

# BALANCED VERSUS SALINE-BASED FLUID REGIMEN FOR ELECTIVE SUPRATENTORIAL CRANIOTOMY: ACID-BASE AND ELECTROLYTE CHANGES

WAN MOHD NAZARUDDIN WAN HASSAN<sup>1</sup>, NORMI SUUT<sup>1</sup>,  
PETER CHEE SEONG TAN<sup>1</sup> AND RHENDRA HARDY MOHAMED ZAINI<sup>1</sup>

## Abstract

**Background:** The aim of this study was to compare the effect of balanced fluid (BF) and saline-based fluid (SF) regimen on the acid-base and electrolyte status during elective supratentorial craniotomy.

**Methods:** 56 patients undergoing elective supratentorial craniotomy were randomized into two groups; Group BF (n=28) received Sterofundin® ISO ± Tetraspan® 6% and Group SF (n=27) received 0.9% normal saline ± Venofundin® 6%. Acid-base, electrolytes, and serum osmolality were measured at baseline and postoperatively.

**Results:** Group SF showed a larger increase in the mean changes of chloride ( $7.7 \pm 4.8$  vs.  $2.6 \pm 3.9$  mmol/l,  $P < 0.001$ ) and a larger reduction in the mean changes of bicarbonate as well as base excess ( $-3.0 \pm 2.1$  vs.  $-1.5 \pm 2.3$  mmol/l,  $P = 0.012$ ;  $-3.1 \pm 3.1$  vs.  $-0.8 \pm 3.1$ ,  $P = 0.009$ ). On actual value, Group SF also showed more post operative hyperchloremia and low serum bicarbonate as well as base excess. Group BF showed a larger increase in the mean changes of magnesium, calcium, and phosphate ( $0.0 \pm 0.2$  vs.  $-0.1 \pm 0.1$  mmol/l,  $P = 0.037$ ;  $0.1 \pm 0.2$  vs.  $-0.1 \pm 0.3$  mmol/l,  $P = 0.021$ ;  $0.3 \pm 0.3$  vs.  $0.0 \pm 0.4$  mmol/l,  $P = 0.013$ ). However, all post-operative levels of electrolytes were within the normal range in both groups except more hypercalcemia in Group BF.

**Conclusions:** BF regimen maintained the acid-base balance and increased in electrolytes changes during neurosurgery, whereas SF regimen showed more hyperchloremia with low bicarbonate and base excess.

## Introduction

The general principles of fluid management for neurosurgical anesthesia are maintaining normovolemia and preventing the reduction of plasma osmolality to avoid the development of cerebral edema. As the blood-brain barrier allows the passage of water along osmotic gradients, plasma osmolality is a determinant of brain water content. Reducing plasma osmolality results in edema in normal and abnormal brains<sup>1</sup>. The other challenges of fluid management during elective neurosurgery are prolonged durations of surgeries and risk of intracranial bleeding, which require high volumes of intraoperative fluid replacement and blood product transfusion.

<sup>1</sup> MD, Master in Medicine (anesthesiology), Department of Anaesthesiology, School of Medical Sciences, Universiti Sains Malaysia (USM), 16150 Kubang Kerian, Kelantan, Malaysia.

**Correspondence Author:** Wan Mohd Nazaruddin Wan Hassan Department of Anaesthesiology & Center for Neuroscience Services & Research-P3Neuro, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia. Tel: +60199630385; Fax: +6097653370. E-mail: drnaza\_anaest@yahoo.co.uk

Table 1  
Composition of The Study Solutions in Comparison with Plasma

Parameters	Plasma	Sterofundin® ISO	NaCl 0.9%	Tetraspan® 6%	Venofundin® 6%
Na <sup>+</sup> (mmol/l)	142	140	154	140	154
K <sup>+</sup> (mmol/l)	4.5	4.0	-	4.0	-
Ca <sup>2+</sup> (mmol/l)	2.5	2.5	-	2.5	-
Mg <sup>2+</sup> (mmol/l)	1.25	1.0	-	1.0	-
Cl <sup>-</sup> (mmol/l)	103	127	154	118	154
HCO <sub>3</sub> <sup>-</sup> (mmol/l)	24	-	-	-	-
Lactate (mmol/l)	1.5	-	-	-	-
Colloid (g/l)	Albumin = 30-52	-	-	HES 130/0.42/6:1=60	HES 130/0.42/6:1=60
Theoretical osmolarity (mOsm/l)	291	304	308	296	308
Osmolality (mosm/kg H <sub>2</sub> O)	287	287	286	292	298

