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Intravenous Fluid Selection for Unruptured Intracranial Aneurysm Clipping : Balanced Crystalloid versus Normal Saline

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Objective : While balanced crystalloid (BC) could be a relevant fluid regimen with buffer system compared with normal saline (NS), there have been no studies on the optimal fluid for surgery of an unruptured intracranial aneurysm (UIA). This study aimed to compare the effects of fluid regimens between NS and BC on the metabolic and clinical outcomes of patients who underwent surgery for UIA.

Methods : This study was designed as a propensity score matched retrospective comparative study and included adult patients who underwent UIA clipping. Patient groups were categorized as NS and BC groups based on the types of pre-operative fluid and the amount of fluid administered during surgery. The primary outcomes were defined as electrolyte imbalance and acidosis immediately after surgery. The secondary outcomes were the length of stay in the intensive care unit (ICU) and duration from the end of the operation to extubation.

Results : A total of 586 patients were enrolled in this study, with each of 293 patients assigned to the NS and BC groups, respectively. Immediately after surgery, serum chloride levels were significantly higher in the NS group. Compared to the NS group, the BC group had lower incidence rates of acidemia (6.5% vs. 11.6%, p=0.043) and metabolic acidosis (0.7% vs. 4.4%, p=0.007). As compared to NS group, BC group had significantly shorter duration from the end of the operation to extubation (250±824 vs. 122±372 minutes, p=0.016) and length of stay in ICU (1.37±1.11 vs. 1.12±0.61 days, p=0.001). Throughout multivariable analysis, use of BC was found to be significant factor for favorable post-operative results.

Conclusion : This study showed that the patients who received BC during UIA clipping had lower incidence of metabolic acidosis, earlier extubation and shorter ICU stay compared to those who received NS. Therefore, using BC as a peri-operative fluid can be recommended for patients who undergo surgery for UIA.

Key Words : Balanced crystalloid · Normal saline · Intracranial aneurysm, Unruptured · Crystalloid solutions · Acidosis · Fluid therapy.

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INTRODUCTION

The incidence of unruptured intracranial aneurysms (UIAs) has exhibited a marked increase owing to an increase in healthcare screenings[11,13]. Although treatment of UIA is effective in preventing subarachnoid hemorrhage, a tailored decision for the treatment of UIA should be made in consideration of possible complication profiles, because window of the benefit over risk is relatively narrow in UIA treatment, unlike treatment for subarachnoid hemorrhage[6,12]. To maximize the risk-benefit ratio of clipping surgery for UIA, surgical and medical complications need to be controlled. Many complementary methods, such as intraoperative neuromonitoring and indocyanine green angiography, have been introduced to reduce the risk of complications during clipping surgery for UIA[4,5,21].

The adequate peri-operative fluid management should be considered, also. The general principle of fluid management for neurosurgical anesthesia is maintaining normovolemia and plasma osmolality to avoid cerebral edema. Hence, normal saline (NS) has been recommended for severe brain injury[1,2]. However, NS can cause metabolic acidosis and can slightly inhibit kidney function[8]. Thus, to lower post-operative adverse events in the setting of UIA, post-operative acidosis (POA) and post-operative electrolyte imbalance (POEI) should be considered with NS administration. In a previous meta-analysis, the use of buffered fluids has been associated with less metabolic derangement, in particular hyperchloremia and metabolic acidosis, compared with non-buffered fluids such as NS[3]. Another prospective randomized controlled study revealed that balanced crystalloid (BC) provided significantly better control over acid-base balance, sodium and chloride levels with elective neurosurgery[7]. Moreover, NS infusion increased variation in serum chloride compared with BC in children undergoing brain tumor resection[14].

As a result, fluid management for UIA clipping has been gradually changed from a NS-based regimen to a buffered BC regimen at our institute. Thus, in this report, we compared the clinical data related with UIA clipping for describing the differences in POA, POEI, and clinical outcomes according to the fluid regimens.

