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Comparison of the trometamol-balanced solution with two other crystalloid solutions for fluid resuscitation of a rat hemorrhagic model

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ABSTRACT

Currently, the optimal resuscitation fluid remains debatable. Therefore, in the present study, we designed a trometamol-balanced solution (TBS) for use as a resuscitation fluid for hemorrhagic shock. Hemorrhagic shock was induced in 18 male Wistar-Kyoto rats, which were assigned to normal saline (NS), Ringer's solution (RS), and TBS groups. During the hemorrhagic state, their hemodynamic parameters were recorded using an Abbott i-STAT analyzer with the CG4+ cartridge (for pH, pressure of carbon dioxide, pressure of oxygen, total carbon dioxide, bicarbonate, base excess, oxygen saturation, and lactate), the CG6+ cartridge (for sodium, potassium, chloride, blood glucose, blood urea nitrogen, hematocrit, and hemoglobin), and enzyme-linked immunosorbent assay kits (calcium, magnesium, creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, and albumin). Similar trends were found for the parameters of biochemistries, electrolytes, and blood gas, and they revealed no significant changes after blood withdrawal-induced hemorrhagic shock. However, the TBS group showed more effective ability to correct metabolic acidosis than the NS and RS groups. TBS was a feasible and safe resuscitation solution in this study and may be an alternative to NS and RS for resuscitation in hemorrhagic shock patients without liver damage.

Keywords: Resuscitation fluid; normal saline; Ringer's solution; hemorrhagic model

INTRODUCTION

After trauma, the hemorrhagic shock is the leading cause of morbidity and mortality in critically ill patients, and hemorrhagic shock is defined as a condition of reduced tissue perfusion that cannot sustain aerobic metabolism [1-3]. Although resuscitation regimens have been discussed over the past decades, the first therapeutic intervention for hemorrhagic shock is still the control of bleeding and fluid resuscitation. Resuscitation fluids are widely

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Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

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considered to be essential for managing emergency patients and can be divided into crystalloids, colloids, or albumin [4]. Crystalloid solutions have lower costs and have a lower risk of anaphylactic reactions compared with albumin and colloid solutions. However, only one-fifth of the infused volume of crystalloid solutions remains in vessels, and the remaining volume shifts to the interstitial space, causing tissue edema and organ dysfunction. The optimal resuscitation fluid is selected based on personal experience, regional variation, and clinician preferences; therefore, the optimal resuscitation fluid has been under debate [5-8].

In hemorrhagic shock, organ injury is caused by vasoconstriction and hypoperfusion, with progression from tissue hypoxia to the release of mediators due to systemic inflammatory responses, and hemorrhagic shock is strongly associated with the occurrence of metabolic acidosis [9-12]. Therefore, to alleviate or prevent metabolic acidosis, which is a challenge in the management of hemorrhagic shock, some strategies have been applied, including using the additives of L-lactate, acetate, gluconate, and bicarbonate in resuscitation fluids [13-15]. In the literature, no evidence has been provided to support the superiority of one type of fluid over another type of fluid in patients with hemorrhagic shock. Principally, acetate and gluconate are metabolised to bicarbonate, which possesses a buffering capacity of approximately 53% for regulating pH through hydrogen cation consumption. According to the reason, a trometamol-balanced solution (TBS) uses trometamol, a biologically inert amino alcohol that has a higher alkalising capacity than bicarbonate for alleviating acidosis [16].

The question concerning which resuscitation fluid should be used during the initial hours of hemorrhagic shock remains to be addressed. Therefore, in the present study, we investigated the influence of normal saline (NS), Ringer's solution (RS), and TBS on biochemistries, electrolytes, hematology, and blood gas in the initial resuscitation of a rat hemorrhagic shock model.

MATERIALS AND METHODS

Animals

A total of 18 male Wistar–Kyoto rats (age, 9–10 weeks; weight, approximately 330–380 g) were randomly assigned to NS, RS, and TBS groups and were treated with different resuscitation fluids. All rats were housed two per cage and had free access to Purina chow and water under a 12-h light/dark cycle. The experiment was conducted at the National Taiwan University (NTU) Laboratory Animal Center (an AAALAC-accredited facility) and was supervised by the Animal Care and Use Committee of NTU (IACUC number: 20140243).