Saline-based fluids (SFs), either crystalloids or colloids, are commonly chosen for neurosurgery because of their isotonicity with plasma. However, their non-physiological levels of chloride may lead to hyperchloremic metabolic acidosis after large volumes of infusion<sup>2,3</sup>. The physiologic significance of this acid-base abnormality is unclear, although animal studies suggest that hyperchloremia causes renal vasoconstriction<sup>4</sup>. The least, it has the potential to confuse the diagnostic picture when acidosis is present. At the same time, SF is also non-physiological in terms of its electrolyte contents.

The search for an ideal fluid therapy for neurosurgery is most likely achieved with the recent availability of both balanced crystalloid and colloid solutions. Balanced fluids (BFs) are isotonic plasma-adapted fluids, which contain inorganic ions (calcium, potassium, or magnesium) and have a smaller chloride concentration. Sterofundin® is a current balanced isotonic crystalloid solution that contains acetate/malate instead of lactate as a bicarbonate precursor, whereas a current balanced colloid is Tetraspan®, which is considered a novel Hydroxyethyl starch (HES) 130/0.42. The combination of these two fluids has the potential to be an ideal fluid regimen during neurosurgery.

The aims of this study were to determine the changes in the intraoperative acid-base balance,

electrolytes, and serum osmolality between BF and SF regimens during elective supratentorial craniotomy.

## Methods

This was a prospective, randomized, double-blinded, and controlled clinical trial in a university hospital. After obtaining institutional ethics committee approval, adult patients (18–65 years old) with American Society of Anesthesiologists (ASA) physical status I–III, who underwent elective supratentorial craniotomy, were included for the study. Exclusion criteria were preexisting acid-base and electrolyte disturbances, history of allergies to the study solutions, coagulopathy, and liver as well as renal impairment.

After obtaining written consent, 56 patients were randomly allocated into either Group SF or Group BF. Randomization was instituted using a permuted block with a size of 4. Patients in Group SF received only SF [0.9% normal saline as crystalloid and Venofundin® 6% (B. Braun, Germany) as colloid], whereas patients in Group BF received only with BF [Sterofundin® ISO (B. Braun, Germany) as crystalloid and Tetraspan® 6% as colloid (B. Braun, Germany)]. The compositions of these solutions are shown in Table 1.

Standard monitoring was started prior to the induction of anesthesia. Non-invasive blood pressure

(BP), heart rate (HR), and pulse oxymetry were recorded at pre-induction. All patients received a standard general anesthetic regimen. They were given intravenous (IV) fentanyl (2 mcg/kg), IV propofol (1–2 mg/kg), and IV rocuronium (0.6 mg/kg) during induction. Intra-arterial cannulation for invasive BP monitoring, central vein cannulation for central venous pressure monitoring, catheterized bladder drainage for urine output monitoring, and nasopharyngeal temperature probe were all inserted after induction. Bispectral index (BIS) monitor was also attached after induction.

Anesthesia was maintained with total intravenous anesthesia using the target controlled infusion (TCI) technique using a TCI pump (Space pump, B. Braun, Germany). TCI propofol was titrated between 4–8 mcg/ml with combination of TCI remifentanyl between 2–8 ng/ml. The aim of anesthesia was to maintain BIS readings in the range of 40–60. An intermittent dose of rocuronium 0.2 mg/kg was given to maintain adequate muscle relaxation. A mixture of oxygen with air at total flow of 2 l/min and inspired oxygen concentration of 0.35–0.40 was maintained throughout the surgery. The ventilation was set up to maintain an end tidal carbon dioxide concentration of 35–40 mmHg.

