Haemodynamic effects of diaspirin crosslinked haemoglobin (DCLHb) given before abdominal aortic aneurysm surgery

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We studied 34 patients undergoing elective repair of an abdominal aortic aneurysm under combined general anaesthesia and epidural block to evaluate the acute effects of diaspirin crosslinked haemoglobin (DCLHb) 50, 100 and 200 mg kg⁻¹ i.v. Haemodynamic variables were measured continuously using pulmonary and radial artery catheters, and oxygen delivery and consumption were calculated at regular intervals. DCLHb was shown to be vasoactive, producing an increase in mean arterial pressure of approximately 25% with each dose, with small decreases in cardiac index and calculated oxygen delivery. These effects persisted beyond the end of infusion and provided a degree of cardiovascular stability during the operative procedure. The effects of DCLHb on oxygen consumption at these doses were minimal.

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Diaspirin crosslinked haemoglobin (DCLHb, Baxter Healthcare Corporation, Deerfield, IL, USA) was developed originally as a ‘blood substitute’. It consists of stroma-free human haemoglobin derived from unused but fully screened and tested blood donations. The haemoglobin is crosslinked at a specific site between the alpha subunits with bis(3,5-dibromosalicyl) fumarate (DBBF) to prevent dissociation of the haemoglobin molecule into dimers. The intravascular half-life of the stabilized tetramer is thereby increased and oxygen binding affinity is decreased, theoretically improving oxygen delivery to tissues. The crosslinked tetramer is of such stability that it can be pasteurized at high temperature to inactivate viruses and precipitate uncrosslinked proteins.¹² Ultrafiltration is used to remove viral particles and precipitated proteins.²⁻⁴

In this study, we have evaluated the effects of low doses of DCLHb in anaesthetized patients undergoing elective repair of abdominal aortic aneurysm. Patients undergoing this procedure were chosen for the study because they have invasive monitoring and are potentially haemodynamically unstable. The study was part of a larger, multicentre study involving 70 patients undergoing elective abdominal aortic repair at three European hospitals. We describe the haemodynamic findings of aortic aneurysm patients enrolled at the Royal Infirmary, Edinburgh only.

Patients and methods

We studied 34 patients after obtaining written informed consent and approval from the Lothian Health Anaesthetic and Dentistry Research Ethics Sub-committee. All patients were undergoing elective repair of an infrarenal aneurysm of the abdominal aorta. Patients with occlusive aortic disease were excluded. A detailed assessment of fitness for surgery (which included evaluation of exercise tolerance, ECG, chest radiograph, pulmonary function tests and radionuclide ventriculogram) was made approximately 1 week before hospital admission. One day before surgery, patient height, weight and ASA status were noted, and full blood count, urea, electrolytes and liver function tests were measured.

This was a single-blind, randomized, dose-incremental study. When the recruitment process was complete, randomization was performed by the hospital pharmacy department. Patients were assigned to either an active (DCLHb) or control (Ringer’s lactate) group. Doses of DCLHb were 50 mg kg⁻¹ (group A), 100 mg kg⁻¹ (group B) and 200 mg kg⁻¹ (group C), corresponding to 35, 70 and 140 ml in a 70-kg patient, respectively. Control patients received the equivalent volume of Ringer’s lactate. The maximum volume of fluid administered to any patient was 160 ml.

One of two consultant anaesthetists and one of three consultant surgeons performed anaesthesia and surgery,
respectively. Standard premedication, including morphine 5 or 10 mg i.m. and oral temazepam 10 or 20 mg in patients less than and more than 50 kg, respectively, was given at 06:00 on the day of surgery. All patients had peripheral venous and radial arterial cannulae and a mid-thoracic epidural catheter inserted under local anaesthesia before induction of general anaesthesia. A test dose of either 2% lidocaine 5 ml (groups A and B) or 0.5% bupivacaine 5 ml (group C) was injected epidurally while the patient was awake. Anaesthesia was induced with thiopental 125–500 mg i.v. and maintained with 1–2% enflurane and 65% nitrous oxide in oxygen. Neuromuscular block was achieved with vecuronium 5–10 mg (with increments of 1–2 mg) to facilitate tracheal intubation and lung ventilation. End-tidal carbon dioxide partial pressure was maintained at 4.5–5.5 kPa.