Resuscitation fluid

The total volume of resuscitation fluids ranged from 19.8 to 22.8 mL according to the Advanced Trauma Life Support guidelines, the estimated resuscitation fluid volume is triple of the bleeding volume because of fluid loss into the interstitial and intracellular spaces. The compositions of three resuscitation fluids used in the experiment were as follows:

1) NS: pH, 5.8; osmolality, 308 mOsml/kg; Na^+, 154 mmol/L; and Cl^-, 154 mmol/L (Y F Chemical Corp., Taiwan).
2) RS: pH, 5.8; osmolality, 309 mOsml/kg; Na^+, 147 mmol/L; K^+, 4 mmol/L; and Cl^-, 156 mmol/L (Y F Chemical Corp.).
3) TBS: pH, 7.4; osmolality, 282 mOsml/kg; Na^+, 135 mmol/L; K^+, 4 mmol/L; Cl^-, 100 mmol/L; Mg^{2+}, 2 mmol/L; acetate, 24.5 mmol/L; gluconate, 25 mmol/L; and trometamol, 10 mmol/L (Resculyte solution, Taiwan Biotech Co. Ltd., Taiwan).

Anesthesia and surgical preparation

Sodium pentobarbital (50 mg/kg; Sigma Chemical Co., USA) was administered intraperitoneally to anesthetize the rats, and intravenous injections (35 mg/kg) were performed per hour. Surgical sites (right and left groin) were shaved, and lungs were ventilated using a ventilator (Model 131, New England Medical Instruments, USA). Ventilation was performed with room air through a 14G plastic catheter (B. Braun Medical, USA) at a tidal volume of 8 mL/kg and a respiratory rate of 70 breaths per minute. The rats were placed in the supine position, and a rectal temperature probe (TP-K01 and TES-1300, TES Electrical Electronic Corp., Taiwan) was inserted for continuous monitoring of the rectal temperature. The rectal temperature was maintained at 36°C by using a circulating warm water circulator (B401H, Firstek Scientific Co. Ltd., Taiwan) and a heat pad (TP22G, Gaymar Industries, Inc., USA). The electrocardiogram (ECG) of lead II was recorded using a Gould ECG/Biotech amplifier (Gould Electronics, USA).

The surgical sites were treated with iodine. The left femoral artery was cannulated using a Millar catheter (model SPC 320, size 2F; Millar Instrument, USA) for arterial pressure monitoring, and the left femoral vein was cannulated using PE-50 tubing for intravenous administration throughout the experiment. PE-50 tubing was also inserted into the right femoral artery for blood sampling.

Hemorrhagic model induction

After surgical preparation, 2% of blood volume of body weight was withdrawn to produce a hemorrhagic and shock-like state, and resuscitation solution was injected through the left femoral vein within 30 min [17]. Thereafter, the 4-h study was initiated, and blood samples were collected during the initial half hour and every hour. Finally, all rats were humanely sacrificed at the end of the experiment. The heart, liver, kidney, spleen, and lung tissues were excised and stored until further analysis.

Blood sampling

Blood samples were collected at the following time points: after surgical preparation (baseline) and 0.5, 1, 2, 3, and 4 h after blood withdrawal (BW + 0.5, + 1, + 2, + 3, and + 4 h, respectively).

Hemodynamic parameter measurement

The collected blood samples were analyzed using an Abbott i-STAT analyzer (Abbott Point of Care, USA). Blood samples for pH, pressure of carbon dioxide (PCO_2), pressure of oxygen (PO_2), total carbon dioxide (TCO_2), bicarbonate (HCO_3), base excess (BE), oxygen saturation (sO_2), and lactate assessments using the i-STAT CG4+ cartridge and for sodium (Na), potassium (K), chloride (Cl), blood glucose, blood urea nitrogen (BUN), hematocrit (Hct), and hemoglobin (Hgb) measurement using the CG6+ cartridge were obtained at baseline and BW + 0.5, + 1, + 2, + 3, and + 4 h. Blood samples for calcium (Ca), magnesium (Mg), creatinine (Cre), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and albumin measurement by using enzyme-linked immunosorbent assay kits were obtained at baseline and BW + 4 h.

Statistical analysis

Statistical analysis was performed using R (version 3.3.2; The R Foundation) for Mac. All data are presented as means ± standard deviations. The two-sample *t*-test was used to determine differences in parameters from baseline to selected time points between the NS and TBS groups and the RS and TBS groups, and $p < 0.05$ was considered statistically significant.

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RESULTS

During the study period, 18 male Wistar–Kyoto rats were randomly assigned to the NS, RS, and TBS groups. All rats underwent surgery for hemorrhagic shock induction and were treated with different resuscitation fluids at the NTU Laboratory Animal Center.

