Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage

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Object. Systemic administration of 23.5% hypertonic saline enhances cerebral blood flow (CBF) in patients with poor-grade spontaneous subarachnoid hemorrhage (SAH). Whether the increment of change in CBF correlates with changes in autoregulation of CBF or outcome at discharge remains unknown.

Methods. Thirty-five patients with poor-grade spontaneous SAH received 2 ml/kg 23.5% hypertonic saline intravenously, and they underwent bedside transcranial Doppler (TCD) ultrasonography and intracranial pressure (ICP) monitoring. Seventeen of them underwent Xe-enhanced computed tomography (CT) scanning for measuring CBF. Outcome was assessed using the modified Rankin Scale (mRS) at discharge from the hospital. The data were analyzed using repeated-measurement analysis of variance and Dunnett correction. A comparison was made between patients with favorable and unfavorable outcomes using multivariate logistic regression.

Results. The authors observed a maximum increase in blood pressure by 10.3% (p < 0.05) and cerebral perfusion pressure (CPP) by 21.2% (p < 0.01) at 30 minutes, followed by a maximum decrease in ICP by 93.1% (p < 0.01) at 60 minutes. Changes in ICP and CPP persisted for longer than 180 and 90 minutes, respectively. The results of TCD ultrasonography showed that the baseline autoregulation was impaired on the ipsilateral side of ruptured aneurysm, and increments in flow velocities were higher and lasted longer on the contralateral side (48.75% compared with 31.96% [p = 0.045] and 180 minutes compared with 90 minutes [p < 0.05], respectively). The autoregulation was briefly impaired on the contralateral side during the infusion. A dose-dependent effect of CBF increments on favorable outcome was seen on Xe-CT scans (mRS Score 1–3, odds ratio 1.27 per 1 ml/100 g tissue × min, p = 0.045).

Conclusions. Bolus systemic hypertonic saline therapy may be used for reversal of cerebral ischemia to normal perfusion in patients with poor-grade SAH. (DOI: 10.3171/JNS-07/08/0274)

Key Words • autoregulation • cerebral blood flow • cerebral ischemia • hypertonic saline • subarachnoid hemorrhage

The diffuse nature of aneurysmal SAH has widespread adverse effects on CBF and metabolism, particularly in patients assigned poor clinical grades.\textsuperscript{6,18} Following primary cerebral ischemia (Days 1–3), another delayed reduction in CBF (secondary cerebral ischemia) may occur, which is usually associated with cerebral vasospasm, brain edema, hydrocephalus, or metabolic derangement.\textsuperscript{44} These episodes of cerebral ischemia have been found to be correlated with the clinical grade and jointly contribute to an unfavorable outcome.\textsuperscript{10} Any interventions aiming to increase CBF may enhance the potential for better outcome.\textsuperscript{18}

Cerebral autoregulation is an intrinsic self-defense mechanism against cerebral ischemia, which maintains a constant CBF under fluctuations in CPP.\textsuperscript{6} During the acute period of aneurysmal SAH and vasospasm, the range of CPP for normal autoregulation may become narrow,\textsuperscript{44,47} and impaired autoregulation has been found to correlate with poorer outcome in patients following aneurysmal SAH.\textsuperscript{32} Indeed, it has been demonstrated that impaired autoregulation precedes ischemic infarction in patients with aneurysmal SAH.\textsuperscript{42}

Cerebral autoregulation can be measured continuously at the bedside by recording correlations between spontaneous fluctuations of flow velocities in the MCA on TCD ultrasonography and the mean ABP over 5-minute intervals (the Mx), thereby avoiding potentially adverse effects from artificial manipulation of the mean ABP.\textsuperscript{7} Values less than 0.3 indicate preserved autoregulation; otherwise, the autoregulation is impaired.\textsuperscript{7}
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The PRx is another bedside index of cerebrovascular pressure reactivity that correlates with Mx. It is an average value of the correlation coefficient between ICP and ABP within a time frame of 3 to 6 minutes.² A value higher than +0.2 reflects a poor reactivity, whereas a value lower than zero demonstrates excellent autoregulation.³ A positive PRx has been found to correlate with higher ICP, lower Glasgow Coma Scale score, and unfavorable outcome at 6 months after head injury,⁴ although its role is undetermined in patients with aneurysmal SAH.⁵

In prospective pilot studies, we have demonstrated that bolus systemic administration of 2 ml/kg 23.5% hypertonic saline enhances CBF and increases substrate delivery in patients with poor-grade spontaneous SAH.⁶⁻⁷ In this study, we continued our investigation to find whether the increments in CBF correlate with the associated changes in autoregulation indices (Mx and PRx) and outcome at discharge.

