Comparison of Permissive Hypotension vs. Conventional Resuscitation Strategies in Adult Trauma Patients with Hemorrhagic Shock: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials.

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Abstract

Background

There is still an ongoing battle against the Permissive Hypotension (PH) through Conventional Resuscitation Strategies (CR). Active fluid resuscitation in patients with traumatic shock can bring many problems, as it is known that standard high-volume resuscitation can exacerbate the lethal triad of acidemia, hypothermia, and coagulopathy. As a part of damage control resuscitation strategy, it can reduce mortality and shorten hospital stay, compared with the use of standard liquids. Moreover, its application is gradually receiving wider attention (1) . This review evaluated the effectiveness and safety of permissive hypotension resuscitation in adult patients with traumatic hemorrhagic shock.

Methods

The systematic review and meta-analysis were conducted according to PRISMA guidelines. We searched PubMed, EMBASE and Cochrane databases for randomized controlled trials (RCTs) from the beginning to March 2021 to compare the therapeutic effects of controlled fluid resuscitation and conventional fluid resuscitation on patients with traumatic hemorrhagic shock. Two reviewers independently conducted screening, data extraction and bias assessment. Data analysis was performed using Cochrane Collaboration Software Revman 5.2. The primary outcome was 30-day or in-hospital mortality. Secondary outcomes included blood routine index, coagulation function, resuscitation fluid use, complications, and length of hospital stay. Pooling was performed with a random-effects model.

Results

8 randomized controlled trials were screened out of 898 studies and 1593 patients were evaluated. The target blood pressure of the intervention group ranged from 50-90 mmHg in systolic pressure or mean arterial pressure ≥ 50 mmHg, while that of the control group was 65-110 mmHg systolic pressure or mean arterial pressure ≥ 60 mmHg. Only patients with penetrating injuries were evaluated in two studies, while the remaining six included blunt injuries. A statistically significant reduction in mortality was observed in the intervention group (RR = 0.70; 95%CI= 0.58-0.84; $P < 0.05$). Small heterogeneity was observed in the included articles ($\chi 2 = 8.9$; $P = 0.18$; $I^2 = 33\%$). The loss of platelet (PLT), hemoglobin (Hb) and body fluid was properly protected, the amount of resuscitation fluid was reduced, and the incidence of some adverse events was effectively reduced. There was no significant difference in coagulation time and hospital stay between the two groups.

Conclusions

This meta-analysis reveals the survival benefits of hypotension resuscitation in patients with traumatic hemorrhagic shock. The significant advantage is to promote the recovery of patients' physical function and reduce the incidence of treatment-related complications such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and multiple organ dysfunction syndrome (MODS), which reduces the mortality. Convincing evidences are provided based on these results, but larger, multicenter, randomized trials are needed to confirm the findings.

Introduction

The concept of permissive hypotension was first proposed by Cannon and his colleagues in the report in 1918(2) . "Injection of a fluid that will increase blood pressure has angers in itself." He pointed out that before achieving definite hemostasis, the application of crystalloid fluid should be limited to keep blood pressure below the normal threshold. Later, Beecher put forward a similar idea in recalling the experience of rescuing the wounded solider in World War II, "elevation of his systemic blood pressure to about 85 mm Hg is all that is, necessary. And when promote internal bleeding is occurring, it is wasteful of time and blood to attempt to get the patient's blood pressure up to normal." (3).

At present, balanced resuscitation has served as an important principle of resuscitation strategy for trauma patients. A growing number of clinicians began to realize that active lens resuscitation can lead to serious clinical complications and hazards, and large amount of fluid resuscitation should be avoided(4-6) . In the early care of trauma patients, the results will be significantly improved if permissive hypotension is used in the process of resuscitation treatment (7) . Permissive hypotension below normal mean arterial pressure and resuscitation goals are beneficial for survival, which has been confirmed in a number of animal studies (8-11) . In 1994, Bickell and his colleagues conducted a landmark study to evaluate and confirm their hypothesis that if fluid is limited to the final hemostasis, hypotension patients with trunk penetrating injury will prove to have survival benefits, which is the first time in history to demonstrate the potential value of delayed resuscitation in humans (12, 13) . Since then, randomized controlled trials on hypotension resuscitation have been carried out, which needs to be updated and analyzed further.

Therefore, the purpose of this review is to identify randomized controlled trials comparing permissive hypotension with conventional resuscitation strategies in adult trauma patients with hemorrhagic injury. The primary outcome was in-hospital or 30-day mortality. Secondary outcomes included blood routine, coagulation function, resuscitation fluid use, complications, and length of hospital stay.

Methods

This systematic review and meta-analysis adhere to the reporting guidelines of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement(14).

Study Eligibility Criteria:

Population: We included studies evaluating adult patients with penetrating or blunt trauma and suspected bleeding, and excluded studies on patients with traumatic brain injury, studies on pregnant or underage patients, studies with insufficient mortality data, and studies without ethical approval.

Intervention: Permissive hypotension is considered in the intervention group. Compared with the control group, the intervention group was fluid limited. Permissive hypotension is defined as limited fluid resuscitation to maintain adequate organ perfusion. Systolic blood pressure is about 50-90 mmHg or mean arterial pressure is about 50 mmHg. There are no restrictions on specific blood pressure targets, type or amount of fluid administration.

Control: Conventional resuscitation strategy is considered in the control group, which was defined as free fluid resuscitation. Systolic blood pressure was 65-110 mmHg or mean arterial pressure ≥ 60 mmHg (normal blood pressure). There are no restrictions on specific blood pressure targets, type or amount of fluid administration.

Outcome: The primary outcome was in-hospital or 30-day mortality. Secondary outcomes included blood routine, coagulation function, resuscitation fluid use, complications, and length of hospital stay.

Study Design: Eligible randomized controlled trials and quasi randomized trials will be included in the study.

Search Strategy

We searched PubMed, EMBASE and Cochrane databases for articles published before February 25, 2021. The strategy was designed under the guidance of adjudicating senior authors Shuguang Zhu and Zhuangrong Huang. In addition, the additional search was carried out for relevant literature and review articles. And we searched references of identified studies closely related to research topics. The medical subject headings (MeSHs) used in our searches included “permissive hypotension”�“Wounds and Injuries” and “Shock, Hemorrhagic”, without language restriction.

