ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 26(3); June 2022 DOI: 10.35975/apic.v26i3.1899

ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Comparison of normal saline and balanced salt solution as a maintenance fluid on acids-base and electrolyte status in traumatic brain injury patients; a prospective randomized double-blind study

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Abstract

Background & objective: Normal saline is the most commonly used fluid in traumatic brain injury (TBI) patients both in resuscitation and maintenance since long time but associated with hyperchloremic metabolic acidosis. Balanced salt solutions (BSS) are recently developed with favorable outcome in resuscitation and intraoperative as a maintenance fluid. We compared normal saline and BSS as maintenance fluids in TBI patients admitted to intensive care unit.

Methodology: After institutional ethical committee approval and written informed consent from patients' relatives, 100 patients who meet inclusion criteria were randomly divided into two equal groups; Group NS: to receive normal saline as a maintenance fluids and Group BSS: to receive BSS as a maintenance fluid. Data of serum electrolyte and acid base status were collected on day 1, 3, 5, 7 and 14. Patient outcome was evaluated on day-8. Data was analyzed with appropriate statistical tests. The $P < 0.05$ indicated that the difference was significant.

Results: In both groups pH gradually increased over time and was more alkaline in normal saline group. Base excess was comparable between two groups. In normal saline group, serum sodium and chloride increased gradually and reached on the higher side on day-14, while potassium level dropped to a lower side. Twenty-eight days mortality was more in Group NS than the Group BSS.

Conclusion: Balanced salt solution causes lesser alterations in acid base and electrolyte status than the normal saline and is associated with more favorable outcome.

Abbreviations: TBI - Traumatic brain injury; BBB - Blood brain barrier; BSS - Balanced salt solution; ABG - Arterial blood gas analysis; GCS - Glasgow Comma Scale; RFT's - Renal function tests; BE - Base excess

Key words: Ringer's lactate; Sodium Chloride / pharmacology; Balanced salt solution; Double-Blind Method; Humans; Hydrogen-Ion Concentration; Isotonic Solutions / pharmacology; Potassium / blood

Citation: Shephali, Singh Y, Mishra M, Sachan S, Pathak NM, Shankar R. Comparison of normal saline and balanced salt solution as a maintenance fluid on acids-base and electrolyte status in traumatic brain injury patients; a prospective randomized double-blind study. Anaesth. pain intensive care 2022;26(3):326-331.

DOI: 10.35975/apic.v26i3.1899

Received: December 18, 2021; **Reviewed:** January 25, 2022; **Accepted:** February 02, 2022

1. Introduction

Trauma is gradually increasing with every passing day and is now a major public health problem all over the world. In our country scientific research and education in the field of trauma is scarce in spite of huge burden of this problem. Traumatic brain injury (TBI) affects a large proportion of trauma victims, road traffic injuries being the leading cause (60%) of TBI. The clinical presentation and prognosis of TBI depends on the individual nature of the injury with often coexisting other injuries. The outcome of the head injury is determined by the extent of the primary injury, being dependent upon the preventive measures, and secondary injury being highly susceptible to neuroprotective therapeutic interventions. [1] Most treatments of TBI are aimed at reducing secondary insults arising from the injury. Intracranial hypertension is the most frequent cause of death and secondary brain insults after brain injury.

Intravenous fluid administration has been an important component of trauma care which influences the patient's outcome, but it may be potentially harmful due to subsequent hyperhydration, or hypo- or hyperosmolar conditions. The fluid therapy and the choice of the fluid depends upon its distribution between intracellular, interstitial, and plasma compartments through blood brain barrier (BBB). [2, 3] Apart from its osmolarity, the concentrations of sodium (Na^+) and other electrolytes in it play an important role as well. The chosen fluids in patients with TBI must preserve the cerebral perfusion, control brain volume and assure appropriate substrate delivery.

