Medicine®

OPEN

Washed cell salvage in surgical patients
A review and meta-analysis of prospective randomized trials under PRISMA

Patrick Meybohm, MD[a],*, Suma Choorapoikayil, PhD[a], Anke Wessels[a], Eva Herrmann, PhD[b], Kai Zacharowski, MD, PhD[a], Donat R. Spahn, MD[c]

Abstract

Background: Cell salvage is commonly used as part of a blood conservation strategy. However concerns among clinicians exist about the efficacy of transfusion of washed cell salvage.

Methods: We performed a meta-analysis of randomized controlled trials in which patients, scheduled for all types of surgery, were randomized to washed cell salvage or to a control group with no cell salvage. Data were independently extracted, risk ratio (RR), and weighted mean differences (WMD) with 95% confidence intervals (CIs) were calculated. Data were pooled using a random effects model. The primary endpoint was the number of patients exposed to allogeneic red blood cell (RBC) transfusion.

Results: Out of 1140 search results, a total of 47 trials were included. Overall, the use of washed cell salvage reduced the rate of exposure to allogeneic RBC transfusion by a relative 39% (RR = 0.61; 95% CI 0.57 to 0.65; $P < 0.001$), resulting in an average saving of 0.20 units of allogeneic RBC per patient (weighted mean differences [WMD] = −0.20; 95% CI −0.22 to −0.18; $P < 0.001$), reduced risk of infection by 28% (RR = 0.72; 95% CI 0.54 to 0.97; $P = 0.03$), reduced length of hospital stay by 2.31 days (WMD = −2.31; 95% CI −2.50 to −2.11; $P < 0.001$), but did not significantly affect risk of mortality (RR = 0.92; 95% CI 0.63 to 1.34; $P = 0.66$). No statistical difference could be observed in the number of patients exposed to re-operation, plasma, platelets, or rate of myocardial infarction and stroke.

Conclusions: Washed cell salvage is efficacious in reducing the need for allogeneic RBC transfusion and risk of infection in surgery.

1. Introduction

Allogeneic blood products can be lifesaving in many conditions but limited in supply. However, inappropriate use of allogeneic red blood cell (RBC) transfusion may even be associated with increased risk of adverse outcome.[1–4] Patient blood management (PBM) is a proactive, patient-centered, and multidisciplinary approach to manage anemia, optimize hemostasis, minimize iatrogenic blood loss, and harness tolerance to anemia. Overall the concept aims to improve patient outcome by promoting and preserving body's own blood source. Cell salvage is used as part of a blood conservation strategy, and covers a wide range of techniques that scavenge blood from the operative field and wound drainages and re-infuse washed autologous RBCs back into the patient. With advances in washing and filtration technology, new cell salvage devices now provide a high quality blood product for re-infusion. The latest updated Cochrane meta-analysis was published in 2010 and included 75 trials with washed and unwashed cell salvage suggesting that cell salvage is efficacious in reducing the need for allogeneic RBC transfusion in adult elective cardiac,vascular and orthopedic surgery.[5]

Here, we examined the overall efficacy of washed cell salvage in different fields of surgery by performing an updated systematic review and meta-analysis of recent published randomized controlled trials.

2. Material and methods

2.1. Registration

The presented study has been registered at PROSPERO register (www.crd.york.ac.uk/PROSPERO, registration number: CRD42016035726).

2.2. Population and intervention

Potentially eligible trials had to be prospective and randomized including surgical patients. Patients in the intervention group received intra- and/or postoperatively washed cell salvage (=cell salvage group) whereas control patients received no cell salvage (=control group). There was neither a limit of age nor type of surgery.

2.3. Search methods for identification of studies

We undertook a systematic search of the literature to identify published reports, which investigated surgical patients receiving either cell salvage or no cell salvage. We searched Medline using the search terms "cell salvage" or "auto transfusion" or "autologous blood transfusion" or "blood salvage" or "cell saver" or "reinfusion system" and "blood transfusion" or "hemorrhage" or "anesthesia" or "transfusion" or "bleeding" or "blood loss" or "hemorrhage" and "randomized controlled trial" or "controlled clinical trial" or "randomized controlled trials" or "random allocation" or "double blind method" or "single blind method" and "humans" not including "stem cell". A total of 954 Medline articles were identified and the abstracts

were searched for reference to mortality and relevant topic. Additionally, we searched Cochrane Library using the same search criteria and found 181 articles. We also hand-searched grey literature and reference lists of identified articles and included 5 studies additionally.

Two independent authors screened the abstracts of identified studies (AW, PM). Discrepancies between the two reviewers were resolved through consensus by discussion with a third reviewer (SC). To be eligible for inclusion, studies had to include patients undergoing surgery randomized to cell salvage or to a control group that did not receive cell salvage. Study reports had to provide data either on the number of patients transfused with red cells or the volume of blood transfused. Transfusion data expressed in milliliters were converted to units by dividing by 300. Flow chart and exclusion criteria are displayed in Fig. 1.

2.4. Risk of bias assessment

To determine the validity of the included trials, we assessed the risk of bias including the domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. If one or more domains were judged as being high or unclear, we classified the trial as having a "high risk of bias." More details are provided in the Supplemental Digital Content 1–3, http://links.lww.com/MD/B173.

2.5. Endpoints

The primary endpoint of the systematic review was the number of patients exposed to allogeneic RBC transfusion. Secondary endpoints were number of units of allogeneic blood transfused, the number of patients exposed to re-operation for bleeding, number of exposed patients to plasma, number of exposed patients to platelets, infectious complications (pneumonia, wound infection, or/and sepsis), myocardial infarction, stroke, mortality, and length of hospital stay.

2.6. Ethical review

No personal data of patients were used in the present study. We only used published statistical data of meta-analysis and therefore ethical approval was not applicable in the current meta-analysis.

