Original Article

Comparison of Preoperative Hypertonic Saline versus Mannitol for Intraoperative Brain Relaxation and Early Postoperative Outcome among Patients with Cerebral Low-grade Glioma: A Prospective Study

Abstract

Introduction: Hypertonic saline (HS) has an important role in the treatment of raised intracranial pressure after traumatic brain injury. This study evaluates the efficacy and safety of HS and its impact on the postoperative course of patients undergoing craniotomy for low-grade gliomas. **Materials and Methods:** Sixty patients with supratentorial low-grade glioma were enrolled. All patients were anesthetized and operated with the same team and protocol. They successively received either HS or mannitol just before surgery. The amount of brain edema was classified according to the dural tension score (I–III) just after craniotomy and before dural opening. Other intraoperative measurements (such as urine output, need, and dosage of other diuretic agents) and postoperative findings (intensive care unit [ICU] and hospital stay, corticosteroid demand, and confusion period) were also assessed. Pre- and postoperative serum S100B levels were documented in both groups. **Results:** The dural tension score was not significantly different among the two groups: severe tension in six and five patients in the mannitol and HS groups, respectively. HS group had a significantly lower amount of diuresis (609 vs. 725 ml) during surgery. Patients in the HS group had shorter ICU stay (16.3 vs. 27.9 h) and shorter duration of corticosteroid therapy after surgery (3.4 vs. 5.2 days). **Conclusion:** HS infusion just before the onset of craniotomy is at least as effective as mannitol in controlling intraoperative brain edema in patients with supratentorial glioma. Improved early postoperative course and lower degrees of S100B rise after craniotomy seen in the HS group needs to be explained in more detailed studies.

Keywords: *Craniotomy, glioma, hypertonic saline, intracranial pressure, mannitol*

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Introduction

Brain edema remains a major challenge in patients undergoing surgery for supratentorial intraparenchymal brain tumors causing difficulties in cortical and subcortical dissection and more parenchymal damage due to brain retraction and ultimately worsening of the final neurological outcome of the patients. Pretreatment with osmotic fluids is one of the main tools to prevent acute brain swelling after dural opening during surgery and to control intracranial pressure (ICP) during the operation.[1,2] Mannitol is a well-known osmotic agent for the reduction of ICP through plasma expansion and decreasing extravascular volume.[3]

Nevertheless, the administration of mannitol has certain side effects such as rebound increase in ICP, electrolyte imbalance, and intravascular volume depletion. Many studies have searched for alternative hypertonic solutions with different concentrations for brain relaxation in neurosurgery, of which the hypertonic saline (HS) is the most popular one.[4,5] The administration of HS initially decreases hematocrit and blood viscosity and increases cerebral perfusion, and eventually, it results in the reduction of ICP and brain's blood volume and finally leads to brain relaxation.[3] In addition to the mentioned properties of HS, it appears to have anti-inflammatory and neuroprotective effects, which has been studied in several studies in recent years.[6-9]

In recent years, researchers tend to measure specific neural biomarkers to estimate the intensity of brain injury in patients suffering

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from brain pathologies. S100B is a known marker of neural cell damage which is specific to brain injury.[10] Serum levels of this biomarker have been shown to increase among patients with brain tumor and traumatic brain injury, and it has been reported to correlate with cerebral perfusion pressure and neural integrity.[11,12]

Although many studies have evaluated HS for the management of raised ICP (RICP) in patients with acute and chronic RICP in the intensive care unit (ICU),[13-16] only a few studies have evaluated the effectiveness of HS in brain relaxation of the patients undergoing elective surgery for brain tumors. This study was to compare the intraoperative findings and early postoperative outcomes of the patients with primary supratentorial low-grade gliomas receiving HS with those receiving mannitol as a well-established osmotic agent.

Materials and Methods

Sixty candidates of elective craniotomy for suspected frontotemporal low-grade glioma between 18 and 65 years of age were enrolled. Written informed consent was obtained from all participants, and the institutional review board confirmed the ethical aspects of the study. Patients with previous neuropsychiatric diseases or cranial operation for any reason, radiation therapy, treatment with chemotherapeutic and/or immunosuppressive agents, chronic systemic diseases (renal, hepatic, cardiopulmonary, poorly controlled diabetes mellitus, and cancer), and/or coagulopathy were excluded from the study.