Biochemistries and electrolytes

During this study, the sodium levels of all groups were within normal ranges. The NS and RS groups showed downward trends, and the TBS group showed fluctuating sodium levels (**Fig. 1A**). The chloride levels of the NS group indicated slight hyperchloremia at BW + 0.5 h, and the chloride levels of the NS group then remained stable and were higher than those of the other two groups (**Fig. 1B**). The chloride levels of the RS and TBS groups fluctuated during the study. The potassium levels of all the groups showed similar trends and were stable within normal ranges (**Fig. 1C**).

Lactate levels increased gradually and peaked at BW + 4 h (**Fig. 2A**), especially in the TBS group; lactate levels of this group were significantly higher than those of the RS and NS groups. Furthermore, the BUN levels of all groups gradually increased and were higher than normal ranges since BW + 0.5 h (**Fig. 2B**). Similarly, the blood glucose levels of all groups showed upward trends and were higher than normal ranges since BW + 0.5 h, and the levels finally peaked at BW + 4 h (**Fig. 2C**).

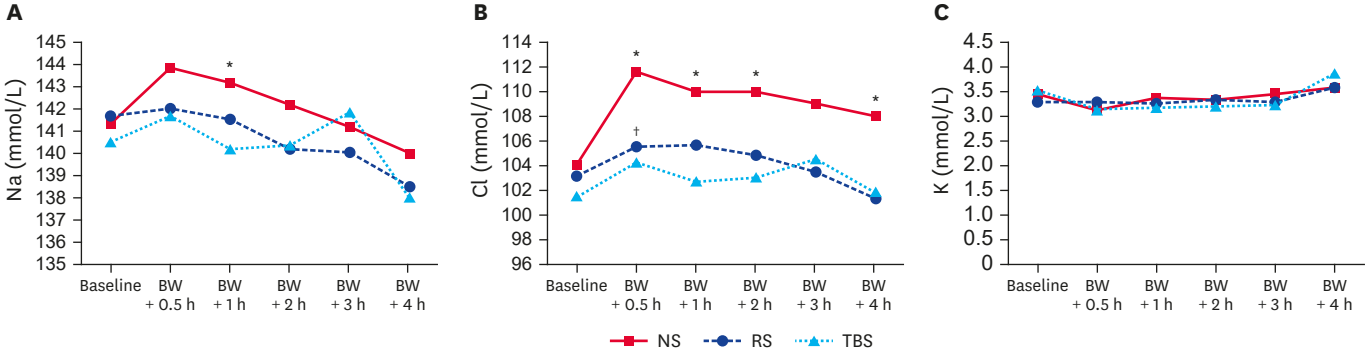

Fig. 1. (A) Na, (B) Cl, and (C) K concentrations at baseline and after BW-induced hemorrhagic shock.
Na, sodium; BW, blood withdrawal; NS, normal saline; RS, Ringer's solution; TBS, trometamol-balanced solution.
*$p < 0.05$ between the NS and TBS groups; †$p < 0.05$ between the RS and TBS groups.

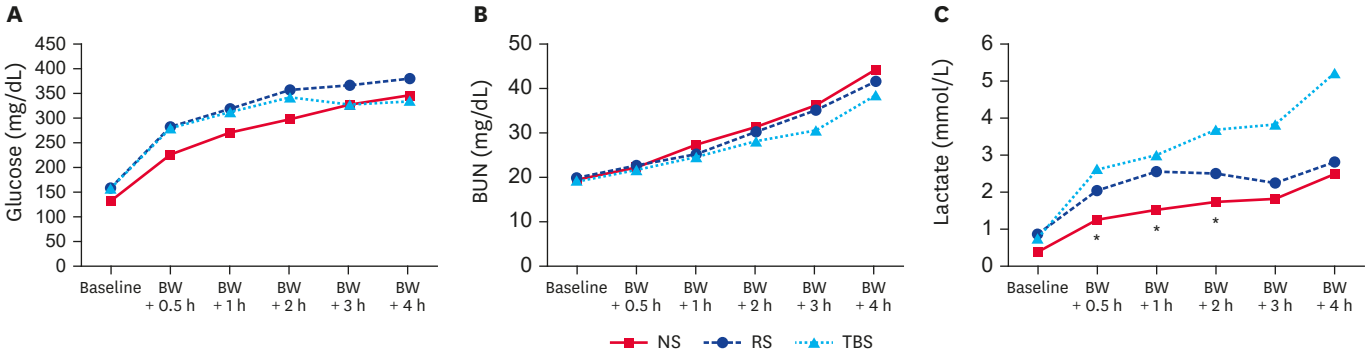

Fig. 2. (A) Lactate, (B) BUN, and (C) glucose concentrations at baseline and after BW-induced hemorrhagic shock.
BW, blood withdrawal; NS, normal saline; RS, Ringer's solution; TBS, trometamol-balanced solution; BUN, blood urea nitrogen.
*$p < 0.05$ between the NS and TBS groups.

