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A Pilot Study to Compare Effects of Mannitol with Hypertonic Saline in Combination with HES on Blood Coagulation and Platelet Function during Elective Craniotomy

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Abstract: ***Neurosurgery requires the use of osmotic agents to reduce intracranial pressure which can adversely affect coagulation. Thromboelastography provides early indicator of derangement of coagulation. A prospective, non randomized pilot study was conducted to compare the effect of administration of either mannitol or hypertonic saline and when combined with hydroxy ethyl starch on coagulation and platelet function, as measured by Thromboelastography. 22 neurosurgical patients, divided into 2 groups, received 20% mannitol (n=12) or 3% hypertonic saline (n = 10) followed by administration of hydroxy ethyl starch (HES). The Thromboelastography parameters were comparable in both the groups at baseline; after administration of the drug and also after HES administration. The results show that combining a single dose of either mannitol or hypertonic saline with hydroxyl ethyl starch does not appear to affect in-vivo coagulation.***

Keywords: 1) Mannitol; 2) Saline solution, Hypertonic; 3) Hydroxyethyl starch; 4) Thromboelastography; 5) Coagulation

1. Introduction

One of the important goals of anaesthetic management for patients undergoing craniotomy is to provide a relaxed brain for the surgeon to operate on. This allows easy surgical manipulations and causes less damage to the normal brain tissue. This in turn, results in less secondary injury to the brain, which improves the patient's neurologic outcome. Therefore, elective neurosurgical procedures often require the use of osmotic agents such as mannitol or hypertonic saline (HS) to reduce intracranial pressure by reducing the brain bulk[1, 2, 3]. Some tumours in the brain such as meningiomas can result in considerable blood loss during surgery due to their high vascularity. Intravascular volume resuscitation in these situations is done with the help of crystalloids and colloids. Consequently, such patients who have received Mannitol or Hypertonic Saline are administered colloids such as Hydroxy ethyl starch. Mannitol, Hypertonic saline and Colloids, such as Hydroxy ethyl starch, interfere with coagulation of blood and are known to cause defects in coagulation. This pilot study was carried out to compare the effects of administration of either mannitol or HS as well as when these two agents are combined with HES on in-vivo blood coagulation and platelet function in patients undergoing elective neurosurgical procedures using Thromboelastography (TEG)[4].

2. Methods

Permission for carrying out the study from Institutional Ethics Committee was obtained. 22 patients, divided into 2 groups (10 studied in HS group and 12 studied in mannitol group), who were subjected to elective decompression/ resection of tumours were recruited in the pilot study. Adult males or females in American Society of Anaesthesiology grade (ASA) I or II (patients with no co-morbid illness or with well controlled co-morbid illnesses) between 18-65 years posted for elective decompression/resection of tumours with preoperative Glasgow coma scale (GCS) 15 were recruited. Pregnant women, paediatric or geriatric age group patients, persons incompetent to give informed consent or prisoners were not recruited for the study. Patients with known allergy to mannitol or HS or HES, or with compromised cardiovascular status or Diabetes mellitus and patients who had history of prolonged anti epileptic drug (AED) ingestion were also excluded, on account of the effects of AEDs and prolonged deranged glycaemic control on the platelet functions. Informed consent was duly obtained.

Patients were divided into two groups, first group received 20% mannitol with a dosage of 1 gram/kg body weight, on beginning of craniotomy, followed by administration of HES. The other group received 3% hypertonic saline with a dosage of 5 ml/kg body weight, on beginning of craniotomy, followed by administration of HES. Monitoring for haemodynamics, oxygentation and ventilation was done intraoperatively. A standardized general anaesthesia technique consisting of induction with propofol and fentanyl, tracheal intubation after muscle relaxation with Vecuronium and maintenance of anaesthesia with air, oxygen and sevoflurane/isoflurane (MAC 0.6-0.8) was followed in all patients. Requirement of fluids was calculated to maintain pulse pressure variation (PPV).

Baseline investigations such as Haemoglobin (Hb), platelet count, Prothrombin Time (PT), Activated Prothrombin Time (APTT) and platelet function test (by Thromboelastograph coagulation analysers (TEGR 5000 Haemostasis Analyser System) were done in all patients before the start of surgery. A second set of similar investigations namely Hb, platelet count, PT, APTT and

platelet function test (by TEG) were performed 15 minutes after the administration of mannitol or hypertonic saline, as Mannitol and HS take 10 – 30 minutes to show their osmotic action. Thereafter, both groups of patients received 20ml/kg of HES (Voluven® - Fresenius Kabi, Bad Homburg, Germany - consisting of a maize derived 6% HES of Molecular weight130 kDa, Molar Substitution 0.40, C2/C6 ratio 9:1 and suspended in normal saline) and the next set of similar investigations Hb, platelet count, PT, APTT and platelet function test (by TEG) were repeated in both the groups, 15 minutes after the administration of HES, for the haemodilution to take place. Primary end points studied were: Hb, PT, and APTT, Platelet function test assessed by TEG and platelet count at three points as already notified. Secondary end points noted were: total amounts of crystalloid, colloid, bleeding, urine output and blood and blood products used during surgery. Postoperative CT was not undertaken routinely to rule out any haematoma.