Clinical Material and Methods

The study was approved by the Cambridge Local Research Ethics Committee (committee numbers 01/354 and 02/392). During the periods between January 2002 and May 2002, and between November 2003 and March 2006, 35 patients (18 men and 17 women; mean age 52.4 ± 11.1 years, range 20–75 years) with poor-grade spontaneous SAH (World Federation of Neurological Societies Grades IV–V) were admitted to the Neurosciences Critical Care Unit at Addenbrooke’s Hospital, University of Cambridge and recruited for this study. The two most common locations of ruptured aneurysms were the MCA (37.1%) and anterior communicating artery (34.3%).

Exclusion criteria were traumatic SAH, confirmed pregnancy, an initial serum sodium higher than 155 mmol/L, an initial serum osmolality higher than 320 mOsm/L,⁸ and impaired renal (serum creatinine > 8.0 mmol/L) or cardiovascular function. For Xe-CT studies, the FiO₂ had to be less than 55%.

All patients were treated according to the SAH protocol, including administration of 60 mg oral nimodipine every 4 hours, continuous monitoring of ABP, heart rate, CVP, hourly urine output, fluid balance, and core temperatures. If necessary, catecholamines were used to support the ABP after adequate fluid supplementation, and were monitored with the assistance of a pulmonary arterial catheter.

When ICP monitoring was required for clinical management, an ICP transducer (Codman MicroSensor, Johnson & Johnson Medical, Ltd.) or an external ventricular drain was inserted into the nondominant frontal region. The CPP was calculated online as the difference between ABP and ICP.

The TCD Ultrasonography and Bedside Monitoring

The TCD ultrasonography examinations (DWL Multi-Dop X4) in which a 2-MHz probe was mounted on a purpose-designed headframe for continuous recording were performed as previously described.⁹ Systolic, diastolic, and mean flow velocities in both MCAs with other analog output (ABP, ICP, and CPP) were digitized through an analog-to-digital converter (DT 2814, Data Translation) and stored on a hard disk using the in-house designed BioSan.¹⁰

Time-averaged values of ICP, ABP, CPP, and the MCA flow velocities were calculated using waveform time integration for 6-second intervals. The Pearson linear moving correlation coefficients between 40 consecutive 6-second averages of flow velocities and CPP (Mx) and correlation coefficients between 40 consecutive samples of values for ICP and ABP averaged for a period of 6 seconds (PRx) were computed.¹¹⁻¹²

Throughout the whole study session (~ 4 hours), ventilator settings and the level of sedation (midazolam) and analgesia (fentanyl) were maintained constant and all physiological variables were closely observed and recorded. No additional treatment aimed at controlling ICP—such as mannitol or barbiturates—was given from 45 minutes before the study until after its completion.

Measurement of CBF

When the patient’s FiO₂ was less than 55%, Xe-CT scans were obtained for quantifying CBF. For at least 20 minutes prior to obtaining these scans, baseline data were collected. The Xe-CT studies were performed using a Somatom Sensation 4 scanner (Siemens) and XeCT System (DDP, Inc.), which had both the hardware and software for delivering Xe gas and calculating CBF. The Xe-CT scanning was performed with an inhalation of 28% Xe gas (Air Products plc.) and FiO₂ 21 to 55% depending on the patients’ ventilation needs. During Xe-CT scanning, all bedside monitoring was continued, except TCD ultrasonography, which had to be dismantled to avoid interfering with the CT scans. During the 4.5 minutes of Xe inhalation, four progressively enhanced scans were obtained.

Immediately after the first Xe-CT scanning session, 2 ml/kg of 23.5% hypertonic saline (equal to the dose of 2.9 g/kg mannitol) was slowly infused via a central venous catheter for 20 to 30 minutes. Ten minutes after the completion of this infusion, a second Xe-CT scan was obtained. After the Xe-CT procedures, TCD ultrasonography was resumed, and the bedside monitoring and recording were continued for at least 3 hours.

Under clinical indications of improving CBF, hypertonic saline was administered more than once, depending on the levels of serum sodium and osmolarity. When the patient was unable to undergo Xe-CT scanning, the entire study was performed using TCD ultrasonography.

