Indian Journal of Clinical Anaesthesia 2021;8(2):221–229

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical Anaesthesia

Journal homepage: www.ijca.in

Original Research Article

"*Balanced hyperosmolar therapy*" using 3% hypertonic saline - 20% mannitol versus an equiosmolar volume of either 3% hypertonic saline or mannitol 20% in supratentorial tumor resection: A new approach to achieve hemodynamic stability

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ARTICLE INFO

Article history:
Received 28-12-2020
Accepted 31-12-2020
Available online 06-01-2021

Keywords:
Balanced
Hyperosmolar
Mannitol
3% hypertonic saline
Supratentorial tumors

ABSTRACT

Background: Both 3% hypertonic saline (3% HTS) and 20% mannitol were proven to be effective in relaxing the brain during supratentorial surgeries. This work aimed to study the effect of consecutive use of both drugs on the brain relaxation score and hemodynamic status during such surgeries.
Materials and Methods: Ninety patients scheduled for supratentorial brain surgeries included in this prospective, randomized and double-blind study. Patients were allocated in three groups; HTS group (n=30) received 3 ml/kg 3% NaCl infusion over 30 minutes, HTS/M group (n=30) received mannitol 20% (1.4 ml/kg) as an infusion over 15 minute followed by 1.5 ml/kg 3% NaCl infused over 15 minutes and M group (n=30) received 3.2 ml/kg mannitol 20% infusion over 30 minutes. Brain relaxation was estimated. MAP and serum Na level were recorded at baseline and then at 30, 90 and 150 min. Total fluid intake, total urine output and operative time were recorded.
Results: Fluid intake and urine output were the highest with 20% mannitol ($p < 0.001$). HTS/M and HTS groups showed no significance when satisfactory and fairly brain relaxation scores were added (p=0.862). MAP and CVP were near to baseline in HTS/M group at 30 and 90 min, while at 150 min no significant difference between groups. Serum hyperosmolarity was noticed in all groups at all check points but maximally with HTS group at 30 min (321.1 mOsm/L).
Conclusion: Balanced hyperosmolar therapy using 3% HTS and 20% mannitol consecutively resulted in a satisfactory brain relaxation and allowed more hemodynamic stability.

1. Introduction

Adequate brain dehydration is supposed to be the most critical factor which facilitates supratentorial brain tumors resection. Perioperatively, the active management of brain water content is one of the fundamental roles of anesthetists. Assuming the blood brain barrier(BBB) is intact, using of Mannitol 20% (in different doses) and 3% hypertonic saline (3%HTS) was introduced to shift brain water to the intravascular compartment leading to brain dehydration and hence a significant decrease in brain volume. With large supratentorial tumors, mass bulk is usually a contributing cause of a firm dura which is usually disappointed by neurosurgeons.

Many doses of mannitol 20% (0.5 – 0.7 – 1.0 – 1.4 gm/kg) were described, where it was evidenced that larger doses had a more brain dehydrating effect.[1–3] Unfortunately, higher doses were accompanied by a lot of side effects, as pulmonary congestion and/or edema, hypotension, venous thrombophlebitis, acidosis and even convulsions.[4]

HTS also was introduced to decrease intracranial pressure (ICP) during supratentorial brain tumor resection with an evidenced superiority over mannitol but some

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https://doi.org/10.18231/j.ijca.2021.044
2394-4781/© 2021 Author(s), Published by Innovative Publication.

adverse reactions were reported such as; venous thrombotic, hypervolemic and hypernatremic effects when used in higher concentrations (> 3%).[5]

Either agents has a different behavior, mannitol depletes intravascular volume through its diuretic effect while HTS expands intravascular space through its hygroscopic action. Subsequently, both agents reduce brain bulk. Owing to their different behaviors regarding the effect on intravascular volume; care must be given while tailoring a hyperosmolar regimen. Maintaining of mean arterial blood pressure (MAP) between 55-65 mmHg to ensure an optimal blood perfusion to the brain is a cornerstone in a better surgical outcome; this can be achieved better when using HTS.[6]

We hypothesize that administration of a balanced regimen of both drugs can minimize the undesired effects on the patient's hemodynamics specially MAP which is usual when each one is administered solely, with the achievement of a satisfactory brain dehydration.

2. Materials and Methods

2.1. Allocation

After El Sahel Teaching Hospital Ethical and Scientific committee (HESC) approval and written informed consents from all patients, 96 patients (ASA II and III) scheduled to supratentorial brain tumor resections between January 2014 and December 2017 were prospectively enrolled in our randomized double – blind study. Patients aged< 18 years with Glasgow Coma Scale (GCS) < 13, ASA over III, hypo/hypernatremia (< 135/>145 mEq/L), congestive heart failure (EF< 55%), Renal impairment (creatinine clearance <30 mL/kg), or preoperative hyperosmolar therapy 24 hours before; were excluded from our study.

