The metabolic load of stored blood. Implications for major transfusions in infants

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SUMMARY Plasma electrolyte, intermediary metabolite, and hormone concentrations were measured in samples of 110 units of citrate phosphate dextrose blood being used for clinical transfusions. The most important changes from the physiological range were in sodium, potassium, glucose, and lactate concentrations. Mean sodium concentrations fell from 170 mmol/l at the beginning of storage to 156 mmol/l at the end and mean potassium concentrations rose from 7 mmol/l to 25 mmol/l. Glucose had a mean concentration of 20 mmol/l at the beginning of storage and had only fallen to 15 mmol/l at the end. Mean lactate concentrations increased from 7 mmol/l at the beginning of storage to 25 mmol/l at the end. Many samples had cortisol, insulin, and growth hormone concentrations within the physiological range. Citrate phosphate dextrose blood contains a large substrate load that changes during storage and that should be taken into account when infants are transfused large volumes of blood. The strong correlation coefficients with duration of storage for sodium, potassium, and lactate (−0.71, 0.91, and 0.90, respectively) indicate that concentrations of these substrates can be predicted within a narrow range if the duration of blood storage is known.

Large quantities of stored blood may have to be transfused into very ill infants in a number of circumstances—for example, exchange transfusion, during and after surgery, or after acute haemorrhage. Stored blood contains metabolically active substrates and electrolytes, which may be poorly tolerated by sick infants if given in large quantities. A number of studies have illustrated the serious metabolic effects of individual substrates from transfused stored blood.1–3 These effects may be modified, however, by other substrates present in abnormal quantities.

A more detailed knowledge of the substrate load of stored blood would enable potential metabolic disturbances to be accurately predicted when infants receive large blood transfusions. Furthermore, this information is essential for the interpretation of metabolic studies in critically ill infants.

Although there is some information on the substrate content of stored blood,4–7 detailed quantitative data on the substrate load and the effects of storage are not available. This study was designed to measure the electrolyte, metabolite, and hormone content of stored blood in relation to duration of storage.

Methods

Aliquots of 10 ml were taken from each of 115 units of citrate phosphate dextrose stored blood being used for clinical transfusions. Samples were taken before the six hour expiry time at room temperature. Blood was available for transfusion from the second day after collection after the completion of virological screening for hepatitis antigens. Eighty one samples were taken from blood between two and eight days after collection, and the remainder of the samples were evenly distributed over the subsequent four weeks from collection.

Glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate concentrations were measured in perchloric acid extracts of 0.5 ml whole stored blood by the method described by Lloyd and colleagues.8 The remaining sample was centrifuged for five minutes and the separated plasma deep frozen for the subsequent batch analysis of electrolytes (routine laboratory autoanalyser (Astra or Chemipak)), total protein (Biuret method), and the hormones insulin,9 cortisol,10 and growth hormone (radioimmunoassay, supraregional assay laboratory, Newcastle upon Tyne).
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As all the above samples were deep frozen before analysis it was necessary to obtain further samples for the measurement of osmolality. Plasma samples were obtained, therefore, from a further 11 units of stored blood within a week of collection after five minutes of centrifugation. Osmotic activity was measured in these samples immediately by the method of freezing point depression, using an Advanced Instruments Micro Osmometer model 3MO.

Statistics. Statistical analyses were performed, using SPSS and SAS statistical packages on an Amndahl mainframe computer. Linear correlation and t test procedures were used as appropriate.

Results

Results of the various assays for the whole period of blood storage are summarised in the Table, which shows correlation coefficients, p values, and normal paediatric ranges.

Sodium. During the period of storage, mean sodium concentrations fell from 170 mmol/l to 156 mmol/l (170 to 156 mEq/l at 35 days (r=-0.71, p<0.001) (Fig. 1). In the 81 samples obtained between two and eight days from collection sodium concentration was in the range of 162-182 mmol/l, with a mean (SD) of 170 (5-0) mmol/l.

Potassium. During the period of storage, mean potassium concentrations increased from 7-0 mmol/l to 25-0 mmol/l (7.0 to 25.0 mEq/l) in the last week of storage (r=0-91, p<0.001) (Fig. 2). Between two and eight days from collection, the mean (SD) potassium concentration was 8-6 (2-0) mmol/l, with a range of 5-5-15-3 mmol/l. Thus the potassium concentration had already reached the upper limit of the physiological range by the second day of storage.

