Effects of hypertonic 75 mg/ml (7.5%) saline on extracellular water volume when used for preloading before spinal anaesthesia

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Background: Prevention of hypotension during spinal anaesthesia is commonly achieved using fluid preloading. This may result in a substantial amount of excess free water retained in the body after spinal anaesthesia. We aimed to evaluate the effects of 7.5% hypertonic saline on extracellular water volume and haemodynamics when used for fluid preloading before spinal anaesthesia.

Methods: This randomised double-blind study evaluated the effects of 75 mg/ml (7.5%) hypertonic saline (HS) on extracellular water volume and haematocrit in patients undergoing arthroscopy or other lower limb surgery under spinal anaesthesia. Amounts of 1.6 ml/kg of HS (20 patients) or 13 ml/kg of 9 mg/ml normal saline (20 patients) were administered for preloading before spinal anaesthesia with a 10 mg dose of 0.5% hyperbaric bupivacaine. Etilefrine was administered in order to maintain mean arterial pressure (MAP) at \( > 80\% \) of its baseline value. Whole-body impedance cardiography-derived cardiac index (CI) and extracellular water (ECW) were measured.

Results: There were no significant differences in demographic data or in the number of blocked segments. ECW remained similar in both groups despite the much smaller amount of infused free water in the HS group. There were no significant differences between the groups in CI values during the study. The amount of etilefrine administered was similar in the treatment groups. Dilution of haematocrit was also similar in both groups.

Conclusion: Hypertonic 75 mg/ml (7.5%) saline is an alternative for preloading before spinal anaesthesia in situations where excess free water administration is not desired. It is effective in small doses of 1.6 ml/kg, which increase the extracellular water, plasma volume and cardiac output, and thus maintain haemodynamic stability during spinal anaesthesia.

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saline had a favourable effect on haemodynamics when used for preloading before spinal anaesthesia (10). In the present study, we evaluated the data collected during our earlier study to investigate the effects of HS on extracellular water volume and haematocrit. Our purpose was to define the mode of action leading to improved haemodynamics after the HS infusion (10).

Methods
Forty day-surgery patients scheduled for knee arthroscopy or other lower limb orthopaedic surgery were randomly allocated according to a list of random digits to two groups of 20 patients (hypertonic saline (HS) and normal saline (NS) groups) after obtaining an institutional study approval and written informed consent. No routine premedication was used. If premedication was needed, 0.05 mg of fentanyl was administered i.v. after the insertion of a venous cannula. The exclusion criteria included any contraindications for spinal anaesthesia.

A radial arterial catheter was inserted and the registration of circulation was started in a separate room for baseline values. CircMon™ B202 (JR Medical Ltd, Tallinn, Estonia) was used for the measurement of whole-body impedance cardiography-derived cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), left cardiac work (LCW) and extracellular water (ECW). Disposable ECG electrodes (Blue sensor type R-00S, Medicotest A/S, Ølstykke, Denmark) were used. A pair of electrically connected current electrodes was placed on the distal parts of the extremities, just proximal to the wrists and ankles. Voltage electrodes were 5 cm apart from the current electrodes (11). Measurements were done in the supine position, and the patient’s limbs were isolated from the trunk to prevent an electrical connection during the bioimpedance measurements. Blood pressure was measured noninvasively at 5-min intervals using Acurror 4 (Datascopc Corp, Montvale, NJ, USA).

ECW (12) was calculated using the equation: $ECW = K \times H^2 / R$, where $H$ is the height (cm) of the patient; $R$ is the resistive part of the whole-body bioimpedance ($\Omega$); and $K$ is the correction factor ($K_{\text{mal}} = 0.078$, $K_{\text{females}} = 0.095$).

In the operating room, a 16-gauge cannula was inserted in a peripheral vein in the cubital fossa. Through this cannula the patients received either 1.6 ml/kg of HS (NaCl 75 mg/ml, 7.5%) or 13 ml/kg of NS (NaCl 9 mg/ml, 0.9%), according to randomisation, for fluid preloading over 10–15 min. All patients received the same amount of sodium (2 mmol/kg) in this preloading, which was given by the anaesthetic nurse caring for the patient in the operating room. After the fluid preloading, saline 4.5 mg/ml (0.45%) infusion was started as maintenance fluid at the rate of 2 ml kg$^{-1}$ h$^{-1}$.

Spinal anaesthesia was induced immediately after the end of the study fluid infusion. It was performed using a 27-gauge Quinke-type spinal needle (Spinocan, B. Braun, Melsungen, Germany) at the L2–3 or L3–4 intervertebral space with the patient in the lateral decubitus position, with the operative side dependent. All patients received 2.0 ml of 0.5% bupivacaine (5 mg/ml, hyperbaric). The patients were kept in the lateral decubitus position for 5 min and then repositioned in the supine position. The surgical procedure was started when the level of sensory blockade was satisfactory.

