# Preoperative acute normovolemic hemodilution: a meta-analysis

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**BACKGROUND:** Acute normovolemic hemodilution (ANH) involves withdrawal of whole blood with concurrent infusion of fluids to maintain normovolemia. The aim of this study was to quantify the efficacy and safety of preoperative ANH with a systematic review and meta-analysis.

**STUDY DESIGN AND METHODS:** Randomized controlled trials were identified through MEDLINE (1966-2002) and the Cochrane Controlled Trials Database and with hand searching of journals. All trials of preoperative ANH reporting on allogeneic transfusion, bleeding, or adverse outcomes were included. Paired reviewers independently abstracted data. Outcomes were pooled using random-effects models.

**RESULTS:** A total of 42 trials compared hemodilution to usual care or to another blood conservation method. The risk of allogeneic transfusion was similar among patients receiving ANH and those receiving usual care (relative risk [RR], 0.96; 95% CI, 0.90-1.01), or another blood conservation method (RR, 1.11; 95% CI, 0.96-1.28). Hemodiluted patients, however, were transfused from 1 to 2 fewer units of allogeneic blood. They had less total bleeding than patients receiving usual care (91 mL; 95% CI, 25-158 mL), although more intraoperative bleeding. Only one-third of studies reported on adverse events.

**CONCLUSIONS:** The literature supports only modest benefits from preoperative ANH. The safety of the procedure is unproven. Widespread adoption of ANH cannot be encouraged.

Acute normovolemic hemodilution (ANH) was introduced into surgical practice in the 1970s to reduce the requirement for allogeneic blood transfusion.[1-3] Potential benefits of ANH include improvement in tissue oxygenation because of decreased blood viscosity, reduction in exposure to blood-borne pathogens from allogeneic blood, and reduction of transfusion reactions from exposure to allogeneic blood antigens.[4-6]Another potential benefit is the availability of whole blood containing clotting factors and fresh PLTs for reinfusion after their removal during the dilution process.[7,8] ANH may be an important alternative to preoperative autologous donation in that it does not require extra patient visits for blood donation before surgery.[5]

The efficacy of ANH, however, is uncertain, with estimates from individual studies ranging from extreme benefits to important increases in the use of allogeneic blood transfusion with ANH. The discrepancies across studies may be due to differences in the degree of hemodilution, in the surgical procedures, in the comparison techniques, in the choice of outcome measures, or other methodologic differences between the studies.[9]

There has been one previous systematic review of the efficacy of ANH, which included studies through August 1996.[10] Additionally, a report following a conference in 1998 systematically reported on the state of the evidence regarding this procedure.[11] Because these reviews were inconclusive regarding the efficacy and safety of this pro-

**ABBREVIATIONS:** ANH = acute normovolemic hemodilution; RR(s) = relative risk(s).

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cedure, we evaluated this topic with a quantitative meta-analysis including several studies completed since publication of earlier reviews. Our goal was to report on the evidence regarding the efficacy and safety of ANH, to investigate whether the degree of hemodilution predicts efficacy and safety, and to identify areas in which data are too scarce to draw conclusions.

## MATERIALS AND METHODS

### Data sources

The MEDLINE database was searched to identify relevant studies. The search strategy combined the words "hemodilution" or "hemodilution" (as text words or MeSH terms) *and* the following study designs: "randomized controlled trial" (as publication type or MeSH term), "comparative studies," "evaluation studies," "follow-up studies," "prospective studies," *or* "case reports" (all of them MeSH terms), excluding animal studies. In addition to MEDLINE, the Cochrane Collaboration Database was also searched to identify additional relevant studies (key words searched: "hemodilution" *or* "hemodilution"). Electronic searches covered the years from 1966 through October 2002.

The electronic search was accompanied by a manual search of the references of the identified original studies and reviews, as well as the indices of the following journals: *Anesthesia and Analgesia*, *Journal of Clinical Anesthesia*, *Transfusion*, and *Anesthesia*, because these were the journals yielding the greatest number of relevant articles in the electronic searches.

### Study selection and data extraction

Studies were eligible for inclusion if they were randomized trials evaluating ANH and included a comparison group that did not receive ANH. We excluded animal or in vitro studies, uncontrolled studies, studies not involving surgery, studies not using ANH, studies published only as abstracts, and studies published in languages other than English. Two investigators independently reviewed all abstracts and potentially relevant articles to confirm eligibility and to extract information about study characteristics, study quality, patient characteristics, interventions, and study results. Discrepancies between reviewers were resolved by discussion.

The main outcomes of interest were the number of subjects who received allogeneic blood transfusion in the perioperative period and the average amount of allogeneic blood received per patient in each study group. Secondary outcomes were the average volume of blood loss perioperatively and all reported adverse events. Units of blood were transformed to milliliters by assuming that 1 unit of whole blood contained 450 mL of blood and that 1 unit of RBCs had a volume of 300 mL, unless stated otherwise in the original article.

The quality of each study was evaluated using versions of the quality scales of Detsky et al.[12] and Jadad et al.[13] adapted for this study. The quality items evaluated included the descriptions of the randomization process, the study outcomes, the patient sample, the interventions, and the statistical analyses.

