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Effect of Fluid Therapy on Acid–Base Balance in Patients Undergoing Clipping for Ruptured Intracranial Aneurysm: A Prospective Randomized Controlled Trial

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Abstract

Objectives Neurosurgical patients often receive 0.9% normal saline (NS) during the perioperative period. Theoretically, a balanced salt solution (BSS) is better than 0.9% saline. We compared the effects of two different fluids on acid–base balance, renal function, and neurological outcome in patients who underwent clipping following subarachnoid hemorrhage from a ruptured intracranial aneurysm.

Materials and Methods Patients in group NS ($n = 30$) received 0.9% saline and group BSS ($N = 30$) received BSS (Plasmalyte-A) in the perioperative period for 48 hours. Comparison of arterial pH, bicarbonate, and base deficit measured preoperatively, intraoperatively (first and second hour), and postoperatively (at 24 and 48 hours) was the primary outcome of the study. The secondary outcome compared serum electrolytes, renal function tests, urine neutrophil gelatinase-associated lipocalin (NGAL), serum cystatin C, and the neurological outcome using modified Rankin score (MRS) at discharge, 1, and 3 months.

Results In group NS, significantly low pH at 1-hour intraoperative period was seen compared with group BSS (7.37 ± 0.06 vs. 7.40 ± 0.05, $p = 0.024$). The bicarbonate level in group NS was significantly lower and the base deficit was higher at second intraoperative hour (bicarbonate: 17.49 vs. 21.99 mEq/L, $p = 0.001$; base deficit: 6.41 mmol/L vs. 1.89 mmol/L, $p = 0.003$) and at 24 hours post-surgery (bicarbonate: 20.38 vs. 21.96 mEq/L, $p = 0.012$; base deficit: 3.56 mmol/L vs. 2.12 mmol/L, $p = 0.034$)). Serum creatinine was higher in group NS at 24 hours (0.66 vs. 0.52 mg/dL,

Keywords
- aneurysmal subarachnoid hemorrhage
- balanced salt solution
- fluid therapy
- acid–base equilibrium
- normal saline
- neurosurgery
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$p = 0.013$) and 48 hours (0.62 vs. 0.53 mg/dL, $p = 0.047$). Serum urea, electrolytes, cystatin, urine NGAL, and MRS were comparable.

Conclusion In neurosurgical patients undergoing clipping for ruptured intracranial aneurysm, using a BSS during the perioperative period is associated with a better acid–base and renal profile. However, the biomarkers of kidney injury and long-term outcomes were comparable.

Introduction

Patients undergoing clipping for a ruptured intracranial aneurysm are at high risk of increased morbidity and mortality.[1] For the maintenance of neuronal homeostasis following acute insult, cerebral perfusion and hemodynamic stability are essential. An adequate circulating intravascular volume is responsible for maintaining adequate cerebral perfusion pressure. Patients with aneurysmal subarachnoid hemorrhage (aSAH) have an altered fluid status in the preoperative period due to inadequate oral intake, altered sensorium, cerebral salt wasting syndrome, and use of osmotherapeutic medication.[2] The primary brain edema ensues following aSAH, and later, secondary brain insult leading to life-threatening consequences occurs due to an imbalance in fluid volume, osmolality, acid–base status, and electrolyte disturbances. Additionally, large-volume intravenous fluid resuscitation is undertaken to treat hypovolemia, maintain perioperative hemodynamic stability, or as a part of therapy for vasospasm. The volume and type of fluids administered during the perioperative period may influence the outcome in aSAH patients.

Crystalloids and colloids are two significant groups of fluids commonly used in the perioperative period. Semisynthetic colloids like starch, dextran, and gelatin are associated with side effects like impaired coagulation profile, acute kidney injury (AKI), and anaphylactic reactions.[3,4] About 0.9% saline is the most used crystalloid in neurosurgical patients.[5] Balanced salt solutions (BSS) are a group of crystalloids that includes Ringer's lactate and multiple electrolyte injection type 1 USP (Plasmalyte A, Karbilyte, Normosol). Ringer's lactate is a hypotonic solution and may increase brain edema.[5] About 0.9% saline is also known as normal saline (NS), but this is not a physiologically normal solution because chloride concentration is higher than plasma (154 vs. 100 mEq/L). Based on the Stewart physiochemical approach, the pH of the fluid is partly determined by its strong ion difference (SID), which is 40 mEq/L for extracellular fluid, while that for 0.9% saline is zero. Thus, a net decrease in plasma SID following 0.9% saline infusion results in metabolic acidosis. On the other hand, BSS could reduce the incidence of hyperchloremic metabolic acidosis because the chloride concentration is reduced by presence of substances like malate and acetate, ensuring isotonicity. Plasmalyte A is a balanced crystalloid solution with an osmolality of 295 mOsm/kg and a pH of 7.4. The composition is 140 mmol/L sodium, 5 mmol/L potassium, 1.5 mmol/L magnesium, 98mmol/L chloride, 27mmol/L acetate, and 23 mmol/L gluconate.[6]

