Published in final edited form as:

Cochrane Database Syst Rev. ; (3): CD004172. doi:10.1002/14651858.CD004172.pub2.

Platelet-rich-plasmapheresis for minimising peri-operative allogeneic blood transfusion

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Abstract

Background—Concerns regarding the safety of transfused blood have generated considerable enthusiasm for the use of technologies intended to reduce the use of allogeneic blood (blood from an unrelated donor). Platelet-rich plasmapheresis (PRP) offers an alternative approach to blood conservation.

Objectives—To examine the evidence for the efficacy of PRP in reducing peri-operative allogeneic red blood cell (RBC) transfusion, and the evidence for any effect on clinical outcomes such as mortality and re-operation rates.

Search methods—We identified studies by searching MEDLINE (1950 to 2009), EMBASE (1980 to 2009), *The Cochrane Library* (Issue 1, 2009), the Internet (to March 2009) and the reference lists of published articles, reports, and reviews.

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CONTRIBUTIONS OF AUTHORS

Danielle Anthony (University of Newcastle) conducted the original literature searches, obtained relevant papers, applied inclusion/exclusion criteria to retrieved papers and quality assessed trials; Paul Carless (University of Newcastle) updated literature searches, extracted study data, quality assessed trials, co-ordinated the project and co-wrote review; David Henry (University of Newcastle) provided methodological expertise and co-wrote review; Dianne O'Connell (University of Newcastle) provided statistical consultancy for the review; Fraser Rubens (Ottawa Heart Institute) provided expert opinion.

Editorial group: Cochrane Injuries Group.

Publication status and date: Edited (no change to conclusions), published in Issue 3, 2011.

Review content assessed as up-to-date: 24 March 2009.

DECLARATIONS OF INTEREST

None known.

NOTES: The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author (Boldt 1990, Boldt 1993, Menges 1996, Menges 1997) on the conclusions of the review.

Selection criteria—Controlled parallel group trials in which adult patients, scheduled for non-urgent surgery, were randomised to PRP, or to a control group which did not receive the intervention.

Data collection and analysis—Primary outcomes measured were: the number of patients exposed to allogeneic RBC transfusion, and the amount of RBC transfused. Other outcomes measured were: the number of patients exposed to allogeneic platelet transfusions, fresh frozen plasma, and cryoprecipitate, blood loss, re-operation for bleeding, post-operative complications (thrombosis), mortality, and length of hospital stay. Treatment effects were pooled using a random-effects model. Trial quality was assessed using criteria proposed by Schulz *et al* (Schulz 1995).

Main results—Twenty-two trials of PRP were identified that reported data for the number of patients exposed to allogeneic RBC transfusion. These trials evaluated a total of 1589 patients. The relative risk (RR) of exposure to allogeneic blood transfusion in those patients randomised to PRP was 0.73 (95%CI 0.59 to 0.90), equating to a relative risk reduction (RRR) of 27% and a risk difference (RD) of 19% (95%CI 10% to 29%). However, significant heterogeneity of treatment effect was observed ($p < 0.00001$; $I^2 = 79\%$). When the four trials by Boldt are excluded, the RR is 0.76 (95% CI 0.62 to 0.93). On average, PRP did not significantly reduce the total volume of RBC transfused (weighted mean difference [WMD] -0.69 , 95%CI -1.93 to 0.56 units). Trials provided inadequate data regarding the impact of PRP on morbidity, mortality, and hospital length of stay. Trials were generally small and of poor methodological quality.

Authors' conclusions—Although the results suggest that PRP is effective in reducing allogeneic RBC transfusion in adult patients undergoing elective surgery, there was considerable heterogeneity of treatment effects and the trials were of poor methodological quality. The available studies provided inadequate data for firm conclusions to be drawn regarding the impact of PRP on clinically important endpoints.

Medical Subject Headings (MeSH)

Blood Loss, Surgical [prevention & control]; Plasmapheresis [*methods]; Platelet Transfusion [*utilization]; Randomized Controlled Trials as Topic; Surgical Procedures, Elective; Transplantation, Homologous

MeSH check words

Adult; Humans

BACKGROUND

Concerns regarding the safety of transfused blood have prompted a reconsideration of the role of allogeneic blood transfusion (whole blood or packed red cells from an unrelated donor). The risks associated with receiving transfusion of allogeneic blood that has been screened by a competent blood transfusion programme are considered minimal, with very low risks of transmission of HIV and hepatitis C (Whyte 1997). However, this only applies where there is a safe, well-regulated supply. The majority of the world's population does not have access to such a system, and the risks of transfusion in developing countries may be

much higher (McFarland 1997). Considerable enthusiasm has been generated for the use of technologies intended to reduce the use of allogeneic blood (Bryson 1998, Forgie 1998, Huet 1999, Laupacis 1997). However, some of the alternatives to allogeneic blood have their own risks, and are expensive (Coyle 1999, Fergusson 1999/a).

The International Study of Peri-Operative Transfusion (ISPOT-a ten-country study of evidence, attitudes and practices relating to the use of alternatives to peri-operative allogeneic blood transfusion) generated a number of systematic reviews (Bryson 1998, Forgie 1998, Huet 1999, Laupacis 1997) that examined the efficacy and safety of various technologies employed to minimise the need for peri-operative allogeneic blood transfusion. Amongst the technologies studied were: the anti-fibrinolytic drugs (aprotinin, tranexamic acid, and epsilon aminocaproic acid); desmopressin (deamino-8-D-arginine vasopressin - DDAVP); autologous blood donation by pre-operative deposit (PAD); acute normovolaemic haemodilution (ANH); and cell salvage (CS)/autotransfusion. Findings from these studies indicate that the use of PAD and ANH (techniques for re-infusing a patient's own blood), were associated with uncertain benefits. However, the use of technologies intended to reduce surgical blood loss, such as aprotinin and tranexamic acid, appear to lead to significant clinical benefits in terms of reducing the need for re-operation due to further bleeding. However, the safety of aprotinin in cardiac surgery was called into question in 2006 and 2007, when the results of a cohort study conducted by Mangano *et al* (Mangano 2006, Mangano 2007) showed that aprotinin increased the risk of renal failure, myocardial infarction, stroke and 5-year mortality (Ray 2008). In November 2007, based on the preliminary results of the BART study (Fergusson 2008), Bayer Pharmaceuticals suspended the world-wide marketing of aprotinin (Trasylol®). The final results of the BART study (a large randomised comparative trial of aprotinin, tranexamic acid and epsilon aminocaproic acid) published in the New England Journal of Medicine, May 29, 2008 (Fergusson 2008) showed that patients treated with aprotinin had a higher rate of death compared to those patients treated with either tranexamic acid (TXA) or epsilon aminocaproic acid (EACA). These results were confirmed by the updated meta-analysis by Henry *et al* (Henry 2009) which showed that the risk of death was consistently higher with the use of aprotinin compared to the lysine analogues, TXA and EACA. The search for a safe, cost-effective blood-conserving strategy continues.

As platelet-rich plasmapheresis (PRP) produces a highly concentrated, autologous platelet product, interest has grown for PRP as an alternative approach to blood conservation in the surgical setting (Triulzi 1995). The use of autologous platelets avoids the potential hazards associated with the use of random donor platelets, such as HLA alloimmunisation, platelet refractoriness and febrile non-haemolytic transfusion reactions. In the case of cardiac surgery, platelet dysfunction secondary to cardiopulmonary bypass (CPB) is one of the most significant factors leading to bleeding diathesis during the post-operative period (Boldt 1995, Safwat 1998). Theoretically, platelet-rich plasmapheresis preserves platelets, which optimises haemostasis and thereby reduces the potential for allogeneic blood transfusion.

Platelet-rich plasmapheresis is either performed pre-operatively (within 24 hours of surgery) or intra-operatively (after the induction of anaesthesia). It involves a patient's own blood (autologous whole blood) being withdrawn via a large bore intravenous catheter into a

plasmapheresis or platelet sequestration device, which separates the blood by centrifugation into a platelet solution, plasma, and red blood cells (RBC) (Ruel 2001). The plasma and red cell component is usually re-administered to the patient immediately, whereas the platelet component is collected, temporarily stored, and then returned to the patient at the end of the surgery (Ruel 2001, Triulzi 1995). In the case of surgery involving CPB, PRP reinfusion usually occurs after the neutralisation of heparin (Gravlee 1994). Haemodynamic stability is maintained during the blood withdrawal phase of the PRP procedure by volume replacement therapy with crystalloid and/or colloid fluids, the reinfusion of withdrawn RBC, and the occasional use of vasopressor agents (Safwat 1998). A number of cycles, taking 10-15 minutes for each cycle, may be required to achieve a PRP target volume of 10-20ml/kg, or approximately 20% of the patient's plasma volume (Gilcher 1989). It has been recommended that the target platelet yield should be at least 20% of the circulating platelet mass or 2.6×10^{11} platelets (in the case of a 70kg male with a platelet count of 250,000u/L) (Gilcher 1989). Such a platelet yield is equivalent to approximately five units of random donor platelets.

This review builds on a systematic review conducted by Rubens *et al.* (Rubens 1998). It examines the evidence of the efficacy of PRP in reducing the need for allogeneic red blood cell transfusion in elective adult surgery, and whether there is a greater reduction in allogeneic transfusion demonstrated in identifiable patient subgroups.

OBJECTIVES

To examine the effects of platelet-rich plasmapheresis (PRP) in minimising peri-operative allogeneic blood transfusion, and on other clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials with a concurrent control group.

Types of participants—The study participants were adults (over 18 years). The surgery being conducted was elective or non-urgent.

Types of interventions—The intervention considered was platelet-rich plasmapheresis, performed during the pre-operative or intra-operative period.

Types of outcome measures

Primary outcomes

- Number of patients in the intervention and control groups who were transfused with allogeneic and/or autologous blood
- Volume of allogeneic and/or autologous blood transfused (expressed as units of blood)

Secondary outcomes

- Number of patients exposed to allogeneic platelet transfusion, fresh frozen plasma (FFP), and cryoprecipitate
- Volume of allogeneic platelets, FFP, and cryoprecipitate transfused
- Blood loss
- Re-operation for bleeding
- Adverse events (e.g. hypotension)
- Mortality
- Thrombosis
- Length of hospital stay

Search methods for identification of studies

Electronic searches—The literature search was conducted using the following electronic databases:

- MEDLINE (1966-March 2009)
- EMBASE (1980-March 2009)
- Cochrane Library (Issue 1, 2009)

The search strategy can be found in Appendix 1.

We searched the bibliographies of eligible trials, review articles, and reports for any potentially relevant studies. In addition to the computer database searches, we searched Google Scholar™ and searched manufacturer web sites to identify any reports or projects relevant to the review.

