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ORIGINAL ARTICLE

Safety and efficacy of acute normovolemic hemodilution during liver surgery: A meta-analysis

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Abstract

Objective The aim of this study was to evaluate the safety and efficacy of acute normovolemic hemodilution (ANH) during liver surgery.

Methods Structured searches of the PubMed, Chinese Biological Medicine Database, and Cochrane Library electronic databases were performed, followed by a meta-analysis of outcomes, including intraoperative blood transfusion(s), intraoperative bleeding, postoperative hematocrit (Hct) levels, postoperative prothrombin time (PT), and number of patients who underwent transfusions during liver surgery.

Results In total, 14 eligible studies were included in the meta-analysis, which revealed that ANH for liver resection was associated with a reduction in intraoperative blood transfusions [weighted mean difference (WMD) −1.99; 95% confidence interval (CI) −2.82 to −1.16; P < 0.00001]. The ANH group experienced less intraoperative bleeding (WMD −72.81; 95% CI −136.12 to −9.50; P < 0.00001) and exhibited a lower postoperative Hct level (WMD −3.38; 95% CI −7.14 to −0.67; P < 0.00001) than the control group. Moreover, meta-analysis revealed that postoperative prothrombin time was not affected by ANH (WMD −0.02; 95% CI −0.18 to −0.32; P = 0.65). Finally, the number of patients requiring allogeneic transfusion was significantly smaller in the ANH group than in the control group (odds ratio 0.13; 95% CI 0.09 to 0.18; P = 0.24).

Conclusion Results of the present meta-analysis indicated that ANH can reduce intraoperative bleeding and the need for blood transfusions. In addition, ANH did not negatively affect the coagulation system after surgery; therefore, ANH appears to be safe and effective during liver surgery.

Key words: safety and efficacy; acute normovolemic hemodilution (ANH); liver surgery; meta-analysis

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Liver resection traditionally requires a blood or blood-product transfusion to compensate for excessive bleeding, which is a common intraoperative complication during this type of surgery. The past several years have witnessed exponential advances in surgical and anesthetic techniques applied during hepatic surgery, together with marked reductions in blood transfusions related to liver resection. However, for complicated liver surgeries, especially those for tumors invading the main blood vessels, or when multiple liver resections are needed, bleeding can be fatal, and leave surgeons with poor visualization of the operative field.

With the increasing number of surgeries performed worldwide annually, the transfusion of allogeneic red blood cells (RBCs) and blood products has become even more widespread. The potential risks related to transfusions are well known and include high incidence of tumor recurrence due to inhibited T-lymphocyte immune function and transmission of infectious diseases such as cytomegalovirus [1], and non-A, non-B hepatitis [2]. Reductions in the number of transfusions required have been particularly noteworthy, and several strategies to reduce hemorrhage during surgery have evolved and are now routinely used, such as low central venous pressure, preoperative autologous blood donation [3], and acute normovolemic hemodilution (ANH). It has been reported [4] that ANH is an effective method to reduce intraoperative RBC loss, to save the patient's blood for later use and reduce thrombosis, and to prevent the spread of blood-borne diseases.

In this study, we evaluated the safety and efficacy of acute ANH, an autologous blood transfusion technique that is different from preoperative autologous blood donation. For ANH, a portion of the patient's whole blood

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is pre-surgically removed through the peripheral vein under general anesthesia while maintaining euvolemia; the same amount of colloid is injected to replace the blood removed. The amount of blood collected from the patient is calculated using the equation:

$$V_L = EBV \times H_0 - H_F / H_{AV},$$

in which V_L represents allowable blood loss, EBV is the estimated blood volume, H_0 is the patient's initial hemoglobin (Hb) level, H_F is a patient's minimal allowable Hb level, and H_{AV} is the average of the initial and minimal allowable Hb levels [5]. The collected blood is stored in an acid citrate dextrose blood collection bag in the operating room at room temperature to accurately record blood collection over time. If blood transfusion is indicated post-surgically [Hb < 80 g/L, hematocrit (Hct) < 25%], the patient's autologous blood is returned. During the entire process, the corpuscular portion of the blood is partially diluted, and the circulating blood volume remains equal and stable.