Data Collection

Two authors (Yang Zhang and Yaping Ding) independently examined each article found in the search process, scanned the full text of relevant articles, applied inclusion and exclusion criteria, and extracted and recorded data. Differences related to any aspect of the data extraction process are resolved through discussion with a third reviewer, and the final decision is made by consensus.

Quality Assessment

The quality of included studies was evaluated using the Cochrane Risk of Bias Tool for randomized controlled studies (15).Disagreements were settled by a third-party reviewer (Liang). Quality metrics assessed include sequence generation, allocation concealment, adequacy of blinding, completeness of outcome data and outcome reporting.

Data Synthesis

All statistical analyses were performed using Review Manager 5.2 software from the Cochrane Collaboration (London, United Kingdom). We extracted the proportions and 95% confidence intervals from each study and pooled them using the random effects model. Statistical heterogeneity and inconsistency were measured by using the Cochran Q test and I^2, respectively(16). Odds ratios (OR) with 95% confidence intervals (CI) were calculated as summary statistics. The pooled OR was calculated with the Mantel-Haenszel method. Weighted mean differences and 95% CIs were computed for continuous variables, again using a fixed-effect method in cases of low statistical inconsistency ($I^2 \leq 50\%$) and using a random-effect method in cases of moderate or high statistical inconsistency ($I^2 > 50\%$) (17). Results were considered statistically significant at $P< 0.05$.

Results

Search results and study characteristics

We selected 898 articles from the search and finally included 8 randomized controlled trials into the analysis (Fig. 1)(12, 18-24) . We didn't come across any quasi-randomized trials. The characteristics of the included studies are described in Table 1. Five studies were conducted in North American civilians who visited major trauma centers, while the other three were conducted in China. Two studies only evaluated patients with penetrating injuries, while the remaining six included penetrating injuries combined with blunt injuries. Two studies only studied preoperative resuscitation, two studies only studied intraoperative resuscitation, and three trials studied patients in two periods. In addition, one trial did not mention surgery related resuscitation strategies. All but one study excluded patients with suspected traumatic brain injury.

Assessment of Reporting Bias

The methodological quality of RCTs was assessed by the Cochrane risk-of-bias tool, which consists of six factors: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting (Fig. 2).

Primary Outcome

The main outcome data of mortality are shown in Table 2. Two studies showed 30-day mortality (18, 21) , while five studies showed in-hospital mortality (12, 19, 20, 22, 23) . One study did not describe mortality(24). The heterogeneity test revealed that there was little heterogeneity between the two groups ($\chi^2 = 8.9$; $P = 0.18$; $I^2 = 33\%$). In these trials, the mortality rates in the PH and CR groups accounted for 133 (18.2%) of 731 and 197 (26.4%) of 745, respectively.

The results showed that limited fluid resuscitation could reduce the mortality of patients with hemorrhagic shock (RR = 0.70; 95% CI = 0.58-0.84; P < 0.05) (Fig. 3).

Secondary Outcomes

Blood routine index (PLT and Hb)

As shown in Figure 4, three trials (12, 21, 23) compared the platelet values of PH group or CR group. According to the heterogeneity test, a high degree of heterogeneity was exhibited between studies (χ2 =131.35; P < 0.00001; I^2 = 98%). Thus sensitivity analysis was conducted to eliminate the heterogeneity. After removing Bickell's data, the two experiments included data of 240 patients (χ2 =0.13; P=0.72; I^2 = 0%). It is indicated that the platelet value in pH group was higher than that in CR group (MD = 9.98; 95%CI=8.03-11.93; P < 0.00001). Three trials (12, 20, 23) , involving 922 patients, investigated the hemoglobin values of patients with hemorrhagic shock after treatment in PH group or CR group, revealing high heterogeneity between studies (χ2 =12.44; P=0.002; I^2 = 84%). The overall effect showed that the hemoglobin value of PH group was higher than that of CR group (MD = 16.74; 95%CI=10.81-22.68; P < 0.00001).

Blood coagulation function (PT, APTT)

As shown in Figure 5, four trials(12, 20, 21, 23) , including 1001 patients, compared the changes of prothrombin time (PT), while three trials (12, 21, 23) , including 842 patients, compared the changes of activated partial thromboplastin time (APTT) between PH group and CR group. Heterogeneity test showed that the comparison results of PT (χ2 =201.75; P < 0.00001; I^2 = 99%) and APTT (χ2 =34.80; P < 0.00001; I^2 = 94%) were highly heterogeneous. The overall effect showed that there was no significant difference in PT and APTT time between PH group and CR group after hemorrhagic shock resuscitation (MD = -2.00; 95%CI=-4.83 to 0.84; P =0.17).

Fluid balance and transfusion requirements

As shown in Figure 6, the overall fluid resuscitation and blood transfusion of PH group and CR group were analyzed by subgroup. Heterogeneity test showed that packed red blood cell (PRBC), prehospital crystal, emergency department crystal volume and total inputs were highly heterogeneous, while intra operative crystal (χ2 =0.07; P=0.79; I^2 = 0%) and estimated blood loss (χ2 =0.51; P=0.48; I^2 = 0%) had no heterogeneity. It is indicated by the overall effect that the total amount of fluid resuscitation in PH group was lower than that in CR group (MD = -564.21; 95%CI=-833.66 to -244.77; P < 0.001), and the estimated blood loss in PH group was less than that in CR group (MD = -721.53; 95%CI=-1326.19 to -116.87; P < 0.05). There was no significant difference in the amount of blood transfusion between the two groups (MD = -144.13; 95%CI=-820.53 to 532.27; P =0.68).

Complications

The included studies described a series of complications, including AKI, anemia, infection, thrombocytopenia, ARDS, differentiated intravascular coagulation (DIC), MODS, etc. As shown in Fig.7, three trials (12, 18, 22) compared the incidence of AKI between PH group and CR group. Heterogeneity test showed high heterogeneity (χ2 =17.08; P =0.0002; I^2 = 88%) among the studies， which was attempted to be eliminated through sensitivity analysis. After removing the data of Schreiber, two experiments (12, 18) compared the data of 41 patients (χ2 =0.02; P =0.90; I^2 = 0%). The incidence of AKI accounted for 13/364 (3.6%) in PH group and 28/375 (37.5%) in CR group. The results showed that limited fluid resuscitation could reduce the incidence of AKI in patients with hemorrhagic shock (RR = 0.43; 95%CI= 0.24-0.79; P < 0.05).