Data collection and analysis

Selection of studies—The titles and abstracts identified in the searches were screened for relevance and selected for inclusion if they fulfilled the eligibility criteria. To be eligible for inclusion, studies had to include adult patients, scheduled for elective or non-urgent surgery, who were randomised to platelet-rich plasmapheresis or to a control group that did not receive PRP treatment. We used an article extraction form to extract information regarding study methodology, length of follow-up, outcomes investigated, the presence or absence of a transfusion protocol, the type of surgery, and treatment outcomes. Two of the authors (PAC, DMA) examined articles for inclusion/exclusion criteria with disagreements resolved by consensus.

Data extraction and management—We extracted data from studies using a data extraction form and then entered data into Review Manager (RevMan). Data on the following outcomes were recorded: the number of patients exposed to allogeneic and/or autologous blood, the amount of blood transfused, the number of patients experiencing post-operative complications (re-operation for bleeding, thrombosis), blood loss, mortality and

hospital length of stay. Information on patient demographics (age and sex) and the presence or absence of a transfusion protocol were also recorded. The number of patients who were enrolled, randomised and completed the study was also documented.

Assessment of risk of bias in included studies—Studies were assessed for methodological quality by two raters using the criteria proposed by Schulz *et al* (Schulz 1995). This criteria contains four items of assessment: double-blinding, allocation concealment, participant exclusion (withdrawal post randomisation), and methods used to achieve randomisation. In the case of double-blinding, allocation concealment, and participant exclusion, three numeric values (i.e. 0, 1, 2) were allocated to each of the three scales within each of these items. For example, trials judged to have adequately concealed treatment allocation scored 2, whereas trials judged not to have concealed treatment allocation scored 0. In the case of the method used to achieve randomisation, two numeric values (i.e. 0, 1) were allocated to each of the two scales within this item of assessment. Therefore, trials scored 1 if the method used to generate allocation sequences was judged to have been adequate (e.g. random number table, computer random number generator), whereas inadequate or unreported methods scored 0.

Inter-rater agreement for each item of methodological quality assessment was assessed by comparing the observed or achieved agreement (the proportion of studies for which the two raters assigned the same score) with that expected by chance (the agreement that would be achieved if the raters assigned scores at random). STATA® statistical software was used to calculate agreement and kappa statistics (κ). Disagreements were resolved by consensus. The methodological quality of included trials was also assessed with particular emphasis on allocation concealment, which was ranked as follows:

- Grade A - Adequate concealment
- Grade B - Uncertain
- Grade C - Inadequate allocation concealment

Assessment of reporting biases—Funnel plots were inspected for evidence of publication bias. Authors were contacted where possible to obtain missing data and/or clarify issues pertaining to study methodology.

Data synthesis—Dichotomous data (e.g. number of patients transfused, patients requiring re-operation for bleeding) and continuous data (e.g. units of blood transfused and blood loss) were analysed using Review Manager (RevMan). If standard deviations (SD) or standard error of means (SEM) were not reported for continuous data (or were unable to be calculated from the reported data) the study was not included in the meta-analysis. Outcomes were expressed as pooled relative risks (RR), risk differences (RD), or weighted mean differences (WMD) using a random effects model. The presence of heterogeneity of treatment effect was assessed using the Q statistic, which has an approximate chi-square distribution with degrees of freedom equal to the number of studies minus one (DerSimonian 1986). A p-value less than or equal to 0.10 was used to define statistically significant heterogeneity. The I^2 statistic was used to quantify inconsistency across trials. The I^2 statistic describes the

percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (Higgins 2002; Higgins 2003). Blood transfusion data reported as millilitres (mls) transfused were converted to units by dividing by 300.

Mathematical notation: Values expressed in scientific notation are interpreted as follows:
Mean platelet yields: $n \times 10^{11}/L = n \times 10$ to the 11th power per litre

Mean platelet counts: $n \times 10^3/\mu L = n \times 10$ to the 3rd power per micro litre

Subgroup analysis and investigation of heterogeneity—We performed analysis of *a-priori* subgroups to determine whether effect sizes varied according to factors such as; the type of surgery, the use of transfusion protocols, the haemoglobin transfusion trigger level, the use of cell salvage, the mean platelet count of PRP, the mean platelet yield, the mean PRP volume collected, and study methodological quality. Funnel plots were inspected for evidence of publication bias.

Sensitivity analysis—The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author on the conclusions of the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search—Of the 34 randomised controlled trials of platelet-rich plasmapheresis identified, 26 fulfilled the inclusion criteria. These 26 trials were conducted in the following countries: United States ($n = 11$), Germany ($n = 5$), Italy ($n = 2$), Switzerland ($n = 2$), Australia ($n = 1$), Egypt ($n = 1$), Taiwan ($n = 1$), France ($n = 1$), Singapore ($n = 1$) and United Kingdom ($n = 1$). Twenty-four trials were conducted in the setting of cardiac surgery and two were conducted in vascular surgery (Godet 1995, Safwat 2002). Trials were published between 1990 and 2003. There were two non-English studies; one was published in German (Klein 2001) and one in French (Godet 1995). These trials were translated before being included in the analysis. Of the 26 included trials, only two (Armellin 1995, Armellin 1997) had more than 100 patients in each trial arm. The remaining 24 trials were generally small. Overall, the mean number of patients in each trial arm was 33 (range: 9-138).

Included studies—Of the 26 included trials, eight were conducted by four similar research groups (two by each group). These trials are as follows: (1) Armellin 1995 (Armellin 1995), Armellin 1997 (Armellin 1997), (2) Boldt 1990 (Boldt 1990), Boldt 1993 (Boldt 1993), (4) Christenson 1996/a (Christenson 1996/a), Christenson 1996/b (Christenson

1996/b), and (4) Menges 1996 (Menges 1996), Menges 1997 (Menges 1997). After a thorough comparative assessment of these trials none were deemed by the authors to be duplicate publications.

Of the 21 trials that provided demographic data, the average age of the study participants ranged from 37.2 to 68 years for those randomised to an intervention group, and 37.6 to 79.7 years for those randomised to a control group. Overall, the ratio of males to females in the PRP group was 3.5:1 compared to 3.2:1 for the controls. These data suggest that patients in the control arms of the included trials were slightly older than those in the intervention arms and that there were slightly more males randomised to the intervention arms than the control arms.

Description of Intervention—Of the 26 included trials, 11 reported the volume of platelet-rich plasma (PRP) harvested per patient (Table 1). Nine trials reported harvesting 10ml/kg of PRP, one reported the harvesting of 8-10ml/kg, and one reported the harvesting of 15 ml/kg of PRP per patient. Fifteen trials reported the actual volumes (mean+/-sd) of PRP collected, and these ranged from 220 ml to 892 ml per patient (Table 1). Fourteen trials reported the mean platelet counts of the harvested PRP product, which ranged from $150 \times 10^3/\mu\text{L}$ to $864 \times 10^3/\mu\text{L}$ (Table 1). The platelet yields also varied considerably, with nine trials reporting mean platelet yields of between $1.2 \times 10^{11}/\text{L}$ and $3.4 \times 10^{11}/\text{L}$ (Table 1).

The majority of devices used to produce the platelet-rich plasma were manufactured by Haemonetics (n = 20). A summary of the types (models) of devices used is provided below.

Summary of PRP devices used:

1. Haemonetics Ultralite Plasma Collecting System (PCS) (n = 3)
2. Haemonetics Plasma Saver (n = 10)
3. Haemonetics MCS3p (n = 1)
4. Haemonetics PCS V50 (n = 2)
5. Haemonetics 5000 (n = 1)
6. Haemonetics 7000 (n = 1)
7. Haemonetics Cell Saver IV (n = 1)
8. Medtronic Elmd-500 (n = 2)
9. Medtronic Electromedics AT 1000 (n = 3)
10. Haemonetics or Electromedics (n = 1)

Co-interventions—The majority of trials (77%) reported the use of co-interventions (Table 2). In the current series of trials co-interventions were those treatments designed to either minimise blood loss (e.g. anti-fibrinolytic drugs), or minimise the need for allogeneic blood (ANH, PAD, CS).

Cell salvage (CS)—Cell salvage was the most frequently used co-intervention, with 16 trials reporting its use in both trial arms (Table 3). Cell salvage involves the reinfusion of blood collected from the operative field, either directly with filtration only or after centrifugation and washing. It is performed during the intra- and/or postoperative periods. Three trials (Jones 1990, Shore-Lesserson 1995, Triulzi 1995) reported re-transfusing shed mediastinal blood to patients during the post-operative period. Six trials (Armellin 1995, Armellin 1997, Boldt 1990, Boldt 1993, Menges 1996, Menges 1997) reported they specifically did not use autotransfused blood from the mediastinal drainage systems during the post-operative period. Trials that exclusively used cell salvage devices to haemo-concentrate the contents of cardiopulmonary bypass circuits were not included in the cell salvage stratum for a-priori subgroup analysis.

Anti-fibrinolytic therapy—Three trials (Liu 1998, Stover 2000, Wajon 2001) reported the use of the anti-fibrinolytic agent, epsilon aminocaproic acid (EACA). Liu *et al* (Liu 1998) administered EACA as a bolus dose of 150mg/kg prior to CPB. Stover *et al* (Stover 2000) administered 150mg/kg of EACA as a loading dose over 30 minutes, added 75mg/kg to the CPB circuit priming volume, and maintained a 20mg/kg/hr infusion of EACA throughout the operation. Wajon *et al* (Wajon 2001) administered 10g of EACA as a bolus dose prior to the commencement of CPB. The use of aprotinin was reported by one trial (Armellin 1995). The administration of this agent was not equally distributed between the intervention and control groups, with slightly more patients in the PRP group (29%) than in the control group (25%) receiving aprotinin treatment. The use of post-operative tranexamic acid (TXA) was reported by one trial (Ford 2002). For this trial two patients randomised to PRP received post-operative TXA whereas no patient randomised to control was treated with TXA at any stage.

Multiple co-interventions—One trial (Godet 1995) reported the use of CS, PAD and ANH. The trial conducted by Jones *et al* (Jones 1990) reported the use of both CS and ANH. Exposure to these co-interventions within trials appeared to be equally distributed across groups.

Transfusion protocols—The number of trials reporting the use of transfusion protocols varied according to the type of blood product (Table 4). Twentyfour trials (92%) reported the use of transfusion protocols for RBCs, 18 trials (69%) reported the use of protocols for platelet transfusion, 18 trials (69%) reported the use of protocols to guide the transfusion of fresh frozen plasma (FFP), and four trials (15%) reported the use of protocols to guide the transfusion of cryoprecipitate.

Red blood cells (RBC): Of the 24 trials that reported the use of transfusion protocols to guide red cell transfusion practice (Table 4), 24 reported the use of a transfusion threshold or “trigger”, that being the haemoglobin (Hb) or haematocrit (Hct) value, at which point a transfusion of allogeneic and/or autologous blood was considered necessary. There was significant variation between trials in the transfusion threshold used. In general, the Hb transfusion thresholds ranged from 6.0 to 8.0 g/dL for the intra-operative period, and ranged from 6.6 to 10.0 g/dL (Hct 20-30%) for the post-operative period.