Although ANH has the advantages of lowering surgery costs, avoids the risk for reduced blood coagulation factors for long-term preservation, and reduces the risk for error in matching blood types, evidence supporting the efficacy and safety of ANH during liver surgery remains lacking. Thus, we performed this meta-analysis to determine the safety and efficacy of ANH in decreasing exposure to allogeneic transfusions in adults undergoing major liver resection procedures.

Methods

Literature search

A structured search of the PubMed, Chinese Biological Medicine Database, and Cochrane Library electronic databases was performed. The search was designed to include articles published between data compilation after the creation of electronic resources and August 1, 2019, with publication language restricted to English and Chinese. The search terms were as follows: ((Hemodilution) AND (((((hepalobectomy) OR "liver resection") OR "hepatic resection") OR hepatectomy)). All abstracts of the retrieved articles were independently reviewed for relevance by the two investigators, and the full-text of the included articles was obtained for a second screening.

Inclusion/exclusion criteria

All studies included in the present meta-analysis fulfilled the following criteria: randomized controlled trials (RCTs) and prospective or retrospective cohort studies comparing intraoperative acute ANH and no intervention in liver surgery; population(s) undergoing liver surgery were > 18 years of age; surgical procedure for ANH was consistent, and all patients received ANH; at least one outcome of interest was reported (e.g., amount of intraoperative bleeding, intraoperative allogeneic blood transfusion, number of patients treated with allogeneic blood transfusion, postoperative Hct level, and prothrombin time). For studies in which the same author or research team reported results for the same patient population more than once, the most recent or most comprehensive was used. The publication language was restricted to English and Chinese.

Studies published as letters, reviews, case reports, conference reports, or expert opinions, and those in which the process of hemodilution was not implemented according to the established formula [5–6], were excluded.

Data extraction

Two authors (MY, JL) independently extracted and summarized the following data from the included articles: study characteristics (author name, year of publication, country of origin, study design, and sample size); outcomes of the ANH and control groups; amount of intraoperative bleeding; intraoperative allogeneic blood volume; number of patients receiving an allogeneic blood transfusion; postoperative Hct level; and postoperative prothrombin time. Any disagreements were jointly resolved by the authors.

Methodological quality of the studies

The Jadad scale [7] was used to score the methodological quality of RCTs, with a maximum total score of 5; studies with scores ≥ 3 were defined as high quality. The Newcastle-Ottawa Scale [8] was used to evaluate the quality of non-RCTs. The maximum total score was 9, and studies with scores ≥ 7 were considered to be high quality.

Statistical analysis

Meta-analysis was performed using Review Manager version 5.3 (RevMan, Cochrane Collaboration, Oxford, United Kingdom). The following outcomes were considered to be continuous data and were analyzed using weighted mean difference (WMD): allogeneic RBC transfusion; intraoperative bleeding; postoperative Hct level; and postoperative prothrombin time. Statistical significance was set at $P < 0.05$.

The number of patients undergoing allogenic blood transfusions was considered to be dichotomous data and analyzed using pooled odds ratio (OR). In the process of data pooling, the Q-test was used to estimate heterogeneity and the I^2 statistic to measure the extent of inconsistency among the results. A fixed-effects model was used when there was no heterogeneity ($P > 0.1$), while a random-effects model was used when there was heterogeneity. An I^2 value > 50% was regarded to be an indicator of significant heterogeneity [9].