The comparison between ARDS and MODS showed similar results. Four trials (12, 19, 20, 24) involving 1034 patients compared the incidence of ARDS between PH group and CR group. No heterogeneity was shown in the heterogeneity test (χ2 =0.12; P =0.99; I^2 = 0%). The incidence of ARDS in PH group and CR group was 24/507 (4.7%) and 58/527 (11.0%) respectively, and the incidence of ARDS was higher (RR = 0.42; 95%CI= 0.27-0.65; P < 0.05) during conventional fluid resuscitation. Four trials compared the incidence of MODS between PH group and CR group. Heterogeneity test showed that there was high heterogeneity between the studies (χ2 =6.48; P =0.09; I^2 = 54%). After removing Bickell's data, three trials (19, 20, 23) compared the data of 434 patients (χ 2 = 0.22; P = 0.89; I^2 = 0%). The incidence of MODS was 17/217 (7.8%) in PH group and 44/217 (20.3%) in CR group. The results showed that the risk of MODS during conventional fluid resuscitation was also higher than that during limited fluid resuscitation (RR = 0.40; 95%CI= 0.24-0.66; P < 0.05).

Days of ICU or hospital

As shown in Figure 8, two trials (12, 22) involving 651 patients compared days of hospital showed less heterogeneity (χ2 =1.32; P =0.25; I^2 = 24%). With 651 patients included, two trials (12, 22) compared days of intensive care unit (ICU). No heterogeneity was exhibited in the test (χ2 =0.66; P =0.42; I^2 = 0%). Based on the overall effect, it is shown that there was no significant difference in hospital stay and ICU treatment time between pH group and CR group during hemorrhagic shock resuscitation (MD = -0.65; 95%CI=-2.14 to 0.84; P =0.39).

Discussion

Hemorrhagic shock poses life-threatening risks for trauma patients. In the history of trauma resuscitation treatment, crystal always serves as the standard of fluid resuscitation. The traditional shock resuscitation method, that is, early active fluid resuscitation, aims to quickly restore effective blood volume and ensure effective perfusion of organs and tissues. However, the infusion of large cold liquid will lead to dilution coagulopathy (loss of coagulation factor in blood or replacement of dilution by fluid without coagulation factor) and hypothermic coagulopathy (hypothermia leads to inhibition of enzyme activity related to platelet and coagulation factor function). At this time, increasing blood flow, perfusion and blood viscosity may contribute to the rupture of blood vessel wall thrombosis, which leads to hypothermia, acidemia and coagulopathy. It will eventually aggravate bleeding and further endangers life. Based on

this theory, reflections have been given to the significance of limited rehydration. Nowadays, the modern management of these patients witnessed a shift from restoring perfusion to maintaining hemostatic capacity. Restrictive fluid resuscitation stands as another option for resuscitation treatment, that is, keeping blood pressure low enough to avoid blood loss and rupture of blood clot, and minimizing the sequelae of hemorrhagic shock, which always maintains the perfusion of final organs (25-27).

Determined by hospitalization or 30-day mortality, this meta-analysis demonstrates that tolerable hypotension brings greater benefits for survival than conventional resuscitation. This conclusion is consistent with the fact that limited fluid resuscitation can improve the survival rate of patients with active hemorrhagic shock in a large number of animal experiments. These studies consistently showed that the blood loss decreased and survival time under blood loss control prolonged in animals resuscitated to normal or near normal MAP or cardiac index (8, 10, 28) . However, in terms of human beings, accurate data are deficient to guide the best mean arterial pressure management during the period of permissive hypotension. At present, the practices derived from this concept are more reflected in the operation. The major purpose is to reduce the bleeding in the operation field, create a good vision and reduce the loss of body fluid. In spite of the reduction of blood loss and controlled hypotension beneficial in some cases, it is generally recommended that systolic blood pressure be 80-90 mmHg or MAP be about 50 mmHg (29-31) for patients without contraindications to antihypertensive therapy. In this study, the blood pressure target of intervention group ranged from systolic blood pressure 50-90 mmHg or mean arterial pressure ≥ 50 mmHg.

The summary of the secondary results shows that the permissive hypotension resuscitation strategy is more effective in preventing the further decline of Hb and PLT indexes, thus improving the tissue oxygen delivery. It also boasts advantages in the balancing fluid resuscitation and reducing the amount of fluid, and appropriately preventing the body fluid loss. Studies showed that before effective control of active bleeding, a large number of fluid resuscitation can be observed that mitochondrial function is seriously damaged, and tissue oxygen supply is reduced, leading to acidosis (11) . The analysis results suggest that the decline of Hb and PLT and the degree of fluid loss are less affected under the permissive hypotension strategy, which can improve the perfusion and oxygen supply of organs and tissues during shock. It is found that permissive hypotension reduced the total amount of resuscitation fluid and is of potential significance with respect to resource utilization. At the same time, it comes to our notice that there was no significant difference in the changes of coagulation indexes and the probability of coagulation related problems between the two groups. Previous studies found that active fluid infusion is associated with dilutive coagulation (32) , thus theoretically fluid should also be minimized to resolve these concerns.

The complication occurrence during resuscitation of adult traumatic hemorrhagic shock is also an important factor affecting the patient survival. According to the results of meta-analysis, permissive antihypertensive strategy can reduce the incidence of complications, including AKI, ARDS and MODS, which may bring about higher survival rate of pH group than CR group. Common resuscitation fluids, such as large amounts of normal saline and lactate Ringer's solution, were revealed to cause various forms of acidosis. Saline can lead to hyperpigmentation metabolic acidosis, which generated decreased cardiac contractility, lowered down renal perfusion and decreased ionic response. Aggressive fluid resuscitation is associated with AKI (33-35) . In contrast, it is in agreement with the research results of cotton et al that hypovolemic fluid resuscitation can effectively eliminate inflammatory factors, improve immune function, maintain the stability of blood components, and reduce the incidence of ARDS and MODS (36-40) . We did not find any consistent difference in the incidence of complications including anemia, infection, thrombocytopenia and DIC between the two groups.

