European Review for Medical and Pharmacological Sciences 2022; 26: 1535-1542

Clinical study of sodium bicarbonated Ringer's solution on fluid resuscitation of patients with hemorrhagic shock

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Abstract. – OBJECTIVE: Fluid resuscitation is a crucial step in shock treatment, but the choice of crystal solution remains controversial. Sodium bicarbonated Ringer's solution can not only effectively expand blood volume, but also reduce tissue damage and acidosis. The study aims to evaluate the resuscitation effect of sodium bicarbonated Ringer's solution on patients with hemorrhagic shock.

PATIENTS AND METHODS: A total of 96 patients with hemorrhagic shock were randomly assigned to receive either normal saline solution (control group) or sodium bicarbonated Ringer's solution (experimental group). The changes in blood lactate, heart rate, arterial pH and mean arterial pressure (MAP) were measured at different time points. The 28-day survival rate, the incidence of complications, and the average length of hospital stay were recorded. Simult

RESULTS: The heart rate, blood lactate, sodium, and chloride in the experimental group were significantly lower than those in the control group, while the MAP, potential of hydrogen (pH), bicarbonate, and base excess in the experimental group were significantly higher than those in the control group at every observed time point after resuscitation ($p<0.05$). Compared with the control group, the experimental group had a lower incidence of acute respiratory distress syndrome (ARDS) (8.3% *vs.* 22.9%, $p<0.05$), shorter mechanical ventilation time (2.2 *vs.* 3.5, $p<0.05$), and shorter intensive care unit length of stay (3.8 *vs.* 4.1, $p<0.05$). The 28-day survival rate between the two groups showed no significant differences ($p>0.05$).

CONCLUSIONS: Early resuscitation with sodium bicarbonated Ringer's solution could better maintain acid-base balance and hemodynamic stability and reduce the risk of related complications.

Key Words:
Sodium bicarbonated Ringer's solution, Normal saline solution, Hemorrhagic shock, Survival.

Introduction

Trauma has become a global health issue with the increase of vehicles and large machinery. Traumatic hemorrhagic shock is responsible for early death in patients with severe trauma, which sets in motion a vicious cycle of outcomes, also known as the lethal triad, consisting of hypothermia, acidosis, coagulopathy, and can be rapidly fatal[1-3]. Despite advances in care, hemorrhagic shock mortality and morbidity remain significant. Controlling bleeding and fluid resuscitation are considered the fundamental part of hemorrhagic shock therapy and hypotensive resuscitation is proposed in the early stage of a hemorrhagic shock to maintain systolic blood pressure[4,5]. However, there is still considerable controversy on the choice of resuscitation fluids. Currently, crystalloids are the most commonly administered intravenous fluids in Intensive Care Units, among which lactated Ringer's and normal saline are the most widely used but both have clinical limits[6,7]. There has been growing evidence that intravenous saline may be associated with hyperchloremic metabolic acidosis and acute kidney injury. Moreover, recent studies[8,9] suggest that acetated Ringer's solution sometimes causes cardiac depression and peripheral vasodilatation. The ideal fluid contains a chemical composition similar to plasma, and it controls bleeding, improves perfusion, reduces or eliminates metabolic acidosis, regains tissue perfusion and organ function. Acid-base disturbances are common in severe trauma patients and reports show that acidosis associated with trauma is caused more frequently by anaerobic metabolism associated with hypotension and hypoperfusion[10]. It is recognized that lactate is a longstanding clinical biomarker to help determine the adequacy of fluid resuscitation of hemorrhagic shock[11-13].