This was a prospective, randomized, double-blinded study. Patients were randomly allocated by the department of anesthesiology, by use of computer-generated random number tables, into one of two treatment groups. Mannitol group received 1 g/kg of mannitol (20%) and the HS group received 3 ml/kg of HS 5%.

The patients successively received either HS or mannitol to reduce ICP just after anesthesia induction and before initiation of the surgery. The tumor location and size was measured on FLAIR sequences of the preoperative brain MRI.

Anesthesia was performed for all patients using the same method, and the same intraoperative monitoring methods were applied for all of them; injecting fentanyl 1.0 μg/kg, midazolam 0.05 mg/kg, thiopental sodium 4.0 mg/kg, atracurium 0.5 mg/kg, and lidocaine 1.0 mg/kg. Maintenance of anesthesia was done using continuous infusion of propofol (80–100 μg/kg/min) and remifentanyl (0.1–0.2 μg/kg/min) and adjusted to maintain the hemodynamic parameters at last 30% less than preoperative baseline values to decrease intraoperative bleeding. Patients in the mannitol group received 1 g/kg of mannitol (20%), whereas in the HS group, 3 ml/kg of HS 5% was administered. Deliberate hypotension was induced in all patients to limit surgical bleeding using a combination of labetalol and TNG drip in a similar manner by the anesthesia team who were blinded to the study protocol. All patients were operated by the same neurosurgical team through pterional approach, and the same craniotomy free bone flap was cut for all patients. Dural tension score was reported immediately after the skull opening by the main surgeon who was blinded to the groups: Grade I, normal dural tension, it was easy for the neurosurgeon to open the dura mater. Grade II, increased dural tension, the dura mater could be opened without additional procedures to lower the ICP. Grade III, markedly increased dural tension, it was necessary to apply additional procedures of lowering the ICP such as hyperventilation in order to open the dura mater.[17]

The primary outcomes of this study were the severity of intraoperative brain edema during surgery and the postoperative course of the patients during their hospital stay. During the immediate postoperative period, the "postoperative confusion period" was defined as the interval between discharge from the recovery room and restoration of full consciousness in the ICU and was documented by the neurosurgeon. Serum concentrations of S100B were used as a surrogate objective marker of neuroprotection. To measure S100B levels, two blood samples were obtained from the patients, the first one 2 h before the surgery and the second one 48 h after surgery, both stored at −70°C for the following measurement procedure. Based on intraoperative observation, the extent of brain edema was classified as low, moderate, or high by a blinded experienced neurosurgeon, immediately after dural opening and before cerebrospinal fluid (CSF) drainage. Furthermore, the amounts of intraoperative blood loss and urine volume during surgery were documented as the secondary outcomes.

Serum concentrations of S100B were measured by BioVendor GmbH, based on the enzyme-linked immunosorbent assay method and expressed in microgram/liter unit.

Statistical analysis

Statistical analysis was performed using the SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp; 2016). The confidence level of at least 95% or maximum error of 5% ($P < 0.05$) has been selected as the level of significance. The normality assumption test was carried out by the Kolmogorov–Smirnov test. Student's *t*-test, Chi-square, and 2-way ANOVA with repeated measure ANOVA were used to compare the main outcomes between the two groups.

Results

Sixty patients completed the study including 25 males and 35 females with the age range of 21–61 years (mean age: 51.6). Table 1 depicts the preoperative characteristics of the two groups. Table 2 summarizes the intraoperative findings and the postoperative hospitalization course among the two groups. The amount of urinary output during surgery was significantly lower in the HS group (609 ml in HS and 725 ml in the mannitol group), but the other intraoperative anti-edema therapies (furosemide and hyperventilation) did not differ significantly among the two groups (applied in 19 and 16 patients in mannitol and HS groups, respectively). The severity of the brain edema reported by the surgeon did not have a significant difference between the two groups (severe edema reported in six patients in mannitol and five in HS group). After surgery, lesser degrees of increment in serum S100B levels were noted in the HS group in comparison to the control group [Figure 1]. The duration of the postoperative confusion and the period of corticosteroid therapy for postoperative brain edema were significantly shorter in the HS (3.8 h and 3.4 days) than the mannitol group (5.3 h and 5.2 days). The length of ICU stay was shorter in the HS group (16.3 vs. 27.9 h), however the total length of hospital stay did not differ significantly among the two groups (6.3 days in the mannitol group and 5.8 days in the HS group).

