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The influence of different resuscitation solution on lactic acid accumulation after hemorrhagic shock: a network meta-analysis

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Abstract. – OBJECTIVE: To compare the effect of various fluid resuscitation procedures after hemorrhagic shock on the lactic acid accumulation by network meta-analysis.

MATERIALS AND METHODS: A number of articles were obtained by searching the databases. Randomized control trials (RCT) were selected by two literature quality assessors; the extracted experimental data were then summarized to compare and analyze the effect of various kinds of infusion procedures at different time points on the concentration of lactic acid in the internal environment of rat models.

RESULTS: 9 articles containing 25 independent reports were enrolled. Results revealed that the accumulation of lactic acid generated in the resuscitation using hydroxyethyl starch solution or gelofusine was significantly different from the one using Ringer solution, hypertonic saline or normal salt solution ($p<0.05$). Compared to the colloidal, the aqueous solution of pyruvate showed a slightly weaker effect in reducing the accumulation of lactic acid. The accumulation of lactic acid is severely affected by hypertonic saline, Ringer lactate solution, and balanced salt solution, i.e., the concentration of lactic acid is increasing with an augment of concentration or prolongation of treatment time.

CONCLUSIONS: In terms of the management of lactic acid accumulation after hemorrhagic shock, the effect of colloidal solution was remarkably better than a crystalloid solution, and hypertonic saline and normal salt solution were not recommended as preferable drugs in the treatment of hemorrhagic shock.

Key Words:
Hemorrhagic shock, Lactic acid accumulation, Network meta-analysis (NMA).

Introduction

Hemorrhagic shock is the most common clinical cause of death among trauma patients. As shown in statistical analysis, the traumatic shock in approximately 50% of the traumatic shock patients will evolve into multiple-organ failure[1] and the mortality rate of trauma induced by this type of serious complication can be up to 40%[2]. In hemorrhagic shock patients, failure in the early and timely expansion of blood volume will cause nearly half of them to die of multiple organ failure (MODS)[3]. However, in early hemorrhagic shock patients, the visceral vessels are still in the status of contraction and filling. If the ischemic duration is prolonged, the risk of reperfusion injuries of organ blood will be increased, leading to an elevation in morbidity and mortality[4,5]. Previously, Duan et al[6] and Liu et al[7] investigated in fluid resuscitation after traumatic injuries and found that reperfusion injuries can induce functional impairment in peripheral organs and lead to the *in vivo* accumulation of multiple toxins and the acid-base imbalance, thereby causing systemic inflammatory response syndrome (SIRS) or MODS. Therefore, the improvement on the internal environment also plays an important role in the late recovery of hemorrhagic shock patients after the excessively long ischemic duration in addition to the crucial expansion of the blood volume at the early stage. Lactic acid in the blood is mainly generated from the transformation of acetone acid catalyzed by

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lactate dehydrogenase. As a final product of anaerobic glycolysis, it is a reliable indicator that can sensitively reflect the tissue oxygen supply-to-demand imbalance[8], thereby playing a role of auxiliary examination on the peripheral circulatory low perfusion and shock severity[4]. Jouffroy et al[9] reveal that the continuous elevation of lactic acid in blood indicates a poor prognosis of circulatory reperfusion. Therefore, it can be served as an indicator of shock severity. Intravenous rapid infusion, with the capability to improve the blood perfusion of patients in hemorrhagic shock rapidly and alleviate the injuries to surrounding organs, has become a primary method in the basic treatment for patients in shock. In clinical practices, the common expanders include lactate Ringer's solution, hypertonic saline solution, hydroxyethyl starch, and balanced salt solution[10,11]. At present, the preferred rehydration procedures for the treatment of patients in shock in an early stage are frequently determined by the doctor's experience, which, however, lacks the support of reference in evidence-based medicines. Network meta-analysis (NMA) can be used to summarize and analyze the same detection indexes from factors collected from various independent studies[12] and qualitatively or quantitatively identify the factors interfering the experiment of subjects. These intervention procedures can be ranked according to their efficacy and the relative efficiency of intervention procedures can be effectively evaluated. Besides, by analyzing the network relation formed by many random control experiments[13], we can, directly or indirectly, compare the efficacy of each intervention procedures enrolled in the random control experiments, identifying the most valuable intervention procedures in various random control tests (RCTs) for the target of the treatment. In this work, through NMA analysis, a new type of evidence-based evaluation method, we summarize the RCT data from a series of different rehydration therapies to investigate the influence of each common rehydration therapy for the treatment of hemorrhagic shock on the accumulation of lactic acid in the internal environment. We hope that the results of this study, together with the summary and analysis of the currently related experimental data, could provide key reference for clinical physicians to stipulate the treatment procedures, thus alleviating the influence of hemorrhagic shock on the patient.