Few studies compared BSS with 0.9% saline, and BSS was found to maintain better metabolic parameters like acid–base balance and electrolyte levels in neurosurgical patients with brain tumors.[7–9] However, there is no study comparing these two fluids in perioperative fluid management of patients with ruptured aSAH. We hypothesize that BSS will give better perioperative acid–base balance parameters like pH, bicarbonate, anion gap, and preserved renal functions.

The study's primary outcome was to assess the effect of fluid therapy on acid–base balance, namely arterial pH, bicarbonate, and base deficit. The secondary outcomes of the study were the effect of fluid therapy on serum lactate, anion gap, serum electrolytes, renal functions, and intraoperative brain condition. Biomarkers of AKI such as urine neutrophil gelatinase associated lipocalin (NGAL), and serum cystatin C were also calculated.[10,11] Neurological status was assessed by modified Rankin Scale (mRS) at discharge, 1 and 3 months after discharge.

Materials and Methods

A prospective randomized, double-blind controlled trial was performed in a tertiary care hospital between October 2020 and November 2021 (including 90 days follow-up period) after ethical approval from the Institutional Ethics Committee (IEC) and registration in the Clinical Trial Registry of India (CTRI; CTRI/2020/09/028078) on 28 September 2020, in accordance with the Helsinki Declaration of 1975, as revised in 2000. Patients between the age of 18 to 75 years of either gender with American Society of Anesthesiologist (ASA) class IE and IIE and World Federation of Neurological Surgeons (WFNS) grade 1 and 2 planned for surgical clipping of intracranial aneurysm were included after consent from the patient or a close relative as applicable. All those patients who had preoperative hyponatremia/hypernatremia (serum sodium < 130 mEq/L or > 150 mEq/L), preoperative serum osmolality more than 320 mOsm/kg, WFNS grade more than 2, ventriculoperitoneal shunt in situ, history of congestive heart failure, and pre-existing renal disease (serum creatinine > 2 mg/dL) were excluded from the study. Findings of computed tomography scan brain and magnetic resonance imaging brain were noted.

The patients were randomized using a computer-generated random number table, and the group allocation was

done with sequentially numbered opaque envelopes. The envelope was opened, and the patient was allocated to one of the two groups during preanesthesia check-up before shifting patient inside the operation room. Fluid bags (according to the assigned group) were wrapped in opaque paper bags and were labeled as "IV fluids" by an operation theater technician not involved in the study to ensure blinding. The anesthesiologist who collected data and the operating surgeon were blinded to the group assigned to the patient. All patients were divided into group NS (n= 30) patients received 0.9% saline (NS) solution and group BSS (n= 30) patients received BSS Plasmalyte A, in the intraoperative period and till 48 hours postoperatively in neurosurgery intensive care unit (ICU).

Standard anesthesia protocol was followed. Standard ASA monitors (pulse oximeter, electrocardiogram, and noninvasive blood pressure) were attached. An arterial cannula was secured under local anesthesia to measure invasive blood pressure and arterial blood gases. Anesthesia was induced with propofol 1 to 2 mg/kg titrated to loss of verbal command and vecuronium 0.1 mg/kg, and the trachea was intubated. Intraoperative analgesia was provided by an initial bolus of fentanyl 2 µg/kg followed by an infusion of 1 µg/kg/h. Maintenance of anesthesia was achieved using propofol and intermittent doses of vecuronium. All patients were mechanically ventilated with a combination of oxygen and air. Minute ventilation was adjusted to keep partial pressure of carbon dioxide around 32 to 35mm Hg. All patients received mannitol (20%) 1 g/kg and levetiracetam 500 mg. After completion of the surgery, patients were shifted to in neurosurgery (ICU) for subsequent management. Brain relaxation score (BRS) was assessed by the operating surgeon, who was blinded to the intravenous (IV) fluid administered to the patient just before the opening of the dura mater.