Discussion

We compared the effects of 20% mannitol with those of 3% HS on the change in ICP among patients undergoing surgery for supratentorial tumors. Both hyperosmolar solutions produced significant decreases in ICP from the baseline.

In the clinical practice, the ICP is not routinely measured during elective neurosurgical procedures, and neurosurgeons evaluate the tension of the dura mater based on their experience before opening the dura mater. If the tension of the dura mater is estimated to be high, brain tissue might protrude through the craniotomy site, which increases the risk of cerebral ischemia with possible worsening of the neurological outcome. Therefore, the dural tension score estimated by the senior surgeon after craniotomy has been shown to be strongly correlated with the degree of cerebral edema and ICP.[18]

Osmotic agents have been used to control RICP since many years ago, however mannitol as the classic osmotic agent in the literature of neurosurgery has important side effects such as volume depletion and electrolyte imbalance that may hinder its application in many clinical conditions. HS has been promising as an osmotic agent to control RICP, especially among patients with traumatic brain injury. Infusion of HS creates an osmotic force that draws the fluid back into the interstitial and intravascular area from the intracellular area due to the impermeability of the blood–brain barrier to sodium.[19] In addition, HS also decreases the formation and/or enhances the reabsorption of the CSF.[20] In an animal model, Toung *et al*. examined the effect of HS on cerebral edema due to tumor. They found that HS was more effective than mannitol in reducing both ipsilateral and contralateral hemispheric water content as measured by wet-to-dry weight ratios.[21] In clinical studies, HS has also been shown to reduce ICP in different intracranial diseases, particularly in head trauma with increased ICP.[22,23] It has been proposed that HS remains effective in intracranial hypertension refractory to treatment with mannitol.[24]

Table 1:Comparison of the preoperative features between the two study groups

Variable	Mannitol group (30)	HS group (30)	*P*
Age (year)	50.23	52.7	0.62
Male/female	13/17	12/18	0.15
Preoperative S100B level	0.147±0.059	0.160±0.166	0.13
Tumor size (ml)	34.4	41.3	0.19
Tumor location			
Frontal	15	13	0.33
Temporal	8	9	
Frontal and temporal	7	8	

HS – Hypertonic saline

Table 2: Comparison of the intraoperative findings and postoperative course between the two study groups

Variable	Mannitol group (30)	HS group (30)	*P*	Power (1-β)* (%)
Urine output (ml)	725.01±106.04	609.33±69.62	0.001	95.8
Bleeding (ml)	778.33±151.06	743.66±198.56	0.45	50.6
Duration of surgery (h)	4.64±0.97	4.20±0.96	0.43	80.2
Dural tension score				
I	5	7	0.729	80.2
II	19	18		
III	6	5		
Need to furosemide/hyperventilation therapy (%)	19 (63)	16 (53)	0.28	-
Extent of tumor resection (%)	87.3 (69-100)	89.6 (73-100)	0.62	-
Confusion period (h)	5.3±1.6	3.8±0.7	0.003	95.9
Duration of corticosteroid therapy (days)	5.2±0.8	3.4±0.6	0.03	100
ICU stay (h)	27.9±2.3	16.3±2.1	0.04	100
Hospital stay after surgery (days)	6.3±1.1	5.8±1.1	0.53	87.9
Postoperative S100B level	0.851±0.058	0.484±0.153	0.001	95

*Estimated by prior power analysis for S100B and by *post hoc* power analysis for the other outcome measures. HS – Hypertonic saline; ICU – Intensive care unit