MATERIALS AND METHODS

This study was approved by Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1909-562-109) and adhered to the recommendations of the Declaration of Helsinki for biomedical research involving human subjects. This retrospective cohort study included adult patients (18 years of age or older) who underwent UIA clipping at our institute between April 1, 2003 and July 31, 2019.

The inclusion and exclusion criteria are summarized in Fig. 1. Patients administered with fluids other than NS or BC were excluded. The NS group consisted of patients administered with NS as pre-operative fluid and administered with NS in an amount greater than 50% of the total fluid volume during surgery. The same criteria were applied to the BC group. The fluid administered to the BC group was a single product (Plasma Solution-A, HK inno.N Corp., Seoul, Korea) containing sodium chloride (5.26 g), sodium gluconate (5.02 g), sodium acetate hydrate (3.68 g), potassium chloride (0.37 g), and magnesium chloride (0.3 g) in 1000 mL of fluid. Propensity score matching was performed to minimize selection bias.

We collected the following data through electronic medical records and a clinical data warehouse system, which was a big data querying platform. The classification of aneurysms targeted for surgery is as follows. Anterior cerebral artery (ACA) aneurysms were defined as aneurysms arose from the ACA, including the anterior communicating artery. Internal carotid artery (ICA) aneurysms included the posterior communicating artery aneurysms, the anterior choroidal artery aneurysms and other aneurysms arose along the ICA. Middle cerebral artery (MCA) aneurysms were all kind of aneurysms belonged to the MCA and bifurcation. Posterior circulation aneurysms were defined as all aneurysm arose from the posterior circulations.

To compare POEI and POA, the laboratory results of arterial blood gas analysis and serum electrolytes were recorded immediately after surgery and on post-operative day 1. Through this study, acidemia was defined as an arterial blood pH <7.35. Metabolic acidosis was defined as a serum bicarbonate concentration <22 mEq/L with acidemia. For analysis of clinical outcomes, we collected information on the length of stay in the intensive care unit (ICU) (in days) and the duration from the end of the operation to extubation (in minutes). Throughout the study period, extubation had been conducted under same criteria (Glasgow coma score ≥13, patient able to initiate an inspiratory effort, and normal PaO_2 without ventilator support).

Age, sex, body mass index (BMI), hypertension, diabetes mellitus, and pre-operative glomerular filtration rate (GFR) were recorded to control potential confounding factors. Factors related with surgery (operation time, total fluid volume and transfusion volume administered) were also investigated.

All statistical analyses were performed using R software (version 3.5.3; The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ±standard deviation and were analyzed by an independent t-test. The chi-square test was used to compare categorical variables. Variables showed statistical significance through univariable analysis were selected for multivariable analysis. Binomial logistic regression was performed to measure the association between incidence rates of acidemia, metabolic acidosis, and other variables. The goodness of fit and the simplicity of the model was evaluated using Akaike information criterion (AIC). For the continuous outcome variable, multi-