Mathematical models of ANH have suggested that removal of a larger volume of blood preoperatively should reduce the risk of allogeneic transfusion compared to the risk associated with a smaller volume hemodilution.[14,15] Before reviewing the distribution of the data, we defined large-volume hemodilution as being when the target Hct was less than 30 percent *or* the mean volume of whole blood removed was 1500 mL *or* 19 mL per kg of body weight. We stratified the studies based on whether large-volume hemodilution was accomplished or not. Trials that provided few details about the hemodilution procedure we classified as having used lower-volume hemodilution.

### Statistical analysis

Intention-to-treat trial results were available for each study and were used in the analysis. The efficacy of ANH in reducing the risk of blood transfusion was summarized by the relative risk (RR; i.e., the ratio of the risk of blood transfusion in the ANH group compared to the control group). An RR of less than 1 indicates that ANH reduced the risk of transfusion compared to the control intervention. If RR estimates or their variances could not be computed because of cells with no patients in the study $2 \times 2$ tables, a small constant (0.5) was added to each table cell to obtain RR estimates useful for the meta-analysis. Studies that do not appear in the accompanying figures did not provide sufficient details for presentation of results for that outcome (generally they lacked estimates of the variance in the reported results).

Estimates were pooled using random-effects models following the method of DerSimonian and Laird,[16] with the estimate of heterogeneity being taken from the Mantel-Haenszel chi-square test of homogeneity.[17] We report the Q statistic and associated p value as an indicator of heterogeneity between studies. Meta-regression using the methods of restricted maximum likelihood estimation was used to investigate the impact of study characteristics on the outcomes, as a way of exploring this heterogeneity. All reported confidence intervals are from random-effects models. Similar methods were used to compute combined estimates of the efficacy of ANH in reducing the volume of allogeneic blood transfusion and the volume of blood loss, although average differences rather than RRs were used.

Results are presented as point estimates and 95 percent CIs. All p values presented are two-sided. Statistical

analyses were performed with computer software (with the commands for meta-analysis in Stata 7.0, Stata Corp., College Station, TX).

## RESULTS

### Description of studies

The search of MEDLINE yielded 918 references, the search in the Cochrane Controlled Trials Register yielded 143 additional references, and the manual searches of retrieved articles and of relevant journals yielded 53 additional articles. From these 1114 references, 1072 papers were excluded because the study was not a controlled trial, did not involve human subjects, did not study ANH in a surgical setting, did not contain original data (review studies), or did not include data on any one of our specified outcomes (Fig. 1).

We stratified the studies by the therapy received by the comparison groups (Tables 1 and 2; Fig. 1). One group of studies we called "ANH versus usual care," which included 1) studies comparing ANH to no blood conservation (23 studies) and 2) studies comparing ANH to no ANH with other blood conservation methods in both arms (10 studies, with one having two comparison groups); the other group we called "ANH versus another blood conservation method" (11 studies). Three studies included two comparisons groups.[18-20]

Two trials provided insufficient information about the volume of blood transfused intra- or postoperatively and were not included in most of the analyses.[21,22] Among the 34 trials comparing ANH to usual care, 11 trials were considered large-volume hemodilution trials.[22-32] Among the 11 trials that compared ANH to another blood-conserving procedure, only four were classified as large-volume hemodilution.[33-36]

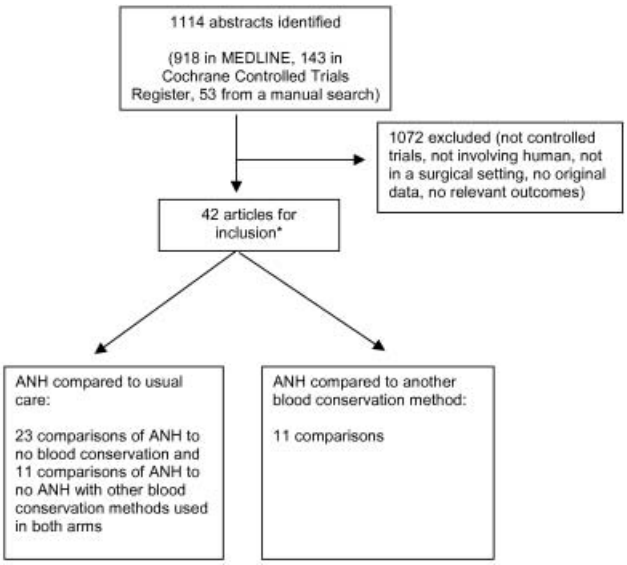


**Fig. 1. Article flow chart. *Three articles included more than one comparison.**

The 42 included studies were published between 1972 and 2002; 10 were conducted in the US, 25 in Europe, and 7 elsewhere. Eighteen of the studies were done during cardiac surgery, most often coronary artery bypass grafting; 10 studies involved hip arthroplasty, four involved radical prostatectomy, three involved spinal surgery, and the rest included a variety of procedures (knee arthroplasty, abdominal aortic aneurysm repair, thoracic procedures, scaphocephaly repair in children, and liver resection). The studies ranged in size from a total of 16 patients to 168 patients. The total number of enrolled patients included in our analyses is 2233; 1 study did not report on the number of enrolled patients.

