Original Article

Comparison of the efficacy of 0.9% normal saline with balanced crystalloid (Plasmalyte) in maintaining the metabolic profile in head injury patients undergoing evacuation of acute subdural haematoma – A randomised controlled trial

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ABSTRACT

Background and Aims: The choice of intravenous fluids is important in patients with traumatic brain injury (TBI), where large volumes may be required for resuscitation. Our study aimed to compare 0.9% normal saline (NS) with balanced crystalloid (Plasmalyte) in TBI patients in terms of metabolic and coagulation profile, brain relaxation score (BRS) and renal functions using serum urea, creatinine and urinary tissue inhibitor of metalloproteinases-2* insulin-like growth factor binding protein-7, [TIMP-2]*[IGFBP7], value to assess the risk of acute kidney injury. **Methods:** This randomised controlled trial on 90 TBI patients undergoing emergency craniotomy and subdural haematoma evacuation was conducted in a tertiary care institute. The patients were randomised to receive either NS (Group NS) or Plasmalyte (Group P) as the intraoperative maintenance fluid. The primary outcome measures included the potential of hydrogen (pH), base excess (BE) and chloride values from an arterial blood gas. The secondary outcomes were the coagulation profile, BRS and urinary [TIMP-2]*[IGFBP7]. The two groups' metabolic profile differences were analysed using two-way repeated analysis of variance. BRS was analysed using the Mann–Whitney U test. A P value < 0.05 was considered to be statistically significant. **Results:** The pH and chloride values were significantly higher, and the BE values were significantly lower in Group P compared to Group NS (P < 0.001). Brain relaxation and coagulation profiles were comparable between the two groups. Serum creatinine (P = 0.002) and urinary [TIMP-2]*[IGFBP7] (P = 0.042) were significantly higher in the NS group. **Conclusion:** Plasmalyte maintains a more favourable metabolic profile than NS in TBI patients without affecting brain relaxation adversely.

Keywords: 0.9% saline, acute kidney injuries, acute subdural haematoma, balanced salt solution, biomarkers, brain injuries, metabolic profile, Plasmalyte, traumatic

INTRODUCTION

Choosing an appropriate intravenous (IV) fluid is crucial in patients with traumatic brain injury (TBI).[1] Although 0.9% normal saline (NS) has been traditionally favoured in neurosurgical patients, its supraphysiological chloride content can lead to hyperchloremic metabolic acidosis and acute kidney

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injury (AKI) when infused in larger volumes (>2 l).[2,3] This, coupled with renal ischaemia and reduced glomerular filtration rate (GFR), heightens the risk of AKI. In addition, physiological derangements produced by overzealous IV fluid administration may necessitate further crystalloid and blood product infusions, establishing a vicious cycle.[4] Consideration of these factors is essential in the management of TBI patients.

Plasmalyte, an isotonic balanced crystalloid (BC) with a composition akin to plasma, maintains a more physiological metabolic profile than NS and does not worsen cerebral oedema like Ringer lactate. It has also been found to produce brain relaxation comparable to NS.[3] Serum creatinine may not be sufficient as a sole diagnostic marker of AKI, especially in the immediate postoperative period, necessitating the early use of urinary biomarkers.[5] Biomarkers like neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, liver fatty acid-binding protein and kidney injury molecule-1 (KIM-1) are not specific and have certain limitations. Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7), exclusive to renal tubular cells, and their combination, that is [TIMP-2]*[IGFBP7], have shown promise in the accurate detection of AKI.[6] However, there is a paucity of literature on the utility of this biomarker in patients with TBI.

Our study aimed to compare NS and Plasmalyte with respect to metabolic profile, brain relaxation, coagulation profile and the risk of AKI in the perioperative period in patients undergoing craniotomy and evacuation of acute subdural haematoma (SDH). The primary objective of our study was to compare the metabolic profile, which included potential of hydrogen (pH), partial pressure of carbon dioxide (pCO_2), bicarbonate (HCO_3), chloride, base excess (BE) and anion gap (AG), between the two groups. Our secondary objectives included the comparison of brain relaxation scores (BRSs), renal function tests (RFT), plasma osmolality, coagulation profile and urinary biomarkers [TIMP-2]*[IGFBP7] between both groups.