In the preoperative area, a wide-bore intravenous access was secured, and intravenous fluid was started according to the assigned group. Point-of-care ultrasonography (POCUS) of inferior vena cava (IVC) was utilized to assess euvolemic status. Euvolemia was defined as an IVC diameter greater than 2 cm, an IVC collapse of less than 50% with each breath, and an IVC collapsibility index greater than 12%. All patients who did not meet the above criteria, that is, were hypovolemic, were given intravenous fluid boluses (as per assigned group) at a rate of 5 to 10 mL/kg over 15 to 30 minutes until euvolemia was achieved. Once euvolemic status was achieved, patients were taken up for induction of anesthesia.

During intraoperative period, maintenance IV fluid was given according to Holliday Segar Eq. (4 mL/kg for the first 10 kg, 2 mL/kg for the next 10 kg, and 1 mL/kg for weight above 20 kg), along with a replacement for blood loss and other insensible losses. In addition, pulse pressure variation (PPV) was monitored continuously. PPV value of more than 12 % was found to accurately predict fluid responsiveness, and the same was used as the threshold for initiating fluid bolus. Throughout surgery, if mean arterial pressure (MAP) fell below 20% of baseline, a further bolus of 200 mL of fluid was given in both groups. If blood loss was beyond the maximum allowable blood loss or the hematocrit value was less than 30%, blood was transfused. Intraoperative hemodynamic parameters like heart rate, systolic and diastolic blood pressure, and MAP were recorded. The total duration of surgery, anesthesia, blood loss, urine output, and volume of fluid, blood/blood products infused were noted.

During the postoperative period till 48 hours in the ICU, the patients continued to receive fluid according to the group assigned. Blinding was ensured by using covered fluid bags throughout the 48 hours study period. The routine fluid therapy was guided by ultrasonography of IVC and urine output. Hemodynamic instability was managed with fluid boluses and vasopressors. Since significant fluid shifts and acid–base imbalances are prone to occur in the perioperative period, the period of study fluid administration was decided to be from immediate preoperative to 48 hours postoperative period.

Arterial blood gas analysis was performed during the preoperative period, then for the first 2 hours in the intraoperative period, at the end of the surgery, and 24 hours and 48 hours after surgery. Arterial pH, bicarbonate, base deficit, serum electrolytes (sodium, calcium, chloride, and potassium), and serum lactate levels were noted.

Blood urea and serum creatinine were assessed preoperatively (as baseline value) and after 48 hours of surgery.

Plasma cystatin C and urine NGAL as a marker of early AKI were measured before and after fluid administration, that is, in the preoperative period and 48 hours after surgery. Plasma cystatin C was measured using the diazyme cystatin C assay based on the latex-enhanced immunoturbidimetric method. For measurement of NGAL, urine from the patient was centrifuged, and the supernatant was stored by freezing to −80°C. Then the samples were analyzed as a batch using the sandwich enzyme-linked immunosorbent assay method.

All patients were assessed for neurological status by mRS at discharge and telephonically at 1 month and 3 months. The scores from 0 to 3 were considered good outcome scores, and 4 to 6 were considered poor outcome scores.

Sample Size

The study of Dey et al observed that pH in the 0.9% saline group was 7.41 ± 0.06 and in the Plasmalyte group was 7.47 ± 0.03 at 2 hours intraoperatively.[7] Taking these values as reference, the minimum required sample size with 99% power and 5% level of significance is 28 patients in each study group. To reduce the margin of error, the total sample size taken was 60 (30 patients per group).

Statistical Analysis

The statistical analysis was performed using Statistical Package for Social Sciences version 22.0 (IBM SPSS Inc., Chicago, Illinois, United states). Categorical variables like gender, ASA category, and WFNS grade were expressed as proportions (percentages). Numerical data were expressed as mean and standard deviation. Normality of data was assessed using Kolmogorov–Smirnov test. The quantitative variables were analyzed using Mann–Whitney and independent t-test, while qualitative variables were analyzed by the chi-squared

test and Fisher's exact test. A probability value (p-value) of less than 0.05 was considered significant.

Results

Sixty-five patients were assessed for eligibility, and 60 patients were randomized to either group NS or group BSS (►**Fig. 1**).

The demographic parameters and brain relaxation scores were comparable between the two groups. The volume of crystalloid infused intraoperative blood loss, duration of surgery, and anesthesia were comparable between the two groups. However, urine output was significantly higher in the BSS group than in the NS group ($p = 0.009$; ►**Table 1**).

Based on the requirement for a fluid bolus assessment by POCUS of IVC, 15 patients in the NS group and 14 patients in the BSS group received a fluid bolus as they were fluid-depleted ($p = 0.796$).

