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Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine®) and 6% hydroxyethyl starch (Voluven®) on blood volume†

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Editor's key points

- This study investigated whether the blood volume-expanding effects of 1 litre intraoperative i.v. infusions of Gelofusine® and Voluven® over 1 h were similar in patients undergoing surgery.
- The blood volume-expanding effects of the two colloids were not significantly different, despite the differences in molecular weight.
- This experimental model may be used safely to study the effects of fixed-volume fluid infusions in the presence of increased capillary permeability.

Background. This study aims to study changes in blood volume after 1 litre infusions of Gelofusine® [4% succinylated gelatine in 0.7% saline, weight-average molecular weight (MWw) 30 kDa] and Voluven® (6% hydroxyethyl starch in 0.9% saline, MWw 130 kDa) in the presence of increased capillary permeability.

Methods. In this randomized double-blind study, adults undergoing laparoscopic cholecystectomy received 1 litre of Gelofusine® (n=12) or Voluven® (n=13) over 1 h at the induction of anaesthesia. No other fluids were given. Haematocrit, serum electrolytes, and osmolality were measured before infusion and hourly thereafter for 4 h. Changes in blood volume were calculated from changes in haematocrit. The urinary albumin:creatinine ratio (ACR) was measured before and after operation.

Results. Baseline parameters before the two infusions were similar (P>0.050). The urinary ACR increased significantly after operation after Gelofusine® (P=0.011) and Voluven® (P=0.002), indicating increased capillary permeability. Voluven® produced a greater increase in serum chloride concentration (P=0.028) and a larger decrease in strong ion difference (P=0.009) than Gelofusine®. There were no significant differences in changes in haematocrit (P=0.523) and blood volume (P=0.404) over the study period when the two infusions were compared, nor were there any differences in serum sodium, potassium, bicarbonate, and albumin concentrations (P>0.050). Urine output, sodium concentration, and osmolality were similar after the two infusions (P>0.050).

Conclusions. The blood volume-expanding effects of the two colloids were not significantly different, despite the increase in postoperative urinary ACR and the 100 kDa difference in MWw.

Keywords: colloid; Gelofusine; hydroxyethyl starch; intravenous; randomized study; succinylated gelatine; surgery; volume loading; Voluven

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It has traditionally been believed that colloids with a low weight-average molecular weight (MWw) escape through the pores in the capillary membrane at a faster rate than colloids with a medium or high MWw and are, therefore, less efficient blood volume expanders.[1] However, in healthy volunteers, we demonstrated that despite the 100 kDa difference in MWw of Gelofusine® (4% succinylated gelatine in 0.7% saline, MWw 30 kDa, B Braun, Chapeltown, UK) and Voluven® (6% hydroxyethyl starch in 0.9% saline, MWw 130 kDa, Fresenius Kabi, Runcorn, UK), there was no significant difference in the blood volume-expanding capacity of the two colloids after a 1 litre infusion over 1 h.[2]

One of the limitations of that study[2] was that as it was undertaken in healthy volunteers in whom the transcapillary escape rate of albumin (TER_{alb}) was presumably normal, the volume-expanding effects of the 30 kDa colloid may have been exaggerated when compared with the effects in patients in whom the TER_{alb} is elevated. Although studies in animals subjected to trauma have suggested that the blood volume expansion produced by iso-oncotic gelatines and hydroxyethyl starch may be similar,[3–5] it is difficult to study this phenomenon in patients with sepsis and trauma and those undergoing major surgery, as it is not practical to give such patients a single bolus of a fixed-volume

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infusion. The aim of the present study was to test the hypothesis that the blood volume-expanding effects of 1 litre intraoperative i.v. infusions of Gelofusine®[6 7] and Voluven®[7 8] over 1 h were similar in patients undergoing surgery. A laparoscopic cholecystectomy model was chosen because this procedure is of sufficient magnitude to evoke an inflammatory response[9 10] and at the same time allows for the administration of a relatively modest fixed-volume infusion.[11]

Methods

Study design

This randomized double-blind study set in an affiliated university hospital was undertaken between February 2009 and July 2011, using an experimental model that has been developed by us[12] and shown to be reproducible.[2 13] We recruited participants aged 18–60 yr with a BMI of 20–26 kg m^{-2} undergoing elective laparoscopic cholecystectomy for uncomplicated gallstone disease, after obtaining written informed consent. Owing to slow recruitment, the BMI criteria were expanded to 20–35 kg m^{-2}. Participants with a history of allergic reaction to colloid infusions, renal, cardiac, or respiratory co-morbidity, and those who were diabetic or pregnant were excluded. The study protocol and the amendment were approved by the Nottingham Research Ethics Committee (approval number 08/H0408/187) and the Medicines and Healthcare products Regulatory Agency of the UK (EudraCT number 2008-005135-15). The study was registered at http://clinicaltrials.gov (NCT00868062) and was performed in accordance with the Declaration of Helsinki of the World Medical Association.