METHODS

After obtaining approval from the Institutional Ethics Committee (vide approval number JIP/IEC/2018/506, dated 29 March 2019), the trial was registered with the Clinical Trials Registry-India (vide registration number CTRI/2019/08/020655, accessible at www.ctri.nic.in). Patients were enroled from August 2019 to July 2021. Patients between 18 and 60 years of age scheduled for craniotomy and evacuation of acute SDH were included in the study. Patients who sustained major thoracic and abdominal injuries or long bone fractures, patients who had preexisting renal failure (defined as serum creatinine >2 mg/dl), patients with dyselectrolytemia, hepatic failure or preoperative altered coagulation status, and pregnant patients were excluded from our study. The study was conducted in accordance with the principles of the Declaration of Helsinki, 2013 and good clinical practice. Informed written consent was obtained from the guardians of patients for participation in the study and for using data for research and educational purposes.

Preoperative complete haemogram, blood urea, serum creatinine, prothrombin time (PT) and international normalised ratio (INR) were noted for all the patients. In the operation theatre, standard monitors [electrocardiogram, non-invasive blood pressure and peripheral capillary oxygen saturation (SpO_2)] were attached, and baseline values were noted. Ninety patients were randomised using block randomisation technique with a randomisation software into either Group NS or Group P. Patients in Group NS received 0.9% saline as the intraoperative maintenance fluid, and patients in Group P received Plasmalyte (Baxter Healthcare Ltd, Thetford Norfolk, UK). Allocation concealment was achieved using the serially numbered, opaque, sealed envelope technique. After preoxygenation with 100% oxygen via a face mask for 3 min, general anaesthesia was induced according to standard induction protocol [IV fentanyl 2 μg/kg, thiopentone 5 mg/kg and rocuronium 1 mg/kg]. After endotracheal intubation and initiation of mechanical ventilation, the right subclavian vein was cannulated with a 7-Fr, triple-lumen central venous catheter, and the radial artery was cannulated for invasive blood pressure monitoring and arterial blood gas (ABG) sampling. Depending on the group randomised, maintenance fluid was given at 2 ml/kg/h and titrated to the haemodynamic parameters. IV mannitol 1 g/kg was administered to all patients before opening the dura. Once the dura was opened, BRS was assessed on a 4-point scale (1- perfectly relaxed, 2- satisfactorily relaxed, 3- firm brain, 4- bulging brain) using tactile evaluation by the neurosurgeon who was blinded to the anaesthetic technique employed.[3] Baseline ABG was obtained for all patients. ABGs were

repeated every 2 h till the end of the surgery and on postoperative day (POD) 1 (POD1). The parameters collected from ABG were potential of hydrogen (pH), pCO_2, HCO_{3-}, partial pressure of oxygen (pO_2), sodium, potassium, chloride, calcium, AG, BE, haematocrit and plasma osmolality. Urine samples were collected at the start of surgery, 1 h after completion of the surgery and on POD1 for the measurement of urinary [TIMP-2]*[IGFBP7], using a commercially available enzyme-linked immunosorbent assay kit (ELK Biotechnology CO., LTD, Wuhan, China) in ng/ml. The value of urinary [TIMP-2]*[IGFBP7] was calculated and expressed in units of $(ng/ml)^2/1000$.

Haemodynamic parameters like heart rate (HR), systolic blood pressure, diastolic blood pressure, SpO_2, end-tidal carbon dioxide and respiratory rate (RR) were recorded at induction and at 10-min intervals after that, till the end of the surgery. Hypotension was managed with fluid boluses and IV mephentermine 3 mg boluses; further haemodynamic management was done with or without blood and blood products and vasopressor support as required. A blood sample for PT–INR was collected 1 h after the commencement of surgery. Blood loss during surgery, the volume of crystalloids given, blood transfused and urine output were also noted. Complete haemogram and RFT were repeated on POD1 and POD5. The primary outcome measures were pH, BE, and chloride, which were measured at specified time points perioperatively. The secondary outcome measures included BRS, coagulation profile, RFT, plasma osmolality and urinary [TIMP-2]*[IGFBP7]. The study participants and the anaesthesiologist, noting the study parameters, were blinded to the type of maintenance fluid used intraoperatively.

