Hypertonic saline (7.2%) in 6% hydroxyethyl starch reduces intracranial pressure and improves hemodynamics in a placebo-controlled study involving stable patients with subarachnoid hemorrhage*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe the effects of hypertonic saline (7.2% saline in 6% hydroxyethyl starch 200/0.5) on intracranial pressure.
2. Compare the effects of hypertonic with normal saline on cerebral perfusion pressure.
3. Use this information in a clinical setting.

All authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

Lippincott CME Institute, Inc., has identified and resolved all faculty conflicts of interest regarding this educational activity.

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Objective: **To compare the effects of a bolus infusion of hypertonic saline hydroxyethyl starch with the effects of normal saline (placebo) on intracranial pressure (ICP) and cerebral perfusion pressure in patients with spontaneous subarachnoid hemorrhage.**

Design and Setting: **Prospective, randomized, single-blinded, placebo-controlled study in a university hospital.**

Patients: **A total of 22 mechanically ventilated patients with spontaneous subarachnoid hemorrhage with stable ICP between 10 and 20 mm Hg.**

Interventions: **During the course of 30 mins, 2 mL/kg of either 7.2% saline in 6% hydroxyethyl starch 200/0.5 (HSS) or of normal saline was infused. The effects were observed for another 180 mins.**

Measurements and Main Results: **Mean change in ICP after intervention (ΔICP) calculated from the average of all observations was −3.3 (SD 2.6) mm Hg in the HSS group vs. −0.3 (SD 1.3) mm Hg in the normal saline group. Mean difference between the groups (HSS − normal saline) was −3.0 mm Hg (95% confidence interval, −4.9 to −1.1; $p = .004$). Mean peak change after HSS was −5.6 (range, −0.8 to −12.2) mm Hg after 64 (range, 40 to 115) mins. Mean difference in cerebral perfusion pressure change between the groups (HSS − normal saline) was 5.4 mm Hg (95% confidence interval, 2.2 to 8.6; $p = .002$), and mean difference in cardiac index change, measured as the area under the curve for the whole study period, corresponded to 0.2 $L \cdot min^{-1} \cdot m^{-2}$ (95% confidence interval, 0.03 to 0.4; $p = .025$).**

Conclusions: **In this placebo-controlled study involving spontaneous subarachnoid hemorrhage patients with normal to moderately increased ICP, 2 mL/kg HSS reduced ICP and increased cerebral perfusion pressure significantly. Maximum effect was reached at twice the infusion time of 30 mins. There were also beneficial hemodynamic effects with increased cardiac index in the HSS group. (Crit Care Med 2006; 34:2912–2917)**

KEY WORDS: brain edema; hypertonic solutions; intracranial hypertension; intracranial pressure; saline solution; hypertonic; subarachnoid hemorrhage

Hypertonic saline solutions are an alternative to mannitol in the treatment of intracranial hypertension (1, 2). Repeated administrations of mannitol are associated with adverse effects such as acute renal failure (3–5), hypovolemia (3, 5, 6), and rebound increase in intracranial pressure (ICP) (2, 7–11). Hypertonic saline has attenuated intracranial hypertension in a number of clinical trials (12–17). In studies comparing hypertonic saline with mannitol, the results generally favor hypertonic saline (18–22).

One of the limitations of these studies has been the lack of placebo control, which makes it impossible to prove how much of the measured effect can be attributed to the hypertonic saline intervention. The administration of osmotherapy is often one of several interventions applied almost simultaneously to unstable patients. The fact that ICP is dangerously high at the time of intervention makes the use of a placebo unethical. We have previously, in a prospective observational study of spontaneous subarachnoid hemorrhage (SAH) patients with ICP of

*See also p. 3037.

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DOI: 10.1097/01.CCM.0000245665.46789.7C

>20 mm Hg, demonstrated an ICP reduction from a mean of 25 mm Hg to a mean of 11 mm Hg after infusion of a hypertonic saline solution (23). We could also report an increase in cerebral perfusion pressure (CPP). This was done in a controlled intensive care setting. All other factors that influence ICP and CPP were kept stable during the trial. The aim of the present study was to validate these findings with an even more laboratory-like trial in which the patients were stable before inclusion and hypertonic saline was compared with a solution that was not expected to influence ICP and CPP. The present study also addresses the question as to when one can expect to reach the maximum effect of a hypertonic saline infusion.