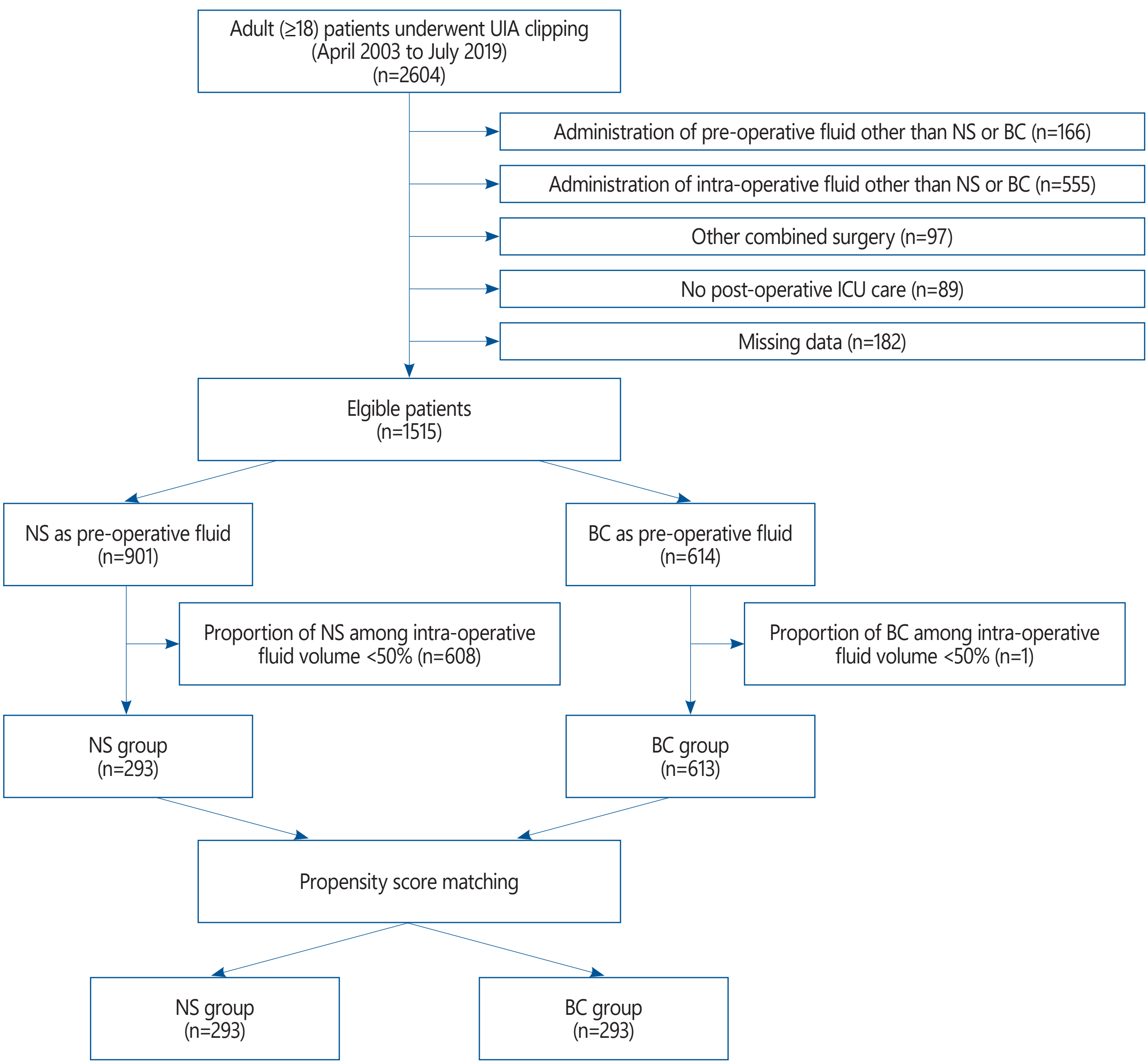

Fig. 1. Flowchart shows enrollment of study subjects. Following the inclusion and exclusion criteria, a total 906 patients (293 NS group and 613 BC group) were matched by propensity score. As a result, 293 patients are allocated to each group. UIA : unruptured intracranial aneurysm, NS : normal saline, BC : balanced crystalloid, ICU : intensive care unit.

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variable linear regression was used to analyze the linear coefficients of variables using bi-directional variable selection based on AIC. With each final model, additional fitting was conducted with variables showing multicollinearity and their interactions. *p*-values <0.05 were regarded as statistically significant.

RESULTS

A total of 906 patients met the inclusion criteria : 293 and 613 patients of NS and BC group, respectively. Throughout propensity score matching with age, sex, BMI, pre-operative measurement of serum levels of sodium, potassium, chloride, GFR, history of hypertension, diabetes mellitus, operation time and the amount of total volume of fluid and transfusion, 293 patients could be allocated to each group. The basic characteristics of patients and distribution of aneurysms are summarized in Table 1. The two groups showed a similar distributions of all variables used in matching process.

