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Original Article

Efficacy of limited fluid resuscitation in patients with hemorrhagic shock: a meta-analysis

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Abstract: Backgrounds: The objective of this meta-analysis was to evaluate the efficacy of limited fluid resuscitation during active hemorrhage compared with regular fluid resuscitation and provide strong evidences for the improvement of fluid resuscitation strategies in uncontrolled hemorrhagic shock. Methods: Electronic searches were performed using PubMed, Medline, Embase and CNKI in accordance with pre-set guidelines. Clinical trials and observation studies were included or excluded according to the criteria. The endpoints examined were mortality, hemoglobin (Hb), platelets (PLT), hematocrit (Hct), prothrombin Time (PT), activated partial thromboplastin time (APTT), base excess (BE), blood lactic acid (BLA) and the main complications, such as multiple organ dysfunction syndrome (MODS) and acute Respiratory Distress Syndrome (ARDS). Risk ratios (RR), mean differences (MDs) and 95% confidence intervals (95% CI) were calculated using fixed/random effect model. Results: The search indentified 11 studies including 1482 subjects. 725 hemorrhagic patients were treated with limited fluid resuscitation while 757 patients undertook regular fluid resuscitation during active hemorrhage. Limited fluid resuscitation had its advantage to reduce the mortality in hemorrhagic shock (RR = 0.67; 95% CI = 0.56-0.81; $P < 0.0001$) and easily controlled the blood routine index close to normal compared with regular fluid resuscitation (Hb: MD = 13.04; 95% CI = 2.69-23.38; P = 0.01. PLT: MD = 23.16; 95% CI = 6.41-39.91; P = 0.007. Hct: MD = 0.02; 95% CI = 0.02-0.03; $P < 0.00001$). LFR also had shorter PT and APTT compared with RFR (PT: MD = -2.81; 95% CI = -3.44--2.17; $P < 0.00001$ and APTT: MD = -5.14; 95% CI = -6.16--4.12; $P < 0.00001$). As for blood gas analysis, LFR reduced the decrease of BE (MD = 2.48; 95% CI = 1.11-3.85; P = 0.0004) and increase of BLA (MD = -0.65; 95% CI = -0.85--0.44; $P < 0.00001$). Besides, LFR may also reduce the occurrence of postoperative complications (MODS: RR= 0.37; 95% CI = 0.21-0.66; P = 0.0008. ARDS: RR = 0.35; 95% CI = 0.21-0.60; $P < 0.0001$). Conclusion: The results provide convincing evidence that support the continued investigation and use of limited fluid resuscitation during active hemorrhage in the trauma setting.

Keywords: Limited fluid resuscitation, hemorrhagic shock, trauma, mortality

Introduction

The complication of large amount of regular fluid resuscitation has always been a problem throughout the world, which triggers refection to traditional fluid resuscitation strategy. Although Cannon has already shown suspect to the regular flood resuscitation (RFR) strategies before operation control bleeding in 1917, the concept of limited fluid resuscitation (LFR) was first put forward by Stern et al. in 1992 [1]. Limited fluid resuscitation refers to maintaining the blood pressure in a low level, which is enough to guarantee blood supply of important organs, through controlling the speed and volume of transfusion in uncontrolled hemorrhagic shock. The aim of LFR is to bring the body compensatory mechanism and fluid resuscitation function into full play, thus achieve the ideal effect of recovery [2].

In recent years, a large amount of studies [3-8] have focused on the selection of crystalloids or colloids in fluid resuscitation and many related meta-analysis [9-15] have been put forward. However, researches on the comparison between regular fluid resuscitation (RFR) and limited fluid resuscitation (LFR) were few and only one meta-analysis was found [16]. Meanwhile, the few related researches hold different opinions on selection between RFR and LFR as well. The report of Feng [16] including 200 patients showed no difference in mortality between hemorrhagic shock patients with LFR and RFR (RR = 0.85; 95% CI = 0.45-1.60; $P = 0.62$). The study of Dutton [17] reported that hypotensive resuscitation during active hemorrhage did not affect mortality. But some other studies showed the advantage of limited fluid resuscitation in reducing morbility of hemorrhagic patients. The study of Bickell [18] including 598 patients reported that delay of aggressive fluid resuscitation until operative intervention improved the outcome. The study of Morrison [19] including 90 patients reported that hypotensive resuscitation strategy reduced transfusion requirements and lowered the risk of early postoperative death and coagulopathy. Therefore, no reliable conclusion could be put forward as for the preference of LFR or RFR during active hemorrhage.

The purpose of this paper aims to evaluate the previous related studies, compare LFR and RFR in mortality and other clinical index through meta-analysis and provide strong evidences for the improvement of fluid resuscitation strategies in uncontrolled hemorrhagic shock.

Methods

Search strategy and data extraction

Electronic searches were performed using PubMed, Medline, Embase and CNKI until Jan 2015. The MeSHs which search headings were as follows: "limited fluid resuscitation", "hypotensive resuscitation", "delayed resuscitation". The terms above were used in different combinations with "hemorrhagic shock". In addition, we reviewed the reference lists of the original articles and reviews on the topic to identify other potentially eligible trials. No language restrictions were made.

Four reviewers working in 2 pairs screened the titles and abstracts to determine potential eligibility, and further indentified by any reviewer proceeded to the full-text eligibility review. The reviewers independently extracted the following parameters from each eligible study: 1) first author and year of publication; 2) number of patients (Total number and numbers in each group); 3) study origin; 4) JADAD scale and 5) hemorrhagic location. Pretested eligibility forms were used for full-text review, which was also done in duplicate. We contacted authors of primary publications for missing or unclear information. Disagreements between the two groups were resolved by a third adjudicator through discussion and consensus. The quality of all selected articles was scored in accordance with JADAD Scale.

