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Study of changes in cardiac output, stroke volume, and cardiac index with two doses of mannitol infusion during supratentorial craniotomy

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Abstract

Background: Mannitol is used extensively in supratentorial surgeries to reduce intracranial pressure. The optimum dose of mannitol is still a matter of debate. We have done this prospective, comparative and randomized study to compare the changes in cardiac output (CO), stroke volume (SV), cardiac index (CI), central venous pressure (CVP), brain relaxation, and side effects in two doses of mannitol infusion. We have divided 60 enrolled patients randomly into two groups. We infused 0.7gm kg^{-1} , 20% mannitol in 20 min duration in Group A and 1.4gm kg^{-1} of 20% mannitol in 20 min in Group B. Flotrac transducer was connected to assess SV, CO, and CI. We recorded and analyzed brain relaxation score, HR, MAP, CVP, SV, CO, and CI at predefined time intervals after mannitol infusion. Chi-square test and unpaired *t* test were used to analyze categorical and continuous variables between two groups.

Results: We have found statistically significant and better brain relaxation in Group B than Group A. Significant ($p < 0.05$) difference in CVP was found between the groups at 10, 20 min after start of infusion, and 5, 10, and 15 min after termination of infusion. We found significant ($p < 0.05$) difference in SV, CO, and CI between the groups at most of the time periods.

Conclusions: We can conclude that higher dose of mannitol provides better brain relaxation intraoperatively without significant adverse effects. We assessed more changes in hemodynamic and cardiac parameters with higher dose of mannitol that did not cause clinical deterioration.

Keywords: Mannitol, Brain relaxation, Stroke volume, Cardiac index

Key message Mannitol infusion does affect hemodynamic profile in different doses. We have done this study to assess these effects and to decide the safe limit with optimal brain relaxation.

Background

Supratentorial tumor resection involves dissection close to the eloquent areas of the brain. The problems in surgery include local and generalized pressure and susceptibility of the brain to damage from retraction and mobilization during surgical exposure (Andrews & Bringas, 1993; Zhong et al., 2003). Optimal brain relaxation helps improve the surgeon's operating conditions and minimizes the severity of retraction injury, improving the patient's outcome (Andrews & Bringas, 1993; Zhong

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et al., 2003; Hans & Bonhomme, 2006; Randell & Niskanen, 2006).

We found the most common agents for osmotherapy are mannitol and hypertonic saline (Rozet et al., 2007). On a traditional basis, mannitol is used as the most common and preferred agent for patients with high intracranial pressure (Brain Trauma Foundation, 2007). Conventional dose of 0.5–1 gm kg⁻¹ of 20% mannitol was used initially. Still, some studies have been done to determine the different doses of mannitol that can provide optimal brain relaxation and decrease intracranial pressure during craniotomy.

The Vigileo/FloTrac system (Edwards Lifesciences, Irvine, CA, USA) allows automatic and continuous monitoring of cardiac output (CO) based on pulse contour analysis and respiratory (Stroke volume variation) SVV. The main advantage of this new device is that it is minimally invasive and can be used with any arterial catheter. The Vigileo monitor can be used to monitor continuous cardiac output with the FloTrac transducer. Most studies mentioned above have used a single dose of mannitol to assess its effect. However, limited research has been done where mannitol has been studied in two different doses.

In the present study, we have compared two doses of 20% mannitol and their impact on cardiac functions using the Vigileo/FloTrac cardiac device with effect on brain relaxation and side effect profile. The research hypothesis of the study is that we anticipated a higher dose of mannitol would provide better brain relaxation with less or no change in hemodynamic profile and side effects. So, we can also use higher doses of mannitol in supratentorial craniotomies with safety.

Methods

The present study is a monocentric comparative prospective randomized and interventional study conducted in our tertiary care hospital and research center. After taking approval from the institutional ethical committee (IEC No. 16/16), we completed the study in 1 year, starting from August 2017 to July 2018. In this study, ethical principles for medical research were strictly followed according to the Helsinki Declaration of 2013.

The study's primary objective is to compare hemodynamic changes like HR, CVP, SV (stroke volume), CO (cardiac output), and cardiac index (CI) between 2 doses of mannitol using a FloTrac monitor.

