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ORIGINAL RESEARCH

Evaluation of the clinical effect of small-volume resuscitation on uncontrolled hemorrhagic shock in emergency

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Objective: The objective of the present study was to explore the resuscitative effect of small-volume resuscitation on uncontrolled hemorrhagic shock in emergency.

Methods: In this study, the resuscitative effects in 200 trauma patients with uncontrolled hemorrhagic shock in emergency were studied. Half of these patients were infused with hypertonic/hyperoncotic fluid (small-volume resuscitation group, n=100), whereas the rest were infused with Hespan and lactated Ringer's solution (conventional fluid resuscitation group, n=100). The changes in hemodynamics, coagulation function, blood biochemistry, blood hematology, and the average infusion volume in both the groups were comparatively studied.

Results: It was found that the hemodynamics were improved in both the groups after resuscitation. Interestingly, compared with trauma patients infused with Hespan and lactated Ringer's solution, the growth rate, range, and time duration of the mean arterial pressure of the patients in small-volume resuscitation group increased significantly, and the shock index decreased progressively; in the 60th min after the resuscitation, blood index including hemoglobin, hematocrit, red blood cells, white blood cells, and platelet declined, whereas prothrombin time and activated partial thromboplastin time were prolonged in both the groups, but these changes were less obvious in the small-volume group. In addition, the average infusion volume of patients in the small-volume group was less than that of patients in conventional fluid resuscitation group.

Conclusion: Featured with small infusion volume and less influence to coagulation function and homeostasis of human body, small-volume resuscitation possesses a significantly higher resuscitative effect. Therefore, trauma patients may have a better chance to maintain the hemodynamic stability and the survival rate, or recovery speed will be increased when traditional aggressive fluid resuscitation is replaced by small-volume resuscitation.

Keywords: small-volume resuscitation, shock, hemorrhage, emergency

Introduction

Trauma that is associated with high mortality is considered to be one of the leading causes of death in young people.[1] Death in trauma patients often results from the rapid evolution and deterioration of secondary complications such as shock and uncontrolled hemorrhage.[2] Rapid recovery and maintaining the stability of physiological environment, definite diagnosis of the injury site, and adequate preparations for the definitive treatment are key elements of the emergency rescue.[3] A highly efficient anti-shock therapy greatly saves time for the following treatments and thereby enhances the success rate of rescue.[4] Intravenous fluid infusion can restore the blood pressure and can reestablish the homeostasis by replenishing the lost liquid components.[5] Traditional anti-shock resuscitation was accomplished by fluid infusion that involved the administration of

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massive (usually 1–3 times the lost blood volume) hyperosmotic crystalloid and isosmotic colloidal solution or whole blood. Such a large volume of fluid or blood infusion will not only reduce the resuscitation efficiency, but also threaten the homeostasis of human body. Moreover, it has been reported that massive fluid resuscitation may increase the blood loss or even cause the dysfunction of normal blood coagulation of uncontrolled hemorrhagic shock patients.[6] In addition, massive fluid resuscitation will take more time, which makes the timely diagnosis and surgery impossible. Consequently, in order to enhance the resuscitation efficiency of uncontrolled hemorrhagic shock in emergency, it is urgent to explore an alternative clinical treatment with easy handling, small transfusion volume, and high efficiency.

Small-volume resuscitation, which refers to the resuscitation using hypertonic NaCl solution (mass fraction =7.2%–7.5%) with a dosage of ~4 mL/kg, could rapidly expand the blood volume and effectively stabilize the hemodynamics.[7–10] During the small-volume resuscitation, there existed an instantaneous mobilization of endogenous fluid along the osmotic gradient from the intracellular to the intravascular compartment.[9] Other substances such as polymerized human serum albumin and hibernation-based fluids have also been used for small-volume resuscitation on animal models.[11,12] For example, the short-term resuscitative effect of low-volume fluid resuscitation using hypertonic saline and hydroxyethyl starch (4 mL/kg) was compared with that of normal saline (10 mL/kg) on a pig model with lung contusion. It was demonstrated that the pulmonary edema that usually occurred in normal saline resuscitation was completely avoided when using the low-volume hypertonic saline and hydroxyethyl starch resuscitation.[13] The efficiency of small-volume resuscitation was also validated by using other animal models such as rats with pancreatitis-caused microcirculatory disorders or endotoxemia-induced kidney injuries.[14,15] In addition, a study has confirmed that hypertonic saline infusion has a far less influence on the coagulation function than that of hemodilution.[16] However, another study has pointed out the concerns related to the safe use of this limited volume resuscitation; for example, intraperitoneal hemorrhage and increase in deaths were reported in the research.[17] The results of these two studies could be ascribed to the differences in resuscitation occasion, infusion volume, and conditions in animal experiments.