Criteria for inclusion and exclusion

We included randomized or quasi-randomized (ie, using systematic methods, such as alternation, assignment based on date of birth, case record number, and date of presentation) controlled trials with or without blind. For inclusion in our meta-analysis, a study had to fulfill the following criteria: (1) The trauma patients in the study presented with a common clinical syndrome - hemorrhagic shock; (2) The study subjects were all human and clinical trials; (3) The study had particular descriptions to the method of fluid resuscitation; (4) The effective information could be extracted in the study; (5) The record of the clinical index (ie, blood rountine test, such as hemoglobin, hematocrit) should be more than 24 h after fluid resuscitation; (6) If two or more studies were reported by the same authors in the same institution, the study of higher quality was selected; (7) JADAD scale score ≥ 3.

The exclusion criteria for our meta-analysis were as follows: (1) The study in which patients were threatened by traumatic brain injury (TBI) was excluded because of substantial clinical literature supporting the absolute prevention of hypotension in TBI patients [20]; (2) only one treatment method was used and no contrastive study was performed; (3) Study on animal observation (i.e., rat, pig, rabbit); (4) JADAD scale score < 3.

Data analysis

Statistical analyses were performed using Review Manager Software (RevMan 5.2; Cochrane Collaboration, Oxford, UK) and quantitative bias analyses were undertaken by Stata 12.0 (Cochrane Collaboration, Oxford, UK). The continuous descriptive data of the LFR and RFR groups were extracted as mean ± standard deviation and reported as Mean difference (MD) and corresponding 95% CIs, while dichotomous data were extracted as case num-

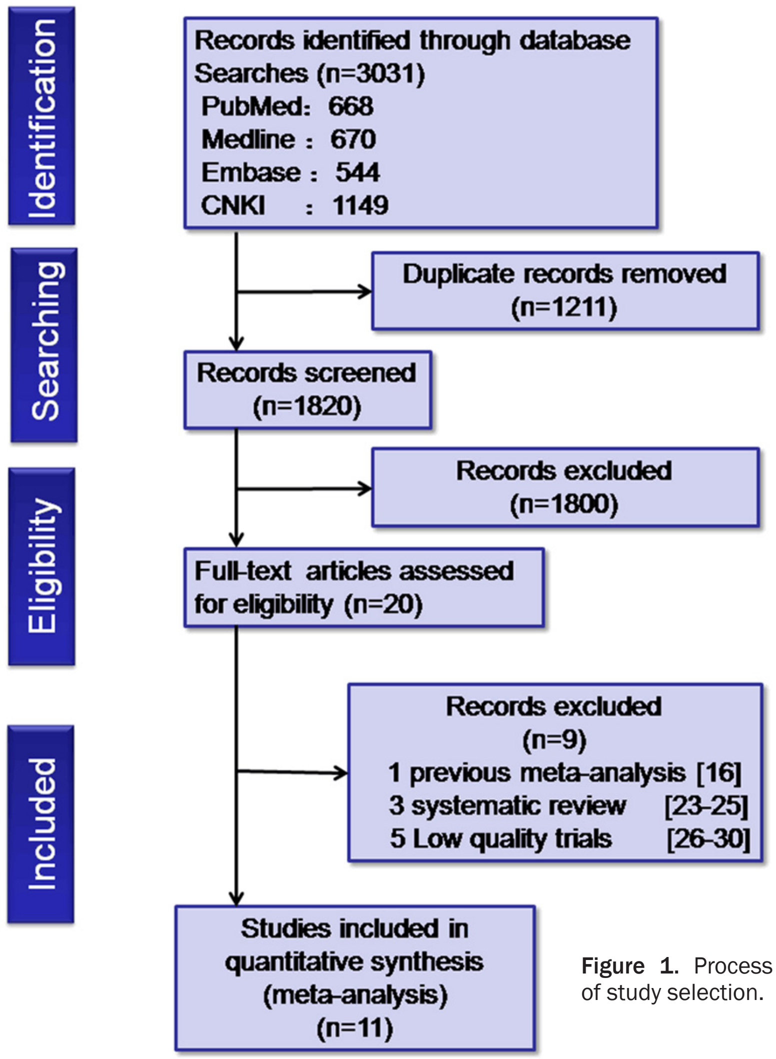


Figure 1. Process of study selection.

ber (*n*) and reported as risk ratio (RR) and corresponding 95% CIs. The Mantel-Haenszel Q-statistic was used to assess heterogeneity among studies, and the I^2 statistic was computed to examine the proportion of total variation in the study estimate due to heterogeneity [21, 22]. We considered $P > 0.10$ or $P \leq 0.10/I^2 \leq 50\%$ to indicate no significant heterogeneity between the trials and, in such cases, a fixed effect model was selected for analysis. Conversely, $P \leq 0.10/I^2 > 50\%$ was considered to indicate high heterogeneity, and a random effect model was used. In the integration results, $P \leq 0.05$ indicated statistical significance. Extensive efforts were made to remove all duplicated data and include all studies published to date. Publication bias in outcomes was assessed and treated using standard methodology. Funnel plots were used to visually inspect the relationship between sample size and treatment effects for the two groups.