The study's secondary objective is to compare brain relaxation and side effects between 2 doses of mannitol. In our study, we have included the patients of ASA I and II, between the age 20 and 60 years, posted for supratentorial surgery having a GCS of more than 10. Exclusion criteria for our study were patient refusal, patients ASA III or higher, Glasgow coma score <10, known history

of hypersensitivity to mannitol, history of drug abuse or alcohol intake, and uncontrolled medical conditions such as hypertension, diabetes mellitus or bronchial asthma, seizure disorder, plasma sodium <130 meq L⁻¹ or >150 meq L⁻¹, creatinine clearance <30 mL kg⁻¹, and any heart disease. The recruited 60 patients were randomly allocated to one of the following two groups (30 each), irrespective of age or gender. Randomization was achieved by block randomization with variable block design using a computer-generated randomization sequence. Allocation was double blinded using SNOPEs.

Group A: Dose of 0.7 gm kg⁻¹ 20% mannitol infused over 20 min.

Group B: Dose of 1.4 gm kg⁻¹ 20% mannitol infused over 20 min. (Quentin et al., 2013)

After preoperative evaluation, consent and premedication of tablet Alprazolam 0.25 mg and tablet Ranitidine 150 mg on the night before the surgery, patients were transferred to the operation theatre. In the operation theatre, we have attached basic monitors like non-invasive blood pressure (NIBP), pulse oximetry (SpO₂), and electrocardiogram (ECG), and 18 gauge intravenous access was taken. Patients were premedicated with inj. Midazolam 0.05 mg kg⁻¹ and inj. Fentanyl 2 µg kg⁻¹ intravenously. General anesthesia was induced with inj. propofol 2-3 mg kg⁻¹ and inj. vecuronium 0.1mg kg⁻¹. Ventilatory parameters were set to maintain EtCO₂ around 30 ± 5 mmHg. Under the aseptic conditions, a 7fr triple lumen central venous catheter was inserted in the internal jugular vein via the seldinger technique and intra-arterial cannulation was performed in the radial artery using a 22G cannula. The FloTrac transducer was then connected to the indwelling intra-arterial line, and the pressure transducer was connected to the central venous catheter and both to the Vigileo TM System. The patient's age, weight, height, and gender were entered. Baseline readings of heart rate (HR), mean arterial pressure (MAP), and cardiac function parameters like central venous pressure (CVP), stroke volume (SV), cardiac output (CO), and cardiac index (CI) were noted. We monitored temperature by the nasopharyngeal probe, and urine output monitoring was done hourly. Anesthesia was maintained using 50%O₂+50% air and inhaled isoflurane to keep the MAC between 0.8 and 1.2 with intermittent boluses of inj. Vecuronium (0.001–0.002 mg kg⁻¹) and fentanyl 50 ug. Target EtCO₂ was kept between 28 and 32 and was monitored continuously. We maintained core body temperature between 36 and 37.4°C. Starting with skin incision, patients received inj. Mannitol (20%) in doses of 0.7gm kg⁻¹ and 1.4gm kg⁻¹ in Groups A and B over 20 min via central line.

The attending neurosurgeon, who was kept blind to study groups, assessed the condition of the brain after

dural opening on a 4-point scale: 1-Perfectly relaxed, 2-Satisfactory relaxed, 3-Firm brain, and 4-Bulging brain (Quentin et al., 2013). Hemodynamic parameters like heart rate (HR), mean arterial pressure (MAP), and cardiac function parameters like central venous pressure (CVP), stroke volume (SV), cardiac output (CO), and cardiac index (CI) were recorded at baseline, 10 and 20 min after the start of mannitol infusion. These indices were again recorded at 5, 10, 15, 30, 45, 60, 90, and 120 min after termination of 20% mannitol infusion.

When we get hypertension that is MAP >20% above baseline value and /or tachycardia that is HR >20% above baseline value, we used inj. fentanyl 0.5–1 ug kg⁻¹ bolus or had increased the inspired isoflurane concentration to a maximum of 1.2 MAC or had infused propofol 0.5 mg kg⁻¹. If all this failed, we used labetalol in 5 mg increments. Hypotension dropping MAP to <20% below the baseline value was treated by escalating isoflurane to the minimum level of 0.8 MAC and intravenous fluids in bolus. We had used inj. Mephentermine 6 mg boluses for decreased blood pressure if the above strategies did not work. Inj Atropine 0.6 mg bolus was given for bradycardia, a heart rate less than 40. All patients were given inj Paracetamol 15 mg kg⁻¹ 30 min before completion of surgery. We had started tapering isoflurane at the time of skin suturing. We had reversed patients using inj. Neostigmine 0.05 mg kg⁻¹ and inj. Glycopyrrolate 0.01 mg kg⁻¹. We assessed for complications like tachycardia, excessive bleeding, excessive diuresis, and the requirement of postoperative ventilation. We had defined excessive bleeding by calculation of more than allowable blood loss. We have taken excessive diuresis as urine output of more than 4 ml kg⁻¹ h⁻¹.