Table 1 Characteristics of the included studies

Author	Year	Country	Study design	Number of patients	Strategy	Age (year)
Sejourne P [22]	1989	France	RCT	22/22	ANH/non-ANH	48 ± 9/52 ± 15
Chen H [17]	1998	America	RE	100/100	ANH/non-ANH	56 ± 5/58 ± 5
Johnson LB [19]	1998	America	RE	13/13	ANH/non-ANH	59.9 ± 3.3/58.1 ± 3.7
Matot I [23]	2002	Israel	RCT	39/39	ANH + LCVP/LCVP	58 ± 12/55 ± 14
Chen GY [10]	2004	China	RE	20/20	ANH/non-ANH	44.9 ± 9.4/43.9 ± 9.9
Yao XH [11]	2006	China	RCT	10/10	ANH/non-ANH	28–65
Lin JQ [12]	2006	China	RCT	20/20	ANH/non-ANH	52.3 ± 4.6/50.3 ± 3.9
Xia KQ [13]	2007	China	RCT	40/40	ANH/non-ANH	60 ± 12/58 ± 14
Balci ST [21]	2008	Turkey	RE	73/41	ANH/non-ANH	36 ± 9/33 ± 8
Jarnagin WR [18]	2008	America	RCT	63/67	ANH + LCVP/LCVP	54 (31–83)/53 (20–77)
Guo JR [14]	2010	China	RCT	15/15	ANH/non-ANH	65.7 ± 8.1/64.3 ± 10.1
Putchakay K [20]	2013	America	RE	96/63	ANH + LCVP/LCVP	62/62
Zhong TM [15]	2013	China	RCT	45/45	ANH/non-ANH	73.1 ± 8.2/72.9 ± 9.5
Sun H [16]	2014	China	RCT	20/20	ANH/non-ANH	45.0 ± 9.4/43.5 ± 7.8

Author	ASA score	Preoperative Hb (g/L)	Intraoperative transfusion trigger	Quality evaluation
Sejourne P [22]	–	13 ± 1.0/12.8 ± 2.0	Hematocrit < 25%	4
Chen H [17]	–	–	–	6*
Johnson LB [19]	–	–	Hematocrit < 28%	6*
Matot I [23]	1 or 2	–	Hematocrit < 20%	4
Chen GY [10]	1 or 2	125.3 ± 12.5/124.1 ± 10.5	Bleeding > 15% blood volume	6*
Yao XH [11]	1 or 2	135.8 ± 9.7/136.6 ± 9.6	Bleeding > 15% blood volume	3
Lin JQ [12]	–	≥ 110	–	4
Xia KQ [13]	1 or 2	–	Hematocrit < 24%	3
Balci ST [21]	1 or 2	13.9 ± 1.6/13.8 ± 1.5	Hematocrit < 25%	6*
Jarnagin WR [18]	3, 46, 14/5, 54, 8#	13.30 (10.60–16.50)/13.20 (10.20–16.10)	Hemoglobin < 7.0 g/dL	4
Guo JR [14]	1 or 2	–	–	4
Putchakay K [20]	3 or 4	13.0/12.6	–	6*
Zhong TM [15]	1 or 2	130.5 ± 16.1/131.9 ± 15.9	Hematocrit < 25%	3
Sun H [16]	1 or 2	138.4 ± 10.8/134.5 ± 9.6	–	3

RCT: randomized controlled trial; RE: retrospective trial; LCVP: low central venous pressure; non-ANH: control group with no intervention; ASA: American Society of Anesthesiologists; #: Number of people distributed in ASA 1, 2, 3. The study score is marked with an *, using the Newcastle-Ottawa Scale to evaluate the quality of non-RCT studies.

Results

Literature selection and characteristics

A total of 482 potentially eligible studies were retrieved in the initial database search. Two authors (MY, JL) independently read the titles and abstracts of the relevant articles, 451 of which were excluded because the abstract or topic did not fulfill the inclusion criteria. Thus, 31 articles were included in the full-text review, of which 17 were excluded: eight because they did not report eligibility data; eight did not calculate the volume of preoperative blood extracted; and one addressed ANH in pediatric liver resections. Ultimately, 14 studies, comprising 1106 patients, were included in the final qualitative analysis (Fig. 1).