Platelets (PLT): Eighteen trials reported the use of transfusion protocols to guide platelet transfusion (Table 4). Eleven trials reported platelet transfusion thresholds of $100 \times 10^9/L$, three trials transfused platelets when the platelet count fell below $50 \times 10^9/L$, and two trials transfused platelets when the platelet count fell below $75 \times 10^9/L$ and $80 \times 10^9/L$, respectively. Platelet transfusion thresholds were either used in isolation or used in combination with other transfusion criteria including, evidence of active or diffuse bleeding post bypass (in the case of trials involving cardiac surgery). Of those 18 trials that reported the use of protocols for platelet transfusion, only one transfused platelets solely on the basis of excessive mediastinal chest tube drainage ($>200\text{ml/hr}$ for two consecutive hours).

Fresh frozen plasma (FFP): Nineteen trials reported the use of transfusion protocols to guide the transfusion of FFP (Table 4). However, there was considerable variation in the transfusion strategies used. Five trials transfused FFP when the prothrombin time (PT) was greater than 150% of control values, whereas one trial transfused FFP when the PT was greater than 120% of control values. Two trials transfused FFP on the basis of diffuse uncontrollable bleeding and laboratory evidence of coagulopathy. Both of these trials failed to describe a specific threshold for FFP transfusion. Fourteen trials transfused FFP on the basis of either prothrombin times (PT), partial thromboplastin times (PTT), or activated partial thromboplastin times (APTT). Prothrombin times ranged from 15-16 seconds and PTT ranged from 20-35 seconds (or a PTT ratio of 1:3). An APTT >45 seconds was used by two trials as an indicator for FFP transfusion. One trial transfused FFP when the INR was >1.4 whereas another trial transfused FFP when the INR was >1.5 and the APTT was >45 seconds. Although one trial (DelRossi 1990) reported FFP transfusion on the basis of an elevated APTT, no specific threshold was described.

Cryoprecipitate: Four trials reported the use of protocols to guide the transfusion of cryoprecipitate (Table 4). Three trials transfused cryoprecipitate for a fibrinogen count $<100\text{mg/dL}$ and one trial transfused cryoprecipitate for a fibrinogen count $<150\text{mg/dL}$. One trial (Triulzi 1995) reported the application of topical cryoprecipitate during surgery for small vessel bleeding not adequately controlled by surgical haemostasis.

Duration of cardiopulmonary bypass (CPB)—Twenty-two of the 24 cardiac trials included in this review reported the duration of cardiopulmonary bypass. The duration of CPB varied considerably between trials ranging from around 73 minutes to 143 minutes (Table 5). Given the varying degree of surgical complexity across these trials this is not an unexpected finding.

Risk of bias in included studies

Twenty-four of the 26 included trials were assessed for methodological quality by two raters. Quality assessment of the two trials requiring translation (Godet 1995, Klein 2001) was performed by one rater. These trials were therefore excluded from the analysis of the reliability of the quality assessment procedure.

Allocation concealment—Using the quality assessment instrument based on the Schulz criteria (Schulz 1995), for the item assessing allocation concealment, all 24 trials scored 0

(out of maximum score of 2). There was 100% agreement between the two raters. As the method used to conceal treatment allocation was not clearly described in any trial, all 24 trials were classified as Grade B using the Cochrane criterion to grade allocation concealment (Figure 1, Figure 2).

Blinding—Using the Schulz criteria (Schulz 1995), one trial (4.2%) was assessed to be double-blind, seven trials (29.2%) the method of blinding was unclear, and for 16 trials (66.7%) outcomes assessment was judged not to be performed in a blinded fashion (Figure 1, Figure 2). There was 83% agreement ($\kappa = 0.60$) between the two raters.

Generation of allocation sequences—For 19 trials, the method used to generate allocation sequences (randomisation) was either inadequate or not reported. Only five trials described methods for generating allocation sequences judged to be adequate. These five trials used either a computer random number generator or a random number table to generate allocation sequences. Using the Schulz criteria (Schulz 1995), for the item assessing the method used to generate allocation sequences, five trials scored 1, and 19 scored 0 (out of a maximum score of 1)(Figure 1, Figure 2). There was 95.8% ($\kappa = 0.88$) agreement between the raters.

Inclusion of all randomised participants—Of the 24 trials assessed for methodological quality, 14 used intention-to-treat analysis or reported no exclusions, and six reported exclusions that were judged unlikely to cause bias. For four trials, exclusions were either not described, or the exclusions created differential loss in the comparison groups. Using the Schulz criteria (Schulz 1995), consensus scores were: 2 for 14 trials, 1 for 6 trials, and 0 for 4 trials (out of a maximum score of 2). There was 83.3% agreement ($\kappa = 0.70$) between the two raters for this item.

Aggregate scores—Based on the Schulz criteria (Schulz 1995) no trial scored more than 4 out of a possible score of 7. Aggregated quality scores were (out of a possible score of 7): 4 for 2 trials, 3 for 4 trials, 2 for 13 trials, 1 for 2 trials, and 0 for 3 trials.

Effects of interventions

Twenty-two trials of PRP reported data on the number of patients receiving an allogeneic RBC transfusion. These trials included a total of 1589 patients, of whom 801 were randomised to PRP. The relative risk (RR) of receiving an allogeneic blood transfusion in patients randomised to PRP was 0.73 (95% CI 0.59 to 0.90), representing a statistically significant relative risk reduction (RRR) of 27%. Heterogeneity of treatment effect was statistically significant ($p < 0.00001$; $I^2 = 79\%$). The absolute risk reduction (ARR) was 19% (RD -0.19, 95% CI -0.29 to -0.10). This equates to a number needing to be treated (NNT) of 5.3 (95% CI 3.5 to 10.0) to avoid a single patient having an allogeneic blood transfusion. (When the Boldt 1990, Boldt 1993, Menges 1996 and Menges 1997 trials were excluded from the analysis, the RR was 0.76 (95% CI 0.62 to 0.93).)

Type of surgery—All but two of the included trials (Godet 1995, Safwat 2002) were conducted in the context of cardiac surgery, so stratification of the data by the type of surgery (subgroup analysis) proved uninformative.

Effect of transfusion protocols—As there were only two trials (Ereth 1993, Farouk 2003) that did not report the use of a transfusion protocol to guide RBC transfusion, subgroup analysis was uninformative.

Transfusion threshold (“trigger”) levels—For the four trials that used Hb transfusion thresholds of 6.6-7.0g/dL the relative risk of receiving an allogeneic RBC transfusion was 0.33 (95%CI 0.18 to 0.62). Heterogeneity of treatment effect was statistically significant ($p = 0.01$; $I^2 = 72\%$). For the seven trials that reported using Hb transfusion thresholds of 8.0-8.5g/dL the relative risk of receiving an allogeneic RBC transfusion was 0.89 (95%CI 0.64 to 1.25). Heterogeneity of treatment effect was statistically significant ($p = 0.07$; $I^2 = 48\%$). (When Menges 1996 and Menges 1997 were excluded, RR was 1.00 (95% CI 0.86 to 1.16).) For the four trials that reported using Hb transfusion thresholds of 9.0g/dL, the relative risk of receiving an allogeneic RBC transfusion was 0.78 (95%CI 0.63 to 0.97; $I^2 = 49\%$). (With Boldt 1990 excluded, RR was 0.79 (95% CI 0.64 to 0.98).) For the three trials that used Hb transfusion thresholds of 10.0g/dL the relative risk of receiving an allogeneic RBC transfusion was 1.10 (95%CI 0.59 to 2.07; $I^2 = 18\%$). (With Boldt 1993 excluded, RR 1.25 (0.85 to 1.85).)

Effect of cell salvage

Intra-operative cell salvage: In 16 trials patients in both the PRP and control groups were exposed to intra-operative cell salvage. For those trials that reported the use of intra-operative cell salvage, the risk of exposure to allogeneic RBC transfusion was reduced by a relative 29% in those patients randomised to PRP (RR 0.71, 95%CI 0.54 to 0.93). Heterogeneity of treatment effect was statistically significant ($p < 0.00001$; $I^2 = 83\%$). (With Boldt 1990, Boldt 1993 and Menges 1997 excluded, the RR was 0.75 (95% CI 0.58 to 0.97).) For the six trials that did not report the use of intra-operative cell salvage the relative risk of receiving an allogeneic RBC transfusion was 0.71 (95%CI 0.45 to 1.11). Heterogeneity of treatment effect was statistically significant ($p = 0.0001$; $I^2 = 79\%$).

Post-operative cell salvage: Only three trials reported the use of post-operative cell salvage. For these trials the relative risk of exposure to allogeneic RBC transfusion was 0.84 (95%CI 0.42 to 1.70). Heterogeneity of treatment effect was statistically significant ($p < 0.002$; $I^2 = 85\%$). For the 19 trials that did not report the use of post-operative cell salvage the relative risk of receiving an allogeneic RBC transfusion was 0.70 (95%CI 0.55 to 0.89). Heterogeneity of treatment effect was statistically significant ($p = 0.0001$; $I^2 = 79\%$). (With Boldt 1990, Boldt 1993, Menges 1996 and Menges 1997 excluded, the RR was 0.74 (95% CI 0.59 to 0.93).)

Effect of PRP volume—Three small trials reported average PRP collection volumes of 701ml or more per patient. These trials included a total of 82 patients, of whom 41 were randomised to PRP. For these trials the relative risk of receiving an allogeneic blood

transfusion was 0.96 (95%CI 0.44 to 2.12; $I^2 = 3\%$). (When the Boldt 1993 trial was excluded from the analysis, the RR was 1.12 (95% CI 0.50 to 2.51).) Five trials reported average PRP collection volumes of between 501-700ml. These trials included a total of 362 patients of whom 181 were randomised to PRP. For these trials the relative risk of receiving an allogeneic blood transfusion was 0.77 (95%CI 0.43 to 1.10). Heterogeneity of treatment effect was statistically significant ($p = 0.002$; $I^2 = 77\%$). Four trials reported average PRP collection volumes of between 301-500ml per patient. These trials included a total of 184 patients of whom 90 were randomised to PRP. The relative risk of receiving an allogeneic blood transfusion was 0.42 (95%CI 0.15 to 1.20). Heterogeneity of treatment effect was statistically significant ($p < 0.00001$; $I^2 = 96\%$). One trial reported an average PRP volume of 233ml per patient. For this trial the relative risk of receiving an allogeneic red cell transfusion was 0.20 (95%CI 0.03 to 1.56).