All patients were shifted to the postoperative ward with good analgesia and standard postoperative care.

Sample size calculation

We had calculated sample size by below mentioned formula (Charan and Biswas, 2013). (Jaykaran & Tamoghna, 2013)

$$n = Z_{1-\alpha/2}^2 \times SD^2 / d^2$$

Z_{1-α/2} = Power of the study

SD = Standard deviation

D = Absolute error (difference in the means).

In a study (Quentin, et al) (Quentin et al., 2013), the mean heart rate was 72±14 in patients of low dose (0.7 gm kg⁻¹) of Mannitol and 70±13 in patients of high dose (1.4 gm kg⁻¹) of Mannitol. We had taken power as 80%, significance level as 5% with 95% confidence interval and absolute error of 2. We had taken SD as 5 and found total sample size of 24 in each group after calculation.

$$N = (1.96 * 1.96) * (5 * 5) / (2 * 2) = 24$$

Statistical analysis

The data of results were recorded in percentages, frequencies, and mean±SD. We used chi-square for the comparison of categorical variables between the groups. For the comparison of continuous variables between the groups, an unpaired t test was used. The repeated measures of analysis of variance were used to find the effect of time and time to group interaction in the change in various continuous variables. The p value < 0.05 was considered significant. We did all statistical analysis using SPSS 16.0 version (Chicago, Inc., USA).