2.7. Statistical analysis

The meta-analysis was done in line with recommendations from the Preferred Reporting Items for Systemic reviews and Meta-Analyses (PRISMA statement).[6] In addition, we used the AMSTAR checklist in terms of the adequacy of conducting this review.[7] All analyses and graphical illustrations were conducted with Review Manager 5.3. for MAC (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), and with the R (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) using
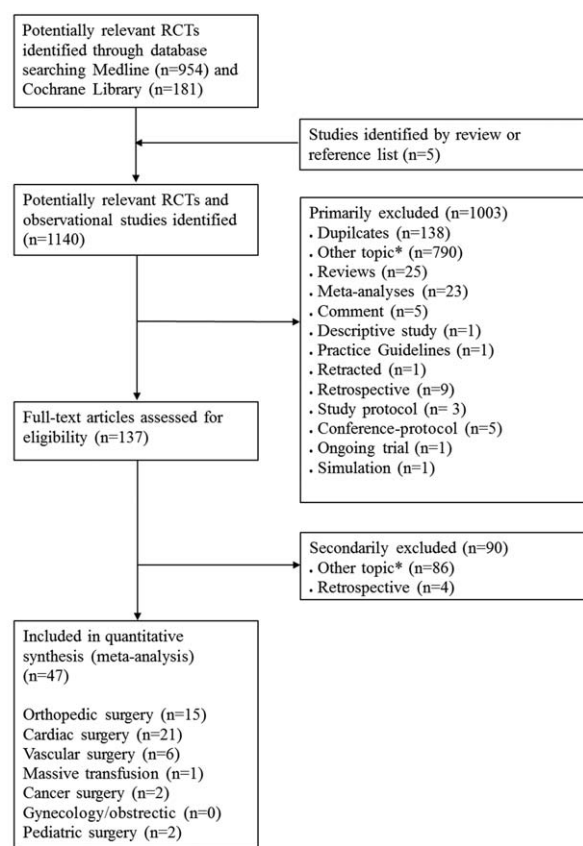
Figure 1. Flow chart of literature search in the systemic review. *Studies were excluded if unwashed preoperative donated blood, unwashed cell salvaged blood was retransfused, cell-salvage was used in all patients, acute normovolemic hemodilution was applied, or retransfused blood has only been filtered but not washed.

package meta of Guido Schwarzer (version 1.6–1) for assessing publication bias. Risk ratio (RR) and 95% confidence intervals (95% CI) were calculated using the fixed effects model (DerSimonian and Laird estimator).[8] RRs were undefined and excluded for studies with no event in either arm.

Dichotomous and continuous data were pooled across trials using a random effects model. The presence of heterogeneity and comparisons of subgroups of trials was tested by Q-test, the χ^2 statistic as well as the I^2 statistic. To find a possible evidence for publication bias, funnel plots of the RR were generated. We considered $P < 0.05$ to be statistically significant. Subgroups were prospectively defined according to type of surgery (orthopedic, cardiac, vascular, multiple trauma/massive transfusion, cancer, gynecology/obstetric, and pediatric) and age (pediatrics/adults) to determine whether effect sizes varied according to the type of surgery.

3. Results

3.1. Study selection

Cross searching of electronic databases yielded a total of 1140 reports that met our inclusion criteria. After screening of all abstracts, 137 reports were considered for full-text review. After excluding of 90 additional reports, 47 studies[9–55] were considered for final quality analysis (Fig. 1, Table 1).

3.2. All types of surgery

Of the 47 trials, 15 included orthopedic surgery,[12,17,18,24–27,30,38,40,42,44,48,54,55] 21 cardiac surgery,[9,14–16,20,22,23,28,29,32,33,35–37,41,43,46,47,50,51,53] 6 vascular surgery,[13,19,31,45,49,52] 1 multiple trauma surgery,[10] 2 cancer surgery,[21,39] and 2 pediatric surgery.[11,34]

Thirty-six trials[9,10,12–16,18–24,26–28,30–34,36,38,41–46,48,50,52–55] reported data on the number of subjects exposed to allogeneic RBC transfusion. These trials included a total of 3433 patients of whom 1783 were randomized to cell salvage. Overall, the use of cell salvage reduced the rate of exposure to allogeneic RBC transfusion by a relative 39% (RR=0.61; 95% CI 0.57 to 0.65; $P < 0.001$). Heterogeneity between these trials was statistically significant ($P < 0.001$, $I^2 = 87\%$) (Fig. 2A). Thirty-five studies[9–11,13–25,27,28,30,32–37,39,40,42,46,50–55] including 3027 patients analyzed the number of allogeneic RBC units per patient. Comparison of 1625 patients using cell salvage with 1402 control patients resulted in an average saving of 0.20 units per patient (WMD=−0.20; 95% CI −0.22 to −0.18; $P < 0.001$) (Fig. 2B). Twenty eight percent less infection were observed in 908 patients with cell salvage compared with 990 control patients (RR=0.72; 95% CI 0.54 to 0.97; $P = 0.03$)[10,11,13,16,19,20,22,27,28,31–33,38,42,43,45,48,49] (Fig. 2C). Mortality was assessed in 22 studies[9–11,13,15,16,19,20,22,31–33,35,36,41,45,46,48–52] with a follow-up of 24 hours,[51] hospital stay[9,11,16,31–33,35,36,41,49,52] and 3 years,[48,50] while 8 trials[10,13,15,19,20,22,45,46] did not report time for follow-up. No statistical difference could be observed in mortality (RR=0.92; 95% CI 0.63 to 1.34; $P = 0.66$; Fig. 2D), the number of patients exposed to re-operation (RR=1.13; 95% CI 0.70 to 1.81; $P = 0.62$), plasma (RR=1.01; 95% CI 0.78 to 1.29; $P = 0.97$), platelets (RR=0.82; 95% CI 0.62 to 1.09; $P = 0.16$), event rate of myocardial infarction (RR=0.76; 95% CI 0.47 to 1.24; $P = 0.27$), and stroke (RR=0.64; 95% CI 0.30 to 1.37; $P = 0.25$). However, length of hospital stay was reduced by 2.31 days in the cell salvage group compared with the control group (WMD=−2.31; 95% CI −2.50 to −2.11; $P < 0.001$) (Supplemental Digital Content 4A-F, http://links.lww.com/MD/B173).

3.3. Subgroups of surgery

3.3.1. Orthopedic surgery.

We found 15 studies[12,17,18,24–27,30,38,40,42,44,48,54,55] with a total of 1207 patients undergoing orthopedic surgery. In 12 trials[12,18,24,26,27,30,38,42,44,48,54,55] including 1103 patients, (n=529 cell salvage vs. n=574 control group) the use of a cell salvage reduced the need of allogeneic RBC by a relative 57% (RR=0.43; 95% CI 0.36 to 0.51; $P \leq 0.001$; Fig. 3A). Ten studies[17,18,24,25,27,30,40,42,53,54] with 590 patients analyzed the number of allogeneic blood units per patient. Comparison of 293 patients in the cell salvage group and 297 patients in the control group resulted in an average saving of 0.80 units per patient (WDM=−0.80; 95% CI −0.89 to −0.70; $P < 0.001$) (Fig. 3B). No statistical difference was observed regarding infection (RR=0.61; 95% CI 0.22 to 1.67; $P = 0.33$) or mortality rate (RR=3.03; 95% CI 0.12 to 73.51; $P = 0.5$) (Fig. 3C, D).