Where specified, the lowest minimum Hb level allowed in enrolled patients was 10 g per dL; most studies specified 12 g per dL as a minimum for enrollment. Nearly all of the studies had extensive exclusion criteria that usually included recent myocardial infarction, coagulopathies, renal or hepatic disease, pulmonary dysfunction, low ejection fraction, or aortic stenosis, but five trials did not report any inclusion or exclusion criteria.[26,28,32,37,38]

### Quality of included articles

By design, we included only studies in which treatment assignment was random; however, only one-third of studies provided any additional description of the randomization process. No other quality characteristics were used to exclude studies. Only 12 studies reported that the outcomes assessor (or the person who decided upon need for allogeneic transfusion) was masked as to treatment assignment. The patients were masked to treatment assignment in only four studies.[29,34,39,40] Only 4 studies reported how many patients were approached and then excluded from participation[27,39,41,42] and 8 reported the number of patient withdrawals.[25,27,35,39,41,43-45] More than three-fourths of the studies reported the threshold at which transfusion was initiated.

### Primary outcome: allogeneic transfusion

**Risk of any allogeneic blood transfusion.** The RR of receiving allogeneic blood, at any time perioperatively, was insignificantly lower in the ANH groups compared to the usual care groups (RR, 0.96; 95% CI, 0.90-1.01; Q = 12; p = 0.98) (Fig. 2A). When the trials were stratified by the degree of hemodilution, large volume or lower volume, the RR reductions were similar. When we looked separately at the subgroup of 10 trials (the study by Boldt et al.[18] from 1992 included two comparisons), which concurrently used other blood conservation methods in both arms, the results were also similar (RR of transfusion, 0.98; 95% CI, 0.91-1.07).[8,25,27,31,39,42,46] When ANH was compared

**TABLE 1. Study population and design: ANH versus usual care**

| First author, year | Location of study | Surgery | Mean age in years or range (SD) | Male (%) | Baseline Hct (%) or (Hb) | Trigger Hct (%) or (Hb) | Number in ANH group | Number in other group | Average volume of blood withdrawn | Fluid to maintain volume | Other therapy in both groups |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bacher, 1998[21] | Austria | Cardiac surgery | 65 (5.8) | 69 | 39 | | 10 | 6 | 500 mL | 6% HES | None |
| Bennett, 1994[23] | Sweden | Hip arthroplasty | 64 (—) | | 42 | 25/30* | 20 | 20 | 900 mL | Gelatin | None |
| Boldt, 1988[64] | Germany | CABG | | | 42 | 20 | 15 | 15 | 10 mL/kg | HES 450 | None |
| Boldt, 1991[65] | Germany | CABG | | | 41 | 27 | 15 | 15 | 10 mL/kg | 6% HES | None |
| Boldt, 1999[19] | Germany | Radical prostatectomy | 65 (—) | 100 | (13 g/dL) | (7 g/dL) | 20 | 20 | 1278 mL | Gelatin | None |
| Casati, 2002[41] | Italy | Cardiac surgery | 63 (12) | 53 | 42 | 20/25* | 103 | 101 | 500 mL | Emagel | None |
| Catoire, 1992[48] | France | Aortic surgery | 66 (—) | 100 | 40 | | 10 | 10 | 875 mL | Dextran 60,000 | None |
| Dietrich, 1989[66] | Germany | CABG | 55 (7.5) | 100 | 42 | 30 | 25 | 25 | 731 mL | HES | None |
| Hallowell, 1972[38] | US | Cardiac surgery | | | 38 | | 25 | 25 | 1252 mL | Ringer's/5% albumin/5% PPF or blood | None |
| Hans, 2000[26] | Belgium | Scaphocephaly/ pachycephaly repair | 0.6 (0.35) | 71 | 33 | 21 | 17 | 17 | 122 mL | 5% albumin | None |
| Herregods, 1997[67] | Belgium | CABG | 62 (8.9) | 93 | 40 | | 39 | 32 | 750 mL | Gelatin | None |
| Kahraman, 1997[68] | Turkey | CABG | 41-70 | 69 | 42 | 30 | 14 | 14 | 5-8 mL/kg | 5% Polygeline & crystalloid | None |
| Kaplan, 1977[37] | US | Cardiac surgery | | | | | 60 | 20 | 742 mL | Plasma and Ringer's | None |
| Karakaya, 1999[20] | Turkey | Hip arthroplasty | 57 (11) | 50 | 36 | 25/30* | 10 | 10 | 874 mL | 6% HES | None |
| Lilleaasen, 1977[47] | Norway | Aortic valve replacement | 53 (11) | 67 | 42 | | 15 | 15 | 855 mL | Ringer's | None |
| Lisander, 1996[28] | Sweden | Fusion for scoliosis | 14 (1.4) | 17 | | (8 g/dL) | 10 | 13 | 1175 mL | 6% dextran then 3% | None |