Laboratory Examinations

Complete blood cell counts, coagulation profiles, and serum biochemistry were assessed just before the hypertonic saline was given at baseline, at the 1st hour, and then every 6 hours, for a total of 24 hours after the infusion. Arterial blood gas was sampled at 1, 2, 3, and 6 hours.

The goal in using hypertonic saline was to increase the serum sodium concentration within the range of 145 to 155 mmol/L, and the maximum rate of increase in the serum sodium was defined at 15 mmol/L/day. After hypertonic saline therapy, physiological saline (0.9%) was supplemented to keep the maximum rate of decrease in serum sodium at 10 mmol/L/day to avoid potential central pontine myelinolysis.¹³

Follow-Up Assessment

Patients were assessed at discharge from the hospital, and outcome was gauged according to the mRS.¹⁴ Favorable
and unfavorable outcomes were defined as mRS Scores 1 to 3 and mRS Scores 4 to 6, respectively.

Statistical Analysis

Analysis was performed using STATA for Windows (Intercools 8.0). Data are expressed as means ± standard deviations with 95% CIs. A probability value less than 0.05 was considered statistically significant.

Data collected from bedside monitoring, such as ABP, ICP, CPP, flow velocity, Mx, and PRx, were averaged every 30 minutes. Continuous variables were checked for normality by using the Kolmogorov statistic and compared with the baseline using the repeated measurement ANOVA. When it was significant within patients, tables of Dunnett correction were applied to identify significant changes over time.11

Analysis of CBF Measured by Xe-CT

The analysis and comparison of CBF were performed using XeCT System software. The anatomical correlation on CBF maps was achieved using an unenhanced CT scan. Each CBF map was divided into 10 ROIs, according to the major arterial areas and the subcortical nuclei. These included the anterior cerebral artery, MCA, posterior cerebral artery, putamen, and thalamus. The rCBF in each ROI was calculated by averaging the pixels in all levels. The global CBF was obtained by summarizing all rCBF values. The cerebral vascular resistance in each ROI was obtained by dividing the CPP by the rCBF. The global cerebral vascular resistance was obtained by dividing the CPP by the global CBF.

Stepwise multivariate logistic regression analysis was applied to determine the factors that might be independent predictors of unfavorable outcome, whereas a significance level of 0.05 was chosen for variable entry into the model. The odds ratio was calculated and is presented with its 95% CI.

Results

A total of 50 infusions was administered to the 35 patients: 22 patients received one infusion, 11 received two, and two received three infusions. Among the 22 patients who received one infusion only, the ICP was well controlled in 12, allowing extubation within 48 hours after the infusion; the conditions of seven continued to deteriorate as medical treatment was withdrawn; and three had persistent hyponatremia (> 155 mmol/L) or hyperosmolarity (> 320 mOsm/L), which excluded them from receiving further doses. Of the 11 patients who received two infusions, four achieved ICP control, the conditions of two deteriorated, and five had persistent hyponatremia or hyperosmolarity. Hence, no further hypertonic saline was given. The third infusion was given to two patients because of persistently high ICP. However, the conditions of both patients continued to deteriorate. Patients who achieved better outcome were more likely to have received a single infusion (p = 0.026, Fisher exact test; Table 1).

Because of the small number of patients who received a third infusion, this treatment episode was excluded from analysis. The mean intervals between the ictus and the first and second treatment episodes were 4.6 ± 3.2 and 6.8 ± 1.9 days, respectively. Seventeen patients underwent Xe-CT scanning. No rebound phenomena were observed during the entire investigation.

First Treatment Episode

Results From TCD Ultrasonography and Autoregulation Indices. Although no difference in the baseline flow velocity was found between the two sides, the baseline Mx was higher on the ipsilateral side (0.20 ± 0.92 compared with 0.01 ± 0.95, p = 0.027), indicating that the autoregulation was weaker on the ipsilateral side (Fig. 2).

As soon as the infusion started, the flow velocity in both MCAs began to accelerate. The flow velocity of the ipsilateral MCA increased maximally by 31.96% (95% CI 13.23–46.81%, p < 0.01) at the end of infusion, followed by a brief reduction by 17.97% (95% CI 9.06–26.88%, p < 0.01) at 90 minutes. These rates indicated an initial plasma expansion, following by volume contraction.
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Fig. 1. Graphs showing hemodynamic monitoring values during the first treatment episode of 2 ml/kg 23.5% hypertonic saline. Boxes represent the median value, and whiskers represent the 75th (upper hinge) and the 25th (lower hinge) percentiles. *p < 0.05 after repeated measurement ANOVA and Dunnett adjustment.