The arterial pH of group NS and group BSS was comparable at all time points between the two groups except at 1st hour of the surgery ($p = 0.024$). At second hour intraoperatively and 24 hours postoperatively, significantly lower bicarbonate values were seen in group NS compared with group BSS, respectively ($p = 0.001$ and $p = 0.012$). Similar trends were seen in base deficit, where group NS had a higher base deficit ($p = 0.003$ and $p = 0.034$; ►**Table 2**).

The anion gap, serum lactate, serum sodium, serum potassium, serum calcium and blood urea levels between the two groups did not differ significantly at baseline or any of the time points measured in the perioperative period. Significantly higher serum chloride levels were seen in group NS compared with group BSS at 24 hours ($p = 0.023$). Serum creatinine level at postoperative 24 hour and 48 hours was significantly higher in group NS (0.66 vs. 0.52 mg/dL, $p = 0.013$ and 0.62 vs. 0.53 mg/dL, $p = 0.047$). A significant rise in urine NGAL was seen in both the groups at postoperative 48 hours compared with the preoperative values (group NS $p = 0.002$, group BSS $p = 0.01$). The serum cystatin C was similar in both groups during preoperative and postoperative time points ($p = 0.10$ and $p = 0.243$; ►**Table 3**).

With regard to clinical outcome, mRS showed no significant difference between the two groups at discharge and on post-discharge 1 month and 3 months follow-up ($p = 0.791$, 0.371, and 0.080; ►**Table 4**).

Discussion

Acid–base balance is an essential factor in maintaining the internal milieu of the body as well as neuronal homeostasis. pH is measured as the negative logarithmic value of hydrogen ion concentration. A large volume of intravenous fluid infusion

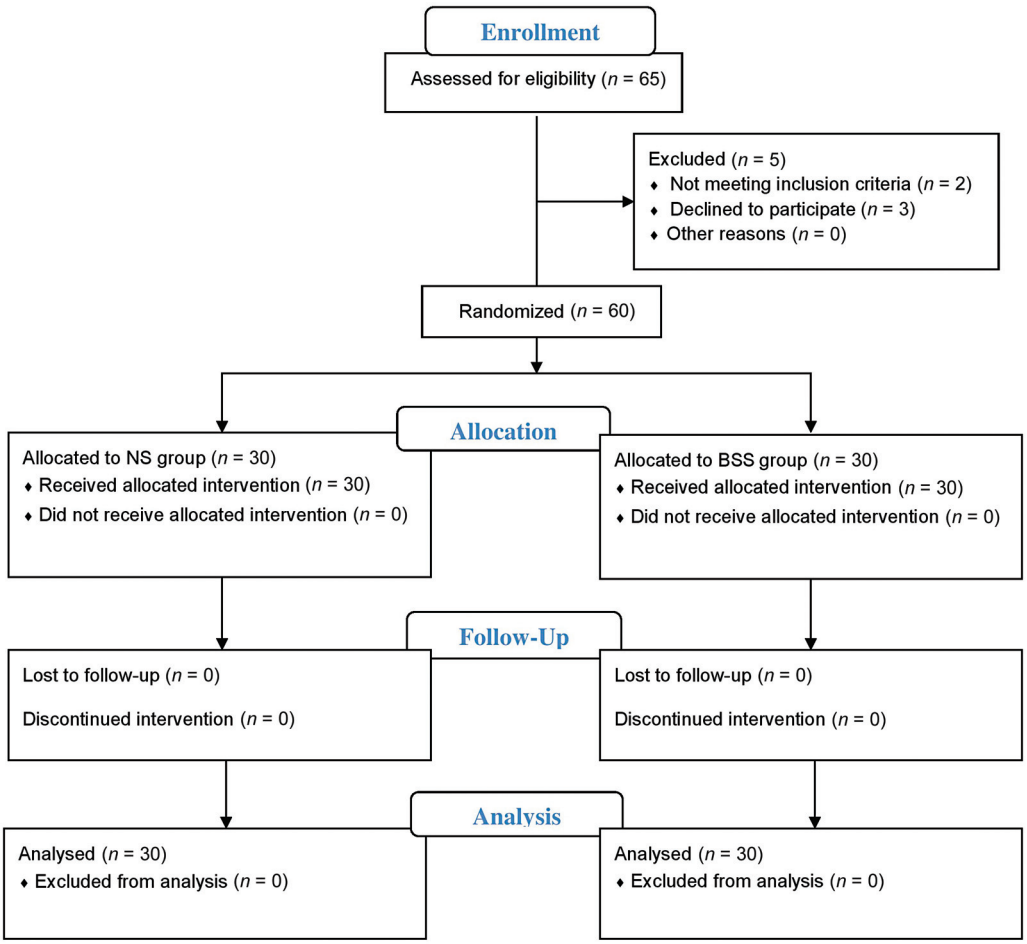

Fig. 1 CONSORT diagram (Consolidated Standards of Reporting Trials). BSS, balanced salt solution; NS, normal saline.

