The Efficacy and Utility of Acute Normovolemic Hemodilution

Michael C. Grant, MD,* Linda M. S. Resar, MD,† and Steven M. Frank, MD*

Acute normovolemic hemodilution (ANH) is a blood conservation technique that was first described in the early 1970s in the setting of cardiac surgery.[1,2] The principle behind this procedure is to reduce the patient's hematocrit by phlebotomy along with infusing crystalloid and/or colloid before the onset of surgical blood loss such that for a given amount of bleeding, a smaller red blood cell (RBC) mass will be lost. The maximum benefit from ANH is achieved when a low, but physiologically adequate, hematocrit is maintained during the blood loss phase of the surgical procedure, after which the fresh whole blood that was removed is given back to the patient near the end of the surgical procedure. Ideally, for ANH to be effective in reducing allogeneic transfusion requirements, the patient should: (1) have a relatively high preoperative hematocrit; (2) undergo the maximum allowable phlebotomy; and (3) lose a substantial amount of blood during surgery. If any of these 3 parameters is not present, the potential benefit of ANH in reducing allogeneic transfusions will be limited.[3]

Whether ANH is effective in reducing transfusion requirements has been a point of controversy. Multiple controlled trials evaluating ANH in patients who underwent a variety of surgical procedures have been published, which allows for meta-analysis to determine efficacy. In fact, 2 previous meta-analyses, including 1 in 1998 with 24 trials[4] and 1 in 2004 with 42 trials,[5] did not show conclusive evidence to support the widespread use of ANH.

Now 11 years later, in the current issue of *Anesthesia & Analgesia*, Zhou et al.[6] report an updated systematic review and meta-analysis that includes additional recent studies (63 studies in total) in an attempt to answer the question of whether ANH is efficacious in reducing allogeneic transfusion. The authors should be commended for conducting the largest and most rigorous analysis of ANH studies to date. Despite their comprehensive meta-analysis, high-quality evidence to support the routine use of ANH is still lacking. Although ANH decreased both the likelihood of any allogeneic transfusion (by 26%) and the volume of allogeneic transfusion (by approximately 1 unit), there was evidence for publication bias leading to an overestimation of benefit from ANH. The primary limitations of this study were the inclusion of small trials, some with as few as 10 patients per group, and the absence of transfusion protocols with a designated hemoglobin trigger or target, which introduces bias when blinding is not possible in such studies. As expected, the type of surgery, the volume of blood withdrawn, the presence or absence of other blood management methods, and even the year of publication all influenced the beneficial impact of ANH. The secondary outcomes were adverse (morbid) events. The only morbid event for which the incidence differed between groups was "any infection," which unfortunately was reported in only 10 of the 63 studies but occurred with less frequency in the ANH group (relative risk, 0.64; $P = 0.037$). Because allogeneic transfusion is known to be associated with hospital-acquired infection,[7] this finding is plausible, interesting, and perhaps understated in the current study. In addition, the inability to assess such outcomes in a blinded fashion is problematic. The authors go on to conclude that based on their findings, in combination with previous mathematical modeling studies,[8] surgical procedures with blood loss of 1 L or greater are the cases in which the benefits of ANH are most likely to be recognized.

Assessing the efficacy of ANH is no simple task. For example, what is the primary outcome that should be measured? Is it the percentage of patients exposed to allogeneic transfusion or the volume of blood transfused? What about other important outcomes that are often not reported in these studies such as length of stay, morbid events, mortality, and overall costs? Is ANH being compared with no blood conservation measures at all? Should ANH be used in combination with other blood management methods, which are now commonly used, such as preoperative anemia management, autologous blood salvage, antifibrinolytic medications, controlled hypotension, new methods of surgical cautery, and hemostatic agents and sealants?[9–11] Many of these measures have now become routine care, given the widespread adoption of patient blood management, with the resulting improved outcomes, as well as reduced costs and risks by avoiding unnecessary transfusions.[12] Although ANH has been touted as easy to perform, it remains labor-intensive and time-consuming. In addition, it frequently requires invasive intravascular access that may

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not otherwise be needed simply to remove the volume of blood required to make a difference.

Another consideration is the evolution of surgery itself over the past 2 decades since the first ANH meta-analysis was published. Surgeries previously associated with high blood loss (e.g., radical prostatectomy or open aortic aneurysm repair) no longer require transfusions in most cases, thanks to minimally invasive approaches with robotic and endovascular surgery. In fact, patients undergoing radical retropubic prostatectomy, for which ANH has been shown to be efficacious in reducing transfusion,[13] are now rarely or never transfused with robotic surgery. For example, only 1 in 800 patients undergoing robotic prostatectomy at our institution was transfused in the past year.[14]

The initial enthusiasm for ANH 20 to 30 years ago was generated when the risk of viral transmission was substantially higher than the current risk. At that time, patients only wanted their own blood for transfusion, which led to the preoperative autologous donation era. Studies from that era showed that ANH was equally efficacious as preoperative autologous donation,[15,16] and less costly,[17] with less chance of a wrong unit error because the blood never leaves the operating room. Of course, over time things have changed. Now the viral risk of allogeneic blood has been compared (seriously and systematically) with the risk of getting killed in an airline crash or being struck and killed by lightening![18] In addition, preoperative autologous donation has fallen out of favor because patients frequently are rendered anemic before their surgery and do not have adequate time for erythropoiesis before surgery. In addition, storing blood is associated with storage lesions, whereby the quality of RBCs decreases over time between the donation and the transfusion.[19] Now that we have other methods of blood conservation, it appears that neither preoperative autologous donation nor ANH is clearly beneficial for the vast majority of cases. In fact, if forced to choose between these 2 methods, there may be more benefit from receiving 2 units of fresh whole blood at the end of surgery, with functional clotting factors and platelets, than stored preoperative autologous donated blood that is near the end of its shelf life with less hemostatic benefit. At our institution, ANH is commonly used for patients undergoing cardiac surgery, especially for those who do not accept transfusion for religious or other reasons.[20] Such patients usually do not accept RBCs, plasma, or platelets, so they benefit from the hemostatic effects of fresh whole blood at the end of the procedure.[21]

In conclusion, the updated meta-analysis published in this issue of *Anesthesia & Analgesia* on the efficacy of ANH is a welcomed addition to the anesthesia literature. Although widespread adoption of this blood conservation measure is not supported by this study, there are certain clinical situations in which ANH may be beneficial. Although still controversial, cardiac surgery may be the ideal setting for ANH when patients arrive with a high hematocrit, undergo a substantial blood loss, and the hemostatic benefits of fresh whole blood may be most apparent.[22] Even then, blood conservation measures such as antifibrinolytics, meticulous surgical techniques, and newer perfusion techniques (retrograde autologous priming, smaller circuit volumes, ultrafiltration) may be equally efficacious. Perhaps a combination of any or all the mentioned blood management techniques, used together for selected patients, under the right circumstances, will become the new standard of care.

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Preoperative Acute Normovolemic Hemodilution for Minimizing Allogeneic Blood Transfusion: A Meta-Analysis

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BACKGROUND: Previous studies have evaluated the efficacy of preoperative acute normovolemic hemodilution (PANH) in reducing the need for allogeneic blood transfusion. However, the results to date have been controversial. In this study, we sought to reassess the efficacy and safety of PANH based on newly emerging evidence.