Effect of platelet yield—Four trials reported mean platelet yields of between $3.0\text{--}3.5 \times 10^{11}/\text{L}$. These trials included a total of 209 subjects, of whom 101 were randomised to PRP. The relative risk of receiving an allogeneic blood transfusion was 0.31 (95%CI 0.05 to 2.02). Heterogeneity between these trials was statistically significant ($p < 0.00001$; $I^2 = 96\%$). Two trials reported mean platelet yields of between $2.5\text{--}2.9 \times 10^{11}/\text{L}$. For these trials the relative risk of receiving an allogeneic blood transfusion was 0.48 (95%CI 0.32 to 0.73; $I^2 = 0\%$). Four trials reported mean platelet yields of less than $1.8 \times 10^{11}/\text{L}$. These trials included a total of 409 patients of whom 205 were randomised to PRP. The relative risk of receiving an allogeneic blood transfusion was 0.98 (95%CI 0.68 to 1.40). Heterogeneity between these trials was statistically significant ($p = 0.05$; $I^2 = 61\%$).

Effect of mean platelet count of PRP—Two trials, conducted by the same group (Christenson 1996/a, Christenson 1996/b), reported mean platelet counts of the PRP of between $700\text{--}870 \times 10^3/\text{uL}$. For these trials the relative risk of receiving an allogeneic blood transfusion was 0.11 (95%CI 0.04 to 0.29).

Two trials (Stover 2000, Wajon 2001) reported a mean platelet count of the PRP between $550\text{--}600 \times 10^3/\text{uL}$. These trials included a total of 139 patients of whom 66 were randomised to PRP. For these trials the relative risk of receiving an allogeneic blood transfusion was 0.89 (95%CI 0.63 to 1.25; $I^2 = 0\%$).

One analysis consists of two trials conducted by Prof. Boldt (Boldt 1990, Boldt 1993), and reported mean platelet counts of the PRP of between $250\text{--}350 \times 10^3/\text{uL}$. These trials included a total of 54 patients of whom 27 were randomised to PRP. For these two small trials the relative risk of receiving an allogeneic blood transfusion was 0.17 (95%CI 0.02 to 1.31; $I^2 = 0\%$).

Two trials, conducted by the same group with Prof. Boldt (Menges 1996, Menges 1997), reported mean platelet counts of the PRP of less than $250 \times 10^3/\text{uL}$. These trials included a total of 80 patients of whom 40 were randomised to PRP. For these two small trials the relative risk of receiving an allogeneic blood transfusion was 0.09 (95%CI 0.01 to 0.67; $I^2 = 0\%$).

Volume of RBCs transfused—Eight trials reported data for the total volume of allogeneic RBC transfused during the intra-operative and post-operative periods. Overall there was no evidence of a significant reduction in the total volume of red blood cells transfused. The reduced volume with PRP was minimal and not statistically significant (WMD - 0.69 units, 95%CI -1.93 to 0.56 units). Heterogeneity between these trials was statistically significant ($p < 0.00001$; $I^2 = 90\%$). Although the use of PRP appeared to reduce the amount of RBC transfused during the intra-operative and post-operative periods, the observed reductions were small and not clinically significant (WMD -0.15 units, 95%CI -0.30 to -0.01 units; WMD -0.44 units, 95%CI -0.65 to -0.22 units; respectively).

Platelet transfusion—Ten trials reported data for the number of patients receiving allogeneic platelet transfusions. These trials included a total of 516 patients of whom 253 were randomised to PRP. The use of PRP reduced the rate of allogeneic platelet transfusion by a relative 51% (RR 0.49, 95%CI 0.28 to 0.85; $I^2 = 7\%$).

Volume of platelet transfusion—Five trials reported data for the volume of allogeneic platelets transfused. These trials included a total of 321 patients of whom 162 were randomised to PRP. On average, the use of PRP reduced the volume of allogeneic platelet transfusions by around one unit per patient (WMD -0.96 units, 95%CI -0.96 to -0.37 units; $I^2 = 45\%$).

Fresh frozen plasma (FFP) transfusion—Nine trials reported data for the number of patients receiving fresh frozen plasma (FFP) transfusions. These trials included a total of 484 patients of whom 248 were randomised to PRP. Although there appeared to be a trend toward a reduction in the number of patients receiving FFP transfusions in the PRP group, the result did not reach statistical significance (RR 0.44, 95%CI 0.17 to 1.12). Heterogeneity of treatment effect was statistically significant ($p = 0.003$; $I^2 = 67\%$).

Volume of FFP transfused—Eleven trials reported data for the volume of FFP transfused (units). These trials included a total of 1027 patients of whom 513 were randomised to PRP. On average, the use of PRP resulted in a saving of around 0.5 units of FFP per patient (WMD -0.49 units, 95%CI -0.79 to -0.20 units). Heterogeneity between these trials was statistically significant ($p = 0.09$; $I^2 = 46\%$).

Cryoprecipitate transfusion—Three trials reported data for the number of patients receiving cryoprecipitate transfusions. These trials included a total of 152 patients of whom 77 were randomised to PRP. The relative risk of receiving a cryoprecipitate transfusion for those treated with PRP compared to control was 0.73 (95%CI 0.20 to 2.61; $I^2 = 33\%$).

Volume of cryoprecipitate transfused—Three trials reported data for the volume of cryoprecipitate transfused (units). These trials included a total of 223 patients of whom 115 were randomised to PRP. On average there appeared to be a trend toward a decrease in the volume of cryoprecipitate transfused in PRP treated patients compared to control, however the result failed to reach statistical significance (WMD -0.76 units, 95%CI -2.18 to 0.66 units; $I^2 = 51\%$).

Blood loss

Intra-operative blood loss: Five trials reported data for intra-operative blood loss. These trials included a total of 210 patients of whom 105 were randomised to PRP. The use of PRP did not appear to impact on intra-operative blood loss (WMD -127.54 mls, 95%CI -402.05 to 146.98 mls). Heterogeneity of treatment effect was statistically significant ($p < 0.00001$; $I^2 = 90\%$).

Post-operative blood loss (0-12 hours): Four trials reported data for blood loss assessed during the first 12 hours of the post-operative period. These trials included a total of 654 patients of whom 324 were randomised to PRP. The use of PRP did not appear to reduce blood loss during this period of assessment (WMD -43.70 mls, 95%CI -89.76 to 2.37 mls; $I^2 = 33\%$).

Post-operative blood loss (0-24 hours): Nine trials reported data for blood loss assessed during the first 24 hours of the post-operative period. These trials included a total of 371 patients of whom 194 were randomised to PRP. PRP reduced blood loss on average by 247 mls per patient (WMD -247.17 mls, 95%CI -396.45 to -97.90 mls). Heterogeneity of treatment effect was statistically significant ($p < 0.00001$; $I^2 = 92\%$). (When the Boldt 1990, Boldt 1993, Menges 1996 and Menges 1997 trial data were excluded, the WMD was -161.05 mls (95% CI -367.59 to -45.49 mls).)

Post-operative blood loss (0-48 hours): Two trials reported data for blood loss assessed during the first 48 hours of the post-operative period. These trials included a total of 58 patients of whom 29 were randomised to PRP. PRP reduced blood loss on average by 284 mls per patient (WMD -284.49 mls, 95%CI -348.75 to -220.24 mls; $I^2 = 39\%$).

Total post-operative blood loss: Seven trials reported data for the total volume of blood lost during the post-operative period. These trials included a total of 787 patients of whom 389 were randomised to PRP. PRP reduced blood loss on average by 230 mls per patient (WMD -230.10 mls, 95%CI -374.42 to -85.79 mls). Heterogeneity of treatment effect was statistically significant ($p < 0.00001$; $I^2 = 82\%$).

Mortality: Five trials of PRP reported mortality data. These trials included a total of 488 patients, of whom 246 were randomised to PRP. There were only two reported deaths, one occurred in the control group of the trial conducted by Christenson *et al* (Christenson 1996/a) and the other occurred in the PRP group of the trial conducted by Wajon *et al* (Wajon 2001).

Re-operation for bleeding: Five trials of PRP reported data for re-operation for bleeding. These trials included a total of 529 patients of whom 265 were randomised to PRP. Ten patients in total, three in the PRP group and seven in the control group, required re-operation for bleeding. The relative risk for re-operation for bleeding in patients randomised to PRP compared to control was 0.56 (95%CI 0.15 to 2.13; $I^2 = 0\%$).

Stroke: Only one trial reported data for stroke (Ford 2002). This single trial reported two events of stroke both occurring in patients randomised to PRP treatment.

Length of hospital stay: Five trials reported data for hospital length of stay. These trials included a total of 351 patients of whom 177 were randomised to PRP. On average the length of hospital stay was reduced by 1.04 days in those randomised to PRP compared to control. However, this result did not reach statistical significance (WMD -1.04 days, 95% CI -2.25 to 0.18 days; $I^2 = 42\%$).

Adverse events

Hypotension: One trial provided data for hypotension (Shore-Lesserson 1995). This trial included a total of 44 patients of whom 25 were randomised to PRP. During the infusion of PRP, 15 of the 25 PRP patients (60%) and three of the 19 control patients (16%) experienced hypotension (mean arterial pressure < 60mmHg) necessitating clinical intervention with intravenous calcium chloride (10-15 mg/kg) and/or epinephrine boluses. The relative risk of developing hypotension (MAP < 60mmHg) during the same time period for PRP treated patients compared to control was 3.8 (95% CI 1.28 to 11.26).

DISCUSSION

We identified 26 randomised trials of PRP carried out in 10 countries over a 13-year time period. These trials evaluated 1712 patients from similar patient populations. The results of the metaanalysis indicated that the use of PRP, in adult patients undergoing elective surgery, reduced the number of patients receiving a peri-operative allogeneic RBC transfusion by a relative 27% (RR 0.73, 95% CI 0.59 to 0.90), and provided an approximate 19% reduction in the average absolute risk (ARR) of receiving an allogeneic blood transfusion (RD -0.19, 95% CI -0.29 to -0.10), equating to a number needing to be treated (NNT) of 5.3. The results also showed that PRP reduced the rate of allogeneic platelet transfusion by a relative 51% (RR 0.49, 95% CI 0.28 to 0.85), reduced the volume of allogeneic platelets transfused (WMD -0.96 units, 95% CI -1.56 to -0.37 units), reduced the volume of FFP transfused (WMD -0.49 units, 95% CI -0.79 to -0.20 units), and reduced post-operative blood loss (0-24 hours) on average by 247 mls per patient (95% CI 97.90 to 396.45 mls). However, for the main outcomes studied, substantial heterogeneity in treatment effect was observed.