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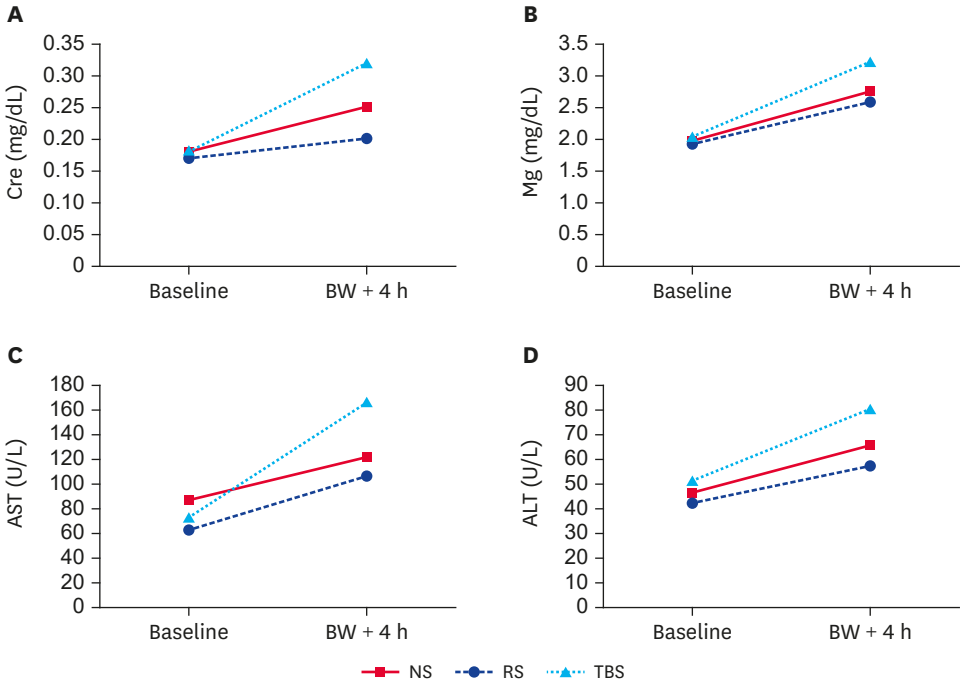

Fig. 3. (A) Cre, (B) Mg, (C) AST, and (D) ALT concentrations at baseline and after BW-induced hemorrhagic shock.
Cr, creatinine; BW, blood withdrawal; NS, normal saline; RS, Ringer's solution; TBS, trometamol-balanced solution; Mg, magnesium; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

In all the groups, the Cre, Mg, AST, and ALT levels all increased from baseline to BW + 4 h, which slightly exceeded normal ranges (**Fig. 3A-D**). By contrast, the Ca and albumin levels of the three groups declined from baseline to BW + 4 h (**Fig. 4A and B**). Furthermore, the bilirubin levels of the three groups were less than 0.2 mg/dL.

Hematology

The Hct and Hgb levels of the three groups were prominently reduced at BW + 0.5 h. Subsequently, these levels remained stable until BW + 4 h (**Fig. 4C and D**). No significant differences were observed in the NS, RS, and TBS groups.

Blood gas

The pH values of the RS and TBS groups remained stable from baseline to BW + 3 h. Subsequently, the pH values increased slightly at BW + 4 h (**Fig. 5A**). By contrast, the pH values of the NS group decreased below normal ranges from baseline to BW + 0.5 h and then gradually increased until the end of the study.

The PCO_2, TCO_2, and HCO_3 levels of all groups exhibited similar trends and declined slightly from within normal ranges at baseline to below normal ranges after BW + 0.5 h during the study period (**Fig. 5B-D**). Specifically, the PO_2 levels of all groups showed similar upward trends; PO_2 levels were within normal ranges at baseline and then increased to more than 105 mmHg until the end of the study (**Fig. 5E**).