Table 1 Comparison of demographic variables, baseline and intraoperative characteristics

Parameters		Group NS ($n = 30$)	Group BSS ($n = 30$)	*p*-Value
Age (y)		52.4 ± 8.1	48.2 ± 11.1	0.105[a]
Gender	F/M	17/13	20/10	0.425[b]
Comorbidities	HTN/DM/Nil	12/2/16	11/0/18	0.531[a]
Neurological scores				
WFNS grade	1/2	23/7	21/9	0.559[b]
Hunt and Hess grade	1/2/3	5/20/5	6 /19/5	0.943[b]
Modified fisher grade	1/2/3/4	9/4/10/7	5/4/10/11	0.566[b]
GCS score	14/15	3/27	4/26	0.688[b]
Site of aneurysm				
ACOM/MCA/PCOM		9/11/4	14/14/1	0.327[a]
ICA-B/ DACA/ PICA	4/1/1	1/0/0		
Intraoperative parameters				
Volume of crystalloid infused (ml)		2270 ± 498	2440 ± 570	0.159[c]
Intraoperative urine output (ml)		603 ± 415	830 ± 439	**0.009**[*c]
Intraoperative blood loss (ml)		343 ± 203	335 ± 118	0.463[c]
Duration of surgery (min)		173 ± 67	169 ± 54	0.257[c]
Brain relaxation score				
Grade 1/2/3/4		5 (16)/14(47)/11(37)/0 (0)	6 (20)/12(40)/12 (40)/0(0)	0.874[b]

Abbreviations: ACOM, Anterior Communicating Artery; DACA, Descending Anterior Cerebral Artery; DM, Diabetes Mellitus; GCS, Glasgow Coma Scale; HTN, hypertension; ICA-B, Internal Carotid Artery Bifurcation; MCA, Middle Cerebral Artery; PCOM, Posterior Communicating Artery; PICA, Posterior Inferior Cerebellar Artery; WFNS, World Federation of Neurological Surgeons.
Values are presented as mean ± SD and number (*n*)/(percentage).
[a]Mann-Whitney U test.
[b]Chi-square test.
[c]Independent *t*-test.
[*]$p < 0.05$ is statistically significant.

Table 2 Comparison of arterial blood gas parameters

		Baseline	Intraoperative 1st hour	Intraoperative 2nd hour	Postoperative 24 hours	Postoperative 48 hours
Arterial pH	Group NS	7.39 ± 0.07	7.37 ± 0.06	7.39 ± 0.07	7.41 ± 0.06	7.42 ± 0.07
	Group BSS	7.41 ± 0.09	7.40 ± 0.05	7.43 ± 0.06	7.40 ± 0.05	7.40 ± 0.05
	p-Value	0.137	0.024[a]	0.195	0.574	0.274
Arterial base deficit (mEq/L)	Group NS	3.62 ± 2.14	4.38 ± 2.34	6.41 ± 2.55	3.56 ± 2.48	2.43 ± 3.35
	Group BSS	2.99 ± 1.66	3.10 ± 2.33	1.89 ± 3.43	2.12 ± 2.51	1.81 ± 2.28
	p-Value	0.167	0.083	0.003[a]	0.034[a]	0.807
Arterial bicarbonate (mEq/L)	Group NS	21.04 ± 1.98	20.30 ± 1.98	17.49 ± 2.02	20.38 ± 2.06	21.46 ± 3.18
	Group BSS	22.00 ± 2.62	21.12 ± 2.16	21.99 ± 2.94	21.96 ± 2.37	22.16 ± 2.12
	p-Value	0.178	0.235	0.001[a]	0.012[a]	0.662

Abbreviations: BSS, balanced salt solution; NS, normal saline; SD, standard deviation.
Values are presented as mean ± SD; data analyzed using Student's *t*-test.
[a]$p < 0.05$ is statistically significant.

may cause deviations in extracellular pH from a resting value of 7.4, which leads to acid–base abnormalities, though buffers exist to maintain the balance.