Sources of heterogeneity

For the main outcomes of this review (number of patients receiving an allogeneic red cell transfusion and volume of blood transfused) significant heterogeneity was observed ($p < 0.00001$; $I^2 = 79\%$). The observed variation in treatment effects was in terms of both the size and the direction of effect with relative risk estimates for red cell transfusion exposure ranging from 0.07 to 1.29. Of the 22 trials that provided data for the proportion of patients exposed to allogeneic red cell transfusion, over half (68%) found that PRP did not statistically significantly reduce the probability of receiving a red cell transfusion. In an attempt to explain this marked heterogeneity for this outcome a number of subgroup analyses were performed. Trials were stratified by the type of operation, the use of a transfusion protocol, the use of cell salvage (a co-intervention), the mean platelet count of PRP, the mean platelet yield, the mean PRP volume collected, and trial methodological quality.

As 91% of the trials were conducted in the setting of cardiac surgery, and 18 of 22 trials reported the use of transfusion protocols, stratification of the data by these subgroups failed to explain the observed variability in treatment effects.

Subgroup analysis of trials that reported the use of cell salvage also failed to adequately explain the marked heterogeneity. For the 16 trials that reported the use of intra-operative cell salvage and provided data for the proportion of patients exposed to allogeneic blood transfusion, heterogeneity was statistically significant ($p < 0.00001$; $I^2 = 83\%$) with the relative risks (for receiving a red cell transfusion) ranging from 0.07 to 1.29. For the six trials that did not report the use of intra-operative cell salvage and provided data for the proportion of patients exposed to allogeneic blood transfusion, heterogeneity was statistically significant ($p < 0.005$; $I^2 = 70\%$) with the relative risks (for receiving a red cell transfusion) ranging from 0.09 to 1.28. Only three trials reported the use of post-operative cell salvage.

Mean platelet yield appeared to explain some of the variability in treatment effects. For the four trials that reported mean platelet yields of less than $1.8 \times 10^{11}/L$ the relative risk (for exposure to red cell transfusion) was 0.98, compared to 0.48 for the two trials that reported mean platelet yields of between 2.5 - $2.9 \times 10^{11}/L$, and 0.31 for four trials that reported mean platelet yields of between 3.0 - $3.5 \times 10^{11}/L$. These results suggest that a higher mean platelet yield may be associated with a decrease in exposure to red cell transfusion. However, with such a small number of trials in each strata, these apparent associations may well be due to the play of chance.

Further subgroup analysis by the mean platelet count of PRP did not convincingly establish the reason for the heterogeneity in treatment effect for red cell transfusion. However, this subgroup analysis was hampered by the small number of trials in each of the four strata analysed. It should be noted that three of these four strata were dominated by trials conducted by the same research groups. In exploring the potential sources of heterogeneity in treatment effect, it was important to determine whether there were differences (imbalance) between the intervention and control groups (within trials) in the proportion of patients exposed to those blood products that augment coagulation in the presence of microvascular bleeding (i.e. platelets, fresh frozen plasma (FFP), cryoprecipitate), potentially minimising exposure to allogeneic red cell transfusion. The concern therefore was confounding introduced by the use of co-interventions.

When the data for platelet, FFP, and cryoprecipitate transfusion were aggregated separately, differential transfusion of these blood products was quite apparent. The pooled relative risks showed PRP treatment was associated with statistically significant reductions in both exposure to platelets (RR 0.49, 95%CI 0.28 to 0.85), the volume of platelets transfused (WMD -0.96 units, 95%CI -1.56 to -0.37 units) and the volume of FFP transfused (WMD -0.49 units, 95%CI -0.79 to -0.20 units). Although there was a trend toward reduced exposure to both FFP and cryoprecipitate transfusion in those patients randomised to PRP, these results did not reach statistical significance (RR 0.44, 95%CI 0.17 to 1.12) and (RR 0.73, 95%CI 0.20 to 2.61), respectively. Overall these results indicate that PRP patients were not exposed any more frequently to these blood components (co-interventions) than the

controls. Had PRP patients been transfused more frequently than the controls, confounding introduced by the use of these co-interventions may have biased the results in favour of PRP treatment.

As the majority of trials reported the use of protocols to guide the transfusion of platelets and FFP (82% of trials for platelets and 86% of trials for FFP), it is assumed that the decision to transfuse patients was based on well-defined haematological indicators rather than clinician subjectivity. Far fewer trials reported the use of protocols to guide the transfusion of cryoprecipitate (18%). However, there were insufficient numbers of studies to look separately at the effects of these transfusion protocols. Moreover, overall compliance with such transfusion protocols was not discussed by any of the trials reviewed. This is a particularly salient issue for randomised controlled trials where the main study outcome is a practice variable, that is, the decision to transfuse a patient with allogeneic red cells, rather than a clinical variable. Due to the degree of subjectivity involved in the decision to transfuse, it is conceivable that the main study outcome in these trials, allogeneic red cell transfusion, may have contributed to the observed heterogeneity.

The impact of trial methodological quality on treatment effect was difficult to determine, as all trials were of poor quality. No trial was judged as having adequate allocation concealment and only one trial were judged to be double-blind.

Trial size is another issue that requires further discussion. Of the 22 trials that provided data for the number of patients receiving an allogeneic red cell transfusion, only two trials had greater than 100 patients in each trial arm. The remaining 20 trials randomised between 10 and 65 patients to each trial arm. It is important to consider whether or not the results of these two larger trials have impacted on the overall results of the meta-analysis. Although the two largest trials (Armellin 1995, Armellin 1997) showed statistically significant reductions in exposure to allogeneic red cell transfusion with relative risk reductions of 31% (RR 0.69, 95%CI 0.55 to 0.86) and 25% (RR 0.75, 95%CI 0.61 to 0.93) respectively, in aggregate they provided 16.5% of the information (weight) in the analysis. Further, by removing the data for these two trials from the analysis, the results remained virtually unchanged, with the relative risk of exposure to allogeneic red cell transfusion changing from 0.73 (95%CI 0.59 to 0.90) to 0.69 (95%CI 0.53 to 0.91). It is also difficult to say, with any great certainty, whether the results of the two larger trials (Armellin 1995, Armellin 1997) represent the true treatment effect of PRP, as both trials were conducted by the same research team and as such may not be generalisable to different populations in different geographical locations. Whether or not trial size had any impact on treatment effect (size and/or direction of effect) is difficult to quantify and answer conclusively. The most salient point of this discussion is that, the majority of trials were particularly small and in most instances, inadequately powered to detect the observed differences in transfusion exposure rates.

When trials were stratified by the transfusion trigger level, the results were inconsistent across subgroups. For the four trials that reported Hb trigger levels of 6.6-7.0g/dL, the risk of receiving an allogeneic RBC transfusion in those patients randomised to PRP was statistically significantly reduced on average by a relative 67% (RR 0.33, 95%CI 0.18 to

0.62). A statistically significant reduction was also observed for the four trials that reported higher Hb transfusion trigger levels of 9.0g/dL (RR 0.78, 95%CI 0.63 to 0.97). However, for the seven trials that reported using Hb transfusion trigger levels of 8.0-8.5g/dL the relative risk of receiving an allogeneic RBC transfusion in those patients randomised to PRP was not statistically significant (RR 0.89, 95%CI 0.0.64 to 1.25). For the three trials that reported using a Hb transfusion trigger of 10.0g/dL, a statistically non-significant increase in risk was observed (RR 1.10, 95%CI 0.59 to 2.07). As three of the four subgroups involved six trials performed by the same investigators (Armellin 1995, Armellin 1997, Christenson 1996/a, Christenson 1996/b, Menges 1996, Menges 1997), it is difficult to draw any firm conclusions from such analyses.

Sources of bias

The majority of trials (85%) were small, with less than 50 participants in each arm. Reliance on small trials raises concerns about the effects of publication bias. Funnel plot assessment revealed some evidence of publication bias in the form of a 'missing' population of small negative trials (Figure 3). As the presence of publication bias may lead to an over-estimation of benefit of treatment effect the results may need to be viewed with some degree of caution.

The main study outcome used in these trials was a practice variable - the decision to transfuse a patient with allogeneic red cells. This requires a degree of subjectivity on the part of clinicians, and as the majority of trials were unblinded, this is a source of bias which may have potentially influenced the results in favour of PRP.

Methodological quality of studies

The overall methodological quality of the trials was poor (Figure 1, Figure 2). Of the 24 trials assessed for methodological quality, only one was judged to be double-blind, the method used to conceal the treatment allocation schedule was not described in any trial, and 79% of the trials failed to describe the method used to generate the allocation sequences (randomisation process). In light of the poor methodological quality of the trials reviewed, substantial biases (e.g. selection bias, performance bias), may have been introduced, exaggerating the true magnitude of beneficial effect of PRP.

Other clinical outcomes

Mortality, re-operation for bleeding, and hospital length of stay did not appear to be influenced by the use of PRP. However, in individual trials the numbers of events were small, therefore it is difficult to draw any firm conclusions regarding the impact of PRP on important clinical outcomes.

Adverse effects of the PRP procedure

As with any medical procedure, plateletpheresis is not without certain risks, the most common of which is hypotension. Of the 26 trials of platelet-rich plasmapheresis reviewed here, only one (Shore-Lesserson 1995) reported complications related to the procedure. This trial reported five episodes (20% of PRP patients) of moderate hypotension (mean arterial blood pressures (MAP) less than 60mmHg) during the collection phase of PRP. Three of these five patients were successfully treated with volume expansion and boluses of IV

phenylephrine. Haemodynamic instability such as this may well be the result of inadequate fluid replacement during the withdrawal of blood into the plasmapheresis circuit leading to hypovolemia. A further 15 patients required treatment for hypotension during the infusion of PRP and were treated with epinephrine infusions and calcium chloride boluses (10-15mg/kg). As postulated by the authors, hypotension such as that experienced in this trial may have been attributable to hypocalcaemia caused by the infusion of large quantities of citrate (preservative agent used in the storage of PRP) during the rapid infusion of PRP.

However, the PRP product, as reported by the authors, was administered slowly in patients with normal hepatic function. Such unexplained hypotension in patients with a history of cardiovascular disease undergoing CABG surgery is of concern. As this trial was the only one of 26 trials to report such significant hypotension in PRP treated patients, it may well be that certain aspects of the techniques employed differed to those of the other trials and therefore it is difficult to generalise these results. Although hypotension appears to be a relatively rare event in the use of PRP, the reviewers caution readers to the potential risk.

Clinical significance of results

The true value of avoiding allogeneic blood transfusion remains debatable. Conceivably, those concerned with the risks of transfusion-transmitted disease will be more interested in avoiding transfusion completely, rather than reducing the volume of blood transfused (Henry 2007). However, the importance of avoiding transfusion depends on the probability of avoiding disease transmission, or other adverse effects that have been attributed to blood transfusion such as alloimmunisation, febrile non-haemolytic transfusion reaction, or immunosuppression (Blumberg 1997). The rate of transmission of HIV or viral hepatitis is very low in most developed countries, because of the quality of donor blood screening (Coyle 1999, Whyte 1997). However, this is not the case in developing countries where donor blood is inadequately screened, and the prevalence of viral pathogens amongst donors is high (Kimball 1995, McFarland 1997). In settings such as these there may be greater clinical value in a range of interventions that diminish or negate the need for allogeneic blood. However, the costs of such interventions may be prohibitive in developing countries.