Characteristics of the included studies

The basic characteristics of the 14 included studies are summarized in Table 1. Study sample sizes ranged from 20 to 200, and ANH was applied to all patients in the experimental group. Seven [10–16] studies involved Chinese populations, four [17–20] American, and one each Turkish [21], French [22], and Israeli [23]. All articles provided adequate data for analysis. Eight studies[10–11, 14–15, 18–19, 21–22] reported that ANH reduced allogeneic RBC transfusion and intraoperative bleeding, five [12, 14–16, 24] reported that ANH did not impact the coagulation system, and one [20] reported that ANH was well tolerated by patients with higher American Society of Anesthesiology scores who underwent partial liver resection.

Results of meta-analysis

A total of 14 studies were included based on the defined criteria (Fig. 1). According to the study aim, five items were compared: allogeneic RBC transfusion, patients requiring allogeneic transfusion, intraoperative bleeding, postoperative Hct level, and postoperative prothrombin time.

Allogeneic RBC transfusion

Among the included studies, eight [10–11, 14–15, 18–19, 21–22] reported data pertaining to allogeneic RBC transfusion in both the ANH and control groups, comprising a total of 494 patients. Pooled data from these eight studies indicated that ANH may reduce the volume of allogeneic RBC transfusion [WMD –1.99; 95% confidence interval (CI) –2.82 to –1.16; P < 0.00001]. There was, however, significant heterogeneity among these studies (P < 0.00001; I^2 = 92%; Fig. 2).

Patients requiring allogeneic transfusion

Eight studies [10–11, 14–17, 19, 22] reported the number of patients who required allogeneic transfusion. The overall number of patients was smaller in the ANH group than in the control group (OR 0.13; 95% CI 0.09–0.18; P = 0.24). There was moderate heterogeneity among these studies (P < 0.00001; I^2 = 23%; Fig. 3).

Intraoperative bleeding

Eight studies [10–11, 14–17, 19, 22] evaluated the amount of bleeding during liver surgery, which was significantly lower in the ANH group (WMD –72.81; 95% CI –136.12 to –9.50; P < 0.00001) than in the control group. There was significant heterogeneity among the studies (P = 0.02; I^2 = 82%; Fig. 4).

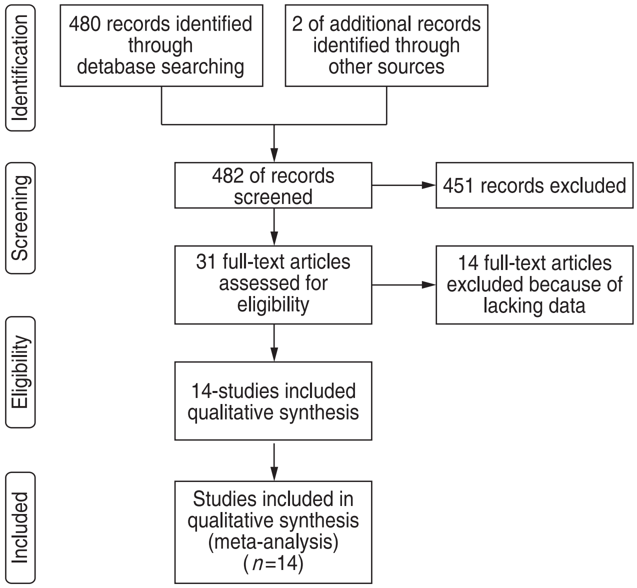

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram depicting the study selection process