Sodium bicarbonated Ringer's solution, a new generation of crystalloid, is composed of a variety of electrolytes, which has a good clinical effect on the supplement of extracellular fluid when circulating blood flow and interstitial fluid decrease[14]. Recent clinical studies[15,16] have demonstrated that sodium bicarbonate ($NaHCO_3$) contained in sodium bicar-

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bonated Ringer's solution can correct electrolyte imbalance and acidosis for its prompt alkalization effect because bicarbonate (HCO_3^-) can be directly produced without a metabolic process. However, there are few studies on its application in the resuscitation effect of hemorrhagic shock, and many aspects remain imperfectly known. In this study, the effects of sodium bicarbonated Ringer's solution on heart rate, mean arterial pressure (MAP), arterial blood gas, and survival rate of patients with hemorrhagic shock were observed by comparing the fluid resuscitation effects of different crystalloids to provide new ideas for clinical treatment.

Patients and Methods

Study Design

The study was a single-center, prospective and randomized trial to assess the efficacy of sodium bicarbonated Ringer's solution on fluid resuscitation in patients with hemorrhagic shock, which was registered on the Chinese Clinical Trial Registry (ChiCTR2000039951, 2020-11-15). The Ethics Committee of Wuwei People's Hospital approved this study, and all patients signed an informed consent form.

Study Population

From December 2020 to December 2021, 96 patients with hemorrhagic shock in Wuwei People's Hospital were enrolled in the study, including 60 males and 36 females with an average age of 50.6±10.9. All patients met the diagnostic criteria of the Task force of the European Society of Intensive Care Medicine for hemorrhagic shock. The patients were randomly divided into the control group and experimental group. Forty-eight patients in the control group received conventional crystalloid fluid, while 48 patients in the experimental group received sodium bicarbonated Ringer's solution. The age, gender, shock index, admission systolic blood pressure, admission heart rate, time from injury to the emergency room, injury severity scale (ISS), type of injury, blunt mechanism, and relative detection indexes of the two groups were recorded.

Inclusion and Exclusion Criteria

Inclusion criteria included: (1) shock index≥ 1; (2) adults aged 18-70 years; (3) time of injury was within 6 hours; (4) arterial blood lactate ≥ 4 mmol/L. The exclusion criteria were as follows: (1) severe hepatic insufficiency (Child grading C); (2) severe renal failure (creatinine>400 μmol/L, urea nitrogen>27 mmol/L); (3) severe coagulation dysfunction (fibrinogen <1.0 g/L, prothrombin activity <30%); (4) patients with hypermagnesemia and hypothyroidism; (5) patients who used acid and basic drugs within 6 hours before admission.

Interventions

Intravenous access and patient monitoring were established. The control group was given 0.9% sodium chloride injection (L220011203; specification 500 mL, Sichuan Kelun Pharmaceutical Co., Ltd., Chengdu Sichuan, China). The patient in the experimental group received intravenously sodium bicarbonated Ringer's solution (16052536; specification 500 mL, Jiangsu Hengrui Medicine Co., Ltd., Lianyungang Jiangsu, China). The liquid dosage of the two groups was adjusted based on age, weight, and clinical signs. The administration rate was determined according to the instructions or the routine infusion rate of fluid resuscitation. Alternatively, fluid was given at a rate of 15 mL/kg/h. The lactate clearance rate at 2h, 6h, and 24h (6h > 10%) were used as the valid endpoint. Albumin or blood products were used as needed. Furthermore, conventional hemostatic therapy was performed for patients and those with indications received a blood transfusion.

Blood Sampling

After admission, 2 ml of peripheral venous blood was collected from patients for evaluation of routine clinical laboratory values. In addition, peripheral arterial blood (5 mL) was collected and anti-coagulated with heparin before and 2h, 6h, and 24h following infusion. The samples were gently shaken, and then, immediately detected by using a blood gas analyzer (GEM5000, Instrumentation Laboratory, Lexington Massachusetts, MA, USA). The analysis results were recorded, including arterial pH, blood lactate, bicarbonate, base excess, and electrolytes.

Observation Indicators

The patients were observed until death or hospital discharge. The primary outcome was 28-day survival. Secondary outcomes included changes in blood lactate, heart rate, arterial potential of hydrogen (pH), and MAP at different times, as well as the incidence of complications and average hospitalization time.

Statistical Analysis

Statistical analyses were performed by the SPSS software (version 22.0, SPSS Inc., Armonk,

Table I. Comparison of demographic and clinical characteristics between the two groups.