The ECG, intra-arterial pressure and arterial oxygen saturation were monitored continuously. A triple-lumen pulmonary artery catheter (Baxter Edwards Vigilance, Irvine, CA, USA) was inserted after induction of anaesthesia to allow continuous monitoring of central venous pressure (CVP), pulmonary artery pressure (PAP) and cardiac output. The latter was checked intermittently by bolus thermodilution. Positioning of the pulmonary catheter was verified by chest x-ray. Pulmonary artery occlusion pressure (PAOP) was measured before each cardiac output calculation. When cardiovascularly stable (5 min minimum), baseline recordings of heart rate, mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), PAOP, CVP and cardiac output were made. In addition, simultaneous blood samples were obtained from the arterial and pulmonary artery catheters for immediate measurement of arterial and mixed venous oxygen saturation and content by co-oximeter (Instrumentation Laboratories, IL3, Lexington, MA, USA) to allow calculation of oxygen consumption (V̇O₂) and delivery (DO₂), according to the following equations:

\[
DO₂=(cardiac\ index×arterial\ oxygen\ content)×10
\]
\[
V̇O₂=(cardiac\ index×venous–arterial\ oxygen\ difference)×10
\]

When the initial data set was complete, DCLHb or control solution was administered via an infusion pump (Imed, Advanced Medical Inc, San Diego, CA, USA) over 15 min into a central (group A) or peripheral (groups B and C) vein. After completion of the infusion, an epidural top-up dose of 0.5% bupivacaine was given and surgery commenced. Haemodynamic data (heart rate, cardiac output, MAP, CVP and MPAP) were recorded continuously for 7 h after the beginning of infusion. Where possible, haemodynamic measurements were made for 24 h after operation. Heart rate and all arterial pressures were measured every 3 min; for cardiac output, the Vigilance provided updated averaged values every 6 min. A Dual 486 notebook computer was interfaced with the patient monitoring system (Hewlett-Packard Merlin, Andover, MA, USA) using an RS232 link to collect all data. Measurements of cardiac output were verified by thermodilution at specific times. Data that could not be verified by thermodilution were excluded (hence the non-availability of data relating to cardiac output at 15 min after infusion). V̇O₂ and DO₂ data were not calculated at 15 min after infusion because of the logistics of collecting arterial and mixed venous samples at commencement of surgery.

Times of specific surgical events were also recorded (to allow subsequent grouped analysis), as were amounts of blood, blood products, fluids and drugs administered during and after operation.

All patients received a minimum of 1 litre of crystalloid (Ringer’s lactate) followed by 1 litre of colloid (Gelofusine) after administration of the study solution. When further fluid was required during surgery, crystalloid (either Ringer’s lactate or 0.9% saline) or blood was given (at the discretion of the anaesthetist) to maintain PAOP within 3 mm Hg of baseline values. No further artificial colloid was used and blood was administered when it was estimated that packed cell volume had decreased to <25%. A standard regimen for administration of fluid and vasopressor drugs was followed. Hypotension was defined as a decrease in MAP of ≥30%, despite a PAOP of >10 mm Hg, and was treated with ephedrine if heart rate was <70 beat min⁻¹ or methoxamine if it was ≥70 beat min⁻¹. The amount of ephedrine and methoxamine used, and the frequency at which they were given, were used as measures of cardiovascular stability. After surgery, patients were transferred to the high dependency unit (HDU) or intensive care unit (ICU) and time spent in each unit was recorded, together with duration of hospital stay.

Haemodynamic data are those collected over the first 6 h after infusion. Values were retrieved from the computer record and verified by written notes at the specified time intervals so that they could be reported directly or used for calculation of cardiac index (CI), systemic vascular resistance index (SVRI), DO₂ and V̇O₂. Values were indexed to allow for variations in patient body size and weight.

Statistical analyses were performed using SAS (version 6.07) (SAS Institute Inc, Cary, NC, USA). Data were analysed by the method of mixed models, using residual maximum analysis to estimate variance components. The dose incremental design required the use of a ‘nested model’, with each active treatment group being considered as a sub-study. An overall test of due difference between control and active conditions was made and, in addition, this comparison was made separately within each sub-study. Interactions between condition, dose and time were also tested. Two-tailed tests were used with P≤0.05 being considered significant. Comparisons of fluid input and output, and dose and frequency of vasoconstrictor administration were made using the Student’s t test. Because of the small sample size, statistical significance at individual times could not often be demonstrated. P values refer to the overall difference between active and control conditions (combined data set).
Table 1  Patient characteristics (mean (range) or number)