Table 1

Studies included in meta-analysis.

Study	Year	Country	Surgical discipline	Number of patients in the control group	Number of patients in the cell-saver group
Aghdaii et al[9]	2012	Iran	Cardiac surgery	25	25
Bowley et al[10]	2006	Republic of South Africa	Trauma surgery/massive bleeding	23	21
Cholette et al[11]	2013	United States	Pediatric surgery	53	53
Cip et al[12]	2013	Austria	Orthopedic surgery	75	76
Clagett et al[13]	1999	United States	Vascular surgery	50	50
Dalrymple-Hay et al[14]	2001	United Kingdom	Cardiac surgery	54	54
Dalrymple-Hay et al[15]	1999	United Kingdom	Cardiac surgery	56	56
Damgaard et al[16]	2006	Denmark	Cardiac surgery	30	30
Ekbäck et al[17]	1995	Sweden	Orthopedic surgery	15	15
Elawad et al[18]	1991	Sweden	Orthopedic surgery	20	19
Farrer et al[19]	1997	United Kingdom	Vascular surgery	27	23
Goel et al[20]	2007	India	Cardiac surgery	25	24
Jacobi et al[21]	1997	Germany	Cancer surgery	12	12
Kelley-Patteson et al[52]	1993	United States	Vascular surgery	18	18
Klein et al[22]	2008	United Kingdom	Cardiac surgery	111	102
Koopman (a)[53]	1993	The Netherlands	Cardiac surgery	20	20
Koopman (b)[54]	1993	The Netherlands	Orthopedic surgery	30	30
Laub et al[23]	1993	United States	Cardiac surgery	19	19
Liang et al[24]	2015	China	Orthopedic surgery	55	55
Lisander and Nordwall[25]	1996	Sweden	Orthopedic surgery	13	11
Lorentz et al[26]	1991	Germany	Orthopedic surgery	15	16
McGill et al[28]	2002	United States	Cardiac surgery	84	84
McShane et al[29]	1987	United States	Cardiac surgery	21	20
Menges et al[30]	1992	Germany	Orthopedic surgery	12	14
Mercer et al[31]	2004	United Kingdom	Vascular surgery	41	40
Murphy et al[33]	2005	United Kingdom	Cardiac surgery	31	30
Murphy et al[32]	2004	United Kingdom	Cardiac surgery	97	99
Nicolai et al[34]	2004	United Kingdom	Pediatric surgery	11	11
Niranjan et al[35]	2006	United Kingdom	Cardiac surgery	40	40
Parrot et al[36]	1991	France	Cardiac surgery	22	44
Perttilä et al[37]	1994	Finland	Cardiac surgery	12	12
Rollo et al[38]	1995	United States	Orthopedic surgery	78	35
Sankarankutty et al[39]	2006	Brazil	Cancer surgery	19	22
Lukic-Sarkanovic et al[27]	2013	Serbia	Orthopedic surgery	55	55
Savvidou et al[40]	2009	Greece	Orthopedic surgery	25	25
Scrascia et al[41]	2012	Italy	Cardiac surgery	17	17
Shenolikar et al[42]	1997	United Kingdom	Orthopedic surgery	50	50
Sirvinskas et al[43]	2007	Lithuania	Cardiac surgery	49	41
Slagis et al[44]	1991	United States	Orthopedic surgery	51	102
Spark et al[45]	1997	United Kingdom	Vascular surgery	27	23
Tempe et al[46]	1996	India	Cardiac surgery	50	50
Tempe et al[47]	2001	India	Cardiac surgery	20	20
Thomas et al[48]	2001	United Kingdom	Orthopedic surgery	116	115
Thompson et al[49]	1990	United Kingdom	Vascular surgery	34	33
Vermeijden et al[50]	2015	The Netherlands	Cardiac surgery	177	364
Xie et al[51]	2015	China	Cardiac surgery	69	72
Zhang et al[55]	2008	China	Orthopedic surgery	20	20

3.3.2. Cardiac surgery. We found 21 studies[9,14–16,20,22,23,28,29,32,33,35–37,41,43,46,47,50,51,53] with a total of 2249 patients undergoing cardiac surgery. Sixteen trials[14–16,20,22,23,28,32,33,36,41,43,46,50,53,54] including 1056 patients in the cell salvage group and 867 control patients showed an overall reduced exposure to allogeneic blood cells by a relative 29% (RR=0.71; 95% CI 0.62 to 0.81; P<0.001) (Fig. 4A). Analysis of 17 trials[9,14–16,20,22,23,28,32,35–37,41,46,50,51,53] involving 1109 patients assigned to the cell salvage group and 908 control

patients revealed an average saving of 0.65 units per patient (RR=−0.65; 95% CI −0.69 to −0.62; P<0.001) (Fig. 4B). The use of cell salvage did neither affect infection (RR=0.94; 95% CI 0.61 to 1.46; P=0.79) nor mortality rate (RR=0.72; 95% CI 0.37 to 1.39; P=0.32) (Fig. 4C, D).

3.3.3. Vascular surgery. We found 6 studies[13,19,31,45,49,52] with a total of 384 patients undergoing vascular surgery, of which 5 trials[13,19,31,45,52] with 316 patients provided data on the number of patients (n=154 cell salvage vs. n=162 control group). The exposure to allogeneic RBC transfusion was reduced