**TABLE 1. *Continued***

| First author, year | Location of study | Surgery | Mean age in years or range (SD) | Male (%) | Baseline Hct (%) or (Hb) | Trigger Hct (%) or (Hb) | Number in ANH group | Number in other group | Average volume of blood withdrawn | Fluid to maintain volume | Other therapy in both groups |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Matot, 2002[29] | Israel | Liver resection | 56 (13) | 40 | 41 | 25 | 39 | 39 | 2020 mL | 6% HES/ 5% albumin | None |
| Moyes, 1985[30] | South Africa | Thoracic surgery | | | | 18 | 10 | 10 | 1500 mL | Dextran 70 | None |
| Spahn, 1996[69] | Switzerland | CABG | 64 (7.3) | 86 | | 20 | 60 | 30 | 12 mL/kg | 6% HES | None |
| Tempe, 1996[70] | India | Valve repair | 27 (9) | 40 | 36 | 25 | 50 | 50 | 303 mL | Ringer's | None |
| Van der Linden, 1994[71] | Belgium | Hip arthroplasty | 60 (9.0) | 45 | 42 | 30 | 10 | 10 | 880 mL | 6% HES and 4.5% albumin | None |
| Vedrinne, 1992[72] | France | Cardiac surgery | 58 (8.6) | 73 | 42 | 24/30* | 30 | 30 | 400 mL | 4% albumin | None |
| Welch, 1993[32] | UK | Aortic surgery | 60 (—) | 59 | 40 | | 20 | 19 | 1500 mL | Dextran 70 then PPF | None |
| Blais, 1996[24] | US | Spine reconstruction | 39 (—) | 66 | 39 | 24 | 27 | 35 | 30% of blood volume | 6% HES | Cell saver device |
| Boldt, 1992[18] | Germany | CABG | 62 (5.3) | | | | 15 | 15 | 12 mL/kg | 6% HES | Hemoconc. on bypass |
| Boldt, 1992[18] | Germany | CABG | 62 (5.3) | | | | 15 | 15 | 12 mL/kg | 6% HES | Hemofiltration on bypass |
| Hohn, 2002[27] | Switzerland | Cardiac surgery | 63 (11) | 78 | 43 | 17/25* | 36 | 41 | 1099 | HES% | Aprotinin infusion and cell saver |
| Gombotz, 2000[25] | Austria | Hip arthroplasty | 59 (14) | 0 | 40 | | 20 | 20 | 1440 mL | 6% HES and Ringer's | EPO (600 U/kg) |
| McGill, 2002[39] | UK | CABG | 63 (8) | 81 | (14 g/dL) | 20/27* | 84 | 84 | 10 mL/kg | Gelatin | Cell saver device |
| Oishi, 1997[46] | US | Hip arthroplasty | 63 (12) | 58 | 37 | | 17 | 16 | | Crystalloid and colloid | PAD in some/cell saver device in all |
| Olsfanger, 1997[31] | Israel | Knee arthroplasty | 69 (—) | 18 | 37 | 28† | 20 | 10 | 994 mL | Ringer's | Tourniquet |
| Shulman, 1998[22] | US | Spine reconstruction | 41 (15) | 58 | 40 | 24 | 80 | 80 | 1050 mL | 6% HES | Cell saver device |
| Suttner, 2001[42] | Germany | Radical prostatectomy | 63 (6) | 100 | 41 | 21 | 14 | 14 | 1000 mL | Gelatin | Controlled hypotension |
| Triulzi, 1995[8] | US | CABG or valve repair | 60 (12) | 77 | | | 18 | 28 | 924 mL | Crystalloid and colloid | Noninvasive methods |

* Intraoperative/postoperative.
† Only stated for control group.
CABG = coronary artery bypass grafting; PAD = preoperative autologous donation; PPF = plasma protein fraction.

**TABLE 2. Study population and design: ANH versus another blood conservation method**

| First author, year | Location of study | Surgery | Mean age in years or range (SD) | Male (%) | Baseline Hct (%) or (Hb) | Trigger Hct (%) or (Hb) | Number in ANH group | Number in other group | Average volume of blood withdrawn | Fluid to maintain volume | Therapy in the comparison group |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Boldt, 1999[19] | Germany | Radical prostatectomy | 65 (—) | 100 | (13 g/dL) | (7 g/dL) | 20 | 20 | 1278 | Gelatin | Controlled hypolension |
| Fredin, 1984[43] | Sweden | Hip arthroplasty | 63 (12) | 32 | 36 | | 27 | 29 | 1100 | Dextran 70 | Low-dose heparin and ergotamine |
| Fukusaki, 1997[33] | Japan | Hip arthroplasty | 61 (8.9) | | 37 | | 10 | 10 | 1000 | 6% HES | PAD; both groups also had controlled hypotension |
| Goodnough, 1999[34] | US | Knee arthroplasty | 69 (6.9) | 39 | 39 | 24 | 15 | 17 | 1100 | HES and Ringer's | PAD |
| Goodnough, 2000[45] | US | Hip arthroplasty | 64 (14) | 55 | 41 | 24 | 23 | 25 | 630 | HES and Ringer's | PAD |
| Karakaya, 1999[20] | Turkey | Hip arthroplasty | 57 (11) | 50 | 36 | 25/30* | 10 | 10 | 874 | 6% HES | Controlled hypotension |
| Mielke, 1997[73] | Germany | Hip arthroplasty | 59 (—) | 59 | 41 | (9 g/dL) | 23 | 26 | 1095 | 6% HES | Hypervolemic hemodilution |
| Monk, 1999[35] | US | Radical prostatectomy | 62 (6.1) | 100 | 43 | 25 | 27 | 26 | 1958 | 6% HES and crystalloid | PAD |
| Ness, 1992[44] | US | Radical prostatectomy | 59 (5.9) | 100 | | 28/25* | 25 | 25 | 1296 | Crystalloid and colloid | PAD |
| Rubens, 2000[40] | Canada | Cardiac surgery | | | | 18 | | | | Ringer's | PAD |
| Zohar, 1999[36] | Israel | Knee arthroplasty | 73 (6.1) | 28 | 39 | 27 | 20 | 20 | 843 | Ringer's | Tranexamic acid |

* Intraoperative/postoperative.
† Only stated for control group.
PAD = preoperative autologous donation.

to another blood conservation method, the RR of transfusion was slightly higher when ANH was used (RR, 1.11; 95% CI, 0.96-1.28; Q = 17; p = 0.01), although not significantly so (Fig. 2B). Again, when the trials were stratified by the intensity of hemodilution, there was not a significant difference in the results (p = 0.3).