Results

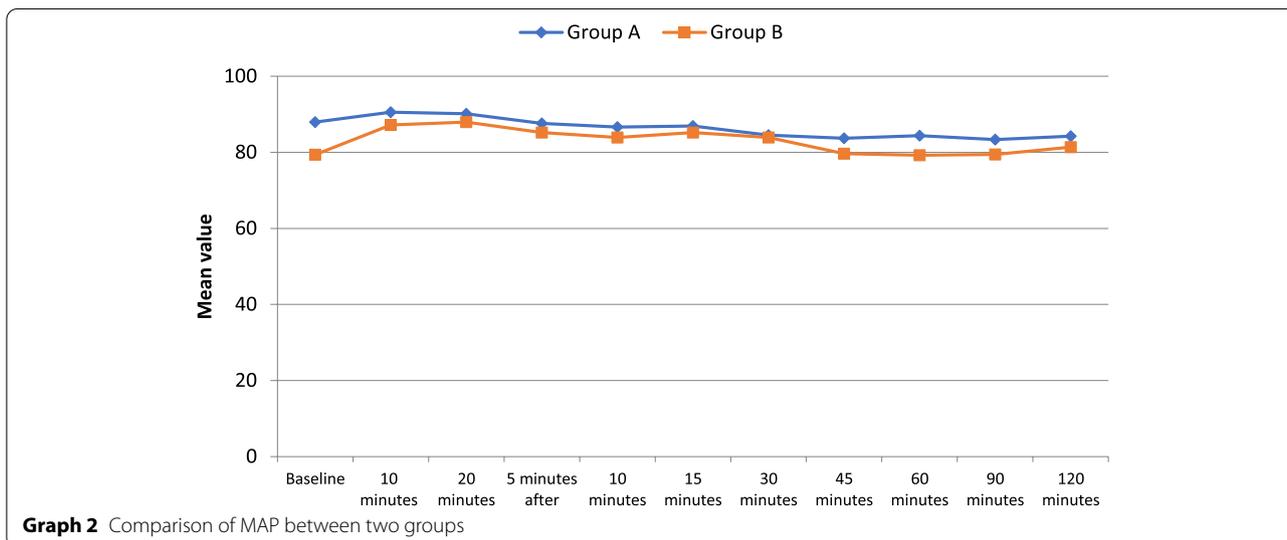
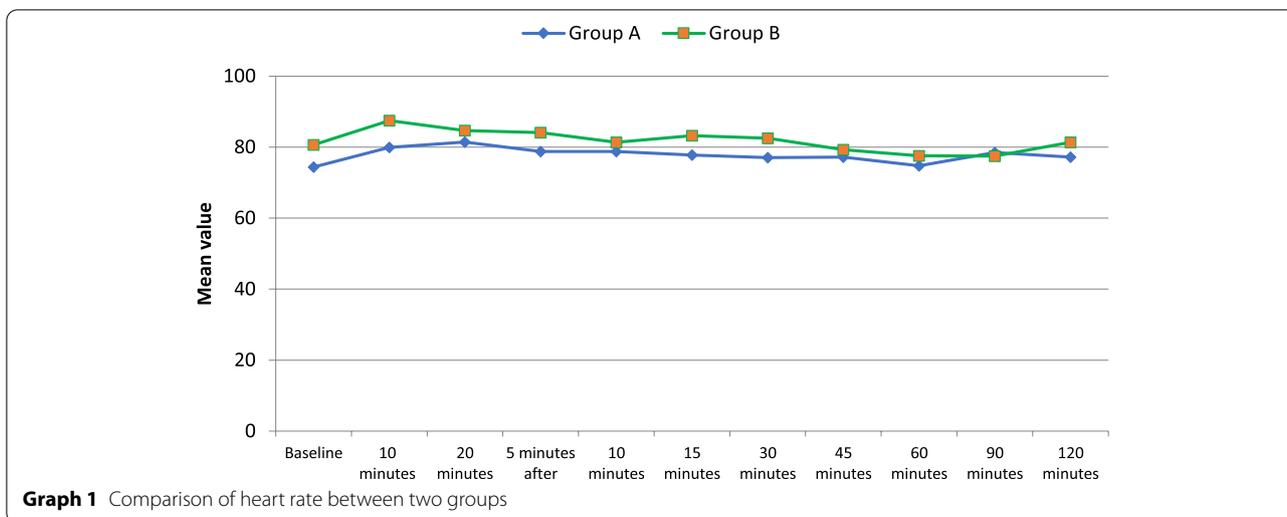
In our study, we have included total of 60 patients and after randomization, divided them into 2 groups of 30 each. We did not find any significant difference between groups A and B in terms of age, sex, anthropometric parameters, ASA grading, and GCS scoring (p>0.05).

As shown in Table 1, we had compared brain relaxation score after dural opening between the groups and found better brain relaxation score in group B that was statistically significant (p=0.002). We have compared heart rate between the groups across and as shown in Graph 1, there was no significant (p>0.05) difference found in heart rate at baseline and other time periods except at 10 min (p=0.02, lower in Group A compared to Group B). The repeated measures of analysis of variance showed that there was no significant effect of time (F=2.30, p=0.07) and time to group interaction (F=3.94, p=0.06) in the change in heart rate from baseline to subsequent time periods. After comparing MAP between the groups across the time periods, we had found no significant (p>0.05) difference in MAP at baseline and all other time periods between the groups (Graph 2). Table 2 shows significant (p<0.05) difference in CVP between the groups at 10, 20 min after start of infusion, and 5, 10, and 15 min after termination of infusion. The repeated measures of analysis of variance showed significant effect of time (F=27.51, p=0.0001) and time to group interaction (F=3.24, p=0.01) in the change in CVP from baseline to

Table 1 Distribution of patients according to brain relaxation score after dural opening between the groups

Brain grade	Group A (n=30)		Group B (n=30)		p value ¹
	No.	%	No.	%	
Score 1	12	40.0	24	80.0	0.002 ²
Score 2	18	60.0	6	20.0	

¹ Chi-square test, ²Significant (p<0.05)



subsequent time periods. As shown in Tables 3 and 4, we found significant ($p < 0.05$) difference in SV and CO between the groups at most of the time periods. The repeated measures of analysis of variance showed significant effect of time ($F = 116.38, p = 0.0001$) and time to group interaction ($F = 4.03, p = 0.01$) in the change in SV from baseline to subsequent time periods. The repeated measures of analysis of variance showed that there was significant effect of time ($F = 25.52, p = 0.0001$) and time to group interaction ($F = 2.56, p = 0.005$) in the change in CO from baseline to subsequent time periods. Table 5 shows significant ($p < 0.05$) difference in CI between the groups at most of the time periods. The repeated

measures of analysis of variance showed that there was significant effect of time ($F = 89.24, p = 0.0001$) and time to group interaction ($F = 3.63, p = 0.006$) in the change in CI from baseline to subsequent time periods.

