Randomized study comparing the effects of hydroxyethyl starch solution with Gelofusine on pulmonary function in patients undergoing abdominal aortic aneurysm surgery


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Background. Restoring blood flow to ischaemic tissue can cause lung damage with pulmonary oedema. Hydroxyethyl starch (HES) solution, when used for volume replacement, may modify and reduce the degree of ischaemia–reperfusion injury. We compared the effects of HES solution with those of Gelofusine solution on pulmonary function, microvascular permeability and neutrophil activation in patients undergoing elective infrarenal abdominal aortic aneurysm surgery.

Methods. Forty patients were randomized into two groups. The anaesthetic technique was standardized. Lung function was assessed with the \( \frac{P_\text{O}_2}{F_\text{I}_2} \) ratio, respiratory compliance, chest x-ray and a score for lung injury. Microvascular permeability was determined by measuring microalbuminuria. Neutrophil activation was determined by measurement of plasma elastase.

Results. Four hours after surgery, the median (quartile values) \( \frac{P_\text{O}_2}{F_\text{I}_2} \) ratio was 40.3 (37.8, 53.1) kPa for the HES-treated patients compared with 33.9 (31.2, 40.9) kPa for the Gelofusine-treated patients (\( P<0.01 \), Mann–Whitney test). The respiratory compliance was 80 (73.5, 80) ml cm\(^{-1}\) H\(_2\)O in the HES-treated patients compared with 60.1 (50.8, 73.3) ml cm\(^{-1}\) H\(_2\)O in the Gelofusine-treated patients (\( P<0.01 \), Mann–Whitney test). The lung injury score 4 h after surgery was less for the patients treated with HES compared with the patients treated with Gelofusine (0.33 vs 0.71, \( P=0.01 \), Wilcoxon rank sum test). Mean (SD) plasma elastase was less in the HES-treated patients on the first postoperative day (1.96 (0.17) vs 2.08 (0.24), \( P<0.05 \)). The log mean microalbuminuria was less in the HES-treated patients (0.41 vs 0.91 mg mmol\(^{-1}\), \( P<0.05 \)). This difference in microvascular permeability was associated with different volumes of colloid required to maintain stable cardiovascular measurements in the two groups of patients studied (3000 vs 3500 ml, \( P<0.01 \), Mann–Whitney test).

Conclusion. Compared with Gelofusine, the perioperative pulmonary function of patients treated with HES after abdominal aortic aneurysm surgery was better.

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The systemic inflammatory response that follows aortic surgery causes increased vascular permeability and interstitial oedema, with a variable degree of multiple organ dysfunction. In the lung this is seen as non-cardiogenic pulmonary oedema.\(^{1}\) Pulmonary dysfunction accounts for a large proportion of deaths after surgery for elective aortic aneurysm repair.\(^{2}\) Ischaemia and reperfusion injury may contribute to postoperative pulmonary dysfunction in these patients. Reducing this source of injury may influence both morbidity and mortality.

In the lung, ischaemia–reperfusion injury can increase pulmonary capillary permeability,\(^{3}\) affect transendothelial
protein and fluid fluxes,\(^4\) cause interstitial oedema\(^5\) and impair gas exchange. These features are similar to those in adult respiratory distress syndrome (ARDS).\(^6\) In this condition, there is an inverse relationship between systemic capillary leak, assessed as microalbuminuria, and pulmonary gas exchange.\(^7\) Capillary permeability, assessed as microalbuminuria, can predict pulmonary dysfunction.\(^8\)

Neutrophils may be a cause of remote lung injury after ischaemia–reperfusion.\(^9\) Activated neutrophils sequester in the pulmonary circulation, degranulate and generate free radicals that cause lung injury.\(^10\) Neutrophil elastase concentrations increase in the plasma of patients with acute lung injury after aortic surgery\(^11\) and in the plasma and the bronchoalveolar fluid of patients with ARDS.\(^12\)\(^13\) Elastase increases vascular permeability\(^10\) and experimental leucocyte depletion prevents pulmonary dysfunction.\(^14\)

The colloid used for intraoperative volume replacement can affect microvascular function and ischaemia–reperfusion damage.\(^15\)\(^16\) Compared with albumin, hydroxyethyl starch (HES) can reduce splanchnic ischaemia and release of circulating adhesion molecules in critically ill patients,\(^17\)\(^18\) reduce post-trauma capillary leak and improve gas exchange.\(^19\) The effects of HES on pulmonary function, capillary permeability and neutrophil activation in patients undergoing aortic surgery have not been compared with those of other low molecular weight colloid solutions.