Randomization, blinding, and preparation of the study solutions

The randomization code was obtained using random assignment software and allocations were concealed in consecutively numbered sealed opaque envelopes that were kept by the hospital's pharmacy department. The latter, who were not involved in collection of study data, randomized patients on the morning of surgery and masked the study solutions (Gelofusine® or Voluven®, Table 1) by placing them in identical opaque bags and connecting them to the infusion sets. The randomization code was broken after completion of data analysis.

Primary endpoint and sample size calculation

The primary endpoint was the magnitude of the blood volume-expanding effects of the two colloids. Our previous work using the same infusion protocol in healthy volunteers has shown that the magnitude and duration of the blood volume expansion produced by Gelofusine® and Voluven® were almost identical.[2] The TER_{alb} in health is 5% h^{-1}, and the stress response to anaesthesia and surgery can result in an increase in TER_{alb} to 10–15% h^{-1}.[14] In our previous study,[2] the mean (SE) blood volume expansion produced at 1 h was 579 (57) ml after Gelofusine® and 574 (92) ml after Voluven®. Assuming that the increase in TER_{alb} would reduce the blood volume expansion produced by Gelofusine® by 20% and have no effect on the expansion produced by Voluven® (because of the higher MWw), a total of 24 (12 in each group) participants was required to demonstrate this difference at the 95% significance level with a power of 90%. Allowing for a 10% dropout rate, we aimed to recruit 27 participants.

Table 1 Characteristics of the infusions.[6–8] *Measured by B Braun Medical SA, Crissier, Switzerland

	Gelofusine®	Voluven®
Sodium (mmol $litre^{-1}$)	154	154
Chloride (mmol $litre^{-1}$)	120	154
Sodium supplied as	NaCl 7.01 g $litre^{-1}$+NaOH 1.36 g $litre^{-1}$	NaCl 9 g $litre^{-1}$
Colloid	Succinylated gelatine	Hydroxyethyl starch
Weight-average molecular weight of colloid (MWw)	30 000	130 000
Number-average molecular weight of colloid (MWn)	23 200	60 000–65 000
Polydispersity ratio (MWw/MWn)	1.29:1	2.0–2.7:1
Molar substitution	—	0.4
Weight of colloid per litre	40 g (4%)	60 g (6%)
pH	7.1–7.7	4.5–5.5
Theoretical osmolarity (mOsm $litre^{-1}$)	274	308
Na^+:Cl^- ratio	1.28:1	1:1
Colloid osmotic pressure at 37°C (mm Hg)	33.3	36
Hydrodynamic particle radius (Rh_w) (nm)*	4.1	6.1
Price per 500 ml bag	£5.15	£12.50

Study interventions

Before inclusion in the study, participants had their height and weight measured, and blood samples (full blood count, urea and electrolytes, liver function tests) were obtained to ensure that they fulfilled the inclusion criteria. On the morning of surgery, having abstained from food for 6 h and clear fluids for at least 2 h (in accordance with the hospital's preoperative fasting guidelines), participants voided urine before entering the anaesthetic room. The voided urine was analysed for sodium, potassium, urea, creatinine, osmolality, and microalbumin. Two venous cannulae were inserted into the forearms, baseline bloods (see below) sampled, followed by the induction of anaesthesia, and bladder catheterization to permit collection of urine. The study infusion (2×500 ml bags) was then commenced and delivered i.v. via an infusion pump (IVAC Corporation, San Diego, CA, USA) over the subsequent hour during which standard laparoscopic cholecystectomy was performed. Patients were

not permitted to receive, and indeed were excluded from the study if they did, any other fluid infusions during the study period. At hourly intervals for a total of 4 h, blood was sampled for haemoglobin, haematocrit, sodium, potassium, chloride, bicarbonate, osmolality, and albumin measurements. Similarly, urine was collected over 4 h and a sample from pooled urine analysed for sodium, potassium, urea, creatinine, osmolality, and microalbumin. The urinary catheter was removed at $t=4$ h and the participants were allowed home at the discretion of the treating team.