2.2. Randomization, blindness and preparation of study fluid

Using 1:1 computerized random number generator; an independent assistant, who didn't contribute in clinical assessment of study subjects, randomized patients into either HTS group (receiving 3ml/kg 3% NaCl infusion(1.027 mOsm/ml) over 30 minutes, or HTS/M group receiving 1.4ml/kg Mannitol 20% (1.099 mOsm/ml) as an infusion over 15 minute followed by 1.5ml/kg 3% NaCl (1.027 mOsm/ml) infused over 15 minutes or M group receiving 3.2 ml/kg mannitol 20% (1.099 mOsm/ml) infusion over 30 minutes. All hyperosmolar fluids were prepared, encoded in a two similar bottles for every patient and distributed to the dedicated anesthetists who were blind to the contained fluids. Attending surgeons were also blind to hyperosmolar regimen to prevent any anticipated outcome.

2.3. Anesthetic Technique

Preoperatively, all patients were checked for any exclusion criteria, and then the routine preoperative evaluation was done, including magnetic resonance imaging (MRI) assessment for every patient by the attending anesthetist and neurosurgeon for the type, location, size of the tumor and presence of any significant midline shifting. On arriving operative theater, all patients had received 0.1 mg/kg midazolam IV. After connecting all the basic monitors' cables (NIBP, pulse oximetry and ECG) and canulating the radial artery to monitor IBP, induction of anesthesia was done to all patients with 2μg/kg fentanyl, 2-3mg /kg propofol IV and 0.5 mg/kg atracurium to facilitate endotracheal intubation. After intubation, central venous catheter, temperature probe through nasopharynx and urinary catheter were inserted. Anesthesia was maintained with Sevoflurane (1 – 1.2% Minimal Alveolar concentration, MAC), propofol at a rate of 2-4mg/kg/h and fentanyl infusion in a rate of 2μg/kg/hour (which was discontinued 60 minutes before recovery). Patients were mechanically ventilated with O_2/Air mixture (FiO_2 50%) in a rate of 10-12/minute and tidal volume of 6-8 ml/kg to insure Spo2 around 99% and end-tidal CO_2 between 28-35 mmHg. Body temperature was kept between 35-37^{o}C using warm fluids and warming blankets.

After induction of anesthesia, a top-up dose of fentanyl (1μg/kg) was given and local infiltration of Mayfield's head clamp pins' sites was done to attenuate its vasopressor effects then head was slightly elevated (30^o). After sterilization and infiltrating surgical incision site with local anesthetic drug, all baseline data were recorded (Baseline). After recording, the dedicated hyperosmolar fluids were started using an infusion pump which was adjusted to infuse both bottles over 30 minutes. Intraoperative fluids were given (2-4ml/kg/hr) guided by central venous pressure (CVP) (to be maintained at 10-12 cmH_2O) and urine output. Hypotension (MAP< 60 mmHg) for more than one minute was managed by lowering concentration of inhalational anesthetic gradually by 0.1. Blood loss was replaced using Ringer's lactate solution in (3-1) volume or 6% hydroxyethyl starch in (1-1) volume. Decision of blood transfusion was considered when haemoglobin level was < 9 mg/dl.

2.4. Recording and data outcome

For every patient, demographic data and tumor characteristics were recorded.

Baseline data were recorded before starting the hyperosmolar therapy which included; HR, MAP, SpO2%, CVP, serum osmolarity, serum Na level and ABG. After finishing the hyperosmolar fluids infusion; we recorded all previous parameters (30 minutes) then after one hour (90 minutes) and at (150 minutes) from the end of infusion.

Fluid intake, urine output and blood loss were recorded hourly then total was calculated for each patient by the end of operation. Hypotensive / hypertensive episodes and the need for rescue bolus dose of hyperosmolar therapy were recorded.

Brain relaxation score (primary outcome) which was scored by the main neurosurgeon after opening of the dura on a one - four scale (1= satisfactory relaxed, 2= fairly relaxed, 3= firm and 4= bulging brain). In case of 3 or 4 scores, 25% of the hyperosmolar regimen was given as a rescue bolus dose.

At the end of surgery, patients were transferred to Surgical Intensive Care Unit (SICU) for immediate post-operative care. SICU team recorded total ventilation hours required, analgesic requirements and if any post-operative complication such as disorientation, headache, convulsions or vomiting.