All types of surgery

Number of patients exposed to allogeneic RBC
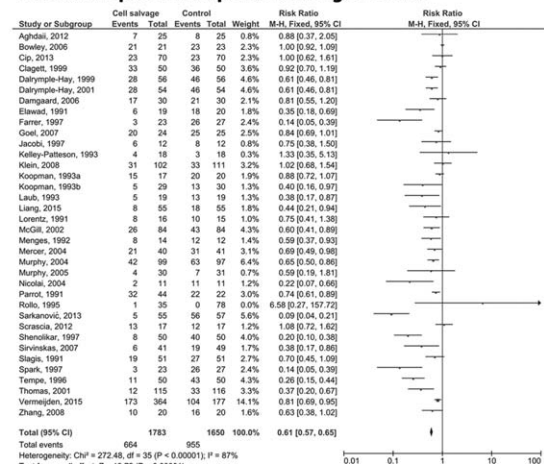
Number of units of allogeneic RBC per patient
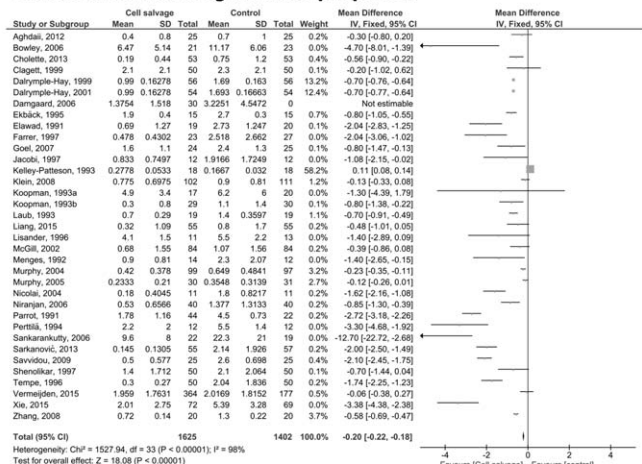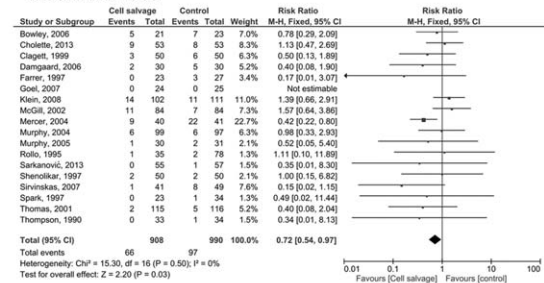
Infections rate
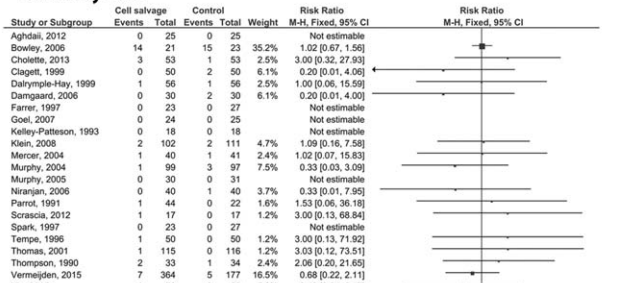
Mortality rate

Figure 2. Forest plot of cell salvage compared with control intervention in all types of surgery. (A) Number of patients exposed to allogeneic RBC, (B) number of units of allogeneic RBC per patients, (C) infections, (D) mortality rate. RBC = red blood cell.

by a relative 45% in the cell salvage group (RR = 0.55; 95% CI 0.44 to 0.68; $P < 0.001$; Fig. 5A). Three studies[13,19,52] including 186 patients (n = 91 cell salvage vs. n = 95 control group) provided data for the usage of RBC units that did not differ

significantly (RR = 0.04; 95% CI −0.11 to 0.19; $P = 0.59$; Fig. 5B). Infection rate was significantly reduced in the cell salvage group (n = 169) compared with control group (n = 179) by relative 62% (RR = 0.38; 95% CI 0.22 to 0.67; $P < 0.001$;

Orthopedic surgery

Number of patients exposed to allogeneic RBC
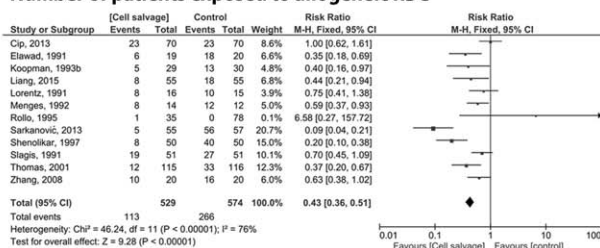
Number of units of allogeneic RBC per patient

Infections rate

Mortality rate

Figure 3. Forest plot of cell saver compared with no cell saver in orthopedic surgery. (A) Number of patients exposed to allogeneic RBC, (B) number of units of allogeneic RBC per patients, (C) infections, (D) mortality rate. RBC = red blood cell.
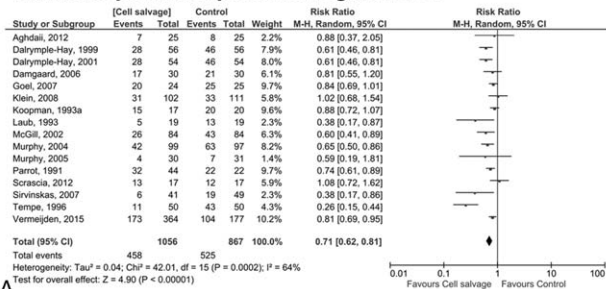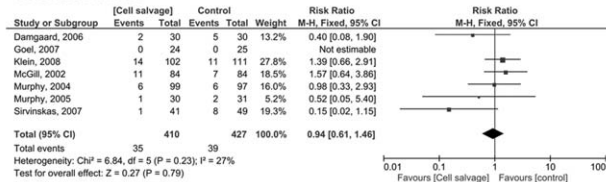
Cardiac surgery

Figure 4. Forest plot of cell saver compared with no cell saver in cardiac surgery. (A) Number of patients exposed to allogeneic RBC, (B) number of units of allogeneic RBC per patient, (C) infections, (D) mortality rate. RBC = red blood cell.

Fig. 5C). The use of a cell saver did not show statistically significant difference in mortality (RR = 0.79; 95% CI 0.20 to 3.13; $P = 0.74$; Fig. 5D).

3.3.4. Multiple trauma/massive transfusion. We found only one trial[10] including 44 patients (n = 21 cell salvage vs. n = 23 control group) with multiple trauma. The use of cell salvage resulted in an overall saving of allogeneic RBC by a relative 99% (RR = 1.00; 95% CI 0.92 to 1.09; $P = 1.00$; Supplemental Digital Content 5A, http://links.lww.com/MD/B173). In average 4.70 units (RR = −4.70; 95% CI −8.01 to −1.39; $P = 0.005$) of RBCs per patient could be saved in the cell salvage group (Supplemental Digital Content 5B, http://links.lww.com/MD/B173). Infection and mortality rate did not vary between the two groups (infection: RR = 0.78; 95% CI 0.29 to 2.09; $P = 0.62$; mortality: RR = 1.02; 95% CI 0.67 to 1.56; $P = 0.92$; Supplemental Digital Content 5C, D, http://links.lww.com/MD/B173).

3.3.5. Cancer surgery. We found 2 studies[21,39] that used cell salvage including 65 participants undergoing cancer surgery. One trial[21] addressed the number of patients exposed to allogeneic blood transfusion (n = 12 cell saver group vs. n = 12 control group), and revealed a reduced exposure by a relative of 25% (RR = 0.75; 95% CI 0.38 to 1.50; $P = 0.42$; Supplemental Digital Content 6A, http://links.lww.com/MD/B173). In average 1.21 units of RBCs (RR = −1.21; 95% CI −2.27 to −0.16; $P = 0.02$) could be saved (Supplemental Digital Content 6B, http://links. lww.com/MD/B173). None of the two studies reported infection or mortality for either the cell salvage or control group.