Haematological and biochemical analyses

Haematological and biochemical parameters were measured by methods we have previously utilized, with coefficients of variance of 0.6–4%.[2 12 13] Urinary microalbumin was used as an indirect measure of increased transcapillary escape rate of albumin (TER_{alb}).[15 16] Microalbumin concentrations were measured by an immunoassay on a Vitros® 5.1 FS Chemistry System (Ortho Clinical Diagnostic, High Wycombe, UK) and the coefficient of variance for the assay was 3%. In order to account for variations in urine flow, results were expressed as the urinary albumin:creatinine ratio (ACR). The normal urinary ACR for ambulatory adults is <2.3 mg mmol^{-1} and this can be as low as 1 mg mmol^{-1} in the recumbent position.[17]

Derived variables

Blood volume at time 0 was estimated according to Nadler's formula:[18]

$$BV_0 = 0.03219 \times BW_0 + 0.3669 \times Ht^3 + 0.6041$$

where BV_0 is the blood volume (litre) at time 0, BW_0 the body weight (kg) at time 0 and Ht the height (m). Changes in blood volume were calculated from changes in haematocrit using formulae we have described previously.[2]

$$\Delta Hct_t\,(\%) = \frac{Hct_0 - Hct_t}{Hct_0} \times 100$$

where ΔHct_t (%) is the percentage reduction in haematocrit at time t, Hct_0 the haematocrit at time 0 and Hct_t the haematocrit at time t.

$$\Delta BV_t\,(\%) = BV_0 \left\lfloor \frac{\Delta Hct_t}{Hct_t} \right\rfloor \times 100$$

where ΔBV_t (%) is the percentage change in blood volume at time t, and

$$BV_t(\text{litre}) = \frac{BV_0 \times [100 + \Delta BV_t(\%)]}{100}$$

where BV_t (litre) is the blood volume in litres at time t

$$\Delta BV_t(\text{litre}) = BV_t - BV_0$$

where ΔBV_t (litre) is the change in blood volume in litres at time t from baseline (time 0).

The strong ion difference (SID) was calculated as described by Stewart:[19]

$$SID\ (\text{mmol litre}^{-1}) = [Na^+] + [K^+] - [Cl^-]$$

Statistical analysis

Statistical analysis was performed with GraphPad Prism v 5.0d for Macintosh software (GraphPad Software Inc., La Jolla, CA, USA). Grouped data (Gelofusine® *vs* Voluven®) are represented as mean (SEM). The significance of differences between the two groups was tested using the repeated measures analysis of variance with Bonferroni's correction for multiple comparisons, the Student *t*-test (paired for within the groups and unpaired for between the groups), and the Fisher exact test. Differences were considered significant at $P<0.050$.

Results

Twenty-seven participants were randomized, 26 completed the study, and the results of 25 (12 Gelofusine® and 13 Voluven®) were analysed (Fig. 1). Baseline parameters of the participants in the two groups before the commencement of infusion were similar (Table 2). None of the subjects experienced infusion-related side-effects.

The urinary ACR was similar in the preoperative urine samples and increased significantly in the postoperative samples, with the differences between the groups not being significant (Fig. 2). Changes in haemoglobin, serum albumin concentration, and haematocrit over the period of the study were not significantly different when the two groups were compared (Fig. 3). Despite the increase in urinary ACR and the 100 kDa difference in MWw of the two colloids, calculated blood volume expansion was not significantly different after the two infusions (Fig. 3). In fact, the blood volume-expanding efficiencies of Gelofusine® and Voluven® at 1 h were 68% and 70%, respectively. However, there was a trend, albeit not statistically significant, for Voluven® to produce a more sustained increase in blood volume than Gelofusine® (Fig. 3).

Changes in serum concentrations of sodium, potassium and bicarbonate, and serum osmolality were similar after both infusions over the course of the study (Fig. 4). A significant and sustained hyperchloraemia was noted after Voluven® but not Gelofusine®, and this difference was reflected in a greater decrease in SID after Voluven®, suggesting a tendency of Voluven® to produce a hyperchloraemic acidosis (Fig. 4).

Postoperative urinary parameters are summarized in Table 3. Apart from urinary potassium concentration, the differences between the two groups were not statistically significant for the other parameters.

