Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study

Dileep N. LOBO*, Zeno STANGA†, J. Alastair D. SIMPSON*, John A. ANDERSON*, Brian J. ROWLANDS* and Simon P. ALLISON†

*Section of Surgery, University Hospital, Queen’s Medical Centre, Nottingham NG7 2UH, U.K., and †Clinical Nutrition Unit, University Hospital, Queen’s Medical Centre, Nottingham NG7 2UH, U.K.

ABSTRACT

Although hypoalbuminaemia after injury may result from increased vascular permeability, dilution secondary to crystalloid infusions may contribute significantly. In this double-blind crossover study, the effects of bolus infusions of crystalloids on serum albumin, haematocrit, serum and urinary biochemistry and bioelectrical impedance analysis were measured in healthy subjects. Ten male volunteers received 2-litre infusions of 0.9% (w/v) saline or 5% (w/v) dextrose over 1 h; infusions were carried out on separate occasions, in random order. Weight, haemoglobin, serum albumin, serum and urinary biochemistry and bioelectrical impedance were measured pre-infusion and hourly for 6 h. The serum albumin concentration fell in all subjects (20% after saline; 16% after dextrose) by more than could be explained by dilution alone. This fall lasted more than 6 h after saline infusion, but values had returned to baseline 1 h after the end of the dextrose infusion. Changes in haematocrit and haemoglobin were less pronounced (7.5% after saline; 6.5% after dextrose). Whereas all the water from dextrose was excreted by 2 h after completion of the infusion, only one-third of the sodium and water from the saline had been excreted by 6 h, explaining its persistent diluting effect. Impedances rose after dextrose and fell after saline (P < 0.001). Subjects voided more urine (means 1663 and 563 ml respectively) of lower osmolality (means 129 and 630 mOsm/kg respectively) and sodium content (means 26 and 95 mmol respectively) after dextrose than after saline (P < 0.001). While an excess water load is excreted rapidly, an excess sodium load is excreted very slowly, even in normal subjects, and causes persistent dilution of haematocrit and serum albumin. The greater than expected change in serum albumin concentration when compared with that of haemoglobin suggests that, while dilution is responsible for the latter, redistribution also has a role in the former. Changes in bioelectrical impedance may reflect the electrolyte content rather than the volume of the infusate, and may be unreliable for clinical purposes.

INTRODUCTION

Although intravenous crystalloids are the most commonly prescribed treatment in hospitalized patients, there are remarkably few studies on their effects in normal subjects with which to compare the response in patients, in particular the extent and time scale of their diluting effects on haematocrit and serum albumin and...
the rate at which they are excreted. An infusion of 2 litres of 0.9% (w/v) saline (NaCl) over 2 h in high-risk pre-operative patients produced a moderate fall in serum albumin concentration (from 34 to 30 g/l) [1], and a bolus infusion of 0.9% saline has been shown to produce a significant decrease in haemoglobin and haematocrit [2]. Experimental work on anaesthetized rabbits has demonstrated that acute expansion of the body water by infusion of 0.9% saline resulted in a greater dilution of serum albumin than could be explained by expansion of plasma volume alone [3]. Studies using mathematical models to analyse volume kinetics of Ringer acetate solution in healthy volunteers demonstrated a more pronounced dilution of serum albumin when compared with that of haemoglobin and blood water, suggesting a larger expandable volume for albumin [4–6].

Hypoalbuminaemia is a well documented sequel to major trauma [7,8], sepsis [9] and surgery [10,11]. The work of Fleck et al. [12] suggested that hypoalbuminaemia, in the acute phase of injury, may be due to redistribution of albumin from the circulation to the interstitial fluid consequent on an increase in vascular permeability. In these situations, however, patients also receive large volumes of crystalloid infusions. This, coupled with the antidiuretic response to trauma and starvation, with inability to excrete a salt and water load normally [13–15], results in oedema and increased total body water (TBW) and extracellular fluid (ECF) volume [9]. This dilutes the serum albumin and reduces its concentration further. We have demonstrated previously, in hypoalbuminaemic oedematous post-operative patients, that as excess salt and water are excreted, the serum albumin concentration rises by 1 g/l for every litre of fluid lost [16], reflecting a reversal of previous dilution.