3.3.6. Pediatric surgery. Two studies[11,34] used cell salvage of which one study[34] assessed the number of patients (11 patients per group) exposed to allogeneic RBC transfusion that was reduced by a relative 78% (RR = 0.22; 95% CI 0.07 to 0.66; $P = 0.007$; Supplemental Digital Content 7A, http://links.lww.com/MD/B173). Both studies examined the number of blood units

applied per patient (n = 56 cell salvage vs. n = 56 control group). In average, a reduction of 0.87 RBC units per patient could be observed upon cell salvage usage (RR = −0.87; 95% CI −1.16 to −0.57; $P < 0.001$; Supplemental Digital Content 7B, http://links. lww.com/MD/B173). One trial[11] reported the number of infections and mortality in which 106 patients were equally randomly distributed into the cell salvage or control group. The use of cell salvage did not reduce infection (RR = 1.13; 95% CI 0.47–2.69; $P = 0.79$) or mortality rate (RR = 3.00; 95% CI 0.32–27.93; $P = 0.33$; Supplemental Digital Content 7C, D, http://links.lww.com/MD/B173).

3.3.7. Transfusion "triggers" / thresholds. Of the 47 included trials 22 studies[9,13–15,18,20–22,24,26–28,31,33,35,37,39,40,42,48,49,51] reported the use of a transfusion protocol for allogeneic RBC transfusion. Transfusion threshold did not vary between cell salvage and control group. Cell salvaged blood was retransfused at the end of surgery. The intra- and postoperative transfusion trigger for hemoglobin (Hb) ranged from 7 to 10 g/dL. Sixteen trials reported an intraoperative transfusion threshold, 2 trials[13,37] reported an Hb transfusion threshold of 10.0 g/dL, 4 trials[20,26,28,48] between 9.0 and 9.5 g/dL, 4 trials[21,27,31,51] between 8.0 and 8.9 g/dL, 6 trials[9,15,22,24,32,40] of 7.0 g/dL. Eighteen trials reported a postoperative transfusion threshold, 5 trials[13–15,26,49] reported a Hb transfusion threshold of 10.0 g/dL, 3 trials[28,42,48] between 9.0 and 9.5 g/dL, 7 trials[18,21,22,27,35,39,51] between 8.0 and 8.9 g/dL, 3 trials[24,33,40] of 7.0 g/dL, and 10 trials[9,13,16,19,20,28,33,36,40,49] transfused patients when the hematocrit value was less than 30%.

3.3.8. Quality management and cost analysis. All included studies did not provide sufficient comparable data to either estimate the quality of salved blood or to perform cost analysis (see Supplemental Digital Content 8–9, http://links.lww.com/MD/B173).
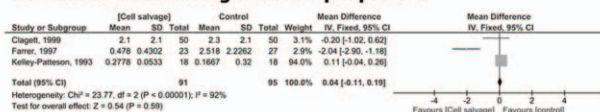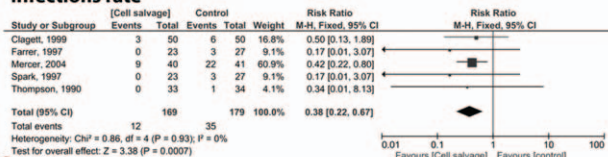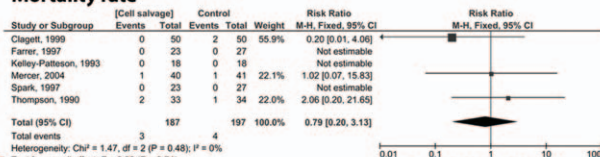
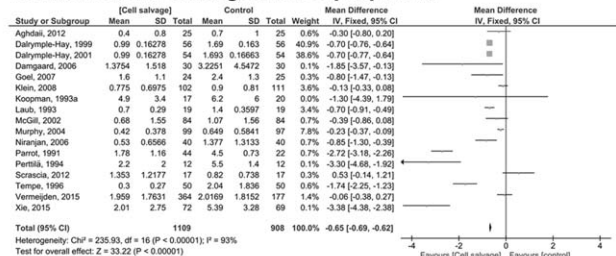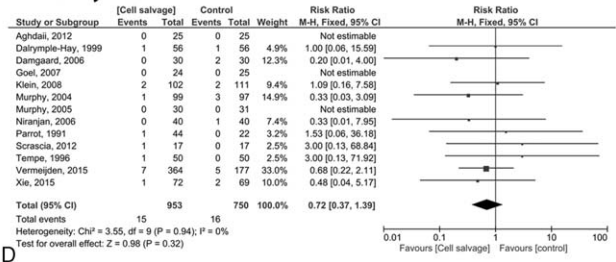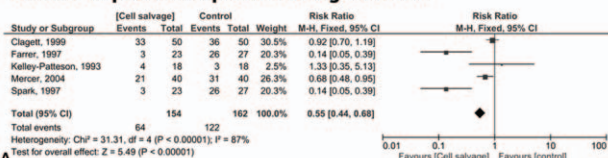**Figure 5.** Forest plot of cell saver compared with no cell saver in vascular surgery. (A) Number of patients exposed to allogeneic RBC, (B) number of units of allogeneic RBC per patient, (C) infections, (D) mortality rate. RBC = red blood cell.

4. Discussion

Patient blood management encompasses multiple blood-sparing techniques that minimize the risk for blood loss and the need for allogeneic RBC transfusion.[56] In this respect, cell salvage is an important tool of blood conservation but is inconsistently used in daily practice due to uncertainties about its efficiency.