Materials and Methods

Literature Retrieval Strategy

Databases such as PubMed, the Cochrane Library, Web of Science, and CNKI were explored using a computer with the major search terms as follows: hemorrhagic shock, resuscitation, lactic acid, saline, ringer, hypertonic, gelofusine, hydroxyethyl starch, and pyruvate. The research was conducted from the moment of establishing the database to August 1st, 2018. In search of the databases, we combined the subjects, i.e., PubMed (MESH) and EMBASE (EMtree), with uncontrolled words as a search strategy, during which suitable adjustments were made in specific databases. To increase the availability of analysis, no restrictions were made on the article types in the research; at the same time, profession-related periodicals and conference papers were searched to cover as much as possible the range of literature correlated with the objective of this study.

Inclusion and Exclusion Criteria of Literature

According to the PICOS principals, we stipulated the inclusion and exclusion criteria. Inclusion criteria: a) Types of study: RCT; b) Subjects of study: the traumatic hemorrhagic shock rat models; c) Intervention measures: different rehydration procedures for the treatment of traumatic hemorrhagic shock, including the different types of rehydration or different concentrations of fluid for infusion; d) Indexes for outcome: concentrations of lactic acid in arterial blood (mean ± SD) were obtained in pairs directly or indirectly. Exclusion criteria: a) Reports that were not RCTs; b) Animals that were used in establishing the model that were not rats; c) Information provided by the article was insufficient, or the quality assessment of the article was excessively low.

Screening the Literature and Retrieving the Information

Two researchers were appointed to independently screen the literature and retrieve the data as follows: according to the inclusion criteria, preliminary screening was carried out by reading titles and abstracts; re-screening was performed by searching and obtaining the full-text; they would discuss on the discrepancy, if any, until they reached a consensus. Information retrieved from the text included the author, publication year, source of search, trauma type, infusion type or concentration, number of models in each group (n), the final mean concentration of blood lactic acid (mean), and standard deviation (SD) obtained in the experiment, etc.

Statistical Analysis

After the data retrieval of the included literature, the data were input into Stata 14.0 statistics software according to the requirement of NMA. The statistical outcome of each subject in the experiment was obtained using the application method of NMA[14], including the correlation between research groups, results of direct comparisons and indirect comparisons, *p*-value, etc. Results of the analysis were used to prepare the intuitional statistical development diagram to anticipate the relative efficacy of the corresponding treatment procedure.

Results

Results of Literature Search

Through the literature search, we obtained the relevant literature (n = 1652), as well as the repeatedly published literature, such as overview, case reports, e-mails, while the literature in which the models were not established using rats was excluded. There were 83 works requiring full-text. After the researchers read the full texts of these works, they excluded those that were not RCTs or those lacking comprehensive test data. Finally, 9 works of literature[15-23] were enrolled in this study (7 articles in English and 2 articles in Chinese), including a total of 25 independent RCTs (Figure 1).

Basic Characteristics of the Subjects Enrolled in the Study

As shown in Table I, the basic information of the enrolled literature included the author, publication year, source of search, trauma type, infusion type or concentration, and infusion strategy. Finally, liquid types included normal saline (NS), lactate ringer (LR), hypertonic saline solution (HSS), pyruvate solution (PYR), and gelofusine (GEL). Meanwhile, the number of models in each group (n) of each RCT, the final mean concentration of blood lactic acid (mean), and standard deviation (SD) in the experiment of blood concentration of lactic acid in different periods were obtained, and data were shown in Supplementary Table I.