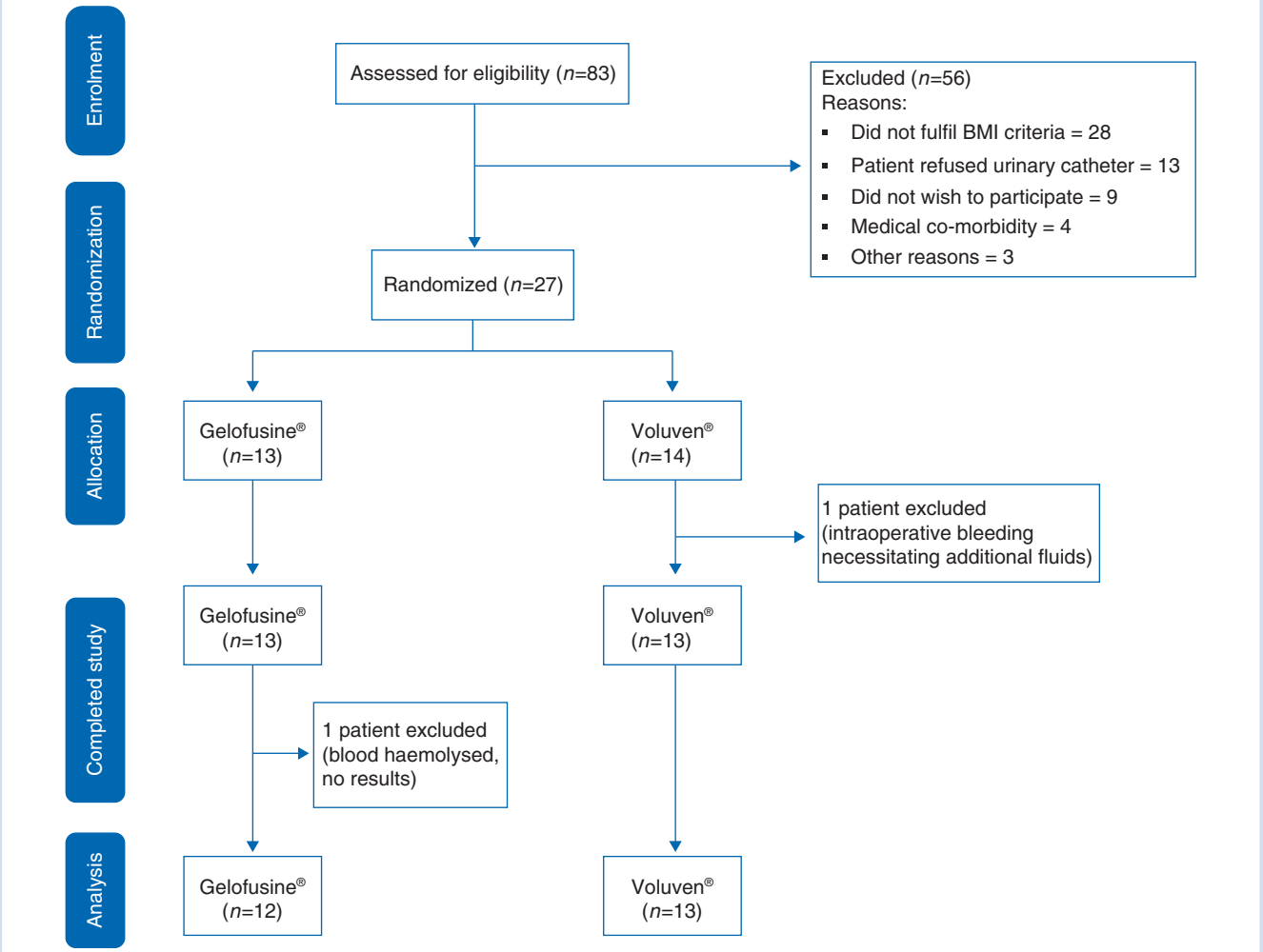

Fig 1 Trial profile.

Discussion

This study has confirmed that in the experimental model used, the blood volume-expanding effects of the two colloids were not significantly different, despite the increase in TER_{alb} (as evidenced by the increase in postoperative urinary ACR) and the 100 kDa difference in MWw of the two colloids. The results are also in keeping with those from previous studies, which have shown that as long the oncotic pressures of the colloids were similar, there was no difference in the volume-expanding effects of gelatines and hydroxyethyl starch during the resuscitation of traumatized animals.[3 5] A recent human study has also shown that in the early phase after cardiac surgery, the effect of a single dose of hydroxyethyl starch solution on the cardiac index and stroke volume index was superior to the effect of gelatine, but that after repeated administration of the colloids, the haemodynamics in the two colloid groups appeared to be similar.[20] The results of the present study also suggest that the laparoscopic cholecystectomy model may be utilized to study the effects of fixed-volume fluid infusions in the presence of an increase in TER_{alb}.