METHODS: Medline, EMBASE, ISI Web of Knowledge, and Cochrane Central Register of Controlled Trials databases were searched using the key words "hemodilution," "autotransfusion," or "hemorrhage" to retrieve all randomized controlled trials examining the benefits of PANH compared with control patients not undergoing PANH in any type of surgery.

RESULTS: Sixty-three studies involving 3819 patients were identified. The risk of requiring an allogeneic blood transfusion and the overall volume of allogeneic red blood cell transfused during the perioperative period were reduced in the PANH group compared with the control group (relative risk, 0.74; 95% confidence interval, 0.63 to 0.88; $P = 0.0006$; weighted mean difference, −0.94 units; 95% confidence interval, −1.27 to −0.61 units; $P < 0.0001$). However, there was significant heterogeneity ($I^2 = 79.6\%$, $\chi^2 = 151.95$, $P < 0.0001$; $I^2 = 95.3\%$, $\chi^2 = 574.28$, $P < 0.0001$) and publication bias ($P = 0.001$; $P = 0.009$) for both outcomes, limiting conclusions regarding the efficacy of PANH for reducing allogeneic transfusion. Perioperative blood loss, adverse events, and the length of hospitalization were comparable between these groups.

CONCLUSIONS: Although these results suggest that PANH is effective in reducing allogeneic blood transfusion, we identified significant heterogeneity and publication bias, which raises concerns about the true efficacy of PANH. (Anesth Analg 2015;121:1443–55)

Allogeneic blood transfusion is associated with well-known complications, including increased risk for infection, transfusion-associated circulatory overload, immune suppression, transfusion-related acute lung injury, transmission of infectious agents, and others.[1] Furthermore, increasing demands and reduced voluntary donation often results in shortage of allogeneic blood.[2] There are several proposed strategies for reducing the need for allogeneic blood transfusion, including preoperative acute normovolemic hemodilution (PANH).[3,4] By reducing the red cell mass of blood loss due to surgical bleeding followed by the retransfusion of the previously withdrawn blood at the conclusion of surgery, PANH is thought to reduce the need for allogeneic blood transfusion while maintaining postoperative hemoglobin level. Meta-analyses that have addressed the effectiveness of PANH are now >10 years old,[5,6] and more recent studies have suggested an inconsistent effect of this strategy.[7–9] We therefore conducted a systematic review and meta-analysis to evaluate the efficacy of PANH for reducing allogeneic blood transfusion.

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METHODS

Search Strategy

The Medline, Excerpta Medica Database (EMBASE), ISI Web of Knowledge, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched electronically using the following key words: "hemodilution," "autotransfusion," "hemorrhage," and "blood loss." Search strategies are found in the Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/AA/B222). Potentially eligible studies were also identified through a manual search of the references and citations in the articles retrieved for full review. The searches were last updated in March 2015.

Selection Process

All clinical trials that used a randomized and controlled study design and assessed the reduced need for allogeneic blood transfusion benefits of PANH compared with no PANH during the perioperative period were included. Two authors initially reviewed the titles and abstracts to exclude irrelevant studies and subsequently screened the studies through a detailed review of the full-text article to determine eligibility. Controversies were resolved by consensus with a third author.

Data Extraction

Two authors independently extracted data from the full-text article of each included study using a standardized data collection form (Table 1). The primary outcomes for the current review were the number of patients undergoing allogeneic blood transfusion, the volume of allogeneic red blood cell (RBC) transfusion, and the volume of blood loss. The secondary outcomes were adverse events (e.g., mortality, reoperation for bleeding, deep vein thrombosis, pulmonary embolus, stroke, myocardial ischemia/infarction, and

Table 1. Main Characteristics of the Included Trials

First author	Type of surgery	Sample (PANH/ Control)	Baseline Hct (%) or Hb	Target Hct or Hb	Average volume of blood withdrawn	Fluid to replace the withdrawn blood	Other active intervention in both groups	Transfusion protocol	Trigger Hb or Hct		Jadad scale
									Intraoperative	Postoperative	
Bennett (1994)[13]	Total hip prosthesis replacement	20/20	42%	25%	900 mL	Gelatin	None	Yes	8 g/dL	8 g/dL	2
Bennett et al. (2006)[7]	Hip surgery	78/77	≥12 g/dL	11.0 g/dL	420 mL	Crystalloids	None	Yes	25%	30%	3
Beveniste et al. (1978)[14]	Abdominal hysterectomy surgery	39/44	32.4% or 8.64 g/dL	—	600–700 mL	Lactated Ringer's	None	No	—	—	2
Boldt et al. (1991)[15]	Aortocoronary bypass grafting surgery	15/15	13.6 g/dL	11.4 g/dL	890 mL	6% HES	None	Yes	7 g/dL	—	3
Bonnet et al. (1986)[16]	Repair craniofacial disjunction surgery	10/10	43.50%	29%	1015 mL	Colloid	None	Yes	28%	30%	2
Bonnet et al. (1986)[16]	Excision of squamous carcinomas of the mouth surgery	10/10	40%	30%	870 mL	Colloid	None	Yes	28%	30%	2
Boussofara et al. (2002)[17]	Cervicofacial oncologic surgery	17/21	41% or 13.4 g/dL	33.6% or 10.8 g/dL	341–496 mL	Colloid	Iron and folic acid	Yes	10 g/dL	10 g/dL	2
Casati et al. (2002)[19]	Open heart surgery	102/100	41.8% or 13.8 g/dL	—	360–576 mL	Colloid	Tranexamic acid and cell salvage	Yes	6.5 g/dL or 20%	8.5 g/dL or 25%	3
Casati et al. (2004)[18]	Off-pump coronary artery bypass surgery	50/50	41.2% or 13.8 g/dL	—	850 mL	4% Succinylated gelatin	Tranexamic acid and cell salvage	Yes	8 g/dL or 24%	8 g/dL or 24%	3
Catoire et al. (1992)[20]	Abdominal aortic surgery	10/10	40%	30%	875 mL	Dextran 60,000	None	No	—	—	2
Chen et al. (2007)[21]	Radical resection for stomach cancer surgery	30/30	>33% or 11.0 g/dL	—	400 mL	Plasma substitute	None	No	—	—	2
Daif et al. (2012)[22]	Brain tumor resection surgery	20/20	39.4% or 13.25 g/dL	33.7% or 11.7 g/dL	900–1000 mL	6% HES	None	Yes	10 g/dL	—	3
Durmus et al. (2003)[24]	Coronary artery bypass grafting surgery	20/20	42%	33.60%	612.5 mL	6% HES	None	Yes	29 (18)%[a]	—	2
Dietrich et al. (1989)[23]	Coronary artery bypass grafting surgery	25/25	42%	30%	731 mL	HES	None	Yes	—	—	2
El-Dessouky et al. (2011)[26]	Spinal fusion surgery	20/20	38.8% or 13.2 g/dL	33.3% or 11.9 g/dL	900 mL	6% HES	None	Yes	9 g/dL or 25%	—	3
Ela et al. (2009)[25]	Off-pump coronary artery bypass surgery	28/29	45.2% or 14.9 g/dL	28%	—	HES	None	Yes	8 g/dL or 25%	8 g/dL or 25%	3
Ervens et al. (2010)[27]	Orthognathic surgery	20/21	13.5 g/dL	9 g/dL	900 mL	6% HES	Induced hypotension	Yes	6.5 g/dL	7 g/dL	2
Fayed et al. (2013)[28]	Liver resection surgery	80/80	41%	27%	1750 mL	6% HES	None	Yes	24%	24%	2
Fischer et al. (2010)[29]	Pancreaticoduodenectomy surgery	65/65	13.2 g/dL	7.9 g/dL	2250 mL	5% Albumin and crystalloid	None	Yes	7 g/dL	8 g/dL	2