Fig. 2. Graphs showing changes in TCD ultrasonography–derived parameters during the first treatment episode of 2 ml/kg 23.5% hypertonic saline. *p < 0.05 after repeated measurement ANOVA and Dunnett adjustment.
tralateral Mx increased briefly by 0.22 ± 0.28 (95% CI 0.10–0.34, p < 0.01), which correlated with the increment in arterial acidosis at 1 hour (coefficient = 0.087, p = 0.050). No significant change was seen in the PRx.

Second Treatment Episode

No statistical differences were found between results from the first and the second treatment episodes. Because of the smaller sample size in the second treatment episode, the results showed shorter-lasting effects on ICP and flow velocity and failed to reveal statistical significance in ABP, CPP, and CVP in the second treatment episode.

Results From Xe-CT Scans. After the infusion, the CBF was augmented in all patients, compatible with the increased flow velocities noted on TCD ultrasonography. The mean increment in global CBF was 18.90% (95% CI 10.91–26.89%, p < 0.001) and was independent of baseline values. All cerebral arterial territories showed similar CBF enhancement, except the ipsilateral putamen, where the increment was of borderline significance. No significant change was seen in cerebral vascular resistance.

Blood Tests. Because there were no differences in the response between the first and the second treatment episodes, only blood tests in the first treatment episode are described. The serum sodium and osmolality increased maximally at 1 hour by 11.23 ± 4.05 mmol/L (95% CI 9.82–12.64 mmol/L, p < 0.01; Fig. 3A) and 23.21 ± 11.85 mOsm/L (95% CI 18.69–27.72 mOsm/L, p < 0.01), respectively. These hypernatremic and hyperosmotic effects persisted for longer than 24 hours. Levels of other serum electrolytes, renal function, cortisol, and adrenal corticotropic hormone were unchanged.

The hematocrit and hemoglobin decreased maximally at 1 hour by 1.47 ± 1.87% (95% CI 0.78–2.15%, p < 0.01; Fig. 3B) and 0.47 ± 0.62 g/dl (95% CI 0.24–0.70 g/dl, p < 0.01), respectively. Both returned to baseline at 3 hours. At 12 hours, a second episode of hemodilution occurred. The reductions were 2.63 ± 2.13% (95% CI 1.45–3.81%, p < 0.01) and 0.67 ± 0.42 g/dl (95% CI 0.39–0.96 g/dl, p < 0.01), respectively. Other hematological parameters were unchanged.

Examination of the arterial blood gas revealed increased acidosis and hypoxia within the first 2 hours; the H+ increased by 4.18 ± 5.00 mmol/L (95% CI 2.20–6.16 mmol/L, p < 0.01; Fig. 3C), the bicarbonate level decreased by 0.75 ± 1.22 mmol/L (95% CI 0.23–1.26 mmol/L, p < 0.05), and the PaO₂ was reduced by 2.37 ± 2.83 kPa (95% CI 1.20–3.54 kPa, p < 0.01) at 1 hour. At 2 hours, the H+ increased by 3.28 ± 4.69 mmol/L (95% CI 0.57–5.99 mmol/L, p < 0.05) and the PaO₂ reduced by 2.71 ± 4.98 kPa (95% CI 0.17–5.58 kPa, p < 0.05), while the bicarbonate level returned to the baseline (Fig. 3C and D). The arterial oxygen saturation (SaO₂, which was constantly maintained ~ 98–100%), glucose, and lactate levels were unchanged. Consequently, the total arterial O₂ content (calculated from 1.39 × hemoglobin × SaO₂ + 0.0031 × PaO₂) was significantly reduced by 0.77 ± 0.85 ml (95% CI 0.39–1.15 ml, p < 0.01) at the 1st hour.