Data was analyzed using SPSS software. Two way repeated measure Anova was utilized to find out any significant difference between different time points. If a statistical difference was found then post hoc analysis applying Bonferroni test was done to know which time points differed statistically. Continuous data was compared with independent t test between the two groups.

3. Results

The age of patients in both the HS and the mannitol groups were comparable with mean age being 45 (±9.7) and 40.8 (±11.4) years respectively. Males and Females were equally distributed in both the groups being 50% each.

The distribution of various type of tumours were: Vestibular Schwannomma (9); Glioma (3); Meningioma (5); Pituitary Macroadenoma (1); Craniopharyngioma (2); Epidermoid tumour (1) and Hemangiopericytoma (1).

Hb (in gm %), PCV, PT, APTT, Platelet Count was comparable in both the groups at baseline. The TEG parameters like the R value, K value, Alpha (α) angle and Maximum Amplitude (MA) values were also comparable in both the groups at baseline. Within group comparison Hb, PCV showed a statistically and clinically significant decline (Table 1). However, these differences were similar in both the groups. The change in R value and K value was not statistically significant, both within as well as between group comparisons (Table 1). The changes in the alpha angle were similar in both the groups and were maintained within normal limits at all times. The change in MA value was not statistically significant both, within as well as between group comparisons (Table 1).

INR was maintained well within normal limits in both the groups. The change in PT, APTT and Platelet Count was statistically significant when compared within group between baseline and after administration of HES. However, PT, APTT and Platelet Count were maintained well within normal limits at all times (Table 2). These changes were similar in between the groups across different time points.

The secondary end points (Table 3) analyzed were the mean intra operative consumption of crystalloids, colloids, Fresh Frozen Plasma (FFP) and Packed Red Blood Cells (PRBC). The mean intra operative consumption of crystalloids was 2535 ml (±1562.1 ml) in the HS group whereas it was 3318.2 ml (±1209.8 ml) in the mannitol group. The p value for this distribution was 0.219. The mean intraoperative consumption of colloids was 1050 ml (±158.1 ml) in the HS group whereas it was 1218 ml (±252.3 ml) in the mannitol group. The p value for this distribution was 0.086. The mean intraoperative consumption of FFP was 0.3 Units (±0.7 Units) in the HS group whereas it was 0.36 Units (±1.2 Units) in the Mannitol group. The p value for this distribution was 0.885. The mean intraoperative consumption of PRBC was 0.9 Units (±1.5 Units) in the HS group whereas it was 1.36 Units (±1.9 Units) in the mannitol group. The p value for this distribution was 0.535.

4. Discussion

In this prospective pilot study to understand the effects of combining mannitol or HS with HES on coagulation, we did not observe any statistically significant changes between the two groups. There was no difference in baseline coagulation status in patients with gliomas and meningiomas. We also analyzed coagulation changes within the same group (within group analysis) as compared to baseline. We did not observe any clinically and statistically significant changes in TEG parameters.

Mannitol or HS are administered in the setting of neurosurgery for providing a relaxed brain[5]. This study was conducted to objectively delineate the effects of Mannitol and HS on blood coagulation when used along with HES in patients undergoing elective craniotomy, by Thromboelastography.

Thromboelastography is a more sensitive test of fibrinolytic activity than conventional measurements of fibrin degradation products. Four values that represent clot formation are determined by this test: the R value (or reaction time), the K value, the angle and the MA (maximum amplitude). The R value represents the time until the first evidence of a clot is detected. The K value is the time from the end of R until the clot reaches 20mm and this represents the speed of clot formation. The alpha angle is the tangent of the curve made as the K is reached and offers similar information to K. The MA is a reflection of clot strength.

In various in-vitro studies, mannitol has been found to alter the coagulation parameters such as, clotting time, clot formation time, and maximum clot firmness (MCF)[6]. In an in-vitro study study by Loustarinen et al, comparing the effects of 15% mannitol with that of 0.9%, 2.5% and 3.5% HS has shown that blood coagulation is disturbed more by 15% mannitol than by equiosmolar 2.5% saline. This disturbance seems to be attributed not only to overall clot formation and strength but also to pure fibrin clot firmness[6].