Variables	All patients	Control group	Experimental group	*p*-value
Simple size	96	48	48	
Age, years	50.6 (10.9)	50.9 (11.0)	50.4 (10.7)	0.822
Female, *n %*	36 (37.5)	19 (39.6)	17 (35.4)	0.673
Shock index	1.67 (0.12)	1.69 (0.11)	1.65 (0.13)	0.107
Systolic blood pressure, mmHg	78.8 (7.9)	77.8 (7.2)	79.7 (8.8)	0.250
Heart Rate, bpm	114.6 (7.4)	113.3 (7.6)	115.9 (7.2)	0.089
Injury Severity Score	26.3 (5.1)	26.9 (4.6)	25. (5.6)	0.296
Time from injury to ED, min	45.9 (11.1)	47.7 (11.4)	44.2 (10.8)	0.126
Type of injury, n%				
Blunt	83 (86.5)	43 (89.6)	40 (83.3)	0.371
Penetrating	13 (13.5)	5 (10.4)	8 (16.7)	
Blunt mechanism, n%				
Motor vehicle accident	54 (56.3)	28 (58.3)	26 (54.2)	0.681
Pedestrian or bicycle collision	12 (12.5)	5 (10.4)	7 (14.6)	0.537
Fall	7 (7.3)	2 (4.2)	5 (10.4)	0.239
Assault	8 (8.3)	5 (10.4)	3 (6.3)	0.460
Other	15 (15.6)	8 (16.7)	7 (14.6)	0.779
Laboratory test on admission				
Hemoglobin, g/L	107.7 (15.4)	108.6 (15.5)	106.4 (15.3)	0.486
pH	7.24 (0.17)	7.24 (0.17)	7.23 (0.16)	0.774
INR	1.30 (0.36)	1.32 (0.39)	1.28 (0.32)	0.584
Blood lactate, mmol/L	5.6 (1.7)	5.7 (1.6)	5.5 (1.8)	0.397
Base excess, mmol/L	-6.7 (2.4)	-6.8 (2.6)	-6.5 (2.3)	0.551
Transfusions/Fluids				
Transfusion in 24h, *n%*	27 (28.1)	12 (25.0)	15 (31.3)	0.496
Packed red blood cells in 24h, units	3.5 (2.5)	3.7 (2.9)	3.4 (2.2)	0.569
Total crystalloid fluid in 24h, L	1.34 (0.54)	1.42 (0.57)	1.26 (0.51)	0.151

ED: emergency room; pH: potential of hydrogen; INR: International normalized ratio.

NY, USA). Continuous variables conforming to the normal distribution were presented as mean ± standard deviation (SD), and the Student's *t*-test was applied for comparison between two groups. The categorical data were expressed as frequency (%) and compared using the χ^2 test or Fisher's exact test. The survival curves of the two groups were constructed and compared by the Kaplan Meier method, and then, the Cox regression model was used to analyze the survival of patients with hemorrhagic shock. *p*-value of <0.05 indicated a significant difference.

Results

The Demographic Data and Clinical Characteristics of Study Population

The demographics and clinical status of the two groups were shown in Table I. All patients were substantially injured (mean ISS: 26.3±5.1) and in shock (mean shock index: 1.67±0.12) when they were admitted. Most of the patients (62.5%) were male and blunt injuries (86.5%) accounted for the majority. The age, gender distribution, injury severity, type of injury, and blunt mechanism were similar in the experimental group and the control group ($p>0.05$). Laboratory test indexes, including hemoglobin, arterial pH, international normalized ratio (INR), lactate, and base excess also exhibited no significant difference between the two groups ($p>0.05$). The total crystalloid fluid first 24h in the experimental group was less than that in the control group, but the differences were not statistically significant ($p>0.05$). No differences in blood transfusion and packed red blood cells were found ($p>0.05$). The groups were well balanced regarding patient characteristics.