PATIENTS AND METHODS

This was a single-center study, performed in the intensive care unit of a university hospital that treats about 170 acute SAH patients annually. The Regional Ethics Committee for Medical Research and the Norwegian Medicines Agency approved the protocol for the study. All patients would be unconscious during inclusion. A thorough evaluation of the risks and possible benefits to the patients was therefore especially important, as underlined in the Helsinki Declaration. Our search of the relevant literature indicated minimal risk of adverse effects. Promising clinical results justified further clinical trials with this critically ill patient population. Informed consent was impossible to obtain. According to Norwegian legislation, one cannot obtain a legally valid consent to medical research by proxy. Thus, in agreement with our ethics committee, close relatives were given oral and written information about the study when present in the intensive care unit.

Study Protocol. To perform a study with a placebo group, we could not address the target patient population for osmotherapy, namely, those with ICP of >20–25 mm Hg. We therefore included intensive care patients with an acute, spontaneous SAH, with stable ICP in the range of 10–20 mm Hg. They needed to be >18 yrs of age, sedated, mechanically ventilated, have stable hemodynamics, and serum sodium of <160 mmol/L. If the inclusion criteria were met, the patients either received a normal saline solution (NS group) or a hypertonic saline solution (HSS group) according to a computer-generated, randomized list. As a continuous intravenous infusion for 30 mins, 2 mL/kg of the study solution was administered into a central venous catheter using an infusion pump. The placebo was a 0.9% saline solution (Fresenius Kabi AG, Bad Homburgh v.d.h., Germany), and the hypertonic solution was a 7.2% saline in 6% hydroxyethyl starch 200/0.5 solution (HyperHAES, Fresenius Kabi AG). The observation period lasted from 10 mins before until 210 mins after the start of the infusion. Need for rescue treatment was defined by treatment failure limits for ICP and CPP, which were an ICP of >20 mm Hg and a CPP of <60 mm Hg. Unless these limits were reached during the observation period, the ventilation variables were kept unaltered, the infusion rates for vasopressors, analgesics, sedatives, and fluids were kept stable, the resistance in the external ventricular drainage (EVD) was unchanged, and the patients were neither stimulated nor moved.

Data Acquisition. ICP (intraparenchymal device, Codman, Raynham, MA), CPP, heart rate, arterial and central venous pressures (zeroed at the level of the right atrium of the heart), and peripheral oxygen saturation (Siemens AG, Munich, Germany) were registered electronically every 30 secs (LabView, National Instruments, Austin, TX). The primary author manually removed false arterial blood pressure values due to blood sampling. This typically affected three consecutive recordings (90 secs). The use of an intraparenchymal device for ICP monitoring is routine practice in our hospital in patients with severe SAH. This allows continuous ICP and CPP monitoring during EVD, even in situations in which the EVD catheter is blocked by blood clots. No additional sensors were used for the purpose of this study.

Arterial blood gases, pH, hemoglobin, and sodium (ABL 725, Radiometer, Denmark) were measured before and 30, 90, and 210 mins after start of the infusion. Cardiac index, intrathoracic blood volume index, and extravascular lung water index were registered before and 30, 90, and 210 mins after start of infusion by use of the PiCCO system (PiCCO, Pulsion Medical Systems, Munich, Germany) (24, 25). The catheters were introduced via the femoral artery and the internal jugular or subclavian vein.

Primary Outcome Variables. Primary outcome variables were: 1) changes in ICP, 2) difference between the two groups in ΔICP calculated from the mean of all observations in each patient during the observation period, and 3) the difference between the groups in maximum ΔICP.

Secondary Outcome Variables. Secondary outcome variables were: 1) changes in CPP; 2) changes in cardiac output, intrathoracic blood volume, and extravascular lung water; and 3) changes in serum sodium levels.

Estimate of Number of Patients Needed for the Study. Study size was calculated based on difference between the groups in maximal effect on ICP. We defined a difference of 4 mm Hg as clinically relevant within the current ICP range. With a SD of 2, we needed ten patients in each group to achieve a power of 90% and alpha of 1%.