We chose the laparoscopic cholecystectomy model because it is the one in which a relatively modest volume single i.v. fluid bolus infusion can be given safely[11] without the need for extra fluid that may have compromised the experiment. Moreover, the procedure is of sufficient magnitude to provoke an inflammatory response, albeit not as pronounced as that produced by open surgery.[9 10] Microalbuminuria refers to the excretion of pathologically significant amounts (30–200 mg $litre^{-1}$) of normal molecular weight albumin, while clinical proteinuria is defined as a urine protein concentration above 200 mg $litre^{-1}$.[16] Microalbuminuria after acute inflammatory insults has been demonstrated in humans and is considered to be a reflection of and a surrogate marker for systemic vascular endothelial dysfunction.[14–16 21–23] Significant increases in TER_{alb} have been demonstrated during surgery, sepsis, and malignancy and have been shown to share a common temporal

Table 2 Baseline preoperative and preinfusion parameters. Data for age are mean (range). All other values except gender are mean (SEM). *Fisher exact test. All other *P*-values calculated using the Student *t*-test (unpaired)

	Gelofusine® (*n*=12)	Voluven® (*n*=13)	*P*-value
Age (yr)	46.1 (24–77)	42.5 (18–65)	0.551
Gender (M:F)	3:9	3:10	1.000*
Weight (kg)	79.5 (3.6)	81.2 (2.9)	0.712
Height (m)	1.66 (0.01)	1.68 (0.01)	0.581
Body mass index (kg m^{-2})	28.8 (1.0)	28.9 (1.1)	0.974
Haemoglobin (g dl^{-1})	13.4 (0.2)	13.1 (0.5)	0.557
Haematocrit (%)	39.4 (0.6)	39.5 (1.3)	0.976
Calculated blood volume (litre)	5.84 (0.3)	5.99 (0.2)	0.703
Serum albumin (g $litre^{-1}$)	34.8 (0.8)	33.5 (1.0)	0.332
Serum sodium (mmol $litre^{-1}$)	139.0 (0.9)	139.5 (0.5)	0.606
Serum potassium (mmol $litre^{-1}$)	4.2 (0.1)	4.1 (0.1)	0.299
Serum chloride (mmol $litre^{-1}$)	103.8 (1.0)	105.3 (0.7)	0.186
Serum bicarbonate (mmol $litre^{-1}$)	23.4 (0.5)	24.2 (0.6)	0.296
Strong ion difference (mmol $litre^{-1}$)	39.4 (0.9)	38.2 (0.7)	0.283
Serum osmolality (mOsm kg^{-1})	291.6 (1.9)	291.7 (1.5)	0.964
Serum creatinine (μmol $litre^{-1}$)	66.5 (3.3)	64.7 (3.9)	0.723
Blood urea (mmol $litre^{-1}$)	4.3 (0.3)	4.2 (0.3)	0.782
Urinary albumin:creatinine ratio (mg $mmol^{-1}$)	1.5 (0.1)	1.3 (0.3)	0.716
Urinary osmolality (mOsm kg^{-1})	513.4 (64.0)	546.9 (57.9)	0.701

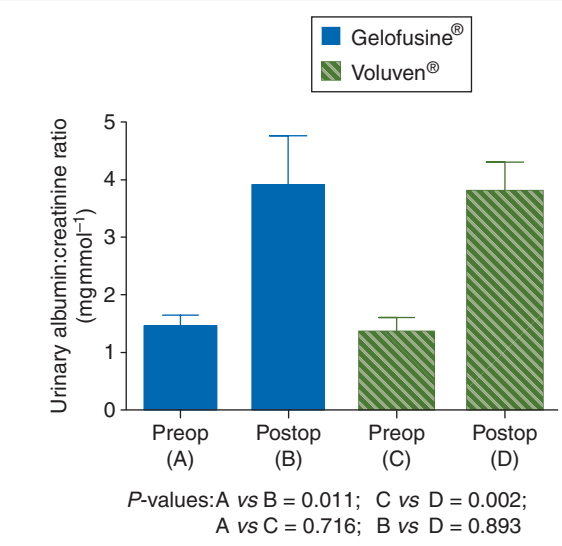

Fig 2 Preoperative/preinfusion (Preop) and postoperative/postinfusion (Postop) urinary ACR. All values are mean (SEM). The *P*-values have been calculated using the Student *t*-test (unpaired for between the groups and paired for within the groups).