During the surgical procedure, invasive arterial pressure was monitored continuosly using a Hewlett Packard monitor (Hewlett-Packard GmbH, Böblingen, Germany). The baseline value of mean arterial pressure (MAP) was measured before preloading in the operating room. A 2 mg bolus of etilefrine was administered i.v. during the course of spinal anaesthesia whenever MAP fell below 80% of its baseline value. The highest cutaneous level of the sensory blockade was determined by loss of cold sensation, and the patients were asked about possible side effects.

Blood samples were taken from the radial arterial cannula before preloading (baseline); after the patient was repositioned in the supine position following the spinal puncture; after the surgical procedure; and after recovery from the spinal anaesthesia (plantar and dorsiflexion of both ankles recovered). Plasma concentrations of sodium, haematocrit and serum osmolality were measured. CO, SV, SVR, LCW and ECW were measured at the same time points.

Before the trial, a power calculation for a 15 mmHg difference in MAP (1 SD in the previous studies in this situation) with a probability of a level of 0.05 and power of 0.80 yielded a sample size of 15–16 patients. Twenty patients were enrolled in each group.

Statistical analysis was performed using the SPSS for Windows (version 7.5) (SPSS Inc., Chicago, IL, USA). The results were analysed using the analysis of variance for repeated measures with group as the factor, and time as the repeating factor (before preloading; after the patient was repositioned in the supine position following the spinal puncture; after the surgical procedure; and after recovery from the spinal anaesthesia). The $t$-test for independent samples (intergroup comparison) and $t$-test for paired samples (intragroup comparison) were performed at different time points. Dichotomous variables were tested using the chi-square test. Results are expressed as mean±SD.
Table 1

Demographic data, effects of spinal anaesthesia and adverse effect of preloading.

<table>
<thead>
<tr>
<th></th>
<th>HS (n=20)</th>
<th>NS (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>7/13</td>
<td>3/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±11</td>
<td>42±11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174±8</td>
<td>177±11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81±16</td>
<td>79±12</td>
</tr>
<tr>
<td>Sensory level of anaesthesia (T6)</td>
<td>16±2</td>
<td>17±2</td>
</tr>
<tr>
<td>Duration of spinal anaesthesia (min)</td>
<td>154±36</td>
<td>156±43</td>
</tr>
<tr>
<td>Etilefrine (mg)</td>
<td>1.0±2.4</td>
<td>1.0±2.1</td>
</tr>
<tr>
<td>Adverse effects* (n)</td>
<td>15**</td>
<td>0</td>
</tr>
</tbody>
</table>

* Sensation of heat and compression around the arm.
** P<0.001 compared to the NS group.

(mean±SEM in figures); P<0.05 was considered statistically significant.

Results

Equal numbers of patients received either NS or HS, and there were no differences in the demographic data or in the number of blocked segments or in the duration of spinal anaesthesia (Table 1). Duration of surgery did not differ between the treatment groups. Adverse effects, including the sensation of heat and compression around the arm during HS infusion and the sense of thirst, were well-tolerated and disappeared immediately after the completion of the HS infusion (Table 1).

The volume of preload was significantly less in the HS group compared to the NS group (129±25 ml vs. 103±161 ml, respectively; P<0.001). The total infused volume before and during spinal anaesthesia was also smaller in the HS group than in the NS group (551±175 ml vs. 1443±243 ml, respectively; P<0.001). However, ECW remained similar in the treatment groups (Fig. 1). The ECW increased from 12.0±1.9 to 12.4±2.2 l in the HS group and from 11.9±1.8 to 12.6±2.0 l in the NS group during the study (P<0.05 in both groups), but the groups did not differ at any time point. There was no notable intraoperative blood loss in either of the study groups. The groups were similar as regards the total amount of etilefrine administered (HS:1.0±2.4 mg vs. NS:1.0±2.1 mg) (Table 1). Five patients in both groups needed etilefrine administration.

There were no significant differences between the groups in MAP and CI values during the study (Table

Table 2

Haemodynamic data.