In our study, we observed that 0.9% saline tended to lower the pH toward acidosis (though the value remained within the normal range) at first hour into the surgery compared with the BSS. This precipitous fall in pH at the first hour can be explained by the large boluses of fluids given in the preoperative period to treat hypovolemia that is frequently observed in patients with aSAH. Dey et al compared NS and

Table 3 Comparison of serum electrolytes, renal function tests, and biomarkers of acute kidney injury

		Baseline	Intraoperative 1st hour	Intraoperative 2nd hour	Postoperative 24 hours	Postoperative 48 hours
Serum sodium (mEq/L)	Group NS	135 ± 5.41	134.06 ± 4.14	134.39 ± 5.18	137.18 ± 5.24	136.87 ± 5.32
	Group BSS	135.10 ± 4.52	134.16 ± 3.14	135.29 ± 3.32	136.68 ± 3.77	135.96 ± 3.59
	p-Value	0.756	0.985	0.616	0.505	0.419
Serum potassium (mEq/L)	Group NS	2.87 ± 0.45	3.19 ± 0.55	3.06 ± 0.55	3.42 ± 0.63	3.48 ± 0.68
	Group BSS	2.98 ± 0.49	3.23 ± 0.47	3.29 ± 0.58	3.50 ± 0.66	3.41 ± 0.53
	p-Value	0.584	0.631	0.351	0.631	0.888
Serum chloride (mEq/L)	Group NS	105.70 ± 5.53	107.13 ± 6.33	105.89 ± 3.95	105.85 ± 5.52	104.02 ± 6.11
	Group BSS	103.47 ± 7.04	105.92 ± 4.59	105.31 ± 5.14	103.23 ± 4.25	102.96 ± 4
	p-Value	0.177	0.547	0.778	0.023[a]	0.423
Serum calcium (mEq/L)	Group NS	0.88 ± 0.18	0.84 ± 0.17	0.81 ± 0.18	0.81 ± 0.18	0.84 ± 0.20
	Group BSS	0.87 ± 0.15	0.87 ± 0.17	0.89 ± 0.20	0.88 ± 0.19	0.85 ± 0.12
	p-Value	0.854	0.437	0.362	0.101	0.524
Anion gap (mEq/L)	Group NS	8.06 ± 5.72	6.48 ± 5.42	10.91 ± 7.27	11.40 ± 4.18	11.39 ± 3.74
	Group BSS	9.67 ± 6.89	7.47 ± 4.20	7.74 ± 5.85	10.52 ± 4.72	10.68 ± 3.43
	p-Value	0.469	0.492	0.271	0.425	0.367
Serum lactate (mEq/L)	Group NS	1.07 ± 0.34	1.25 ± 0.77	1.77 ± 1.52	1.34 ± 0.43	1.30 ± 0.59
	Group BSS	1.15 ± 0.40	0.96 ± 0.36	1.47 ± 1.53	1.20 ± 0.59	1.09 ± 0.52
	p-Value	0.564	0.2	0.65	0.062	0.11
Blood urea (mg/dL)	Group NS	31.31 ± 14.36			18.58 ± 9.85	16.44 ± 8.43
	Group BSS	27.64 ± 8.75			16.83 ± 9.08	18.89 ± 22.17
	p-Value	0.367			0.594	0.756
Serum creatinine (mg/dL)	Group NS	0.79 ± 0.27			0.66 ± 0.23	0.62 ± 0.20
	Group BSS	0.76 ± 0.23			0.52 ± 0.14	0.53 ± 0.13
	p-Value	0.79			0.013[a]	0.047[a]
Urine NGAL (pg/dL)	Group NS	5638.15 ± 3905.15				8671.05 ± 5084.60
	Group BSS	5175.11 ± 4630.46				7724.39 ± 4656.20
	p-Value	0.677				0.455
Serum cystatin C (mg/L)	Group NS	0.96 ± 0.37				0.91 ± 0.31
	Group BSS	0.82 ± 0.23				0.83 ± 0.17
	p-Value	0.106				0.243

Abbreviations: BSS, balanced salt solution; mEq/L, milliequivalent per liter; mg/L, milligram per liter; mmol/L, millimol per liter; NGAL, neutrophil gelatinase-associated lipocalin; NS, normal saline; pg/dL, picogram per liter; SD, standard deviation.
Values are presented as mean ± SD, data analyzed using Student's *t*-test.
[a]$p < 0.05$ is statistically significant.

