A COMPARISON OF MANNITOL VERSUS 3% HYPERTONIC SALINE FOR BRAIN RELAXATION DURING ELECTIVE SUPRATENTORIAL CRANIOTOMY (NEUROSURGICAL ANESTHESIA)

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Summary:

Introduction: Brain relaxation is essential in anesthesia for intracranial surgery; it has been considered a neuroprotective measure as it can reduce surgical compression, local hypoperfusion, cerebral ischemia, and blood loss. To ease surgical tumor removal, measures are taken to reduce brain swelling, often referred to as brain relaxation. In the present study, we aimed to compare the effects of 20% mannitol and 3% hypertonic saline (HS) on brain relaxation during supratentorial craniotomy. Fluid input, urine output, arterial blood gases and serum sodium concentration were also measured.

Methods: We conducted a prospective, randomized, double blind controlled trial. Sixty patients, ages 18 to 50, belonging to American Society of Anesthesiologist (ASA) physical status (II-IV), posted for craniotomy were divided into two equal groups in a double-blinded selection by using computer-generated random numbers (Thirty patients in each group). The surgeon and anesthesiologist were unaware of the identity of the study agents. Each patient was administered 150 ml of either 20% mannitol (Group M) or 3% HTS over 20 minutes (min) (Group H) after skin incision. The neurosurgeon assessed the brain conditions on a four-point scale as “Perfectly relaxed,” “Satisfactory relaxed,” “Firm brain,” or “Bulging brain,” immediately after opening the dura mater.

Results: Intraoperative brain relaxation was comparable between the two groups. Brain relaxation observed in Group M (perfectly relaxed/satisfactory relaxed/firm brain/bulging brain, n = 8/13/5/4) was similar to that observed in Group H (perfectly relaxed/satisfactory relaxed/firm brain/bulging brain, n = 7/13/8/2; P= 0.77). Urine output was significantly higher in the mannitol group (P <0.05). Administration of HTS was associated with a transient increase in serum sodium concentrations, which was statistically significant but returned to normal within 48 h (P < 0.05). There were no significant differences in fluid input and arterial blood pressure during surgery in between two groups.

Conclusion: Our results suggested that hypertonic saline and mannitol both had a similar effect on brain relaxation during elective supratentorial craniotomy.

Keywords: Brain relaxation; Craniotomy; Hypertonic saline; Mannitol

Introduction:

Brain relaxation is essential in anesthesia for intracranial surgery; it has been considered a neuroprotective measure as it can reduce surgical compression, local hypoperfusion, cerebral ischemia, and blood loss. Supratentorial brain tumor patients usually have swollen brain tissue with results in increased intracranial pressure. To ease the surgical tumor removal, measures are taken to reduce brain swelling, often referred to as brain relaxation. Hyperosmotic agent is used to relax swollen brain tissue before opening of the dura mater in elective supratentorial brain tumor surgeries. The commonly used osmotic agent for treatment of brain edema irrespective of intracranial hypertension is mannitol. During the past few years, hypertonic saline has also been chosen for treatment of brain edema.

Mannitol and hypertonic saline produce an osmotic gradient resulting in transfer of extravascular to intravascular water across the blood–brain

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barrier. Hypertonic saline is a more effective osmotic agent than mannitol, due to its higher osmotic reflection coefficient (1 vs. 0.9)\textsuperscript{4}.

The aim of the present study was to compare brain relaxation after using hypertonic saline (3%) and mannitol (20%) in patients undergoing supratentorial brain tumor surgery.

**Objective:**

The primary objective of our study was to compare the brain relaxation during elective supratentorial craniotomy in both groups.

The brain relaxation as assessed by a neurosurgeon was on a four-point scale as: 1. Perfectly relaxed, 2. Satisfactory relaxed, 3. Firm brain, 4. Bulging brain.

The secondary objective was comparing fluid input, urine output, arterial blood gases and serum sodium concentration level in both groups.

**Methods:**

After obtaining the Institutional Ethical Committee approval [Reference number 55/2020, dated 28/2/2020] and written informed valid consent, this prospective, randomized, double blind controlled study was conducted in the Neurosurgery Operation Theatre, Department of Anesthesiology, in our institute, between March 2020 to November 2021.