Traumatic brain injury (TBI) is common in trauma population, accounting for about half of all trauma deaths (41) . A large number of literatures pointed out that hypotension resuscitation is controversial in patients with suspected TBI. The most fatal problem of permissive hypotension is that the decrease of cerebral perfusion and oxygenation will aggravate the secondary brain injury and increase the mortality. In addition to its advantages, the active fluid resuscitation has potential harms as well, particularly for cerebral perfusion. Higher crystalloid infusion to maintain blood pressure results in increased fluid extravasation, microvascular damage, brain edema, and increased intracranial pressure, thereby offsetting any benefit from increased arterial blood pressure (27, 42).For the patients with hemorrhagic shock complicated with craniocerebral injury, we should focus on whether there is a threshold to maintain proper cerebral perfusion and give full play to the advantages of hypotension resuscitation. A retrospective study of more than 15000 patients with moderate and severe traumatic brain injury showed that the hypotension threshold of traumatic brain injury should be defined as SBP < 110 mmHg(43).

Strengths and Limitations

Only randomized studies were included in this review, which represents the highest quality of available evidence. By collecting the latest evidence and combining with the previous meta-analysis of this study, this review provides a strong theoretical basis for the survival benefits of hypotension resuscitation strategy(13, 44-46).However, we have to consider some limitations in the comprehensive analysis of these review results. Firstly, the quality of the included randomized trials was uneven due to the lack of systematic bias associated with blinding. Secondly, in addition to Bickell's articles, the scale of included studies is generally small, and there are some heterogeneities in research methods. Such results tend to report a larger range of effects, thus it is urgent to carry out large-scale, multicenter, randomized controlled trials to confirm the conclusions. Most of the studies focused on penetrating injury combined with blunt injury. Whether the conclusions drawn from this meta-analysis are applicable to trauma patients caused by other injury mechanisms is still questionable. In addition, in terms of the arterial pressure, with four studies related to arterial pressure and other studies related to systolic blood pressure, a unified data reference was not provided for the evaluation of allowable hypotension threshold. It is noteworthy that this study failed to collect enough data to analyze the duration of permissive hypotension in order to avoid the occurrence of adverse events. The specific implementation plan of permissive hypotension resuscitation needs to be further explored.

Conclusion

Based on a comprehensive analysis of eight randomized controlled trials, this systematic review compares the overall survival benefits of permissive hypotension resuscitation and conventional resuscitation strategies for adult patients with traumatic hemorrhagic shock. The current research results show

that permissive hypotension resuscitation strategy serves as a better option, as it can reduce the mortality of shock patients, promote the recovery of physical function and reduce the incidence of adverse events, such as AKI, ARDS and MODS. However, there are complex questions to be answered, such as the role of lens in hemostasis and resuscitation, coagulation disorders and treatment caused by trauma, duration of permissible hypotension and specific implementation plan. All of those need further high-quality and dynamic experiments to clarify.

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PH: Permissive Hypotension; CR: Conventional Resuscitation Strategies; RCTs: randomized controlled trials; PLT: Platelet; Hb: Hemoglobin; ARDS: Acute Respiratory Distress Syndrome; AKI: Acute Kidney Injury; MODS: Multiple Organ Dysfunction Syndrome; OR: Odds Ratios; CI: Confidence Intervals; PRBC: Packed Red Blood Cell; DIC: Differentiated Intravascular Coagulation.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yang Zhang and Yaping Ding reviewed, extracted and recorded data. Liang made consensus in final decision on selected literatures. Dongbin Zheng, Junhui Zhang and Xusheng Huang processed manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of Included Studies

Study	Country	Population	Study design	n	Participants	Mechanism	Time Period	Intervention	Control
Bickell 1994	USA	Civilian	Single-center,prospective, RCT	598	Gunshot or stab wounds to the torso who had SBP<90 mmHg	Penetrating Torso	Preoperative	No resuscitation for SBP < 90mmHg	Immediate resuscitation for target SBP >100mmHg
Carrick 2016	USA	Civilian	Multi-center,RCT	168	Penetrating trauma patients with SBP < 90 mmHg who were brought emergently to OR for bleeding control	Penetrating	Intraoperative	Maintain MAP>50mmHg	Maintain MAP >65mmHg
Dutton 2002	USA	Civilian	Single-center,prospective, RCT	110	Traumatic hemorrhagic shock with SBP <90 mmHg and evidence of ongoing bleeding	Blunt and Penetrating	Preoperative+ Intraoperative	Low SBP of 70mmHg	Conventional SBP > 100mmHg
Gu 2020	China	Civilian	Single-center,prospective RCT	160	Traumatic hemorrhagic shock	Blunt and Penetrating	Fluid resuscitation only	restricted fluid resuscitation kept in 50-60 mmHg	routine fluid resuscitation kept in 60-80 mmHg
Lu 2018	China	Civilian	Single-center,prospective RCT	164	Severe multiple hemorrhagic shock with MAP< 65mmHg or SBP < 40 mmHg,who have undergone hemostatic treatment one or two hours after admission	Blunt and Penetrating	Preoperative	MAP 40-50 mmHg	MAP 60-80 mmHg
Morrison 2011	USA	Civilian	Single-center,prospective,two-arm,intention totreat, RCT	90	Patients undergoing laparotomy or thoracotomy for blunt and penetrating trauma who had SBP < 90mmHg	Blunt and Penetrating	Intraoperative	Maintain MAP>50mmHg	Maintain MAP >65mmHg
Schreiber 2015	USA and Canada	Civilian	Multi-center,prospective RCT	191	Blunt or penetrating trauma patients with SBP <90mmHg	Blunt and penetrating	Preoperative+ Intraoperative	250 mL bolus if SBP <70 mmHg and maintain SBP >70 mmHg	2L bolus and maintain SBP >110 mmHg
Yu 2018	China	Civilian	RCT	112	Patients diagnosed with uncontrolled hemorrhagic shock	Blunt and Penetrating	Preoperative+ Intraoperative	Maintain MAP >50mmHg	Maintain MAP >60mmHg

Table 2 Primary Outcome Data of Mortality

Study	Primary Outcome	Group	Mortality	Significance
Bickell 1994	In-Hospital Mortality	PH	86/289(29.70%)	0.04
		CR	116/309(37.50%)	
Carrick 2016	30-Day Mortality	PH	18/86(21.40%)	NS
		CR	21/82(26.30%)	
Dutton 2002	In-Hospital Mortality	PH	4/55(7.30%)	NS
		CR	4/55(7.30%)	
Gu 2020	In-Hospital Mortality	PH	5/80(6.30%)	0.045
		CR	13/80(16.30%)	
Lu 2018	In-Hospital Mortality	PH	2/82(2.40%)	0.041
		CR	15/82(18.30%)	
Morrison 2011	30-Day Mortality	PH	10/44(22.70%)	NS
		CR	13/46(28.20%)	
Schreiber 2015	In-Hospital Mortality	PH	8/95(8.40%)	NS
		CR	15/91(16.50%)	