However, in the in vivo study by Singh GP, comparison of TEG parameters in patients who received mannitol and HES with that of mannitol and saline did not show major alterations in clotting parameters as assessed by TEG. The MCF though, differed in both the groups, were still within normal range and hence the authors have concluded that mannitol can be safely administered in patients undergoing craniotomy for supratentorial tumors, without clinically significant changes in coagulation parameters as measured by rotational TEG[7]. Our results are also consistent with these findings.

In our pilot study the mean R and mean K values in Mannitol group did not change significantly as compared to the baseline values. The mean alpha angle and mean MA also showed variation which was not statistically significant.

In our study the mean R (reaction time) in HS group fell from 4.9 to 4.2 minutes after HS. The mean α angle in HS group increased from 45.3 to 55.3 after HS. The mean MA in HS group decreased from 51.4 to 46.9 after HS. These changes were not statistically significant and the values of all parameters remained within clinically accepted range.

Hydroxy ethyl starch solutions are plasma volume expanders which affect haemostasis. Infusion of HES is shown to interfere with coagulation by decreasing Factor VIII plasma concentration and by interference with fibrin polymerization and thus decreasing clot strength[8,9,10]. Newer HES 130/0.4 is said to be safer[11].

TEG parameters changed from normal values in all patients. In HES group, R and K times increased, however, the alpha angle and MA decreased ($P < 0.05$). Our results showed that the TEG parameters were within normal limits at both baseline as well as at after delivery of HES and HS.

Our pilot study showed that there was a statistically significant prolongation of PT and APTT and reduction in Platelet count, haemoglobin and PCV after administration of either mannitol or HS and later with HES, as compared with baseline within the groups. However, these changes were similar in both the groups.

There are some limitations of this study. This is a pilot study with only 22 subjects. We used only a single bolus dose of either mannitol or HS. The dose of HES was also limited to 20ml/kg body weight. The results are limited to a subset of patients who were not suffering from diabetes mellitus nor had a long standing exposure to Antiepileptic drugs. We excluded patients with diabetes mellitus and patients on long standing Antiepileptic treatment from our study protocol because both the conditions are related to some alteration in platelet function. Diabetes mellitus is considered to be prothrombotic state, with chronic platelet activation, activation of coagulation system and decreased fibrinolytic potential[12].

Antiepileptic drugs on chronic use also lead to various abnormalities in platelet quantity and quality. Leukopenia, thrombocytopenia and various anaemia's have been reported in isolated cases with the all the AED[13,14] except gabapentin and lamotrigine. A dose-dependent thrombocytopenia and/or platelet dysfunction (due to inhibition of platelet aggregation) has been reported infrequently in patients on valproic acid[15,16]. Hence patients on chronic antiepileptic medication were also excluded from the study protocol.

5. Conclusion

The results of this pilot study show that combining a single dose of either mannitol or hypertonic saline and with hydroxyl ethyl starch does not appear to affect in vivo coagulation as measured by TEG. However further studies involving a large number of patients are required to confirm this finding.

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Tables

Table1: Comparison of Parameters between the Mannitol and HS groups

Parameter		Mannitol			HS		
		Point A	Point B	Point C	Point A	Point B	Point C
HB	Mean ± SD	12.8 ± 1.4	11.6 ± 1.3	8.9 ± 1.6	12.2 ± 1.6	11.0 ± 1.4	8.1 ± 0.9
	N	12	12	12	10	10	10
	p value	0.323[a]	0.324[b]	0.180[c]			
PCV	Mean ± SD	38.8 ± 4.7	35.6 ± 4.7	27.8 ± 6.1	37.1 ± 4.7	33.7 ± 3.6	25 ± 2.9
	N	12	12	12	10	10	10
	p value	0.404[a]	0.303[b]	0.206[c]			
MA	Mean ± SD	46.5 ± 13.0	50.5 ± 12.2	38.8 ± 16.9	51.4±16.8	46.9±9.1	45.9±22.0
	N	12	11	12	10	10	09
	p value	0.457[a]	0.465[b]	0.409[c]			
α	Mean ± SD	41.4±13.8	48.1±12.7	42.6±14.5	45.3±12.4	55.3±13.6	43.7±17.0
	N	12	11	12	10	10	09
	p value	0.496[a]	0.222[b]	0.869[c]			
R	Mean ± SD	5.7±1.8	3.8±2.4	5.4±2.5	4.9±1.6	4.2±1.9	4.8±2.4
	N	11	11	10	8	8	7
	p value	0.677[a]	0.710[b]	0.642[c]			
K	Mean ± SD	4.7±2.7	4.1±1.8	4.7±2.1	4.3±2.4	3.4±2.9	4.6±2.9
	N	11	11	10	8	10	7
	p value	0.749[a]	0.530[b]	0.959[c]			

Point A = Values at Baseline
Point B = Values about 15 minutes after Mannitol or HS administration
Point C = Values about 15 minutes after HES administration
N = Number of subjects
SD = Standard Deviation
a = p value calculated for significance between the two corresponding Point A in the Mannitol and HS groups
b = p value calculated for significance between the two corresponding Point B in the Mannitol and HS groups
c = p value calculated for significance between the two corresponding Point C in the Mannitol and HS groups

Statistical Analysis: Two way repeated measure Annova was utilized to find out any significant difference between different time points. If a statistical difference was found then post hoc analysis applying Bonferroni test was done to know which time points differed statistically. Continuous data was compared with independent t test between the two groups.