We set out to study the effect of volume expansion with HES solution compared with Gelofusine solution on pulmonary function, capillary permeability and neutrophil activation in patients undergoing aortic surgery.

### Methods

Approval for the study was obtained from the local research ethics committee. Forty patients scheduled for elective abdominal aortic aneurysm surgery were randomized to receive either HES (eloHAES 6%; Fresenius-Kabi, Milton Keynes, UK) or gelatine solution (Gelofusine 4%; Braun, Sheffield, UK) for colloid volume replacement. The characteristics of the colloid studied are given in Table 1. We excluded patients with an ejection fraction of <40%, with poor pulmonary function (\(P_{aO_2} < 8.9\) kPa), with microalbuminuria (albumin excretion rates of 20–200 \(\mu g\) min\(^{-1}\)) and a creatinine concentration of >150 \(\mu mol\) litre\(^{-1}\). Randomization was by sealed envelopes that were opened before surgery. All patients were anaesthetized using a standard technique of i.v. etomidate, fentanyl and vecuronium followed by tracheal intubation. Anaesthesia was maintained with a mixture of nitrous oxide, oxygen and isoflurane. Intraoperative and postoperative analgesia was with an epidural catheter placed after induction of anaesthesia, through which morphine 2.5 mg in bupivacaine 0.35%, 5 ml was given. Cardiovascular measurements were by a transoesophageal Doppler probe, a triple-lumen catheter in the internal jugular vein for central venous pressure (CVP) measurement, and a radial artery cannula for arterial pressure measurement and arterial blood gas sampling. All patients received the same crystalloid. Sodium chloride 0.9%, 1 litre was given over 8 h before their operation. Immediately after induction of anaesthesia, patients were given Hartmann’s solution 15 ml kg\(^{-1}\) over 1 h followed by a maintenance infusion at 3 ml kg\(^{-1}\). Colloid was given to obtain a stable heart rate, CVP of 8–10 cm H\(_2\)O, a steady mean arterial pressure and cardiac output. After surgery, maintenance fluid replacement was crystalloid at 2 ml kg\(^{-1}\) h\(^{-1}\). Colloid was infused to maintain a stable heart rate, CVP of 8–10 cm H\(_2\)O, a steady mean arterial pressure and cardiac output. Blood was given to maintain a haemoglobin of more than 10 g dl\(^{-1}\). The volume of crystalloid infused was adjusted to maintain a urine output of greater than 40 ml h\(^{-1}\) after surgery. Mannitol 10% solution was given as an infusion of 0.5 g kg\(^{-1}\) before applying the aortic cross-clamp. Blood and urine samples were collected for analysis at the following times: T0 = before surgery; T1 = before aortic cross-clamp; T2 = after aortic cross-clamp release; T3 = 4 h after clamp release; T4 = 8 h after clamp release; T5 = 12 h after clamp release; T6 = 24 h after clamp release; T7 = 48 h after clamp release, and T8 = 48 h after clamp release. The \(P_{O_2}/F_{IO_2}\) ratio was measured at similar times for the first 24 h after clamp release. Respiratory compliance was measured for 8 h after reperfusion (T1 to T4). Patients were mechanically ventilated using a tidal volume of 10 ml kg\(^{-1}\). All patients were started with 5 cm H\(_2\)O of positive end-expiratory pressure (PEEP), which was then adjusted according to their \(P_{aO_2}\). As most patients had their operations in the late afternoon, they were weaned from mechanical ventilation the following morning.