The present study was conducted to measure the responses of normal subjects to crystalloid infusions as a basis for comparison with those in patients. In particular, the extent and time course of the diluting effects of the infusions on haematocrit and serum albumin were measured.

This study was presented to the British Association for Parenteral and Enteral Nutrition, Harrogate, November 2000, and to the Association of Surgeons of Great Britain and Ireland, Birmingham, April 2001. It will be published in abstract form [16a,16b].

**METHODS**

This double-blind, crossover study was conducted on 10 healthy young adult male volunteers after obtaining informed consent. Only those subjects with a body weight of 65–80 kg and a body mass index of 20–25 kg/m² were included. Subjects with chronic medical conditions or acute illness in the 6-week period preceding the study, on regular medication or with a history of substance abuse were excluded.

Subjects reported for the study at 09.00 hours after a fast from midnight. After voiding of the bladder, height was recorded to the nearest 0.01 m, weight measured to the nearest 0.1 kg using Avery 3306ABV scales (Avery Berkel, Royston, U.K.), and body mass index calculated. Bioelectrical impedance analysis was performed with single-frequency (50 kHz) and dual-frequency (5 and 200 kHz) devices (Bodystat 1500 and Bodystat Dualscan 2005 respectively; Bodystat Ltd., Isle of Man, U.K.) using tetrapolar distal limb electrodes [17,18]. TBW and ECF volume were calculated using regression equations programmed into the devices.

The equations for dual-frequency bioelectrical impedance analysis are as follows:

ECF (litres) = \([0.178458 \times \text{height}^2] / \text{impedance (5 kHz)} + (0.06895 \times \text{weight}) + 3.794\]

TBW (litres) = \([0.24517 \times \text{height}^2] / \text{impedance (200 kHz)} + (0.18782 \times \text{weight}) + 8.197\]

The equation for single-frequency bioelectrical impedance analysis is:

TBW (litres) = \([0.3963 \times \text{height}^2] / \text{impedance (50 kHz)} + (0.143 \times \text{weight}) + 8.4\]

Height was measured in cm, weight in kg and impedance in \(\Omega\).

Two venous cannulae were inserted, one in each forearm, and blood was sampled for full blood count, packed cell volume, serum electrolytes (sodium, potassium, chloride and bicarbonate), albumin and osmolality, and blood glucose. The urine collected was analysed for osmolality and concentrations of sodium and potassium.

Serum and urinary osmolality were measured on a Fiske 2400 Osmometer (Vitech Scientific Ltd., Partridge Green, W. Sussex, U.K.) using a freezing point depression method, which has a coefficient of variance (CV) of 1.2%. A Vitros 950 analyser (Ortho Clinical Diagnostics, Amersham, Bucks., U.K.) was used to measure serum sodium (CV 0.6%), potassium (CV 1.0%), chloride (CV 1.1%), bicarbonate (CV 4.0%), urea (CV 2.0%) and albumin (CV 1.6%) and blood glucose (CV 1.2%). Urinary sodium (CV 1.5%) and potassium (CV 1.5%) were assayed on a Vitros 250 analyser (Ortho Clinical Diagnostics). Haematological parameters were measured on a Sysmex SE 9500 Analyser (Sysmex UK Ltd, Milton Keynes, U.K.) using direct-current hydrodynamic focusing and cumulative pulse-height detection. The CV for haemoglobin and packed cell volume estimation was 1.0–1.5%. Urinary samples were tested with Combur2 Test® D sticks (Roche Diagnostics Ltd, Lewes, E. Sussex, U.K.) for glucose content.

A volume of 2 litres of 0.9% (w/v) saline or 5% (w/v) dextrose was then infused over 60 min, with subjects in
Responses to crystalloid infusions

Figure 1  Changes in body weight, and percentage changes in serum albumin concentration, haemoglobin concentration and
packed cell volume (haematocrit) after infusion of 2 litres of 0.9% saline or 5% dextrose over 1 h

All values are means (95% CI). P values are for tests of between-subjects effects (saline compared with dextrose) obtained using the general linear model repeated measures procedure.

the supine position. The infusions were administered in random order on separate days. A nurse who was not involved in the study masked all labels on the infusion bags with opaque tape and also performed the randomization. The infusion started at time 0. Pulse rate and blood pressure were recorded at 15 min intervals for 2 h and then at 30 min intervals for a further 4 h. Subjects were not allowed to eat or drink for the duration of the study and remained supine for most of the time. They stood up to void urine and to be weighed, but blood samples were taken after lying supine for at least 15 min.