The BE levels of the RS and TBS groups decreased gradually from baseline to BW + 3 h and increased at BW + 4 h (**Fig. 5F**). The BE of the NS group declined sharply from within normal ranges at baseline to fluctuation at approximately –7.5 after BW + 0.5 h during the study

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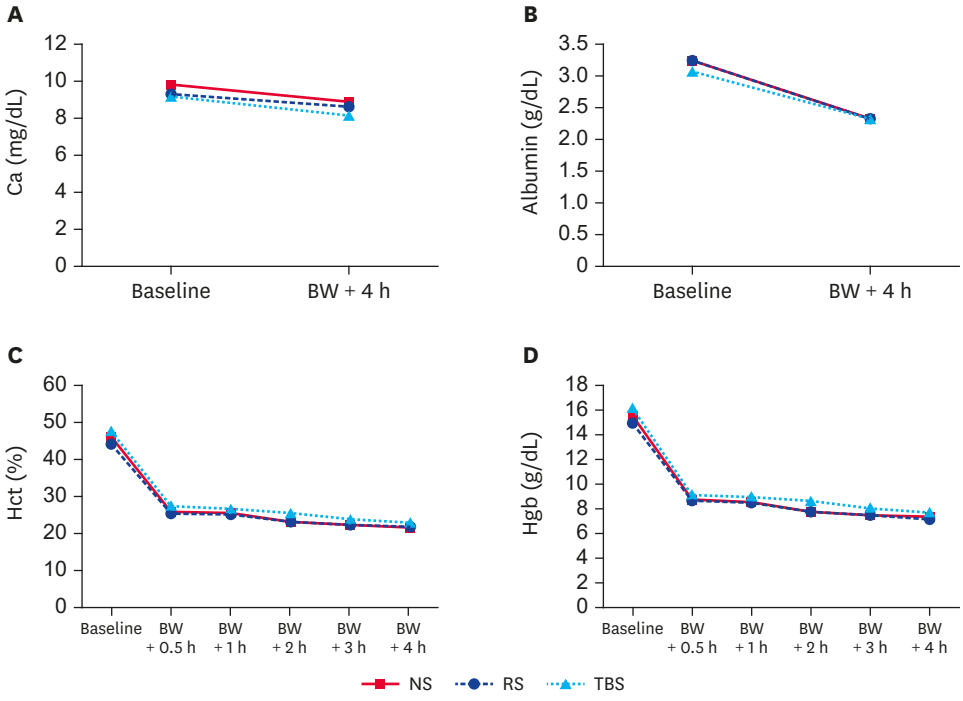

Fig. 4. (A) Ca and (B) albumin (C) Hct and (D) Hgb concentrations at baseline and after BW-induced hemorrhagic shock.
Ca, calcium; BW, blood withdrawal; NS, normal saline; RS, Ringer's solution; TBS, trometamol-balanced solution; Hct, hematocrit; Hgb, hemoglobin.

period. The sO_2 levels of all the groups showed upward trends and remained stable within normal ranges (**Fig. 5G**).

DISCUSSION

Many compositions of resuscitation fluids have been developed using crystalloids, colloids, or albumin as primary constituents [4]. However, the ideal resuscitation fluid for critically ill patients remains debatable. Compared with albumin and colloid solutions, crystalloid solutions are more advantageous because they have lower costs and have a lower risk of anaphylactic reactions [5-8].

Currently, crystalloid solutions, including lactated RS, RS, and NS, are used as resuscitation fluids. These solutions have similar sodium concentrations and may contain physiological concentrations of potassium. Acid resuscitation fluids, such as RS and NS, are widely used in Taiwan and are considered to alter the pH values of patients and increase their medical expenditure. In this study, we designed a new resuscitation fluid, TBS, and compared TBS with RS and NS in a rat hemorrhagic model. TBS comprises acetate and gluconate, which are metabolised to bicarbonate in the liver and works to regulate pH. In addition, trometamol is the most important component of TBS. The buffering capacity of trometamol is better than bicarbonate because of acid dissociation constant (pK_a) of 7.82 and 6.1, respectively, and is effective buffer in the physiological range of blood pH; therefore, compared with RS and NS, TBS has a higher alkalising capacity for alleviating acidosis [16].