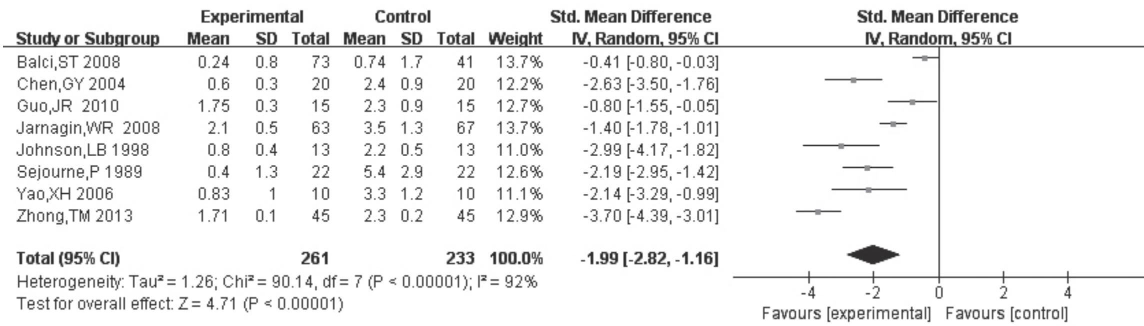

Fig. 2 Meta-analysis of allogeneic red blood cell transfusion

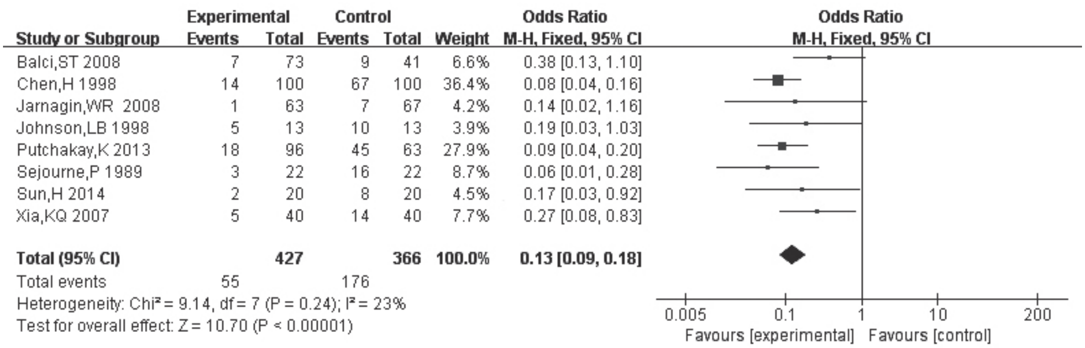

Fig. 3 Meta-analysis of patients requiring allogeneic transfusion

Postoperative Hct level

Eight studies [10–11, 13, 15–17, 19, 23], comprising 574 patients who underwent liver resection, evaluated postoperative Hct level. Meta-analysis revealed that postoperative Hct level was significantly lower in the ANH group than in the control group (WMD –3.38; 95% CI –7.14 to 0.67; P = 0.10); however, there was high heterogeneity among these eight studies (P = 0.00001; I^2 = 99%; Fig. 5). After further analysis, this high heterogeneity may be explained by the lack of a unified indicator for transfusion. In some studies [14, 21, 23], patients in whom Hct level did not reach the level set before surgery did not receive an autologous blood transfusion. The remaining patients received autologous blood transfusion in the ANH group; therefore, the heterogeneity of Hct level significantly increased.

Postoperative prothrombin time

Six studies [12–16, 23], comprising 358 patients who underwent liver resection (ANH, n = 179; control, n = 179), reported postoperative prothrombin time. Meta-analysis indicated no significant difference in postoperative prothrombin time (WMD –0.02; 95% CI –0.68 to 0.32; P = 0.49). There was no significant heterogeneity among these studies (P = 0.65; I^2 = 0%; Fig. 6).

Publication bias

Funnel plots for intraoperative blood transfusion (Fig. 7a), the number of patients who underwent allogenic blood transfusion (Fig. 7b), intraoperative bleeding (Fig. 7c), postoperative Hct level (Fig. 7d), and postoperative prothrombin time (Fig. 7e) demonstrated basic symmetry. As such, no significant publication bias was evident (Fig. 7).