Randomization. A person not otherwise involved in the study prepared a computer-generated list with alternating block sizes of four and six. The examiners were unaware of the randomization method and unaware of the block size. Group allocations for all patients were stored in sealed envelopes marked with consecutive patient numbers only. To avoid examiner bias, the envelopes remained unopened until inclusion was decided on and baseline data logging was established. No patients were withdrawn after inclusion. The randomization code was not revealed until the study was completed and all data had been entered and validated.

Statistics. The mean value of each patient's measured variables from the 5 mins of registration before the infusion served as the baseline. For data acquired electronically every 30 secs, the mean values of all 5-min periods throughout the 210-min observation period were calculated and used for analysis. As recommended for statistical analysis of serial measurements by Matthews et al. (26), we calculated the area under the curve for the different variables in each patient and standardized by the length of the study, 210 mins, to get the mean change for the whole period. For variables for which time intervals between successive observations were constant, the simple mean of the observations was used. To assess differences between the groups, unpaired Student's *t*-tests were used, with Welch correction when there was unequal variance or Mann-Whitney tests when normality tests failed (GraphPad InStat version 3.05, GraphPad Software, San Diego, CA).

RESULTS

From April 2002 through October 2004, 22 patients with acute, spontaneous SAH were included, 11 in each group. A total of 21 patients had hemorrhaged because of a ruptured aneurysm, and one patient was diagnosed with a fusiform dilation of the left vertebral artery. Except for this last patient, all patients either were coiled or clipped (Table 1). All patients were mechanically ventilated. They were all treated with nimodipine and all but one with vasopressors. A majority of the patients had ongoing EVD (i.e., drainage of cerebrospinal fluid from one or both cerebral lateral ventricles). Hemodynamics and ICP were stable before inclusion in the study. There were no significant demographic differences between the groups (Table 1).

All patients included were reported according to the intention-to-treat principle. No patients were withdrawn after inclusion. One patient in the NS group needed rescue treatment at 96 mins after the start of infusion due to increased ICP and reduced CPP. This patient was then given 2 mL/kg HSS during the course of 20 mins. ICP decreased from 24 mm Hg

to 13 mm Hg and remained stable for the next 3 hrs. CPP increased to above our treatment threshold of 60 mm Hg. We did not strengthen the results by extrapolating the ICP and CPP values measured at 96 mins to the remaining observation period. Instead, baseline values were used for the period of 97 to 210 mins in this patient. Only 5 of 946 scheduled measurements of the different variables were lacking because of technical failure. Missing values were replaced by the mean of the preceding and the following measurement.

Changes in ICP. The reduction in ICP from baseline, measured as average ΔICP during the study period, was significantly greater in the HSS group compared with the NS group ($p = .004$) (Table 2). The same variable's temporal development is shown in Figure 1. The mean maximal change in ICP from baseline in the HSS group was −5.6 (range, −0.8 to −12.2) mm Hg and came after 64 (range, 40 to 115) mins. As the curve in Figure 1 shows, this was not a meaningful value to calculate for the NS group. Mean ICP for the last 5 mins of the study were still less than baseline in 8 of 11 patients administered HSS. The last three had a mean ΔICP between 0 and +1 mm Hg compared with baseline.

Changes in CPP. The average ΔCPP during the study period was significantly higher in the HSS group ($p = .002$) (Table 2, Fig. 2). The average ΔCPP after HSS was 5.6 mm Hg higher than baseline, whereas ICP decreased 3.3 mm Hg. This indicates that HSS has a separate effect on blood pressure. Average change in mean arterial pressure was 2.3 mm Hg after HSS, but this was not statistically different from the change in mean arterial pressure in the NS group. There was also no significant difference in heart rate (Table 2).

Changes in Cardiac Index, Intrathoracic Blood Volume Index, and Extravascular Lung Water Index. These data were collected at baseline and at 30, 90, and 210 mins after start of the infusion. There were no significant differences between the groups at baseline (Table 2). Cardiac index increased in the HSS group. Mean change in cardiac index compared with baseline, measured as area under the curve divided by 210 mins, was 0.2 $L \cdot min^{-1} \cdot m^{-2}$ higher than in the NS group (Table 2). The difference is statistically significant. Given the small number of measurements taken, we can draw no conclusion about time of maximum effect on cardiac index, but we measured peak effect at the 30-min recording. At that point, change in cardiac index was 0.5 (range, −0.1 to 1.5) $L \cdot min^{-1} \cdot m^{-2}$ in the HSS group. Intrathoracic blood volume index and extravascular lung water index were not significantly different between groups at baseline, nor were there significant differences in the area under the curve values between the groups (Table 2).