The crystalloid solutions were administered at approximately 4 ml/kg/h in addition to the maintenance fluid. The triggers for infusion of HES 6% solutions were a systolic BP of less than 90 mmHg and/or a reduction of more than 20% from baseline, an HR of more than 110 beats/min and/or an increase of more than 20% from baseline, and/or urine output of less than 0.5 ml/kg/h and/or pulse pressure variations of more than 12%. The maximum dose of HES 6% solutions allowed was 50 ml/kg. The packed red blood cell (RBC) transfusion was considered when hemoglobin concentration dropped less than 7 g/dl and hemodynamics were compromised during ongoing surgical bleeding. Platelet, fresh frozen plasma (FFP), and cryoprecipitate transfusion were considered based on intraoperative clinical judgement if the bleeding was still active after 3–4 pints of packed RBC were transfused. The aims were for platelet levels more than  $50 \times 10^9 \text{ l}^{-1}$ , a prothrombin time and activated partial thromboplastin time greater than 1.5 of the control mean, and serum fibrinogen of more than  $1.0 \text{ g l}^{-1}$

The arterial blood was sampled immediately after intra-arterial cannulation, as the baseline values and the postoperative samples were taken after the completion of skin closure. These samples were analyzed for pH, arterial carbon dioxide ( $P_a\text{CO}_2$ ), bicarbonate ( $\text{HCO}_3^-$ ), standard base excess (BE) sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ), and serum lactate levels using a blood gas analyzer GEM Premier 3000 (Instrumentation Laboratory, USA), whereas serum chloride ( $\text{Cl}^-$ ), phosphate ( $\text{PO}_4^{3-}$ ), magnesium ( $\text{Mg}^{2+}$ ), calcium ( $\text{Ca}^{2+}$ ) and serum osmolality were analyzed using a COBAS Integra® 800 system (Roche, USA).

Statistical analysis was carried out with SPSS version 22.0. The demographic data between groups were compared using an independent t-test, chi-square test, or Fisher's exact test where appropriate. The intragroup and intergroup differences were analyzed using an independent t-test or paired t-test where appropriate. The results were expressed as means and standard deviations (SDs) or frequencies as appropriate. The level of significance was determined as  $p < 0.05$ .

The sample size was calculated based on previous study by Wilkes et al<sup>5</sup>, using Power & Sample Size Calculations, version 3.0.10 software. If based on the value of mean BE changes, we required 28 patients in each group to detect a difference of 4.6 in mean changes of BE with an assumed SD of 5, power of 90%, alpha of 0.05, and consideration of 10% potential dropouts. Therefore, for final sample size, we took the calculation based on the BE calculation, which was a total of 56 subjects.

## Results

A total of 56 patients were recruited and divided into 28 patients in each group. One patient from Group SF was withdrawn from the study, as the patient developed major complications intraoperatively and the surgery had to be abandoned. This resulted in only 27 patients in Group SF for analysis. Both groups were comparable in terms of demographic data and surgical and anesthetic-related parameters (Table 2).

The results of acid-base and electrolytes changes are shown in Table 3. Both groups showed an increment in chloride from the baseline, but Group