PH: Permissive Hypotension; CR: Conventional Resuscitation Strategies; NS: No Significance

Figures

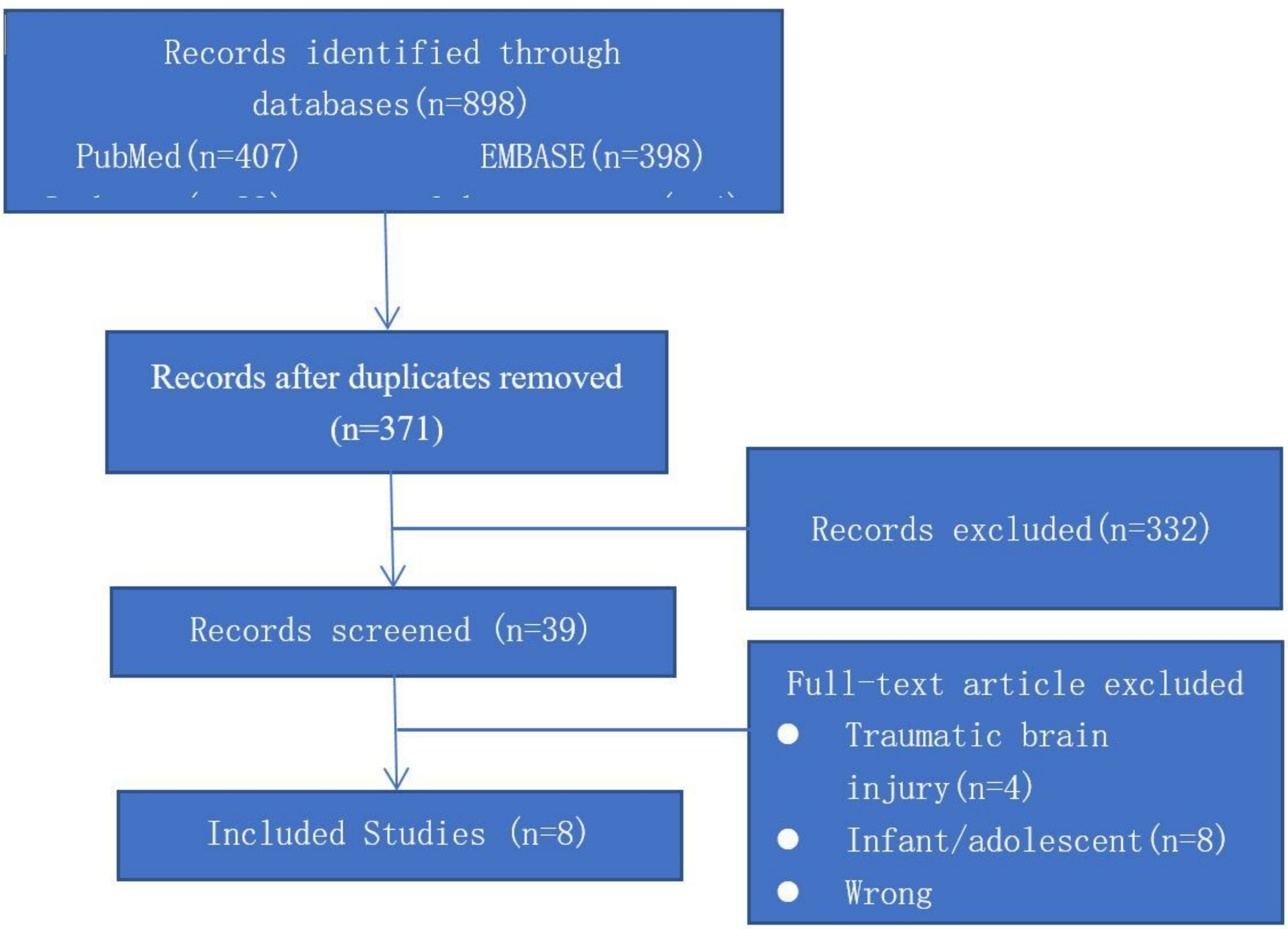

Figure 1

PRISMA Flow Diagram

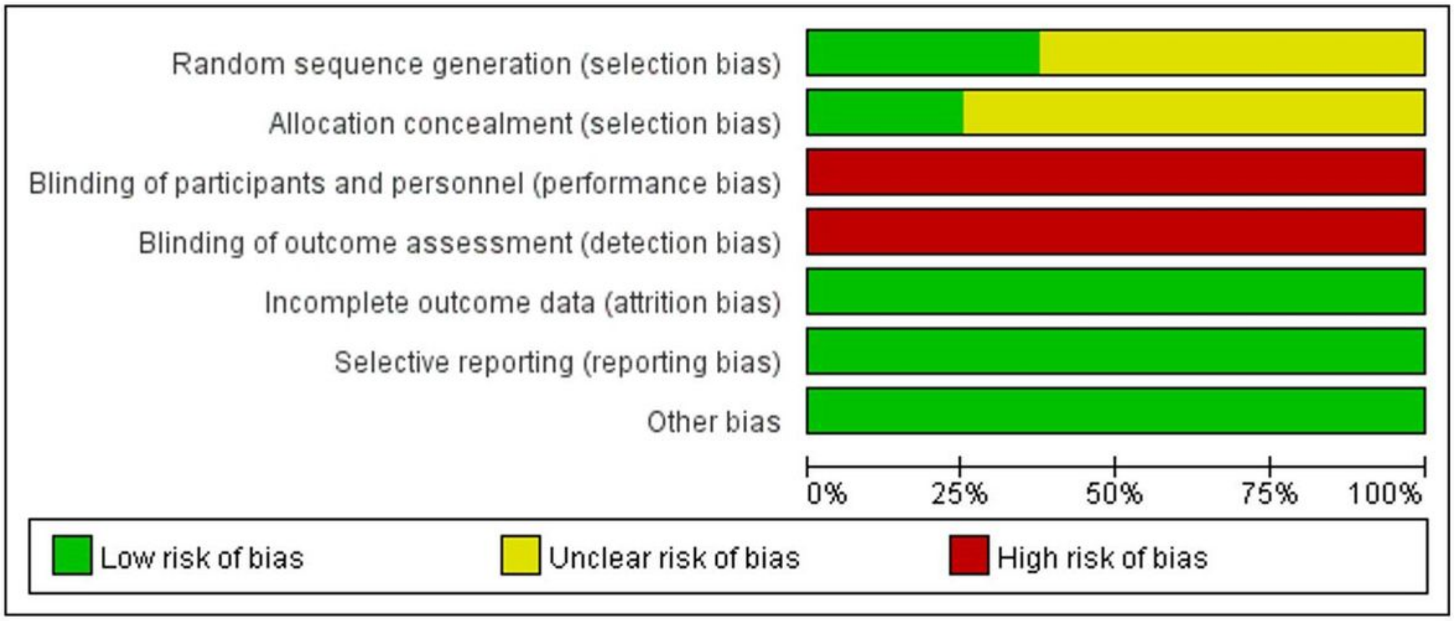

Figure 2

Risk of Bias Graph—review authors' judgments about each risk of bias item presented.