### Assessment of lung function

**\(P_{O_2}/F_{IO_2}\) ratio**

Arterial blood gas analysis was done with a Bayer 865 RapidLab blood gas system. During mechanical ventilation, \(F_{IO_2}\) was recorded from the ventilator setting. In spontaneously breathing patients the \(F_{IO_2}\) was taken as 0.3, 0.4 and 0.5 with 1, 3 and 5 litres min\(^{-1}\) respectively of supplementary 100% oxygen delivered to the patient via a face mask.
Table 2. Patients’ characteristics. *Mean (range); †median (range)

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<th>HES (n=20)</th>
<th>Gelofusine (n=20)</th>
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<tr>
<td>Age (yr)</td>
<td>71.2 (56–82)*</td>
<td>73.8 (50–86)*</td>
</tr>
<tr>
<td>Male:female</td>
<td>14:6</td>
<td>16:4</td>
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<tr>
<td>Duration of operation (min)</td>
<td>140 (80–240)†</td>
<td>135 (70–180)†</td>
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<td>Clamp time (min)</td>
<td>54 (30–120)†</td>
<td>51 (22–105)†</td>
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The postoperative hypoxaemia score at 4 h was determined as follows: PO2/FIO2 ratio \(\geq 40=0;\) PO2/FIO2 ratio 30–39.9=1; PO2/FIO2 ratio 23.3–29.9=2; PO2/FIO2 ratio 13.3–23.2=3; and PO2/FIO2 ratio <13.3=4.

**Determination of respiratory compliance**

Static respiratory compliance was measured during mechanical ventilation using an inflation hold during ventilation. The tidal volume, plateau pressure during an end-expiratory occlusion of 5 s, and PEEP were recorded. The respiratory compliance was calculated as the tidal volume divided by the difference between the plateau pressure and the PEEP. Four hours after the end of surgery, a compliance score was determined as follows: \(^20\) compliance \(\geq 80\) ml cm\(^{-1}\) H\(_2\)O=0; compliance 60–79 ml cm\(^{-1}\) H\(_2\)O=1; compliance 40–59 ml cm\(^{-1}\) H\(_2\)O=2; compliance 20–39 ml cm\(^{-1}\) H\(_2\)O=3; and compliance <19 ml cm\(^{-1}\) H\(_2\)O=4.

**Determination of the degree of non-cardiogenic oedema on chest x-ray**

A chest x-ray was taken the day before surgery as part of the routine assessment. Another chest x-ray was taken 4 h after surgery. The x-rays were taken at end-inspiration with a portable machine with the patient propped up. The films were assessed by a radiologist unaware of the patient’s status in the study and were assigned a score of 0–4 according to defined criteria, as follows: mild interstitial oedema=1; severe interstitial oedema=2; alveolar oedema in 1–2 quadrants=3; and alveolar oedema in 3–4 quadrants=4.

**Calculation of the lung injury score**

The lung injury score was determined from the PO2/FIO2 ratio, lung compliance, chest x-ray and the amount of PEEP. The PEEP score was assigned as follows: PEEP \(<5\) cm H\(_2\)O=0; PEEP 6–8 cm H\(_2\)O=1; PEEP 9–11 cm H\(_2\)O=2; PEEP 12–14 cm H\(_2\)O=3; and PEEP \(\geq 15\) cm H\(_2\)O=4. A lung injury score was computed 4 h after surgery by dividing the aggregate score by the number of components used.\(^20\)

**Measurement of neutrophil elastase**

Plasma concentrations of elastase, measured as the \(\alpha_1\)-antiprotease–elastase complex, were assayed by the latex-enhanced immunoassay using Ecoline® PNM elastase (Merck Diagnostica, Darmstadt, Germany). The elastase values were measured before surgery, after release of the aortic cross-clamp, four-hourly for the first 12 h and then daily for the next 2 postoperative days.

**Measurement of microalbuminuria**

Aliquots of urine were saved preoperatively, after induction of anaesthesia, after clamp release and four-hourly for 12 h and then daily for 3 days. The urinary excretion of microalbumin was determined using automated immunoturbidimetry. The results were expressed as a protein:creatinine ratio in mg mmol\(^{-1}\), to correct for variations in urine flow rate. Values in normal subjects were less than 2.3 mg mmol\(^{-1}\).