Table 2  
Demographic Data, Surgical and Anesthetic Related Parameters

Parameters	Group		P-value
	BF (n=28)	SF (n=27)	
Age (years)	38.9 ± 15.3	40.6 ± 15.4	0.676
Weight (kg)	63.8 ± 9.4	69.4 ± 14.5	0.092
Height (meter)	1.6 ± 0.1	1.6 ± 0.1	0.552
Sex [n (%)]			
male	13 (44.8%)	16 (55.2%)	0.341
female	15 (57.7%)	11 (42.3%)	
ASA class [n (%)]			
I	11 (44.0%)	14 (56.0%)	0.285
II	15 (62.5%)	9 (37.5%)	
III	2 (33.3%)	4 (66.7%)	
Diagnosis [n (%)]			
Meningioma	11 (50.0%)	11 (50.0%)	0.983
Cerebral Aneurysm	7 (50.0%)	7 (50.0%)	
Others (metastases, clival chordoma)	10 (52.6%)	9 (47.4%)	
Duration of surgery (hours)	6.6 ± 1.7	6.7 ± 2.1	0.797
Estimated blood loss (ml)	978.6 ± 409.3	990.7 ± 466.6	0.918
Total fluid transfusion (ml)	4803.6 ± 1796.8	4500.0 ± 1896.4	0.545
Crystalloid (ml)	4500.0 ± 1683.3	4185.2 ± 1732.9	0.497
Colloid (ml)	285.7 ± 286.4	296.3 ± 286.2	0.892
Packed cells (ml)	810.0 ± 355.7	706.3 ± 367.4	0.431
Blood product (ml)			
Fresh frozen plasma	380.0 ± 44.7	600.0 ± 282.8	0.468
Cryoprecipitate	133.3 ± 57.7	200.0 ± 141.4	0.624
Platelets	166.7 ± 57.7	150.0 ± 70.7	0.789
Post op Hb (g/dL)	10.6 ± 0.3	10.7 ± 0.32	0.528
Total propofol TCI (mg/kg/hr)	8.2 ± 3.3	6.9 ± 1.8	0.090

\* Data are mean ± SD, or number of patients (%).

ASA Physical Status indicates American Society of Anesthesiologists Physical Status; TCI, Target Controlled Infusion

SF showed a larger significant increase in the mean changes in chloride ( $7.7 \pm 4.8$  vs.  $2.6 \pm 3.9$  mmol/l,  $P < 0.001$ ). Based on the actual post-operative levels, Group SF also showed more hyperchloremia than Group BF. Group BF showed an increment whereas Group SF showed a reduction of magnesium and calcium levels from the baseline. The mean changes

in magnesium and calcium were significantly larger in Group BF ( $0.0 \pm 0.2$  vs.  $-0.1 \pm 0.1$  mmol/l,  $P = 0.037$ ;  $0.1 \pm 0.2$  vs.  $-0.1 \pm 0.3$  mmol/l,  $P = 0.021$ ). Based on the actual post-operative levels, both groups showed normal serum magnesium, but Group BF showed more hypercalcemia than Group SF. Both groups showed an increase in the mean changes of phosphate, but Group