However, there are still some technical bottlenecks such as the potential microcirculatory disturbances that need to be explored to further promote the clinical applications of small-volume resuscitation using hypertonic/hyperoncotic solution. Taking this into consideration, the clinical efficiency of small-volume resuscitation on 100 patients of uncontrolled hemorrhagic shock hospitalized in the Emergency Department of Shanghai Sixth People's Hospital from October 2005 to December 2015 was retrospectively studied, and these 100 patients were immediately diagnosed by using imaging technology such as computed tomography to determine the location of trauma. The resuscitative effects of another 100 trauma patients who were infused with Hespan and lactated Ringer's solution were also summarized for comparison. The present study concentrated mainly on the changes of hemodynamics, coagulation function, hemoglobin (HB), hematocrit (HCT), and average infusion amount, in order to provide more guiding instructions for better health care of patients with uncontrolled hemorrhagic shock in emergency.

Research objects and methods

Research objects and grouping

This research was approved by the State Food and Drug Administration of China (2005L02080). The clinical data of the 200 trauma-caused hemorrhagic shock patients (each of whom with multiple injuries) with the need of immediate bleeding control were retrospectively tested and statistically analyzed. Approval for collecting medical records was provided by the Medical Affairs Department of Shanghai Sixth People's Hospital. All of these 200 patients have signed an informed consent form for the collection of patient-identifiable information and medical records, and they were separated into two groups: small-volume resuscitation group (n=100) and conventional fluid resuscitation group (n=100) according to the type of resuscitation fluid that was initially used. Small-volume resuscitation group included 79 men and 21 women, with an average age of 34 years (ranging from 19 to 60 years). Among them, 28 patients suffered from liver and spleen rupture injuries, 53 patients were diagnosed with pelvic and limb fracture–caused great vessels rupture, and 19 patients were diagnosed with urinary system injuries. The mean arterial pressure (MAP) of these 100 patients was 48 mmHg, and the average preclinical time and average total treatment time were 95±44 min and 140±40 min, respectively. Conventional fluid resuscitation group included 87 men and 13 women, with an average age of 34 years (ranging from 20 to 60 years). Table 1 shows other general information about the patients in these two groups. Among the patients in conventional fluid resuscitation group, 35 patients suffered from liver and spleen rupture, 52 patients were diagnosed with pelvic and limb fracture–caused great vessels rupture, and 13 patients were diagnosed with urinary system injuries. The MAP of these 100 patients was 47 mmHg, and the

Table 1 General information (average height, average body weight, average GCS, T-RTS, mean administration time, and average observation time) of the two groups (n=100, $x \pm s$)

Group	Height (cm)	Body weight (kg)	GCS	T-RTS	Administration time (min)	Observation time (min)
A	169±7	62±8	14.5±1.4	7.0±0.3	25±10	30
B	165±8	60±8	14.5±0.8	7.0±0.3	27±6	30

Notes: Groups A and B stand for conventional fluid resuscitation group and small-volume resuscitation group, respectively.
Abbreviations: GCS, Glasgow Coma Score; T-RTS, mean revised trauma score.

average preclinical time and average total treatment time were 94±45 min and 152±45 min, respectively. Table 1 shows other general information about these two groups. These two groups were comparable in terms of gender, age, shock degree, injury time, and trauma score.