Sixty patients belonging to ASA physical status II-IV, between 18 and 50 years of age scheduled for supratentorial brain tumor surgery were included in this study (Figure 1.). After taking informed consent, patients were classified randomly into two equal groups of thirty each. Patients with history of drug allergy, pregnant and nursing women, major cardiac, hepatorenal or endocrine dysfunction and refusal for consent for the study were excluded from the study.

The research methodology was prospectively randomized with the help of computer-generated coded envelopes and patients were divided into two groups: Group H and Group M.

A detailed history was taken. The majority of the patients PRESENT with history of headache, seizures, vomiting and or progressive neurological deficit in the form of hemiparesis, visual symptoms (diminished vision) on admission.

In patients without satisfactory brain relaxation another bolus of the same osmotic agent was administered after demand from neurosurgeon.

Ventilation was set to keep an end-tidal carbon dioxide value between 35 and 40 mmHg.

We managed the fluid input according mainly to urine output (i.e., 100 ml urine output using 100 ml of 0.9% saline or Ringer lactate solution supplement). Additionally, 2 ml/kg/h fluid (0.9% saline or Ringer lactate solution) was given to maintain positive fluid balance. Blood loss was assessed and replaced accordingly.

Measurement of arterial blood gases and serum sodium concentration were done at the baseline as well as at the end of surgery. At the end of surgery, reversal of the neuromuscular blockade was
The mean intraoperative fluid input in Group H was 1312 ± 158 ml, and 1340 ± 140 ml in Group M (P > 0.05). We did not find any statistically significant difference between both the groups.

The mean blood loss during surgery was 350 ± 60 ml in Group H and 375 ± 55 ml in Group M (P > 0.05).

The mean intraoperative urine output was less in Group H (612 ± 112 ml) as compared to Group M (1156 ± 142 ml) respectively. There was statistically significant difference in both the groups (P < 0.05) (Table 3).

The serum sodium concentration level was significantly higher in Group H compared to Group M at the end of surgery. (P < 0.05) (Table 4).

Discussion:

Through continuous development and expansion of neuroanesthesia, the basic principles of neuroanesthesia like provision of good operative field, assessment with preservation of neurological function, and a speedy, high-quality recovery remain the same.

Neuroanesthesia must emphasize the stability of hemodynamics, adequate cerebral perfusion pressure, and avoidance of intracranial hypertension. Patients with edematous brain tissue usually manifest with increased intracranial pressure. Neuroprotective anesthesia for craniotomy includes brain relaxation with resultant reduction in surgical compression, cerebral ischemia, blood loss and local hypoperfusion.

Supratentorial brain tumors produce a circumscribed mass lesion, often with a surrounding area of brain edema. In a study, it is summarized that intraoperative intracranial hypertension is associated with greater amounts of preoperative brain swelling surrounding supratentorial tumors\(^5\). Thus, control of intraoperative intracranial pressure is mandatory for satisfactory brain relaxation during craniotomy.

During neurosurgical procedures under general anesthesia, satisfactory brain relaxation is a great challenge\(^6,7\). Cerebral swelling (tight brain) with increased intracranial pressure in patients undergoing craniotomy has many harmful effects like poor outcome with neurological deficits and also results in poor surgical exposure, making the operative procedure more difficult\(^7,8\). Different methods used during neurosurgery to provide brain relaxation and reduction in intracranial pressure done with an inj. of neostigmine 0.05mg/kg and inj. glycopyrrolate 0.01 mg/kg intravenously. Extubation was done in all patients when they were wide awake and obeying commands, after which they were shifted to the neurologic Intensive Care Unit for further observation. Most of the patients had GCS scores of more than 10 after extubation. All patients in both the groups were neurologically improved after craniotomy.

Other variables measured were total urine output, fluid input, blood loss, serum Na concentration, arterial blood gases.