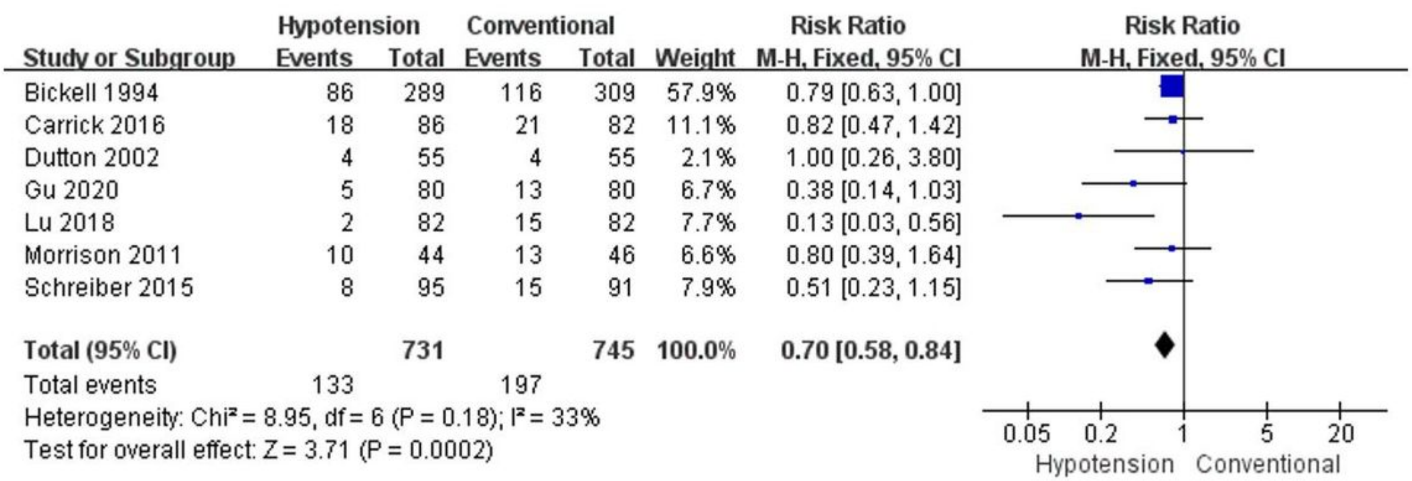

Figure 3

Forest plot of Permissive Hypotension vs. Conventional Resuscitation Strategies, relative to Mortality.

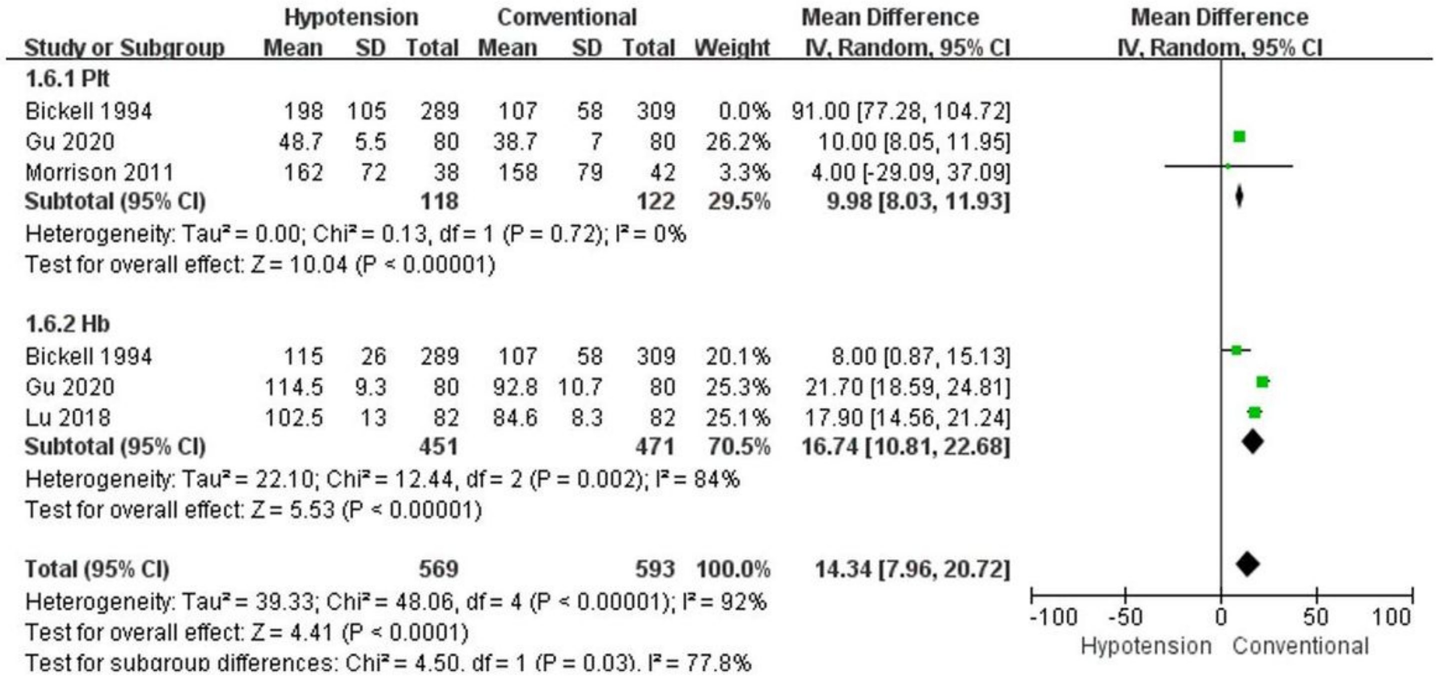

Figure 4

Forest plot of Permissive Hypotension vs. Conventional Resuscitation Strategies, relative to Blood Routine Index (PLT, Hb).