The RRs of transfusion in studies comparing ANH to usual care were not significantly related to the year of the study, the number of participants, any measure of the degree of hemodilution (volume removed, volume removed per kilogram, or target Hct), the Hct value used to trigger transfusion, or the type of procedure (orthopedic, cardiac, prostate surgery, or other). Nevertheless, in the trials comparing ANH to another blood conservation method, ANH was ineffective in the most recent trials. The two most recent trials demonstrated that the alternate intervention had significantly greater efficacy at preventing allogeneic transfusion than did ANH. One of these compared hemodilution (average volume withdrawn, 843 mL) to tranexamic acid for knee arthroplasty,[36] and the other compared hemodilution (average volume withdrawn, 630 mL) to preoperative autologous donation for hip arthroplasty.[45]

**Volume of allogeneic transfusion.** The mean volume of allogeneic blood transfused intraoperatively was lower in hemodiluted patients than in patients in the usual care group (weighted mean difference, 303 mL; 95% CI, 55-551 mL; Q = 862; p < 0.001). The one trial that was an extreme outlier in the volume of blood transfused was removed from these analyses.[47] The two studies that used the largest volume hemodilution (mean of 1500 mL of blood withdrawn) reduced the volume of intraoperative allogeneic transfusion most extremely (weighted mean difference, 720 mL; 95% CI, 475-982 mL).[30,32]

In exploring the reasons for the heterogenous outcomes across trials, we found that the savings in the volume of allogeneic blood transfused intraoperatively varied directly with the volume of blood withdrawn in the hemodilution procedure (p = 0.007). Also, the savings in transfusion volume were greater in studies that used a higher Hct value to trigger transfusion (p ≤ 0.0001). The more recent studies were less likely to show a reduction in the volume of transfusion than the older trials (p = 0.003).

The total volume of allogeneic blood transfused both intra- and postoperatively was also less in the ANH group than in the usual care group (Fig. 3). The weighted mean difference in total transfusion was 201 mL (95% CI, 92-309 mL; Q = 198; p < 0.001), with little difference between the large-volume and lower-volume studies (p = 0.6). As above, trials using higher Hct levels to trigger transfusion demonstrated greater savings with ANH (p < 0.001), as did older trials (p = 0.04).

Only one study comparing ANH to another blood conservation method reported a measure of variability around the volume transfused, demonstrating a differ-

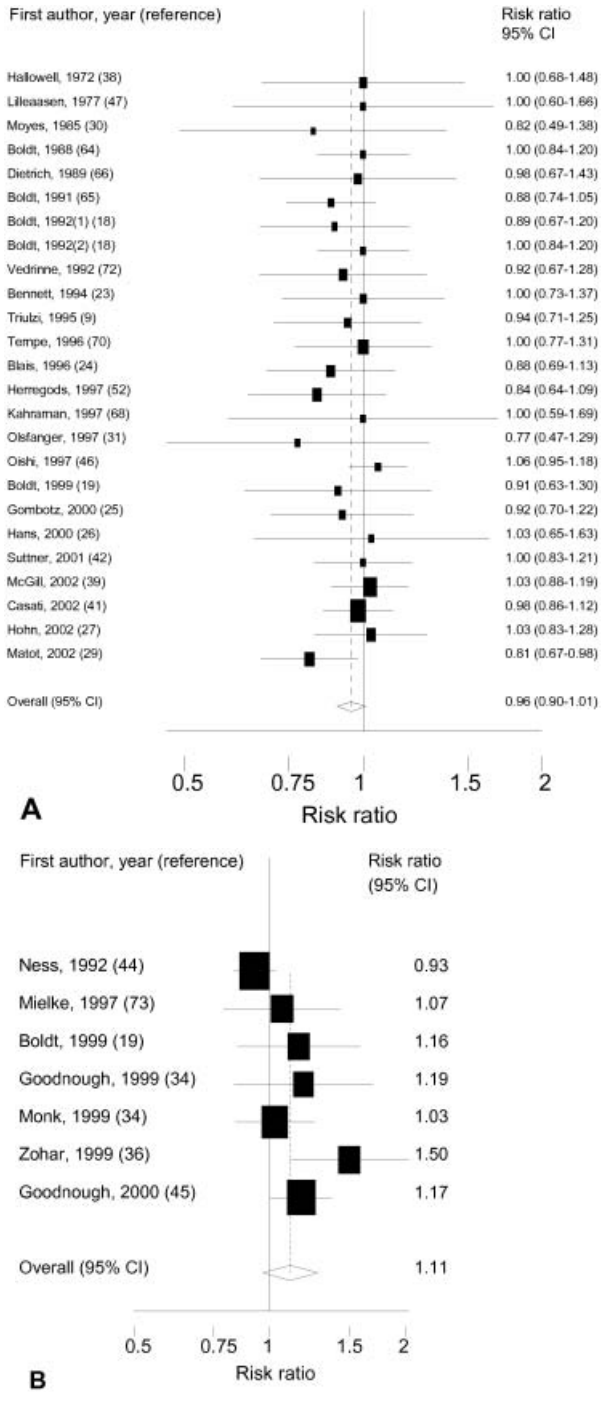


**Fig. 2. (A) ANH versus usual care: forest plot of RR of allogeneic transfusion. RR of allogeneic transfusion, intra- or postoperatively, comparing groups receiving ANH to those receiving usual care. Results are from a fixed-effects model (p value for heterogeneity, 0.98). Symbol size is proportional to weight of study. (B) ANH versus another blood conservation method: forest plot of RR of allogeneic transfusion. RR of receiving an allogeneic transfusion, intra- or postoperatively, comparing groups receiving ANH to those receiving another blood conservation method. Results are from a random-effects model (p value for heterogeneity, 0.009). Symbol size is proportional to weight of study.**