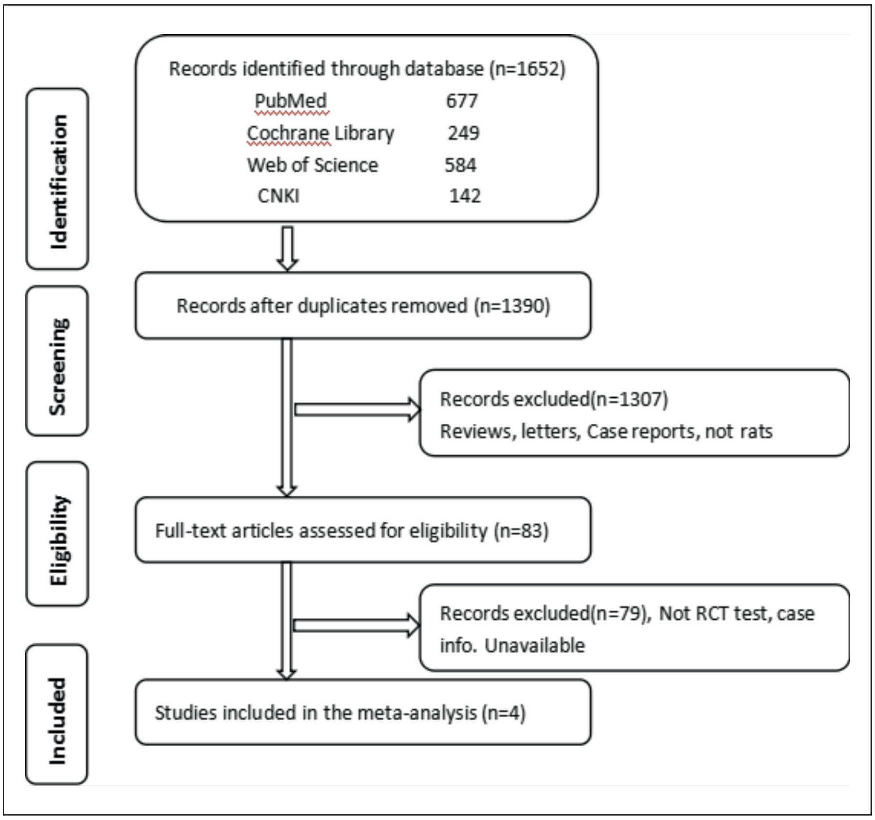

Figure 1. Literature screening process.

Table I. Characteristics of included studies.

Study	Author	Year	Country	Trauma type	Type of rat	Solution type	Resuscitation strategy
1	Jiang et al[16]	2016	China	Intestinal Ischemia Reperfusion Injury after shock	Male SD rats (n=60; 10/group)	① Glucose-lactate-based peritoneal dialysis ② Pyruvate solution (1.1%/1.6%/2.2% grams/dl) ③ SHAM ④ Intravenous resuscitation only	Maintain MAP at 40 mmHg for 60 min, Intravenous resuscitation volume: two times of shed blood. Intraperitoneal pump 20 ml LR or PYR in 30 min.
2	Gao et al[18]	2013	China	Hemorrhagic Shock and infection	SD rats (n=60; 12/group)	① Lactate Ringer ② Lactate Ringer ③ 7.5% hypertonic saline solution ④ Hydroxyethyl starch ⑤ Sham operation	Maintain MAP at 35-40 mmHg for 60 min and followed by infection of LPS, LR-3 times volume of shed blood; HSS-4 ml/kg 7.5% hypertonic saline; HES-equal to the shed blood volume.
3	Hirano et al[17]	2006	Brazil	Hepatic ischemia and reperfusion after hemorrhagic shock	Male Wistar rats (n = 18; 6/group)	① Lactate Ringer's solution ② Physiologic saline Solution ③ 7.5% hypertonic saline solution	MAP=40 mmHg for 20 minutes. LR/NS group- LR/saline and blood to volemic replacement; HSS group- 7.5% HSS (4 ml/kg) complement with LR and blood.
4	Lee et al[15]	2005	China	Hemorrhagic shock	Male Wistar rats (n = 24; 8/group)	① Lactate Ringer's solution ② 4% Hydroxyethyl starch ③ 4% Modified fluid gelatin	Maintain hypovolemia (30% body blood loss) for 30 min before resuscitation. LR-three times volume of blood loss; HES-volume equal to blood loss; GEL-volume equal to blood loss.