2.5. *Statistical analysis*

Data were statistically described in terms of mean ± standard deviation (± SD), range or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test with post-hoc (Holm-Bonferroni) multiple 2-group comparisons when significance was achieved by ANOVA to decrease α error. Within group comparison of numerical variables was done using repeated measures analysis of variance (ANOVA) test with post-hoc multiple comparisons. For comparing categorical data, Chi-square (c^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Sample size calculation was done using 1-point difference in brain relaxation score was considered clinically significant. Based on α error of 0.05 and β error of 0.2, power analysis was done. Total size of 75 subjects was required for 95% confidence interval and 5% level of significance but we increased sample size to 90 for more accuracy of prediction.

3. Results

Ninety six patients were enrolled in this study, four patients were excluded due to high MAP (2 patients) and two patients declined to participate. Ninety two patients were randomized into 3 groups; HTS group (31 patients), HTS/M group (30) patients and M group (31 patients). During follow up, two patients excluded one from HTS group due to out-of- goal hemodynamics for more than 5 minutes and other patient in M group because operation was aborted due to excessive bleeding. Thirty patients in each group completed the analysis of this study (Diagram 1).

No significant difference was detected between the three groups regarding age, sex, BMI and ASA classification (Table 1). Tumor characteristics including type, location, maximum diameter and presence of midline shift showed no significance between three groups (Table 2).

3.1. *Brain relaxation score*

Based on one – four scale (1= satisfactory relaxed, 2= fairly relaxed, 3= firm and 4= bulging brain), M group showed a significant lower satisfactory relaxed percentage (16.7%) compared with other groups (p =0.01), while HTS was the highest (76%) (Figure 1). Total of satisfactory relaxed and fairly relaxed brain showed no significant difference between HTS and HTS/M groups (26, 86.7% and 25, 83.3% patients) while it was 14 patients in M group (46.7%). Firm and bulging brain were significantly higher in M group (16, 53.3%) compared with other groups (p =0.02). No significant difference was detected between HTS and HTS/M groups regarding four grades of the scale (Table 3). Need for rescue bolus dose was the highest in M group (16 patients) which was significant when compared with HTS/M group (p =0.004) and M group (p =0.003). No significant difference was detected between HTS and HTS/M groups (p = 0.224) (Figure 2).

Fig. 1: Brain relaxation score in different groups

3.2. *Intraoperative hemodynamics*

As shown in Table 4; total operative time and blood loss during operations showed no significant differences between three groups (p =0.927 and 0.231 respectively).

MAP showed no significance between all groups at baseline (p =0.74). But at 30 min; higher readings were detected in HTS and HTS/M groups (71.4, 65.03 mmHg), but a decline in MAP was observed in M group (61.5 mmHg). Between groups comparison showed a highly significant difference (P < 0.001). At 90 min, decrease in MAP was noticed in the three groups with the highest mean

Table 1: Patients characteristics

	Group HTS (n=30)	Group HTS/M (n=30)	Group M (n=30)	P value
Age(yrs.)	57.4±8.7	56.6±8.3	51.2±10.8	0.023
Male/Female	16/14	20/10	19/11	0.545
BMI(Kg.m2)	28.7±5.7	27.6±5.3	27.4±4.3	0.600
ASA(II/III)	23/7	26/4	24/6	0.602