Methods

A reliable chronic venous access was established by using a peripherally inserted central catheter for each patient immediately when they were hospitalized. The patients in Group B were initially treated with 7.2%–7.5% NaCl/hydroxyethyl starch solution with a dosage of 4 mL/kg, whereas the patients in Group A were treated with Hespan and lactated Ringer's solution with the same dosage. The average injection rates of both the groups were 20 mL/min (with the range of 15–25 mL/min). After the resuscitation, all of the 100 patients in Group B were administered with a continuous supplement of 7.2%–7.5% NaCl/hydroxyethyl starch solution. It was noteworthy that the injection dosage and rate should be adjusted according to the systolic blood pressure (not <80 mmHg) of individual patients. More specific diagnoses and relevant preoperative preparations such as blood preparation should timely be carried out for the immediate operation. Routine blood pressure and heart rate (HR) examinations were performed every 5 min during the first hour postresuscitation. The coagulation function indexes including HB, HCT, and plasma fibrinogen content of each patient before and 60 min after the resuscitation were monitored to calculate the total infusion volume before the effective bleeding control.

Blood biochemistry and blood routine examination

The typical coagulation parameters including prothrombin time (PT) and activated partial thromboplastin time (APTT) were analyzed by using the ACL™ 200 blood coagulation analyzer with the guidance of HemosIL™ kit. The Beckman Coulter Unicel DxC 800 automatic biochemical analyzer was used to record the blood biochemistry parameters such as aspartate aminotransferase, alanine aminotransferase, total bilirubin, and carbamide. Routine blood test was carried out by using Sysmex XS-800i automated hematology analyzer. The tested parameters included white blood cell (WBC), HB, platelet (PLT), red blood cell (RBC), HCT, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red cell distribution width.

Statistical analysis

Statistical analyses were conducted by using Statistical Package for the Social Sciences (SPSS) Version 17.0 software for windows. Data were expressed as mean ± standard deviation ($x \pm s$). Between-group data were compared by using the Student's *t*-test, whereas within-group data were compared by using *q*-test and analysis of variance. A *P*-value <0.05 was considered as significant.

Results

Comparison of hemodynamics

As illustrated in Table 2, the hemodynamics including MAP and shock index of both the groups were significantly improved

Table 2 Change of hemodynamics before and after resuscitation in the two groups (n=100, $x \pm s$)

Group		Before resuscitation	0 min	10 min	30 min	60 min
B	MAP (mmHg)	48±3.8	66±7.0*	72±6.5*,Δ	74±6.3*,Δ	70±7.7*,Δ
A		48±3.5	49±5.7	57±3.9*	63±5.1*	59±2.7*
B	HR (bpm)	121±11	125±9	126±10	130±24	121±15
A		120±13	121±12	123±11	142±23#	147±21#
B	Shock index	1.73±0.15	1.10±0.16*	1.17±0.13*,Δ	1.05±0.20*,Δ	1.13±0.19*,Δ
A		1.70±0.13	1.65±0.13	1.35±0.32*	1.40±0.19*	1.39±0.28*

Notes: *Versus before resuscitation, $P<0.01$; #versus before resuscitation, $P<0.05$; Δsmall-volume group versus conventional group, $P<0.01$.
Abbreviations: HR, heart rate; MAP, mean arterial pressure.

Table 3 Comparison of coagulation function, HB, HCT, and average infusion volume between the two groups before and after resuscitation (n=100, $x \pm s$)

Group	HB (g/L)		HCT (%)		PT (s)		APTT (s)		Infusion volume (mL)
	Before	After	Before	After	Before	After	Before	After	
B	103±13	85±7.9*,Δ	31±5	28±7#,Δ	13.6±1.5	16.1±1.8#,Δ	31.5±4.5	39±4.8*,Δ	851±230Δ
A	101±19	74±5.3*	30±7	22±5*	13.9±2.5	17.5±2.1*	31.9±4.6	45±5.5*	1,403±334

Notes: *Versus before resuscitation, $P<0.01$; #versus before resuscitation, $P<0.05$; Δsmall-volume group versus conventional group, $P<0.01$.
Abbreviations: APTT, activated partial thromboplastin time; HB, hemoglobin; HCT, hematocrit; PT, prothrombin time.