Normal saline is the most common fluid to be used in TBI patients because of its iso-osmolarity, both in resuscitation and as maintenance fluid. However, a large number of studies show its potential to produce hyperchloremic metabolic acidosis. [4] This masks the diagnosis of perfusion deficit and hence leads to inappropriate intervention. In a previous study a chloride-restrictive strategy was associated with a significant decrease in renal failure in critical patients and significantly affected electrolyte and acid-base status. [5]

So, use of balanced salt solution (BSS) came into play as its composition is similar to plasma and is iso-osmolar. BSS decreases the rate of hyperchloremic acidosis in healthy volunteers and during perioperative care compared with saline solutions. [6] BSS was used in TBI patients during resuscitation and found to reduce the incidence of hyperchloremic acidosis. It may have other benefits as well, which involve stable acid-base and electrolyte parameter without causing cerebral edema.

We compared BSS with normal saline as a maintenance fluid in TBI patients. We hypothesized that BSS will cause lesser incidence of acid base and electrolyte imbalance.

2. Methodology

This prospective randomized double-blind study was conducted in Trauma Intensive Care Unit (TICU) of Tertiary Trauma Center of India between January 01, 2019 to February 29, 2020 (Clinical Trial Registration No CTRI/2018/12/016728 dated 19/12/2018). The protocol was approved by institutional ethical approval committee (Dean/2018/EC/451 dated 23/02/2018) and

Table 1: Comparative demographic profile and baseline parameters between two groups.

Parameters	Group NS	Group BSS	p-value
Age (Years)	40.48 ± 13.81	40.48 ± 13.81	0.255
Sex (Male: Female)	36:14	39:11	0.488
GCS	5.68 ± 1.87	5.68 ± 1.87	0.235
Ph	7.33 ± 0.11	7.32 ± 0.09	0.892
BE/Deficit	-1.61 ± 2.58	-1.60 ± 2.34	0.990
Serum Na^+ (meq/L)	138.26 ± 7.41	137.73 ± 5.56	0.690
Serum K^+ (meq/L)	3.29 ± 0.51	3.27 ± 0.51	0.860
Serum $HCO3^-$ (meq/L)	23.48 ± 3.32	22.57 ± 2.77	0.142
Serum Cl^- (meq/L)	98.83 ± 4.45	97.66 ± 2.84	0.119
$PaCO_2$ (mmHg)	34.7 ± 05.81	35.96 ± 6.52	0.310
Serum lactate (mmol/l)	3.8 ± 11.96	3.81 ± 1.68	0.996

Data is presented as mean ± SD; P value < 0.05 considered as significant

written informed consent from the next of kin of the patents was obtained before enrollment.

A total of 113 patients of TBI were included, with age between 18-60 y, nonoperative isolated head injury, and who reached the TICU from trauma emergency within 24 h of the initial injury. Patients with baseline electrolytes outside the normal range, on inotropic support, with any systemic illness like diabetes, hypertension, end stage organ damage e.g. hepatic, renal or cardiovascular disorder or who expired within 24 h of TICU admission, were excluded from the study. One hundred patients completed the study.

Table 2: Comparison of pH between two groups at different time interval

Parameters	Group NS	Group BSS	p-value
baseline	7.33 ± 0.11	7.32 ± 0.09	0.83
Day 1	7.39 ± 0.06	7.37 ± 0.06	0.06
Day 3	7.44 ± 0.03	7.42 ± 0.04	0.02
Day 5	7.44 ± 0.04	7.43 ± 0.04	0.04
Day 7	7.45 ± 0.05	7.41 ± 0.04	< 0.001
Day 14	7.46 ± 0.05	7.43 ± 0.04	0.007

Data is presented as mean ± SD; P value < 0.05 considered as significant

Table 3: Comparison of base excess between two groups at different time interval

Parameters	Group NS	Group BSS	p-value
baseline	-1.61 ± 2.58	-1.60 ± 2.34	0.98
Day 1	0.58 ± 1.69	-1.02 ± 1.68	0.19
Day3	-0.07 ± 1.53	0.07 ± 1.15	1.00
Day 5	0.83 ± 1.53	1.08 ± 0.68	0.29
Day 7	-0.03 ± 1.70	0.45 ± 1.66	0.16
Day 14	-0.48 ± 2.24	0.72 ± 0.62	0.47

Data is presented as mean ± SD; P value < 0.05 considered as significant

Randomization was done using computer generated random number table. A total of 100 envelopes were numbered indicating the sequence of the patients on the outside. The group allocation and study fluid were kept inside the opaque envelope and sealed. These envelopes were given to the fluid administrator. The participants and the investigator involved in collecting data and in assessment of variable were blinded. The group allocation was revealed only after analysis of data.