Results are in mean± SD and Numbers; ASA: American Society of Anesthesiologists

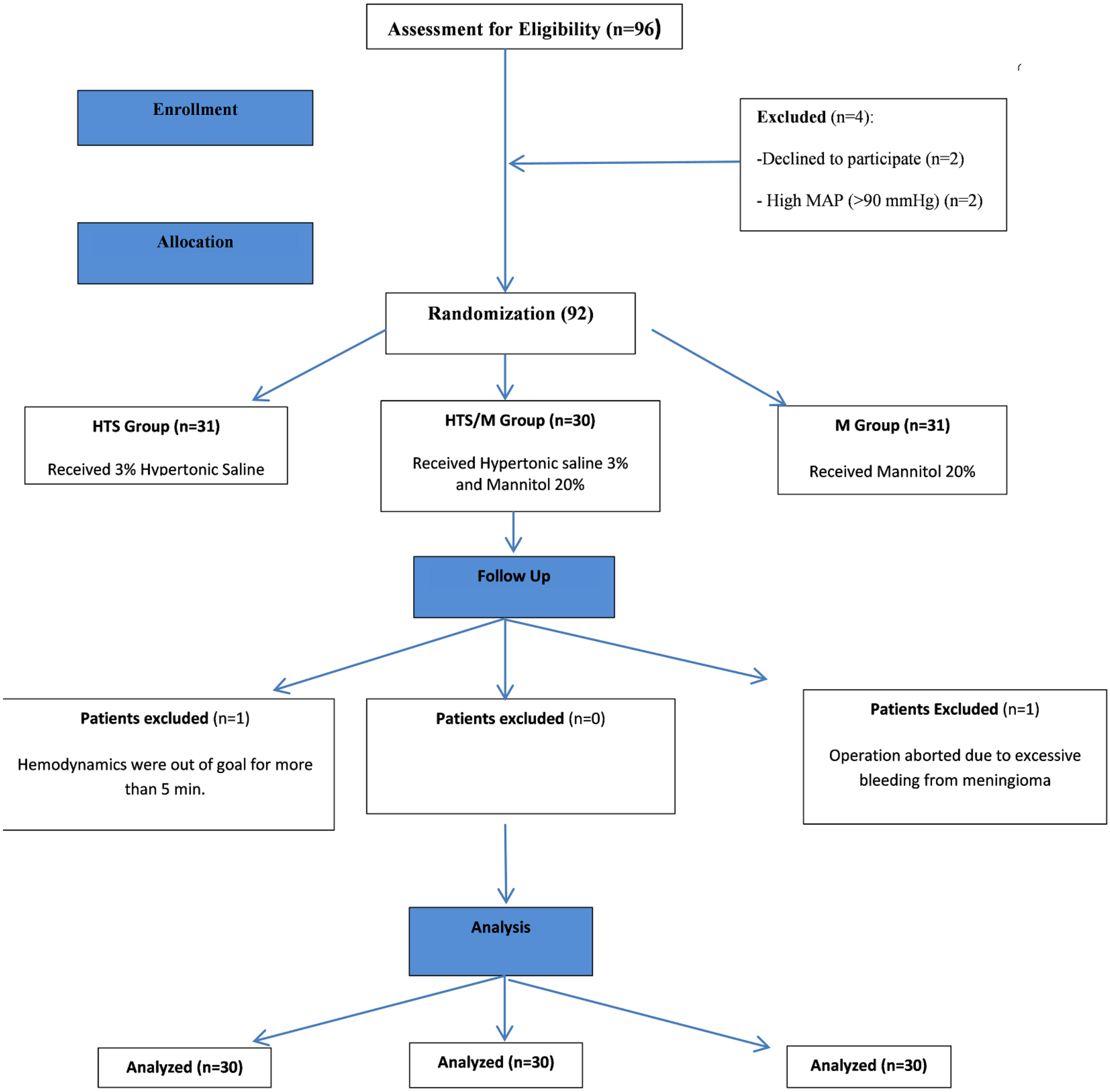

Diagram 1: Study flow chart

Table 2: Tumor characteristics

	Group HTS (n=30)	Group HTS/M (n=30)	Group M n=30)	P value
Type(n) G/M/Met.*	10/16/4	11/16/3	9/14/7	0.693
Location (n) F/P/T/O**	13/8/6/3	9/6/13/2	11/10/7/2	0.503
Midline shift(n) Yes/No	20/10	20/10	23/7	0.621
Maximum diameter (mm) (Means ±SD)	30.3±17.3	39.2± 20.8	38.7± 18.4	0.124

*G= Gliomas M= Meningioma, Met= Metastasis. **F= Frontal, P=parietal, T= Temporal, O= Occipital

Table 3: Brain relaxation score (n, %) and need for rescue doses

	Group HTS (n=30)	Group HTS/M (n=30)	Group M (n=30)	P value
Satisfactory relaxed	20(76%)	16(53.3%)	5(16.7)	0.01
Fairly relaxed	6 (20%)	9(30%)	9(30%)	0.687
Firm	2(6.7%)	3(10%)	10(33.3%)	0.02
Bulging	2(6.7%)	2(6.7%)	6(20%)	0.202

Data expressed in number (n) andpercentage (%)