The latest Cochrane meta-analysis of prospective trials was published in 2010 and included 75 studies focusing on the field of cardiac, vascular, and orthopedic surgery that used both washed and unwashed cell salvage reporting an overall reduction by a relative 38%.[5] Recent studies, however, demonstrated that the use of unwashed cell salvage negatively affect recovery after surgery. Unwashed salvaged blood may be enriched with inflammatory mediators,[57–59] fibrin degradation products[60,61] and interleukins[62,63] that exceed body's own circulating levels leading to enhanced coagulopathy, systemic inflammation, or acute respiratory distress syndrome. Additionally, some concerns emerged during the last years upon the observation that total drain output was shown to be significantly greater after unwashed salvaged blood retransfusion during total knee arthroplasty compared with patients receiving allogeneic transfusion only.[64–66] In this study, we performed an up-dated meta-analysis of randomized controlled trials focusing on washed salvage in which patients of all ages were randomized either to washed cell salvaged or to a control group scheduled for all types of surgery with a broad spectrum of relevant clinical endpoints. Our search resulted in 8 additional trials published beyond 2010 and 10 trials with a total of 1630 patients that were not included in the latest Cochrane Analysis. We showed that the overall use of washed cell salvaged blood reduces perioperative allogeneic RBC transfusion exposure by a relative 39% with the most significant result in orthopedic surgery where the use of cell salvage reduced the exposure by 57% in 15 trials. Thus, the overall consumption decreased by 0.80 RBC units per patient. A recent observational study including approximately 1.6 million patients revealed that transfusion of a single unit allogeneic RBC already double the risk for myocardial infarction and/or ischemic stroke.[4] Notable, Rohde et al performed a systematic review and meta-analysis including 7456 patients assigned either to a restrictive or liberal transfusion practice. A restrictive transfusion strategy with less RBC transfusion was associated with a reduced risk of serious infections.[67] In accordance, our meta-analysis demonstrated a reduced infection rate upon usage of cell salvage reduced allogeneic RBC transfusion rate.

In cancer surgery, however, the use of cell salvage is controversially debated and much reservation exists among surgeons. Retransfusion may increase the risk of cancer recurrence, while allogeneic RBC transfusion may also be associated with increased risk of cancer recurrence. However, a recent systematic review emphasizes that the use of a leucocyte depletion filter enables the elimination of tumor cells from blood–tumor cells mixture, whereas a standard filter did not. Overall the study showed that the use of cell salvage in patients having cancer surgery was not associated with a greater risk of tumor dissemination or metastasis. However, caution must be given when tumor rupture occurs during surgery as washed blood remained positive for tumor cells.[68] A statistically powered trial is essentially needed to finally elucidate whether cell salvaged blood or allogeneic RBC transfusion is superior in terms of cancer recurrence.

To our knowledge no results of prospective randomized controlled trials have been published in the last decade describing the use of cell salvage within multiple trauma surgery. The technique has not been widely accepted for trauma patients undergoing urgent surgery because of various reasons. Firstly, logistic issues exist for implementing an immediate auto-transfusion protocol. In addition, trauma induced injuries persist a high potential for infections and bacterial contamination. However, our analysis of one trial including multiple traumata surgeries confirmed the beneficial use of cell sever in that 4.70 units of blood could be saved per patient, thereby strongly supporting it's use within trauma patients. Cholette et al[11] showed impressively, that cell saver blood can safely be stored at the bedside for immediate transfusion for 24 hours after collection disclosing an additional opportunity to retransfuse autologous blood. It would be of interest to conduct a randomized controlled study that is statistically powered to confirm these results.

Till now, cell salvage is not widely used during cancer or trauma surgery, however current evidence justify further evaluation of its use in clinical studies.

Technical limitations generally restrict the use of cell salvage for infants during surgery. Yet advancements and increasing knowledge may allow volume-independent collection and retransfusion of salvaged blood.[69] Our search revealed two

trials that support the use of cell salvage technique during pediatric surgery. Analysis of 106 infants undergoing cardiac surgery with cardiopulmonary bypass weighing less than or equal to 20 kg and 22 patients between 6 and 17 years undergoing acetabulosplasty revealed a 5-fold less exposure to allogeneic RBCs and 0.87 less RBC units per patient in the cell salvage group compared with the control group. Thus, our analysis supports and recommends the use of cell salvage during pediatric surgery.

Inappropriate allogeneic RBC transfusion may be associated with increased morbidity and mortality. From the urgent need to formulate common transfusion threshold the World Health Assembly has endorsed PBM, requesting the World Health Organization to provide its member states with training on the safe, rational use of allogenic RBC transfusion and transfusion alternatives (WHA63.12) in 2010.[70] In accordance with this release we observed a change in transfusion practice in the trials outlined in this study. Initially, we detected a broad transfusion range between 7 and 10 g/dL in studies published until 2005 that became more restricted in the last decade with a transfusion trigger ranging between 7 and 8 g/dL. In most studies, transfusion thresholds did not vary between the cell salvage and control group. Due to the different benefit-risk-ratio, we rather suggest that salvaged blood should be routinely retransfused irrespective of the Hb level. It is noteworthy, that in addition to a restrictive transfusion policy an improvement in patient outcome (reduced RBC transfusion rate, infection rate and length of hospital stay) could be observed upon utilization of cell salvage within the surgical setting. Our meta-analysis could not clarify whether the use of cell salvage is associated with increased or decreased costs. Three trials[10,16,22] observed no cost differences; one[48] reported an increased cost investment for the use of cell salvage usage and one[40] estimated reduced costs of 225 € per patient upon retransfusion of salvaged blood. Thus, estimation of cost is challenging as different parameters were defined for cost calculation.

With regard to the pooled analysis, some limitations must be taken into account. In our meta-analysis we found that most of the studies were of limited methodological quality and risk of bias could not be fully judged in any of the included trials. The majority of the included trials did not provide detailed information about procedure or blinding. Analyses of individual trials suggest that some effect sizes were overestimated, for example participants with long hospitalization were excluded from the analysis.[54] Investigation of publication bias by generating funnel plots showed no obvious deviations from symmetry excluding the possibility of potential publication bias. However, a tendency may exist to publish more likely trials in favor of the studied intervention and may challenge the significance of the meta-analysis presented in this study.[71] The times of re-infusion of autologous RBCs differed widely from the time point of surgery, to skin closure up to 6 hours post-surgery or were not described at all and might affect study outcome.

5. Conclusion

On the basis of this meta-analysis, washed cell salvage is efficacious in reducing the need for allogeneic RBC transfusion in surgery and even in decreasing the risk of infection. Thus, we recommend the use of cell salvage for surgery in which blood loss is a concern. However, the methodical qualities of the presented study are poor in quality, and further large randomized prospective trials are still needed.

References

[1] Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011;114:283–92.

[2] Hopewell S, Omar O, Hyde C, et al. A systematic review of the effect of red blood cell transfusion on mortality: evidence from large-scale observational studies published between 2006 and 2010. BMJ open 2013;3:

[3] Shander A, Fink A, Javidroozi M, et al. Appropriateness of allogeneic red blood cell transfusion: the international consensus conference on transfusion outcomes. Transfus Med Rev 2011;25:232.e53–46.e53.