Continued

Table I (continued). Characteristics of included studies.

Study	Author	Year	Country	Trauma type	Type of rat	Solution type	Resuscitation strategy
5	Zhang et al[19]	2014	China	Intestinal ischemia reperfusion injury after hemorrhagic shock	Male SD rats (n = 50; 10/group)	① Normal saline ② Lactate-based PDS ③ Pyruvate based PDS ④ SHAM ⑤ Intravenous resuscitation only	Maintain MAP at 40 mmHg for 60 min before resuscitation. NS (twice volume of blood loss), intraperitoneally infused with 20 ml NS, LR, PYR over 30 min.
6	Sharma et al[20]	2012	USA	Hemorrhagic shock	Male SD rats (6-8 /group)	① Normal saline ② Lactate Ringer ③ 7.5% hypertonic saline solution ④ Sham ⑤ HSS without resuscitation	Maintain MAP at 40 mmHg for 30min. NS group-0.9% saline, 5 ml/kg; LR group-3 times the volume of blood shed; HSS group-7.5% hypertonic saline, 5 ml/kg.
7	Hu et al[21]	2013	China	Hemorrhagic shock	Male SD rats (n = 54; 18/group)	① Lactate Ringer's solution ② Pyruvate Ringer's solution ③ Sham	Maintain MAP at 40 mmHg for 60 min. LR -three times volume of shed blood; PYR -three times volume of shed blood.
8	Yi et al[22]	2015	China	Hemorrhagic shock	Male SD rats (n = 50; 10/group)	① Lactate Ringer's solution ② 6% hydroxyethyl starch ③ LR+HES ④ Sham ⑤ HSS without resuscitation	Maintain MAP at 40 mmHg for 60 min. LR group-reinject LR solution to MAP at 80 mmHg; HES group-reinject 6% hydroxyethyl starch to MAP at 80 mmHg.
9	Zhang et al[23]	2012	China	Severe hemorrhagic shock	Male SD rats (n = 37) ① :12; ② 12; ③ 13.	① 0.9% Normal saline ② 6% hydroxyethyl starch ③ Whole blood	35% blood loss and stop for 10 min, and then another 30% blood loss. Blood flow rate: 0.5 mL/min. MAP: 46±14 mmHg for 60 min. Volume of LR/HES are equal to blood shed.

(MAP: Mean Artery Pressure; LR: Lactate Ringer; PYR: Pyruvate solution; HSS: hypertonic saline solution; GEL: gelofusine; NS: normal saline; HES: hydroxyethyl starch; SD: Sprague-Dawley).

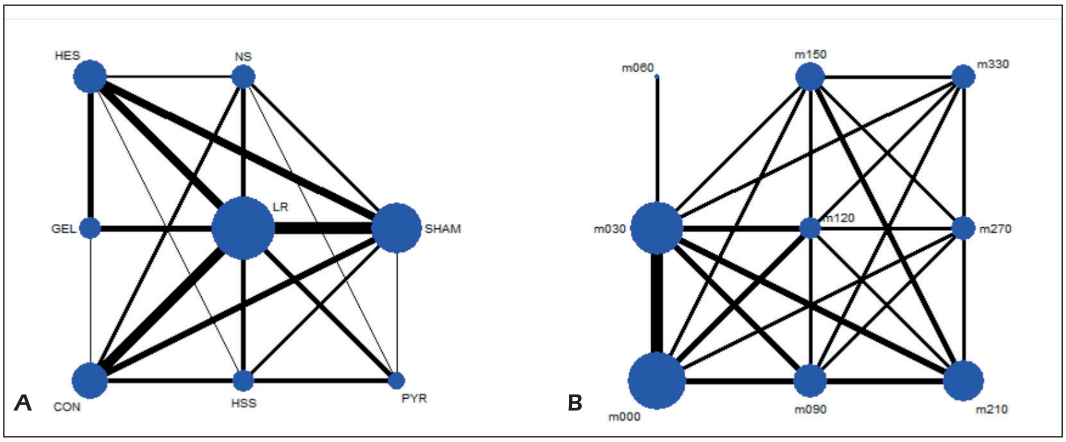

Figure 2. Evidence network of eligible comparisons for network meta-analysis. ***A,*** Comparisons with different resuscitation solution. ***B,*** Comparisons with different period. (Each line represents direct comparisons between included studies. The width of the lines reflects the cumulative number of trials for each comparison and the size of every cycle is proportional to the number of included sample size.)