Table 4: Intra-operative hemodynamics

						Between groups	
	Group HTS (n=30)	Group HTS/M (n=30)	Group M) (n=30)	P-value	HTS/C	HTS/M	M/C
Operative time (min)	332.3± 60.4	335.1± 64.9	328.23±76.2	0.927	———	———	———
Fluid Intake (total, ml)	2134.5±335.8	2878.3± 317.4	3037.7± 403.2	< 0.001	< 0.001	< 0.001	0.272
Urine output(total, m)	794.2± 142.6	1069.7± 260.1	1177.3± 223.3	< 0.001	< 0.001	< 0.001	0.165
Blood Loss (ml)	401± 201.4	360± 305.7	370± 260.3	0.241	———	———	———
Hypotensive Episodes (n)	3/30(10%)	6/30(20%)	12/30(40%)	0.020	0.075	0.006	0.028
MAP (mmHg)							
Baseline	63.0± 3.6	62.3± 3.7	64.7± 4.7	0.74	1.0	0.348	0.80
30 min	71.4 ± 4.1	65.03 ± 3.2	61.5± 3.2	0.001	0.001	0.001	0.001
90 min	68.6 ± 3.5	63.1 ± 2.7	60.1± 3.5	0.001	0.001	0.001	0.002
150 min.	62.2 ± 4.0	61.7± 3.4	63.1± 2.7	0.261	1.0	0.877	0.322
CVP (cmH2O)							
Baseline	9.2 ± 1.9	8.9 ± 1.7	8.5 ± 1.6	0.333	———	——-	——-
30 min	11.2 ± 1.4	10.1 ± 2.4	6.2± 1.2	0.001	0.32	< 0.001	< 0.001
90 min.	12.1 ± 1.1	9.5 ± 1.3	6.8 ± 1.6	0.001	< 0.001	< 0.001	< 0.001
150 min.	9.7 ± 1.8	9.1 ± 2.1	9.2 ± 2.2	0.166	———	———	——-
Rescue doses needed (n.)	9 (30%)	8(26.7%)	16(53.3%)	0.01	0.224		

in HTS group (68.6 mmHg) and the lowest in M group (60.1 mmHg). At that time point, MAP differed significantly between groups ($p < 0.001$). At 150 min., no significant difference was detected between groups (p =0.261). Heart rate (HR) showed no significant difference between groups either at baseline or subsequent time points (p = 0.438, 0.237, 0.672 and 0.521 respectively).

CVP showed no significant difference between groups at baseline (p =033), but at 30 min. it was the lowest in M group (9.5 cm H_2O) which was significantly lower when compared with HTS group and C group (p =0.001) but when comparing HTS and HTS/M groups showed no significance (p =0.32). At 90 min., average reading was the highest in HTS group (12.1 cmH_2O) and the lowest in M group (6.8 cm H_2O) with significant difference between all groups ($P < 0.001$). At 150 min., no significant difference was detected between groups (p =0.166). Within group comparisons revealed significant difference in HTS group

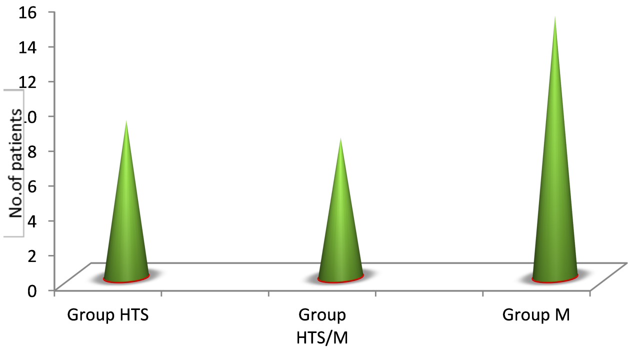

Fig. 2: Need for resue hyperosmolar dose in different groups

at 30 and 90 min averages compared to baseline (p =0.001), in HTS/M group it was only significant at 30 min(p =0.04) and in M group it was significantly lower at 30 and 90 min (p=0.001) compared to baseline.

Intraoperative total fluid intake was the least in HTS group (2134 ml average) which was significantly lower when compared to HTS/M and M groups (p < 0.001), but no significance was detected when comparing fluid intake between HTS/M and M groups (p =0.272). Total urine output was maximum in M group (1177 ml in average) which was highly significant when compared with HTS group (p < 0.001), but was not significant when compared to HTS/M group (p =0.165). Comparing of total volume of urine output between HTS and HTS/M groups revealed a highly significant result(p < 0.001). Hypotensive episodes intraoperatively were more frequent in M group (12 patients), and showed significant differences when compared with HTS (P = 0.006) and HTS/M groups (p =0.028). The least frequent hypotensive attacks were noticed in HTS group (only 3 patients).

3.3. *Serum osmolarity and electrolytes*

Sharp rise in serum Na level was noticed in HTS group at 30 min (145.7 mEq/L) while significant decline in M group was noticed (133.7 mEq/L, p < 0.001) without significant change in HTS/M group. At 90 min serum Na levels started to decrease in HTS and HTS/M groups without significant change in M group, no significance was observed between HTS/M and M groups (p =0.143). At 150 min, HTS group showed significantly higher levels compared with M group (p =0.003) but no significance between HTS and HTS/M groups was detected (p =0.341) (Table 5).