**Table 1: Demographic data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group H (N = 30)</th>
<th>Group M (N = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.87 ± 6.35</td>
<td>37.03 ± 7.12</td>
<td>0.6314**</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.9 ± 5.91</td>
<td>55.73 ± 7.02</td>
<td>0.4878**</td>
</tr>
<tr>
<td>Male/Female</td>
<td>16/14</td>
<td>17/13</td>
<td>1.000**</td>
</tr>
<tr>
<td>ASA(^5) grade II/III</td>
<td>18/12</td>
<td>16/14</td>
<td>0.79*</td>
</tr>
<tr>
<td>Duration of surgery(min)</td>
<td>194.4 ± 22.46</td>
<td>190.2 ± 24.74</td>
<td>0.4939**</td>
</tr>
</tbody>
</table>

\(^5\)ASA-American Society of Anesthesiologist;  
\(^*\)Chi-square test  
\(^**\)Student’s t-test  
Data presented as mean ± standard deviation or number: P > 0.05 considered not significant

Statistical analysis:
Table 2: Brain relaxation data

<table>
<thead>
<tr>
<th>Brain relaxation</th>
<th>Group H (N = 30)</th>
<th>Group M (N = 30)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfectly relaxed</td>
<td>7</td>
<td>8</td>
<td>0.77</td>
</tr>
<tr>
<td>Satisfactorily Relaxed</td>
<td>13</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Firm Brain</td>
<td>8</td>
<td>5</td>
<td>0.35</td>
</tr>
<tr>
<td>Bulging Brain</td>
<td>2</td>
<td>4</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Chi-square test
Data presented as number : P > 0.05 considered not significant

Table 3: Intraoperative parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group H (N = 30)</th>
<th>Group M (N = 30)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fluid input (ml)</td>
<td>1312 ± 158</td>
<td>1340 ± 140</td>
<td>0.4705</td>
</tr>
<tr>
<td>0.9% Saline (ml)</td>
<td>410 ± 76</td>
<td>428 ± 78</td>
<td>0.3691</td>
</tr>
<tr>
<td>Ringer Lactate (ml)</td>
<td>326 ± 68</td>
<td>332 ± 72</td>
<td>0.7412</td>
</tr>
<tr>
<td>Packed Cell Volume (ml)</td>
<td>250 ± 40</td>
<td>255 ± 35</td>
<td>0.6083</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>350 ± 60</td>
<td>375 ± 55</td>
<td>0.0979</td>
</tr>
<tr>
<td>Total Urine output (ml)</td>
<td>612 ± 112</td>
<td>1156 ± 142</td>
<td>0.0040</td>
</tr>
</tbody>
</table>

** Student's t-test
Data presented as mean ± standard deviation or number: P < 0.05 is significant

Table 4: Serum sodium concentration level

<table>
<thead>
<tr>
<th>Na+</th>
<th>Group H (meq/l)</th>
<th>Group M(meq/l)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>138.77 ±2.80</td>
<td>140.00 ± 3.18</td>
<td>0.1165</td>
</tr>
<tr>
<td>At the end of surgery</td>
<td>141.90 ± 1.99</td>
<td>140.13 ± 2.44</td>
<td>0.0032</td>
</tr>
</tbody>
</table>

** Student's t-test
Data presented as mean ± standard deviation
P < 0.05 considered as a significant

In this study, calculation of sample size was done by using formula n= 4pq/E², based on Hardy-Weinberg principle. According to this formula p means prevalence of craniotomy at our institute.

Data was presented as mean values ± standard deviation. Analysis of categorical variables was done by using chi-square with Yates’ correction and Fisher’s exact test (two tailed) as and when appropriate. Unpaired student’s t-test was used for analysis of continuous variables. Microsoft Office Excel 2010 and Graph Pad Prism 6.05 (QuickCalcs) Software (Graph Pad software Inc., La Jolla CA, USA) were used for statistical calculations. A P-value <0.05 was considered to be statistically significant.

Results:

Both groups were comparable in terms of age, sex, weight, and American Society of Anesthesiologist (ASA) grade and operation time (Table 1). Mannitol and hypertonic saline had similar effects on brain relaxation. There was no statistically significant difference regarding brain relaxation in both the groups (P >0.05) (Table 2).
are hyperventilation, usage of hyperosmotic agents and drainage of cerebrospinal fluid\(^9\).

Mannitol is first preference and the gold standard hyperosmotic agent for reduction of raised intracranial pressure in various intracranial pathologies\(^9\). Nowadays, hypertonic saline is an alternative to mannitol as a hyperosmotic agent to produce brain relaxation and to decrease intracranial hypertension in various neurosurgical procedures\(^10,11\). Various studies have observed that hypertonic saline is as effective as mannitol, for reduction of intracranial hypertension\(^12,13\).