Changes in Serum Sodium. At baseline, mean serum sodium in the HSS group was 148 (range, 139 to 157) mmol/L vs. 145 (range, 141 to 151) mmol/L in the NS group. The mean difference was 3.0 mmol/L (95% confidence interval, −1.2 to 7.2 mmol/L; $p = .15$). There were no significant changes in the NS group during the study. In the HSS group, a maximum serum sodium increase of 5.6 (range, 4 to 7) mmol/L was measured at 30 mins (i.e., at the end of the study's drug infusion). At the conclusion of the observation period, the level was 3.3 (range, 1 to 5) mmol/L greater than baseline. Both the peak value and the end value increased significantly compared with baseline ($p < .0001$). The highest osmolality measured was 332 mOsm/kg.

Changes in EVD. As shown in Table 1, all but three patients had ongoing EVD. The amounts drained during the hour before the study showed no difference between the groups: mean of 12.5 (range, 5 to 28) mL in the HSS group vs. 12.2 (range, 2 to 25) mL in the NS group, with

Table 1. Demographic data

	HSS	NS	*p* Value
Age in years, mean (SD)	50.1 (10.5)	55.2 (10.8)	.28[a]
Men/women	3/8	1/10	.58[b]
SAPS II score, mean (SD)	40.5 (11.1)	47.0 (12.1)	.20[a]
Hunt and Hess score, median (range)	5 (3 to 5)	5 (2 to 5)	.42[c]
Days since insult, mean (SD)	3.9 (2.9)	2.6 (1.7)	.23[a]
EVD	10/11	9/11	.53[b]
IVH	8/11	8/11	1.0[b]
Number of patients coiled[d]	7/11	5/11	.67[b]

HSS, 7.2% saline in 6% hydroxyethyl starch; NS, normal saline; SAPS, Simplified Acute Physiology Score; EVD, external ventricular drainage; IVH, intraventricular hemorrhage.

[a]Unpaired *t*-test; [b]chi-square test; [c]Mann-Whitney test; [d]remaining patients were clipped, except for one patient in the HSS group for whom no option was available for securing the source of bleeding.

Table 2. Physiologic data and differences in physiologic data between the groups

	HSS, Mean (SD)	NS, Mean (SD)	Mean Difference[a]
ICP, mm Hg, baseline	15.1 (2.9)	15.5 (2.5)	−0.4 (−2.8 to 2.0), $p = .74$
ΔICP, mm Hg, average during study period	−3.3 (2.6)	−0.3 (1.3)	−3.0 (−4.9 to −1.1), $p = .004$[b]
CPP, mm Hg, baseline	71.6 (7.9)	70.6 (5.4)	1.0 (−5.0 to 7.0), $p = .73$
ΔCPP, mm Hg, average during study period	5.6 (4.2)	0.2 (2.8)	5.4 (2.2 to 8.6), $p = .002$
MAP, mm Hg, baseline	87.0 (7.6)	84.5 (2.9)	2.4 (−3.2 to 8.1), $p = .36$[b]
ΔMAP, mm Hg, average during study period	2.3 (3.9)	0.1 (2.8)	2.2 (−0.8 to 5.2), $p = .15$
HR, mm Hg, baseline	71(13)	67 (14)	4 (−8 to 16), $p = .48$
ΔHR, mm Hg, average during study period	2.0 (3.0)	0.9 (3.4)	1.1 (−1.8 to 4.0), $p = .44$
CI, $L \cdot min^{-1} \cdot m^{-2}$, baseline	4.0 (0.8)	3.7 (0.5)	0.3 (−0.3 to 0.9), $p = .36$
ΔCI, $L \cdot min^{-1} \cdot m^{-2}$, AUC standardized by time	0.27 (0.23)	0.06 (0.18)	0.21 (0.03 to 0.39), $p = .025$
ITBI, mL/m^2, baseline	883 (192)	932 (174)	−49 (−212 to 114), $p = .54$
ΔITBI, mL/m^2, AUC standardized by time	17.3 (38.3)	14.2 (78.3)	3.1 (−53.3 to 59.5), $p = .91$[b]
ELWI, mL/kg, baseline	8.0 (2.3)	9.2 (3.5)	−1.2 (−3.8 to 1.4), $p = .36$
ΔELWI, mL/kg, AUC standardized by time	−0.03 (0.4)	0.5 (1.0)	−0.6 (−1.3 to 0.2), $p = .12$[b]