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Baseline</th>
<th>After preload</th>
<th>After spinal puncture</th>
<th>After surgery</th>
<th>After spinal anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>HS</td>
<td>95±15</td>
<td>100±14</td>
<td>92±15</td>
<td>88±10*</td>
<td>89±11*</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>101±8</td>
<td>103±9</td>
<td>97±10*</td>
<td>94±9*</td>
<td>95±9*</td>
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<tr>
<td>CI</td>
<td>HS</td>
<td>2.82±0.40</td>
<td>3.19±0.50*</td>
<td>3.13±0.45*</td>
<td>2.67±0.56</td>
<td>2.75±0.62</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>2.76±0.63</td>
<td>3.02±0.65*</td>
<td>3.14±0.75*</td>
<td>2.54±0.48*</td>
<td>2.49±0.49*</td>
</tr>
<tr>
<td>SV (l/min/m²)</td>
<td>HS</td>
<td>86±12</td>
<td>91±16*</td>
<td>88±13</td>
<td>88±11</td>
<td>88±11</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>85±17</td>
<td>88±18*</td>
<td>88±20</td>
<td>84±14</td>
<td>81±15</td>
</tr>
<tr>
<td>LCWI (kg/m²)</td>
<td>HS</td>
<td>3.4±0.6</td>
<td>4.1±1.0*</td>
<td>3.7±0.9</td>
<td>3.0±0.7*</td>
<td>3.1±0.7</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>3.5±0.9</td>
<td>4.0±0.9*</td>
<td>3.8±1.1</td>
<td>3.1±0.7*</td>
<td>3.0±0.6*</td>
</tr>
<tr>
<td>SVRI (dyn·s/cm⁵/m²)</td>
<td>HS</td>
<td>2678±613</td>
<td>2477±438</td>
<td>2292±413*</td>
<td>2648±504</td>
<td>2623±608*</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>2962±675</td>
<td>2799±792</td>
<td>2549±770*</td>
<td>2960±646</td>
<td>3087±752</td>
</tr>
</tbody>
</table>

Mean arterial pressure (MAP), cardiac index (CI), stroke volume (SV), left cardiac work index (LCWI) and systemic vascular resistance index (SVRI).

† P<0.05 compared to the NS group, but the change from the baseline did not differ between the groups.
* P<0.05 compared to the baseline.

Fig. 1. Extracellular water (ECW) before (1) and after (2) preloading, after spinal puncture (3), after surgery (4) and after spinal anaesthesia (5) in the hypertonic saline and normal saline groups. ECW differed significantly from the baseline after spinal puncture and thereafter in both groups (P<0.05). The groups did not differ at any time point.
Effects of hypertonic saline during spinal anaesthesia

2. SV and LCWI were also similar in both groups (Table 2). SVRI was lower in the HS group after spinal anaesthesia; however, the baseline value was also slightly lower in the HS group. The change from the baseline did not differ between the groups (Table 2).

The plasma sodium levels as well as serum osmolality increased after preloading. The maximum level of plasma sodium after preloading was 150 mmol/l. All values were within the normal limits after surgery. The plasma sodium levels and the serum osmolality are presented in Table 3. The haematocrit value decreased in both groups, and no significant difference was seen between the groups (Table 3).

Discussion

We found that 75 mg/ml (7.5%) hypertonic saline was effective in small doses of 1.6 ml/kg, which increased the extracellular water and plasma volume, and prevented the haemodynamic changes as effectively as 13 ml/kg of 9 mg/ml (0.9%) normal saline in ASA I–II patients undergoing knee arthroscopy or other lower limb orthopaedic surgery. When the same amount of sodium was infused during fluid preloading, the patients required similar amounts of etilefrine in order to maintain adequate arterial pressure during spinal anaesthesia. This is in line with the results of Veroli and Benhamou (13). They used saline 5 mg/ml (5%) for preloading before extradural anaesthesia.

The sympathetic nervous blockade did not reach the level of the heart (T1–T5) in all patients, but the level of sensory block did not differ between the treatment groups. Whole-body impedance cardiography (ICGWB) has been shown to be a reliable method compared with other methods of measuring cardiac output: comparison with the thermodilution (TD) and direct Fick methods showed that the ICGWB measures CO accurately in different conditions (in the supine position, during head-up tilt, after induction of anaesthesia, and after coronary artery bypass surgery) (11, 14, 15). The differences in CO values between the ICGWB and TD methods were comparable to those between the direct Fick and TD methods, and the repeatability of ICGWB was nearly twice as good as that of TD (14, 15). Therefore, ICGWB is an adequate method to estimate CO and its changes.