Results

Search results

A total of 3031 titles were identified in a combined search of MEDLINE, PubMed, Embase and CNKI databases covering studies published before Feb 2015 (1211 after duplicates were removed). In total, 1800 articles were excluded after scanning the title/abstract because they were not relevant to the purpose of our meta-analysis, leaving 20 studies for full-text review (**Figure 1**). This total included a previous meta-analysis [16], 3 related systematic reviews [23-25] and 5 low quality clinical trials [26-30]. 11 eligible RCTs [17-19, 31-38] were left after excluding 9 studies mentioned above. The characteristics of the 11 included studies were listed in **Table 1**.

A total of 1482 subjects were included in the meta-analysis. 725 hemorrhagic shock patients who required emergent surgery selected limited fluid resuscitation (LFR) while 757 patients underwent regular fluid resuscitation (RFR) during active hemorrhagic shock. The mean arterial blood pressure (MAP) of patients in LFR group were all under 70 mmHg while MAP of hemorrhagic shock patients in RFR group were 80~90 mmHg. The baseline characteristics such as age and sex were similar between the two groups in all included studies ($P > 0.05$). The 11 included studies all used the definition of hemorrhagic shock consistent with international consensus. The blood gas analysis and blood routine examination were all tested after fluid intervention for 24 h. And the end of active bleeding was determined on the basis of one or more of the following criteria: visible control of hemorrhage in the operating room, stable

Table 1. Characteristics of the studies included in the meta-analysis

Study, Year (Reference)	Country	Patients (LFR/RFR)	Jadad scale			Total score	Hemorrhagic location
			R	B	D		
Bickell, 1994 [18]	America	289/309	2	2	1	5	Abdomen or thorax
Morrison, 2011 [19]	America	44/46	2	2	1	5	Abdomen or thorax
Tang, 2013 [36]	China	38/36	2	2	1	4	Acute upper gastrointestinal bleeding
Lu, 2015 [34]	China	27/24	1	2	1	4	Acute upper gastrointestinal bleeding
Dutton, 2002 [17]	America	55/55	1	2	1	4	Abdomen
He, 2012 [32]	China	30/27	1	2	0	3	Acute upper gastrointestinal bleeding
Li, 2012 [33]	China	63/63	1	1	1	3	Abdomen or thorax
Fan, 2011 [31]	China	43/42	1	1	1	3	Abdomen
Wei, 2008 [37]	China	56/62	1	1	1	3	Abdomen or thorax
Zheng, 2007 [38]	China	60/72	1	1	1	3	Abdomen or thorax
Lu, 2006 [35]	China	20/21	1	2	0	3	Abdomen

Abbreviation: LFR: limited fluid resuscitation; RFR: Regular fluid resuscitation; R: Randomisation; B: Blinding; D: Withdrawals and dropouts.

blood pressure not requiring fluid administration for support and diagnostic studies such as computed tomography scan or angiography showing no evidence of ongoing hemorrhage.

Meta-analysis

The clinical data were prospectively gathered through the 11 eligible studies [17-19, 31-38]. The index, which were extracted for meta-analysis, included mortality, the blood routine index (hemoglobin, Hb; Platelets, PLT; Hematocrit, Hct), blood coagulation function (Prothrombin Time, PT; activated partial thromboplastin time, APTT), blood gas analysis (base excess, BE; blood lactic acid, BLA) and the main postoperative complications, such as MODS (multiple organ dysfunction syndrome) and ARDS (Acute Respiratory Distress Syndrome).

Mortality

Nine studies [17-19, 31, 33, 34, 36-38] including 1,384 patients compared the mortality of hemorrhagic shock patients between limited fluid resuscitation (LFR) and regular fluid resuscitation (RFR). The heterogeneity test indicated that there was little heterogeneity between LFR and RFR groups ($\chi^2 = 12.35$; $P = 0.14$; $I^2 = 35\%$) and fixed model was used. In these trials, mortality for LFR group vs. RFR group was 131 of 675 (19.4%) vs. 208 of 709 (29.3%). The results indicated that limited fluid resuscitation may reduce the mortality in patients with hemorrhagic shock (RR = 0.67; 95% CI = 0.56-0.81; $P < 0.0001$) (**Figure 2**).

In order to investigate whether human species influence the mortality of hemorrhagic shock after LFR or RFR, we did subgroup analysis to 3 trials from America and 6 trials from China, respectively. The consequences of subgroup analysis were consistent with the total analysis. However, the difference of mortality between LFR and RFR groups in America descent was not significant as that in Asian descent (**Figure 2**).

Blood routine index (Hb, PLT and Hct)

Five trials [18, 32-35] investigated the hemoglobin (Hb) values after treated with LFR or RFR in hemorrhagic shock patients and showed a high heterogeneity across studies ($\chi^2 = 27.84$; $P < 0.0001$; $I^2 = 86\%$), which called for random model to correct the bias. The overall effect showed that Hb value in LFR group was higher than that in RFR group (MD = 13.04; 95% CI = 2.69-23.38; $P = 0.01$). (**Figure 3A**). Four trials [18, 31, 35, 38] including 856 patients compared the PLT values between LFR and RFR groups. The heterogeneity test showed a moderate degree of heterogeneity across studies ($\chi^2 = 8.05$; $P = 0.04$; $I^2 = 63\%$), which need to select random model for analysis. The overall effect suggested that PLT value in LFR group was higher than that in RFR group (MD = 23.16; 95% CI = 6.41-39.91; $P = 0.007$). (**Figure 3B**). As for the Hct values in hemorrhagic shock patients, we computed data from five trials [31, 33, 35-37] (n = 359). There was little heterogeneity between LFR and RFR groups ($\chi^2 = 5.25$;