relationship with microalbuminuria.[14 21] In the present study, the urinary ACR was normal before operation and increased significantly after operation (although there was no statistically significant difference between the groups), indicating that the procedure did produce vascular endothelial dysfunction and that the experimental model could be used to study physiological responses to fixed-volume i.v. fluid infusions in the presence of increased capillary permeability. This endothelial dysfunction is unlikely to be due to the infusions as previous experimental work has shown that dextran, gelatine, and hydroxyethyl starch do not affect permeability for albumin in cat skeletal muscle.[24] It must be emphasized, however, that the magnitude of increase in urinary ACR in the present study was much smaller than that seen after major injury such as extensive burns.[16]

The fact that the preoperative urinary osmolality was <700 mOsm kg^{-1} in both groups and not statistically different (Table 2) suggests that both groups of patients were in a similar state of hydration before operation and that they were not dehydrated.[25] This is corroborated by the normal values obtained for preoperative serum osmolality and blood urea concentration. Although both groups of patients excreted more than 300 ml of urine over the 4 h study period, the increase in osmolality of the postoperative pooled urine samples in both groups (Table 3) is reflective of the metabolic response to trauma, where there is retention of sodium and water, with an increase in potassium excretion and excretion of concentrated urine.[26–28] The blood volume expansion seen at the end of the infusions (~70% of the infused volume) in the present study was greater than what we observed (~60% of the infused volume) when the same study was performed in healthy volunteers.[2] The reason for this is not entirely clear, but it is possible that it could be related to the sodium and water retention mediated by the metabolic response to injury.[26–28] This may also reflect the fact that the healthy volunteers were in a fluid deficit (urinary osmolality >800 mOsm kg^{-1}) at the start of the infusion after an overnight fast[2] while the patients in the present study were euhydrated as they were drinking clear liquids up to 2 h before the commencement of the infusion.

Interestingly, there was a relative decrease in urinary potassium concentration after Voluven® when compared with Gelofusine® and may explain why some studies have shown that there may be a hyperkalaemia associated with 0.9% saline-based solutions rather than balanced solutions.[29] This may also be a consequence of the hyperchloraemic acidosis caused by saline. Although not statistically significant, there was a greater concentration of sodium in the urine after Gelofusine® than after Voluven® and this supports the hypothesis that the hyperchloraemic acidosis