**Measurement of plasma oncotic pressure**

The plasma oncotic pressure was measured using a Genotec Osmomat 050 (Hants., UK) with 20 kDa membrane. Blood for colloid oncotic pressure measurement was taken before operation, 4 h after release of the aortic cross-clamp (T3), and on each of the first 2 postoperative days (T6 and T7 respectively).

**Statistical analysis**

Where appropriate, the numerical data were compared using the Mann–Whitney test. Intragroup data were analysed using ANOVA. Lung injury scores were compared using the Wilcoxon rank sum test. Log transformation was used to normalize the data on plasma elastase and urinary excretion of albumin before statistical analysis. These data were analysed using Student’s t-test.

**Results**

No patient suffered any adverse reactions from the colloid used in the study. The patients’ characteristics are shown in Table 2. The PO2/FIO2 ratios are summarized in Fig. 1. Gas exchange deteriorated throughout the study period in both groups of patients. The PO2/FIO2 ratio was significantly greater in the HES-treated patients compared with the gelatine-treated patients. After aortic cross-clamp release, the PO2/FIO2 ratio was 50.5 (44.9, 63.6) kPa for the HES-treated patients compared with 36.8 (33.2, 39) kPa for the gelatine-treated patients (median values and quartiles) \((P<0.001,\) Mann–Whitney test). Four hours after reperfusion of the extremities, the PO2/FIO2 ratio for the HES-treated patients was reduced to 40.3 (37.8, 53.1) kPa compared with 33.9 (31.2, 40.9) kPa for the gelatine-treated patients \((P<0.05,\) Mann–Whitney test). Although the PO2/FIO2 ratio continued to decrease in both groups of patients, on the first postoperative day it was greater for the HES-treated patients (32.8 (30.0, 42.7) kPa vs 29.8 (27.0, 34.8) kPa, \(P<0.05,\) Mann–Whitney test).

The respiratory compliance for the two groups of patients is summarized in Fig. 2. Compliance decreased during
surgery in all the patients studied. The decrease in compliance after cross-clamp release was significantly greater in the gelatine-treated patients than in the HES-treated patients, and this persisted throughout the first 8 h after clamp release.

The logarithm of the plasma α₁-antiprotease–elastase complex concentration was plotted against time for the two groups of patients studied. Plasma α₁-antiprotease–elastase complex increased in both groups of patients during surgery and continued to increase during the first 2 postoperative days. There was no significant difference in the mean plasma α₁-antiprotease–elastase complex concentration in the two groups of patients during surgery and in the first 12 h after surgery. There was a weak negative correlation between $P_{O_2}/F_{IO_2}$ ratio and the logarithm of the plasma α₁-antiprotease–elastase complex concentration ($r_s = -0.079$). Twenty-four and 48 h after reperfusion, the plasma α₁-antiprotease–elastase complex concentration was less in the HES patients, but this difference was statistically significant only at 24 h (1.96 (0.17) vs 2.08 (0.24), $P<0.05$) (Fig. 3).

Compared with the patients treated with HES, patients treated with gelatine had a greater urinary excretion of albumin during surgery, indicating a greater systemic capillary leak (Fig. 4). The urinary excretion of albumin peaked after release of the aortic clamp (1.31 (0.45) vs 0.93 (0.54) mg mmol⁻¹, $P<0.05$) and remained significantly increased 4 h after clamp release (0.91 (0.42) vs 0.41 (0.57) mg mmol⁻¹, $P<0.01$). However, by the first postoperative day, the microalbuminuria values in the two groups of patients were similar.

**Discussion**

Our findings support previous observations that clamp release impairs gas exchange and reduces compliance. An increase in pulmonary capillary permeability is usually inferred from isotopic methods, changes in lung compliance, chest x-ray and pulmonary shunt. We computed a lung injury score using clinical, radiographic and physiological abnormalities. We found that perioperative and postoperative pulmonary function was better in patients treated with HES infusion in comparison with Gelofusine infusion. Compared with patients treated with Gelofusine,
patients treated with HES had better gas exchange, greater respiratory compliance and a smaller lung injury score.