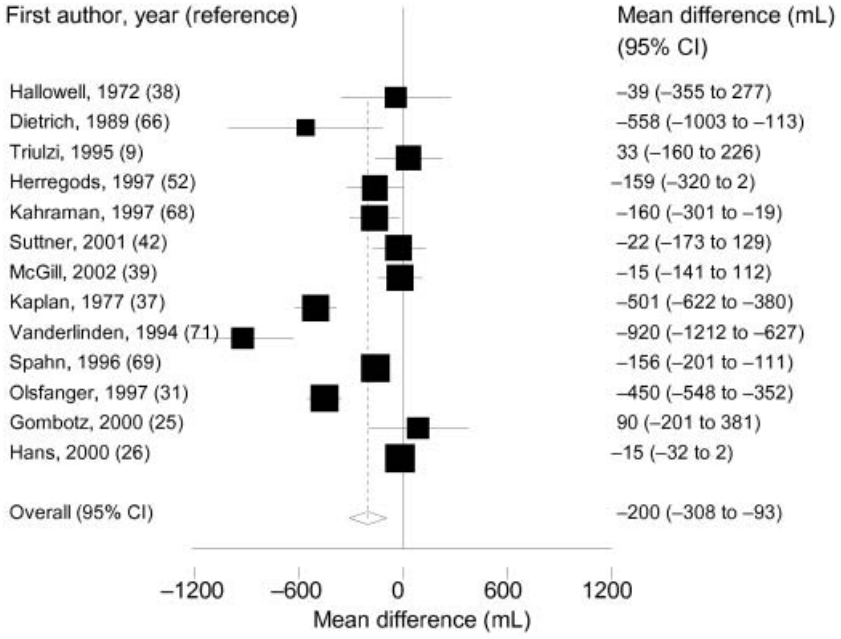


**Fig. 3. ANH versus usual care: forest plot of difference in volume of total allogeneic transfusion. Mean difference in the total volume of allogeneic blood transfused comparing groups receiving ANH to those receiving usual care. Results are from a random-effects model (p value for heterogeneity, < 0.0001). Symbol size is proportional to weight of study.**

ence of 210 mL (95% CI, 61-680 mL) in intraoperative transfusion and 240 mL (95% CI, 284-764) in total volume of transfusion.[43]

### Secondary outcomes: blood loss and adverse events

**Intraoperative and postoperative blood loss.** The volume of intraoperative blood loss was similar in the ANH groups and in the usual care groups (pooled average difference, 15 mL; 95% CI, –27 to 58 mL; Q = 11; p = 0.26), with little difference between the large-volume and lower-volume trials for this outcome (p = 1.0). None of the characteristics of the trials influenced the savings in intraoperative blood loss, although ANH was less effective at reducing blood loss in the "other" surgeries compared to in the orthopedic or cardiac surgeries (p = 0.02). The pooled average difference in blood loss in these "other" surgeries (two of aortic bypasses,[32,48] one of liver resection,[29] and one of diverse thoracic procedures[30]) was 380 mL (95% CI, 59-700 mL) favoring the usual care group.

Nevertheless, there was significantly less total (intra- and postoperative) blood loss in the ANH groups than in the usual care groups; the weighted mean difference in blood loss was 91 mL less in the ANH arms (95% CI, 25-195 mL; Q = 48; p < 0.001) (Fig. 4A). The difference in blood loss between arms was similar in the trials with large-volume hemodilutions and those with lower-volume hemodilutions (p = 0.8) and was not influenced by any trial characteristics.

Similarly, when ANH was compared to another blood conservation method, there was little difference in the pooled intraoperative blood loss between study arms (mean, 45 mL less blood loss in the other blood conservation arm; 95% CI, –48 to 139 mL; Q = 10; p = 0.11). Nevertheless, there was more total (intra- and postoperative) blood loss with ANH than in the groups with other conservation methods (weighted mean difference, 153 mL; 95% CI, 2-309 mL; Q = 30; p < 0.001) (Fig. 4B). The difference in blood loss between arms was significantly less among the studies that used large-volume hemodilutions compared to lower-volume hemodilutions (p < 0.0001).

**Adverse events.** There was sparse and inconsistent reporting on adverse events in these 42 studies. The absolute numbers of adverse events are shown in Table 3. Approximately one-third of the studies reported on in-hospital mortality, and fewer reported on any other adverse event. Few adverse events occurred in any study. Only one-fourth of the studies reported on hypotension during the procedure and, of these, only one had any events (two in the ANH arm).[36] No study noted any transfusion reactions. One patient in an ANH group who developed unilateral pulmonary edema was described as having had a potential adverse consequence of therapy.[46]

## DISCUSSION

Current evidence does not support a reduction in the risk of allogeneic transfusion in the perioperative period with use of ANH. Furthermore, the lower bound of the CI for the pooled estimate is 0.90 suggesting that, at best, ANH may reduce the risk of transfusion by 10 percent. For this outcome, there was little heterogeneity between these studies, strengthening our confidence in this pooled estimate. We did not identify any subgroup of trials in which this risk reduction was substantially lower.