Body weight, bioelectrical impedance analysis and the above blood tests were repeated at hourly intervals for 6 h. Subjects voided their bladders as the need arose and, in all cases, at the end of 6 h. The time of each micturition was noted and urine volume was measured. Urine samples were analysed for osmolality and concentrations of sodium and potassium. Urinary glucose content was assessed using dipsticks.

The experiment was repeated with a 2-litre infusion of 5% dextrose in those who had received 0.9% saline initially, and vice versa, 7–10 days later. The randomization code was broken at the end of the study. The University of Nottingham Medical School Ethics Committee granted ethical approval for the study, which was carried out in accordance with the Declaration of Helsinki of the World Medical Association.

Statistical analysis was performed with SPSS® for Windows™ Release 9.0 software (SPSS Inc., Chicago, IL, U.S.A.). Data were expressed as mean [95% confidence intervals (CI)]. Data were tested for statistical significance using the paired Student’s t-test, and tests of between-subject effects (saline compared with dextrose) were performed using the general linear model repeated measures procedure. Graphs were created with GraphPad Prism 2 Software (GraphPad Software Inc., San Diego, CA, U.S.A.). Differences were considered significant at $P < 0.05$.

RESULTS

The 10 male volunteers had a mean (S.E.M.) age of 22.1 (0.3) years, height of 1.78 (0.01) m, initial weight of 73.6 (1.8) kg and body mass index of 23.2 (0.5) kg/m$^2$. The mean (95% CI) baseline values for serum albumin concentration, haemoglobin and packed cell volume of the volunteers were 44.0 (39.4–48.6) g/l, 14.9 (13.9–15.9) g/dl and 44.8 (43.4–46.2)% respectively before infusion of saline, and 43.8 (40.1–47.6) g/l, 15.2 (14.2–16.3) g/dl and 45.1 (43.4–46.9)% respectively before infusion of dextrose (not significant; paired t-test). Six volunteers received 0.9% saline as the first infusion and
Table 1  Urinary changes
All values are means (95 % CI) for n = 10. Student’s paired t-test was used to calculate the statistical significance of differences between saline and dextrose; NS, not significant.

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Dextrose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first micturition (min)</td>
<td>212 (141–283)</td>
<td>78 (68–88)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of micturitions over 6 h</td>
<td>1.7 (0.9–2.5)</td>
<td>3.4 (2.4–4.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total post-infusion urine volume over 6 h (ml)</td>
<td>563 (441–685)</td>
<td>1663 (1512–1813)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total post-infusion urinary sodium over 6 h (mmol)</td>
<td>95 (75–116)</td>
<td>26 (15–38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total post-infusion urinary potassium over 6 h (mmol)</td>
<td>37 (29–45)</td>
<td>10 (8–13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Osmolality of pre-infusion urine (mOsm/kg)</td>
<td>880 (381–1379)</td>
<td>773 (372–1174)</td>
<td>0.87 (NS)</td>
</tr>
<tr>
<td>Osmolality of pooled post-infusion urine (mOsm/kg)</td>
<td>630 (540–721)</td>
<td>129 (115–144)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Figure 2  Changes in serum osmolality, blood glucose and serum concentrations of sodium, potassium, chloride and bicarbonate after infusion of 2 litres of 0.9% saline or 5% dextrose over 1 h
All values are means (95 % CI). P values are for tests of between-subjects effects (saline compared with dextrose) obtained using the general linear model repeated measures procedure.

Four received 5% dextrose initially. All volunteers remained haemodynamically stable throughout the study.