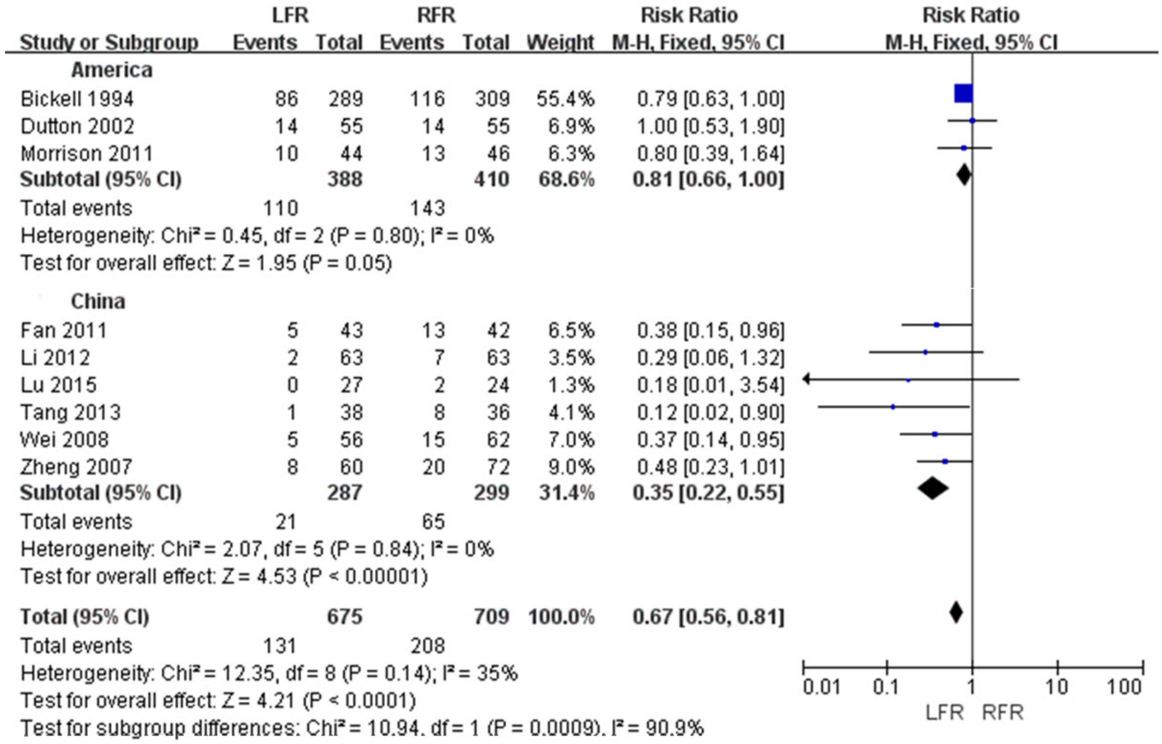


Figure 2. Forest plot illustrating the mortality between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; M-H, Mantel-Haenszel.