Table 2 shows the results of the laboratory tests immediately after surgery. The serum levels of sodium and potassium did not show statistical differences, however, the mean serum chloride level of the NS group (109.1±2.9 mmol/L) was significantly higher than that of the BC group (107.8±3.1 mmol/L) (p<0.001). The arterial blood gas analysis results showed that the arterial pH was significantly lower in the NS group (7.39±0.04) than in the BC group (7.42±0.05, p<0.001). HCO_3^- level was also significantly lower in the NS group compared to that of the BC group (22.7±1.8 vs. 24.1±2.1, p<0.001). On the other hand, partial pressure of carbon dioxide (pCO_2) showed similar results. There were three patients in the BC group and zero

Table 1. Patients characteristics

	NS group (n=293)	BC group (n=293)	*p*-value
Age (years)	56.5±9.7	56.9±10.2	0.660
Female sex	194 (66.2)	198 (67.6)	0.792
BMI (kg/m^2)	25.0±3.3	24.8±3.6	0.616
Sodium (mmol/L)	140.8±2.3	140.8±2.2	0.971
Potassium (mmol/L)	4.20±0.39	4.20±0.38	0.966
Chloride (mmol/L)	103.8±2.4	104.1±2.4	0.197
GFR (mL/min/1.73 m^2)	91.0±31.5	93.0±24.7	0.481
Hypertension	155 (52.9)	158 (53.9)	0.868
Diabetes	26 (8.9)	31 (10.6)	0.577
Operation time (minutes)	240.9±86.4	241.0±109.7	0.996
Total fluid volume (mL)	1699±619	1683±852	0.799
Total transfusion volume (mL)	215±444	164±447	0.167
Location of aneurysms			
MCA	144 (49.1)	157 (53.6)	
ACA	75 (25.6)	62 (21.2)	
ICA	34 (11.6)	40 (13.7)	
POST	1 (0.3)	4 (1.4)	
ACA+MCA	16 (5.5)	15 (5.1)	
ICA+MCA	11 (3.8)	4 (1.4)	
ACA+ICA	7 (2.4)	7 (2.4)	
MCA+POST	2 (0.7)	2 (0.7)	
ICA+POST	1 (0.3)	0 (0.0)	
ACA+ICA+MCA	2 (0.7)	0 (0.0)	
ACA+MCA+POST	0 (0.0)	1 (0.3)	
ICA+MCA+POST	0 (0.0)	1 (0.3)	

Values are presented as mean±standard deviation or number (%). NS : normal saline, BC : balanced crystalloid, BMI : body mass index, GFR : glomerular filtration rate, MCA : middle cerebral artery, ACA : anterior cerebral artery, ICA : internal carotid artery, POST : posterior circulation

Table 2. Immediate post-operative laboratory tests and clinical outcomes by fluid types

	NS group (n=293)	BC group (n=293)	*p*-value
Sodium (mmol/L)	142.4±2.4	142.5±2.6	0.476
Potassium (mmol/L)	3.91±0.33	3.96±0.32	0.070
Chloride (mmol/L)	109.1±2.9	107.8±3.1	<0.001*
GFR (mL/min/1.73 m^2)	112.9±45.7	111.9±28.9	0.763
pH	7.39±0.04	7.42±0.05	<0.001*
pCO_2 (mmHg)	37.9±4.9	37.8±6.3	0.836
HCO_3^- (mmol/L)	22.7±1.8	24.1±2.1	<0.001*
Anion gap (mmol/L)	10.51±2.23	10.74±2.40	0.244
Base excess (mmol/L)	-1.67±1.78	-0.05±2.35	<0.001*
Acidemia	34 (11.6)	19 (6.5)	0.043*
Metabolic acidosis	13 (4.4)	2 (0.7)	0.007*
Vasopressor	0 (0.0)	3 (1.0)	0.249
Length of stay in ICU (days)	1.37±1.11	1.12±0.61	0.001*
Duration from the end of the operation to extubation (minutes)	250±824	122±372	0.016*

Values are presented as mean±standard deviation or number (%). *Indicates statistical significance (p<0.05). NS : normal saline, BC : balanced crystalloid, GFR : glomerular filtration rate, ICU : intensive care unit patients in the NS group who required the administration of vasopressor after surgery, but there was no statistical difference. The incidence of acidemia was significantly higher in the NS group compared to the BC group (11.6% vs. 6.5%, p=0.043). The rate of metabolic acidosis was also significantly higher in the NS group compared to the BC group (4.4% vs. 0.7%, p=0.007). An analysis of the clinical outcomes showed that the length of stay in the ICU was significantly shorter among patients in the BC group (1.37±1.11 days) compared to those in the NS group (1.12±0.61 days, p=0.001). With regards to the mean duration from the end of the operation to extubation, the NS group required twice as much time (250±824 minutes) compared to the BC group (122±372 minutes) (p=0.016).