The serum albumin concentration had fallen significantly (20 % after saline; 16 % after dextrose) at 1 h after both infusions (Figure 1). The decrease was more pronounced and prolonged after saline (P < 0.001). Changes in packed cell volume and haemoglobin were similar, but of a smaller magnitude (7.5 % after saline; 6.5 % after dextrose) (Figure 1). Sequential changes in serum osmolality, sodium, potassium, chloride and bicarbonate and blood glucose are shown in Figure 2. Despite the changes in serum biochemistry, mean corpuscular volume in each individual subject did not change by more than ± 1 fl from baseline during the course of each experiment. Urinary responses are summarized in Table 1. All subjects had glycosuria (4; ≥ 55 mmol/l) in the first sample voided after infusion of dextrose. Glycosuria was not detected in pre-infusion or subsequent samples.

Changes in body weight were equivalent to the volume of fluid infused and urine excreted (Figure 1; Table 1). Although all volunteers had gained 2 kg in weight at the end of each infusion, weight returned to baseline more slowly after saline than after dextrose, because of the different rates of excretion of these two solutions.

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It was interesting to note, however, that measured impedance decreased initially after saline infusions and increased after dextrose infusions. Calculated TBW increased by up to 2 litres after a lag period of 1 h in volunteers who received saline infusions, but remained unchanged or decreased after dextrose infusions (Figure 3). The mean increase in TBW after saline infusions was closer to 2 litres when measured by single-frequency bioelectrical impedance analysis than by the dual-frequency device.

One subject developed transient periorbital oedema after both infusions, and another developed the same complication after infusion of saline. Five subjects felt light-headed for a short period about 2 h after the start of the dextrose infusion, and this corresponded with the documented reactive hypoglycaemia (Figure 2). No other side effects were observed.

**DISCUSSION**

It is extraordinary that one of the most commonly administered treatments in medical and surgical practice, intravenous crystalloids, has been so rarely tested in normal subjects, and that there is so little information concerning normal responses with which to compare those in patients. The present study shows that, even in normal subjects, the administration of 0.9% (w/v) saline precipitated falls in serum albumin of 20% and in haematocrit of 7.5%. This effect was sustained for more than 6 h, because only one-third to one-half of the infused dose of sodium and water had been excreted during this period. This illustrates the contribution of crystalloid infusions to the fall in serum albumin concentration in patients after surgery or during illness, when the ability to excrete an excess salt and water load is even less [13–15]. The effects of a 5% (w/v) dextrose infusion were more transient, since almost all the water had been excreted by 2 h after infusion, and the volume of distribution was the whole-body water rather than just the ECF volume as with saline. The diuretic effect of dextrose was probably partly due to the osmotic effect of hyperglycaemia in the first 1 h after infusion, as well as reduced secretion of vasopressin in response to a lower plasma osmolality in the first 2 h after infusion.

Although saline infusion may be expected to induce a diuresis in a patient who is salt- and water-depleted by excess losses, the mechanism for disposing of a salt and water load in excess of normal (dependent, perhaps, on atrial natriuretic peptide) may be less efficient than that for excreting excess water (changes in osmolality causing a decrease in vasopressin secretion). If there is a volume
deficit (blood, plasma or salt and water), there is an oliguric response, which is reversed by volume repletion with crystalloid or colloid. However, if one administers water or its equivalent (5% dextrose) to a normovolaemic subject, the osmoreceptors ‘switch off’ vasopressin and there is a diuresis. Similarly, if one administers an isotonic solution with sodium as the osmotic agent holding that fluid in the extracellular space, the water component of saline will only be excreted equivalently or secondary to the sodium excretion. This is borne out by our results, which suggest that, although the mechanisms for adjusting water balance are sensitive and efficient, the mechanisms for disposing of excess sodium, even in normal individuals, are remarkably sluggish by comparison. These observations have implications for fluid management in clinical situations, where the margin of error between adequate fluid replacement and overload is much narrower.