Initially patient was resuscitated as per protocol of trauma emergency. Primary survey was done in emergency and any life-threatening injury was addressed. After stabilizing and taking care of airway, breathing, circulation, and disability, the patient was shifted to TICU.

After shifting to ICU, baseline investigation and arterial blood gas analysis (ABG) were ordered. Glasgow Comma Scale (GCS) was evaluated. A total of 100 patients were randomized into two equal groups (n = 50): Group NS received normal saline as maintenance fluid and Group BSS received BSS as maintenance fluid. Daily maintenance fluid requirement was calculated on basis of fluid deficit and daily urine output. Thereafter, ABG's and renal function tests (RFT) were repeated on day 1, 3, 5, 7 and 14. Urine output was assessed on the same days. On 28th day, patient's outcome, in the form of survival or otherwise, was recorded.

Patients were managed according to the set protocols of TICU. Secondary brain injuries were prevented by avoiding hypotension, hypoxemia and anemia (Hb < 10 g/dl), maintaining body temperature between 36°C and 37°C, ensuring normoglycemia (140 - 180 mg/dl) and normocapnia (35 – 45 mmHg). Position was changed every 8 hourly and air mattresses were used to reduce the chances of bedsores. Injection mannitol (20%) 100 ml

was infused 8 hourly for the first three days followed by as required basis. Inj, furosemide 20 mg was given along with mannitol for initial three days after that given as per requirement. Anti-epileptic prophylaxis was done in the form of maintenance dose of inj. fosphenytoin (5 mg/kg) in three divided doses. Inj leveraticetam (500 mg) twice

a day was administered to all females of reproductive age group

General care of the patient was done as per TICU protocols. Primary outcome of study was comparison of acid base and electrolyte status between two groups. Secondary outcome of study was 28 days mortality between two groups.

Statistical analysis

Calculation of sample size was based on presumption that there will be minimum expected differences in between two groups of 25%. For the results to be of statistically significant with alpha = 0.05 and beta = 0.08, we needed to recruit 47 patients in each group; to take

Table 4: Comparison of serum electrolyte (meq/L) between two groups at different time intervals

Time period	Group NS			Group BSS			p-value
	Na+	Cl_	K	Na+	Cl	K+	
Baseline	138.26 ± 7.41	98.83 ± 4.45	3.29 ± 0.51	137.73 ± 5.56	97.66 ± 2.84	3.27 ± 0.51	0.690, 0.119, 0.860
Day 1	139.55 ± 6.67	99.13 ± 4.66	3.42 ± 0.56	139.19 ± 5.30	98.31 ± 2.41	3.56 ± 0.44	0.765, 0.270, 0.182
Day3	141.22 ± 7.63	101.08 ± 3.47	3.53 ± 0.45	141.12 ± 3.66	99.35 ± 2.36	3.86 ± 0.48	0.935, 0.004, 0.001
Day 5	145.73 ± 5.94	101.99 ± 4.00	3.61 ± 0.44	141.87 ± 3.54	100.05 ± 2.07	3.92 ± 0.47	< 0.001, 0.003, 0.001
Day 7	146.67 ± 5.22	103.60 ± 3.25	3.58 ± 0.37	141.32 ± 2.31	99.58 ± 1.36	4.00 ± 0.36	< 0.001, < 0.001, < 0.001
Day 14	149.15 ± 5.05	102.70 ± 2.27	3.43 ± 0.42	141.95 ± 2.22	99,01 ± 1.47	4.21 ± 0.21	< 0.001, < 0.001, < 0.001

Data is presented as mean ± SD; P value < 0.05 considered as significant

care of any drop outs, we enrolled 50 patients in each group.