We had also compared adverse events occurred during study. Hypotension was observed 10 and 16.6% in group A and group B, respectively. Sudden tachycardia episodes were observed in groups A and B were 6.6% and 10%. 6.6% and 3.3% patients develop excessive bleeding in groups A and B, respectively. Incidence of postoperative ventilation is 6.6% in both groups A and B. All the adverse effects between the groups were found insignificant statistically $p > 0.05$ (Table 6).

Table 2 Comparison of central venous pressure (CVP) between the groups across the time periods

Time periods	Group A (n=30)		Group B (n=30)		p value ¹
	Mean	SD	Mean	SD	
Baseline	6.57	2.78	7.13	13.31	0.07
10 min	8.00	1.58	9.90	1.99	0.0001 ²
20 min	9.23	1.76	11.23	2.29	0.0001 ²
5 min after	10.47	2.39	12.13	2.81	0.01 ²
10 min after	9.97	2.54	11.63	3.21	0.03 ²
15 min after	7.77	2.39	9.23	2.86	0.03 ²
30 min after	6.90	2.20	7.03	2.47	0.82
45 min after	6.50	1.96	5.83	1.68	0.16
60 min after	5.67	1.79	4.97	1.81	0.13
90 min after	5.33	1.58	4.97	2.31	0.47
120 min after	5.23	2.10	5.10	2.72	0.83

¹ Unpaired t test, ²Significant (p<0.05). SD standard deviation

Table 3 Comparison of stroke volume (SV) between the groups across the time periods

Time periods	Group A (n=30)		Group B (n=30)		p value ¹
	Mean	SD	Mean	SD	
Baseline	53.67	15.50	59.40	8.18	0.07
10 min	60.97	15.50	68.90	10.93	0.02 ²
20 min	65.27	12.39	75.97	9.13	0.0001 ²
5 min after	70.13	14.18	85.23	8.27	0.0001 ²
10 min after	71.13	14.45	87.20	9.41	0.0001 ²
15 min after	63.70	11.93	76.50	7.26	0.0001 ²
30 min after	58.60	13.79	68.13	9.29	0.003 ²
45 min after	54.20	12.34	63.50	14.52	0.01 ²
60 min after	51.17	10.74	59.60	16.40	0.02 ²
90 min after	48.17	10.93	55.17	15.37	0.04 ²
120 min after	48.17	13.31	52.43	15.72	0.26

¹ Unpaired t test, ²Significant (p<0.05). SD standard deviation

Discussion

We have done this study to compare the effects two different doses of 20% mannitol on brain relaxation and cardiac function parameters in patients, posted for supratentorial craniotomy. In our study, we observed that the brain relaxation score was 1 in 40% patients of Group A while in 80% patients of Group B (Table 1). Our observation was compared to Hyungseok Seo et al. (Seo et al., 2017) who did prospective randomized study in 124 patients to find out the best intraoperative brain relaxation by different doses of 20% mannitol. They have compared doses of 0.25 gm kg⁻¹ (Group A), 0.5gm kg⁻¹ (Group B), 1.0gm kg⁻¹ (Group C), and 1.5 gm kg⁻¹ (Group D). They also observed that in groups C and D, brain relaxation was found better than groups

Table 4 Comparison of cardiac output (CO) between the groups across the time periods

Time periods	Group A (n=30)		Group B (n=30)		p value ¹
	Mean	SD	Mean	SD	
Baseline	4.10	1.70	4.80	1.13	0.06
10 min	4.91	1.65	6.04	1.31	0.005 ²
20 min	5.23	1.37	6.35	1.06	0.001 ²
5 min after	5.53	1.61	7.13	0.95	0.0001 ²
10 min after	5.53	1.48	7.16	1.34	0.0001 ²
15 min after	4.96	1.47	6.19	0.88	0.0001 ²
30 min after	4.56	1.48	5.50	1.09	0.007 ²
45 min after	4.10	1.29	5.00	1.26	0.009 ²
60 min after	3.92	5.24	4.62	1.39	0.76
90 min	3.74	1.16	4.24	1.21	0.10
120 min after	3.62	1.26	4.19	1.26	0.08