NMA Analysis Results

The results of network linear head to tail comparison (Figure 2) revealed that among the experiment groups of models enrolled in this study, the weight of crossover studies on hydroxyethyl starch and Ringer's solution ranked first followed by GEL, NS, and HSS in sequence, in accordance with the results in different resuscitation solution and different periods. Results obtained in the analysis of probability sequencing graphs (Figure 3) in the experiments using different resuscitation solutions revealed that the best order was HSS, GEL, and PYR. HSS, LR, and PYR were characterized as the factors exerting the largest influences on the accumulation of lactic acid. With the increase in concentration or the extension in time, the concentration of lactic acid was continuously increased. Besides, the grade-probability histogram (Figure 4) could intuitively reflect the significant differences in comparisons of the accumulation of lactic acid in experiments using different resuscitation solutions, at different time points between the groups. According to the results obtained in direct and indirect comparisons among the combinations through the analysis of NMA (Table II, Supplementary Table II), we found that the accumulation rate of lactic acid in blood could be slowed down by expanding the capacity using HSS, GEL or PYR, suggesting that the application use in early stage could alleviate the occurrence of lactic aci-

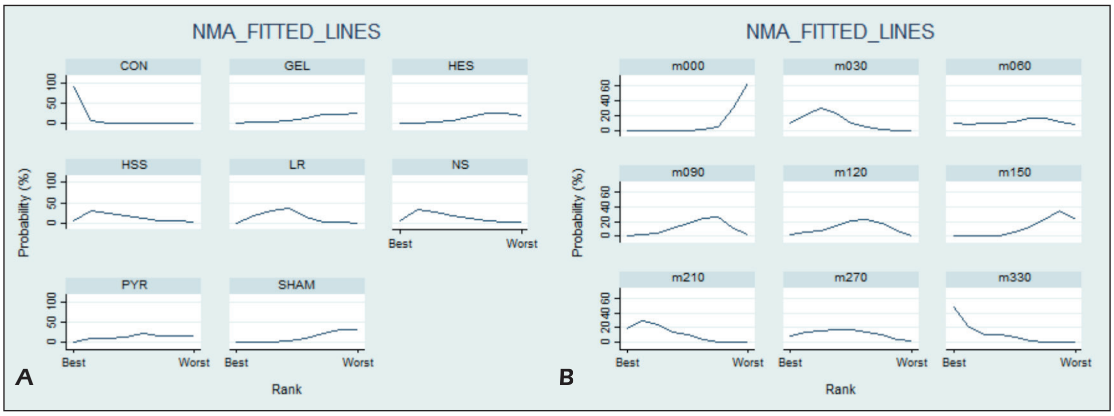

Figure 3. Ranking grams showing probability of each strategy having each specific rank for lactate accumulation. ***A,*** Probability based on different resuscitation solution. ***B,*** Probability based on different period of detect lactate concentration.

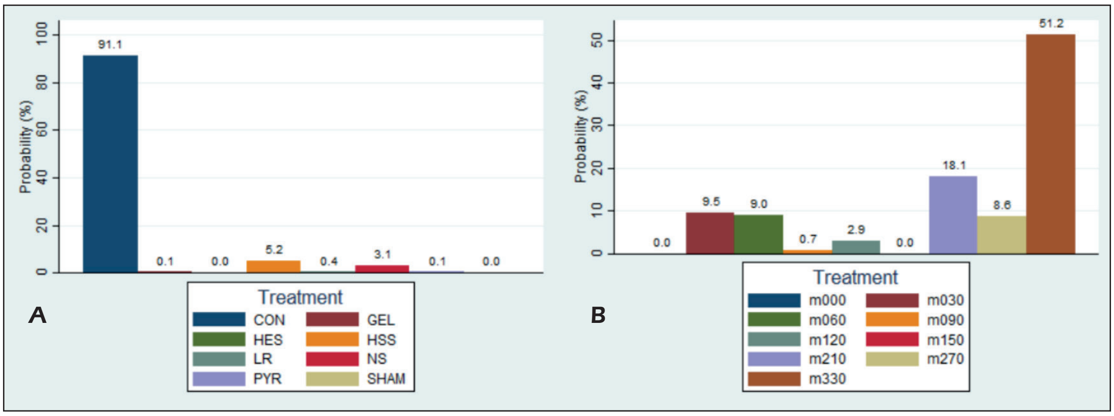

Figure 4. Network plotting bars showing the probability of lactate accumulation based on different resuscitation and period. ***A,*** Treatment divided by different resuscitation type. ***B,*** Treatment divided by different period.