Table 3  
 Mean of Actual Values and Mean Changes of Electrolytes and Acid Base

Parameters		Group		P-value
		BF (n=28)	SF (n=27)	
Na <sup>+</sup> (mmol/l)	Baseline	136.3± 4.1	137.7± 5.0	
	Post-op	138.9± 3.6	140.2± 6.0	
	Mean Changes	2.6 ±3.8	2.5 ±4.0	0.933
K <sup>a+</sup> (mmol/l)	Baseline	3.4 ± 0.3	3.6 ± 0.5	
	Post-op	3.7 ± 0.3	3.7 ± 0.4	
	Mean Changes	0.3 ±0.3	0.1 ±0.6	0.083
Cl <sup>-</sup> (mmol/l)	Baseline	109.2± 5.3	110.1 ± 4.8	
	Post-op	111.8 ± 5.2	117.8± 5.6	
	Mean Changes	2.6 ±3.9	7.7 ±4.8	<0.001
PO <sub>4</sub> <sup>3-</sup> (mmol/l)	Baseline	1.1 ± 0.2	1.1 ± 0.3	
	Post-op	1.3 ± 0.3	1.1 ± 0.4	
	Mean Changes	0.3 ±0.3	0.0 ±0.4	0.013
Mg <sup>2+</sup> (mmol/l)	Baseline	0.9 ± 0.2	0.9 ± 0.2	
	Post-op	0.9 ± 0.1	0.8 ± 0.1	
	Mean Changes	0.0 ±0.2	-0.1 ±0.1	0.037
Ca <sup>2+</sup> (mmol/l)	Baseline	2.1 ± 0.4	1.7 ± 0.5	
	Post-op	2.2± 0.3	1.6 ± 0.3	
	Mean Changes	0.1 ±0.2	-0.1 ±0.3	0.021
pH	Baseline	7.47± 0.06	7.42±0.06	
	Post-op	7.42±0.04	7.36± 0.05	
	Mean Changes	-0.05±0.05	-0.06±0.06	0.301
P <sub>a</sub> CO <sub>2</sub> (mmHg)	Baseline	33.1 ± 4.2	33.2 ± 6.1	
	Post-op	35.0 ± 3.7	34.3 ± 3.1	
	Mean Changes	1.9 ±5.9	1.1 ±5.9	0.624
Base excess	Baseline	1.1 ± 3.2	-2.0 ± 3.7	
	Post-op	0.3 ± 3.7	-5.0 ± 3.4	
	Mean Changes	-0.8 ±3.0	-3.1 ±3.1	0.009
HCO <sub>3</sub> <sup>-</sup> (mmol/l)	Baseline	25.7 ± 3.0	23.3 ± 2.8	
	Post-op	24.3 ± 3.0	20.3 ± 2.6	
	Mean Changes	-1.5 ±2.3	-3.0 ±2.1	0.012
Lactate (mmol/l)	Baseline	1.2 ± 0.6	1.3 ± 0.8	
	Post-op	1.9 ± 1.2	1.4 ± 0.8	
	Mean Changes	0.6 ±0.9	0.2 ±0.5	0.025
Albumin (mmol/l)	Baseline	32.5 ± 5.1	34.6 ± 4.6	
	Post-op	27.8 ± 6.1	30.0 ± 5.5	
	Mean Changes	-4.8 ±5.7	-7.7 ±3.8	0.029
Serum osmolality (mOsmol/kg)	Baseline	285.6 ± 7.5	288.4 ± 8.2	
	Post-op	294.0 ± 8.7	295.6 ± 11.1	
	Mean Changes	8.4 ± 8.1	7.2 ±8.1	0.593

\*Data are mean ± SD

BF showed a larger significant increase ( $0.3 \pm 0.3$  vs.  $0.0 \pm 0.4$  mmol/l,  $P = 0.013$ ). However, the actual post-operative serum phosphate levels were still normal in both groups.

Both groups showed a reduction in the bicarbonate levels and base excess from the baseline, but Group SF also showed a larger significant reduction in the mean changes of bicarbonate levels and base excess ( $-3.0 \pm 2.1$  vs.  $-1.5 \pm 2.3$  mmol/l,  $P = 0.012$ ;  $-3.1 \pm 3.1$  vs.  $-0.8 \pm 3.0$ ,  $P = 0.009$ ). The actual post-operative value was lower than the normal range only in Group SF. Both groups also showed an increase in the lactate levels from the baseline, but there was a significantly greater mean lactate level increase in group BF ( $0.6 \pm 0.9$  vs.  $0.2 \pm 0.5$  mmol/l,  $P = 0.025$ ). However, the actual post-operative value was normal in both groups. There were no significant differences in pH,  $P_aCO_2$ , and serum osmolality. In general, the hemodynamic parameters were stable in both groups.

## Discussion

Our study demonstrated that the mean changes in chloride indicated a significantly larger increase in SF than BF with more hyperchloremia in the actual post-operative values. Although the mean pH changes were not significant with a normal range of actual post-operative pH values in both groups, the mean bicarbonate changes and base excess demonstrated a significantly larger reduction in SF than BF with actual post-operative values also lower than the normal range. This demonstrated that SF causes hyperchloremia without significant metabolic acidosis, but with decreasing changes of base excess and bicarbonate levels. In terms of electrolyte profiles, our study showed that patients who received BF recorded significant larger increases in mean changes in magnesium, calcium, and phosphate levels than SF. However, based on the actual post-operative values, all serum electrolytes were within the normal range, except there was more hypercalcemia in BF. This demonstrated that BF contributed more toward preserving electrolyte status than SF. There were no significant changes in terms of serum osmolality and  $P_aCO_2$ .