Aneurysm surgery is usually associated with an increase in pulmonary capillary permeability, allowing the extravasation of osmotically active macromolecules, such as albumin, into the interstitial space. Fluid movement across a capillary membrane is governed, according to Starling’s law, by a balance between the hydrostatic and colloid osmotic forces across the capillary wall and the permeability of the capillary membrane. In the Gelofusine-treated patients there was more systemic loss of albumin, as determined by the microalbuminuria. This shift in protein allows movement of water across the pulmonary endothelium into the interstitial space. This is borne out by studies of permeability oedema in both human subjects and experimental animal models. Normally, an increase in transendothelial fluid is removed by pulmonary lymph flow. Interstitial oedema develops when the colloid leak overwhelms the lymph drainage rate. Previous studies in animal models of ischaemia–reperfusion injury have suggested that the use of starch colloids of the right shape and size can reduce capillary permeability and oedema formation. The HES molecules may act as a sealant to the leaky capillary pores. While this could explain the differential excretion of urinary albumin and the disparity in lung function, recent studies on the endothelial barrier function would suggest that this mechanism of action is simplistic.

The $\alpha_1$-antiprotease–elastase complex, a marker of neutrophil activation, was increased in both groups of patients. In animal models of ischaemia–reperfusion injury, the increase in microvascular permeability in the pulmonary circulation depended on the pulmonary sequestration of activated neutrophils. Reperfusion was associated with a transient decrease in neutrophil count, presumably related to the tissue sequestration, followed by an increase in circulating neutrophils. The plasma neutrophil elastase activity was not significantly different between the two groups of patients during the early postoperative period, yet there were significant differences in the pulmonary function during that time. The $\alpha_1$-antiprotease–elastase complex measured in the plasma in the early postoperative period is derived from the degranulation of activated neutrophils from the initial reperfusion and not from primed neutrophils that are sequestered in the pulmonary circulation. Sequestered neutrophils are relatively harmless unless they are activated by a second stimulus, such as endotoxins, by-products of dead cells that have been affected by the initial ischaemia–reperfusion injury, and mediators released after protracted tissue ischaemia. Rittoo and colleagues have shown that microvascular perfusion and splanchnic oxygenation are better preserved with HES infusion than with Gelofusine. Further activation of the neutrophils by a second stimulus, such as endotoxins, could account for the secondary rise in plasma $\alpha_1$-antiprotease–elastase complex in the first 2 days after surgery. Intravital microscopy studies of haemodilution in controlled ischaemic conditions have shown that HES can reduce leucocyte adherence in ischaemic conditions. The weak inverse correlation between the $P_{O_2}/F_{I\text{O}_2}$ ratio and the log $\alpha_1$-antiprotease–elastase complex ($r=-0.079$) suggests that more than one mechanism may be operational. While HES may modulate the neutrophil endothelial activation, the similar plasma elastase values in the two groups do not support this mechanism of lung protection.

COP normally decreases during surgery. In unstable general surgery patients, a low COP–pulmonary wedge pressure difference of $>3$ mm Hg was weakly associated with ADRS and pulmonary oedema. However, in the presence of low COP, when the hydrostatic pressure is normal, the lung can resist oedema formation. There was no significant difference in COP in the two groups of patients studied, so a beneficial effect of HES is probably not related to the COP.

The treatment of non-cardiogenic oedema is aimed at preventing further damage and improving tissue oxygenation. As it is not always possible to achieve the former, attention has been aimed at improving the rate of extraction or reducing the rate of accumulation of oedema fluid in the lungs. Synthetic colloid solutions such as HES contain a heterogeneous mixture of macromolecules of varying molecular weight. Some of these molecules are too large to escape through the leaky endothelium and can help prevent excessive fluid flux across the endothelial layer. HES, particularly in the narrow molecular weight range, may therefore offer certain advantages over Gelofusine. However, the role of HES molecules may be more than biophysical. We found that perioperative pulmonary function was better after HES than after Gelofusine.

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