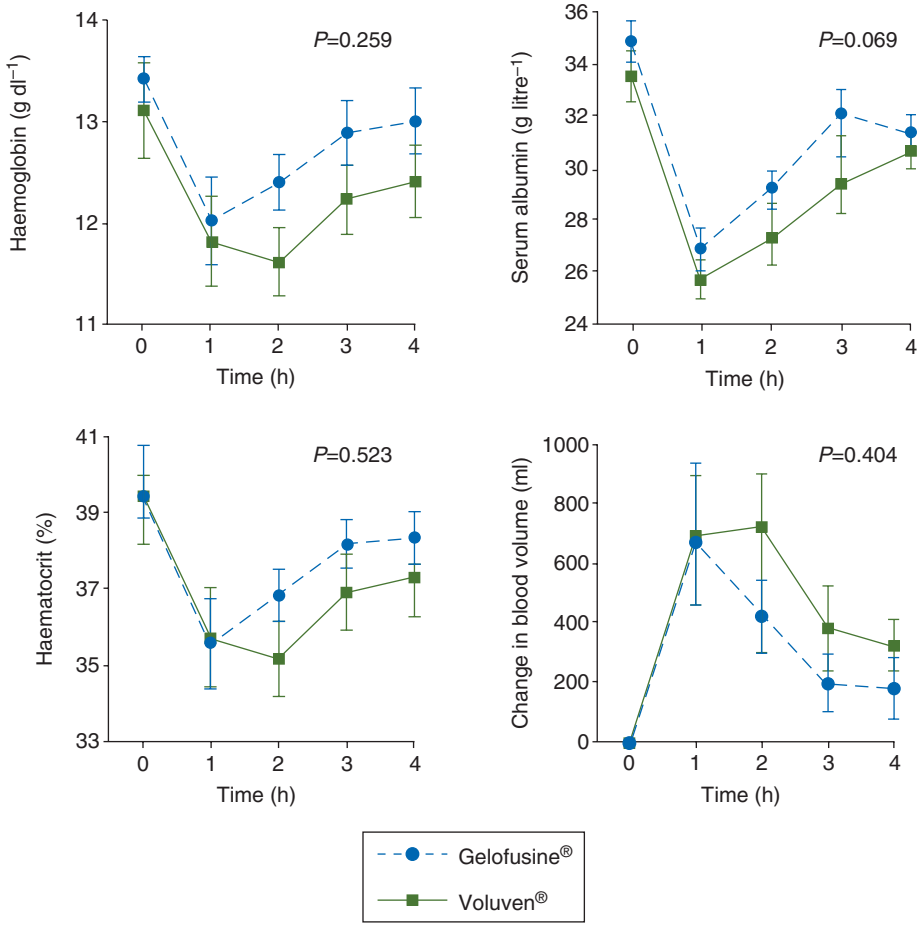

Fig 3 Changes in haemoglobin, serum albumin concentration, haematocrit, and calculated blood volume after 1 litre infusions of the two colloids over 1 h. All values are mean (SEM). The *P*-values are for the test of Gelofusine® *vs* Voluven® using the analysis of variance and a repeated measures model.

induced by 0.9% saline-based fluids results in a decreased ability of the kidney to excrete salt and water[2 12 13] because of a decrease in renal blood flow and cortical perfusion.[30]

Despite the increased urinary ACR (and, hence, the increase in endothelial dysfunction) and the 100 kDa difference in MWw of the two colloids, changes in haematocrit and calculated blood volume expansion were not significantly different after the two infusions, suggesting that the increase in capillary permeability did not play a major role in determining the blood volume-expanding efficiencies of the two colloids. Nevertheless, it must be pointed out that there was a trend, albeit not statistically significant, for Voluven® to produce a more sustained increase in blood volume than Gelofusine®. We have previously proposed an explanation for the lack of significant difference between the blood volume-expanding effects of the two colloids when used in healthy volunteers[2] and that explanation may also be valid in the presence of moderate endothelial dysfunction. The two-pore theory for transport of macromolecules across the microvasculature suggests that small solutes pass through small pores (radius: 2.5–3 nm) in the capillary membrane along the entire microvascular bed, while larger molecules only pass through the large pores (radius: 10–11 nm) on the venous side of the capillary network and in venules,[31 32] with the ratio of large to small pores being 1:3000–1:3600.[31] As the oncotic pressure on both sides of the large pores is in equilibrium, flow of fluid across these pores is governed solely by hydrostatic pressure. The loss of macromolecules across the pores is along the direction of fluid flux and occurs mainly by convection.[32–35] Hence, even in health, an increase in capillary hydrostatic pressure caused by volume expansion can result in leakage of larger molecules from the intravascular compartment to the extravascular space. Hypervolaemia may disrupt endothelial integrity, which is maintained by the endothelial glycocalyx which binds to large anionic molecules and prevents their extravasation.[36 37] In addition, the escape of a molecule across the pores is dependent more on the diameter of the molecule than the MWw.[38] The measured hydrodynamic radii (Rh_w) of succinylated gelatine and hydroxyethyl starch (Table 1) are greater than the Rh_w of human serum albumin (2.6–3.3 nm),[39] but larger than the small-pore radius, and smaller