HSS, 7.2% saline in 6% hydroxyethyl starch; NS, normal saline; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MAP; mean arterial pressure, HR, heart rate; CI, cardiac index; ITBI, intrathoracic blood volume index; ELWI, extravascular lung H_2O index.

[a]Results from unpaired *t*-test, mean (HSS - NS) difference (95% confidence interval); [b]*p* value with Welch correction.

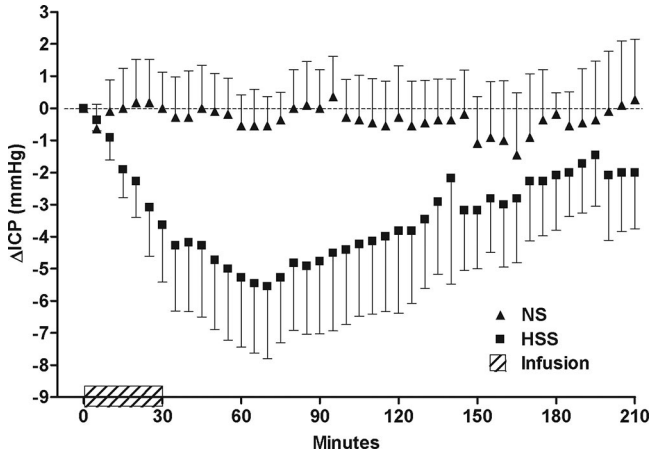

Figure 1. Changes in intracranial pressure (*ICP*). Each *time point* represents the mean of the registrations of the preceding 5 mins; *error bars* display the 95% confidence interval. *NS*, normal saline group; *HSS*, 7.2% saline in 6% hydroxyethyl starch group.

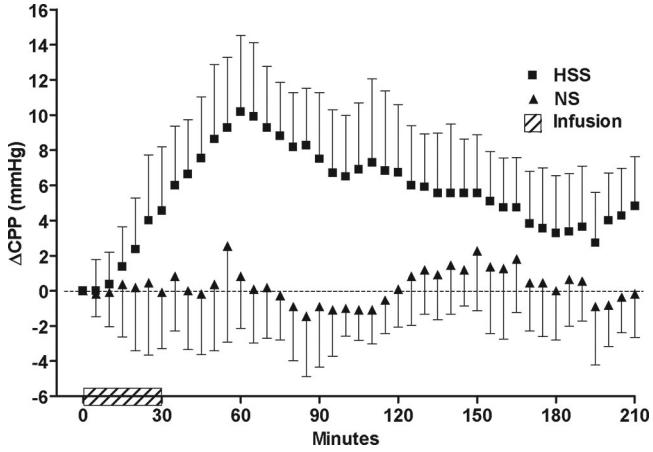

Figure 2. Changes in cerebral perfusion pressure (*CPP*). Each *time point* represents the mean of the registrations of the preceding 5 mins; *error bars* display the 95% confidence interval. *NS*, normal saline group; *HSS*, 7.2% saline in 6% hydroxyethyl starch group.

a mean difference 0.3 mL (95% confidence interval, −6.6 to 7.2 mL; $p = .93$). The volume was significantly less during the first hour of the study in the HSS group, with a mean difference compared with the previous hour of −8.2 mL (95% confidence interval, −13.9 to −2.5 mL; $p = .008$). This reduction was also significantly greater than in the NS group, with a mean difference (HSS − NS) of −6.3 mL (95% confidence interval, −11.5 to −1.1 mL; $p = .02$).

Protocol Violation. The fifth patient in the HSS group had a baseline ICP of 16 mm Hg when included and ICP remained at ±1 mm Hg throughout the observation period. Two days later, it was discovered that the zero level of the measuring device had drifted. The correct ICP was 15 mm Hg lower than displayed. We therefore have reason to suspect that this patient's ICP at the time of inclusion was significantly less than 10 mm Hg, perhaps close to zero. If so, this patient should not have been included. Still, the results are included according to the intention-to-treat principle. If excluded for a "per protocol" analyses, this would enhance statistical significance because this patient represents a nonresponder in the HSS group.