(*Continued*)

Table 1. Continued

First author	Type of surgery	Sample (PANH/ Control)	Baseline Hct (%) or Hb	Target Hct or Hb	Average volume of blood withdrawn	Fluid to replace the withdrawn blood	Other active intervention in both groups	Transfusion protocol	Trigger Hb or Hct		Jadad scale
									Intraoperative	Postoperative	
Gombotz et al. (2000)[30]	Hip replacement surgery	20/20	11.0 g/dL	8 g/dL	1440 mL	6% HES and Ringer's lactate	rHu-EPO and iron	Yes	8 g/dL	8 g/dL	2
Guo et al. (2010)[31]	Hepatic carcinectomy surgery	15/15	>35%	28%	—	6% HES	None	Yes	8 g/dL or 25%	—	2
Hallowell et al. (1972)[32]	Cardiac surgery	25/25	38%	—	1252 mL	Ringer's/5% albumin/5% PPF or blood	None	No	—	—	2
Hans et al. (2000)[33]	Repair craniosynostosis surgery	17/17	33.20%	25%	122 mL	5% Albumin	None	Yes	21%	21%	2
Hensel et al. (1996)[34]	Gastric surgery	30/20	40.50%	35%	672 mL	6% HES	None	Yes	30%	30%	2
Herregods et al. (1995)[35]	Coronary artery bypass grafting surgery	15/15	39.70%	34.80%	785 mL	Succinyl-linked gelatin	None	No	—	—	2
Herregods et al. (1997)[36]	Coronary artery bypass grafting surgery	39/32	39.60%	35%	750 mL	Succinyl-linked gelatin	None	No	—	—	3
Höhn et al. (2002)[37]	Cardiac surgery	36/41	43.25%	27.90%	1099	HES	Aprotinin and cell salvage	Yes	25 (17)%	—	3
Hurpe et al. (1987)[38]	Cardiac surgery	79/81	37.30%	36.90%	734.4	Gelatin	None	No	—	—	2
Jalali et al. (2008)[8]	Coronary artery bypass grafting surgery	50/50	44.60%	9 g/dL	—	0.9% saline	None	Yes	8 g/dL	8 g/dL	3
Jarnagin et al. (2008)[39]	Hepatic resection surgery	63/67	13.25 g/dL	8 g/dL	2250 mL	5% albumin and crystalloid	None	Yes	7 g/dL	8 g/dL	3
Juelsgaard et al. (2002)[40]	Total knee arthroplasty surgery	14/14	38.40%	30.40%	877 mL	6% HES	Controlled hypotension	Yes	28%	28%	3
Kahraman et al. (1997)[41]	Coronary artery bypass grafting surgery	14/7	41.80%	—	369–590 mL	Crystalloid and 3.5% polygeline	None	Yes	—	30%	2
Kahraman et al. (1997)[41]	Coronary artery bypass grafting surgery	14/7	41.80%	—	743–1114.5 mL	Crystalloid and 3.5% polygeline	None	Yes	—	30%	2
Karakaya et al. (1999)[42]	Primary total hip arthroplasty surgery	10/10	35.75% or 11.95 g/dL	29.3% or 9.8 g/dL	1000 mL	6% HES	None	Yes	25%	30%	2
Khanna et al. (1998)[43]	Major general surgical	20/20	—	9.19 g/dL	836.6 mL	3% Polygeline	None	Yes	—	—	2
Licker et al. (2005)[44]	Coronary artery bypass grafting surgery	41/39	40.50%	28%	—	6% HES	Aprotinin and cell salvage	Yes	25(18)%	—	3
Licker et al. (2007)[45]	Aortic valve replacement	19/21	14.4 g/dL	9 g/dL	—	6% HES	Aprotinin and cell salvage	Yes	25(18)%	—	3
Lim et al. (2003)[46]	Spinal surgery	15/15	40%	28%	717 mL	6% HES and Ringer's lactate	Controlled hypotension	Yes	20%	—	2
Lisander et al. (1996)[47]	Idiopathic scoliosis	10/13	13.65 g/dL	8 g/dL	1125 mL	6% dextran 70 or 3% dextran or 4% albumin	None	Yes	8 g/dL	8 g/dL	2

(*Continued*)

Table 1. Continued

First author	Type of surgery	Sample (PANH/ Control)	Baseline Hct (%) or Hb	Target Hct or Hb	Average volume of blood withdrawn	Fluid to replace the withdrawn blood	Other active intervention in both groups	Transfusion protocol	Trigger Hb or Hct		Jadad scale
									Intraoperative	Postoperative	
Lisander et al. (1996)[47]	Idiopathic scoliosis	13/11	14.1 g/dL	8 g/dL	1215 mL	6% dextran 70 or 3% dextran or 4% albumin	Cell salvage	Yes	8 g/dL	8 g/dL	2
Lorentz et al. (1991)[48]	Total hip arthroplasty surgery	16/15	—	9 g/dL	700 mL	Polygeline	None	Yes	—	—	2
Mahoori et al. (2009)[9]	Coronary artery bypass grafting surgery	54/47	39.5% or 13.45 g/dL	—	490 mL	Gelatin	None	Yes	10 g/dL or 30%	—	3
Matot et al. (2002)[49]	Major liver resections surgery	39/39	41.20%	23.50%	2020 mL	6% dextran and 5% albumin	None	Yes	20%	—	3
McGill et al. (2002)[50]	Cardiac surgery	84/84	>36% or 12 g/dL	—	843 mL	Gelatin	Cell salvage	Yes	20 (20)%	9 g/dL or 27%	3
Moyes et al. (1985)[51]	Thoracic surgery	10/10	—	28.20%	500 mL	Dextran 70	None	No	—	—	2
Nuttall et al. (2000)[53]	Coronary artery bypass grafting or/and cardiac valve surgery	32/45	—	—	859 mL	—	Tranexamic acid and cell salvage and reinfusion of shed mediastinal blood	Yes	8(7) g/dL	—	4
Naqash et al. (2011)[52]	Intracranial meningioma surgery	20/20	12.98 g/dL	10.44 g/dL	802 mL	6% HES	None	Yes	—	—	2
Oishi et al. (1997)[54]	Primary total hip arthroplasty surgery	16/16	37.50%	28.80%	—	Crystalloids and/or colloids	PAD and cell salvage	No	—	—	3
Olsfanger et al. (1997)[55]	Total knee replacement surgery	10/5	—	28%–30%	1003 mL	Lactated Ringer's	None	Yes	—	28%	3
Olsfanger et al. (1997)[55]	Total knee replacement surgery	10/5	—	28%–30%	985 mL	Lactated Ringer's	None	Yes	—	28%	3
Payen et al. (1997)[56]	Maxillofacial surgery	13/13	37.50%	30%	862.5 mL	4% Albumin	None	No	—	—	2
Peillon et al. (1995)[57]	Mandibular osteotomy surgery	16/16	41.80%	30%	828 mL	4% Albumin	None	Yes	25%	—	2
Saricaoglu et al. (2005)[59]	Hip arthroplasty surgery	10/10	41.20%	32.50%	1065 mL	6% HES	None	Yes	9 g/dL	—	2
Sanders et al. (2004)[58]	Major gastrointestinal surgery	78/82	13.5 g/dL	8 g/dL	—	Gelofusine and lactated Ringer's	None	Yes	8 g/dL	8 g/dL	2
Soltanzadeh et al. (2012)[60]	Coronary artery bypass grafting surgery	50/50	>12 g/dL	—	500 mL	Lactated Ringer's	None	No	—	—	2
Triulzi et al. (1995)[61]	Cardiac surgery	18/28	14.1 g/dL	10.6 g/dL	924 mL	Colloid and/or crystalloid	None	Yes	20%	24%	3
Van der Linden et al. (1994)[62]	Total hip replacement surgery	10/10	42.20%	28.20%	880 mL	6% HES or/and 4.5% albumin	None	Yes	30%	30%	2
Vedrinne et al. (1992)[63]	Cardiac surgery	30/30	14.16 g/dL	11.61 g/dL	400 mL	4% Albumin	None	Yes	27 (24)	30%	2
Virmani et al. (2010)[64]	Valve surgery	88/100	12.25 g/dL	—	270.8	HES	None	Yes	8 (6) g/dL	—	3