The total BF regimen has the potential to be an ideal

fluid of choice during neurosurgery, or at least a better choice than the SF regimen. We chose a combination of Sterofundin® and Tetraspan® as the BF regimen for our study. Sterofundin® is an isotonic solution that contains full electrolytes and acetate/malate as a bicarbonate precursor, whereas Tetraspan® is HES 130/0.42/6:1 in a balanced full electrolyte solution with acetate/malate as a bicarbonate precursor as well. Theoretically, total BF can prevent hyperchloremic metabolic acidosis, maintain the electrolyte profile, and prevent cerebral edema compared to SF or lactated Ringer's solution.

The data on the potential benefits of BF in neurosurgery are still limited. At the time of our literature search, we only found two studies providing evidence on the use of BF in neurosurgery population. Thirty-six consecutive patients with subarachnoid hemorrhage were randomized and double-blinded to either 0.9% normal saline and HES dissolved in 0.9% normal saline (Voluven® and saline) or balanced crystalloid and colloid solutions (Ringerfundin® and Tetraspan®) for 48 h. Laboratory samples and fluid balance were evaluated at baseline, 24 h, and 48 h. The results showed that treatment with SF resulted in a greater number of patients with hyperchloremia, hyperosmolality, and positive fluid balance  $>1,500$  ml early after subarachnoid hemorrhage, while the administration of BF did not cause more frequent hyponatremia or hypo-osmolality<sup>6</sup>. This was similar to our study in term of hyperchloremia in SF, but our serum osmolality was maintained as iso-osmolar in both groups. In terms of osmolality changes, our study showed that both types of fluid regimens were suitable for use in neurosurgery. In another study on brain-injured patients, either severe traumatic brain injury or subarachnoid hemorrhage demonstrated that balanced solutions reduce the incidence of hyperchloremic acidosis compared to saline solutions. However, intracranial pressure did not appear to differ between groups<sup>7</sup>.

Several other non-neurosurgical studies have been done on the use of BF regimens. In the resuscitation of trauma patients, Plasma-Lyte A, a calcium-free balanced crystalloid solution, resulted in improved acid-base status and less hyperchloremia 24 hours post injury when compared to resuscitation

with 0.9% normal saline<sup>8</sup>. In a rat hemorrhagic shock model, balanced crystalloid solution with Plasma-Lyte resuscitation seems to be superior to unbalanced crystalloid (0.9% normal saline) in protecting the kidneys after hemorrhagic shock. However, neither solution was able to correct systemic inflammation or oxidative stress associated with hemorrhagic shock<sup>9</sup>. A study in cardiac surgery, comparing 6% HES130/0.4 balanced (Volulyte; Fresenius Kabi, Bad Homburg, Germany) and 6% HES130/0.4 saline (Voluven; Fresenius Kabi, Bad Homburg, Germany) for intra- and post-operative hemodynamic stabilization, demonstrated significantly lower serum chloride levels in the HES balanced group, which reflected the lower chloride load of similar infusion volumes as well as significantly less acidosis<sup>10</sup>. A study of 12 healthy volunteers showed that a totally BF concept, which is a combination of balanced crystalloid and colloid, had similar coagulation effects in vitro as their respective combination of unbalanced solutions<sup>11</sup>. The resuscitation of diabetic ketoacidosis patients with balanced solution (Plasma-Lyte) results in lower serum chloride and higher bicarbonate levels than patients receiving 0.9% normal saline, consistent with the prevention of hyperchloremic metabolic acidosis<sup>12</sup>. Most of these studies demonstrated hyperchloremia in the SF group with or without significant acidosis, consistent with our results.

There are few conditions that might lead to acidosis related to fluid therapy. Tavernier B et al. mentioned four conditions that must be combined for plasma expanders-induced acidosis to be observed post operatively after major surgery and in intensive care: 1) the type of solutions administered is isotonic saline-based plasma expanders (typically isotonic saline solution alone or as colloid solvent), 2) the volume infused is large, 3) the rate of infusion is rapid, and/or 4) the renal function is impaired<sup>13</sup>. Even under these conditions, a study by Scheingraber et al showed that the administration 6 l of 0.9% normal saline over 2 hours during elective gynecological surgery only induced mild acidosis, where the pH decreased to 7.28 (vs. 7.40 with lactated Ringer's solution)<sup>2</sup>. In another study, the administration of 50 ml/kg of 0.9% normal saline over 1 hour to healthy volunteers lowered the pH by  $0.04 \pm 0.04$  compared to lactated Ringer's solution, which increased the pH by  $0.04 \pm$