Table 4 Neurological outcome by mRS

Time	Outcome (mRS)	Group NS (*n*)	Group BSS (*n*)	*p*-Value
Discharge	Good (0–3)	19	18	0.791
	Poor (4–6)	11	12	
1 month	Good (0–3)	21	24	0.371
	Poor (4–6)	9	6	
3 months	Good (0–3)	19	25	0.08
	Poor (4–6)	11	5	

Abbreviations: BSS, balanced salt solution; mRS, modified Rankin Scale; NS, normal saline.
Values are presented as actual numbers (*n*), data analyzed using Mann–Whitney U-test.
$p < 0.05$ is statistically significant.

Plasmalyte-A in patients undergoing elective craniotomy for supratentorial tumors and found a significant difference in acid–base balance throughout the intraoperative period with Plasmalyte-A maintaining a better acid–base status compared with NS.[7] They also observed that the pH of both the groups was well within physiological limits throughout the study period, like our study. Another study in neurosurgical population by Arora et al yielded similar results.[9] Furthermore, when 0.9% saline and Plasmalyte A were used for the resuscitation of trauma patients, it was found that the pH in the 0.9% saline group consistently remained acidic for 24 hours.[12] In a study by Roquilly et al, balanced solutions reduced the incidence of hyperchloremic acidosis in brain injured patients compared with saline solutions.[13]

The base deficit indicates the amount of base needed to titrate serum pH back to the physiological range. A study was performed by Lehmann et al on SAH patients where 0.9% saline and saline based colloid solution was compared with balanced crystalloid and colloid solution (Ringerfundin and Tetraspan).[14] They found that the 0.9% saline-based fluids had a base deficit of more than 2 with a maximum value of 12. Also, 0.9% saline was compared with Plasmalyte A for resuscitation of trauma patients by Young et al, and the primary outcome of the study was base deficit a day after injury.[12] The authors found a significant improvement in base deficit in the Plasmalyte A group 6 hours after the fluid infusion was started. The base deficit was uncorrected in the 0.9% saline group even after 24 hours. These results are in concordance with our results, where we noted a base deficit of more than two throughout the study period with a significant difference at second hour intraoperatively and at 24-hour postoperative period with a higher deficit (maximum value of 6.41 ± 2.55 mEq/L) in group NS.

The arterial bicarbonate values were significantly lower in the group NS at the 2nd hour intraoperatively and 24 hours postoperatively. The BSS group was found to have a stable bicarbonate value throughout the perioperative period. The observed effect may be due to the presence of acetate in the Plasmalyte-A solution that was responsible for maintaining normal bicarbonate. In traumatic brain injury patients, NS was compared with Stereofundin (BSS) by Hassan et al and found that the 0.9% saline group had significantly lower bicarbonate values than the balanced fluid group.[15] The findings are similar to our study. The tendency of 0.9% saline to lower the bicarbonate values and increase the base deficit did not produce any noticeable effect on the clinical outcome at any time point in our study.

The serum lactate values were not statistically different at any time in our study. Similar findings were seen in traumatic brain injury patients.[15] In another study on renal transplant patients by Saini et al, a significant difference was found in serum lactate between the BSS group and 0.9% saline group at the end of surgery, though they were within normal physiological limits.[16]

The serum chloride level was higher in the 0.9% saline group at all time periods of measurement in this study, with a significantly higher value found at the 24-hour postoperative time point. This can be explained by the supra physiological chloride content of 0.9% saline (154 mmol/L) compared with the Plasmalyte A, which has lesser chloride content (98 mmol/L). In another study, authors observed that chloride levels in the 0.9% saline group were persistently higher than the Plasmalyte A group throughout the study period.[9,12] Similarly, rise in chloride levels (up to 115 mEq/L) was noted in patients undergoing surgery for supratentorial tumors when NS was used.[7]

In literature, 0.9% saline is known to cause hyperchloremic metabolic acidosis.[17,18] In a study by Chowdhury et al, it was observed that this acidosis causes an adverse effect on kidney function.[19] They found a decreased glomerular filtration rate and renal artery blood flow in subjects infused with 0.9% saline. This can translate into reduced creatinine clearance. The creatinine values in our study were significantly higher at 24 and 48 hours postoperative period in the group NS compared with the group BSS, though they remain within physiological limits. In a similar study in neurosurgical population, creatinine was significantly elevated in NS group at 4 hours after surgery.[9]

The urine NGAL and serum cystatin C emerged as biomarkers of AKI in medical literature.[10,11] Urine NGAL is an early biomarker of AKI seen to rise as early as 6 hours after insult. In our study, the urine NGAL values in both groups were comparable during the preoperative and 48 hours postoperative period. The NGAL values at 48 hours of any of the patients in either of the groups did not approach a value denoting AKI. From these findings, we conclude that neither of the study fluids caused a predisposition to AKI after 48 hours of infusion. Though there was no difference in urine NGAL values between the groups, there was a significant difference in NGAL values between preoperative and postoperative period. This may be due to the acute stress response and a subclinical insult to the kidney following aSAH.