<table>
<thead>
<tr>
<th>Group A (50 mg kg⁻¹)</th>
<th>Group B (100 mg kg⁻¹)</th>
<th>Group C (200 mg kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCLHb</td>
<td>Control</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/1</td>
<td>3/2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.8 (71–82)</td>
<td>64.4 (65–73)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>75.9</td>
<td>69.5</td>
</tr>
<tr>
<td>ASA (I/II/III)</td>
<td>2/3/0</td>
<td>1/3/1</td>
</tr>
<tr>
<td>Hypertensive (yes/no)</td>
<td>2/3</td>
<td>2/3</td>
</tr>
</tbody>
</table>

Results

The majority of the 34 patients enrolled at this site were male and elderly; all were Caucasian and 40% had a history of essential hypertension (Table 1). There were minimal differences in patient characteristics between the sub-groups. Two patients were excluded because they did not undergo aortic aneurysm repair. One had aneurysm repair abandoned because of previous adhesions, preventing surgical access; laparotomy and repair of perforated bowel were performed. The other patient was found to have an extension of his aneurysm into the thorax, which prevented surgery as planned, and his results were excluded from analysis.

There were no differences between groups in the time spent in the HDU, ICU or in hospital. There were no deaths reported during the study or at a 4-month follow-up visit.

Major cardiovascular effects

Before infusion, there were no significant differences in cardiovascular variables between groups. In group A, baseline MAP was 66.2 (SEM 6.4) mm Hg in the control group and 79.6 (4.4) mm Hg in the DCLHb group; in group B, MAP was 80 (4.6) in the control group and 73 (2.8) mm Hg in the DCLHb group; and in group C, MAP was 88 (6.9) mm Hg in the control group and 76 (5.7) mm Hg in the DCLHb group. After DCLHb infusion, MAP increased significantly in all three groups from baseline values (Fig. 1). This effect was consistent, immediate and persisted well beyond the end of infusion. There was no significant decrease in heart rate corresponding with the increase in MAP.

After infusion of DCLHb, SVRI increased significantly in all three groups compared with baseline values. In group B, baseline SVRI was 2231 (SEM 425) dyn s cm⁻⁵ m⁻² in controls and 1819 (167) dyn s cm⁻⁵ m⁻² in the DCLHb group; and in group C, values were 2867 (777) dyn s cm⁻⁵ m⁻² in controls and 2159 (301) dyn s cm⁻⁵ m⁻² in the DCLHb group. The effect on SVRI was the most marked for DCLHb at these small doses (Fig. 2). It persisted for 2 h in patients receiving dose B and for 6 h in those receiving dose C.

The effects of DCLHb on CVP and SVRI are not reported for group A as some patients received the study solution centrally and others did not. When using the central venous route, we noted that the use of the infusion pump caused an artificial increase in CVP. From Dose B onwards, all control and test solutions were given by a peripheral vein to exclude this source of error.

Heart rate

Heart rate did not change throughout the study in control patients or with any of the doses of DCLHb. Mean heart rate at the start of infusion in group A was 63 (SEM 4) and 61 (4) beat min⁻¹ for control and treated patients, respectively, in group B, 62 (7) and 63 (4) beat min⁻¹ and in group C, 77 (6) and 67 (8) beat min⁻¹, respectively. Mean heart rate for all three groups did not decrease to less...
Haemodynamic effects of DCLHb

Fig 2 Systemic vascular resistance index (SVRI) in group B (DCLHb 100 mg kg\(^{-1}\)) and group C (DCLHb 200 mg kg\(^{-1}\)). \(*P<0.05\), \(**P<0.01\) and \(****P<0.001\) compared with control in each group.

Table 2 Summary of the effect of DCLHb vs control solution on central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), cardiac index (CI), oxygen delivery (\(DO_2\)) and oxygen consumption (\(VO_2\)) (mean (SEM) [% change compared with baseline]). Times (start, 1 and 2 h) are times after start of infusion