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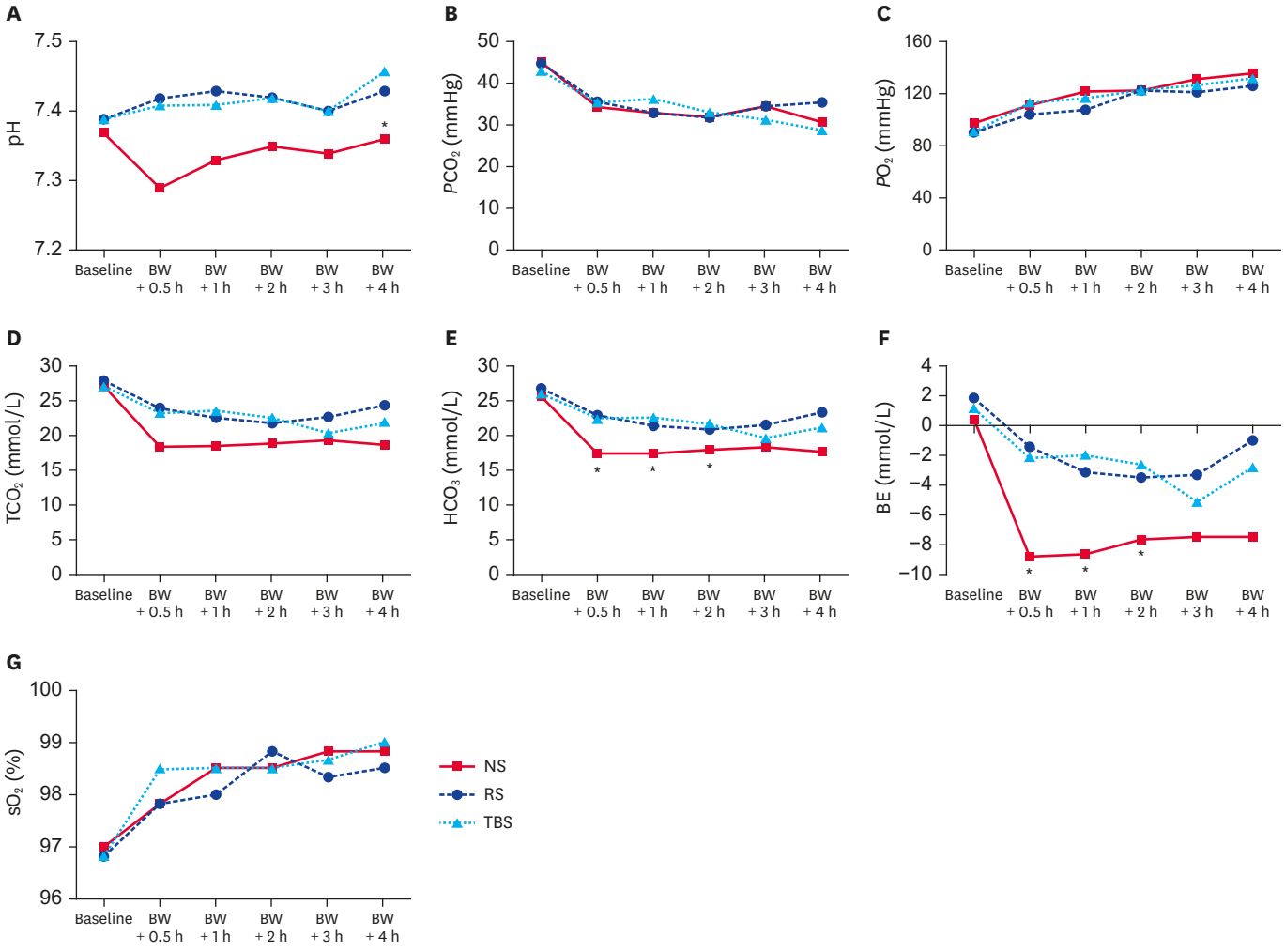

Fig. 5. (A) pH, (B) PCO_2, (C) PO_2, (D) TCO_2, (E) HCO_3, (F) BE, and (G) sO_2 levels at baseline and after BW-induced hemorrhagic shock.
BW, blood withdrawal; NS, normal saline; RS, Ringer's solution; TBS, trometamol-balanced solution; PCO_2, pressure of carbon dioxide; PO_2, pressure of oxygen; TCO_2, total carbon dioxide; HCO_3, bicarbonate; BE, base excess; sO_2, oxygen saturation.
*$p < 0.05$ between the NS and TBS groups.