(*Continued*)

Table 1. Continued

First author	Type of surgery	Sample (PANH/ Control)	Baseline Hct (%) or Hb	Target Hct or Hb	Average volume of blood withdrawn	Fluid to replace the withdrawn blood	Other active intervention in both groups	Transfusion protocol	Trigger Hb or Hct		Jadad scale
									Intraoperative	Postoperative	
Welch et al. (1993)[65]	Infrarenal aortic surgery	20/19	40.20%	28%	1500 mL	Dextran 70 or/and plasma	None	No	—	—	2
Wolowczyk et al. (2003)[66]	Abdominal aortic aneurysm repair surgery	16/18	14.0 g/dL	9.4 g/dL	890 mL	6% HES	Cell salvage	Yes	8 g/dL	9.5 g/dL	3
Yao et al. (2006)[67]	Liver tumorectomy surgery	10/10	41% or 13.62 g/dL	34.7% or 11.42 g/dL	705 mL	6% HES	None	Yes	—	—	2
Zisman et al. (2009)[68]	Cardiac surgery	27/35	14.3 g/dL	—	600 mL	6% HES	None	Yes	—	9 g/dL	2

See Supplemental Digital Content 3, Supplemental Table 1, http://links.lww.com/AA/B224, for more details.
PANH = Preoperative acute normovolemic hemodilution; Hct = hematocrit; Hb = hemoglobin; HES = hydroxyethyl starch; rHu-EPO = recombinant human erythropoietin; PPF = plasma protein fraction; PAD = preoperative autologous donation.
[a]Criteria for intraoperative allogeneic transfusions: number in brackets means during cardiopulmonary bypass; number out of brackets means after cardiopulmonary bypass.

renal dysfunction) and length of hospital stay. If necessary, authors were contacted to obtain further data.

Quality Assessment of Studies

A quality assessment was independently performed by 2 authors using an established tool, the Jadad scale, to assess the methodological quality of clinical trials.[10] This scale included the method of randomization (2 points), double-blinding (2 points), and the description of dropouts (1 point) (Supplemental Digital Content 2, Supplemental Appendix 2, http://links.lww.com/AA/B223). Discrepancies were resolved by consensus with a third author.

Statistical Analysis

All calculations were performed using STATA Software version 11.0 (StataCorp LP, College Station, TX). Dichotomous and continuous data were expressed as the relative risk (RR) and weighted mean difference (WMD) with 95% confidence intervals (CIs), respectively. We used WMD to pool the results as all included studies measured outcomes on the same scale and data with zero were excluded. Data were first pooled using a fixed-effect model. The random effects model was subsequently used when between-study heterogeneity was obvious ($I^2 > 50\%$, $P \leq 0.05$). Heterogeneity was tested using the I^2 statistic and the χ^2 test, with values >50% and $P \leq 0.05$ indicating significant heterogeneity, respectively.[11] If the heterogeneity was strong, subgroup analyses and meta-regression analyses were used to identify the sources of heterogeneity. Sensitivity analyses were performed to assess the contributions of a single study to the pooled results. Publication bias was assessed using a funnel plot when the number of studies was >10.[12] If bias was suspected, the meta-trim method was used to re-estimate the effect size.

RESULTS

Our search strategy identified 5440 potentially relevant studies. After a number of studies were excluded, 63 studies involving a total of 3819 patients were finally included in this meta-analysis (Fig. 1).[7–9,13–68] The characteristics of these studies and quality scores are presented in Table 1 (see more detail in Supplemental Digital Content 3, Supplemental Table 1, http://links.lww.com/AA/B224).

Primary Outcomes

Risk of Perioperative Allogeneic Blood Transfusion

Of the 63 included studies, 37 (n = 2711) compared the efficacy of PANH versus a control group to evaluate the risk of allogeneic blood transfusion during the perioperative period.[7–9,13,17–19,23,25,27–30,32–37,39–41,43–46,48–50,55,58,61,63,64,66] These 37 studies found that the number of allogeneic blood transfusion was significantly reduced in the PANH group versus the control group (RR, 0.74; 95% CI, 0.63 to 0.88; P = 0.0006). These results are summarized in the forest plot in Figure 2. Moreover, our results demonstrated that the use of PANH was associated with a fewer allogeneic blood transfusion during the intraoperative (RR, 0.54; 95% CI, 0.38 to 0.78; P = 0.0009; Supplemental Digital Content 4, Supplemental Figure 1, http://links.lww.com/AA/B225) and postoperative (RR, 0.61; 95% CI, 0.43 to 0.87; P = 0.007; Supplemental

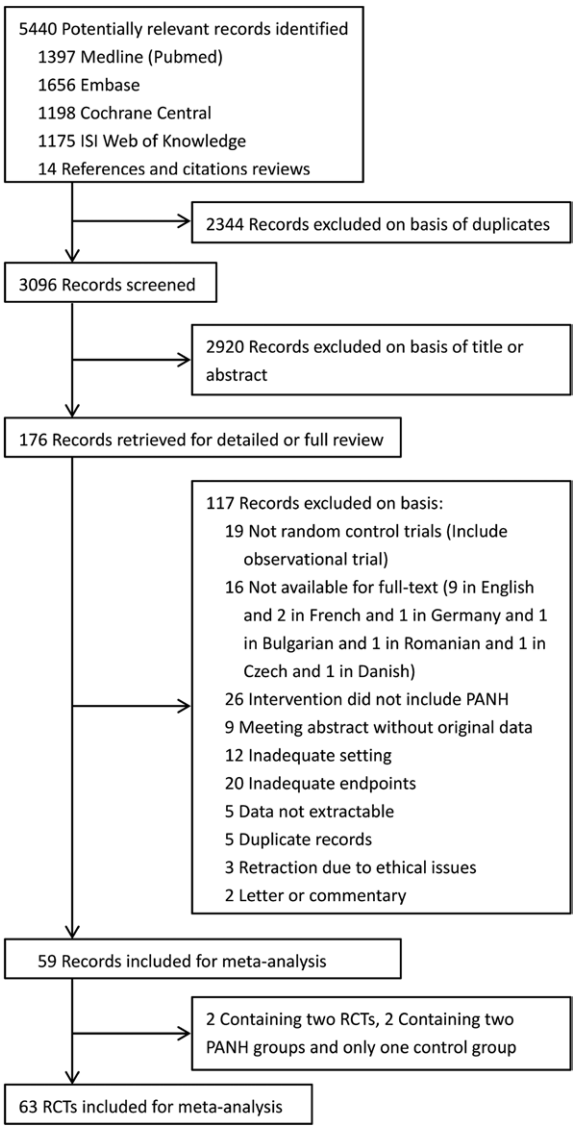

Figure 1. Flowchart of the literature search and manuscript selection. PANH = preoperative acute normovolemic hemodilution; RCT = randomized controlled trials.