The volume of allogeneic blood transfused in the ANH groups was less than that transfused in the comparison groups, by 1 to 2 units. Nevertheless, the results were heterogeneous across studies, likely owing to marked differences in the volumes transfused in both arms, with substantially more blood transfused in the older studies. The recent studies were less likely to show a benefit with ANH. Also, in studies employing a greater volume of hemodilution, a lower volume of allogeneic blood was required, as

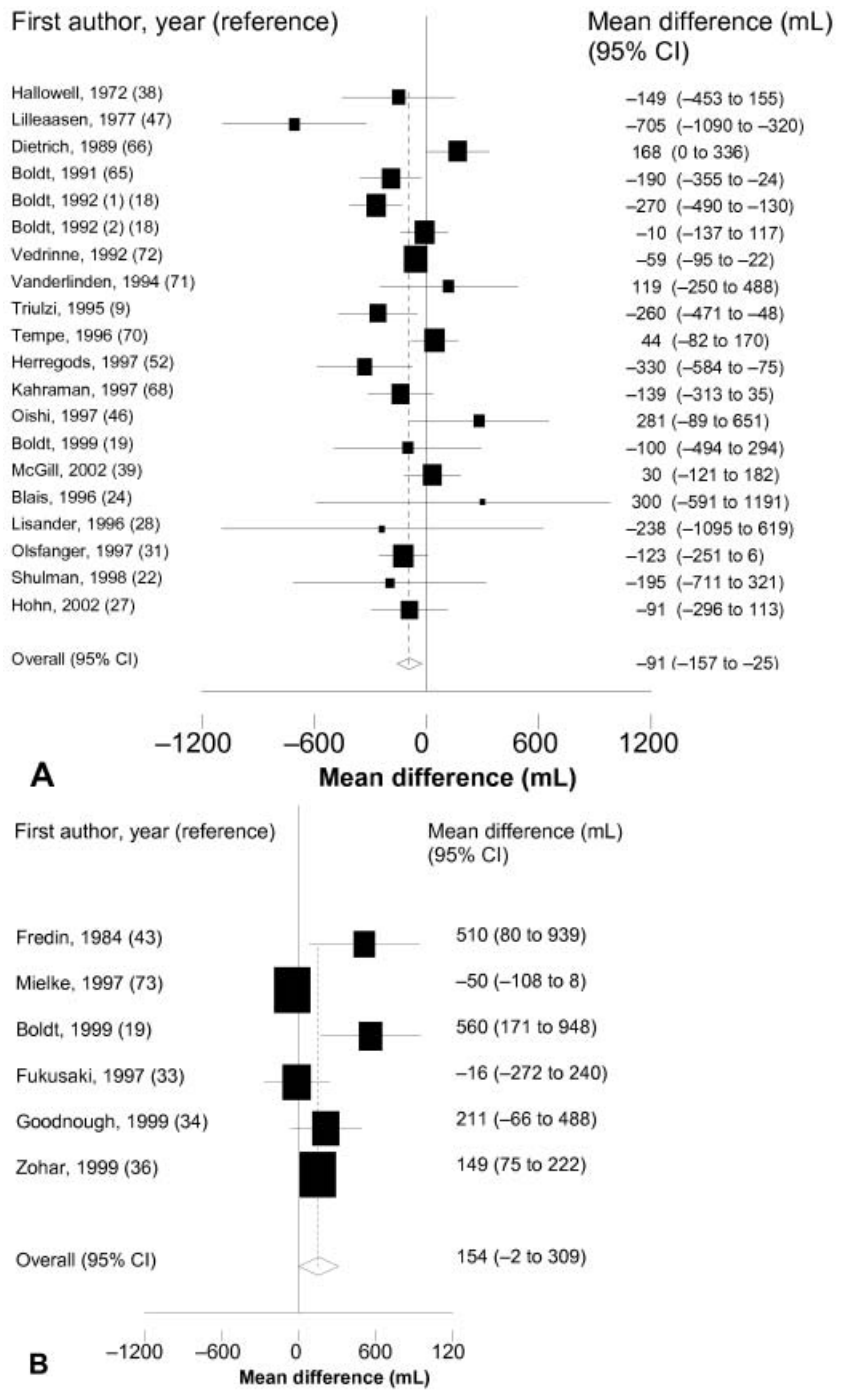


**Fig. 4. (A) ANH versus usual care: forest plot of difference in volume of total allogeneic transfusion. Mean difference in the total volume of blood loss, intra- or postoperatively, comparing groups receiving ANH compared to those receiving usual care. Results are from a random-effects model (p value for heterogeneity, < 0.0001). Symbol size is proportional to weight of study. (B) ANH versus another blood conservation method: forest plot of difference in volume of total allogeneic transfusion. Mean difference in the total volume of blood loss, intra- or postoperatively, comparing groups receiving ANH compared to those receiving another blood conservation method. Results are from a random-effects model (p value for heterogeneity, < 0.0001). Symbol size is proportional to weight of study.**

has been predicted by mathematical modeling.[15] Given the heterogeneous outcomes across studies, this 1- to 2-unit difference that we report can only be considered an approximation. It is more instructive to note the differences in results between trials and recognize what drives these differences.