after the resuscitation ($P<0.01$). The MAP level in Group B increased after the first resuscitation. In marked contrast, it showed only a slight increase in the 10th min after the resuscitation in Group A. Moreover, the increase of blood pressure in Group B was much greater than that in Group A ($P<0.01$). The patients in Group B had steady heartbeats without detectable HR change before and after the resuscitation. However, their heartbeats increased quickly at 30 min after the resuscitation and were significantly higher than before resuscitation in Group A ($P<0.05$). The shock index in Group B showed an immediate decrease after the first resuscitation, whereas in Group A this decrease happened only in the 10th min after the resuscitation. Moreover, the decrease of shock index in Group B was much greater than that in Group A ($P<0.01$).

Comparison of coagulation function, blood hematology, blood biochemistry, and average infusion volume

Blood clotting assay suggested that the PT and APTT in both the groups were significantly prolonged in the 60th min after resuscitation (Table 3; $P<0.05$ or <0.01, versus before resuscitation). Importantly, the change degrees of PT and APTT in Group B were less than those in Group A ($P<0.01$). In addition, HB, HCT, RBC, WBC, and PLT also declined progressively in both the groups (versus before resuscitation, $P<0.05$ <0.01; Tables 3 and 4), and the decrease in Group B was much less than that in Group A ($P<0.01$). Besides, the average fluid infusion volume of individual patients in Group B before effectively controlling the bleeding was also smaller than that in Group A (Group B: 851±230 mL versus Group A: 1,403±334 mL, $P<0.01$; Table 3). However, the difference in the mean volume of blood transfusion in the two groups was not significant (data not shown). Moreover, although other blood biochemistry parameters (Table 4) and blood hematology parameters (Table 5) changed after the resuscitation in Group B, these changes were not obvious when compared with Group A.

Table 4 Change of blood biochemistry of patients before and after resuscitation in the two groups (n=100, $x \pm s$)

Blood hematology index	Group A		Group B	
	Before	After	Before	After
RBC	3.82±0.55	3.08±0.58	3.59±0.54	3.06±0.71
WBC	16.31±5.44	15.14±3.81	18.07±10.40	16.69±7.07
PLT	217.67±63.04	170.68±60.87	219.14±75.71	195.00±62.61
MPV	9.89±1.04	9.7±0.93	10.48±1.28	9.99±2.06
PDW	14.04±3.29	13.16±2.91	12.92±2.61	12.26±1.99
PCT	25.15±8.18	23.22±6.83	28.78±9.97	26.75±9.72

Abbreviations: MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Discussion

Typically, restricting the infusion volume, delaying the resuscitation, and maintaining the moderate hypotension so as to facilitate the infusion are well-established principles for the uncontrolled hemorrhagic shock resuscitation. Although a sufficient fluid resuscitation is necessary for anti-shock, recent studies have suggested that the massive fluid resuscitation before effectively controlling the active bleeding may increase the blood loss or lead to dilutional coagulopathy. In the meantime, the increase of blood pressure can peel away the scar tissue and lead a rebleeding, which may increase the probability of complications.[18] In addition,

Table 5 Change of blood hematology of patients before and after resuscitation in the two groups (n=100, $x \pm s$)

Blood biochemistry index	Group A		Group B	
	Before	After	Before	After
ALT	30.06±16.86	27.94±13.13	35.47±18.62	32.09±16.77
AST	35.16±12.73	29.67±12.73	34.94±18.15	28.63±14.79
ALB	34.47±10.64	24.62±7.05	34.68±8.46	25.41±9.50
TBIL	10.41±6.29	8.53±4.83	7.36±4.68	7.94±2.34
GLU	8.36±3.10	8.91±3.21	9.58±4.16	9.23±3.87
SCR	74.71±24.36	72.14±24.36	76.57±24.73	75.71±22.03
BUN	5.87±1.55	6.00±1.45	6.59±1.91	6.45±2.03
Na	140.43±4.82	140.05±6.18	141.45±4.30	145.15±4.79
K	3.86±0.95	3.57±0.47	3.60±0.34	3.84±0.44
Cl	107.33±4.05	109.76±6.11	108.31±4.96	116.55±6.76