dosis; however, effects of HSS, NS, and LR were significantly weaker than that of HSS in terms of alleviating the lactic acid accumulation. Also, all the abbreviations were listed in Table III. The grouping of combined effect size in forest plots (Figure 5) showed the relative ratio of the solution in the comparative analysis influencing the concentration of lactic acid. We found that the influences on the lactic acid concentrations would increase with the augmentation of ratio or the ratio being shifted to the right. The size of the block represented the weight of the corresponding study in comparative group, the length of line represented the relative position of 95% confidence interval of the effect size, and the red line represented the combined effect size between groups, which could indirectly reflect the influences of the studied solution on the accumulation of lactic acid.

Discussion

The major pathophysiological changes in the hemorrhagic shock are characterized by the reduction in the effective circulating blood volume, which can lead to the insufficient tissue perfusion and increase in lactic acid accumulation, resulting in the lactic acidosis, aggravating the degree of shock, and forming a vicious circle[10]. D'Alessandro et al[10] showed that the concentration of lactic acid in blood can directly reflect the degree of anaerobic metabolism, showing a better sensitivity and reliability to the reduction of blood volume caused by hemorrhagic shock compared to the oxygen dynamics and pH of blood, which is of great significance for guiding the resuscitation of hemorrhagic and hypovolemic shock. Thus, searching for a more efficient and reliable method for treating the accumulation of lactic acid through evidence-based medicine makes a big difference in the treatment of hemorrhagic shock caused by trauma[24]. In this work, from a peculiar perspective for analysis, we, directly and indirectly, compared the influences of several expanding solutions on the treatment of lactic acid accumulation caused by hemorrhagic shock using NMA of the shock rat model experiment to provide further guidance for the exploration of clinical medication. Based on the NMA analysis results above, HSS and NS, among the five resuscitation solutions for hemorrhagic shock, can significantly increase the concentration of accumulated lactic acid in the blood. In the literature that previously reported the application of HSS in liquid treatment of hemorrhagic shock, it was believed that the major mechanism in the high permeability of solution, i.e., the rapid increase in the sodium concentration in serum, would generate a concentration gradient of osmotic pressure inside and outside the vessels and cells. This would further lead to the re-distribution of interstitial fluid, increase of the effective circulating blood volume of the body, and maintenance of the regular cardiac output and perfusion in organs and tissues. However, recent studies have indicated that a massive infusion of the salt solution after the hypovolemic shock may cause hyperchloremic acidosis.

Table II. Network Rank results. In the "best" rows: the smaller number represents lower impact on accumulation of lactate.

Study and Rank	Treatment							
	CON	GEL	HES	HSS	LR	NS	PYR	SHAM
Best	87.7	0.1	0	6.4	0.2	5.3	0.3	0
2nd	10.2	2.5	0.8	32.6	13.7	32.8	7.3	0.1
3rd	1.8	3.8	3	22.5	29.9	28.2	10.2	0.6
4th	0.3	7.2	7.2	15.1	37.7	17.5	12.2	2.8
5th	0	15.4	17.9	11.8	15.5	9.3	20.3	9.8
6th	0	22.1	26.4	5.5	2.1	3.6	16.7	23.6
7th	0	20	24.2	3.9	0.9	2.3	14.4	34.3
Worst	0	28.9	20.5	2.2	0	1	18.6	28.8

Study and Rank	Treatment								
	m000	m030	m060	m090	m120	m150	m210	m270	m330
Best	0	10.3	8.8	0.9	2.3	0	18.4	8.7	50.6
2nd	0	22.9	10.2	1.8	4.1	0	28.4	14.4	18.2
3rd	0	26.9	8.8	3.6	9.7	0.2	23.2	14.6	13
4th	0	22.2	11	10.3	15.2	1.8	16.9	15.4	7.2
5th	0	13.4	11.4	18.7	23.6	3.8	8.6	15.7	4.8
6th	1.1	4	13.4	24.6	21.6	13	3.5	15.1	3.7
7th	6	0.2	15.8	25.7	15.4	23.6	1	10.5	1.8
8th	31.5	0.1	11.2	11.3	6.7	34.2	0	4.3	0.7
Worst	61.4	0	9.4	3.1	1.4	23.4	0	1.3	0

Table III. List of abbreviations.