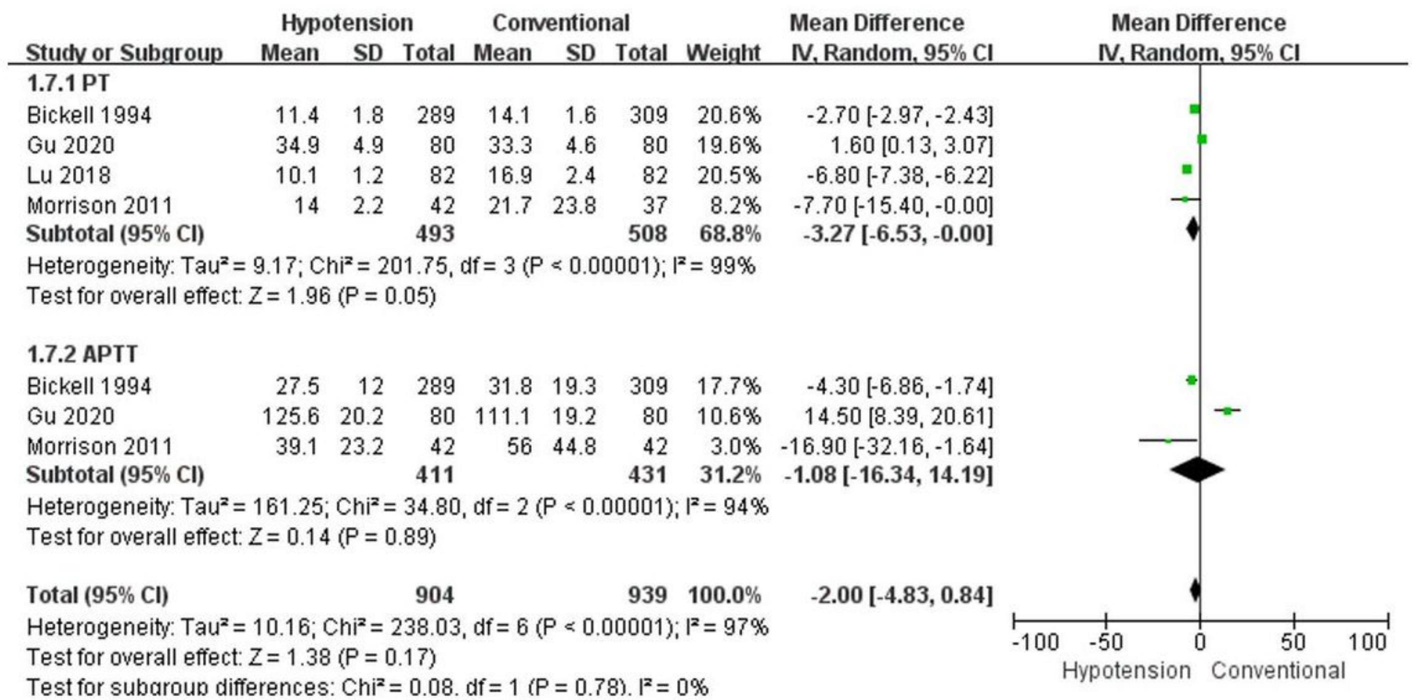

Figure 5

Forest plot of Permissive Hypotension vs. Conventional Resuscitation Strategies, relative to Blood Coagulation Function (PT, APTT).