Apparent polyuria was seen during the first 3 hours after hypertonic saline therapy. The increments in urine output were 94.0 ± 135.33 ml (95% CI 47.51–140.49 ml, p < 0.01) at 1 hour, 94.29 ± 148.75 ml (95% CI 43.19–145.38 ml, p < 0.01) at 2 hours, and 52.97 ml (95% CI 12.74–93.20 ml, p < 0.05) at 3 hours (Fig. 3E). The hourly fluid balances were −121.83 ± 192.44 ml (95% CI −187.93 to −55.72 ml, p < 0.01) at the 1st hour, and −116.80 ± 227.37 ml (95% CI −194.90 to −38.70 ml, p < 0.05) at the 2nd hour (Fig. 3F). However, no significant changes were found in urine osmolarity.

Correlation of CBF Enhancement and Outcome

Of the 35 patients with poor-grade SAH, 14 (40.0%) achieved a favorable outcome (mRS Score 1–3) and 21 (60%) had an unfavorable outcome (mRS Score 4–6). Eleven patients died during hospitalization (mortality rate 31.4%).

Compared with patients with an unfavorable outcome, the increment in CBF after hypertonic saline therapy was more than double in those with a favorable outcome (29.04 ± 19.40% compared with 13.37 ± 10.14%, p = 0.042, or the mean difference in increments 7.16 ml/100 g × min, 95% CI 0.17–5.58 ml/100 g × min, p = 0.014; Fig. 4). Furthermore, patients with a favorable outcome at discharge from the hospital tended to have a higher cortisol level (p = 0.093), lower ICP (p = 0.068), and higher arterial bicarbonate levels (p = 0.068) before the hypertonic saline therapy. They also demonstrated a higher serum osmolality at 24 hours (p = 0.130, Table 2).

Logistic regression analyses showed that the degree of CBF enhancement following hypertonic saline therapy was associated with a favorable outcome. Each 1–ml/100 g tissue × min increment in CBF was associated with 27% increase in the chance of a favorable outcome (odds ratio 1.27 per ml/100 g tissue × min, 95% CI 1.01–1.62 per ml/100 g tissue × min, p = 0.045).

Discussion

Significance of the Study

Following aneurysmal SAH, neurological deficits are potentially reversible if low CBF can be avoided. Given the diffuse nature of aneurysmal SAH, local vascular therapies (such as angioplasty) for CBF augmentation have proved unsatisfactory. In this study we adopted a global approach to enhance CBF in patients with poor-grade aneurysmal SAH who are very likely to suffer cerebral ischemia. Despite the transient hyperchloremic and hemodilutional acidosis in the 1st hour after the hypertonic saline infusion, no detectable clinical impact was seen.

Characteristics of the CBF augmentation by hypertonic saline therapy can be summarized as follows: 1) The CBF enhancement is independent of the baseline. 2) The CBF enhancement is nonsselective and does not compromise any particular type of brain tissue. 3) The CBF enhancement by hypertonic saline is much more durable than other commonly prescribed hyperosmotic agents, that is, mannitol or glycerol. 4) Increased CBF has been shown to deliver more energy substrates and O₂ available for cerebral metabolism.

Mechanisms of CBF Augmentation by Hypertonic Saline

Mechanisms of CBF enhancement by hypertonic saline
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include the built-up hyperosmolarity, creating a gradient to remove free water from the interstitial and intracellular compartments into the intravascular space. This causes an associated acute plasma expansion with hemodilution, increased ABP, and reduced vascular resistance.\textsuperscript{21,34} The prolonged hyperosmolarity seems beneficial, because patients with a favorable outcome had higher serum osmolarity levels at 24 hours.

Hypertonic saline has been found to have inotropic effects, derived from improvement in cardiac microcirculation and contractility.\textsuperscript{45} Stroke volume is increased, but the heart rate is unchanged.\textsuperscript{17} Furthermore, it has been discovered that the plasma level of endogenous epinephrine and sympathetic activities also increase during hypertonic saline therapy.\textsuperscript{27} The hypertensive, hypervolemic, and hemodilution effect mentioned earlier is similar to the triple-H therapy commonly used to reverse vasospasm-related cerebral ischemia,\textsuperscript{26} and the magnitude of CBF enhancement seems to be compatible with the extent of CPP increment.

However, we have observed significant polyuria in the first 3 hours. In addition to the hyperosmolarity, the diuresis may be caused by enhanced renal perfusion,\textsuperscript{23} which in

\textbf{Fig. 3.} Box plots showing physiological parameters obtained during the first treatment episode of 2 ml/kg 23.5% hypertonic saline. *p \textless 0.05 after repeated measurement ANOVA and Dunnett’s adjustment.