Abbreviations	Full names	Abbreviations	Full names
RCT	Randomized control trials	HSS	Hypertonic Saline Solution
MODS	Multiple Organ Failure	GEL	Gelofusine
SIRS	Systemic Inflammatory Response Syndrome	NS	Normal Saline
NMA	Network meta-analysis	HES	hydroxyethyl starch
SD	Sprague-Dawley	SHAM	negative control
LR	Lactate Ringer	CON	positive control
PYR	Pyruvate solution	MAP	Mean Artery Pressure

After the shock, various weak acidic metabolites generated by the anaerobic metabolism can ionize some H^+, which can bind with the infused Cl^- in a high concentration, forming HCL that can promote the accumulation of acidic substances. For the lactated Ringer's solution, it can increase the effective circulating blood volume by itself; however, a massive liquid infusion in a short period can increase the hydrostatic pressure in the vessel and decrease the colloidal osmotic pressure, finally resulting in repeated decreases in the intravascular volume. A failure of the

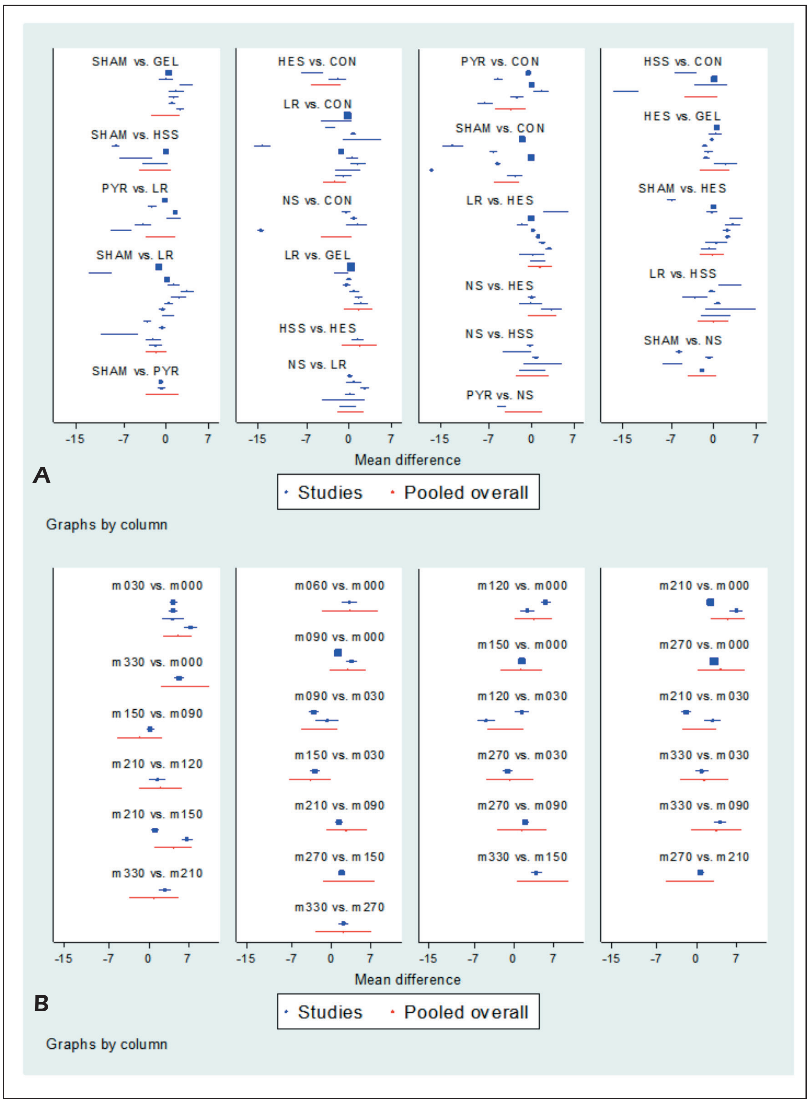

Figure 5. Forest analysis of different resuscitation solution for lactate accumulation. ***A,*** NMA forest between different resuscitation solution. ***B,*** NMA forest between different period for detected concentration of lactate. Squares indicate study-specific odds ratios (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% CIs; the diamond indicates the summary odds ratios estimate with its 95% CI.