Serum osmolarity showed no significant difference at baseline (p =0.448), but at 30 min it was significantly higher in all groups (p = 0.001) compared to baseline with highest average in HTS group (312.1 mOsm/L). At 90 min., it showed a significant higher averages from baseline but no significance was detected between HTS/M and M groups (p =0.419). At 150 min., no significant difference either between groups (p =0.122) or within group compared to baseline (p =0.524) (Figure 3).

Serum lactate showed a significant rise in M group at 30 min and 90 min (1.428, 1.492 mmol/L) which was significant compared with other groups (p < 0.001). At 150 min, no significance was observed between HTS and HTS/M groups (p =0.189). Meanwhile, M group showed significant higher level when compared with other groups (p < 0.001)

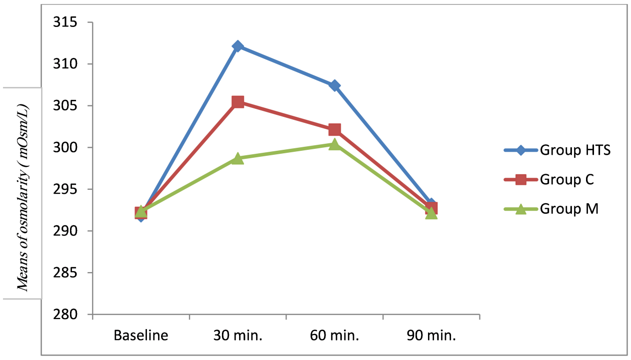

Fig. 3: Comparison of serum osmolarity in groups at different time points

3.4. *Outcome at SICU*

Total hours of postoperative ventilation (when needed) was calculated in each group and showed no significant difference between groups (p =0.147) (Table 4). No serious postoperative complications were recorded in all groups.

4. Discussion

Our study compared the effects of the traditional hyperosmolar therapy using either 20% Mannitol or 3% HTS with a new balanced therapy of both agents on brain relaxation and hemodynamic stability during supratentorial brain tumors resection, and showed that:[1] the administration of equiosmolar volume of either 3% HTS or balanced therapy of 3% HTS and 20% mannitol had a similar satisfactory brain relaxation score which was comparable to the effect of 20% mannitol;[2] MAP was significantly preserved near to its baseline values when using both agents consecutively;[3] no difference was found between HTS and HTS/M as regarding the need for a second hyperosmolar dose, meanwhile; it was significantly higher with 20% mannitol[4] total fluid intake and total urine output during surgery were significantly higher with 20% mannitol when compared with 3% HTS or the balanced regimen. Collectively, these effects were the same as we hypothesized before this study.

The effect of osmolarity on reducing brain bulk was firstly described by Weed and McKibben in 1919.[7] Since

Table 5: Serum Na, osmolarity and serum lactate

	Group HTS (n=30)	Group HTS/M (n=30)	Group M (n=30)	P-value	Between groups HTS/C	HTS/M	M/C
Serum Na (mean ± SD)							
Baseline	139.9±2.1	139.03 ± 2.2	138.9 ± 2.4	0. 18	——-	——-	——-
30 min	145.7± 1.9	138.9 ± 2.4	133.7± 2.4	0.001	0.001	0.001	0.001
90min.	142.5 ±2.3	135.5 ± 2.1	134.8± 2.2	0.001	0.001	0.001	0.143
150 min.	136.1±2.2	135.4 ± 2.2	133.8±2.2	0.001	0.341	0.003	0.02
Osmolarity (mOsm/L)							
Baseline	291.8± 1.6	292.2 ± 1.74	292.4 ± 2.19	0.448	———	——-	———
30 min.	312.1 ± 3.2	305.5 ± 4.1	301.4 ± 5.8	0.001	< 0.001	< 0.001	< 0.001
90 min.	307.4 ± 4.4	302.1± 3.6	300.4 ± 5.2	0.001	< 0.001	< 0.001	0.419
150 min.	293.2 ± 3.8	292.7± 2.5	292.1 ± 2.4	0.122	———	< 0.001	——-
Serum Lactate (mmol/L)							
Baseline	1.287± 0.7	1.294± 0.7	1.293± 0.8	1.00	———	———	———
30 min.	1.295 ± 0.7	1.345 ± 0.9	1.428 ± 1.2	< 0.001	< 0.001	< 0.001	< 0.001
90 min.	1.317 ± 0.9	1.366 ± 1.1	1.492 ± 1.4	< 0.001	< 0.001	< 0.001	< 0.001
150 min.	1.359 ±1.2	1.389 ±1.4	1.460 ± 1.4	< 0.001	0.189	< 0.001	< 0.001

that time, investigators tried to use many agents like glucose, magnesium sulphate, sucrose, urea, mannitol and saline to decrease intracranial pressure (ICP).[8] Mannitol was introduced in the 1960s[9] and adopted solely through 1980s, but in the last decades HTS (in different concentrations) was introduced as an alternative hyperosmolar therapy during supratentorial brain surgeries.[10]