<table>
<thead>
<tr>
<th></th>
<th>Dose A (50 mg kg(^{-1}))</th>
<th>Dose B (100 mg kg(^{-1}))</th>
<th>Dose C (200 mg kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start 1 h 2 h</td>
<td>Start 1 h 2 h</td>
<td>Start 1 h 2 h</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>10 (1) 11 (2) [10]</td>
<td>8 (2) [−20]</td>
<td>8 (3) 7 (1) [−12]</td>
</tr>
<tr>
<td>DCLHb (n=6)</td>
<td>10 (1) 11 (1) [10]</td>
<td>9 (2) [−10]</td>
<td>10 (2) 9 (2) [−10]</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>21 (2) 18 (3) [−14]</td>
<td>23 (2) [10]</td>
<td>19 (1) 17 (3) [−10]</td>
</tr>
<tr>
<td>DCLHb (n=6)</td>
<td>24 (2) 25 (2) [+4]</td>
<td>27 (4) [13]</td>
<td>21 (1) 17 (2) [−19]</td>
</tr>
<tr>
<td>CI (litre min(^{-1}) m(^{-2}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>2.9 (0.2) 3.0 (0.4) [3]</td>
<td>3.5 (0.3) [21]</td>
<td>2.7 (0.3) 3.3 (0.3) [+22]</td>
</tr>
<tr>
<td>DCLHb (n=6)</td>
<td>2.1 (0.13) 1.9 (0.3) [−10]</td>
<td>1.9 (0.3) [−10]</td>
<td>2.5 (0.3) 2.3 (0.4) [−8]</td>
</tr>
<tr>
<td>(DO_2) (ml min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=6)</td>
<td>970 (77) 1006 (143) [+4]</td>
<td>979 (91) [+1]</td>
<td>940 (116) 995 (177) [+6]</td>
</tr>
<tr>
<td>DCLHb (n=6)</td>
<td>796 (58) 591 (71) [−25]</td>
<td>562 (35) [−30]</td>
<td>840 (108) 1062 (197) [+26]</td>
</tr>
<tr>
<td>(VO_2) (ml min(^{-1}))</td>
<td></td>
<td></td>
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</tbody>
</table>

than 56 or increase to more than 83 beat min\(^{-1}\) throughout the study. There were no significant differences in heart rate between the DCLHb and control groups for any of the doses.

Other cardiovascular variables

A summary of the data for MPAP, CVP and CI is given in Table 2. Recordings of these variables were made at the same times indicated in Figure 2, but limitation of space prevented full publication of every value. There were no significant changes in any of these variables at individual times. When the variables were analysed statistically over time, there were no significant differences between groups.

Oxygen delivery and consumption

Table 2 also shows values for oxygen delivery and consumption. Delivery and consumption are reported only for doses B and C because of problems with sample handling leading to errors in oxygen content calculation at the 50 mg kg\(^{-1}\) dose. These problems were overcome with the two higher doses.

The only significant change was a decrease in mean delivery of oxygen by 30% to 555 (SEM 28) ml min\(^{-1}\) within 30 min of commencement of infusion in those patients treated with DCLHb 100 mg kg\(^{-1}\) \((P=0.002)\). This effect lasted for 2 h. Oxygen delivery never decreased to critical levels during this time. The lowest absolute level of oxygen delivery was 336 ml min\(^{-1}\) which occurred in one patient 2 h after administration of DCLHb 100 mg kg\(^{-1}\).

Other measured variables

There were no significant or clinically notable differences between control and treatment groups in blood loss during operation or in the total volume or type of i.v. fluids given. On the day of operation, control patients lost an average of 3016 (range 1025–4696) ml of blood and received 8005 (5485–9792) ml of i.v. fluids. The equivalent values for DCLHb patients were 2720 (1180–4557) ml and 8458 (5698–14013) ml, respectively. More than 50% of patients required blood transfusions.

All patients received vasopressor agents during anaesthesia and surgery, but fewer administrations and lower cumulative doses of both ephedrine \((P=0.023)\) and methoxamine...
Table 3 Use of vasoconstrictor drugs from the start of infusion to the end of surgery. Intervention refers to each time that the anaesthetist gave a drug to increase arterial pressure during surgery and up to 6 h after surgery.

<table>
<thead>
<tr>
<th>No. of interventions to increase arterial pressure</th>
<th>Mean dose of drug used (mg)</th>
<th>Range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DCLHb</td>
</tr>
<tr>
<td>Group A (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Methoxamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B (n=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Methoxamine</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Group C (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>54</td>
<td>35</td>
</tr>
<tr>
<td>Methoxamine</td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>


time of the anaesthetist gave a drug to increase arterial pressure during surgery and up to 6 h after surgery.

\( P = 0.045 \) were required in patients who received DCLHb compared with those in the control group (Table 3).

**Discussion**

Our intention was to observe the vasoactive properties of low-dose DCLHb in a human population. A single-blind design was used because of the distinctive red colour of DCLHb. Ringer’s lactate cannot be altered to mimic this colour. The history of adverse events associated with other haemoglobin solutions led to the view that an early clinical study should be open in design and involve progressive dose increments. The two lower doses used (50 and 100 mg kg\(^{-1}\)) had already been evaluated in young healthy volunteers. The higher dose was felt to be a reasonable progression in the absence of adverse events at the two lower doses.