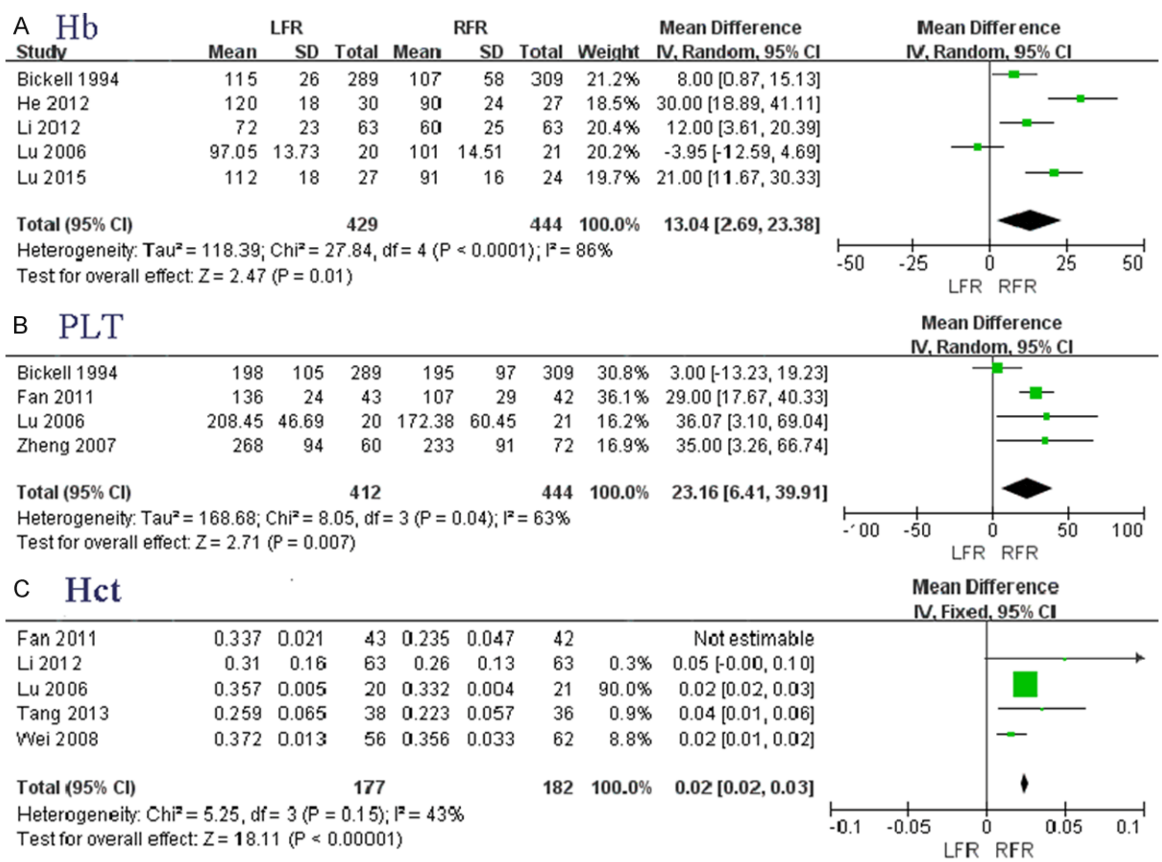


Figure 3. Forest plot illustrating the blood routine index between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; MD, Mean difference; A. Hb, hemoglobin; B. PLT, Platelets; C. Hct, Hematocrit.

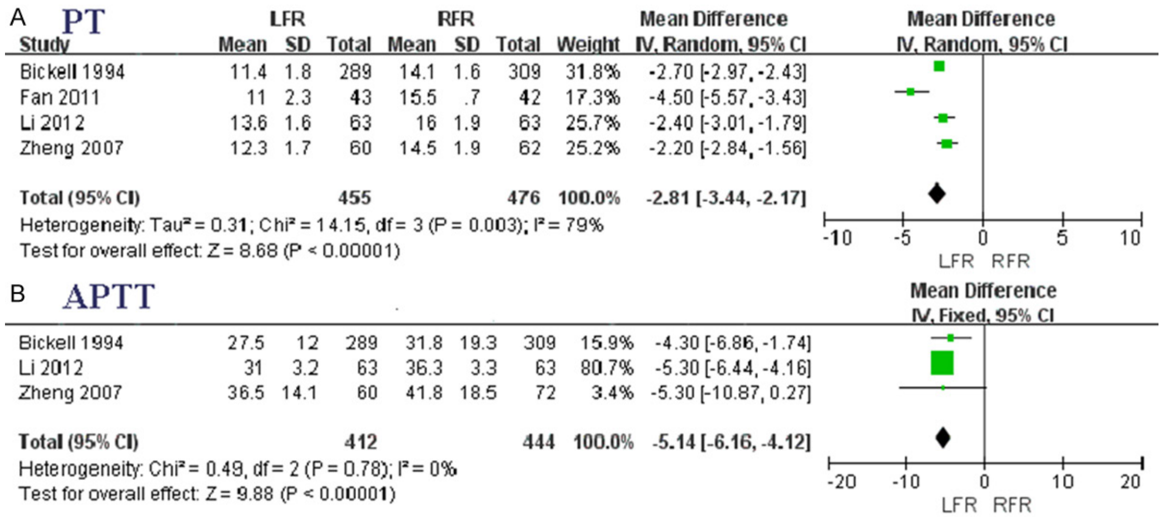


Figure 4. Forest plot illustrating the blood coagulation function between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; MD, Mean difference; A. PT, Prothrombin Time; B. APTT, activated partial thromboplastin time.

P = 0.15; I^2 = 43%) and fixed model was used. The overall effect suggested that Hct value in LFR group was higher than that in RFR group (MD = 0.02; 95% CI = 0.02-0.03; P < 0.00001). (**Figure 3C**).

Blood coagulation function (PT, APTT)

Four trials [18, 31, 33, 38] including 931 patients compared Prothrombin Time (PT) while three trials [18, 33, 38] including 856 patients compared activated partial thromboplastin time (APTT) between LFR and RFR groups. The heterogeneity test showed high heterogeneity in PT comparison (χ^2 = 14.15; P = 0.003; I^2 = 79%) but low heterogeneity in APTT (χ^2 = 0.49; P = 0.78; I^2 = 0%). The overall effect suggested that RFR group prolong PT and APTT in hemorrhagic shock compared with that in LFR group (PT: MD = -2.81; 95% CI = -3.44--2.17; P < 0.00001 and APTT: MD = -5.14; 95% CI = -6.16--4.12; P < 0.00001) (**Figure 4A** and **4B**).

Blood gas analysis (BE, BLA)

Analysis of four trials [32, 33, 36, 37] (n = 389) investigating the base excess (BE) value after treated with LFR or RFR in hemorrhagic shock showed substantial heterogeneity across studies (χ^2 = 15.37; P = 0.002; I^2 = 80%). The analysis showed that BE values in the two groups were both inferior to the normal value, but the BE value in the RFR group decreased more seriously than that in LFR group (MD = 2.48; 95% CI = 1.11-3.85; P = 0.0004) (**Figure 5A**). Five trials [31-33, 35, 36] (n = 383) investigating the blood lactic acid (BLA) value in LFR and RFR groups showed no heterogeneity across studies (χ^2 = 0.52; P = 0.97; I^2 = 0%). The analysis showed that the blood lactic value in RFR group was much higher than normal (MD = -0.65; 95% CI = -0.85--0.44; P < 0.00001) (**Figure 5B**).