The best evidence reviewed here applies to the use of platelet-rich plasmapheresis in elective adult surgery. The vast majority of the data have been collected in the context of cardiac surgery, where blood loss is often substantial. This review identified only one randomised trial of platelet-rich plasmapheresis in a setting other than cardiac surgery. Consequently, the applicability of the results to clinical settings where blood loss is minor are questionable. Although there are a number of interventions used in cardiac surgery to reduce perioperative allogeneic red cell transfusion, some are particularly expensive and do not represent cost-effective alternatives (Fergusson 1999/a). In the field of cardiac surgery, there is growing evidence that the use of anti-fibrinolytic drugs (aprotinin, tranexamic acid, epsilon aminocaproic acid), and the acceptance of lower transfusion thresholds, may offer the most effective approaches for managing the transfusion requirements of patients in this high-risk setting (Henry 2007, Hill 2001). However, the use of aprotinin in cardiac surgery has been questioned, with the results of the large randomised comparative trial conducted by Fergusson *et al* (Fergusson 2008) showing a higher rate of death in those patients

randomised to aprotinin compared to those patients treated with either tranexamic acid (TXA) or epsilon aminocaproic acid (EACA). Although this trial (BART study) showed a modest reduction in the risk of massive bleeding in those patients treated with aprotinin (RR 0.79, 95% CI 0.59 to 1.05) the relative risk of death in the aprotinin group, as compared with that in both groups receiving lysine analogues (TXA and EACA), was 1.53 (95% CI 1.06 to 2.22). An updated meta-analysis conducted by Henry *et al* (Henry 2009), including the data from the BART study (Fergusson 2008), showed that the risk of death was consistently higher with the use of aprotinin compared to the lysine analogues. Based on their findings, Henry *et al* (Henry 2009) recommended that either TXA or EACA should be used to prevent bleeding after cardiac surgery rather than aprotinin.

As a relatively new technology the true efficacy of platelet-rich plasmapheresis is yet to be definitively ascertained. It is a procedure not without certain risks to patient health. This and other reviews (Hardy 1996, Rubens 1998, Ruel 2001) have highlighted the potential for hypovolaemia, hypothermia (during the sequestration procedure), and citrate-induced hypocalcaemia (during the transfusion of the harvested platelets). Questions have also been raised about the quality of platelets harvested. Centrifugation during plateletpheresis has been shown to significantly impair platelet function to an extent that the platelets remain refractory to stimulation for a four to six-hour period (Gutensohn 1997). Although platelet-rich plasmapheresis has been shown to reduce post-operative blood loss, it cannot limit intra-operative blood loss which can be significant in re-operative cardiac patients due to vascular adhesions (Rubens 1998). Therefore, the use of PRP in this sub-group of patients appears not to be warranted. Another important issue is time. The trials reviewed here described sequestration times of 20-92 minutes. Whether plateletpheresis extends operative times is difficult to determine from the current literature as the studies generally reported 'surgery times' which do not necessarily include the time taken to insert lines, or prepare and operate equipment specific to PRP. Where platelet-rich plasmapheresis fits within the spectrum of potential alternatives to allogeneic red cell transfusion is currently unclear, as studies that examine its cost-effectiveness are yet to be identified.

On the basis of the current available evidence it is difficult to recommend the use of PRP for the purpose of minimising perioperative allogeneic blood transfusion in elective adult surgery. Further large, methodologically rigorous, randomised controlled trials of PRP are needed.

AUTHORS' CONCLUSIONS

Implications for practice

The use of platelet-rich plasmapheresis in adult elective surgery cannot be justified on the basis of the evidence reviewed, as better proven technologies are currently available.

Implications for research

Further large, methodologically rigorous, randomised controlled trials of PRP, using clinical outcomes, in different surgical procedures need to be conducted to clarify the efficacy of this technique.

Acknowledgments

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council of Australia, Australia.

Appendix 1. Search strategy

The Cochrane Library and the databases MEDLINE and EMBASE were initially searched using unrestricted search terms with exploded MeSH (Medical subject heading) terms and specific text-word terms for platelet-rich plasmapheresis.

- The exploded MeSH terms included:exp Plateletpheresis/
- The specific text-word terms included: plateletphere\$, platelet rich plasma, platelet rich, platelet rich plasmapheresis, thrombocytophoresis, thrombocytophere\$, thrombocyte rich plasma and autologous platelet\$
- To maximise the sensitivity for the retrieval of all potentially relevant studies, electronic searches were initially unrestricted. To improve the specificity of the searches, two search filters were used.
- Firstly, the ISPOt filter (Laupacis 1997), which identifies blood transfusion studies using the MeSH terms: 'blood transfusion', 'hemorrhage', and 'anesthesia'. The ISPOt filter combines these MeSH terms with the text-word terms: transfusion\$, bleed\$, blood loss\$, hemorrhag\$.
- Secondly, a modified version of the Cochrane Collaboration filter (Dickersin 1996, Robinson 2002), which primarily identifies randomised controlled trials.
- These search filters were combined with the MeSH and text-word terms specific for platelet-rich plasmapheresis.
- Reference lists of relevant reviews and identified articles were searched for additional relevant studies.

NB: The truncation character "\$" (dollar sign) indicates the use of unlimited truncation to retrieve all possible suffix variations of the root word or phrase.

MEDLINE and EMBASE - unrestricted search strategy

1. exp Plateletpheresis/
2. plateletpheres\$.tw
3. platelet rich plasma\$.tw
4. (platelet and rich and pheresis).tw
5. (platelet and rich).tw

6. plasmapheres\$.tw
7. thrombocytopheres\$.tw
8. (thrombocyte and rich and plasma\$).tw
9. autologous plateletpheres\$.tw
10. or/1-9

MEDLINE and EMBASE - restricted search strategy (ISPOT search filter)

1. exp Plateletpheresis/
2. plateletpheres\$.tw
3. platelet rich plasma\$.tw
4. (platelet and rich and pheresis).tw
5. (platelet and rich).tw
6. plasmapheres\$.tw
7. thrombocytopheres\$.tw
8. (thrombocyte and rich and plasma\$).tw
9. autologous plateletpheres\$.tw
10. or/1-9
11. exp Blood Transfusion/
12. exp HEMORRHAGE/
13. exp ANESTHESIA/
14. transfusion\$.tw.
15. bleed\$.tw.
16. blood loss\$.tw.
17. hemorrhag\$.tw.
18. or/11-17

MEDLINE - restricted search strategy (ISPOT & RCT filter)

1. exp Plateletpheresis/
2. plateletpheres\$.tw
3. platelet rich plasma\$.tw
4. (platelet and rich and pheresis).tw
5. (platelet and rich).tw
6. plasmapheres\$.tw

7. thrombocytopheres\$.tw
8. (thrombocyte and rich and plasma\$).tw
9. autologous plateletpheres\$.tw
10. or/1-9
11. exp Blood Transfusion/
12. exp HEMORRHAGE/
13. exp ANESTHESIA/
14. transfusion\$.tw.
15. bleed\$.tw.
16. blood loss\$.tw.
17. hemorrhag\$.tw.
18. or/11-17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized controlled trials.sh.
22. random allocation.sh.
23. double blind method.sh.
24. single blind method.sh.
25. or/19-24
26. (animal not human).sh.
27. 25 not 26
28. clinical trial.pt.
29. exp Clinical trials/
30. (clin\$ adj25 trial\$).ti,ab.
31. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
32. placebos.sh.
33. placebo\$.ti,ab.
34. random\$.ti,ab.
35. research design.sh.
36. or/28-35
37. comparative study.sh.
38. exp Evaluation studies/

39. follow up studies.sh.
40. prospective studies.sh.
41. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
42. or/37-41
43. 42 not 26
44. 43 not 26
45. 27 or 36 or 43
46. 10 and 18 and 45

EMBASE - restricted search strategy (ISPOT & RCT filter)

1. exp Plateletpheresis/
2. plateletpheres\$.tw
3. platelet rich plasma\$.tw
4. (platelet and rich and pheresis).tw
5. (platelet and rich).tw
6. plasmapheres\$.tw
7. thrombocytopheres\$.tw
8. (thrombocyte and rich and plasma\$).tw
9. autologous plateletpheres\$.tw
10. or/1-9
11. exp Blood Transfusion/
12. exp HEMORRHAGE/
13. exp ANESTHESIA/
14. transfusion\$.tw.
15. bleed\$.tw.
16. blood loss\$.tw.
17. hemorrhag\$.tw.
18. or/11-17
19. exp clinical trial/
20. controlled study/
21. randomized controlled trial\$.tw.
22. comparative stud\$.ti,ab.

23. random allocation.tw.
24. crossover trial.ti,ab.
25. double blind procedure.sh.
26. (cli\$ adj25 trial\$).ti,ab.
27. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
28. placebo\$.sh.
29. placebo\$.ti,ab. or placebo\$.tw.
30. random\$.ti,ab. or random\$.tw.
31. or/19-30
32. animal/ not (human/ and animal/)
33. 31 not 32
34. "COMPARATIVE STUDY".mp.
35. "EVALUATION STUDIES".mp.
36. "FOLLOW UP STUDIES".mp.
37. "CROSSOVER TRIAL".mp.
38. exp prospective study/
39. exp longitudinal study/
40. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
41. or/34-40
42. 41 not 32
43. 31 or 41
44. 10 and 18 and 43

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Armellin 1995

Methods	Method of blinding, randomisation and allocation concealment was not described
Participants	261 consecutive cardiac surgery patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Intraoperative plasmapheresis group: n = 128; M/F = 111/17; mean (+/-SD) age = 58.4 (12.5) years 2 Control group: n = 128; M/F = 86/42; mean age (+/-SD) = 60.8 (11.3) years

Interventions	1	Intra-operative plasmapheresis was performed after the induction of anaesthesia harvesting 10 ml/kg autologous platelet-rich plasma (PRP) using the PCS Haemonetics Ultralite system.
	2	Control group were managed without PRP.

Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels.
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Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used.
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Reported to be double-blind study but control group received standard care without PRP treatment

Armellin 1997

Methods	Method of randomisation and allocation concealment was not described. Only the anaesthesiologist and the perfusionist were aware of group allocations
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Participants	293 consecutive cardiac surgery patients were randomised to one of two groups: 1 Intraoperative plasmapheresis group: n = 137; M/F = 92/50; mean (+/-SD) age = 59 (12.3) years. 2 Control group: n = 138; M/F = 92/50; mean (+/-SD) age = 61.1 (12) years
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Interventions	1	Intra-operative plasmapheresis (IP) was performed after the induction of anaesthesia harvesting 10 ml/kg autologous platelet-rich plasma (PRP) using the PCS Haemonetics Ultralite system.
	2	Control group were managed without PRP.

Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Excessive bleeding (n).
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Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Single blinding

Boey 1993

Methods	Method of randomisation and allocation concealment was not described. All patients were operated on by the same surgeon.	
Participants	40 consecutive primary myocardial revascularisation patients were randomised to one of two groups: 1 Plateletpheresis group: n = 19; M/F = 17/2; mean (+/-SD) age = 59.1 (9.1) years. 2 Control group: n = 20; M/F = 14/6; mean (+/-SD) age = 63.4 (8.4) years	
Interventions	1 Plateletpheresis was performed immediately before surgery harvesting 10 ml/kg autologous platelet-rich plasma (PRP) using the PCS Haemonetics Ultralite system. 2 Control group were managed without PRP.	
Outcomes	Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Mortality (n).	
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Single blinding

Boldt 1990

Methods	Method of randomisation and allocation concealment was not described	
Participants	45 aortocoronary bypass surgery patients were randomised to one of three groups: 1 APP-PPP group: n = 15; M/F = not specified; mean (+/-SD) age = 62.8 (5.1) years. 2 APP-PRP group: n = 15; M/F = not specified; mean (+/-SD) age = 59.0 (3.3) years. 3 Control group: n = 15; M/F = not specified; mean (+/-SD) age = 63.7 (4.4) years	
Interventions	1 Acute pre-operative plasmapheresis (APP) was performed after the induction of anesthesia harvesting 10 ml/kg autologous platelet-poor plasma (PPP) using the PCS V50 Haemonetics system. 2 Acute pre-operative plasmapheresis (APP) was performed after the induction of anesthesia harvesting 10 ml/kg autologous platelet-rich plasma (PRP) using the PCS V50 Haemonetics system. 3 Control group were managed without PRP or PPP. NB: All groups received intra-operative cell salvage.	
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused.	

	Blood loss (mls). Haematological levels. Coagulation levels.	
Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol used.	
<i>Risk of bias</i>		
Item	Authors' 2019; judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP or PPP)

Boldt 1993

Methods	Method of randomisation and allocation concealment was not described. The surgical team were blinded to patient grouping.	
Participants	36 coronary artery bypass surgery (CABG) patients wererandomised to one of three groups: 1 PPP group: n = 12; M/F = 12/0; mean (+/-SD) age = 56.0 (8.8) years. 2 PRP group n = 12; M/F =12/0; mean (+/-SD) age = 60.5 (9.2) years. 3 Control group: n = 12; M/F = 12/0; mean (+/-SD) age = 58.9 (8.2) years	
Interventions	1 Acute pre-operative plasmapheresis(APP) was performed before the onset of the operation harvesting 10 ml/kg of autologous platelet-poor plasma (PPP) using the Haemonetics PCS V50 system. 2 Acute pre-operative plasmapheresis (APP) was performed before the onset of the operation harvesting 10 ml/kg of autologous platelet-rich plasma (PRP) using the Haemonetics PCS V50 system. 3 Control group were managed without PRP or PPP.	
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels.	
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP or PPP)

Christenson 1996/a

Methods	Method of randomisation and allocation concealment was not described
Participants	40 redo coronary artery bypass grafting (CABG) patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 latelet-rich plasma group: n = 20 2 Control group: n = 20 NB: M/F of both groups = 33/7; mean (range) age of both groups = 63.4 (42-80) years
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis (PRP) was performed after the induction of anaesthesia harvesting 20-30% circulating platelets using the Elmd-500 autotransfusion/platelet sequestration device (Medtronic). 2 Control group were managed without PRP.
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Hospital length of stay (days). Mortality (n). ICU length stay (hrs).
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Christenson 1996/b

Methods	Method of randomisation and allocation concealment was not described
Participants	60 primary and redo coronary artery bypass grafting (CABG) patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Platelet sequestration group: n = 30 2 Control group n = 30 NB: M/F of both groups = 51/9; mean (range) age of both groups = 62 (38-82) years
Interventions	<ol style="list-style-type: none"> 1 Platelet sequestration harvesting platelet-rich plasma (PRP) was performed after the induction of anaesthesia using the Elmd-500 system (Medtronic). 2 Control group were managed without PRP.
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Hospital length of stay (days). ICU length of stay (hrs).

Notes
Quality assessment score (Schulz criteria): 2/7
Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

DelRossi 1990

Methods	Method of randomisation and allocation concealment was not described
Participants	18 heart operation patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n = 9; M/F = not reported; mean (+/-SD) age = 59.0 (1.8) years. 2 Control group: n = 9; M/F = not reported; mean (+/-SD) age = 58.2 (3.4) years
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis (PRP) was performed after the induction of anaesthesia using the Haemonetics Plasma Saving system. 2 Control group were managed without PRP.
Outcomes	Units of allogeneic blood transfused. Blood loss (mls). Haematological levels Coagulation levels.
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Ereth 1993

Methods	Method of randomisation and allocation concealment was not described. Once patients were positioned and the PRP device connected, the anaesthesia staff were replaced by new anaesthesia staff. One member of the new staff was an anaesthesiologist-investigator. To blind all other operating room staff, PRP equipment and autotransfusion staff were visually isolated by surgical drapes. Collection tubing in the Sham procedure group was clamped simulating PRP collection
Participants	56 repeat valvular surgery patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n = 28; M/F = 18/10; mean (+/-SD) age = 68.0 (11.1) years.

	2	Control group: n = 28; M/F = 18/10; mean (+/-SD) age = 66.0 (11.6) years
Interventions	1	Platelet-rich plasmapheresis (PRP) harvested 15-20% of plasma volume using the Haemonetics Plasma Saver system.
	2	Control group received a sham procedure involving the same preparation as for the experimental group. The patient's blood in this group was drawn only through the collection tubing. Both ends were clamped and the tube remained filled with blood, simulating ongoing PRP collection
Outcomes		Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Deep venous thrombosis (n).
Notes		Quality assessment score (Schulz criteria): 4/7 No transfusion protocol described.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Double blind

Farouk 2003

Methods	Methods of randomisation and allocation concealment were not described	
Participants	30 patients undergoing coronary artery bypass grafting (CABG) or valve replacement surgery were randomised to one of three groups:	
	1	Platelet-rich plasmapheresis group: n = 10; M/F = 4/6; mean (+/-SD) age = 37.2 (13.3) years
	2	Acute normovolaemic haemodilution group: n = 10; M/F = 6/4; mean (+/-SD) age = 34.1 (12.1) years
	3	Control group: n = 10; M/F = 6/4; mean (+/-SD) age = 37.6 (12.1) years
Interventions	1	Platelet-rich plasmapheresis (PRP) group had 20-25% of plasma volume harvested. Plasma volume collected was replaced by Haes-Steril 6% solution. Blood collected was transferred to the blood bank where it was centrifuged by the JOUAN CR 412 centrifugation machine (at a speed of 2400 rpm, a temperature of 22°C and for a 10-minute interval) into platelet-rich plasma and packed red blood cells. Erythrocytes separated were returned to the patient immediately before initiation of CPB, while collected PRP remained undisturbed in an insulated bag until after protamine neutralisation of heparin, when it was given 10 minutes later
	2	Acute normovolaemic haemodilution group had 20% of the blood volume withdrawn immediately after the induction of anaesthesia. The final haematocrit was not allowed to decrease below 30%. The same amount was replaced by Haes-Steril 6%. Blood was collected in a citrate-phosphate-dextrose-adenine blood donor bag, remained undisturbed until after protamine neutralisation of heparin, when it was given 10 minutes later
	3	Control group received the same preparation and operative techniques as the PRP group. There was no collection of any autologous blood product and the patient was managed in a standard manner

Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Number of patients transfused fresh frozen plasma (n). Volume of fresh frozen plasma transfused (mls). Blood loss (mls). Haematological levels.
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Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Ferraris 1993

Methods	Patients were divided into high and low risk categories initially. This categorisation was made according to a ratio of template bleeding time to packed red blood cell volume. Within these groups, patients were randomised according to a simple blocked randomisation scheme. The method used to conceal treatment allocation was not described
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Participants	100 patients undergoing coronary artery bypass grafting (CABG) were randomised to one of three groups: 1 Platelet-rich plasmapheresis group: n = 35 2 Whole blood group: n = 30 3 Control group: n = 35 NB: Demographic data were not reported
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Interventions	1 Platelet-rich plasmapheresis (PRP) group had 8-10 ml/kg of autologous PRP harvested immediately before the operation using the Haemonetics Plasma Saver system. 2 Autologous whole blood was harvested after systemic heparinization and immediately before institution of CPB. 3 Control group were managed without PRP.
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Outcomes	Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Mortality (n).
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Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol used. Data used in the analysis came from the high risk groups only, due to a lack of data in other groups
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear

Blinding? All outcomes	No	Control group received standard treatment (no PRP)
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Ford 2002

Methods	Patients were randomly assigned to either pheresis or control group by a process of minimisation using computer software	
Participants	54 patients undergoing elective routine coronary artery bypass graft surgery and valve replacement were randomly allocated to one of two groups:	
	1	Platelet-pheresis group: n = 25; M/F = 17/8; median (range) age = 65 (59-73) years
	2	Control group: n = 29; M/F = 22/7; median (range) age = 69 (62-73) years
Interventions	1	Platelet-pheresis was performed in the anaesthetic room before the induction of anaesthesia using the Haemonetics MCS3p apheresis system. Approximately 6 cycles were required to achieve a standard donation in excess of 2.5×10^{11} platelets in a plasma volume of 300 ml. The platelet harvest was retransfused over a 20-minute period
	2	Control group were managed without PRP.
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Stroke (n). Re-exploration for bleeding (n).	
Notes	Quality assessment score (Schulz criteria): 4/7 Transfusion protocol used.	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer randomisation
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Single blinding

Godet 1995

Methods	Method of randomisation and allocation concealment was not described	
Participants	20 abdominal infra-renal aortic aneurysmectomy patients were randomly allocated to one of two groups:	
	1	Platelet-rich plasmapheresis group: n = 10
	2	Control group: n = 10
	NB: Demographic data not reported	
Interventions	1	Platelet-rich plasmapheresis (PRP) harvesting 10 ml/kg of platelet-rich plasma was performed over 40-50 minutes prior to the induction of anaesthesia using the PCS Haemonetics system. Each unit of PRP was transfused to the patient after aortic declamping.
	2	Control group were managed without PRP.