The sample size was calculated based on the study by Dey *et al*.[3] By comparing two independent means, considering the minimum expected difference in pH between the two groups as 0.0315, with a standard deviation (SD) of 0.05, the sample size was estimated to be 90 patients (45 in each group) with 5% level of significance and 80% power of the study. Statistical Package for the Social Sciences version 19.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Comparison of age, duration of surgery, blood loss, blood transfused, the volume of crystalloids given and urine output between the groups was done using an unpaired Student's *t*-test. Categorical variables were expressed as proportions or percentages. The difference in metabolic parameters (pH, pCO_2, HCO_{3-}, lactate, AG, BE), electrolytes, haematocrit, plasma osmolality, RFT and urinary biomarkers between the two groups was analysed using two-way repeated measures analysis of variance (ANOVA) after analysing the baseline values. Partial η^2 was used as effect size for two-way repeated measures ANOVA. Cohen's D value was calculated for unpaired *t*-test using the formula [D = M1 − M2/Sp], where M1 and M2 denote the sample means for groups 1 and 2 and S_p denotes the standard deviation of the pooled estimated population. BRS was analysed using the Mann–Whitney U test. A *P* value of less than 0.05 was considered significant.

RESULTS

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is depicted in Figure 1. The demographic parameters, including the duration of surgery, were comparable between the two groups [Table 1]. We observed lower pH and higher BE values at all time points in group NS, with statistically significant differences noted between the two groups; however, the remaining parameters like pCO_2, HCO_{3-} and AG were comparable [Table 2]. At all time points, sodium and chloride levels were significantly elevated in group NS [Table 3]. Plasma osmolality and BRS were comparable between the two groups [Tables 3 and 4]. There was an increasing trend of serum urea and creatinine in group NS on POD1 and POD5, and the difference between the two groups was statistically significant; however, all the measured values were well within the normal range in both groups [Table 5]. The two groups had a concurrent correlation with a change in urinary [TIMP-2]*[IGFBP7] levels and significant differences on POD1 [Table 5]. The two groups were comparable in terms of intraoperative blood loss, fluid requirement, urine output, blood transfusion requirement, and coagulation profile.

DISCUSSION

Our results indicate that Plasmalyte is better than 0.9% saline in maintaining the metabolic profile of patients

Table 1: Comparison of demographic parameters

Parameters	Group P (*n*=45)	Group NS (*n*=45)
Age (years)	44.62 (10.82)	40.29 (12.26)
Gender: male/female	32/13	36/9
Duration of surgery (min)	243.60 (46.2)	236.40 (42.0)
Glasgow Coma Scale	9.80 (2.17)	9.88 (2.07)
Number of patients received tracheally intubated to the operating room	12	13

Data expressed as mean (standard deviation) or numbers. NS=normal saline, P=Plasmalyte, n=number of patients