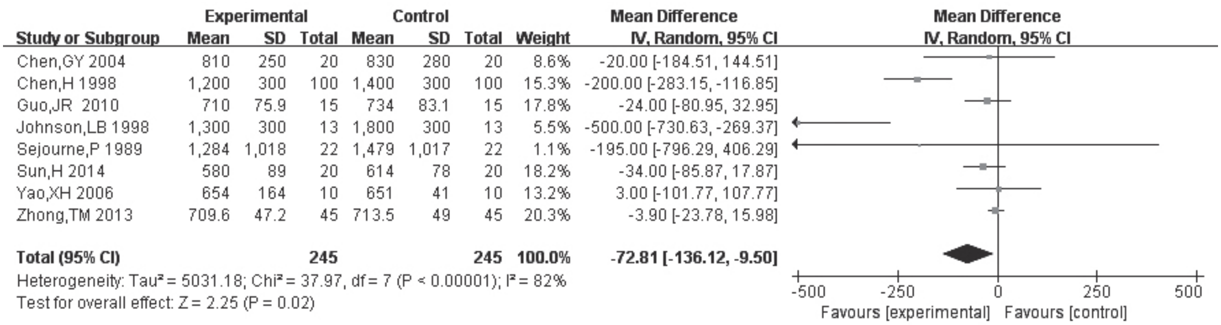

Fig. 4 Meta-analysis of intraoperative bleeding

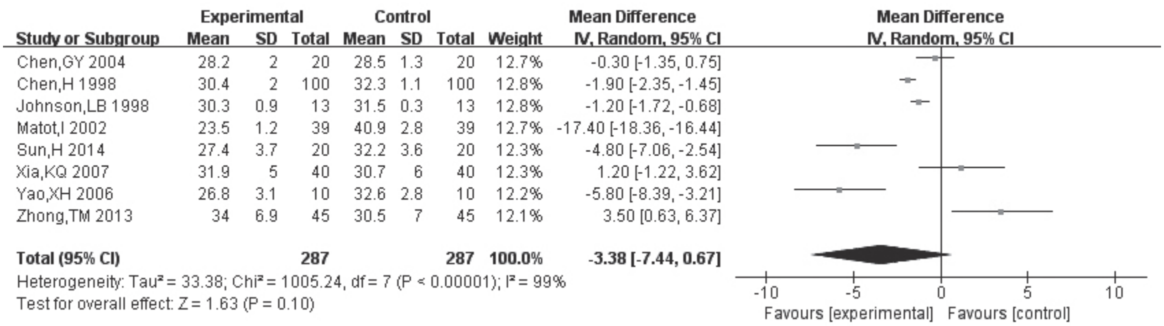

Fig. 5 Meta-analysis of postoperative hematocrit level

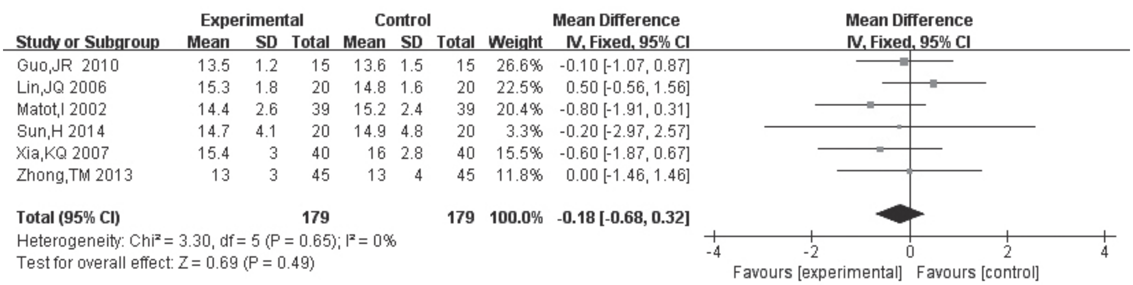

Fig. 6 Meta-analysis of postoperative prothrombin time

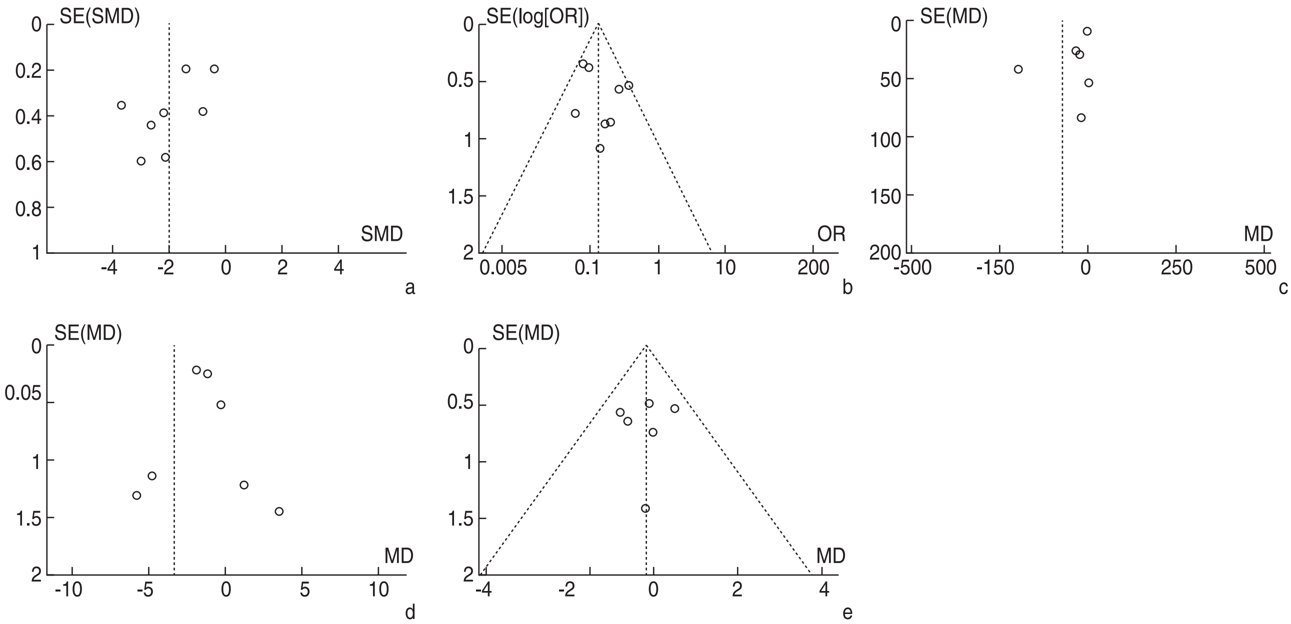

Fig. 7 Funnel plots for meta-analyses. (a) Eight articles in the meta-analysis of blood transfusion; (b) Eight articles in the meta-analysis of number of patients underwent allogenic blood transfusion; (c) Eight articles in the meta-analysis of intraoperative bleeding; (d) Eight articles in the meta-analysis of postoperative hematocrit; (e) Six articles in the meta-analysis of postoperative prothrombin time

Discussion

Although perioperative preparation is usually sufficient for patients with liver cancer, liver resection is still associated with a significant risk for major morbidity, and this is often directly correlated with blood loss and transfusion of allogeneic blood products during surgery [25]. Developing blood conservation techniques has had a positive impact on preventing the risk(s) associated with allogeneic transfusions, including transmission of infectious agents, anaphylaxis, sodium citrate poisoning, and hemolysis. These risks may be a trigger for poor patient prognosis and can aggravate the effects of surgery [26–28]. In addition, for patients undergoing resection for cancer, allogeneic transfusions have the added potential of increasing the risk for cancer recurrence [29–30]. Furthermore, additional important reasons to reduce allogeneic blood transfusions are increased cost and the occasionally tenuous state of the national blood supply, which is sometimes exceeded by demand [31]. A reduction in the need for blood transfusions has been particularly noteworthy, and ANH may be a useful method to resolve the abovementioned risks.

ANH is performed on the day of surgery, which decreases the time the blood is stored *in vitro*. In theory, after surgery, all of the drawn blood is returned to the patient, which reduces the cost of transfusing allogeneic blood. Second, compared with intraoperative cell salvage, ANH does not require additional equipment or specially trained clinicians and is easy to perform. Therefore, among the strategies for reducing intraoperative bleeding and salvaging blood, ANH is preferred in terms of ease of operation and cost. However, ANH has not been widely used in liver resection primarily due to persistent uncertainty regarding its safety and efficacy. Findings from our study may provide the supportive evidence needed to apply ANH during liver surgery.