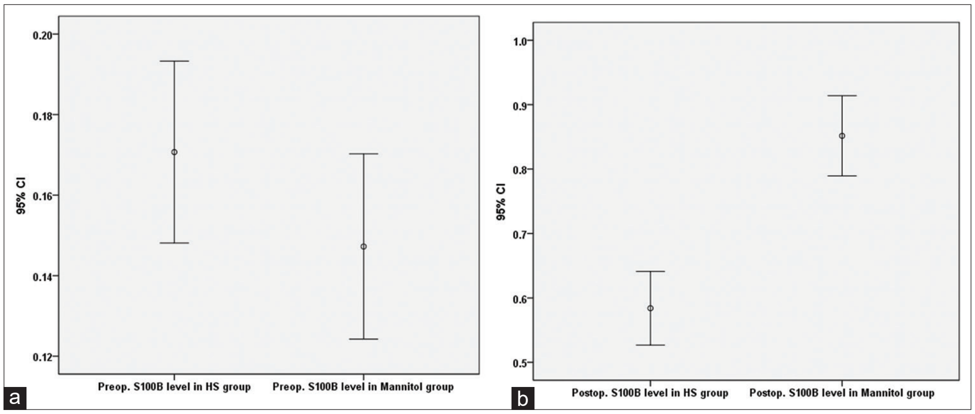

Figure 1: Comparison of the rise in serum S100B levels after surgery between the control (blue line) and intervention (orange line) groups. Serum S100B levels before surgery (a) and after the operation (b), showing no significant difference among the two groups before the operation (overlapping error bars) in contrast to the significantly lower S100B levels after surgery in the hypertonic saline group

Our study included a relatively homogenous group of the patients in terms of pathology (low-grade astrocytoma) and location (frontotemporal) to compare the effectiveness of HS versus mannitol in achieving brain relaxation during elective craniotomy. The severity of the brain edema reported by the surgeon did not have a significant difference between the two groups (severe edema reported in six patients in mannitol and five in HS group, *P*: 0.729), and our data show that HS is at least as effective as mannitol in terms of controlling brain edema during surgery.

Although all hyperosmolar agents cause diuresis, the amount of urinary output during surgery was significantly lower in the HS group (609 ml in HS and 725 ml in the mannitol group, *P*: 0.001), whereas the dosage of other intraoperative anti-edema therapies (furosemide and hyperventilation) did not differ significantly among the two groups (applied in 19 and 16 patients in mannitol and HS groups, respectively, *P*: 0.28). This finding may result from the stimulation of natriuretic peptide (ANP) release by HS and not merely a direct osmotic diuresis, which might assist in avoiding hypovolemia and hypotension.[18]

We also observed that the duration of the postoperative confusion and the period of corticosteroid therapy for postoperative brain edema were significantly shorter in the HS than the mannitol group (3.8 h vs. 5.3 h, *P*: 0.003 and 3.4 days vs. 5.2 days, *P*: 0.03). The length of ICU stay was shorter in the HS group (16.3 vs. 27.9 h, *P*: 0.04); however, the total length of hospital stay did not differ significantly among the two groups (6.3 days in mannitol group and 5.8 days in the HS group, *P*: 0.53). All of these findings may not completely be explained just on the basis of the osmotic effects of the HS and considering the well-known immune modulatory effects of HS;[6,8,9] there may be a neuroprotective role beyond its circulatory benefits. Although it is still considered a research tool rather than a valid clinical measurement, Vos *et al*. have suggested that the S100B is a known inflammatory factor specific to brain injury which increases in brain tumor patients.[10] The range of S100B blood level is between 0.02 and 0.05 μg/l in normal individuals and 0.19 μg/l in patients with brain tumor and increased to 1.07 μg/l after tumor resection in one study.[11] The uniform rise in postoperative serum S100B levels seen in our patients also supports the role of S100B as a marker of neural damage and/or inflammation. Although the serum levels of S100B before surgery in both groups were similar, the amount of rise in S100B level was significantly lower in patients who received HS in contrast to those who received mannitol (0.484 ± 0.153 μg/L vs. 0.851 ± 0. 058 μg/L, *P*: 0.001) [Figure 1]. Usui *et al*. reported that S100B is excreted and eliminated completely through the kidneys.[25] Considering the significantly higher urine volume in the mannitol group, one may expect lower S100B levels in these patients, while our data show higher serum S100B levels in this group despite their higher urinary outputs. Nevertheless, S100B has been used only as an ancillary objective measurement in this study, and deriving a clear conclusion regarding the relation between S100B and the clinical outcome of the patients receiving HS before surgical resection of brain tumors is not possible from this study.

Limitations

One major shortcoming of our study was the lack of direct measurement of cerebral perfusion and rheological properties of blood. In addition, the potential long-term beneficial effects of the HS on the neurological outcome of the patients remain to be evaluated. We suggest that anti-inflammatory and neuroprotective effects of HS be further studied in addition to its brain relaxation and circulatory features. There remain other aspects of HS to be evaluated by further studies, such as its effect on the coagulation pathways and platelet function.

Conclusion

In summary, the administration of HS seems to be safe and effective in achieving brain relaxation needed for elective craniotomies to resect intra-axial brain tumors and at the same time may have additional benefits by improving neuroprotection during the neurosurgical procedures.

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Conflicts of interest

There are no conflicts of interest.

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