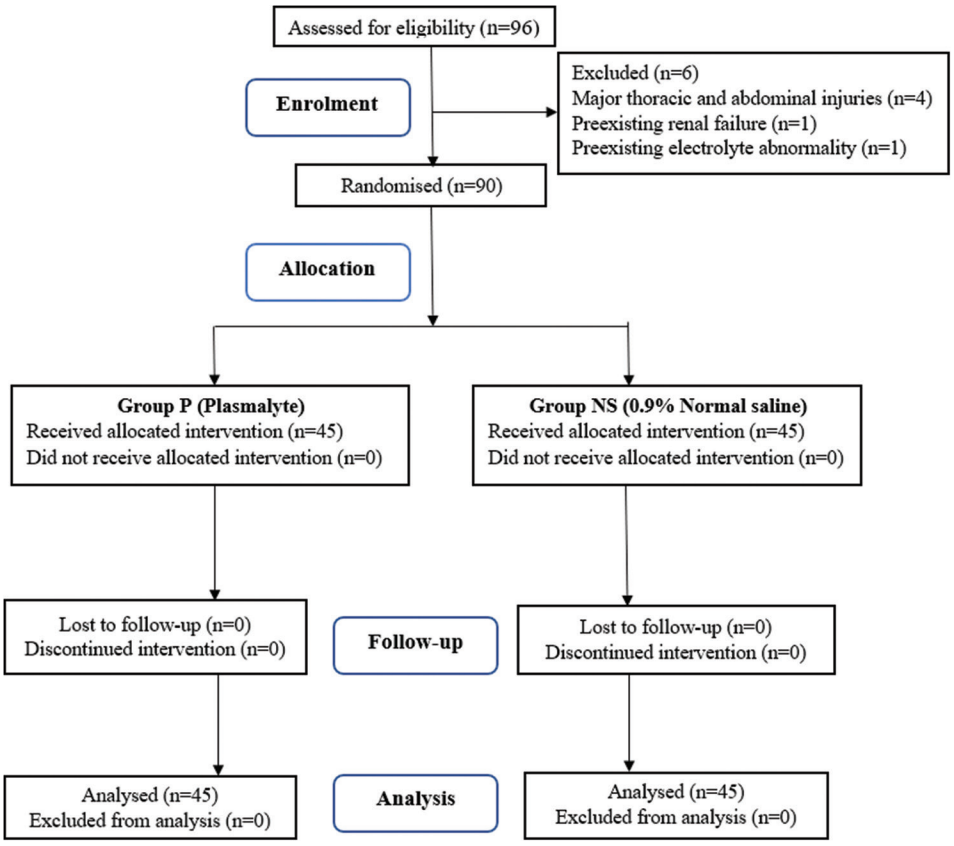

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Table 2: Comparison of metabolic parameters

Parameters	Group P (*n*=45) Mean (SD)	Group NS (*n*=45) Mean (SD)	Mean difference	95% CI of mean difference		Two-way repeated measures ANOVA *P* (effect size)
				Lower	Upper	
pH-baseline	7.39 (0.04)	7.38 (0.04)	0.01	0.00	0.03	
Second hour	7.41 (0.03)	7.37 (0.02)	0.03	0.02	0.05	<0.001 (0.335)
Fourth hour	7.42 (0.04)	7.37 (0.03)	0.05	0.04	0.07	
POD1	7.43 (0.05)	7.39 (0.05)	0.04	0.02	0.07	
pCO_2-baseline	32.22 (1.78)	32.71 (5.38)	-0.49	-2.17	1.18	
Second hour	31.4 (1.81)	30.91 (2.27)	0.50	-0.36	1.36	0.758 (0.002)
Fourth hour	29.45 (2.05)	29.93 (2.45)	-0.48	-1.63	0.67	
POD1	33.19 (2.51)	32.27 (2.20)	0.92	-0.07	1.91	
HCO_3- baseline	20.60 (2.10)	20.7 (2.00)	-0.17	-1.04	0.70	
Second hour	21.90 (2.60)	19.90 (1.30)	2.02	1.15	2.88	0.001 (0.169)
Fourth hour	21.80 (2.00)	19.60 (1.20)	2.19	1.31	3.08	
POD1	20.58 (3.32)	19.96 (1.82)	0.63	-0.49	1.75	
Anion gap-baseline	14.90 (1.70)	13.90 (1.70)	0.94	0.24	1.64	
Second hour	13.60 (1.80)	13.60 (2.20)	-0.02	-0.86	0.81	0.840 (0.001)
Fourth hour	14.10 (1.50)	14.30 (2.40)	-0.15	-1.15	0.86	
POD1	13.90 (1.50)	14.40 (1.60)	-0.45	-1.09	0.20	
Base excess-baseline	-1.50 (1.60)	-2.50 (1.30)	0.95	0.34	1.56	
Second hour	-2.31 (2.53)	-2.91 (1.64)	0.59	-0.30	1.49	<0.001 (0.243)
Fourth hour	-2.10 (1.70)	-3.80 (1.40)	1.68	0.87	2.48	
POD1	-2.10 (1.60)	-4.40 (2.10)	2.29	1.51	3.07	

ANOVA=Analysis of variance, CI=Confidence interval, HCO_3- =Bicarbonate, NS=Normal saline, P=Plasmalyte, pCO_2=Partial pressure of carbon dioxide, POD1=Postoperative day 1, SD=Standard deviation, n=number of patients

undergoing emergency craniotomy for evacuation of acute SDH without adversely affecting brain relaxation.

TBI is a global health issue associated with significant morbidity and mortality.[7,8] Fluid management in TBI