Digital Content 5, Supplemental Figure 2, http://links.lww.com/AA/B226) periods.

Sensitivity Analysis

Sensitivity analyses were performed to determine the effects of omitting a single study on the overall effect. The omission of a single study using the random method did not change the overall RR of perioperative allogeneic blood transfusion; the overall RR was changed from 0.72 (95% CI, 0.61 to 0.86; $P = 0.0003$) to 0.78 (95% CI, 0.67 to 0.91; $P = 0.001$; Supplemental Digital Content 6, Supplemental Table 2, http://links.lww.com/AA/B227).

Subgroup Analysis and Meta-Regression

Because the heterogeneity among studies was significant ($I^2 = 79.6\%$, $\chi^2 = 151.95$, $P < 0.0001$; Fig. 2), subgroup analyses and meta-regression were performed to identify the sources of the heterogeneity. The results of the subgroup analyses revealed that the type of surgery, the presence or absence of a transfusion protocol, and the volume of withdrawn blood could not explain the heterogeneity; thus, heterogeneity persisted in the included studies (Supplemental Digital Content 7, Supplemental Table 3, http://links.lww.com/AA/B228). We then performed further analyses using the meta-regression method. Similarly, the results of meta-regression could not identify the sources of the heterogeneity. Factors such as the type of surgery, the presence or absence of a transfusion protocol, the volume of withdrawn blood, the type of fluid for replacing the withdrawn blood, the presence or absence of other active interventions, the quality of the study, the year of publication, the sample size, and the mean age did not appear to be the source of the observed heterogeneity (Supplemental Digital Content 8, Supplemental Table 4, http://links.lww.com/AA/B229).

Publication Bias Analysis

A funnel plot of the risk of perioperative allogeneic blood transfusion revealed that 6 studies exceeded the 95% confidence limits (Supplemental Digital Content 9, Supplemental Figure3,http://links.lww.com/AA/B230).TheEggerregression asymmetry test yielded a significant publication bias ($P = 0.001$). To produce a more robust estimation, trim and fill tests were performed using the random effects model. Two virtual studies were filled, and the overall RR of the trim and fill method was 0.77 (95% CI, 2.57 to 8.49; $P = 0.001$). The overall RR was slightly higher than that of the crude meta-analysis (RR, 0.74; 95% CI, 0.63 to 0.88; $P = 0.0006$) but was still significant.

Units of Perioperative Allogeneic RBC Transfusion

Of the included studies, 31 ($n = 1781$) compared the effect of PANH versus control on the units of perioperative allogeneic RBC transfusion.[8,9,16,23,25,27,28,30,33,38–47,49,50,55,60–63,65] These 31 studies revealed that the units of perioperative allogeneic RBC transfusion was significantly decreased in the PANH group compared with the control group (WMD, –0.94 units; 95% CI, –1.27 to –0.61 units; $P < 0.0001$). The results are presented in the forest plot in Figure 3. We further analyzed the volume of intraoperative and postoperative allogeneic RBC transfusion; the results revealed that the volume of allogeneic RBC transfusion was reduced in the PANH group versus the control group during the intraoperative period (WMD, –0.76 units; 95% CI, –1.22 to –0.30 units; $P = 0.001$; Supplemental Digital Content 10, Supplemental Figure 4, http://links.lww.com/AA/B231) but not in the postoperative period (WMD, –0.73 units, 95% CI, –1.63 to 0.17 units; $P = 0.11$; Supplemental Digital Content 11, Supplemental Figure 5, http://links.lww.com/AA/B232).

Sensitivity Analysis

The results of the sensitivity analyses showed that omission of a single study did not change the overall WMD of the units of perioperative allogeneic RBC transfusion; the overall WMD was changed from –0.86 units (95% CI, –1.18 to –0.53 units, $P < 0.0001$) to –1.04 units (95% CI, –1.37 to –0.72 units, $P < 0.0001$; Supplemental Digital Content 12, Supplemental Table 5, http://links.lww.com/AA/B233).

Subgroup Analysis and Meta-Regression

The heterogeneity among studies with respect to the units of perioperative allogeneic RBC transfusion was strong