circulatory function, as well as an excessive infusion of liquid will cause tissue edema or cell outside the vessels. Reports[25-27] have already showed that a massive infusion of LR can induce the hyperlactatemia, leading to an increased cell apoptosis in intestinal mucosa, liver, and lung; however, when the lactic acid in LR is replaced by pyruvate, the cell apoptosis in liver and lung is significantly reduced. Further researches revealed that eliminating the D-lactate in LR can also improve the lactic acid accumulation. Pyruvic acid, the final product of glycolysis, is an important link in the transformation among the three major nutrients, i.e., sugar, fat, and amino acid. As a substrate in energy metabolism, the pyruvate solution is characterized by a strong anti-inflammation and anti-oxidation effect. Existing researches[28,29] have found that in the liquid resuscitation of hemorrhagic shock, pyruvate, except for the effect to expand the blood volume, can also provide energy for the myocardium, inhibit the inflammatory response, ameliorate the oxidative damage to increase the survival rate of animals in hemorrhagic shock, and preserve the functions of major organs. In this study[30], we found that the pyruvate solution can improve the acidosis caused by shock in a certain degree, which might be associated with the consumption of H^+ in the metabolism of endogenous pyruvic radicals and the alkalified extracellular fluid. The exogenous pyruvate solution can, through the TCA cycle, supplement the quantity of substrate and adjust the PDH activity to promote the process of TCA to decrease the accumulation of lactic acid with continuous consumption of H[28]. Also, the NMA analysis showed that the effect of the colloidal solution on the accumulation of lactic acid in the blood of hemorrhagic shock model was the least. The colloidal solution, as a kind of macromolecular substance, shows better effects to improve the microcirculation and ameliorate the cellular swelling compared to the crystalloid solution. In addition, hydroxyethyl starch contains the bicarbonate ions. Therefore, except for its function in expanding the capacity, it can also supplement the electrolyte in the extracellular liquid, increase the base excess, and improve the lactic acid accumulation caused by the shock. Nevertheless, side effects of colloidal solution, such as decreasing the GFR, affecting the clotting mechanism, and a certain incidence rate of an allergic reaction, should not be neglected and improvements in resuscitation procedures of the colloidal solution are urgent to decrease the side effects. Although some reports have revealed that HSS shows more disadvantages than advantages in treating the septic shock[31], and the recommendations of PRAC to restrict the use of HSS in patients of septic shock, the key role of colloidal solution in hemorrhagic shock has not been denied and HSS is still suggested for hypovolemic shock patients who exhibit poor efficacy after the application of crystalloid solutions.

For various objective factors, there are some inevitable limitations in this study, which may affect its final results. For example, only some literature that met the criteria was enrolled, the sample size was too small, only the hemorrhagic shock rat model was included, there was no detailed description for random methods, blind methods, and concealment in grouping. Furthermore, the bleeding volume was not strictly controlled to reach the degree of shock when hemorrhagic shock models were established by each group. Due to the above factors that can affect the analysis in this study, we will collect further relevant studies in the future, expand the scale of enrolled studies, and improve the reliability of the analysis.

Conclusions

We investigated the most valuable intervention procedures for the goal of treatment among various RCTs in this study with the advantages of NMA and found that colloidal solution and pyruvate solution can significantly decrease the accumulation of lactic acid after the hemorrhagic shock; however, in resuscitation using crystalloid solution, we found that the accumulation of lactic acid was continuously increased with an increase in the concentration of crystalloid solution or the time to be prolonged. Therefore, given that the accumulation of lactic acid in hemorrhagic shock is an important index, we do not recommend the HSS or NS as the preferred choice for the treatment of hemorrhagic shock.

Conflict of Interests

The Authors declared that they have no conflict of interests

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