Table 3: Comparison of electrolytes (Na^+ and Cl^-) and plasma osmolality

Parameters	Group P (*n*=45) Mean (SD)	Group NS (*n*=45) Mean (SD)	Mean difference	95% CI of mean difference		*P* (effect size)
				Lower	Upper	
Na^+-Baseline	137.50 (4.40)	139 (3.10)	-1.49	-3.09	0.12	
Second hour	137.10 (3.80)	140.80 (4.10)	-3.70	-5.36	-2.05	<0.001 (0.277)
Fourth hour	138.20 (3.80)	142 (2.50)	-3.79	-5.47	-2.11	
POD1	139.10 (3.60)	141.50 (2.80)	-2.40	-3.75	-1.05	
Cl^--baseline	101.20 (5.20)	102.30 (4.80)	-1.04	-3.14	1.05	
Second hour	101.40 (4.60)	108.60 (4.70)	-7.20	-9.16	-5.24	<0.001 (0.696)
Fourth hour	100.30 (5.90)	112.90 (3.70)	-12.66	-15.22	-10.11	
POD1	101.30 (7.20)	115.20 (4.0)	-13.98	-16.41	-11.54	
Plasma osmolality-baseline	300.05 (9.51)	301.20 (9.70)	-1.42	-5.46	2.62	0.160 (0.010)
Third hour	301.39 (8.86)	301.9 (9.05)	-0.64	-4.38	3.09	
POD1	296.39 (9.25)	303.58 (9.36)	-3.02	-6.80	0.76	

Na^+- Sodium, Cl^--Chloride, CI=confidence interval, NS=normal saline, P=Plasmalyte, POD1=postoperative day 1, SD=standard deviation, n=number of patients

Table 4: Comparison of brain relaxation score between the two groups

Brain relaxation score	Number of patients in Group P (*n*=45)	Number of patients in Group NS (*n*=45)	*P*
1 (Perfectly relaxed)	0	0	
2 (Satisfactorily relaxed)	1	5	0.110
3 (firm brain)	33	25	
4 (Bulging brain)	11	15	

NS=normal saline, P=Plasmalyte, n=number of patients

has been a contentious area due to the correlation between the osmolality of fluids and cerebral oedema. Mildly hyperosmolar fluids, such as 0.9% saline, have been traditionally preferred for fluid resuscitation in TBI patients. However, the indiscriminate use of hyperchloremic IV fluids has been associated with an increased risk of adverse outcomes, including death in critically ill adults.[9–12] Conversely, a few large randomised controlled trials (RCTs) have failed to demonstrate a mortality benefit with using BC in critically ill adults.[13,14] Interestingly, in a large RCT, even though there was no difference in the incidence of AKI and requirement for renal replacement therapy (RRT) between the BC and saline groups, among patients who received larger volumes of isotonic crystalloids, those who received saline had a higher incidence of major adverse kidney events (MAKE).[13] Similarly, in another study conducted on non-critically ill adults, even though there was no difference in hospital-free days between patients who received BC and NS, the incidence of MAKE at 30 days was significantly lower in those who received BC for resuscitation.[15] This finding underscores the importance of choosing an appropriate crystalloid for resuscitation. In two recent RCTs comparing Plasmalyte and NS in neurosurgical patients, including only TBI patients, the authors found that Plasmalyte maintained the metabolic profile better than 0.9% saline.[2,16] Our results were in agreement with these two studies. In a subgroup analysis of the BaSICS RCT conducted on TBI patients, the authors found that using BCs was associated with a higher 90-day mortality. It should be noted that this increase in mortality was more pronounced in those patients who had a Glasgow Coma Scale score <6 at admission. In addition, this study could not prove conclusively whether the requirement of RRT was reduced in those who received BC, which is an important end point in studies evaluating clinically important outcomes of fluid management. Another drawback of this study was that they did not delineate the type of head injury, which in itself plays an important role in influencing patient outcomes.[17]

Among patients admitted to the intensive care unit following TBI, approximately 10% developed AKI, and 2% required RRT.[18] AKI requiring RRT is reportedly associated with a mortality rate of 45%–55%.[19] Therefore, early diagnosis and treatment of AKI is imperative to reduce mortality related to TBI. The conventional diagnosis of AKI, based on serum creatinine and urine output, results in a considerable delay in diagnosis because serum creatinine elevation occurs only after a significant reduction in GFR.[20] Urine output also may not be a reliable diagnostic marker of AKI in TBI patients on hyperosmolar therapy. This has led to the increasing use of biomarkers for the early detection of AKI. Among the various urinary biomarkers available for the detection of AKI, urinary [TIMP-2]*[IGFBP7] has been demonstrated to have a sensitivity of 89% for predicting AKI beyond a threshold value of 0.3 (ng/ml) ^{2}/1000 and a specificity approaching 95% for a threshold value ≥2 (ng/ml) ^{2}/1000.[20–22] It was found to outperform all the other biomarkers of AKI in a report by Kashani *et al.*[23] In a study conducted by Funke *et al.*[24] on critically ill adults, BCs were also associated

Table 5: Comparison of renal parameters, urinary biomarkers, coagulation parameters, blood loss and blood transfusion between the two groups