¹ Unpaired t test, ²Significant (p<0.05). SD standard deviation

Table 5 Comparison of cardiac index (CI) between the groups across the time periods

Time periods	Group A (n=30)		Group B (n=30)		p value ¹
	Mean	SD	Mean	SD	
Baseline	2.50	1.03	2.93	0.77	0.07
10 min	3.00	0.95	3.60	0.86	0.01 ²
20 min	3.20	0.89	3.86	0.57	0.001 ²
5 min after	3.42	0.98	4.18	0.58	0.001 ²
10 min after	3.39	0.97	4.22	0.85	0.001 ²
15 min after	3.07	0.96	3.62	0.48	0.006 ²
30 min after	2.79	0.98	3.36	0.68	0.01 ²
45 min after	2.53	0.91	2.98	0.71	0.03 ²
60 min after	2.44	0.84	2.72	0.81	0.20
90 min after	2.26	0.74	2.48	0.72	0.24
120 min after	2.20	0.86	2.44	0.78	0.26

¹ Unpaired t test, ²Significant (p<0.05). SD standard deviation

Table 6 Comparison of patients according to adverse events during study

Adverse events	Group A (N=30)		Group B (N=30)		P value
	Number	Percentage	Number	Percentage	
Sudden hypotension	3	10%	5	16.6%	>0.05
Sudden tachycardia	2	6.6%	3	10%	>0.05
Excessive diuresis	3	10%	5	16.6%	>0.05
Excessive bleeding	2	6.6%	1	3.3%	>0.05
Postop ventilation	2	6.6%	2	6.6%	>0.05

A and B. Sorani et al. (Sorani et al., 2008) found that at high mannitol concentration ICP was decreased accordingly in traumatic brain injury patients.

In our study, we have not used colloids, blood products, and diuretics. We have used only maintenance fluid and mannitol. Therefore, we can say that all the hemodynamic changes are depicted due to effect of mannitol. No statistically significant difference in heart rate was found between the groups except at 10 min after starting the mannitol infusion (Graph 1). Similar to our study, Quentin et al. (Quentin et al., 2013) also found no significant difference ($p=0.5$) heart rate in both group that received 0.7 gm kg^{-1} and 1.4 gm kg^{-1} of 20% mannitol. Also, no significant difference in heart rate was observed by Chatterjee et al. (Chatterjee et al., 2012) in their study after giving 1 gm kg^{-1} of 20% mannitol.

In our study, we had not observed any significant difference in MAP between the groups at all time periods (Graph 2). The study by Quentin et al. also showed that no significant change in MAP was observed ($p=1$) in both groups received 0.7 gm kg^{-1} and 1.4 gm kg^{-1} , respectively. Raghava et al. (Raghava et al., 2015) also found no significant change in SBP, diastolic BP, and MAP with respect to time after giving 1 gm kg^{-1} of 20% mannitol. Similar result was obtained by Malik et al. (Malik et al., 2014) and Soriano et al. (Soriano et al., 1996) after giving 1 gm kg^{-1} mannitol (20%). Gayatri et al. (Gayatri et al., 2014) suggested that the reason no change in MAP may be due to time duration of infusion that is around 30 min. Greater fall in MAP is occurred due to high rate of infusion of mannitol. Chatterjee et al. observed similar result and quoted that after infusing mannitol, in start SVR is decreased, but this decrease is neutralized by increase in cardiac output. So, MAP is maintained. In later stage, SV, CO, CI, and CVP were decreased and neutralized by increase in SVR, so again no change used to occur in MAP. In contrast, Sokhal et al. (Sokhal et al., 2017) observed transient decrease of MAP in mannitol group at 10 min after the start of infusion ($P < 0.01$). The reason for that was high rate of infusion of mannitol, given over 10 min.