The binomial logistic regression analysis showed that BMI, operation time, total fluid volume and fluid type were significantly related with development of acidemia. Throughout multivariable analysis, interaction variable between operation

Table 3. Binomial logistic regression for immediate post-operative acidemia and metabolic acidosis

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Outcome : acidemia						
Age	0.99	0.95–1.03	0.574			
Sex (female)	0.98	0.51–1.81	0.957			
BMI (kg/m^2)	1.14	1.04–1.25	0.007*	1.12	1.03–1.21	0.006*
Pre-OP sodium (mmol/L)	0.92	0.79–1.06	0.242			
Pre-OP potassium (mmol/L)	0.94	0.44–2.03	0.874			
Pre-OP chloride (mmol/L)	1.11	0.96–1.27	0.152			
Pre-OP GFR (mL/min/1.73 m^2)	1	0.98–1.01	0.480			
Hypertension	1.05	0.55–1.97	0.891			
Diabetes	0.76	0.27–2.13	0.596			
Operation time (minutes)	1	1.00–1.01	0.035*		Eliminated	
Total fluid volume (mL)	1	1.00–1.00	0.006*		Eliminated	
Total transfusion volume (mL)	1	1.00–1.00	0.950			
NS group	1.96	1.07–3.58	0.030*	1.9	1.05–3.44	0.033*
Outcome : metabolic acidosis						
Age	0.91	0.84–0.98	0.011*		Eliminated	
Sex (female)	2.73	0.59–12.70	0.200			
BMI (kg/m^2)	1.23	1.01–1.49	0.036*		Eliminated	
Pre-OP sodium (mmol/L)	0.87	0.66–1.15	0.321			
Pre-OP potassium (mmol/L)	0.89	0.21–3.82	0.870			
Pre-OP chloride (mmol/L)	1.17	0.92–1.50	0.210			
Pre-OP GFR (mL/min/1.73 m^2)	0.95	0.92–0.98	0.003*	0.97	0.95–0.99	0.009*
Hypertension	1.08	0.30–3.90	0.908			
Diabetes	0.72	0.08–6.76	0.771			
Operation time (minutes)	1.01	1.00–1.01	0.106			
Total fluid volume (mL)	1	1.00–1.00	0.263			
Total transfusion volume (mL)	1	1.00–1.00	0.529			
NS group	5.16	1.060–25.06	0.042*	6.14	1.36–27.70	0.018*

*Indicates statistical significance (p<0.05). OR : odds ratio, CI : confidence interval, BMI : body mass index, OP : operation, GFR : glomerular filtration rate, NS : normal saline

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time and the total fluid volume was added and evaluated. Throughout additional fitting, operation time, total fluid volume and their interaction variable were eliminated from the final model. According to the final model, BMI of patients (adjusted odds ratio [OR], 1.12; 95% confidence interval [CI], 1.03–1.21; p=0.006) and the use of NS for fluid management (adjusted OR, 1.90; 95% CI, 1.05–3.44; p=0.033) were significant predictors for the development of acidemia.

With regards to metabolic acidosis, age, BMI, pre-operative GFR and fluid type were statistically significant variables by univariable analysis. Interactions were found between BMI and pre-operative GFR, and between age and pre-operative GFR. Using two second-ordered interaction variables among them, age, BMI and interaction variables were eliminated from the final model. According to the final model, pre-operative GFR (adjusted OR, 0.97; 95% CI, 0.95–0.99; p=0.009) and the use of NS for fluid management (adjusted OR, 6.14; 95% CI, 1.36–27.70; p=0.018) were significantly associated (Table 3).