The statistical analysis was done using SPSS for Windows version 23.0 software (IBM Inc.). For categorical data Chi-square and Fischer's Exact test was used. For comparing means of two groups independent Student's 't' test was used. For paired samples paired 't' test was applied. P < 0.05 was considered to be significant**.**

3. Results

Out of 113, one hundred patients completed the study; thirteen were excluded from the study (Figure 1).

Demographic profile and base line parameters of the studied patients are summarized in Table 1.

Baseline pH in both groups was on the acidic side of normal range and comparable between the two groups (p = 0.83). In both groups pH gradually increased over time and on day 14 this was more alkalotic (7.46 ± 0.05) in Group NS than the Group BSS (7.43 ± 0.04). Statistically significant difference was found between the two groups from day3 onwards (Table 2).

Baseline base excess (BE)/deficit was comparable between the two groups. BE/deficit remained within the normal range of -2 to +2 during the study period (Table 3).

Baseline electrolyte values were comparable between the two groups. In Group NS, serum Na^+ and Cl^- increased gradually and reached on the higher side on day-14 (Na^+ = 149.15 ± 5.05, Cl^- = 102.70 ± 2.27) while potassium remained on the lower side (3.43 ± 0.42). In Group BSS electrolytes increased from baseline value over time but remained within normal range. On comparison between the two groups, there was statistically significant differences in the electrolyte status from day-5 (p < 0.05) (Table 4).

The percentage mortality in Group NS was 54%, while it was 40% in Group BSS, but the difference was not statistically significant between the groups (p = 1.61) (Figure 2).

Other parameters, including serum calcium, lactate, urea/creatinine, 24 hour urine output, were within normal range and no statistically significant difference was observed between the groups. Amount of mannitol administered was also comparable between two groups.

4. Discussion

BSS is being used as new approach in fluid management in intraoperative and intensive care settings both in pediatric and adult patients. [7] Its electrolyte composition is close to the plasma composition, but has lower Cl^- concentrations than normal saline. This solution can prevent the risk of iatrogenic derangement in electrolytes and acid-base status.

We found significant differences in acid-base and electrolyte status between the two groups after day-3 of fluid administration.

There is a traditional thinking that normal saline infusion causes hyperchloremic acidosis. It is true when infused in large quantities over a shorter span of time. When it is infused very slowly, the body tries to compensate for high Cl^- and the net result is maintenance of normal pH over time. TBI patients usually hyperventilate, so pH is towards alkalotic side in both the groups. [8, 9] In the Group

NS, more respiratory alkalosis may be due to two reasons: first, the patients receiving normal saline may hyperventilate more than patient receiving balanced crystalloid solution. Second, there may be possibility that Group NS patients may have increased baseline respiratory rate.

However, the BE was found to be within normal range in both the groups with being on negative side for NS and positive side for BSS. A previous study that compared saline-based fluid and BSS in surgical patients demonstrated a significant decrease in BE with NS in comparison to BSS. [10] NS showed a more negative value of BE than BSS. This finding is inevitable because NS contains more Cl^-, which subsequently leads to this condition. According to previous studies, the BSS caused significant acid-base stability compared with saline-based solution in elderly surgical patients and healthy volunteers. [11]

A significant difference in bicarbonate level was found between the two groups over 14 days period. The mean serum bicarbonate in the balanced solution was higher than that in the saline group but was still in the normal range. It was on the lower side in Group NS, this may be due to compensation over a period for respiratory alkalosis. A pilot study by Hofmann–Kiefer showed that slight advantages were observed in the acetate-buffered solution in terms of pH and plasma HCO_3^- stability in comparison with the lactate-based balanced solution. [12] The balanced solution with acetate buffer is also more advantageous than a lactate-based buffer in terms of metabolism and clearance because it does not depend on the intact liver function.