Calcium and magnesium. Both stored blood calcium concentrations (mean (SD) 2-3 (0-4) mmol/l, (9-2 (1-6) mg/100 ml), range 1-8-3-7 mmol/l and magnesium concentrations (mean (SD) 0-8 (0-2) mmol/l (1-9 (0-5) mg/100 ml), range 0-6-2-0 mmol/l) increased gradually during the period of blood storage (r=0-53, p<0.001, and r=0-33, p<0-001, respectively). There was a very wide scatter.

Table Results of assays of electrolyte, metabolite, and hormone concentrations of stored blood

<table>
<thead>
<tr>
<th>Index</th>
<th>No of samples</th>
<th>Mean (ND) concentration (mmol/l)</th>
<th>Range (mmol/l)</th>
<th>Normal range</th>
<th>Pediatric range</th>
<th>Correlation with duration of storage</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>115</td>
<td>168 (6)</td>
<td>155 - 182</td>
<td>136 - 145</td>
<td>-0.71</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>115</td>
<td>11.1 (4-6)</td>
<td>5.5 - 24.6</td>
<td>3.5 - 5.6</td>
<td>0.91</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>115</td>
<td>78 (5)</td>
<td>69 - 86</td>
<td>98 - 106</td>
<td>-0.31</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>114</td>
<td>2.3 (0-4)</td>
<td>1.8 - 3.7</td>
<td>2.2 - 2.75</td>
<td>0.53</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>114</td>
<td>0.8 (0-2)</td>
<td>0.6 - 2.0</td>
<td>0.6 - 0.95</td>
<td>0.33</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total carbon dioxide</td>
<td>115</td>
<td>11.1 (2.8)</td>
<td>4.0 - 19</td>
<td>18 - 25</td>
<td>-0.25</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>114</td>
<td>91 (14)</td>
<td>9.0 - 141</td>
<td>5.5 - 106</td>
<td>-0.04</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>115</td>
<td>4.6 (1-2)</td>
<td>1.3 - 8.2</td>
<td>2.5 - 6.6</td>
<td>0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>112</td>
<td>59.4 (4-7)</td>
<td>50 - 70</td>
<td>64 - 75</td>
<td>0.17</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>49</td>
<td>36.7 (3.3)</td>
<td>31 - 45</td>
<td>37 - 50</td>
<td>0.3</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>115</td>
<td>19.2 (3-7)</td>
<td>8.4 - 31.4</td>
<td>3.3 - 5.5</td>
<td>-0.49</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>115</td>
<td>10.5 (4-6)</td>
<td>3.3 - 23.3</td>
<td>0.4 - 1.3</td>
<td>0.9</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Pyruvate</td>
<td>114</td>
<td>0.24 (0-10)</td>
<td>0.01 - 0.57</td>
<td>0.03 - 0.16</td>
<td>-0.27</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Alanine</td>
<td>114</td>
<td>0.38 (0-10)</td>
<td>0.02 - 0.08</td>
<td>0.18 - 0.86</td>
<td>0.51</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Glycerol</td>
<td>113</td>
<td>0.05 (0-2)</td>
<td>0.01 - 0.15</td>
<td>0.03 - 0.18</td>
<td>0.04</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>3-Hydroxybutyrate</td>
<td>109</td>
<td>0.04 (0-04)</td>
<td>0.01 - 0.26</td>
<td>0.01 - 0.34</td>
<td>-0.04</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Non-esterified fatty acids</td>
<td>104</td>
<td>0.65 (0-22)</td>
<td>0.25 - 1.54</td>
<td>0.2 - 1.45</td>
<td>0.52</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>114</td>
<td>+12.2</td>
<td>&lt;1.0 - 33.4</td>
<td>5.0 - 40</td>
<td>0.13</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Cortisol (mmol/l)</td>
<td>111</td>
<td>+301</td>
<td>62 - 906</td>
<td>200 - 700</td>
<td>0.03</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Growth hormone (mU/l)</td>
<td>110</td>
<td>+3.2</td>
<td>0.1 - 62.3</td>
<td>&lt;12 (Unstressed)</td>
<td>-0.14</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>11</td>
<td>314 (4)</td>
<td>308 - 320</td>
<td>270 - 320</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unless otherwise stated.
1Non-Gaussian distribution.
NS=Not significant.
Conversion: SI to traditional units—Sodium: 1 mmol/l=1 mEq/l; potassium: 1 mmol/l=1 mEq/l; chloride: 1 mmol/l=1 mEq/l; calcium: 1 mmol/l=4 mg/100 ml; magnesium: 1 mmol/l=2.4 mg/100 ml; total carbon dioxide: 1 mmol/l=1 mEq/l; creatinine: 1 mmol/l=0.01 mg/100 ml; urea: 1 mmol/l=5.9 mg/100 ml; total protein: 1 g/l=100 mg/100 ml; glucose: 1 mmol/l=18 mg/100 ml; lactate: 1 mmol/l=9 mg/100 ml; pyruvate: 1 mmol/l=0.009 mg/100 ml; alanine: 1 mmol/l=1 mg/l; glycerol: 1 mmol/l=2 mEq/l; 3-hydroxybutyrate: 1 mmol/l=1 mEq/l; non-esterified fatty acids: 1 mmol/l=1 mEq/l; insulin: 1 mU/l=1.1 U/ml; cortisol: 1 mmol/l=0.04 U/ml; growth hormone: 1 mU/l=0.4 ng/ml.
Fig. 1 Results of assays of sodium concentrations for whole period of blood storage. Hatched area represents the normal range.

Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l.

Fig. 2 Results of assays of potassium concentration for whole period of blood storage. Hatched area represents the normal range.

Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l.
however, for both calcium and magnesium throughout storage.

**Total protein and albumin.** Both total protein concentrations (n=112), mean (SD) 59.4 (4.7) g/l and range 50–70 g/l, and albumin concentrations (n=49), mean (SD) 38.7 (3.3) g/l and range 31–45 g/l, increased slightly during storage (r=0.17, p<0.05, and r=0.3, p<0.05, respectively).

**Glucose.** The glucose concentrations of all units of citrate phosphate dextrose stored blood were markedly above the normal non-fasting range throughout the period of storage (Fig. 3). There was a significant fall in glucose concentration during storage from around 20 to 15 mmol/l (360–270 mg/100 ml) (r=−0.49, p<0.001). (Fig. 3). Between the second and eighth days of storage, mean (SD) glucose concentrations were 19.2 (3.5), mmol/l (n=81), with a range of 8.4–31.4 mmol/l.

**Lactate.** Lactate concentrations rose significantly from around 7 mmol/l (63 mg/100 ml) at the beginning of storage to around 25 mmol/l at the end of storage (r=0.9, p<0.001) (Fig. 4). From the second up to the eighth day from collection, mean (SD) lactate concentrations were 7.8 (1.8) mmol/l, with a range of 3.3–14.3 mmol/l.

**Pyruvate.** Pyruvate concentrations in stored blood were widely scattered during the first week of storage, with a mean (SD) of 260 (110) μmol/l (2.3 (1.0) mg/100 ml) and a range of 10–570 μmol/l. There was a slight but significant fall in pyruvate concentrations during the storage period (r=−0.37, p<0.001).

**Alanine.** Stored blood alanine concentrations also showed a wide scatter during storage, with a mean of 0.38 (0.10) mmol/l (0.38 (0.40) mEq/l) and a range of 0.02–0.68 mmol/l, but did increase slightly during storage (r=0.31, p<0.001).

**Insulin, cortisol, and growth hormone.** Neither insulin nor cortisol were totally degraded in stored blood and both showed appreciable concentrations throughout the period of storage. The mean insulin concentration was 12.2 μU/l, with a range of <1–33.4 μU/l, and mean cortisol concentration was 301 nmol/l (10.9 μg/100 ml), with a range of 62–906.

![Fig. 3](http://adc.bmj.com/) Results of assays of glucose concentrations for whole period of blood storage. Hatched area represents normal range.

*Conversion: SI to traditional units—Glucose: 1 mmol/l = 18 mg/100 ml.*
nmol/l. These concentrations were not significantly correlated with duration of storage. The mean growth hormone concentration was 3.2 mU/l, with a range of 0.1-6.2 mU/l. Concentrations were not correlated with the age of blood.

**Osmolality.** The osmolality of all the 11 units of blood less than one week old analysed was above the upper limit of the physiological range (290 mOsm/kg). The mean (SD) osmolality in the samples was 314 (4) mOsm/kg, with a range of 308-320 mOsm/kg.

**Discussion**

The electrolyte and substrate content of stored blood is derived from the addition of:

(i) citrate phosphate dextrose adenine anticoagulant preservative solution;
(ii) the metabolism of stored blood cells;
(iii) the volume and plasma constituents of the donor blood.

The anticoagulant preservative solution increases both the sodium and glucose concentrations of stored blood by roughly 20 mmol/l.

Even during storage at 4°C, red cell metabolism continues anaerobically and lactate is produced by glycolysis.

The data presented in this study show that citrate phosphate dextrose stored blood contains a large substrate load, which alters during storage. Further, it is possible to predict accurately the sodium, potassium, glucose, and lactate load of a given unit of blood if the duration of storage is known.