Changes in MAP and Heart Rate Before and After Resuscitation

As shown in Table II, MAP and heart rate did not differ between the two groups at baseline. During the 24h after resuscitation, the MAP increased continuously across time in two groups and reached the highest level at 24h. Conversely, the heart rate of both groups showed a continuous decrease with time, reaching the lowest level at

Table II. Comparison of MAP and heart rate between two groups at different time.

Variables	Baseline	2h	6h	12h	24h
MAP, mmHg					
Control group	53.5 (8.5)	60.5 (6.0)**	67.5 (5.8)**	70.4 (7.3)**	79.1 (7.9)**
Experimental group	55.2 (7.6)	65.2 (6.3)**##	72.4 (6.2)**##	77.6 (6.7)**##	84.3 (7.4)**##
Heart Rate, bpm					
Control group	113.3 (7.6)	109.4 (10.2)*	103.6 (9.3)**	97.3 (9.5)**	92.8 (8.8)**
Experimental group	115.9 (7.2)	105.2 (9.3)**#	99.4 (8.7)**#	90.1 (10.6)**##	86.5 (8.4)**##

MAP: mean arterial pressure.
*p<0.05, **p<0.01, significantly different from baseline.
#p<0.05, ##p<0.01, significance between experimental group and control group.

24h. Compared with the control group, the MAP at 2h, 6h, 12h, and 24h after resuscitation in the experimental group increased significantly, while the heart rate decreased significantly ($p < 0.05$).

Changes of Blood Gas Analysis Results Before and After Resuscitation

The average values of blood gas analysis before and after infusion in the control group and the experimental group were summarized in Table III. No significant differences were observed in the blood gas analysis data before infusion ($p > 0.05$). The pH and sodium bicarbonate increased after infusion in both groups, with the highest values recorded at 24h, whereas the blood lactate and base excess decreased, reaching the lowest at 24h ($p < 0.05$). Compared with the control group, the pH and bicarbonate of the experimental group were significantly increased within 24h after infusion, while the blood lactate and base excess were significantly reduced ($p < 0.05$). In the control group, sodium and chloride increased from 2h to 12h after infusion, and then, gradually decreased, whereas the experimental group showed no fluctuation and had considerably lower values than the control group ($p > 0.05$).

Analysis of Adverse Events Between the Two Groups

During the observation period, there was no statistical difference in the number of multiorgan failures, nosocomial infections, and the average

Table III. Comparison of blood gas analysis data between two groups at different time.

Variables	Baseline	2h	6h	12h	24h
pH					
Control group	7.24 (0.17)	7.27 (0.14)	7.30 (0.11)*	7.34 (0.11)**	7.37 (0.10)**
Experimental group	7.23 (0.16)	7.28 (0.12)	7.34 (0.08)**#	7.38 (0.09)**#	7.40 (0.08)**#
Bicarbonate, mmol/L					
Control group	16.24 (5.07)	17.05 (4.26)	19.13 (3.52)**	21.25 (3.19)**	22.70 (2.14)**
Experimental group	15.98 (5.23)	18.13 (4.11)*	20.75 (4.04)**#	22.64 (3.51)**#	23.89 (2.56)**#
Blood lactate, mmol/L					
Control group	5.7 (1.6)	4.9 (1.4)*	4.4 (1.3)**	3.8 (1.2)**	3.2 (1.2)**
Experimental group	5.5 (1.8)	4.3 (1.5)**#	3.9 (1.1)**#	3.3 (1.1)**#	2.5 (1.3)**##
Base excess, mmol/L					
Control group	-6.8 (2.6)	-4.5 (2.1)**	-3.1 (1.5)**	-2.4 (1.2)**	-1.1 (0.8)**
Experimental group	-6.5 (2.3)	-3.5 (1.8)**#	-2.3 (1.7)*8#	-1.8 (1.3)**#	0.7 (0.6)**#
Sodium, mmol/L					
Control group	137.8 (6.5)	139.3 (8.5)	142.8 (6.7)*	143.1 (6.2)**	140.6 (4.9)*
Experimental group	136.5 (7.4)	138.0 (10.9)	139.2 (8.1)#	139.7 (7.9)*#	138.1 (6.5)#
Chloride, mmol/L					
Control group	101.4 (5.5)	102.1 (6.3)	103.9 (7.1)*	104.4 (7.2)*	104.2 (5.6)*
Experimental group	100.2 (5.3)	100.7 (5.6)	99.5 (8.1)##	101.3 (6.6)#	99.4 (6.2)##