The basic mechanism of action of hyperosmotic agent is shifting of the water from brain tissue to the intravascular space by the hyperosmolarity of hypertonic saline and mannitol as the blood brain barrier is not permeable to sodium and mannitol as well. When hypertonic saline or mannitol is administered, they increase serum osmolality and decrease intracranial pressure and brain water content in normal brain areas.

The “reflection coefficient” of hyperosmolar solution is responsible for effectiveness of the hyperosmolar therapy in determining the relative impermeability of the blood brain barrier to the solute. The reflection coefficient of 1 denotes an absolutely impermeable solute and 0 denotes an ideally permeable solute. The reflection coefficient of hypertonic saline and mannitol is 1 and 0.9 respectively indicating hypertonic saline as theoretically better osmotic agent than mannitol.

Wu et al\(^14\) concluded that hypertonic saline is better in terms of brain relaxation as compared to mannitol in patients posted for elective supratentorial craniotomy.

Mishra et al\(^15\) also concluded that routine use of HS is superior in place of mannitol for providing brain relaxation, better hemodynamic stability and neurosurgical access in elective supratentorial craniotomies.

In an in vitro study done by Wang LC et al\(^16\), it was observed that mannitol reduced brain water content to a large extent over the entire period of the 5-hours experiment when compared to equivalent, equiosmolar administration of hypertonic saline. In our study we observed similar effect on brain relaxation in elective supratentorial craniotomies with 20 % mannitol and 3% hypertonic saline.

Our findings are in accordance with the findings of Namrata Kumari et al\(^17\), who noticed that mannitol is as effective as hypertonic saline in decreasing intracranial hypertension and maintaining adequate intraoperative brain relaxation. Same result was found with another study done by Rozet et al\(^18\), who concluded that mannitol and hypertonic saline produce rise in cerebrospinal fluid osmolality and comparable brain relaxation score along with arteriovenous oxygen and lactate difference in craniotomy.

In our study as per the four-point scale assessment for brain relaxation from a neurosurgeon, when the brain was found to be relaxed during surgery, it was assumed to have no intracranial hypertension.

In our study we maintained end tidal carbon dioxide between 35 and 40 mmHg and arterial blood pressure within baseline values ± 20% to avoid the effect of carbon dioxide and blood pressure on brain bulk. There were no significant differences in heart rate, systolic, diastolic, and mean blood pressure in both the groups.

The mean intraoperative fluid input in Group H was 1312 ± 158 ml and 1340 ± 140 ml in Group M. We observed no significant difference between the groups (\(P > 0.05\)). Our findings are similar to earlier studies\(^14,15\).

The mean intraoperative urine output was found to be higher in the mannitol than hypertonic saline (\(P < 0.05\)) in our study. Being an osmotic diuretic, infusion of mannitol leads to significant diuresis. Earlier studies also found similar results regarding urine output\(^14,15\).

In our study, significantly higher levels of serum sodium and a decreased diuretic effect were seen with 3% hypertonic saline group compared to the mannitol group. These results are in line with other studies\(^14,18\).

The lower diuretic effect of hypertonic saline is due to release of antidiuretic hormones because of increase in serum sodium. It leads to the absorption of free water from the kidney, which may explain less diuresis with hypertonic saline as compared to mannitol.

In our prospective randomized controlled study, we found that: 1. Brain relaxation was similar in both study groups; 2. Group M has higher urine output owing to its diuretic property; 3. Group H has higher serum sodium levels at the end of surgery.
**Limitation:**

We did not measure intracranial pressure as it does not work and we don’t get accurate measurement of ICP once brain is opened, so it is not a routine practice in our institute to measure it in craniotomy. Another limitation of our study is the use of 150 ml doses and is not expressed in gr/kg for the 20% mannitol or ml/kg for the 3% NaCl.

**Conclusion:**

Administration of the mannitol and hypertonic saline provided similar brain relaxation in elective supratentorial craniotomies. The serum sodium concentration was significantly higher, without diuretic effect in hypertonic saline as compared to mannitol.

**References:**