A significant difference was found in the mean Na^+ level in Group NS than Group BSS from the 5th day onwards. This may be attributed to high Na^+ load in NS (154 meq/l) with respect to plasma. While for BSS, the level of Na^+ was increased but remained within the normal range only. [13]

A significant difference was found in the mean Cl^- and increment of Cl^- level in NS in comparison with BSS from the 3rd day itself. The balanced group showed a downward trend of Cl^- level keeping it within the normal range. This condition can be due to the high concentration or load of Cl^- in the NS in comparison with the plasma Cl^- concentration to produce iso-osmolar fluid. [14] Various studies found that hyperchloremia could impair end-organ perfusion and interfere with the cellular exchange mechanism. [14] Previous studies found that the infusion of NS would lead to increased time to first urination and that a greater frequency of abdominal discomfort has a negative effect on renal blood flow and the glomerular filtration rate. [15] However, we didn't find any such changes in our study. The urea and creatinine levels were almost same in both the groups compared to their baseline with no significant difference between the two groups.

Prolonged infusion of NS led to reduced potassium and calcium levels. Mild hypokalemia was observed after 14 days of NS infusions, but potassium level was seen to be within normal range in Group BSS. There was

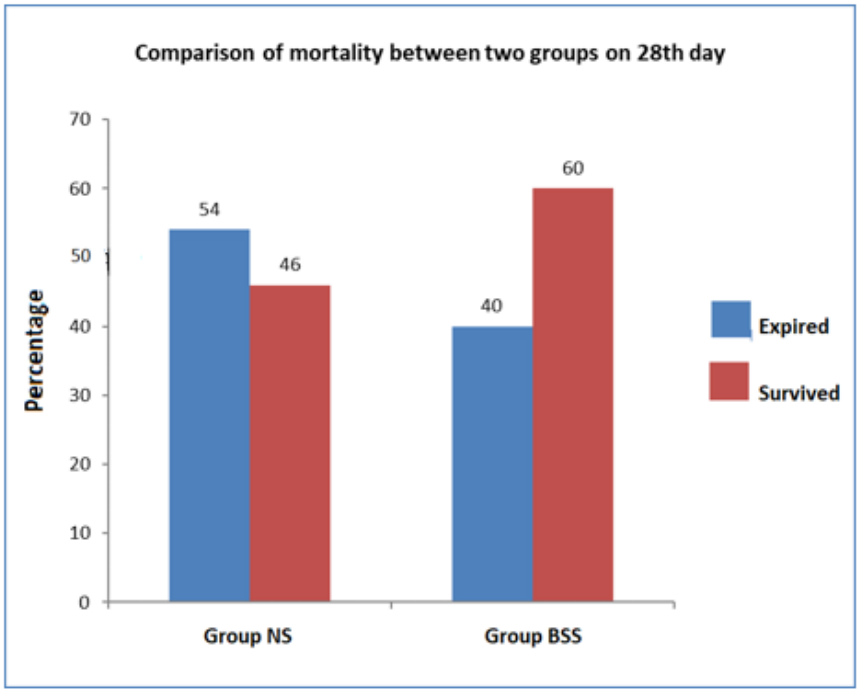

Figure 1: Comparative mortality in the two groups

significant difference between the two groups after day-3. This situation is particularly true as NS does not contain potassium ion.

Serum lactate showed downward trends from baseline value in both groups and was comparable between the groups. Various studies showed serum lactate as a prognostic marker in TBI patients.

28 days mortality was higher in Group NS than Group BSS, but statistically the difference was not significant between the groups.

5. Limitation

Our study had several limitations due to various factors influencing the acid base status and final patient outcome. Severity of injury and ventilatory parameters may influence the survival and acid-base status of the patients. Various medications used for patient management can also influence the outcome of patients. Our sample size was small, so large multi-center studies are required which may open new era of fluid management in TBI patients.

6. Acknowledgment

We express our sincere thanks to all TICU staff for their constant help and support in conduction of this study.

7. Conflict of Interest

None declared by the authors.

8. Funding

No internal or external funding was involved in the study.

9. Data availability

Numerical data pertaining to this study is available with the authors.

10. Authors' contribution

Sh - Conduct study work and manuscript writing

YS - Study design, patient analysis, data analysis, proof reading

MM - Data analysis

RSP - Proof reading, analysis

NMP - Manuscript editing

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