Biochemistries and electrolytes

Studies have suggested that hemorrhagic shock may lead to disturbances in electrolyte homeostasis. The initial response to hemorrhage is sensed a decrease in blood pressure through baroreceptors within the aortic arch and atrium, and shunting blood to vital organs. Neural reflexes then activate sympathetic adrenergic system to increase heart rate and systemic vascular resistance. Chemoreceptors reflexes are activated by systemic acidosis, leading by low blood flow and arterial pressure, activate sympathetic adrenergic system and also reinforce baroreceptor reflexes. Furthermore, a hormonal response occurs and stimulates adrenocorticotropic hormone, epinephrine and norepinephrine into the blood, which reinforces the effects of compensatory mechanisms. Activation of the renin system in kidneys contributes to increase circulating levels of angiotensin II and aldosterone and then causes vascular constriction. In addition, sympathetic activity also stimulates vasopressin release, thirst mechanisms and retention of sodium and water to increase blood volume. In blood loss, the renal mechanism is important for long-term recovery. Hypotension also results in a fall of hydrostatic pressure in capillary vessels, which less fluid leaves the

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capillaries, and net reabsorption of fluid can occur in moderate to severe hemorrhage to increase the plasma volume [18-21].

The sodium levels of the NS group were higher than those of the RS and TBS groups, especially at BW + 0.5 h after the administration of the resuscitation fluid. The higher sodium and chloride levels of the NS group may be due to solutions containing higher sodium and chloride concentrations and sodium retention because of renal impairment by renal hypoperfusion of hemorrhage. Afterwards, the sodium levels of NS and RS groups showed downward trends and the TBS group showed fluctuating sodium levels after BW + 0.5 h, that the major factors for sodium levels disturbed are hyperglycemia and aldosterone releasing. Hyperglycemia usually cause hyponatremia with hyperosmolality by shifting fluid from intracellular to extracellular compartment, which a 1.6 mEq/L decrement is sodium for each 100 mg/dL increment in glucose. The formula works well up to 440 mg/dL in blood glucose and is much accurate at higher blood glucose levels [22]. Furthermore, aldosterone is produced by adrenal glands and acts on the late distal tubule and collecting duct of nephrons to impact sodium absorption and potassium excretion. As for the sodium levels at BW + 4 h, glucose levels of all groups were higher at this time point and cause sodium at lower levels. Sodium constituents in NS are higher and in TBS are lower, which is the possibility the sodium levels ranked from high to low were NS, RS and TBS during the study.

The potassium levels remained stable within normal ranges until the end of the study and showed no remarkable differences in all groups. At BW + 0.5 h, the potassium levels of all groups revealed subtle decline and might result from sodium reabsorption and potassium excretion by aldosterone. After that, hyperglycemia of stress response and metabolic acidosis by hemorrhagic shock might cause slight potassium levels increase at BW + 4 h.

Hypomagnesemia and hypocalcemia are common electrolyte disorders observed in critically ill patients, especially in those with hemorrhagic shock, and their prevalence in the intensive care unit is as high as 90% and 50%, respectively [23-25]. In our study, these disorders were not found, and the major reason is that no blood transfusion was conducted, which reduced the potential of chelation or precipitation by citrate and ethylenediaminetetraacetic acid added for preserving stored blood [19]. The magnesium levels of all groups indicated slight hypermagnesemia, which may be due to the impairment of renal function caused by poor renal perfusion [23]. In addition, at BW + 4 h, the magnesium levels of the TBS group were higher than those of the NS and RS groups, because TBS solution contained 2 mmol/L magnesium.

The calcium levels of all the groups declined from baseline to BW + 4 h, and the levels were all within normal ranges. Most importantly, the calcium levels of the TBS group were lower than those of the NS and RS groups at BW + 4 h; no significant difference was observed in the three groups ($p < 0.05$). Studies have suggested parenteral administration for treating hypocalcemia [25,26]. However, animal model experiments have not provided evidence to support the treatment [27,28]. Therefore, no calcium was added to TBS.

In this study, blood glucose levels increased gradually from baseline to BW + 4 h and indicated hyperglycemia since BW + 0.5 h. Hyperglycemia is a normal response to hypoxia by hemorrhagic shock and called “stress hyperglycemia.” These alterations may be caused by activation of central nervous system, neuroendocrine axis, pancreatic hypersecretion and inflammation, which releases cytokines and catecholamines to enhanced glycogenolysis

and gluconeogenesis. In addition, more recent studies indicate persistent hyperglycemia is associated with organ failures and detrimental outcomes [29-31]. Trometamol has been known to increase insulin release and therefore lower blood glucose. But no differences were observed among all groups in the study. The short experiment episode causes insulin-release response by trometamol late and significant stress hyperglycemia response are the possible reasons to attribute no variations for glucose levels in all groups.