The aggregate data suggest a modest hemostatic benefit (less blood loss) with use of ANH relative to the use of no blood conservation method, but the clinical benefit of reducing blood loss by this small volume is unknown. It has been suggested that ANH can only be expected to be efficacious when there is substantial intraoperative blood loss.[15] Interestingly, in the studies we reviewed, the mean amount of intraoperative blood loss in the ANH arms was highly correlated with the mean volume of blood removed by hemodilution. One possible explanation is that when sizable blood loss was anticipated, large-volume hemodilutions were planned. Alternatively, it can be hypothesized that large-volume hemodilutions generated coagulopathies resulting in greater intraoperative blood loss. These explanations need further study. Importantly, the scarcity of reporting on adverse events does not allow for conclusions regarding the safety of ANH compared to usual care or to alternative blood conservation methods.

Our results regarding risk of transfusion differ in magnitude from those in a previous meta-analysis on this topic.[10] The authors, writing for the International Study of Perioperative Transfusion, reported a combined OR for allogeneic transfusion of 0.31 (95% CI, 0.15 to 0.62), favoring ANH. Twenty-eight studies were included in their systematic review, including five that we excluded from our pooling for not meeting our inclusion criteria—one involved hemodilution in both arms,[49] one used intraoperative autotransfusion and probably not ANH,[50] one was not a controlled trial,[51] one did not involve a surgical procedure,[52] and one had no relevant outcomes.[53] Additionally, five were published in languages other than English that, at the outset, we opted to

**TABLE 3. Adverse events**

| Adverse event | Number of studies reporting outcome | Number of events/ number of patients in acute normovolemic groups | Number of events/ number of patients in comparison groups | Studies (reference numbers) |
|---|---|---|---|---|
| Death | 17 | 6/607 | 10/584* | 19, 27, 28, 29, 31, 32, 35, 36, 39, 41, 48, 52, 66, 68, 69, 70, 72 |
| Myocardial infarction | 15 | 7/502 | 9/480* | 19, 27, 28, 29, 30, 31, 35, 36, 39, 41, 48, 52, 68, 69, 71 |
| Cardiac ischemia | 6 | 8/140 | 9/137 | 27, 35, 42, 48, 52, 68 |
| Left ventricular dysfunction | 4 | 2/133 | 7/110 | 27, 43, 48, 69 |
| Venous thromboembolism | 7 | 3/180†‡ | 2/180 | 28, 30, 35, 36, 41, 43, 71 |
| Cerebral infarction | 9 | 3/323 | 2/343* | 19, 28, 29, 30, 35, 36, 39, 41, 71 |
| Hypotension during hemodilution | 10 | 2/234 | 0/243 | 24, 32, 36, 44, 45, 65, 68, 70, 71, 72 |
| Transfusion reaction | 7 | 0/131 | 0/153§ | 19, 34, 32, 65, 68, 71, 72 |

* Includes two comparison arms from Boldt et al. [19]
† One event was after discharge.
‡ Does not include study in which active deep vein thrombosis surveillance was done 2 weeks postoperatively (Fredin et al.[43]).
§ Includes two comparison arms from Boldt et al.[18]

exclude owing to resource limitations. The five non-English language articles included by these authors involved only 218 patients (ranging from 20 patients to 103 patients per study).[54-58] Exclusion of trials involving these few patients cannot explain the differences between this current meta-analysis and the previous.

One partial explanation for why our results differ from the earlier study involves the use of the OR. ORs overestimate the RR when events are common.[59] Transfusion occurred in roughly 50 percent of all participants across studies—not a rare event. Another explanation may be our inclusion of very recent studies with lower efficacy. Only one of the four high-quality trials published in 2002 demonstrated a reduction in risk of transfusion with ANH.[29] The authors of the earlier meta-analysis concluded that the observed heterogeneity in reported results suggested that the benefit of ANH was inconsistent and that the benefits they demonstrated in their meta-analysis may have been due to design flaws in the original studies.[10] Our results support this conclusion.

A systematic review published after the Royal College of Physicians Consensus conference of 1998 reported on 12 trials of ANH.[11] Of these 12, we excluded 5 for not meeting our inclusion criteria: 1 was an abstract,[60] 1 used historical controls,[61] 1 did not involve surgery,[52] 1 was in German,[62] and 1 compared ANH to hypervolemic hemodilution.[63] The authors concluded that the quality and size of the trials still, at that time, did not allow definitive conclusions. They suggested that more and higher quality research was required before ANH could be endorsed for general use in elective surgery patients.

The evidence suggests that the efficacy of ANH is likely to be small. It appears to modestly reduce bleeding and the volume of allogeneic blood requirements, but its efficacy with regard to avoidance of allogeneic transfusion is unproven. Furthermore, the safety of ANH has not been addressed adequately. There is the need for additional large, carefully controlled, prospective, randomized clinical trials, which must include strict transfusion protocols that minimize the effects of incomplete blinding and that have sufficient power to investigate both the risks and the benefits of the technique. Until additional studies demonstrate that ANH is both effective and safe, there is little justification to support widespread use of this procedure. ANH may be considered in surgical patients with an absolute contraindication to allogeneic blood transfusion, such as patients for whom blood cannot be cross-matched. In these patients, a 1- or 2-unit savings may be clinically relevant, but its routine use in the elective surgical population cannot be recommended. A 1- or 2-unit savings may have relevance on a population level, but this requires further study balanced against the costs of the procedure.

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