What are the implications of these findings? The clinical situations of exchange transfusion in the neonate and transfusion after surgery and haemorrhagic shock can be used to illustrate some of the important metabolic effects.

**Hypernatraemia.** Citrate phosphate dextrose blood within the first week of collection is used for exchange transfusions. From the data presented in this paper, therefore, the mean (SD) sodium concentration of the donor blood will be 170 (5) mmol/l. After an exchange transfusion 85–90% of the blood volume may be derived from stored blood. The osmolality of the stored blood plasma is higher than that of normal plasma (see above) and will cause considerable water and electrolyte flux. The plasma sodium concentration will rapidly increase to hyper-

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**Fig. 4** Results of assays of lactate concentrations for whole period of blood storage. Hatched area represents normal range.

*Conversion: SI to traditional units—Lactate: 1 mmol/l = 9 mg/100 ml.*
The metabolic load of stored blood

Hyperkalaemia. Hyperkalaemia has been documented as a 'transient phenomenon' after exchange transfusions and is more common in infants of low birth weight. This transient phenomenon cannot be related to rapid excretion, as even full term healthy neonates cannot rapidly excrete a sodium load. It is probable that this excess sodium will be distributed throughout the extracellular space, thus expanding it at the expense of intracellular water.

These changes in intracellular water will also result in a reduction of brain cell volume, may cause overall shrinkage of the brain, and may result in low intracranial pressure, causing capillary dilatation and subsequent vessel rupture. Exchange transfusion is a known aetiological factor in neonatal cerebral haemorrhage.

Hyperglycaemia. Hyperkalaemia sufficient to induce serious cardiac arrhythmias has been described during exchange transfusions. Our data show a significant rise of potassium concentration during the first week of storage, which is related to a pronounced reduction in the activity of cell membrane Na⁺/K⁺ adenosine triphosphatase during storage at 4°C. As a result, sodium and potassium are pumped back against their concentration gradients more slowly than the rate of passive diffusion.

Hyperglycaemia. The glucose load of all citrate phosphate dextrose stored blood has a mean concentration of 19.2 mmol/l. Thus a rapid large volume exchange transfusion may induce severe hyperglycaemia. Hyperglycaemia is known to interfere with platelet function and is now known to affect adversely neurological recovery from cerebral ischaemia. Less mature infants respond to a glucose stimulus with a lower insulin output whose peak concentration may occur up to two hours later, thus making them susceptible to the development of hypoglycaemia.

Hyperglycaemia unrelated to infusion of glucose has been described in infants with hypernatraemia whose insulin responses were inappropriately low. Insulin facilitates active transport of glucose into brain cells, but in those clinical circumstances glucose would be an extracellular obligate osmole and, therefore, along with sodium, increase the cellular dehydration.

The metabolic stress response to surgery and haemorrhagic shock with the associated increase in glucagon, catecholamine, and cortisol concentrations may modify the handling of the substrate load of blood transfused during the perioperative period. In contrast to these hormones that stimulate gluconeogenesis, insulin secretion is suppressed during surgical stress, and cellular glucose uptake is consequently reduced. In these clinical circumstances lactate is also used for gluconeogenesis.

Anaerobic metabolism secondary to poor tissue perfusion in haemorrhagic shock produces lactic acidemia. The transfusion of stored blood with a raised lactate concentration, mean concentration of 8.0 mmol/l during the first week of storage, will accentuate the metabolic acidosis.

Conclusions

The use of very recently stored citrate phosphate dextrose blood does not prevent the administration of large sodium and glucose loads. The effect of each of these substrates may increase the adverse effects of the other, particularly in relation to neurological damage. Potassium and lactate concentrations rise rapidly, and, even within the first week of blood storage, may have produced concentrations considerably above the physiological range.

The changes in concentration of other electrolytes and intermediary metabolites illustrate the alteration in red cell permeability and continuing metabolism during blood storage. These results and the preservation of some hormones in stored blood are important considerations in metabolic studies carried out in infants.

The good correlation coefficients with duration of storage for sodium, potassium, and lactate indicate that concentrations of these substrates can be predicted within a narrow range in a given unit of blood if the duration of storage is known.

These data would support the use of fresh blood collected in heparin for large volume transfusions both in infants who have short gestational ages and infants who are very ill to avoid these potential problems.

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References


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1989 April 11-15

At University of Warwick:
1990 April 3-7
1991 April 16-20
1992 April 7-11
1993 April 19-23 (provisional)
1994 April 11-15 (provisional)
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