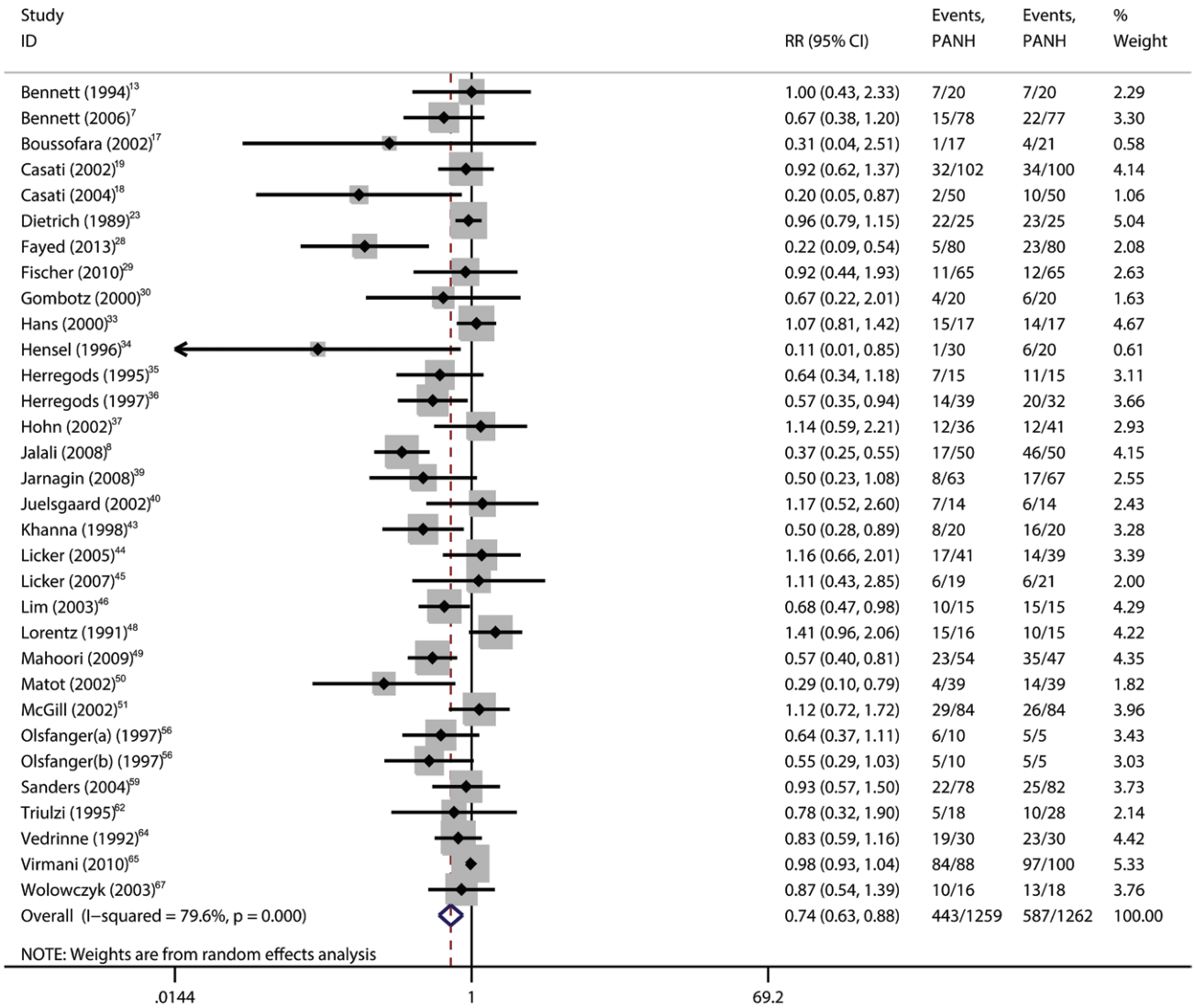

Figure 2. Forest plot of the number of perioperative allogeneic blood transfusion in PANH group versus control group. PANH was effect in reducing the number of perioperative allogeneic blood transfusion. Results are from a random effects model. The data with zero has been excluded. PANH = preoperative acute normovolemic hemodilution; RR = relative risk; CI = confidence interval.

(I^2 = 95.3%, χ^2 = 574.28, P < 0.0001; Fig. 3); thus, subgroup analyses and meta-regression were performed. The results of subgroup analyses revealed that the type of surgery, the presence or absence of a transfusion protocol, and the volume of withdrawn blood could not explain the heterogeneity; thus, heterogeneity persisted in the included studies (Supplemental Digital Content 13, Supplemental Table 6, http://links.lww.com/AA/B234). We then performed a meta-regression analysis. Similarly, the results of the meta-regression could not identify the sources of the heterogeneity, which indicates that the factors included in the analysis of meta-regression were not the sources of the observed heterogeneity (Supplemental Digital Content 14, Supplemental Table 7, http://links.lww.com/AA/B235).

Publication Bias Analysis

A funnel plot of the overall volume of perioperative allogeneic RBC transfusion revealed that half of the included studies (14/28) exceeded the 95% confidence limits (Supplemental Digital Content 15, Supplemental Figure 6, http://links.lww.com/AA/B236). The Egger regression asymmetry test identified a significant publication bias (P = 0.009). The included smaller studies tended to report greater benefits of PANH. Trim and fill analysis was performed, and 6 virtual studies were filled. The overall WMD of the trim and fill method was 0.30 units (95% CI, 0.21 to 0.45 units, P < 0.0001), and this overall WMD was significantly different from that of the crude meta-analysis (−0.94 units, 95% CI, −1.27 to −0.61 units, P < 0.0001). This finding raises concerns over the true efficacy of PANH in reducing the overall volume of perioperative RBC transfusion.

Volume of Perioperative Blood Loss

Eight studies (n = 317) compared the effectiveness of PANH versus a control group with respect to the overall volume of perioperative blood loss.[14,21,30,40,47,62,65] These studies revealed that the overall volume of perioperative blood loss was similar in the PANH group and the control group (WMD, 21.98 mL; 95% CI, −46.90 to 90.86 mL; P = 0.53). These results are presented in the forest plot in Figure 4. Our results further

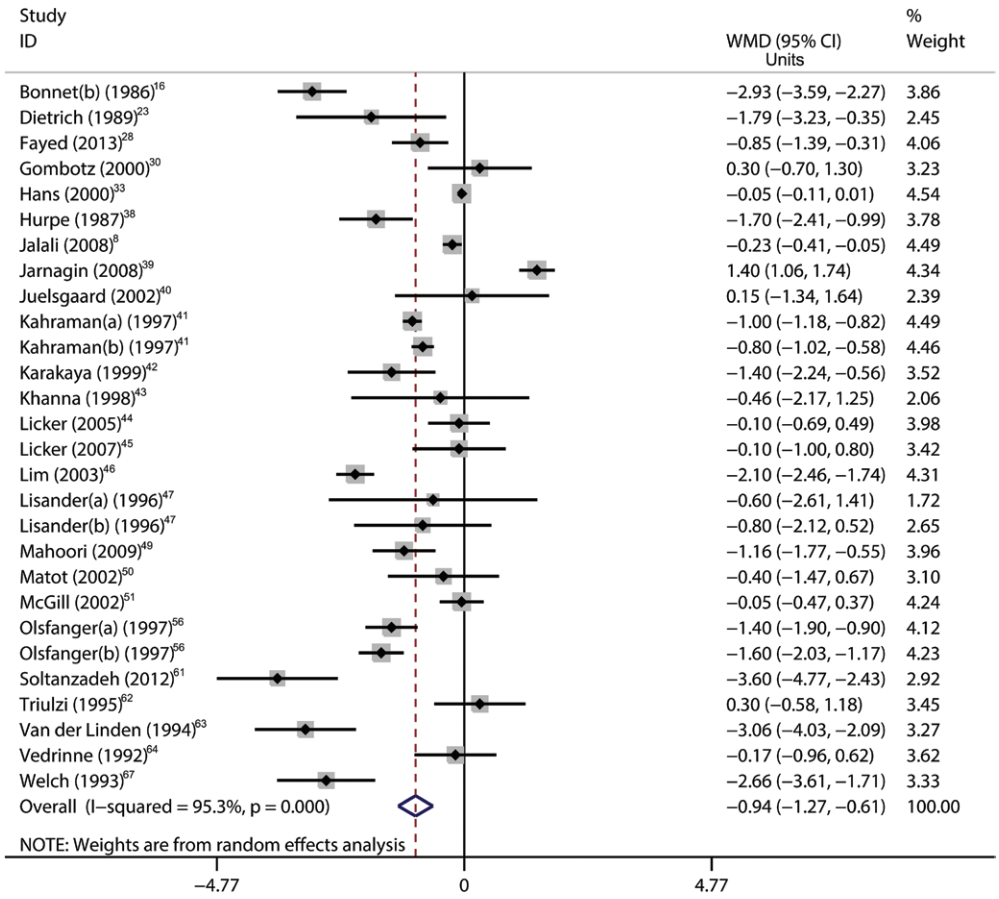

Figure 3. Forest plot of the units of perioperative allogeneic red blood cell transfusion in PANH group versus control group. PANH was effect in reducing the volume of perioperative allogeneic blood transfusion. Results are from a random effects model. The data with zero has been excluded. PANH = preoperative acute normovolemic hemodilution; WMD = weighted mean difference; CI = confidence interval.

revealed that the volume of blood loss was significantly reduced in the PANH group versus the control group during the postoperative period (WMD, −120.72 mL; 95% CI, −167.10 to −74.34 mL; $P < 0.0001$; Supplemental Digital Content 16, Supplemental Figure 8, http://links.lww.com/AA/B237) but not during the intraoperative period (WMD, −12.18 mL, 95% CI, −63.35 to 38.99 mL, $P = 0.64$; Supplemental Digital Content 17, Supplemental Figure 7, http://links.lww.com/AA/B238).