Main postoperative complications (MODS, ARDS)

The main postoperative complications of fluid resuscitation include multiple organ dysfunction syndromes (MODS), Acute Respiratory Distress Syndrome (ARDS), etc. Four trials [31, 33, 34, 36] including 336 patients compared the occurrence of MODS after resuscitation. The heterogeneity test showed no heterogeneity across studies (χ^2 = 1.98; P = 0.58; I^2 = 0%). MODS complication for LFR vs. RFR group was 13 of 171 (7.6%) vs. 34 of 165 (20.6%). The results indicated that limited fluid resuscitation

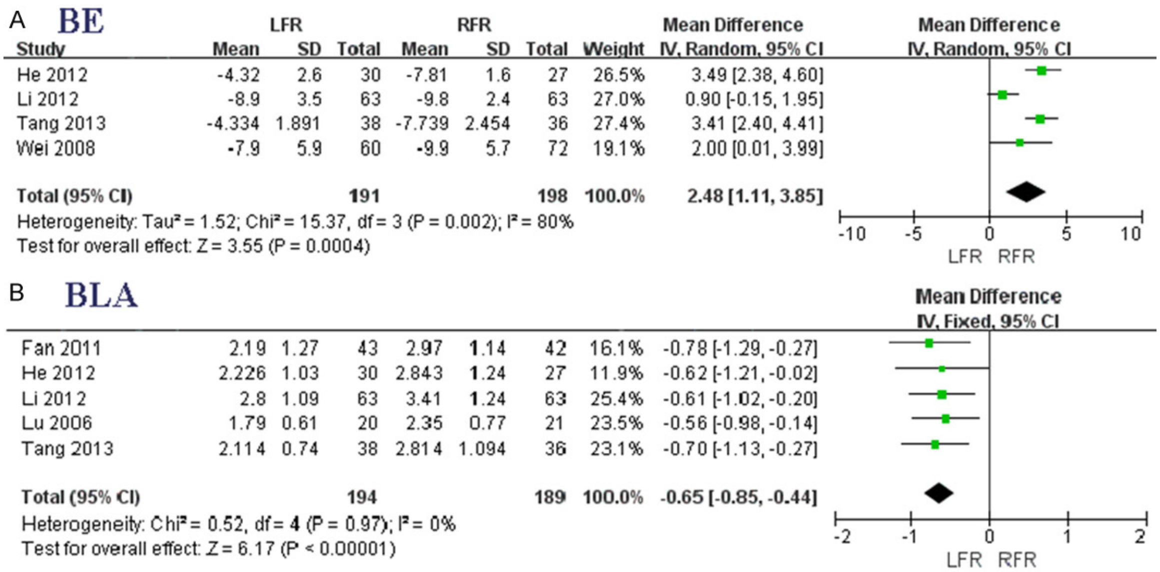


Figure 5. Forest plot illustrating BE and blood lactic acid between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; MD, Mean difference; A. BE, base excess; B. BLA, blood lactic acid.

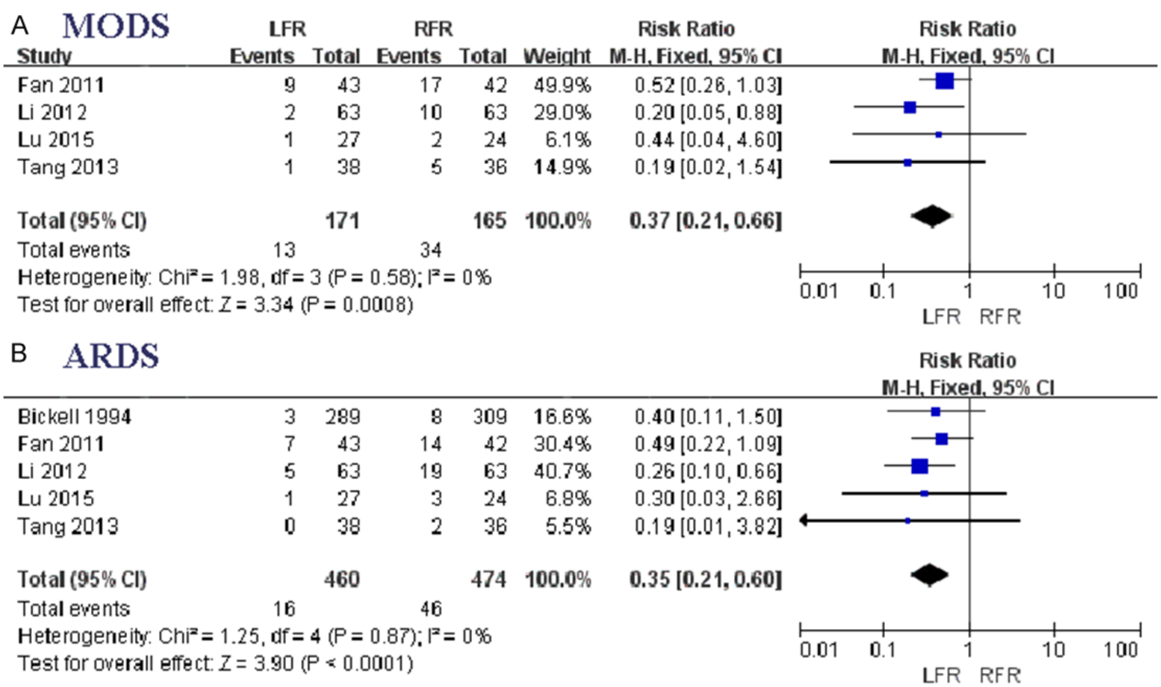


Figure 6. Forest plot illustrating main postoperative complications between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; M-H, Mantel-Haenszel; A. MODS, multiple organ dysfunction syndrome; B. ARDS, Acute Respiratory Distress Syndrome.

may reduce the occurrence of MODS in patients with hemorrhagic shock (RR = 0.37; 95% CI = 0.21-0.66; P = 0.0008) (**Figure 6A**). The similar result also showed in the result of ARDS. Five trials [18, 31, 33, 34, 36] including 934 patients compared the occurrence of ARDS complication between LFR and RFR groups. The heterogeneity test show no heterogeneity (χ^2 = 1.25; P = 0.87; I^2 = 0%) and the complication ARDS was also more frequent occurrence in regular fluid resuscitation (RR = 0.35; 95% CI = 0.21-0.60; $P < 0.0001$) (**Figure 6B**).