As anesthetists, the major challenge we face during such surgeries is always related to the proper brain relaxation. Meanwhile, the extreme alterations of MAP during brain surgeries may carry a significant risk regarding surgical outcome and ICU stay. So, the need for a satisfactory brain relaxation is weighed against stability of hemodynamics during such surgeries.

Both 3% HTS and 20% mannitol had been investigated, either in humans or animals, for their physical effects on brain dehydration.[10,11] Both agents were evidenced to be effective in reducing brain bulk as showed by Min Li et al.[12] and Wu et al.,[6] but which is more effective ?. Sakellaidis et al.[13] found no statistically significant difference using 20% mannitol and 15% HTS regarding ICP reduction, while Battison et al.,[14] Wu et al.[6] and others showed that HTS was superior to Mannitol 20%.

The mechanisms of both agents to decrease the bulk of brain tissues is dedicated to their hyperosmolar effect which shifts water from the intracellular and intercellular spaces to the intravascular compartment due to the increased osmotic gradient across BBB which is normally impermeable to both. Reflection Coefficient (RC) is usually used to determine the relative permeability of BBB to solutes, where (RC=1) means absolute impermeable and (RC=0) means completely permeable. Because of its higher reflection coefficient, HTS was shown to be more effective than mannitol (1.0 and 0.9 respectively).[6] Once water is shifted from brain tissues; both agents differ in their behavior, mannitol - as an inert agent- has a strong diuretic effect which leads consequently to a significant water loss through the kidneys. In contrast, HTS - as an active substance - preserves the intravascular volume with minimal water loss.[12]

In fact, efficacy of hyperosmolar therapy during brain surgeries is influenced by many factors; patient's BMI, type and maximum diameter of the tumor and presence of midline shift. All these factors contribute in the related increase of ICP and hence the brain bulk prior to surgery. Fortunately, all these variables were not significantly different during this study.

Administration of HTS evidenced to cause a risky hyperosmolarity, cerebropontine myelinosis, hypokalaemia, congestive heart failure and intracerebral bleeding specially in a higher concentrations (>3%),[5] while mannitol may predispose to a lowered MAP, K depletion, acute renal failure, pulmonary congestion, acidosis and is claimed to produce rebound intracranial hypertension.[4] Hence came the hypothesis of this study which stated that: "can we optimize the brain relaxation score during brain surgeries without expanding or depleting the intravascular space through the administration of a balanced hyperosmolar regimen?".

Rozet et al.[15] and Wu et al.[6] compared 3% HTS and 20% mannitol and showed a significant increase in Na load and decrease in urine output with 3% HTS. Our present study showed that the administration of 3% HTS alone was accompanied by higher serum Na load and a lower urine output compared with a balanced equiosmolar volume of both 3% HTS and 20% mannitol specially at 30 and 90 minutes. Hypernatremic state leads to the release of antidiuretic hormone which enhances the reabsorption of water by the kidneys. In contrast, mannitol causes decrease in serum Na load due to the initial hemodilution then its diuretic effect comes, leading to gradual hypernatremia.[1] So, both agents have opposed mechanisms.

When measured at 30 and 90 min; serum osmolarity showed a significant increase compared to baseline readings, then returned near to baseline at 150 min with mannitol and combination group, while it was slightly higher in HTS groups which was explained by the fade of osmotic load of both agents with time and the more prolonged action of HTS. Maximum osmolarity achieved during this study was 312.1 mOsm/L (HTS group) which was lower than the recommended maximum levels (320 mOsm/L and 360 mOsm/L for mannitol and HTS respectively).[16] This explained the lack of any serious complications in all groups throughout the study.

During supratentorial brain tumor resection, a MAP between 55 -65 mmHg is always desired to minimize blood loss even in small sized tumors. In present study, a good correlation was found between serum Na level and MAP within each group at 30 and 90 Minutes. In HTS group, higher MAP values were dedicated to the high osmotic pressure gradient which shifted water to intravascular space, this necessitated the administration of 20 mg furosemide in 18 (20%) patients; meanwhile the combined hygroscopic and diuretic actions in the HTS/M group were responsible to the more stable MAP, only 2 (6.7%) patients needed a bolus of diuretic. But at 150 min there was no significant difference between groups regarding serum Na level which was correlated with MAP means .We recorded the same pattern with CVP measures which showed significant difference between groups at 30 and 90 min, but at 150 min no significance was detected although all groups showed higher CVP levels compared to baseline. Heart rate (HR) showed no significant difference between groups all through check points which can be explained by the proper anesthetic management protocol intraoperatively regarding depth of anesthesia and analgesics administration.