Acute kidney injury (AKI) is common in patients with hemorrhage. And hemorrhage-induced AKI results from reduced tissue perfusion and inadequate oxygen and nutrient supply [32-34]. In the end, the BUN and Cre levels of all groups showed upward trends during the study. The levels of the TBS group were higher than those of the other two groups; however, no significant differences were observed among all groups.

In hemorrhagic shock, liver injury is caused by vasoconstriction and hypoperfusion, with progression from endothelial cell dysfunction and tissue hypoxia to the release of mediators caused by systemic inflammatory responses and finally to liver failure [9-12]. Therefore, in this study, the AST and ALT levels of all the groups increased from normal ranges at baseline to the end of the study. Most importantly, the levels of the TBS group were higher than those of the RS and the NS groups; this may be attributed to the trometamol content in TBS, which increased hepatic metabolite loads. Furthermore, the albumin levels of all the groups decreased at BW + 4 h and showed no differences. Hypoalbuminemia can be divided into four factors, including decreasing synthesis, increasing loss, redistributing albumin and albumin diluting. In this study, hemorrhage may be attributed to hypoalbuminemia by loss of all constituents of whole blood.

In hemorrhagic shock, hyperbilirubinemia is not a common complication and usually occurs 8–10 days after the shock episode [35,36]. In this study, the experiment was ended after 4 h of hemorrhage induced. Therefore, the bilirubin levels of all groups were less than 0.2 mg/dL and were within normal ranges during the study. But the bilirubin levels are predicted to reveal upward trends in the following days.

Lactate levels are indicators of inadequate tissue perfusion caused by hypotension and lower cardiac outputs and are influenced by multiple factors, including hypothermia, cardiopulmonary bypass flow, liver failure, drugs, anaerobic muscle activity, and shock [36-38]. All the groups in the study exhibited hyperlactatemia after baseline, which resulted from poor perfusion caused by hemorrhage. Nevertheless, the lactate levels of the TBS group were significantly different from those of the other groups ($p < 0.05$). This may be because impaired hepatic and renal functions affected the clearance of lactate and caused hyperlactatemia in the TBS group.

Hematology

The blood volume of rats is usually estimated using 5.5%–7% of body weight [39]. In this study, 2% of blood volume of body weight was withdrawn, and the volume of resuscitation fluids was triple of the volume of blood withdrawn. This was the reason why Hct and Hgb revealed moderate anemia after baseline. Furthermore, blood sampling also contributed to lower Hct and Hgb levels in the study; all groups showed gradually decreased Hct and Hgb levels, although the sampling volume was low. No differences were found in haematology between the TBS group and the RS and NS groups.

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Blood gas

Studies have revealed that hemorrhagic shock induces metabolic acidosis, which in turn contributes to acid–base imbalance, eventually causing the dysfunction of different organs [5,8]. In the present study, to prevent and alleviate acidosis, TBS containing trometamol was designed as a neutralising solution. After BW + 0.5 h, pH values were 7.35 and 7.45, and PCO_2 levels and HCO_3 levels were lower than normal ranges, indicating compensated metabolic acidosis. The situation may be caused by inadequate tissue perfusion resulting from hemorrhagic shock. Notably, the pH values of the TBS and RS groups were more stable than those of the NS group. The stable pH values of the TBS group were attributed to trometamol, whose buffering capacity is approximately three times that of bicarbonate; therefore, compared with RS, TBS has a higher alkalising capacity for alleviating acidosis [14]. In addition, the BE levels of the NS group revealed severe metabolic acidosis since BW + 0.5 h without significant improvement. The BE levels of the TBS group showed considerable differences compared with those of the NS group and were similar to those of the RS group. Although the BE levels of the TBS group peaked to −5.17 at BW + 3 h, the levels instantly returned to −2.83 at BW + 4 h, indicating the great alkalising capacity of TBS for alleviating acidosis.

In conclusion, the RS and TBS groups showed similar hemodynamic alterations without significant differences during the study, and their blood gas parameters were more favourable than those of the NS group. The results revealed the great potential of TBS to alleviate metabolic acidosis during hemorrhagic shock compared with NS and RS. However, TBS is contraindicated in patients with pre-existing liver disease because trometamol, acetate, and gluconate increase liver metabolites. To sum up, TBS appears to be feasible and safe for use as a resuscitation solution in rats, but further study is recommended for use in practice of pigs and companion animals.

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