pH: potential of hydrogen.
*p<0.05, **p<0.01, significantly different from baseline.
#p<0.05, ##p<0.01, significance between experimental group and control group.

Table IV. Comparison of adverse events between the two groups.

Variables	All patients	Control group	Experimental group	*p*-value
Simple size	96	48	48	
ARDS, *n%*	15 (15.6)	11 (22.9)	4 (8.3)	0.045
Multiorgan failure, *n%*	13 (13.5)	8 (16.7)	5 (10.4)	0.371
Vasoactive drugs, *n%*	45 (46.9)	27 (56.3)	18 (37.5)	0.064
Nosocomial infections, *n%*	13 (13.5)	8 (16.7)	5 (11.4)	0.371
Mechanical ventilation time, days	3.7 (2.7)	4.4 (3.5)	2.8 (2.2)	0.009
Intensive care unit length of stay, days	6.6 (4.0)	7.5 (4.1)	5.4 (3.8)	0.011
Average hospitalization, days	10.4 (9.2)	11.8 (9.7)	9.2 (8.3)	0.162

ARDS: acute respiratory distress syndrome.

hospitalization between the two groups ($p > 0.05$). Although the number of vasoactive drugs was lower in the experimental group compared to the control group, the difference was not statistically significant ($p > 0.05$). Moreover, the incidence of acute respiratory distress syndrome (ARDS), mechanical ventilation time, and intensive care unit length of stay of the experimental group was significantly lower compared to that of controls ($p < 0.05$). The results were presented in Table IV.

Survival Analysis of Two Groups

The 28-day survival rate of the experimental group was 79.17%, and that of the control group was 68.75%. Kaplan Meier survival curve (Figure 1) showed that there was no significant difference between the two groups regarding the 28-day survival rate ($p > 0.05$).

Cox regression analysis was used to analyze the factor affecting the 28-day survival (Table V). Univariate analysis indicated that shock index, injury severity score, interventions, hemoglobin, and INR could influence 28-day survival. Further analysis showed that a higher shock index, higher injury severity score, and lower hemoglobin levels were independently associated with decreased survival.

Discussion

Severe insufficiency of circulating blood volume in hemorrhagic shock can lead to tissue hypoperfusion, cell hypoxia, tissue injury, and death. The key treatment of shock is fluid resuscitation, which directly affects the prognosis of patients[17,18]. Sodium bicarbonated Ringer's solution is weak-