$0.04$ <sup>14</sup>. Our study showed that the administration of SF for 6.7 hours of surgery with a total volume of 4.5 liters caused a pH reduction of only  $0.06 \pm 0.06$ , which was not significant. However, a reduction of the base excess and bicarbonate with the presence of hyperchloremia still showed a trend toward acidosis. This result showed that even though large volumes of SF were administered in our cases, the slow rate of administration during prolonged neurosurgery in patients with normal renal function could have prevented the development of significant metabolic acidosis.

Little information exists on the clinical importance of hyperchloremic acidosis. A study of elderly surgical patients showed that it may impair splanchnic perfusion<sup>5</sup>. It may also interfere with cellular exchange mechanisms, reduce renal blood flow by vasoconstriction, and have a negative effect on the glomerular filtration rate<sup>15</sup>. Several other studies have shown that hyperchloremic acidosis caused a significant increase in the time to first urination and needed significantly more blood products<sup>14,16</sup>. A recent study that examined the association of a chloride-restrictive vs. chloride-liberal intravenous fluid strategy with acute kidney injury in critically ill patients revealed that the implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant reduction in the incidence of acute kidney injury and use of renal replacement therapy<sup>17</sup>. The extension of this study to another 12 months of observation also revealed that the overall impact of restricting chloride-rich fluids on acute kidney injury remained, even though sensitivity analysis suggested that other unidentified confounders might have also contributed to fluctuations in the incidence of acute kidney injury<sup>18</sup>. These two studies showed the potential effects of hyperchloremia from chloride-liberal intravenous fluid strategy in ICU to renal complications in ICU.

The observation of a better electrolyte profile in BF is self-explanatory in view of the presence of magnesium and calcium as the constituents in BF. The infusion of 10 ml/kg Hextend®, a balanced 6% HES in 21 healthy volunteers, demonstrated that plasma components remained unchanged during and after the infusion, which reflected the benefit of a balanced

electrolyte solution in biochemical stability<sup>19</sup>. Although both fluid regimens do not contain phosphate, the mean changes in phosphate indicated a significantly larger increase in BF. We could not find a plausible explanation for these changes. Nevertheless, whether these differences have clinical relevance has yet to be investigated.

The other advantage of BF given in our work is their content of acetate-buffer, which is more stable in terms of their influence on plasma pH,  $\text{HCO}_3^-$  and base excess. This finding was demonstrated by Hofmann-Kiefer and colleagues in comparison with the administration of lactate-based balanced solution<sup>20</sup>. Its clinical relevance is yet to be determined, but small differences in the acid-base stability of the concerned solutions may be important successively if increased volumes of fluids are given, for instance, during major surgeries. Furthermore, balanced solutions with acetate-buffer also offer another advantage over lactate-based fluids. Acetate is rapidly metabolized in several extrahepatic tissues, especially muscles. Therefore,

it is less accumulated during shock states or severe hepatic impairment. Acetate is also unlikely to result in hyperglycemia. Moreover, oxygen consumption and carbon dioxide elimination are less affected by acetate<sup>21</sup>. We could not offer a plausible explanation for the significantly higher mean changes in the lactate levels in the BF regime compared to SF. However, the changes did not lead to pH changes, and the lactate level only increased  $0.62 \pm 0.85$  mmol/l from the baseline. The actual post-operative values were still within the normal range in both groups. Furthermore, the estimated blood loss was comparable between the two groups and indeed slightly lower in Group BF.

In conclusions, the BF regimen demonstrated more stable electrolytes, particularly chloride, magnesium, calcium, and phosphate levels as well as an acid-base balance during prolonged elective supratentorial craniotomy. On the other hand, the SF regimen demonstrated hyperchloremia with a greater propensity to develop metabolic acidosis.

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