Sensitivity Analysis

Sensitivity analyses revealed that omission of a single study did not change the overall WMD of the volume of perioperative blood loss; the overall WMD was changed from −6.05 mL (95% CI, −78.57 to 66.47 mL, $P = 0.87$) to 78.69 mL (95% CI, −26.28 to 183.65 mL, $P = 0.43$; Supplemental Digital Content 18, Supplemental Table 8, http://links.lww.com/AA/B239).

Subgroup Analysis and Meta-Regression

Heterogeneity among studies with respect to the overall volume of perioperative allogeneic RBC transfusion was not obvious ($I^2 = 31.8\%$, $\chi^2 = 10.27$, $P = 0.174$; Fig. 4). Therefore, subgroup analyses and meta-regression were not performed.

Publication Bias Analysis

Because the number of included studies was <10,[12] we did not perform publication bias analysis.

Secondary Outcomes

Adverse Events

The pooled RRs for the adverse events are presented in Table 2. Adverse events (e.g., mortality, reoperation for bleeding, deep vein thrombosis, pulmonary embolus, stroke, myocardial ischemia/infarction, and renal dysfunction) did not differ significantly between the PANH group and the control group. However, the risk of any infection was inclined to reduce in the PANH group versus the control group (RR, 0.64; 95% CI, 0.42 to 0.97; $P = 0.037$).

Length of Hospitalization

Seven studies ($n = 263$) compared the length of hospitalization for patients with or without PANH.[17,30,37,41,61,62] The length of hospitalization was similar in the PANH group and the control group, and the pooled WMD value for the hospital length of stay is presented in Table 2.

DISCUSSION

The perioperative use of PANH is based on the principle of reducing the red cell mass of blood loss into the surgical field by euvolemic removal of the patient's blood before surgery.[19,39,69] The return of the patient's collected blood at the conclusion of surgery should restore hemoglobin levels and augment coagulation factor and platelet concentrations, reducing bleeding and the need for allogeneic blood

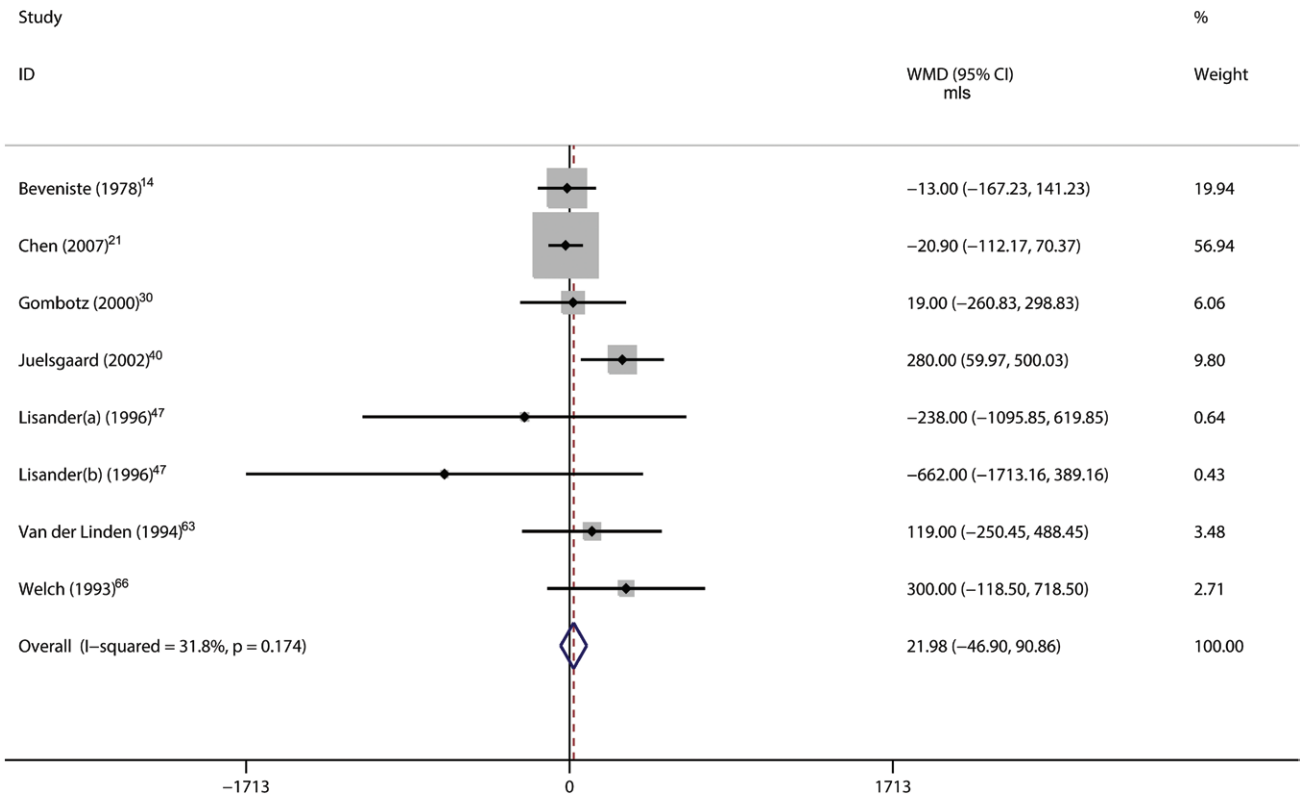

Figure 4. Forest plot of the volume of perioperative blood loss in PANH group versus control group. PANH did not show an effect in reducing the volume of perioperative blood loss. Results are from a fixed effects model. The data with zero have been excluded. PANH = preoperative acute normovolemic hemodilution; WMD = weighted mean difference; CI = confidence interval.

transfusion.[70,71] In this meta-analysis of 63 randomized controlled trials (3819 patients), we showed that PANH significantly lowered the risk of allogeneic blood transfusion and the volume of allogeneic RBC transfused compared with the control group. However, blood loss, adverse events, and the length of hospitalization were comparable between these groups.

Evidence of Benefit

Although PANH is commonly used during the perioperative period, the true efficacy of PANH in reducing perioperative allogeneic blood transfusion continues to be debated. Two previous meta-analyses reported no definite benefit of PANH for reducing perioperative allogeneic blood transfusion.[5,6] More recent studies have found inconsistent effects of PANH as a strategy for reducing the need for perioperative allogeneic blood transfusion compared with controls. On the basis of the current evidence, PANH appears to reduce exposure to allogeneic blood by 26% (RR, 0.74; 95% CI, 0.63 to 0.88; $P = 0.0006$). Furthermore, the volume of allogeneic blood transfused in the PANH groups was lower than that transfused in the control groups, by approximately 1 unit (WMD, −0.94 units; 95% CI, −1.27 to −0.61 units; $P < 0.0001$). Nevertheless, the results were heterogeneous across studies ($I^2 = 79.6\%$, $\chi^2 = 151.95$, $P < 0.0001$; $I^2 = 95.3\%$, $\chi^2 = 574.28$, $P < 0.0001$, respectively). In the present study, we considered a number of factors that might explain variation in the benefits of PANH. These factors included the type of surgery, the presence or absence of a transfusion protocol, the volume of withdrawn blood, the type of fluid for replacing the withdrawn blood, the presence or absence of other active interventions, the quality of the study, the year of publication, the sample size, and the mean age of the patients. However, none of the subgroup analyses or meta-regression analyses performed established a clear reason for the observed heterogeneous results (Supplemental Digital Content 7, Supplemental Digital Content 8, Supplemental Digital Content 13, Supplemental Digital Content 14, Supplemental Tables 3, 4, 6, and 7, http://links.lww.com/AA/B228, http://links.lww.com/AA/B229, http://links.lww.com/AA/B234, http://links.lww.com/AA/B235). We speculate that these analyses were hampered by the small number of trials included in some subgroups. In our analysis, 14 of 37 trials were conducted in patients undergoing cardiac surgery,[8,9,18,19,23,35–37,44,45,50,61,63,64] whereas only 1 trial was conducted in patients undergoing noncardiac thoracic surgery.[51] Stratification of the data by the type of surgery provided only limited information. Nevertheless, other factors also potentially contributed to the heterogeneous. Mathematical modelings have previously shown that the benefits of PANH for reducing allogeneic transfusion are dependent on the volume of intraoperative blood loss.[72] Thus, PANH is effective in reducing allogeneic blood loss transfusion only when blood loss is 1 L or when it exceeds 20% of the patients' blood volume. Furthermore, the use of a restrictive transfusion threshold may limit the clinical justification for PANH.[73]