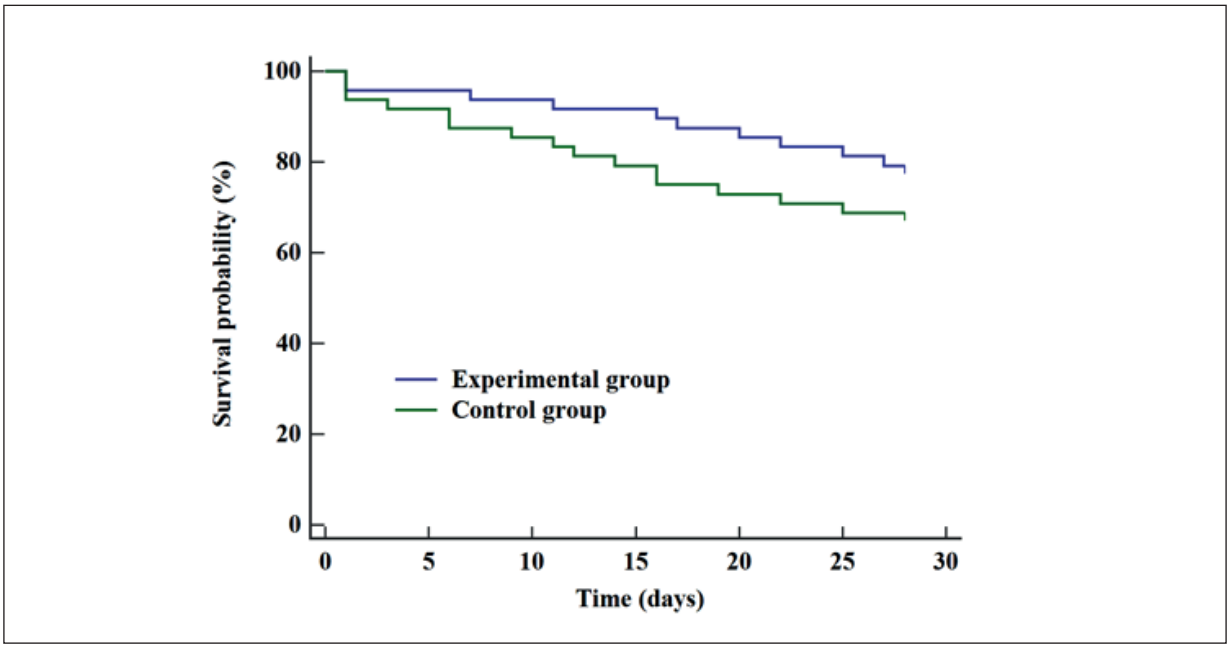

Figure 1. Comparison of 28-day survival time between two groups.

Table V. Cox regression analysis for 28-day survival among patients with hemorrhagic shock.

Variables	Univariate analysis			Multivariate analysis		
	Hazard Ratio	95% CI	*p*-value	Hazard Ratio	95% CI	*p*-value
Age	1.029	0.985-1.075	0.197	1.053	0.995-1.115	0.073
Gender (Female *vs.* male)	0.773	0.334-1.790	0.548	1.663	0.652-4.244	0.287
Shock index	3.245	1.168-5.078	0.010	2.118	1.122-4.879	0.039
Injury Severity Score	1.153	1.042-1.276	0.006	1.126	1.021-1.242	0.018
Interventions (experiment *vs.* control)	2.640	1.075-6.482	0.034	2.495	0.947-6.575	0.064
Hemoglobin	0.972	0.946-0.999	0.044	0.965	0.932-0.998	0.037
INR	3.814	1.048-13.886	0.042	2.647	0.554-12.648	0.223

CI: confidence interval; INR: international normalized ratio; CI: confidence interval.

ly alkaline with a pH of 7.3, containing sodium, potassium, magnesium, calcium ions, which can maintain the physiological activities of cells. In addition, the HCO_3^- buffer system in the solution helps lessen acidosis damage without putting additional strain on the kidneys and liver[14,16]. Compared with traditional crystalloids, sodium bicarbonated Ringer's solution has certain potential strengths in the trauma and perioperative period. Earlier studies by Satoh et al[19] found that the alkalization effect of sodium bicarbonated Ringer's solution was more pronounced than that of acetated solution in partially hepatectomized rabbits. It showed better Mg^{2+} stability as compared to lactated Ringer's solution. Further investigation in an animal by Wang et al[20] analyzed the effect of sodium bicarbonated Ringer's solution on early resuscitation of rabbits with hemorrhagic shock and found that sodium bicarbonated Ringer's solution was more effective than normal saline in maintaining acid-base balance and protecting tissues and organs. In another study, Satoh et al[21] also indicated that the sodium bicarbonated Ringer's solutio significantly improved the blood base excess values compared with lactate Ringer's and Ringer's solution in an experimental hemorrhagic shock model with dogs. These results suggest that sodium bicarbonated Ringer's solution is an appropriate treatment for metabolic acidosis in shock patients. The study aims are to further determine and compare the clinical efficacy of sodium bicarbonated Ringer's and clinical commonly used crystalloid fluid in early resuscitation of shock patients with high lactate levels.