Parameters	Group P (*n*=45)	Group NS (*n*=45)	Mean difference	95% CI of mean difference		*P* (effect size)
				Lower	Upper	
Urea pre-op (mg/dl)	30.20 (24.07)	26.69 (13.09)	3.51	-4.61	11.63	
POD1	28.67 (15.80)	33.0 (19.60)	-4.33	-11.83	3.16	0.050 (0.012)
POD5	27.80 (12.74)	36.29 (18.24)	-8.49	-15.08	-1.90	
Creatinine pre-op (mg/dl)	0.89 (0.30)	0.82 (0.36)	0.07	-0.07	0.21	
POD1	0.67 (0.25)	0.85 (0.38)	-0.18	-0.31	-0.04	0.002 (0.042)
POD5	0.63 (0.27)	0.86 (0.49)	-0.23	-0.40	-0.06	
UrinaryTIMP2*IGFBP7 [(ng/ml)^2/1000] pre-op	0.29 (0.47)	0.21 (0.39)	0.08	-0.10	0.26	0.042 (0.024)
First hour	0.72 (0.68)	0.73 (0.92)	-0.01	-0.35	0.34	
24th hour	0.58 (0.64)	1.12 (1.50)	-0.54	-1.03	-0.06	
PT pre-op	10.93 (0.45)	11.18 (0.43)	-0.25	-0.43	-0.06	0.782 (0.076)
First hour	11.01 (0.40)	11.24 (0.48)	-0.23	-0.42	-0.05	
INR pre-op	0.87 (0.08)	0.90 (0.07)	-0.03	-0.06	0.00	0.813 (0.049)
First hour	0.89 (0.08)	0.92 (0.07)	-0.03	-0.07	0.00	
Crystalloids given (ml)	3908 (745.2)	3806.7 (581.7)	102.22	-177.84	382.29	0.470 (0.153)
Urine output (ml)	645.6 (116.7)	637.6 (130.5)	8.00	-43.85	59.85	0.760 (0.064)
Blood loss (ml)	735.1 (168)	762.2 (174.2)	-27.1	-44.59	98.79	0.450 (0.15)
Blood transfused (ml)	224.4 (221)	233.3 (255.6)	-8.9	-91.2	109	0.430 (0.037)

INR=International normalised ratio, PT=Prothrombin time, POD=Postoperative day, TIMP2*IGFBP7=Product of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 [(ng/ml)^2/1000], CI=Confidence interval, n=number of patients

with lower urinary concentrations of NGAL and KIM-1 compared to NS. In another study by Dey *et al.*[3] on adults scheduled for elective craniotomy for excision of supratentorial tumours, serum NGAL measured within 6 h of surgery was significantly elevated in patients who received NS perioperatively, compared to Plasmalyte. However, similar to our study, none of the patients in this study developed AKI.

Intraoperative brain relaxation in craniotomies is affected by the osmolality of the IV fluid used. Our findings concur with Dey *et al.*,[3] who also found no difference in BRS between patients who received either NS or BC intraoperatively during excision of supratentorial tumours. However, the authors did not comment on intraoperative BRS in another RCT comparing NS and Plasmalyte in TBI patients, where Plasmalyte was found to maintain a better metabolic profile.[16]

The prevalence of coagulopathy in TBI reportedly varies from 32.7% to 35.2% and has been found to be associated with poor outcomes.[25] Our findings were consistent with those of other studies, where the coagulation profile was comparable between two groups of neurosurgical patients who received intraoperatively NS or Plasmalyte.[2,16]

Our study has a few limitations. We used PT/INR to assess coagulation instead of the more reliable viscoelastic haemostatic assays, which is in accordance with the general practice in most centres. Although we found a significant difference between the two groups with respect to urinary [TIMP-2]*[IGFBP7], we could only repeat this test within 24 h, owing to financial constraints. Larger RCTs across the entire spectrum of TBI are warranted to provide further insights into fluid management in these patients.

CONCLUSIONS

Plasmalyte maintains a more favourable metabolic profile than NS in patients scheduled for emergency craniotomy for evacuation of SDH while providing adequate brain relaxation. The coagulation profile was comparable between the two groups. Serum creatinine and urinary [TIMP-2]*[IGFBP7] were significantly lower in those who received Plasmalyte. However, none of the patients in our study developed AKI.

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Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the

corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest

There are no conflicts of interest.

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