In our study, the serum cystatin C values did not change in both the groups during preoperative and 48 hours postoperative time periods. This could confirm that both the study fluids do not predispose to AKI, though our study was not powered to detect this as the endpoint. In comparing serum cystatin C and serum creatinine values in patients undergoing cardiac surgery, a rise of more than or equal to 30 % baseline serum cystatin C was considered to be suggestive of AKI.[20] In our study, none of the patients demonstrated such an increase. In our study, both the creatinine and cystatin C are found to point toward a normal physiological limit meaning that there is no predisposition to AKI by infusion of the study fluids. These findings are in accordance with other investigators' findings where none of the patients developed clinically significant AKI in either of the study groups.[7]

The statistically significant variations found in the various biochemical and metabolic parameters did not produce difference in clinical outcome as seen in other fluid studies on neurosurgical population[21] and also no adverse renal outcomes.[7]

We assessed the effect of study fluid infusion on the condition of the brain using a BRS by the surgeon blinded

to the study fluid.[22] The intraoperative BRS could be affected by the change in the plasma osmolality from the study fluids because BSS is iso-osmolar to plasma (294 mOsm/kg) compared with 0.9% saline (308 mOsm/kg). However, we observed no significant difference in the BRS between the two groups. These results are consistent with the findings of Dey et al, in which patients undergoing craniotomies for supratentorial tumors were given 0.9% saline or BSS, and brain relaxation was similar between the two groups.[7]

All the patients included in our study were followed and assessed for neurological outcomes using the MRS at discharge and 1 and 3 months after discharge. There was no significant difference seen between the two groups with respect to neurological outcomes. Neurological outcome in patients with aSAH is based on many factors like volume and location of initial bleed, hemodynamic factors, surgical factors, postoperative complications like vasospasm, and delayed cerebral ischemia; thus, the type of fluid infused alone was not found to affect it significantly.

The strength of the study was that it was a prospective randomized, double-blinded study that was statistically well powered to find a significant difference in pH between the two groups of study fluids. Additionally, the same study fluid was administered to the patient during preoperative fluid resuscitation, intraoperative period, and till 48 hours after surgery. So, the effect of study fluid was extensively evaluated in our study. The various parameters of acid–base balance, serum electrolytes, serum lactate, and anion gap were all measured in the intraoperative period and till 48 hours in the postoperative period. Thus, the in-depth analysis of the effect of study fluid on the acid–base parameters was possible.

The study has some limitations. The study's sample size was statistically powered to find significant differences in pH. However, it was not adequately powered to find significant differences in other secondary outcomes like biomarkers of AKI, brain relaxation score, and neurological outcome. Our study was conducted in a subgroup of population with good grade aneurysms. Generalization to poor-grade aneurysms and other neurosurgical populations may not be possible.

Conclusion

The BSSs maintain acid–base balance, do not produce acute renal injury, and provide comparable intraoperative brain conditions and neurological outcomes. On the other hand, 0.9% saline infusion exhibits a tendency to shift the pH toward acidosis. Hence, BSS may be preferred to 0.9% saline for perioperative use in patients undergoing clipping for ruptured intracranial aneurysm.

Authors' Contributions

S.K.S., N.B.P., and N.K. were involved in study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. S.L.S. helped in study conception and design, data collection, and manuscript preparation. S.M. contributed to analysis and interpretation of results and manuscript preparation. M.K., S.P., and A.P. helped in study conception and design and data collection. S.S. and S.D. helped in data collection and analysis. M.T. contributed to study conception and design.

Note

This study was presented at 23rd Annual National Conference of Indian Society of Neuroanaesthesiology and Critical Care (ISNACC-2022) on January 21–23, 2022, Kolkata (Virtual mode) under Free Paper Original Article Category.

Ethical Approval

Ethical approval of this study was obtained from the Institutional Ethics Committee (INT/IEC/2020/SPL - 1088) on August 31, 2020, and the study was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000.

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Clinical Trial Registration Number

Clinical Trial Registry of India (CTRI/2020/09/028078) on 28 September 2020 (www.ctri.nic.in).

Conflict of Interest

None declared.

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