Sensitivity analysis and publication bias

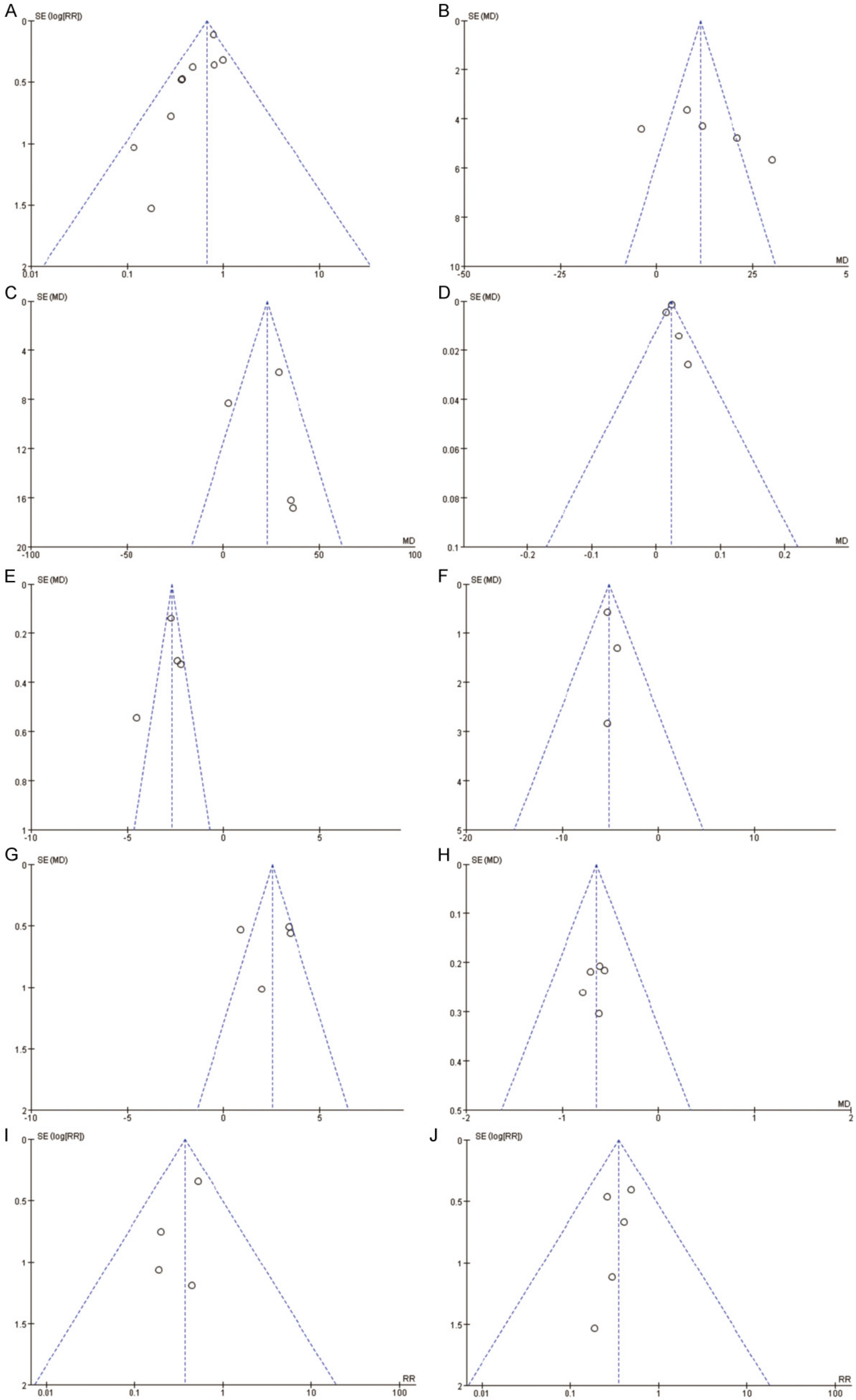
Funnel plots obtained from *RevMan 5.2* may illustrate the publication bias of each analysis visually. The results showed that except for the funnel plot of Bickell et al. [18], the other nine plots were basically inverted and funnel-shaped with bilateral symmetry, which indicated that low publication bias across studies (**Figure 7**). In order to test the bias through quantitative analysis, Egger's test and Begg's test were undertaken to binary variables (Mortality, MODS and ARDS) through *Stata 12.0*. The results were consistent with our observation to funnel plots (Mortality--Begg's test, u = 0.42; Egger's test, $P = 0.00$; MODS--Begg's test, u = 0.00; Egger's test, $P = 0.389$; ARDS--Begg's test, u = -0.49; Egger's test, $P = 0.818$), which further proved the confidence level of our meta-analysis. As for the high bias of mortality, we removed the possibly high impact study of Bickell [18] by circulation eliminating method and the updated overall effect was also consistent with the previous result (RR = 0.52; 95% CI = 0.37-0.71; $P < 0.0001$).