Hemorrhagic shock impairs microcirculation and therefore enhances anaerobic digestion and lactate production, leading to lactic acidosis. As a core treatment for shock, fluid resuscitation and correction of acidosis must be effective and quick to preserve hemodynamic functions and reduce mortality[22-24]. The MAP, lactate concentration, base excess, and osmotic pressure are the traditional indicators of metabolic disorder in the post-shock. In this study, arterial pressure, heart rate, and blood gas analysis indexes were measured at different time points. The results showed that there were significant differences in MAP and heart rate between the control group and the experimental group after rehydration. The hemodynamics of patients with hemorrhagic shock who received sodium bicarbonated Ringer's solution was more stable. Moreover, the blood test results also showed that the arterial blood pH value and lactate concentration were significantly decreased, and the sodium bicarbonate and base excess were notably improved in the experimental group compared with the control group. Lactate is a key indicator of treatment decision thresholds, resulting from insufficient oxygen supply to meet metabolic demand[25]. Multiple publications[26,27] demonstrated that high levels of arterial lactate are associated with increased mortality in shock patients. Therefore, serial lactate monitoring has important clinical implications. The data of the present study suggested that sodium bicarbonated Ringer's solution could rapidly improve microcirculation, attenuate acidosis, and contribute to maintaining acid-base balance in patients with hemorrhagic shock. Its curative effect was better than that of conventional crystalloid fluid.

Although crystalloid solutions commonly used in clinical practice such as 0.9% sodium chloride and Ringer's solution produce the near osmotic pressure as plasma, the concentrations of sodium and chloride are higher than those of plasma. Excessive fluid amounts cause electrolyte disturbances, leading to hypernatremia and hyperchloremia[28,29]. On the other hand, such solutions lack a buffer system and are prone to acid-base imbal-

ance[30]. In contrast, sodium bicarbonated Ringer's solution does not suffer from these drawbacks. The electrolyte composition of the sodium bicarbonated Ringer's solution is close to the plasma, and the citrate in solution tends to form stable chelates with calcium and magnesium ions to avoid precipitation[31]. This is also evident in our results which showed that the sodium and chloride in the control group were significantly higher than those in the experimental group after infusion. We also observed a lower incidence of ARDS and shorter mechanical ventilation time and intensive care unit stay in the experimental groups than in the control groups, suggesting that sodium bicarbonated Ringer's solution can maintain the stability of the internal environment and improve the prognosis of patients. This finding was supported in the study by Ma et al[32].

In this study, the use of sodium bicarbonated Ringer's solution did not lead to a significant reduction in 28-day mortality compared with conventional crystalloid fluids. In the univariate Cox regression model, we found that the 28-day survival of shock patients treated with sodium bicarbonated Ringer's solution was higher. However, this variable did not reach significance in the multivariable model.

There are some limitations to our study. First, the sample size was relatively limited, and further investigations with a large sample size are required. Second, unblinded design may introduce bias because strict blind methods are inappropriate or infeasible in this study. However, the investigators who collected and analyzed the 28-day survival rate and secondary outcomes were unaware of treatment assignments. Third, the study population was limited to emergency or intensive care units and may not be generalizable in some cases.

Conclusions

Sodium bicarbonated Ringer's solution has superior effects on the acidosis and electrolyte balance in patients with hemorrhagic shock and resulted in a lower risk of complications than the conventional crystalloid fluid.

Authors' Contributions

All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript. LY, CM, and XJ conducted the study; LY, CM, XJ, and JC collected and analyzed data; LY, CM, XJ, and JC wrote the manuscript.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Ethics Committee of Wuwei People's Hospital approved this study.

Clinical Trial Registration

This study was registered on the Chinese clinical trial registry (ChiCTR2000039951, 2020-11-15).

Funding

Supported by China primary health care foundation (YLGX-JZ-2020005).

Data Availability

The data during the current study are available from the corresponding author on reasonable request.

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