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GLU, glucose; TBIL, total bilirubin; SCR, serum creatinine.

intra-abdominal bleeding and increased death rate were reported for uncontrolled hemorrhagic shock animals that were perfused with the hypertonic saline.[17] Therefore, the concept of limited fluid resuscitation which indicates that fluid infusion should be restricted before controlling the active bleeding was proposed.[19]

In recent years, the application of hypertonic saline solution containing 7.2%–7.5% NaCl for early recovery of uncontrolled hemorrhagic shock has received an ever-increasing interest. After entering into the blood circulation, this hypertonic saline solution causes an increase in swift plasma osmolality to 2,400 mOsm/L, which is 8 times higher than the normal plasma osmolality. Under such a high plasma osmolality, the interstitial fluid and intercellular fluid swiftly move to the blood vessel and cause an increase in the effective circulating blood volume, cardiac output, and blood pressure (this effect can last about 40 min[7]). A subsequent study has shown that hypertonic saline salt solution supplemented with colloid such as dextran or hydroxyethyl starch can further facilitate the blood circulation and increase the blood pressure for up to 2 h, which thereby obviously increases the survival rate of patients.[20] An obvious characteristic of this treatment is the relatively small clinical dose (3–4 mL/kg, also called "small-volume resuscitation"). It was detected that the plasma volume can reach 20% of the former volume when the dosage of the hypertonic saline solution was 4 mL/kg, and ~400–800 mL of interstitial fluid and intercellular fluid entered the blood vessels. This present study concentrated mainly on the resuscitation effect of the small-volume resuscitation 1 h after the treatment. The resuscitation time of the 100 patients in the two groups was ~90 min after injury and the infusion volume were identical to maintain the basic blood pressure. It was found that the hypertonic/hyperoncotic fluid infusion tends to exert less influence on the blood coagulation function, HB, HCT, RBC, WBC, and PLT than the conventional fluid infusion, whereas the blood coagulation function changes and hemodilution may be related to the uncontrolled bleeding. Moreover, both the conventional fluid resuscitation group and small-volume resuscitation group showed a negligible influence on the other blood biochemistry parameters and blood hematology parameters, which clearly proved the admirable hemocompatibility of the small-volume resuscitation modality[21] and the excellent resuscitation potency of small-volume resuscitation on uncontrolled hemorrhagic shock in emergency. The results from the present study also uncovered a significant increase in MAP immediately after the application of 250 mL hypertonic saline solution. In addition, the increase of blood pressure and the duration of the higher blood pressure were much greater than in those patients infused with hydroxyl ethyl starch or balance fluid.

Another noteworthy point is the potential influence of hypertonic solution on the microcirculatory disturbances. Although there are different points of view,[22] it is generally accepted that the hypertonic solution alleviates the microcirculatory disturbances;[23–25] for example, a previous study has uncovered that the hypertonic/hyperoncotic saline could attenuate the microcirculatory disturbances after traumatic brain injury. With the capacity of significantly decreasing the shock index with a little fluid infusion and blood transfusion before controlling the bleeding in trauma patients, small-volume resuscitation exhibited an admirable expansion and resuscitation efficiency in clinic experience.

Conclusion

In summary, the primary goal of infusion for uncontrolled hemorrhagic shock patients during emergency is to save time to enable the swift and accurate diagnosis and fast hemostasis. This clinical experience showed that before controlling the bleeding, massive and repeated administration of hypertonic saline is not recommended, and compared with the conventional fluid resuscitation, the recently proposed small-volume resuscitation possesses a high resuscitative efficiency toward trauma patients with uncontrolled hemorrhagic shock in emergency. Moreover, small-volume resuscitation could reduce the infusion volume, thus effectively avoid the interference to the homeostasis of human body. Therefore, small-volume resuscitation is an effective and safe protocol that is recommended for the traumatic hemorrhagic shock treatment in clinical reality.

Disclosure

The authors report no conflicts of interest in this work.

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