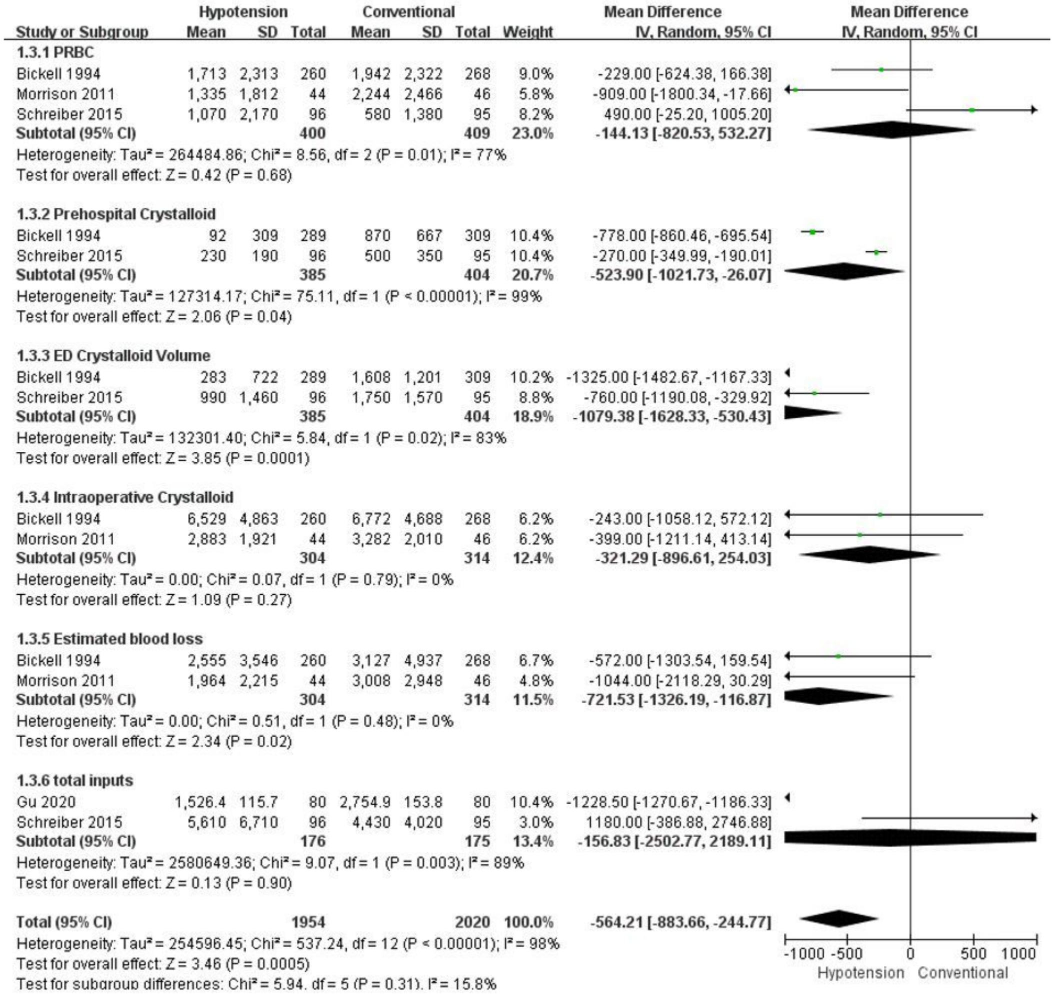

Figure 6

Forest plot of Permissive Hypotension vs. Conventional Resuscitation Strategies, relative to Fluid Balance and Transfusion Requirements.

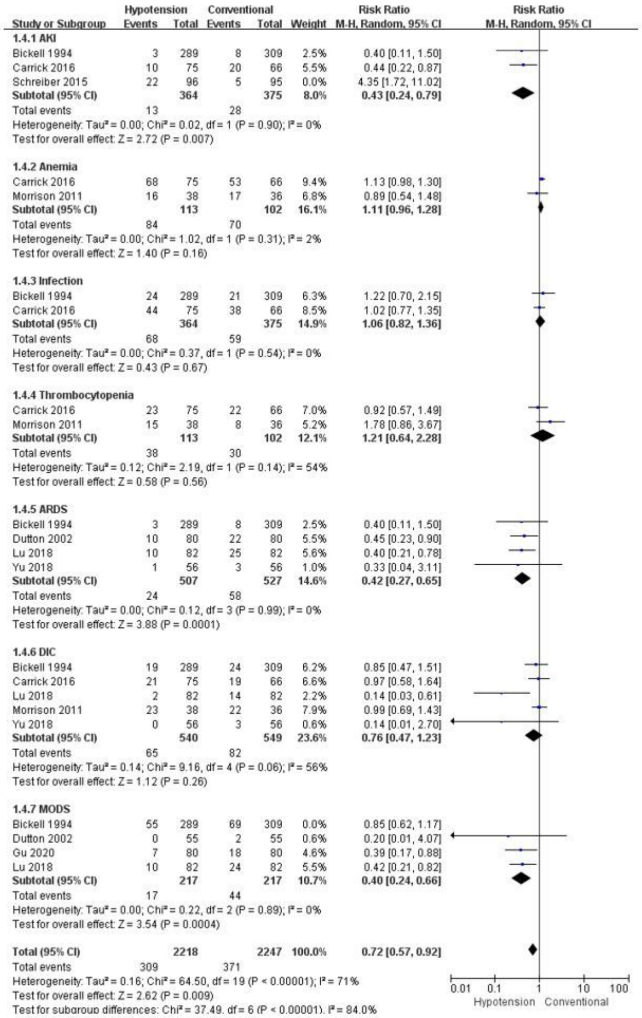

Figure 7

Forest plot of Permissive Hypotension vs. Conventional Resuscitation Strategies, relative to Complications.

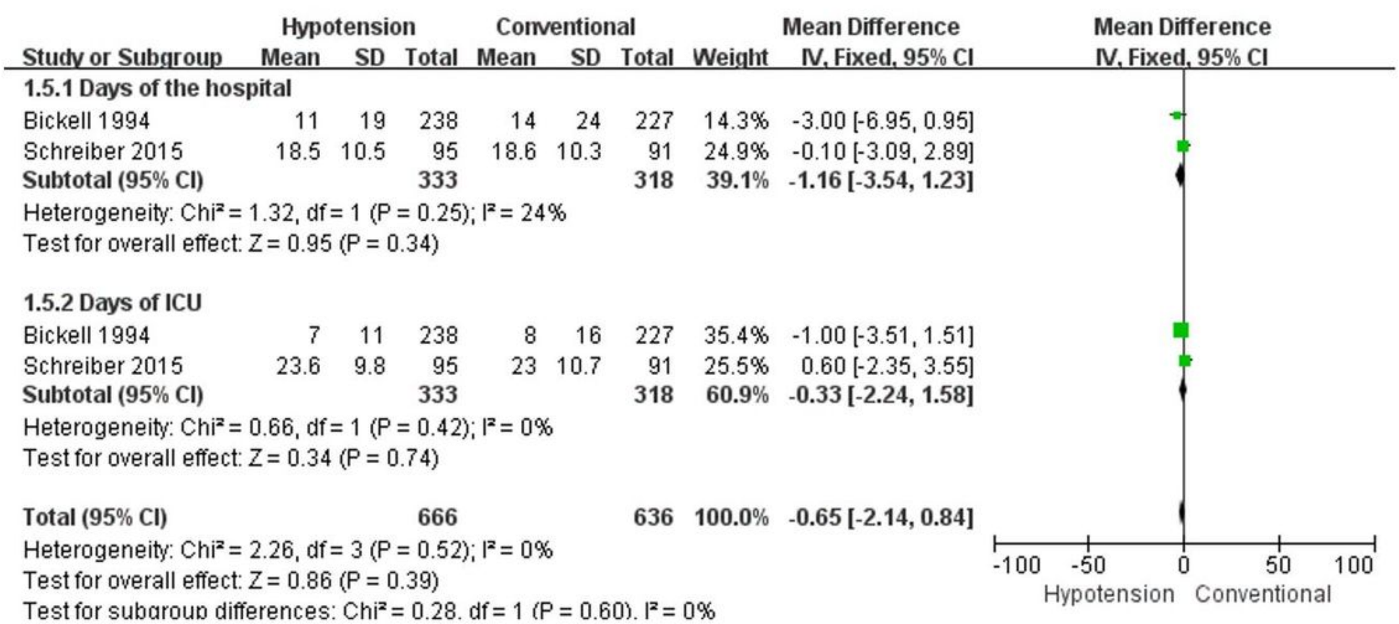

Figure 8

Forest plot of Permissive Hypotension vs. Conventional Resuscitation Strategies, relative to Days of ICU or Hospital.