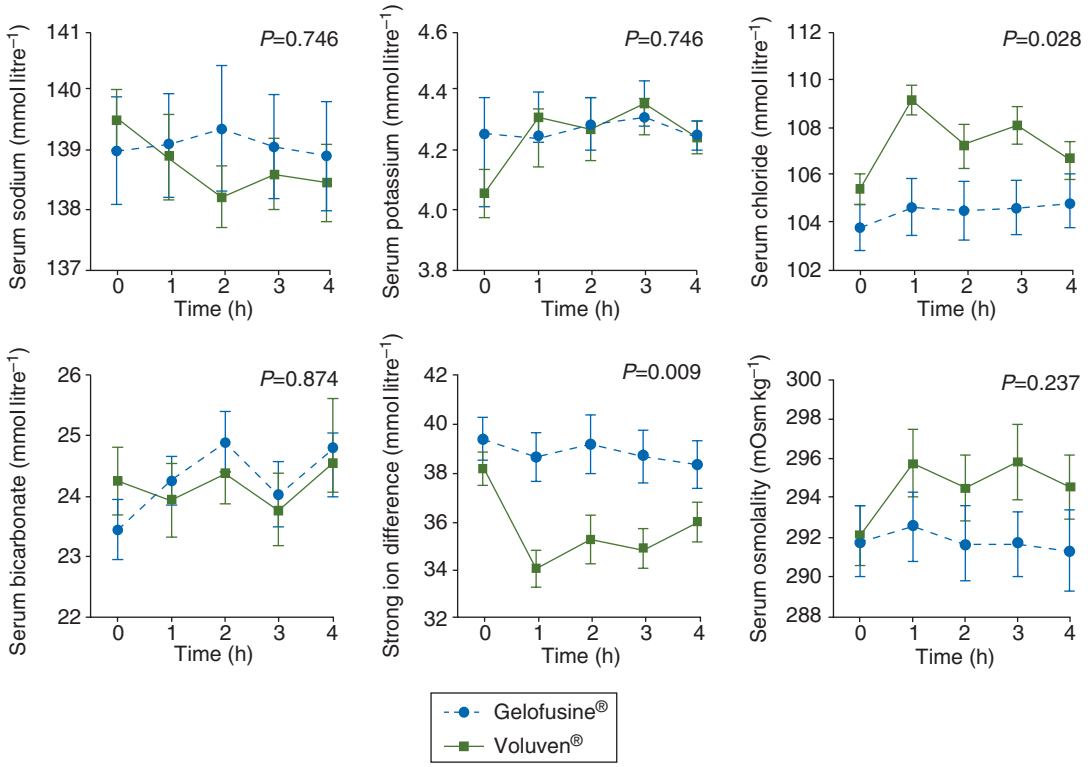

Fig 4 Changes in serum concentrations of sodium, potassium, chloride, and bicarbonate, and changes in strong ion difference (SID) and serum osmolality after 1 litre infusions of the two colloids over 1 h. All values are mean (SEM). The *P*-values are for the test of Gelofusine® *vs* Voluven® using the analysis of variance and a repeated measures model.

Table 3 Analysis of postinfusion urine pooled over 4 h. All values are mean (SEM); *P*-values calculated using the Student *t*-test (unpaired)

	Gelofusine® (*n*=12)	Voluven® (*n*=13)	*P*-value
Volume (ml)	335.4 (75.6)	312.9 (58.6)	0.819
Sodium (mmol litre^{-1})	133.9 (19.1)	92.9 (18.6)	0.141
Potassium (mmol litre^{-1})	117.0 (15.7)	75.2 (11.3)	0.043
Osmolality (mOsm kg^{-1})	830.1 (86.5)	839.4 (85.8)	0.940
Total urinary sodium (mmol)	51.5 (16.9)	26.9 (7.6)	0.234
Total urinary potassium (mmol)	33.8 (7.2)	18.8 (1.6)	0.083

than the large-pore radius of the capillaries.[31] It may be possible that the increase in small-pore size induced by the endothelial dysfunction produced by laparoscopic cholecystectomy did not result in the radius of the pores being greater than the Rh_w of succinylated gelatine. The similar effects of Gelofusine® and Voluven® may also be because hydroxyethyl starch molecules are broken down into smaller units by the cleavage action of amylase.[40]

Some limitations of this study must be emphasized. Although we were able to demonstrate endothelial dysfunction induced by the surgical procedure, the magnitude of increase in the urinary ACR was much less than that induced by major trauma such as burns[16] and it is possible that our results may not hold validity in the latter situation. However, it is very difficult to study changes produced by moderate fixed-volume infusions in critically ill patients as they usually require continuous infusions of larger volumes and the heterogeneity of critical illness may also be a confounding variable. We used theoretical calculations, based on changes in haematocrit to determine changes in blood volume in the present study, and these may be different from actual changes in blood volume measured using more complex techniques such as isotope or dye labelling. However, the former technique has been utilized on numerous occasions and errors, if any, should be applicable to both groups.

It must also be emphasized that the results of this study may not be applicable to other forms of gelatine such as urea-linked gelatine. Succinylation of gelatine results in stretching of the polypeptide chains, which in combination with the negative charge on the molecule, may make it a more efficient plasma volume expander than non-succinylated gelatines of the same molecular weight (e.g. urea-linked gelatine, polygelines). Equally, the results of the study may be extrapolated to preparations of 6%

hydroxyethyl starch in 0.9% saline made by other manufacturers.

In conclusion, we have shown that the blood volume-expanding effects of 1 litre infusions over 1 h of Gelofusine® and Voluven® in patients undergoing laparoscopic cholecystectomy were not significantly different, despite the increase in postoperative urinary ACR and the 100 kDa difference in MWw. This experimental model may be used safely to study the effects of fixed-volume fluid infusions in the presence of increased capillary permeability.

Declaration of interest

S.A. has received educational support and travel expenses from Baxter Healthcare. D.N.L. has received speaker's honoraria from B. Braun, Baxter Healthcare and Fresenius Kabi. D.N.L. has also received grant support from Fresenius Kabi and Baxter Healthcare for unrelated work.

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