The exact volume of ECW in man is unknown. In invasive diagnostics, the distribution space of substances used for ECW volume estimation ranges from about 15% (inulin and mannitol) to 23% (ions such as bromide, chloride) of body weight (16). Bioimpedance-derived ECW volume equations are usually fitted to some particular dilution method. The CircMon™ device calculates ECW volume on the basis of the equation derived by Kolesnikov et al. (12), which is fitted to thiosulphate space giving ECW values around 16% of body weight. The ECW values estimated in healthy adults using this equation (17) agree well with the reference values reported by Albert (18). The relatively low initial ECW values in some patients may also be explained by slight overweight. In addition, relative preoperative ECW volume deficit may occur in patients undergoing operation after the preoperative fasting (19). Experimental correlations between whole-body bioimpedance and clinical findings related to ECW have been established recently (17, 20). The solutions infused in our study have different conductivities, which may have influenced the bioimpedance-derived ECW. It is difficult to establish the significance of the conductivity-related errors, since the effects are quantitatively complex involving also varied physiological responses, such as renal excretion. Logically, the electrical conductivity of NS roughly equals the average conductivity of the human body, and consequently, it has negligible effect on the results. As HS is a better conductor than NS, the bioimpedance-derived ECW may be slightly overestimated in this group. As the ECW changes in the HS and NS groups were in agreement with the results of the previous studies using dilution techniques (21, 22), we believe that the differences in conductivity of the

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Haematocrit (Hct), plasma sodium (P-Na) and serum osmolality (S-Osmol) data.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
</tr>
<tr>
<td>Hct</td>
<td>HS</td>
</tr>
<tr>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>P-Na (mmol/l)</td>
<td>HS</td>
</tr>
<tr>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>S-Osmol (mosm/kg)</td>
<td>HS</td>
</tr>
<tr>
<td></td>
<td>NS</td>
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</tbody>
</table>

† P<0.05 compared to the NS group.
* P<0.05 compared to the baseline.
study fluids did not substantially influence the findings of the present study. The vasodilatation caused by spinal anaesthesia results in the fluid distribution from the central to peripheral vasculature. We do not believe that this would significantly influence the measured R in the equation, and thereby increase the calculated ECW values. We saw a slow positive trend in the ECW volume, which reflects the physiological distribution of the study fluid from the intravascular to interstitial space.

The increase of the plasma sodium concentration and the serum osmolality was significantly greater in the HS group, despite the similar amounts of infused sodium. This created an osmotic gradient between the extra- and intracellular spaces. The cellular membrane is semipermeable, allowing only water but no solute to pass through (22). Sodium is mainly an extracellular electrolyte owing to the active transport mechanism of the cell membrane. Sodium is also the most important electrolyte participating in the regulation of the distribution of water. Isotonic 9 mg/ml (0.9%) saline did not change the osmolality of extracellular water in our patients. Therefore, it increased ECW by its own volume. Hypertonic 75 mg/ml (7.5%) saline increases ECW more than its own volume, because it draws water from the intracellular space in order to equilibrate the osmotic gradient. This was also seen in our patients; ECW did not differ between the groups despite the significant difference in the infused water volume. Hypotonic 4.5 mg/ml (0.45%) saline infusion during spinal anaesthesia weakened this effect to some degree. We did not see any considerable change in ECW immediately after the infusion of the study fluids. This can be partly explained by the fact that the patients’ position was changed when they were prepared for the surgical procedure, which caused deviations in the baseline impedance independently of the changes in the fluid status.

Another factor that has probably influenced our results is related to the infusion protocol. We infused the study fluids during a short period of time, which means that during this period the fluid remained mostly in the central circulation. It is known that the whole-body bioimpedance method underestimates the central regions in the measurement of ECW (23). Therefore, the bioimpedance method may not adequately reflect the changes of the intravascular volume. The method is more reliable after the distribution of fluid into the peripheral extracellular space. Consequently, because of the short time interval between the first two measurements no conclusions can be drawn from these two phases. The decrease in the haematocrit values was similar in both groups indicating similar increase in the plasma volume. In addition to haemodilution, the decrease in haematocrit may have been partly due to the shrinkage of erythrocytes in the HS group, since the erythrocytes are one of the first sources where water is drawn out along the osmotic gradient (24). The plasma volume increase indicated by haemodilution is more rapid than the increase in ECW volume because the bioimpedance method is not sensitive to fast intravascular volume increases.

Hypertonic saline increases preload (25) and decreases afterload (26). We were not able to measure preload because of the noninvasive technique used. The decrease in SVRI was similar in both groups. Thus it was rather due to the vasodilator effect of the spinal anaesthesia than an effect of the hypertonic saline. HS solution also increases myocardial contractility (27, 28). This effect, together with the plasma volume expansion, could explain its ability to maintain haemodynamic stability during spinal anaesthesia. In our patients, CI was maintained in the HS group at least at the same level as in the NS group. Stroke volume was as good in the HS group as in the NS group.

Preloading with normal saline may require large fluid volumes, and still fail to maintain adequate arterial pressure (29). We conclude that hypertonic 75 mg/ml (7.5%) saline is an alternative method for pre-loading before spinal anaesthesia in situations where excess free water administration is not desired. It is effective in small doses of 1.6 ml/kg, which increase the extracellular water, plasma volume and cardiac output, and thus maintain haemodynamic stability during spinal anaesthesia.

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References
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