12	103±12	104±10
HR_{GEL}	116±30	110±26	108±26	110±28
PaO_2/FiO_{2HES}(mmHg)	207±114	206±100	189±52	189±78
PaO_2/FiO_{2GEL}	182±85	197±85	189±87	182±85
$\Delta ITBV/100\ ml_{HES}$	–	26±19	–	–
$\Delta ITBV/100\ ml_{GEL}$	–	30±19	–	–

* $P<0.05$ compared to baseline values

difference between the groups (Table 2). There was also no significant difference in the PaO_2/FiO_2 either within or between groups.

Discussion

The main finding in this study is that volume resuscitation with small (GEL) or large molecular weight (HES) colloids in patients with sepsis with ALI significantly improved ITBVI, cardiac output, and oxygen delivery but did not result in increased EVLW and/or worsening oxygenation.

It has been suggested that the inflammatory cascade reactions in sepsis induce increased capillary permeability, which results in albumin loss and interstitial oedema [8]. There is firm experimental evidence that albumin does escape from the circulation in animals with sepsis and the measurement of radio-labelled albumin escape rate is an accurate method to quantify increased capillary leakage [11, 17, 18]. Therefore, the use of higher molecular weight colloids than that of albumin would certainly carry theoretical advantages in patients with sepsis, such as haemodynamic stability without interstitial and/or pulmonary oedema, hence better oxygenation.

In our patients in severe sepsis, similar haemodynamic improvement was observed following fluid resuscitation with GEL and HES as indicated by significantly higher CI and DO_2I. This improvement was solely due to the increase in preload (ITBV), which resulted in larger stroke volume. The amount of fluid required to achieve this improvement was also very similar in the two groups as expressed by the ΔITBVI/100 ml infusion value (Table 2). These results are in accord with previous and recent reports, in which no significant difference was observed in haemodynamic effects of HES and GEL [10, 11, 19, 20]. An important finding in our current study is that despite significant increase in ITBVI and CI, the EVLW remained unchanged. Furthermore, in contrast to the previously cited papers, we also observed a significant improvement in DO_2I, meaning that the haemoglobin did not drop to such an extent as the CI improved. One of the main differences between our study and the earlier works is that our patients were managed according to the ITBV and not the CVP or PAOP values. For haemodynamic monitoring we used the single transpulmonary thermodilution as determinations of ITBV and EVLW. This method has been shown to agree closely with the corresponding values from the double-indicator technique; however, it has also been described that in edematous lung, this method may underestimate the EVLW [21, 22]. It is an interesting finding that although CI improved significantly neither the CVP, nor the HR or MAP reflected this change in cardiac performance. ITBVI-guided fluid challenge did not result in an increased EVLW, which may explain why there was no significant change in oxygenation.

Our results are to some extent in contrast to those found by Allison et al. [12]. In their study, 48 h after fluid resuscitation in trauma patients, significantly better PaO_2/FiO_2 was found in the HES group, mean: 325 (95% confidence interval: 44) mmHg, as compared to the GEL group: 267 (43) mmHg, P=0.029. This difference between the two studies could be explained by the different design. In our protocol the measurements were done 60 min after the end of fluid challenge with regard to the pharmacodynamic properties of HES and GEL [10], whilst in the Allison study the daily mean values were recorded, therefore it is difficult to exclude that other influences than the fluid challenge itself effected oxygenation. Furthermore, the total amount of fluid infused in our study was HES: 750±274 ml, GEL: 714±254 ml over about 1 h (250 ml/15 min) under strict haemodynamic control, whilst there was no target end point in the Allison trial. They also observed significantly lower renal albumin excretion rate in the HES group and they concluded that this means decreased capillary permeability in HES-treated patients. However, despite recent descriptions of different non-invasive determinants, the diagnosis of systemic capillary leakage remains difficult [23, 24, 25]. The clinical applicability of the "gold-standard" albumin escape rate is limited due to radioactive contamination and dye accumulation. Therefore, the problem of diagnosing endothelial permeability by the bedside remains unsolved.

In a recent paper by Marx et al., albumin escape rate was found to be higher in animals with sepsis but they could not show any escape of HES or GEL molecules from the circulation and both colloids maintained plasma volume [11]. In accord with our results, it seems that colloids—regardless of their molecular weight—may remain in the circulation even in septic shock. Colloid oncotic pressure and/or changes at the endothelial or subendothelial matrix proteins' charges could provide the physiological explanation [11, 26, 27]. Unfortunately, any explanation seems to be speculative at present as there is no firm evidence to support either theory [28].

The appropriate choice of colloid during fluid resuscitation, especially in sepsis, remains unknown. The results of recent meta-analyses suggest that the effect of resuscitation fluid choice on mortality, if any, is minor [29]. However, in a recent paper it was found that HES as compared to GEL worsened gastric mucosal acidosis [10].

In conclusion, this study investigated the short-term effect of fluid resuscitation with small molecular weight GEL and 200,000 Dalton molecular weight HES in patients with sepsis with ALI. Both colloids improved ITBVI, CI, and DO_2, whilst neither increased EVLW or worsened oxygenation.

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