The factors affecting the duration from the end of the oper-

Table 4. Linear regression for clinical outcomes

	Univariable analysis		Multivariable analysis	
	Coefficient±SE	p-value	Coefficient±SE	p-value
Outcome : duration from end of operation to extubation (minutes)				
Age	-0.753±3.284	0.819		
Sex (female)	18.7±53.6	0.726		
BMI (kg/m^2)	9.73±8.13	0.232		
Pre-OP sodium (mmol/L)	10.7±12.0	0.376		
Pre-OP potassium (mmol/L)	26.3±63.0	0.676		
Pre-OP chloride (mmol/L)	-5.19±11.44	0.650		
Pre-OP GFR (mL/min/1.73 m^2)	-1.09±1.25	0.385		
Hypertension	77.3±51.8	0.136		
Diabetes	-145±82	0.078		
Operation time (minutes)	-0.397±0.368	0.280		
Total fluid volume (mL)	0.0731±0.0491	0.137		
Total transfusion volume (mL)	0.651±0.065	<0.001*	0.655±0.053	<0.001*
NS group	95.1±47.4	0.045*	99.8±47.4	0.036*
Outcome : length of stay in ICU (days)				
Age	0.00136±0.00463	0.768		
Sex (female)	-0.0957±0.0764	0.211		
BMI (kg/m^2)	0.00885±0.01149	0.442		
Pre-OP sodium (mmol/L)	0.00861±0.01716	0.616		
Pre-OP potassium (mmol/L)	0.0225±0.0894	0.802		
Pre-OP chloride (mmol/L)	-0.00797±0.01629	0.625		
Pre-OP GFR (mL/min/1.73 m^2)	-0.00246±0.00165	0.136		
Hypertension	-0.0707±0.0734	0.335		
Diabetes	0.0861±0.1178	0.465		
Operation time (minutes)	0.00124±0.00052	0.016*	0.00154±0.00039	<0.001*
Total fluid volume (mL)	0.0000718±0.0000695	0.302		
Total transfusion volume (mL)	0.000608±0.000092	<0.001*	0.000627±0.0000867	<0.001*
NS group	0.210±0.068	0.002*	0.217±0.067	0.001*

*Indicates statistical significance (p<0.05). SE : standard error, BMI : body mass index, OP : operation, NS : normal saline, ICU : intensive care unit ation to extubation and the length of stay in the ICU are summarized in Table 4 with the results from the linear regression. By univariable analysis for extubation time, total transfusion volume and fluid type were selected for multivariable regression. As there was no collinearity between two variables, the final model was fitted to use total transfusion volume and fluid type as a predictive variable for extubation time. The use of NS resulted delay of 99.8 minutes of extubation time. The R^2 of this model was 0.22 (95% CI, 0.16–0.28).

As to length of stay in ICU, operation time, total transfusion volume and fluid type showed statistical significance by univariable linear regression. Because there was strong linear correlation between operation time and total transfusion volume, further fitting including interaction variable resulted in the elimination of only interaction variable, leaving each variable related. According to the final model, the use of NS, a longer operation time and a larger total transfusion volume were significantly correlated with a longer stay in the ICU. The use of NS resulted delay of 0.2 days of ICU stay. The R^2 of this model was 0.19 (95% CI, 0.14–0.25).

DISCUSSION

In this study, the use of BC as a management fluid during surgery for UIA was related with a lower occurrence of POEI and POA. Furthermore, duration from the end of the operation to extubation and ICU stay were significantly shorter among patients in the BC group compared to those in the NS group.