Discussions

With more and more clinical trials and animal researches on fluid resuscitation strategies, regular fluid resuscitation faced the challenge and limited fluid resuscitation has been put forward.

In mortality, both total meta-analysis and subgroup analysis indicated that limited fluid resuscitation reduce the mortality, which was consistent with the fact that limited fluid resuscitation during active hemorrhagic shock improve survival in a large number of animal trials. The moderate difference between mortality of LFR and RFR in America studies could be explained that there was little gap between the goal controlled pressure in LFR group and RFR group. The European trauma guidelines recommend SBP not higher than 80-100 mmHg in bleeding trauma patients [39]. Furthermore, our previous studies also indicated that the mean artery pressure (MAP) should be no more than 60 mmHg in limited fluid resuscitation [40, 41]. However, the blood pressure in study of Bickell et al. [18] was that 79 mmHg (systolic blood pressure, SBP) in RFR group, which should moderately increase at least higher than 80 mmHg (SBP). Besides, just as Dutton mentioned [17], when fluids are administered in small, titrated amounts in response to decreases in blood pressure, the blood may be oscillation. There is also a possibility that the results of some studies were skewed by a Hawthorne effect. These reasons may all cause the bias of the results.

The results of this meta-analysis in blood routine index between LFR and RFR group showed that limited fluid resuscitation during active hemorrhagic shock may prevent Hb, PLT and Hct values from further decreasing, which may improve tissue oxygen delivery. In regular fluid resuscitation, the rapid recovery of blood pressure may relieve protective vasospasm, and then the dilated artery increased the hemorrhage. What's worse, compared with limited fluid resuscitation, regular fluid resuscitation prolonged PT and APTT of patients with hemorrhagic shock. Besides, in all included studies, the transfusion volume in RFR group was much more than that in LFR group. The large quantity of fluid may reduce the blood viscosity and dilute clotting factors. The excessive blood dilution in regular fluid resuscitation may also increase hemorrhage, which significantly weaken the body's self-adjustment ability and decrease the defense response ability. This may also be one of the reasons why regular fluid resuscitation have more mortality than limited fluid resuscitation during active hemorrhagic shock. Base excess (BE) is an important index for tissue acidosis and can accurately reflect the effect of fluid resuscitation. The series of hemorrhagic shock cases of Randolph et al. [42] indicated that low base excess may cause high oxygen consumption and low oxygen utiliztion. The serious decrease of base excess in RFR group indicated that regular flood resuscitation easily induces the occurrence of metabolic acidosis while limited flood resuscitation may reduce the occurrence of acidosis. Lactic acid is one of the reliable indicators to inadequate tissue oxygen and its value is closely related to oxygen debt, the degree of low perfusion as well as the severity of shock [43]. The study of Sobhian et al. [44] showed that blood lactic acid level in hemorrhagic shock had a strong hint to the sensitivity of blood volume decrease. Compared with regular fluid resusci-


A
SE (log[RR])
B
SE (MD)
MD
C
SE (MD)
MD
D
SE (MD)
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SE (MD)
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SE (MD)
G
SE (MD)
H
SE (MD)
MD
I
SE (log[RR])
RR
J
SE (log[RR])
RR

Figure 7. Funnel plot for each comparison. A. Mortality; B. Hb, hemoglobin; C. PLT, Platelets; D. Hct, Hematocrit; E. PT, Prothrombin Time; F. APTT, activated partial thromboplastin time; G. BE, base excess; H. BLA, blood lactic acid; I. MODS, multiple organ dysfunction syndrome; J. ARDS, Acute Respiratory Distress Syndrome.RR, risk ratio; MD, mean difference.

tation, the consequence of meta-analysis indicated that limited fluid resuscitation may improve the blood perfusion and oxygen delivery of tissues, which is consistent with the result of Lu et al. [45] in animal research. The reason can be explained that LFR improve aerobic metabolism of body and weaken anaerobic glycolysis pathway, which is convenience for the removal of lactic acid metabolites in vivo.

Furthermore, the occurrence of postoperative complications, such as MODS and ARDS, is a big problem to fluid resuscitation and the survival of hemorrhagic shock patients. According to the result of our meta-analysis, the incidence rate of complications in limited fluid resuscitation is less than that in regular fluid resuscitation, which may contribute to the high survival rate in LFR. The study of Li et al. [46] showed that limited fluid resuscitation may reduce the production of inflammation factors, oxygen radical, decrease the level of ET and vasoactive peptides, which contribute to the balance of proinflammatory and anti-inflammatory medium. Besides, LRF also enhances the anti-lipid peroxidation and reduces the damage of ischemia reperfusion injury.

These preliminary results provided convincing evidences that support the continued investigation and use of hypotensive resuscitation in the trauma setting. But there are also some limitations and points to improve: (1) There have been few high quality RCTs comparing LFR and RFR in hemorrhagic shock up till now and only two trials [18, 19] which were scored 5 points through JADAD Scale were included in our meta-analysis. Therefore, more and larger, well-designed RCTs are eager for further investigation. (2) All included studies were divided into LFR and RFR groups, but the blood pressure was only controlled in a certain range for each group. More trails with detailed or fixed values of blood pressure are needed to further increase credibility of our analysis. (3) Most included studies described the random allocation methods but the methods were few random hidden properly. So the subsequent trials should make independent units undertake the random allocation. Further studies in this area should focus on specific patient populations most likely to benefit from deliberate hypotensive resuscitation, and on the development of better markers for assessing tissue perfusion and ischemic risk.

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Disclosure of conflict of interest

None.

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