In our study, MAP and SVRI increased with all DCLHb doses and smaller amounts of vasopressor drugs were used in patients who had received DCLHb. In the absence of an increase in cardiac output, the primary cause of the increase in arterial pressure appeared to be related to peripheral vasoconstriction. Several mechanisms could explain this: DCLHb, in common with free intravascular haemoglobin, is thought to scavenge intravascular nitric oxide. It may affect directly vascular smooth muscle by interacting with adrenoreceptors or it may stimulate endothelin release or up-regulation of endothelin receptors. The increase in arterial pressure after infusion of DCLHb was associated with a clinically notable but not statistically significant reduction in cardiac index which, in part, may be caused by increasing afterload associated with the vasoactive properties of DCLHb. This was not simply a result of a few outlying values as reductions in cardiac index were noted in almost all patients receiving DCLHb. The outcome from surgery was universally good with no deaths and no excess morbidity or evidence of malperfusion in DCLHb patients. Therefore, we conclude that depression of cardiac output and possible increased cardiac work was benign. The common use of drugs to increase afterload, such as methoxamine, almost certainly has a similar effect and yet clinical practice allows for the use of such agents without undue concern. The absence of clinically significant increases in CVP or MPAP make it unlikely that a reduction in myocardial performance was the cause of compensatory vasoconstriction. In addition, a study observing the effect of DCLHb in patients after cardiopulmonary bypass did not demonstrate any myocardial depressant effect.

Decreases in calculated \( \text{DO}_2 \) were associated with changes in cardiac index. When the effect of DCLHb was analysed by dose (100 and 200 mg kg\(^{-1}\) only), calculated global \( \text{DO}_2 \) decreased significantly only in patients who received DCLHb 100 mg kg\(^{-1}\) (\( P = 0.002 \)). The value of 555 (28) ml min\(^{-1}\) was the lowest mean oxygen delivery recorded which occurred at 30 min after DCLHb 100 mg kg\(^{-1}\). The lowest absolute oxygen delivery in any patient was 336 ml min\(^{-1}\). This was not clinically significant. It must be remembered that these patients were anaesthetized and as such did not have a high demand for oxygen. Oxygen delivery being depressed to supply dependent consumption levels was therefore not demonstrated at these doses of DCLHb. Also, the smaller size and lower viscosity of DCLHb allows rapid administration and it is possible to speculate that it may deliver oxygen to poorly perfused tissues, improving the status of the microcirculation despite reduction in cardiac index and global oxygen delivery.

DCLHb has been developed as an adjunct to resuscitation of patients suffering from haemorrhagic shock. The vasoactive properties of DCLHb have been studied and characterized in several animal models and demonstrated in humans. Results of animal work suggested that DCLHb may have potential use as a resuscitation fluid. Unfortunately, the results of two, unpublished, controlled studies of the use of DCLHb in patients with haemorrhagic shock in Europe and the USA have proved disappointing. Baxter Healthcare have since stopped manufacturing this solution but haemoglobin solutions with similar properties to DCLHb may well be developed in the future.

At a dose of DCLHb 200 mg kg\(^{-1}\), \( \text{DO}_2 \) was depressed but not significantly, and we speculate that this may have been because the total haemoglobin content of blood was increased sufficiently to have compensated for decreased cardiac output. This may also explain the apparent boost in oxygen delivery at 60 min after the start of DCLHb 200 mg kg\(^{-1}\).
V̇O₂ (calculated) was not appreciably decreased despite the decrease in ḊO₂. This implies that the tissues were able to maintain oxygenation in the presence of a decreased ḊO₂ (i.e. there was greater oxygen extraction in the presence of DCLHb). A similar associated reduction in flow after administration of erythrocytes modified to enhance oxygen dissociation at the tissues has been reported in animals.²⁴ Recently, haemoglobin has been postulated to have greater influence on vascular control in the microcirculation than was thought previously.²⁵ This may explain some of the observed effects of DCLHb on ḊO₂ and V̇O₂ in this study.

We noted decreased use of vasopressor agents after DCLHb which has also been noted in a study in critically ill patients.²⁶ The doses used in the DCLHb group suggest a useful clinical effect, but the single-blinded nature and small size of our study must be taken into account.

The primary haemodynamic effect of DCLHb at the doses described here was an increase in arterial pressure associated with peripheral vasoconstriction. An agent with these properties may be of considerable value in the initial management of hypovolaemic or septic shock, particularly if preservation of splanchnic and renal blood flow seen in animals is confirmed in humans. It remains to be seen if the other haemoglobin therapeutic agents currently under development can usefully deliver oxygen and thus preserve cellular function in such circumstances.

Acknowledgement
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