DISCUSSION

Comparing infusion of 2 mL/kg 7.2% saline in 6% hydroxyethyl starch (HSS) with NS in a laboratory-like model, this study has confirmed the ability of HSS to reduce ICP and increase CPP in SAH patients. All the physiologic variables measured in the NS group fluctuated around baseline values throughout the 210-min study period, except for the one patient who needed rescue therapy. This demonstrates that the patients included were stable and the study design was valid, allowing us to conclude that the statistically significant effects measured for ICP, CPP, and cardiac index in the HSS group can be attributed to the infusion of the hypertonic saline solution.

The study design implies that the patient population has normal to only moderately increased ICP. This was necessary to conduct a placebo-controlled trial. In a clinical setting, these patients would not be candidates for osmotherapy. The question is whether our results can be extrapolated to SAH patients with severe intracranial hypertension. We think they can. The results are in accordance with the results from our previously published, uncontrolled study that was conducted in very much the same manner (23). That study had an equally long observation period of 210 mins and used the same inclusion criteria, except that the patients were to have ICP of >20 mm Hg. The change in ICP with time is very much alike in the two studies. The absolute effect on ICP after HSS was less in the current study, with a mean maximum ICP reduction of 5.6 mm Hg, compared with our previous study, which had a mean reduction of 14.3 mm Hg. This is most likely related to the fact that baseline ICP was lower in the current study. With ICP in the range of 10 to 20 mm Hg we are not on the steep part of the intracranial pressure-volume curve. Equal changes in volume will have less effect on pressure compared with patients having ICP of >20 mm Hg. The current placebo-controlled study clearly describes the effects of HSS. It greatly strengthens our previous findings obtained with a relevant patient population. The magnitude of the expected effects in clinical practice would be in the range documented in that study (23).

Maximum effect was reached at a mean of 64 mins in the current study when 2 mL/kg hypertonic solution was infused in 30 mins. In the previous study, the infusion was given in 20 mins. Peak effect was reached at a mean of 40 mins. In a recent study involving patients with traumatic brain injury by Battison et al. (21), 100 mL of 7.5% saline/6% dextran was infused in 5 mins in comparison with mannitol. The exact time of maximum ICP reduction was not stated, but from the enclosed time-series plot, it seems that maximum effect was typically reached between 20 and 30 mins. The majority of the effect is thus not instan-

taneous, like the effect of manipulating $Paco_2$. This corresponds to the idea that the osmotic effect is a major contributor to the overall effect (27, 28).

The fact that 10 of 11 patients receiving HSS had ongoing EVD, most likely reduced the magnitude of ICP change. The HSS infusion was accompanied by a reduction of the EVD volume, which was probably primarily caused by the ICP reduction *per se*. There may also be other explanations. There is documentation that mannitol decreases the production of cerebrospinal fluid (29, 30), but we have found no publications directly addressing the effect of hypertonic saline on cerebrospinal fluid formation. Indirectly, however, HSS might reduce cerebrospinal fluid formation via the increase in serum osmolality. This has been demonstrated with glycine (31).

Was the choice and volume of study solutions adequate? As the placebo, we chose normal saline. This, of course, is a slightly hypertonic solution with a sodium content of 154 mmol/L. Given normal serum sodium levels of 140 mmol/L, this would weaken its perceived "placebo" effect. We reasoned that this was more acceptable than strengthening the results by using a slightly hypotonic solution such as lactated Ringer. As it turned out, both groups had increased sodium levels of 148 and 145 mmol/L. This made normal saline more suited as the placebo than we had foreseen. Saline solutions of 7.2% to 7.5% in hetastarch or dextran have been extensively studied in trials on small-volume resuscitation (32). The usual dose has been 4 mL/kg. This dose can be regarded as safe. From previous experience, we expected 2 mL/kg to be sufficient for a reliable effect on ICP without increasing serum sodium more than 5 to 6 mmol/L. We would also argue that inter-individual differences were reduced by using a volume based on patient weight rather than a fixed volume. For comparison, it was important to use the same dose as used in our previous study (23). Based on the results from that study, we would now recommend that the initial bolus be <2 mL/kg 7.2% HSS to not create larger fluctuations in ICP than needed or to exhaust too rapidly the therapeutic possibilities of hypertonic saline.