Most trials that have evaluated PANH are small and likely underpowered to evaluate all end points, particularly safety and health resource utilization end points. Reliance on

Table 2. Adverse Events and Other Outcomes

Events	Number of studies	PANH		Control		M-H pooled RR/I-V pooled WMD			Heterogeneity		
		n+	Total	*n*+	Total	RR/WMD (95% CI)	*z*	*P*	χ^2	I^2 (%)	*P*
Mortality	22[7,18,19,29,35–41,44,45,49,50,55,58,63–65]	9	968	11	960	0.82 (0.37, 1.84)	0.48	0.634	3.04	0.0	0.80
Reoperation for bleeding	18[7,9,18,20,28,35,36,39,41,44,45,49,50,63,64,68]	15	798	16	764	0.93 (0.49, 1.79)	0.21	0.836	4.93	0.0	0.90
Any infection	10[7,14,17,20,34,38,39,49,50,64]	31	527	49	543	0.64 (0.42, 0.97)	2.08	0.037	7.66	21.6	0.26
Deep vein thrombosis	7[7,20,29,46,58,62,63]	9	286	5	289	1.82 (0.63, 5.32)	1.10	0.271	0.51	0.0	0.92
Pulmonary embolus	9[7,19,20,29,46,47,62,63]	4	333	2	331	1.56 (0.42, 5.75)	0.67	0.504	1.29	0.0	0.73
Stroke	11[19,20,29,40,44–47,50,63]	7	405	4	402	1.59 (0.53, 4.76)	0.83	0.408	0.78	0.0	0.94
Myocardial ischemia/infarction	18[18–20,29,36,37,39–41,44,45,47,50,63,64,67]	9	646	10	634	0.90 (0.39, 2.04)	0.26	0.794	1.66	0.0	0.95
Renal dysfunction	9[18,19,40,44,45,47,50,65]	15	353	24	351	0.61 (0.34, 1.11)	1.62	0.105	3.57	0.0	0.61
Length of hospital stay	7[17,30,37,41,61,62]	129		134		−0.15 (−0.89, 0.58)	0.41	0.679	2.65	0.0	0.85

n+ = The number of patient with adverse event; Total = the number of the total patients; RR = relative risk; WMD = weighted mean difference; M-H = Mantel-Haenszel; I-V = inverse-variance.

small trials further raises concerns about the effects of publication bias (as small positive trials are more likely to be published than small negative trials), as well as other concerns.[74] Funnel plot assessment revealed some evidence of publication bias in the form of a "missing" population of small negative trials (Supplemental Digital Content 9 and Supplemental Digital Content 15, Supplemental Figures 3 and 6, http://links.lww.com/AA/B230 and http://links.lww.com/AA/B236). To produce a more robust estimation, trim and fill tests were performed, and the units of perioperative allogeneic RBC transfusion were different from those obtained in the crude meta-analysis (WMD, 0.30 units; 95% CI, 0.21 to 0.45 units; $P < 0.0001$ versus WMD, −0.94 units, 95% CI, −1.27 to −0.61 units; $P < 0.0001$). As the presence of publication bias may lead to an overestimation of benefit of PANH, the results should be evaluated with some degree of caution.

Given the heterogeneous outcomes across studies and the publication bias, this benefit of PANH that we report can only be considered an approximation.

Safety of PANH

In our analysis, there were no significant differences between the PANH group and the control group in the occurrence of adverse events such as mortality, reoperation for bleeding, deep vein thrombosis, pulmonary embolus, stroke, myocardial ischemia/infarction, renal dysfunction, and length of hospitalization, with the exception of infection (Table 2). We found that the risk of any infection tended to be lower in the PANH group versus the control group (RR, 0.64; 95% CI, 0.42 to 0.97, $P = 0.037$). However, the rate of adverse events presented here was small. Therefore, it is difficult to draw firm conclusions regarding the impact of PANH on important clinical outcomes.

Limitations

There are some limitations of this meta-analysis. First, the source data were drawn from diverse surgical procedures and settings, leading to considerable heterogeneity, which made it difficult to compare the studies. This is confirmed by the fact that in the subgroup analyses and meta-regression, none of the investigated factors reduced the heterogeneity between studies. Second, the number of eligible trials was small; thus, statistical power was low, and results were likely biased. In the Egger regression asymmetry test, obvious publication biases were detected in the results of the risk perioperative allogeneic blood transfusion and volume of perioperative allogeneic RBC transfusion. This may lead to an overestimation of benefit of PANH. Third, most of the studies reviewed did not present data for the magnitude of hemodilution, transfusion triggers, the presence or absence of restrictive transfusion threshold, or the blood loss volume. The contribution of these factors to the marked observed heterogeneity is not explored in the present meta-analysis. Finally, the rates of adverse events were low, and the sample size of most reviewed studies was small. Thus, it is difficult to draw firm conclusions regarding the safety of PANH.

CONCLUSIONS

Although these results suggest that PANH is effective in reducing allogeneic blood transfusion, we identified

significant heterogeneity and publication bias, which raises concerns about the true efficacy of PANH. The safety and cost-effectiveness of PANH has not been adequately addressed. Large, methodologically rigorous, controlled trials to assess the relative efficacy, safety, and cost-effectiveness of PANH in different surgical procedures are needed.

DISCLOSURES

Name: Xuelong Zhou, MD.
Contribution: This author undertook the search, selection, extraction, data analysis, and wrote the initial manuscript.
Attestation: Xuelong Zhou approved the final manuscript.
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Contribution: This author undertook the search, extraction, and wrote the initial manuscript.
Attestation: Chenjing Zhang approved the final manuscript.
Name: Yin Wang, MD.
Contribution: This author undertook the search, selection, extraction, and data analysis.
Attestation: Yin Wang approved the final manuscript.
Name: Lina Yu, MD.
Contribution: This author undertook the data analysis and helped with the manuscript preparation.
Attestation: Lina Yu approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
Name: Min Yan, MD.
Contribution: This author undertook the data analysis and helped with the manuscript preparation.
Attestation: Min Yan approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript. Min Yan is the archival author.
This manuscript was handled by: Charles W. Hogue, MD.

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