Table 2: Comparison of Parameters within the groups

Parameter		Mannitol			HS		
		Point A	Point B	Point C	Point A	Point B	Point C
HB	Mean ± SD (in gm%)	12.8 ± 1.4	11.6 ± 1.3	8.9 ± 1.6	12.2 ± 1.6	11.0 ± 1.4	8.1 ± 0.9
	N	12	12	12	10	10	10
	Mean Difference	Between A& B	Between A & C	Between B & C	Between A & B	Between A & C	Between B & C
		0.3	0.6	0.4	0.3	0.8	0.5
	p value	0.001	0.000	0.019	0.004	0.000	0.000
PCV	Mean ± SD (in %age)	38.8 ± 4.7	35.6 ± 4.7	27.8 ± 6.1	37.1 ± 4.7	33.7 ± 3.6	25 ± 2.9
	N	12	12	12	10	10	10
	Mean Difference	Between A& B	Between	Between B	Between A & B	Between A & C	Between B & C

			A & C	& C			
		3.2	11.0	7.8	3.4	12.0	8.7
	p value	0.000	0.000	0.000	0.001	0.000	0.000
PT	Mean ± SD (in secs)	13.0 ± 4.2	14.8 ± 0.9	17.1 ± 1.4	14.0 ± 0.9	14.8 ± 0.9	16.6 ± 0.9
	N	12	12	12	10	10	10
	Mean Difference	Between A& B	Between A & C	Between B & C	Between A & B	Between A & C	Between B & C
		1.7	4.1	2.4	0.8	2.6	1.8
	p value	0.194	0.008	0.000	0.016	0.000	0.000
APTT	Mean ± SD (in secs)	30.9 ± 4.7	35.6 ± 4.7	27.8 ± 6.1	37.1 ± 4.7	33.7 ± 3.6	25 ± 2.9
	N	12	12	12	10	10	10
	Mean Difference	Between A& B	Between A & C	Between B & C	Between A & B	Between A & C	Between B & C
		0.8	4.9	4.1	0.2	5.3	5.2
	p value	0.428	0.001	0.017	0.867	0.011	0.005
Platelet Count	Mean ± SD (in lacs)	2.7 ± 0.6	2.5 ± 0.5	2.1 ± 0.5	2.8 ± 0.6	2.5 ± 0.5	2.0 ± 0.3
	N	12	12	12	10	10	10
	Mean Difference	Between A& B	Between A & C	Between B & C	Between A & B	Between A & C	Between B & C
		0.3	0.6	0.4	0.3	0.8	0.5
	p value	0.001	0.000	0.019	0.004	0.000	0.000

Point A = Values at Baseline
Point B = Values about 15 minutes after Mannitol or HS administration
Point C = Values about 15 minutes after HES administration
N = Number of subjects

Statistical Analysis: Two way repeated measure Annova was utilized to find out any significant difference between different time points. If a statistical difference was found then post hoc analysis applying Bonferroni test was done to know which time points differed statistically. Continuous data was compared with independent t test between the two groups.

Table 3: Comparison of Secondary end points

		Mean	p
Urine output	Mannitol (N = 12)	1029.2 ± 515.4	0.009
	HS (N = 10)	520.0 ± 238.3	
Bleeding	Mannitol (N = 12)	216.7 ± 173.6	0.135
	HS (N = 10)	130.0 ± 25.8	
Total Blood Loss	Mannitol (N = 11)	1077.3 ± 628.2	0.209
	HS (N = 10)	790.0 ± 316.9	
Total Crystalloid	Mannitol (N = 11)	3318.2 ± 1209.8	0.212
	HS (N = 10)	2535.0 ± 1562.1	
Total Colloid	Mannitol (N = 11)	1218.2 ± 252.3	0.086
	HS (N = 10)	1050.0 ± 158.1	
PRBC	Mannitol (N = 11)	1.4 ± 0.9	0.534
	HS (N = 10)	0.9 ± 0.4	
FFP	Mannitol (N = 11)	0.4 ± 0.2	0.885
	HS (N = 10)	0.3 ± 0.1	

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