\textbf{Fig. 4.} Box plots showing a comparison of CBF-enhancing effects by hypertonic saline therapy between patients with unfavorable and favorable outcomes. The mean difference in increments was 7.16 ml/100g × min (95% CI 1.65–12.66 ml/100g × min, p = 0.014).
The lowering effect of hypertonic saline on the ipsilateral side of the ruptured aneurysm may have profound dehydrating effects on the intracranial components. The lowering of ICP can be seen as soon as plasma expansion and hemodilution occur. The time taken to reach the maximum reduction in ICP and the total duration of the effect depend on the dose of sodium. The integrity of the BBB may be important for hypertonic saline to achieve this effect, given that the CPP generally improves at the same time.

We did not find significant changes in the PRx during or after hypertonic saline therapy, because the ICP-derived property of the PRx cannot efficiently detect the side-related differences. Moreover, a radical decrease in ICP may counteract detrimental changes caused by short-term vasodilation. Therefore, the value of applying the PRx measurement to patients with aneurysmal SAH needs to be assessed using a larger number of patients in the future.

Limitations of Using Hypertonic Saline

Although hypertonic saline has been used for reversing the effects of hypovolemic shock, the safety of repeated application is limited by serum sodium levels and osmolarity. The beneficial effects of hypernatremia are associated with potentially deleterious effects of hyperchloremia and inhibition of resorption of bicarbonate from the proximal renal tubules. Hence, the induced acidosis by hypertonic saline is proportional to the hemodilution and extracellular volume expansion. Because we have found that a higher arterial bicarbonate level before hypertonic saline therapy seems to be associated with favorable outcome, additional measures to reduce the potentially adverse effects from hyperchloremic and hemodilutional acidosis may be beneficial in selected patients. Although additional sodium bicarbonate and sodium lactate have been used for this purpose, neither can significantly alleviate the acidosis. Hypertonic saline made from a 50:50 acetate/chloride mixture has been shown to effectively buffer against metabolic acidosis; therefore, an additional supplement of sodium acetate could be explored if hypertonic saline therapy is to be repeated.

The borderline association between the baseline cortisol level and the outcome after hypertonic saline therapy implies that additional hydrocortisone before treatment may assist osmotherapy. Indeed, a prophylactic supplement of hydrocortisone has been shown to buffer against possible detrimental changes caused by short-term vasodilation. Moreover, an additional supplement of hydrocortisone may facilitate alleviating acidosis induced by hypernatremia.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unfavorable (95% CI)</th>
<th>Favorable (95% CI)</th>
<th>Difference (95% CI)</th>
<th>p Value</th>
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<td>baseline level ICP (mm Hg)</td>
<td>18.25 ± 8.83 (14.12–22.38)</td>
<td>12.59 ± 7.69 (7.94–17.23)</td>
<td>-5.66 (-11.77–0.44)</td>
<td>0.068</td>
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<tr>
<td>cortisol (nmol/L)</td>
<td>338.36 ± 189.50 (211.06–467.67)</td>
<td>496.29 ± 171.32 (337.84–654.73)</td>
<td>157.92 (-29.54–345.38)</td>
<td>0.093</td>
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<tr>
<td>arterial bicarbonate (mmol/L)</td>
<td>21.47 ± 3.09 (19.98–2.96)</td>
<td>23.50 ± 2.57 (21.87–25.13)</td>
<td>2.03 (-0.16–4.22)</td>
<td>0.068</td>
</tr>
<tr>
<td>osmolarity at 24 hrs (mOsm/L)</td>
<td>311.99 ± 16.51 (304.26–319.71)</td>
<td>361.19 ± 141.52 (259.95–462.43)</td>
<td>49.21 (-15.36–113.77)</td>
<td>0.130</td>
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* Mean values are presented as the means ± standard deviations.
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Limitations of the Study

Although this is a prospective observational study, the sample size is relatively small and is not powered to detect a clinically relevant difference in the outcome between combined therapies. The results encourage further use and observation of the hypertonic saline therapy. Appropriate use of acid-base buffers and supplements with hydrocortisone may be an avenue to pursue further investigation in the clinical environment.

Conclusions

The results of this study demonstrate a correlation between bolus systemic hypertonic saline therapy and outcome in patients with poor-grade SAH. These effects may be associated with integrities of BBB or cerebral autoregulation. Combined therapy to reduce the accompanying hyperchloremic hemodilutional acidosis may need further investigation in future studies.

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