Evidence-based data regarding ANH from other meta-analyses [32–33] during large-scale surgeries did not demonstrate the safety and efficacy of ANH in liver resection. An investigation by Barile [32] included 23 studies addressing ANH use during cardiac surgery. Although the outcomes demonstrated that ANH can be successfully used during cardiac surgery, its application during liver surgery, and whether it can achieve the same effect, was not determined. Another analysis [33] included only two clinical studies on liver surgery and a subgroup analysis of the two articles [10, 34]. The subgroup outcomes indicated that, although ANH reduced the number of blood transfusions, it did not reduce the amount of bleeding. Furthermore, it has not been proven that ANH is safe and effective during liver surgery, and there was high heterogeneity in the subgroup analysis. In a study by Moggia *et al* [35], the included studies focused on the surgical techniques used to reduce bleeding during liver resection, rather than on blood conservation methods. A meta-analysis by Segal [36] published in 2004 noted that ANH does not play an active role in reducing intraoperative allogeneic blood input. The type of surgery using ANH was not reported in this article, and our meta-analysis only included studies addressing liver surgery. With advances in imaging and surgical techniques, we have a better understanding of the anatomy of the liver, which leads us to believe that ANH is now safer for patients.

Our meta-analysis comprised 14 studies investigating the effects of ANH during liver surgery. In agreement with our hypothesis, the results demonstrated that ANH can safely and effectively reduce blood transfusions and bleeding during liver surgery. Moreover, our pooled analysis of postoperative prothrombin times revealed that patient coagulation systems were not impaired, which suggests that ANH is safe. Therefore, if patients tend to lose a significant volume of blood during liver surgery, ANH may be an alternative method of preserving blood.

One of the results of our meta-analysis demonstrated a statistically significant decrease in the number of allogeneic RBC transfusions (WMD –1.99; 95% CI –2.82 to –1.16; $P < 0.00001$). This suggests that ANH can reduce the possibility of blood transfusions during liver resection; however, there was high heterogeneity ($P < 0.0001$; $I^2 = 92\%$) among the studies, the main reason for which may be the results of the intraoperative transfusion trigger being different among the eight studies, with some having an Hb level < 7.0 g/dL [18] and Hct levels < 28% [19], 25% [21] and 20% [23], and autogenous blood transfusions that were not counted in the total number of blood transfusions [18]. Our findings suggest that, in future studies, the transfusion threshold should be strictly designated when attempting to optimize outcomes.

Furthermore, in our study, compared with the control group, a slightly lower postoperative Hct level was found in the ANH group after surgery and the difference was statistically significant (WMD –3.38; 95% CI –7.14 to –0.67; $P < 0.00001$); however, the lowest Hct level was > 25% in the seven articles. Habler *et al* [37] reported that if the Hct level is not < 20%, the oxygen supply to the patient's tissues and organs is stable [38–39]. Due to the decrease in viscosity when blood is diluted, cardiac output increases, and tissue perfusion improves and is compensated [40]. These results suggest that the effect of ANH on Hct level is safe.

Although the results of this meta-analysis support the safety and efficacy of ANH and its positive outcomes during liver surgery, the heterogeneity of the allogeneic RBC transfusion group and intraoperative bleeding group remains high. We cannot definitively explain this heterogeneity; however, we propose several possible reasons. First, this meta-analysis lacked recent research on ANH use during liver resection, given that one-half of the included studies were published before 2010. Second, among the included studies, blood transfusion indicators were not uniform, which may have affected the anesthesiologist's tendency to suggest transfusions to the patients. Finally, because there are many ways to evaluate intraoperative bleeding, accurate assessment is difficult [41].

Conclusion

Results of the present review and meta-analysis demonstrated that ANH can reduce bleeding during liver resection and the necessity for blood transfusions without affecting the patient's coagulation system postoperatively. Nevertheless, a well-designed multicenter study of ANH use during liver surgery is needed to further support its safety and efficacy.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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