The changes in packed cell volume and haemoglobin after saline infusions were very similar to those demonstrated by Grathwohl et al. [2], who infused 0.9% saline at 30 ml/kg into normal volunteers over 30 min. The greater proportional change at 1 h in serum albumin concentration (20% after saline and 16% after dextrose) compared with those in haemoglobin and packed cell volume (7.5% after saline and 6.5% after dextrose) partly reflects the fact that albumin is distributed only in the plasma space, while red blood cells (and haemoglobin) are distributed in the whole blood space. Plasma volume expansion is equal to blood volume expansion in absolute terms (ml), but the relative expansion and dilution (%) is greater in the smaller plasma and albumin space. A decrease in haematocrit (or haemoglobin) of 7.5% is the result of expansion of the blood volume by 8.1% \[\frac{(100 \times 100)}{(100 - 7.5)} - 100\]. With a pre-infusion haematocrit of 45% (and a plasma volume of 55%), this expansion in total blood volume would result in a 14.7% increase in plasma volume \[\frac{(55 + 8.1) \times 100}{55} - 100\]. Nonetheless, the 20% decrease in serum albumin concentration after saline infusion cannot be explained by dilution alone, and suggests a change in albumin distribution as well [1,3,4,19,20]. Although it has been suggested that plasma volume expansion may increase the transcapillary escape rate of albumin [21], the greater than expected fall in serum albumin concentration resulting from a net loss of albumin from the intravascular compartment in response to the crystalloid infusions [1,3] appears not to be a result of increased capillary permeability [22], but a consequence of increased convective transport of albumin across the microvasculature into the interstitium because of dilution of the plasma colloid oncotic pressure by the infusion [1,2,3,24]. The mechanism of escape of albumin by convection could be used to explain part of the differences noted after the saline and dextrose infusions. We speculate that one of the immediate effects of both infusions was to produce a shift of albumin, water and sodium (after saline infusion) into the interstitial space, which reverses more slowly with saline because of its slower excretion. The secondary falls in serum albumin and haemoglobin after dextrose could be a result of a return of water from the intracellular to the extracellular compartment following the water diuresis.

All subjects developed hyperchloraemia after saline infusions, and serum chloride concentrations remained elevated even 6 h after the infusion (Figure 2). This is consistent with published data [28] and reflects the greater chloride content of 0.9% saline (154 mmol/l) compared with that of serum (95–105 mmol/l). Bicarbonate concentrations remained normal and, in contrast with an earlier study in which subjects received much greater volumes of 0.9% saline (50 ml/kg over 1 h) [25], we were unable to demonstrate an acidosis.

Subjects emptied their bladders earlier and more frequently after infusion of dextrose than saline. They also voided greater volumes of urine of low osmolality and low sodium and potassium content after dextrose infusions (Table 1). Body weight had returned to baseline by the end of 6 h following dextrose infusions, while weight at 6 h following saline infusions remained more than 1 kg above baseline (Figure 1), reflecting retention of over half of the infused sodium and water. All subjects developed hyperglycaemia at the end of the dextrose infusion, resulting in an osmotic diuresis. This is borne out by the fact that the first urine sample voided after infusion of dextrose contained \(\geq 55\) mmol glucose/l. In addition, serum osmolality and sodium concentration decreased substantially at the end of the dextrose infusion (Figure 2).

It was interesting that body impedance at all three measured frequencies decreased after saline infusion and increased after dextrose infusion (Figure 3). This may be because the electrolytes in saline conduct electricity and, therefore, decrease resistance. On the other hand, infusion of dextrose provides electrolyte-free water, which, being a poor conductor, increases resistance. These findings corroborate preliminary work from our group [17] suggesting that the ability of bioelectrical impedance analysis to detect changes in body water depends on whether the change is in pure water or in water and electrolytes. This greatly limits the role of bioelectrical impedance analysis in the clinical situation, as a pure water (or electrolyte-poor water) excess registers as a decrease in TBW because of the increase in impedance (TBW \(\propto\) height\(^2\)/impedance), and may explain, to some extent, why previous studies have not been able to document accurately fluid shifts using bioelectrical impedance analysis [26–29]. In addition, calculated changes in TBW after saline infusion were more accurate when using single-frequency compared with dual-frequency bioelectrical impedance analysis, corroborating previous studies showing that single-frequency bioelectrical im-
pedance analysis is correlated more closely with dilutional techniques for TBW estimation than dual-frequency [18] and multifrequency [30] bioelectrical impedance analysis.

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