[4] Whitlock EL, Kim H, Auerbach AD. Harms associated with single unit perioperative transfusion: retrospective population based analysis. BMJ 2015;350:h3037.

[5] Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2010;Cd001888.

[6] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Int Med 2009;151:264–9. w64.

[7] Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.

[8] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[9] Aghdaii NKM, Yazdanian F, Ghaffarinejad MH. Effect of retransfusion of heparin remaining in the salvaged blood on postoperative blood loss in coronary artery bypass grafting: comparison with homologous blood transfusion. Iran Heart J 2012;13:10.

[10] Bowley DM, Barker P, Boffard KD. Intraoperative blood salvage in penetrating abdominal trauma: a randomised, controlled trial. World J Surg 2006;30:1074–80.

[11] Cholette JM, Powers KS, Alfieris GM, et al. Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: results of a prospective, randomized, clinical trial. Pediatr Crit Care Med 2013;14:137–47.

[12] Cip J, Widemschek M, Benesch T, et al. Does single use of an autologous transfusion system in TKA reduce the need for allogenic blood? A prospective randomized trial. Clin Orthop Relat Res 2013;471:1319–25.

[13] Clagett GP, Valentine RJ, Jackson MR, et al. A randomized trial of intraoperative autotransfusion during aortic surgery. J Vasc Surg 1999;29:22–30. discussion -1.

[14] Dalrymple-Hay MJ, Dawkins S, Pack L, et al. Autotransfusion decreases blood usage following cardiac surgery—a prospective randomized trial. Cardiovasc Surg 2001;9:184–7.

[15] Dalrymple-Hay MJ, Pack L, Deakin CD, et al. Autotransfusion of washed shed mediastinal fluid decreases the requirement for autologous blood transfusion following cardiac surgery: a prospective randomized trial. Eur J Cardiothorac Surg 1999;15:830–4.

[16] Damgaard S, Steinbruchel DA. Autotransfusion with cell saver for off-pump coronary artery bypass surgery: a randomized trial. Scand Cardiovasc J 2006;40:194–8.

[17] Ekbäck GSK, Axelsson K, Carlberg M. Perioperative autotransfusion and functional coagulation analysis in total hip replacement. Acta Anaesthesiol Scand 1995;39:390–5.

[18] Elawad AA, Ohlin AK, Berntorp E, et al. Intraoperative autotransfusion in primary hip arthroplasty. A randomized comparison with homologous blood. Acta Orthop Scand 1991;62:557–62.

[19] Farrer A, Spark JI, Scott DJ. Autologous blood transfusion: the benefits to the patient undergoing abdominal aortic aneurysm repair. J Vasc Nurs 1997;15:111–5.

[20] Goel P, Pannu H, Mohan D, et al. Efficacy of cell saver in reducing homologous blood transfusions during OPCAB surgery: a prospective randomized trial. Transfus Med 2007;17:285–9.

[21] Jacobi K, Walther A, Kuhn R, et al. Advantages and limitations of intraoperative mechanical autotransfusion in al prostatectomies. Anaesthesist 1997;46:101–7.

[22] Klein AA, Nashef SA, Sharples L, et al. A randomized controlled trial of cell salvage in routine cardiac surgery. Anesth Analg 2008;107:1487–95.

[23] Laub GW, Dharan M, Riebman JB, et al. The impact of intraoperative autotransfusion on cardiac surgery. A prospective randomized double-blind study. Chest 1993;104:686–9.

[24] Liang J, Shen J, Chua S, et al. Does intraoperative cell salvage system effectively decrease the need for allogeneic transfusions in scoliotic patients undergoing posterior spinal fusion? A prospective randomized study. Eur Spine J 2015;24:270–5.

[25] Lisander BJR, Nordwall A. Combination of blood-saving methods decreases homologous blood requierments in scoliosis surgery. Anaesth Intens Care 1996;24:555–8.

[26] Lorentz A, Osswald PM, Schilling M, et al. A comparison of autologous transfusion procedures in hip surgery. Anaesthesist 1991;40:205–13.

[27] Lukic-Sarkanovic M, Gvozdenovic L, Savic D, et al. Autologous blood transfusion in total knee replacement surgery. Vojnosanit Pregl 2013;70:274–8.

[28] McGill N, O'Shaughnessy D, Pickering R, et al. Mechanical methods of reducing blood transfusion in cardiac surgery: randomised controlled trial. BMJ 2002;324:1299.

[29] McShane AJ, Power C, Jackson JF, et al. Autotransfusion: quality of blood prepared with a red cell processing device. Br J Anaesth 1987;59:1035–9.

[30] Menges T, Rupp D, van Lessen A, et al. Measures for reducing the use of homologous blood. Effects on blood coagulation during total endoprosthesis. Anaesthesist 1992;41:27–33.

[31] Mercer KG, Spark JI, Berridge DC, et al. Randomized clinical trial of intraoperative autotransfusion in surgery for abdominal aortic aneurysm. Br J Surg 2004;91:1443–8.

[32] Murphy GJ, Allen SM, Unsworth-White J, et al. Safety and efficacy of perioperative cell salvage and autotransfusion after coronary artery bypass grafting: a randomized trial. Ann Thorac Surg 2004;77:1553–9.

[33] Murphy GJ, Rogers CS, Lansdowne WB, et al. Safety, efficacy, and cost of intraoperative cell salvage and autotransfusion after off-pump coronary artery bypass surgery: a randomized trial. J Thorac Cardiovasc Surg 2005;130:20–8.

[34] Nicolai P, Leggetter PP, Glithero PR, et al. Autologous transfusion in acetabuloplasty in children. J Bone Joint Surg 2004;86:110–2.

[35] Niranjan G, Asimakopoulos G, Karagounis A, et al. Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial. Eur J Cardiothorac Surg 2006;30:271–7.

[36] Parrot D, Lancon JP, Merle JP, et al. Blood salvage in cardiac surgery. J Cardiothorac Vasc Anesth 1991;5:454–6.

[37] Perttila JT, Salo MS, Jalonen JR, et al. Blood transfusion with autologous and leukocyte-depleted or standard allogeneic red blood cells and the immune response to open heart surgery. Anesth Analg 1994;79:654–60.

[38] Rollo VJ, Hozack WJ, Rothman RH, et al. Prospective randomized evaluation of blood salvage techniques for primary total hip arthroplasty. J Arthroplasty 1995;10:532–9.

[39] Sankarankutty AK, Teixeira AC, Souza FF, et al. Impact of blood salvage during liver transplantation on reduction in transfusion requirements. Acta Cir Bras 2006;21(suppl 1):44–7.