We have found only two other studies comparing hypertonic saline with a normal saline placebo in patients with increased ICP. Both were done in children with traumatic brain injury. Fisher et al. (33) compared a bolus of 3% saline with a placebo, demonstrating lower ICP in the hypertonic saline group. Simma et al. (34) compared 1.7% saline with Ringer lactate infusion during the course of 72 hrs, targeting a serum sodium level of 145 to 150 mmol/L in the saline group. They found lower ICP, fewer complications, and need for fewer interventions in the hypertonic saline group. The study by Simma et al. (34) utilizes a model very different from our study, whereas the model used by Fisher et al. (33) is not so different. A bolus was given, and the effect was observed for 2 hrs. They reported a significant difference between average ICP during the observation period of 15.8 mm Hg and an ICP baseline of 19.9 mm Hg in the hypertonic saline group. This corresponds to our finding of ΔICP of -3.3 mm Hg in the HSS group; the differences being, however, lower baseline ICP, lower osmotic load, and longer infusion time in our study. In addition, the differences between children and adults and traumatic brain injury vs. SAH are important. Our study offers a description of how ICP and CPP change with time, which is lacking in previous studies, and our study contains more detailed information on hemodynamics.

Baseline serum sodium was increased in both groups. This was most probably caused by our use of normal saline as a standard solution in patients with intracranial diseases in the days before inclusion in this study. The patients were not subject to volume restriction. This is supported by baseline intrathoracic blood volume index in the normal range (Table 2). The changes in serum sodium show an inverse pattern to the changes in ICP. We found this both in the current and in the previous trial. After an initial increase caused by HSS infusion, the sodium level decreases with time toward baseline. The clinical implication of this is that it makes sense to continue with a slow infusion of HSS after the initial bolus to maintain the increased serum sodium level. Doing this, one could expect to maintain the desired effect on ICP for a longer period. Indeed, promising results have been published concerning the use of continuous infusion of hypertonic saline in pediatric patients with traumatic brain injury (16, 34). On the other hand, others have found unfavorable results in adult head trauma patients given prophylactic infusions of hypertonic saline (35). The results are conflicting, and none of these trials included SAH patients. SAH patients with limited ischemic damage have relatively limited disruption of the blood–brain barrier and might therefore be well suited for osmotherapy compared with patients having widespread disruption of the blood–brain barrier. The problems with vasospasm after SAH can strengthen the indication for hypertonic saline. Suarez et al. (36) have published a retrospective study on hyponatremic patients with vasospasm after SAH. Their focus was not on intracranial hypertension, and the authors only concluded on the safety of hypertonic saline infusion. The question as to whether bolus doses or continuous infusion represent the better strategy remains unanswered.

Hypovolemia is among the possible adverse effects related to mannitol. It is therefore reassuring to see that hemodynamic stability is well maintained with HSS. Intrathoracic blood volume is maintained and cardiac index is improved in the HSS group. Based on documentation from small-volume hypertonic resuscitation research, one can expect this hemodynamic effect to be longer lasting after an infusion of hypertonic saline in hetastarch or dextran compared with hypertonic saline alone (32). This is beneficial in patients needing vasopressor support to maintain a sufficient CPP. From the fact that there were no changes in intrathoracic blood volume index or extravascular lung water index, we can also conclude that there were no signs of overhydration or extravasation of water in the lungs.

We have not recorded any adverse effects in the current study. In particular, we saw no indications of an increase in ICP needing intervention at the conclusion of the observation period. However, it is important to recognize that issues concerning safety can only be studied to a very modest degree in a small, short-period study like the present.

CONCLUSIONS

A volume of 2 mL/kg 7.2% saline in 6% hydroxyethyl starch 200/0.5 (HSS) reduced ICP and increased CPP significantly in SAH patients with normal to moderately increased ICP, whereas there were no changes in the placebo group. The effects of HSS reached their maximum at twice the infusion time of 30 mins. There were also beneficial hemodynamic effects with increased cardiac index in the HSS group. All changes can be attributed to HSS because the patients

were otherwise stable and there were no changes in the placebo group.

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