Although there had been no reports regarding the effects of using BC instead of NS during surgery for UIA, the superiority of BC has been reported in critically ill adults when comparing clinical results such as mortality, hospital days, and renal function[3,9]. Similar to previous reports, the use of BC rather than NS also resulted in a shorter length of stay in the ICU in this study. These clinical findings might be due to the substances and buffer system making up the fluid and the resulting metabolic acidosis. Several reports corroborated our findings : the use of BC was superior to that of NS, especially when comparing serum pH and chloride levels[3,8]. A previous study showed that the major determinant of [H+] was the strong ion difference in the body[22]. Changes in [Cl–], which is a major anionic contributor, affects changes in [H+] homeostasis. The development of significant hyperchloremia with large volumes of NS for fluid resuscitation would result in a decrease in strong ion differences and metabolic acidosis[16]. Hyperchloremic metabolic acidosis is a pathological state that results from bicarbonate loss, rather than acid production or retention. The major pH buffer system in the human body is the bicarbonate/carbon dioxide (HCO_3^-/CO_2) chemical equilibrium system. A decrease in HCO_3^- will shift the acid-base balance towards acidic. The pulmonary system regulates CO_2 levels through respiration; this condition increases the respiratory rate as the body attempts to decrease CO_2 to compensate and then delays the time to extubation[18,20]. In this study, those who received BC required approximately half as much time from the end of the operation to extubation compared to those who received NS.

Neurological manifestations, headache, lethargy, stupor, and coma in most severe cases can result from metabolic derangement. Additionally, during periods of profound acidosis, cerebral hypoxia may occur. Signs and symptoms of raised intracranial pressure occur less often when the acidosis is secondary to a metabolic cause rather than a respiratory cause, as alluded to previously, because the development of respiratory acidosis is often more acute[24]. Therefore, our findings indicating that NS was six times more likely to trigger metabolic acidosis provided important clinical insights for caring of patients who underwent neurologic surgery, as metabolic acidosis was considered as a risk factor potentially leading to poor clinical course in these patients.

Also, some studies found the development of moderate hyperchloremia to be associated with increased in-hospital mortality in patients who experienced an intracerebral hemorrhage[19]. For those who were hyperchloremic during ICU admission, every 5 mmol/L increase in chloride was associated with a 37% increase in odds for hospital mortality. This can be explained by the fact that hyperchloremic metabolic acidosis has been linked to an increased rate of infection via a theoretical augmented neutrophil response and a proinflammatory imbalance[17]. Infection has been associated with increased hospital mortality as well as worse 3-month outcomes in patients who experienced intracerebral hemorrhage[15]. Other studies have demonstrated a possible hypocoagulable state and the need for a large volume of blood products after administration of sodium chloride-based fluids during surgical procedures[23]. In addition, one study found that BC therapy

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was more effective in maintaining normal potassium level and reducing the trend toward hyperchloremic metabolic acidosis than NS therapy during prolonged fluid therapy post-operatively in patients treated for traumatic brain injury[10]. Similar to these studies, hyperchloremic metabolic acidosis could affect the clinical outcomes of patients in the neurocritical ICU.

This study had some limitations. This was a retrospective study, and the data were derived from a single center, which could not completely exclude a selection bias. Furthermore, the two groups might be not fully comparable due to chronological differences. Thus, we performed propensity score matching to reduce the bias. As a result, statistical differences were not observed between two groups indicating that comparative groups were secured with a certain degree of homogeneity. Furthermore, compared to previous studies that analyzed the effects of fluid regimens in critically ill patients who had various primary diagnoses, one strength of our study was the focus on patients who underwent UIA clipping; therefore, relatively homogeneous characteristics of the patients group could show better comparable effects of fluid management in POEI, POA, and clinical outcomes. Still, further prospective randomized clinical trials are needed to determine a more solid recommendation for the selection of fluid regimen during surgery for UIA.

CONCLUSION

BC resulted in lower serum chloride ion levels, lower incidence of metabolic acidosis, and shorter duration of intubation and ICU stay. Therefore, using BC can be recommended as an appropriate fluid than NS for managing patients who undergo surgery for UIA in the pre- and intra-operative periods.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : JK, YJS, TK
Data curation : JK, YJS
Formal analysis : JK, YJS, TK
Funding acquisition : TK
Methodology : TK
Project administration : TK
Visualization : TK
Writing - original draft : JK, YJS
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