[40] Savvidou C, Chatziioannou SN, Pilichou A, et al. Efficacy and cost-effectiveness of cell saving blood autotransfusion in adult lumbar fusion. Transfus Med 2009;19:202–6.

[41] Scrascia G, Rotunno C, Nanna D, et al. Pump blood processing, salvage and re-transfusion improves hemoglobin levels after coronary artery bypass grafting, but affects coagulative and fibrinolytic systems. Perfusion 2012;27:270–7.

[42] Shenolikar A, Wareham K, Newington D, et al. Cell salvage auto transfusion in total knee replacement surgery. Transfus Med 1997;7:277–80.

[43] Sirvinskas E, Veikutiene A, Benetis R, et al. Influence of early re-infusion of autologous shed mediastinal blood on clinical outcome after cardiac surgery. Perfusion 2007;22:345–52.

[44] Slagis SV, Benjamin JB, Volz RG, et al. Postoperative blood salvage in total hip and knee arthroplasty. A randomised controlled trial. J Bone Joint Surg 1991;73:591–4.

[45] Spark JI, Chetter IC, Kester RC, et al. Allogeneic versus autologous blood during abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 1997;14:482–6.

[46] Tempe D, Bajwa R, Cooper A, et al. Blood conservation in small adults undergoing valve surgery. J Cardiothorac Vasc Anesth 1996;10:502–6.

[47] Tempe DK, Banerjee A, Virmani S, et al. Comparison of the effects of a cell saver and low-dose aprotinin on blood loss and homologous blood usage in patients undergoing valve surgery. J Cardiothorac Vasc Anesth 2001;15:326–30.

[48] Thomas D, Wareham K, Cohen D, et al. Autologous blood transfusion in total knee replacement surgery. Br J Anaesth 2001;86:669–73.

[49] Thompson JF, Webster JH, Chant AD. Prospective randomised evaluation of a new cell saving device in elective aortic reconstruction. Eur J Vasc Surg 1990;4:507–12.

[50] Vermeijden WJ, van Klarenbosch J, Gu YJ, et al. Effects of cell-saving devices and filters on transfusion in cardiac surgery: a multicenter randomized study. Ann Thorac Surg 2015;99:26–32.

[51] Xie Y, Shen S, Zhang J, et al. The efficacy, safety and cost-effectiveness of intra-operative cell salvage in high-bleeding-risk cardiac surgery with cardiopulmonary bypass: a prospective randomized and controlled trial. Int J Med Sci 2015;12:322–8.

[52] Kelley-Patteson C, Ammar AD, Kelley H. Should the cell saver autotransfusion device be used routinely in all infrarenal abdominal aortic bypass operations? J Vasc Surg 1993;18:261–5.

[53] Koopman G. Peri-operative Autotransfusion by Means of a Blood Cell Separator. Processed Autotransfusion and Homologous Red Cell Requirement in Elective Cardiac and Orthopaedic Surgery: a Randomised Prospective Study. 1993;Den Haag:Cip-Data Koninklijke Bibliotheek, 1993a(chapter 5): 96–112.

[54] Koopman G. Peri-operative Autotransfusion by Means of a Blood Cell Separator. Processed Autotransfusion and Homologous Red Cell Requirement in Elective Cardiac and Orthopaedic Surgery: A Randomised Prospective Study. 1993;DenHaag:Cip-Data Koninklijke Bibliotheek, 1993b; chapter 5: 96–112.

[55] Zhang XF, Dong JM, Gong ML, et al. Effectiveness of preoperative autologous plateletpheresis combined with intraoperative autotransfusion on the blood coagulation in orthopaedic patients. Zhonghua wai ke za zhi 2008;46:118–21.

[56] Spahn DR, Goodnough LT. Alternatives to blood transfusion. Lancet 2013;381:1855–65.

[57] Andersson I, Tylman M, Bengtson JP, et al. Complement split products and pro-inflammatory cytokines in salvaged blood after hip and knee arthroplasty. Can J Anaesth 2001;48:251–5.

[58] Bengtsson A, Avall A, Hyllner M, et al. Formation of complement split products and proinflammatory cytokines by reinfusion of shed autologous blood. Toxicol Lett 1998;100–101:129–33.

[59] Sinardi D, Marino A, Chillemi S, et al. Composition of the blood sampled from surgical drainage after joint arthroplasty: quality of return. Transfusion 2005;45:202–7.

[60] Krohn CD, Reikeras O, Bjornsen S, et al. Fibrinolytic activity and postoperative salvaged untreated blood for autologous transfusion in major orthopaedic surgery. Eur J Surg 2001;167:168–72.

[61] Duchow J, Ames M, Hess T, et al. Activation of plasma coagulation by retransfusion of unwashed drainage blood after hip joint arthroplasty: a prospective study. J Arthroplasty 2001;16:844–9.

[62] Tylman M, Bengtson JP, Avall A, et al. Release of interleukin-10 by reinfusion of salvaged blood after knee arthroplasty. Intensive Care Med 2001;27:1379–84.

[63] Handel M, Winkler J, Hornlein RF, et al. Increased interleukin-6 in collected drainage blood after total knee arthroplasty: an association with febrile reactions during retransfusion. Acta Orthop Scand 2001;72:270–2.

[64] Matsuda K, Nozawa M, Katsube S, et al. Reinfusion of unwashed salvaged blood after total knee arthroplasty in patients with rheumatoid arthritis. Int Orthop 2009;33:1615–8.

[65] Matsuda K, Nozawa M, Katsube S, et al. Activation of fibrinolysis by reinfusion of unwashed salvaged blood after total knee arthroplasty. Transfus Apher Sci 2010;42:33–7.

[66] Singh VK, Singh PK, Javed S, et al. Autologous transfusion of drain contents in elective primary knee arthroplasty: its value and relevance. Blood Trans 2011;9:281–5.

[67] Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA 2014;311:1317–26.

[68] Kumar N, Chen Y, Zaw AS, et al. Use of intraoperative cell-salvage for autologous blood transfusions in metastatic spine tumour surgery: a systematic review. Lancet Oncol 2014;15:e33–41.

[69] Booke M, Hagemann O, Van Aken H, et al. Intraoperative autotransfusion in small children: an in vitro investigation to study its feasibility. Anesth Analg 1999;88:763–5.

[70] Organization WH. Global Forum for Blood Safety: Patient Blood Management. 2010

[71] Dickersin K, Chan S, Chalmers TC, et al. Publication bias and clinical trials. Controll Clin Trials 1987;8:343–53.