Fluid management was done through the study guided by our standard recommendations; in the HTS/M group total fluid intake was significantly higher than 3% HTS group which was understood due to the diuretic effect of mannitol, while it was the highest in M group. Hetastarch was used in addition to different crystalloids to reserve the intravascular volume except when Hb fall < 9 mg/dl which was an indication for blood transfusion.

Serum lactate was measured at the same check points and showed an increase at all points; its highest value (1.492 mmol/L) was with mannitol at 90 min. High serum lactate levels can be dedicated to the hypovolemia resulting from the diuretic effect of mannitol which causes relative increase in its level,[17] meanwhile, the slight increase in lactate level in HTS group can be explained by the use of diuretic drugs to stabilize MAP.

Different dural tension scores are used to estimate brain relaxation intraoperatively as an alternative to ICP direct measurement which is not routinely measured in clinical practice. These scores showed a positive correlation with ICP.[16] Brain relaxation score (4 – point scale) - as a very subjective measure – was taken by the most senior surgeons who were –fortunately – the same through the whole study and who were blind to the regimen. While keeping $PaCo_2$ and core body temperature within normal range throughout this study, our results showed that HTS either alone or within the balanced regimen provided satisfactory brain relaxation in 20 patients (76%) and 16 patients (53.3%) respectively whereas in mannitol group only 5 patients(16.7%). Firm and bulging brain were reported in a higher incidence in mannitol group, 10 patients (33.3%) and 6 patients (20%) respectively which necessitated the higher need for hyperosmolar rescue bolus doses in 16 patients (53.3%), while in HTS and HTS/M groups 9 patients (30%) and 8 patients (26.7%) needed rescue doses. The superiority of HTS when compared with mannitol in reducing brain bulk was investigated widely in literature, but most of investigators used 3-point scale which is less objective than the 4-point scale we used in our study. Same results were shown by Wu et al.[6] who used equiosmolar volumes of both agents. Most of the previous studies either used unequal osmolar loads of mannitol and HTS[18,19] or studied both agents in traumatized brain injuries which is characterized by impaired BBB[15,20–22] which resulted in different conclusions. To the best of our knowledge, this is the first time to investigate a balanced regimen of both 20% Mannitol and 3% HTS in such surgeries with almost similar added satisfactory relaxed and fairly relaxed scores; 25 patients (83.3%) in HTS/M group while 26 patients (86.7%) in HTS group without significant difference in the need for rescue doses (p=0.224).

The mean postoperative ventilation hours was compared between groups as an indicator of good recovery, it showed no significant difference (P=147) without any serious complication observed during SICU stay for all groups.

A limitation to this study was the lack of correlation between the intraoperative administration of this balanced regimen and both postoperative clinical outcome and hospital stay. More studies are needed to evaluate long-term postoperative follow-up of such regimen.

Despite of being evidenced as a more effective agent in dehydrating the brain tissues during supratentorial surgeries compared to mannitol; HTS still needs a concrete titration because of its potential risks. To our knowledge, this study is the first to use "Balanced Hyperosmolar Therapy" via administrating both 3% HTS and 20% mannitol consecutively during such surgeries.

It is to be concluded that; the tailoring of a consecutive doses of both agents equivalent to the osmolar load of 3 ml/kg 3% HTS resulted in a satisfactory brain relaxation with a more stable and steady hemodynamic status and hence a better surgical comfort than using 3% HTS or 20%

Mannitol alone during supratentorial tumor resection.

5. Source of Funding

None.

6. Conflicts of Interest

There are no conflicts of interest.

Acknowledgements

Our deep thanks go to our intimate friend Prof. Abdelfattah Hegazy ; the General manager of ElSahel Teaching Hospital for his respected and unlimited help. We are also grateful to Dr. Laila Al Awamy for her help in statistics and our OR staff and colleagues for their help during this study.

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Cite this article: Elkafrawy SA, Khames MK, Kandeel IM. "*Balanced hyperosmolar therapy*" using 3% hypertonic saline - 20% mannitol versus an equiosmolar volume of either 3% hypertonic saline or mannitol 20% in supratentorial tumor resection: A new approach to achieve hemodynamic stability. *Indian J Clin Anaesth* 2021;8(2):221-229.