In our study, while comparing CVP between the groups across the time periods (Table 2), we found significant ($p < 0.05$) difference in CVP between the groups at 10, 20 min after start of infusion, and 5, 10, and 15 min after termination of infusion. In each group, initially an increase in CVP was observed sequentially from 10 min of start of infusion and remains increasing up to 30 min in groups A and 15 min in group B after stopping of infusion. After that decrease in CVP was started and the final CVP value of study was lower than the baseline in both groups. So there is a dose dependent change observed in our study. Larger doses cause more change in CVP. Sokhal et al. also observed similar result in his study that CVP is changed significantly than baseline values, increased initially till 25 min of end of infusion followed by decrease after

giving 1 gm kg^{-1} of 20% mannitol. Chatterjee et al. showed in their study that CVP became increased significantly after 5 min of mannitol infusion (1 gm kg^{-1}), in comparison to baseline value ($P < 0.001$) and continued to be elevated till 15 min that was not significant. After that, CVP started decreasing from 15 min onwards and at 45 min CVP was found insignificantly lower than baseline value.

In our study, we have not found any significant ($p > 0.05$) difference in baseline SV, CO, and CI between the groups. There was significant ($p < 0.05$) difference seen in SV between both groups at most of the time periods as starting from 10 min after starting of infusion to 90 min after end of infusion. In both groups, the increase in SV started at 10 min after initiation of infusion increases with time and remains increased for 30 min in group A and for 60 min in group B after end of infusion (Table 3). Higher doses cause more variability in both direction and for prolong period of time. Likewise significant difference ($p < 0.05$) was seen in CO and CI between both groups at 10 and 20 min after starting of infusion to 45 min after end of infusion (Tables 4 and 5). In both groups, cardiac output and cardiac index start increasing 10 min after the start of infusion and remained above baseline up to 45 min after end of infusion. The value of all three parameters at the end of study was lower than the baseline in both groups.

Sabharwal et al. (Sabharwal et al., 2009) observed the same in his study of 11 patients using noninvasive cardiac output monitor and found that after giving 1 gm kg^{-1} of 20% mannitol, and SV and CO increased significantly for 15 min ($P < 0.05$) and after that decreased significantly at 45 min after end of infusion and became lower than that from 1 to 30 min ($P < 0.05$). Most probably, the cause for that change was initial expansion of volume due to high oncotic pressure followed by decrease in SV and CO due to diuresis. Cardiac index followed the same trend that it increased significantly at 1 to 10 min and afterwards it decreased at 40 to 45 min compared with 1 to 15 min. Chatterjee et al. also showed same results of increased CO, CI, and SV at 5–15 min after start of infusion that decreased at 45 min after completing infusion of mannitol. There are 3 factors that explains increase in SV and CO after starting mannitol infusion. First is increase in intravascular volume that in turn increases preload and so SV and CO. Secondly, it is considered that mannitol causes decrease in SVR due to decrease in viscosity of the blood, vasodilatation of the skeletal muscle, and histamine release. Third factor is positive inotropic effect of mannitol that increases SV and CO.

Limitations

Limitations in our study were small sample size and 4-point scale used for brain relaxation. We have not

described preoperative factors that may affect brain relaxation, such as the size and histological type of the tumor, peritumoral edema, and also high-risk patients with increased ICP were not included. Thus, a further study can be proposed by taking larger sample size and while considering peritumoral edema, CT grading of disease, and high-risk patients also.

Conclusions

On the basis of our study, we suggest the higher dose of mannitol (1.4g kg^{-1} v/s 0.7g kg^{-1}) provide better brain relaxation intraoperatively without significant adverse side effects, although we had observed alteration in hemodynamic and cardiac functions that did not cause clinical deterioration in patients undergoing supratentorial craniotomy.

Abbreviations

ASA: American Society of Anesthesiologists; CO: Cardiac output; SV: Stroke volume; CI: Cardiac index; CVP: Central venous pressure; MAP: Mean arterial pressure; GCS: Glasgow coma scale.

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Not applicable.

Authors' contributions

PKR has taken the patient data and analyzed the data. DM contributed to the hypothesis and methods of the article. MH analyzed and interpreted the patient data. MT has contributed to the hypothesis and was the major contributor of writing the manuscript. DKS had contributed to the surgery and given the data about the brain relaxation. SM contributed to the methods and writing of the manuscript. The authors read and approved the final manuscript.

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Availability and data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Consent to participate

Informed written consent to participate in the study was provided by all participants (or their parent or legal guardian in the case of children under 16).

Ethics approval and consent to participate

Approved by the Institutional Ethical Committee, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Reference no- 243/RMLIMS/2017, IEC No- 16/16.

Consent for publication

Written informed consent to publish this information was obtained from study participants.

Competing interests

The authors declare that they have no competing interests.

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