NB: Autologous transfusion techniques were available to all patients (i.e. predonation of autologous blood, pre-operative normovolaemic haemodilution, and intra-operative cell salvage)

Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels.	
Notes	French language publication. Transfusion protocol used.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Control group received standard treatment (no PRP)

Jones 1990

Methods	Method of randomisation and allocation concealment was not described	
Participants	100 consecutive coronary artery bypass patients were randomised to one of two groups: <div><div>1</div><div>Platelet-rich plasmapheresis group: n = 50; M/F = 39/11; mean (+/-SD) age = 61.37 (9.2) years.</div></div> <div><div>2</div><div>Control group: n = 50; M/F = 37/13; mean (+/-SD) age = 61.27 (10.6) years</div></div>	
Interventions	<div><div>1</div><div>Platelet-rich plasma (PRP) was harvested after the induction of anaesthesia using the Haemonetics 5000 system. PRP harvesting was terminated either at the accumulation of 1000 ml of PRP or at the administration of heparin sodium. The PRP was reinfused when the sternum was closed.</div></div> <div><div>2</div><div>Control group were managed without PRP.</div></div> NB: Patients in both groups received normovolaemic haemodilution and cell salvage	
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Mortality (n). Re-operation for bleeding (n).	
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Klein 2001

Methods	Method of randomisation and allocation concealment was not described	
Participants	40 low-risk coronary artery bypass grafting (CABG) patients were randomised to one of two groups: <div><div>1</div><div>Plateletpheresis group: n = 20; M/F = 20/0; mean (+/-SD) age = 60.6 (6.7) years.</div></div> <div><div>2</div><div>Control group: n = 20; M/F= 20/0; mean (+/-SD) age = 60.0 (8.6) years</div></div>	
Interventions	<div><div>1</div><div>Plateletpheresis harvesting of platelet-rich plasma (PRP) was performed 15-25 hours before cardiopulmonary bypass (CPB). The PRP contained yields of 2.93×10^{11} platelets. Platelets were retransfused post-operatively after the administration of protamine.</div></div> <div><div>2</div><div>Control group were managed without PRP.</div></div>	
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Re-operation for bleeding (n).	
Notes	German language publication. Transfusion protocol used.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Liu 1998

Methods	Method of randomisation and allocation concealment was not described	
Participants	60 open-heart surgery patients were randomised to one of three groups:	
	1	Platelet-rich plasmapheresis + epsilon aminocaproic acid group: n = 20; M/F = not reported; mean (+/-SD) age = 67 (12) years.
	2	Epsilon aminocaproic acid group: n = 20; M/F = not reported; mean (+/-SD) age = 65 (9) years.
	3	Control group: n = 20; M/F = not reported; mean (+/-SD) age = 64 (11) years
Interventions	1	Platelet-rich plasmapheresis (PRP) was performed before CPB, harvesting 10 ml/kg using a Haemonetics plasma saver. PRP was reinfused at the end of CPB with heparin completely neutralised by protamine. Patients also received 150 mg/kg of intravenous epsilon aminocaproic acid (EACA) before CPB.
	2	EACA group received 150 mg/kg of intravenous EACA before CPB.
	3	Control group were managed without PRP or EACA.
Outcomes	Units of allogeneic blood transfused. Blood loss (ml). Haematological levels. Coagulation levels.	

Notes
Quality assessment score (Schulz criteria): 2/7
Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Menges 1996

Methods	Method of randomisation and allocation concealment was not described	
Participants	60 coronary artery bypass grafting (CABG) patients were randomised to one of three groups:	
	1	Platelet-poor plasmapheresis group: n = 20; M/F = 20/0; mean (+/-SD) age = 55.3 (8.2) years.
	2	Platelet-rich plasmapheresis: n = 20; M/F = 20/0; mean (+/-sd) age = 60.5 (9.2) years.
	3	Control group: n = 20; M/F = 20/0; mean (+/-SD) age = 58.7 (8.1) years
Interventions	1	Platelet-poor plasmapheresis (PPP) harvesting 10 ml/kg was performed after the induction of anesthesia using a Haemonetics Plasma Collecting System (PCS - V250).
	2	Platelet-rich plasmapheresis (PRP) harvesting 10 ml/kg was performed after the induction of anesthesia using a Haemonetics Plasma Collecting System (PCS - V250).
	3	Control group were managed without PRP or PPP.
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Re-bleeding events (n).	
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Menges 1997

Methods	Method of randomisation and allocation concealment was not described	
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Participants	40 coronary artery bypass grafting (CABG) patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n = 20; M/F = 11/9; mean (+/-SD) age = 61.1 (8.6) years. 2 Control group: n = 20; M/F = 13/7; mean (+/-SD) age = 79.7 (7.3) years
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis (PRP) harvesting 10 ml/kg over 25 minutes was performed before incision using a Haemonetics device (discontinuous flow centrifugation technique). PRP was returned to the patient at the end of surgery after heparin reversal with protamine. 2 Control group were managed without PRP. <p>NB: All patients received intra-operative cell salvage.</p>
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (ml). Haematological levels. Coagulation levels.
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Quigley 1995

Methods	Method of randomisation and allocation concealment was not described
Participants	126 consecutive patients undergoing elective cardiopulmonary bypass were randomly allocated to one of two groups: <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n = 64; M/F = 51/13; mean (+/-SD) age = 64 (12) years 2 Control group: n = 52; M/F = 39/13; mean (+/-SD) age = 66 (11) years
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: after heparinisation and institution of CPB, blood was diverted from the venous portion of the CPB circuit to the cell saver (Haemonetics Cell Saver IV) at 300 ml/min with a centrifuge speed of 4750 rpm. Blood elements were separated according to density into PRP and erythrocytes. PRP was diverted into a blood storage bag as the cell saver bowl filled. Upon completion of the PRP sequestration, the red blood cells were returned to the circuit. The PRP was stored at room temperature without agitation and had an expiry time of 4 hours. 2 Control group: standard CPB circuit was used. No autologous blood components were sequestered
Outcomes	Number of patients transfused allogeneic blood (n). Coagulation profiles. Platelet activation analysis. Blood loss (mls).
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Safwat 2002

Methods	Patients were randomised to groups by drawing coded slips of paper from a bag. These slips of paper were placed in a bag in groups of 10 (5 APP and 5 control) to ensure equal patient numbers in the two groups. The patients were blinded from treatment	
Participants	<p>33 patients undergoing elective aortic reconstruction were randomly allocated to one of two groups:</p> <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n = 15; M/F = 14/1; mean (+/-SD) age = 68 (6) years 2 Control group: n = 15; M/F = 14/1; mean (+/-SD) age = 65 (13) years <p>NB: Two patients from the control group and one patient from the PRP group were excluded from the final analysis</p>	
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group underwent plasmapheresis using the Electromedics AT1000 (Medtronic) autotransfusion unit. An average of 20 minutes was required to complete blood withdrawal and separation of the blood components. A volume of blood was withdrawn to obtain approximately 300 ml of PRP from each patient. After the reversal of heparin with protamine and all arterial clamps were released, the autologous PPP and PRP were re-infused 2 Control group were managed without PRP. <p>NB: An autotransfusion device (cell salvage) was used to collect and re-infuse autologous red blood cells during the course of the operation in both groups</p>	
Outcomes	<p>Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels.</p>	
Notes	<p>Quality assessment score (Schulz criteria): 4/7 Transfusion protocol was used.</p>	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Coded slips of paper were drawn from a bag
Allocation concealment?	No	Used sealed envelopes to conceal treatment allocation
Blinding? All outcomes	Yes	Single blinded

Shore-Lesserson 1995

Methods	Generation of allocation sequences was made by a table of 52 random numbers with prospective assignment of patients. Concealment of treatment allocation was not described. Investigators recruiting patients were unaware of the treatment group to which patients would be assigned. Eight patients were withdrawn from the study
Participants	52 repeat open-heart surgery patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis: n = 25; M/F = not reported; mean (+/-SD) age = 64 (11) years. 2 Control group: n = 19; M/F = not reported; mean (+/-SD) age = 77 (15) years
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis (PRP) harvesting 15 ml/kg was performed after the establishment of appropriate invasive monitoring and intravascular access using Haemonetics Plasma Saver®. 2 Control group were managed without PRP. <p>NB: Patients in both groups received intra- and post-operative cell salvage</p>
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Hypotension during procedure (n). Re-operation for bleeding (n).
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table was used to randomise patients
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Although investigators recruiting patients were unaware of the treatment group to which patients would be assigned the control group received standard treatment with no PRP treatment. Study was assessed as being single blinded

Stammers 1993

Methods	Method of randomisation and allocation concealment was not described. Study reports that post-operative management and care staff were blinded
Participants	115 cardiac surgery patients were randomised to one of two groups: <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n = 63; M/F = 54/9; mean (+/-SD) = 60.4 (10.0) years. 2 Control group: n = 52; M/F = 45/7; mean (+/-SD) = 61.8 (10.8) years
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis (PRP) harvesting 20% of circulating plasma volume was performed using the Haemonetics Plasma Saver®. 2 Control group were managed without PRP. <p>NB: Autotransfusion with a cell washing system (Cell Saver 4, Haemonetics) was employed and ultrafiltration was included when deemed necessary by the perfusionist</p>

Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (ml). Haematological levels. Coagulation levels. Hospital length of stay (days).
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Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used.
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Single blinding

Stover 2000

Methods	Method of randomisation and allocation concealment was not described. Seven patients were withdrawn from the study
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Participants	62 repeat coronary artery bypass grafting (CABG) or CABG/valve surgery patients were randomised to one of two groups: 1 Platelet-rich plasmapheresis group: n = 26; M/F = 22/4; mean (+/-SD) age = 67 (11) years. 2 Control group: n = 29; M/F = 21/8; mean (+/-SD) = 70 (8) years
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Interventions	1 Platelet-rich plasmapheresis (PRP) was performed using an AT1000, Medtronic, Electromedics device. Blood was initially removed from the patient at a rate of 100 ml/min at a centrifuge speed of 5600 rpm. Once the centrifuge bowl was filled the centrifuge speed was reduced to 2400 rpm and the PRP was removed at a blood draw rate of 50 ml/min. The PRP removed consisted of the buffy coat and a 1-min elution of the red cell layer. A maximum of six passes was permitted. Platelet-poor plasma (PPP) and red cell components were returned to the patient. 2 Control group were managed without PRP. NB: Cell salvage (Electromedics AT1000, Medtronic) was used for both groups. All patients received 150 mg/kg of epsilon aminocaproic acid (EACA) over 30 minutes, followed by an infusion of 20 mg/kg/hr throughout the operation, in addition 75 mg/kg of EACA was added to the cardiopulmonary circuit priming volume
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Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Haematological levels. Coagulation levels. Blood loss (mls).
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Notes	Quality assessment score (Schulz criteria): 0/7 Transfusion protocol used.
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Triulzi 1995

Methods	Patients were randomised to treatment or control by use of a random number table. Concealment of treatment allocation was not described	
Participants	70 primary or repeat cardiac surgery patients were randomised to one of three groups: <div><div>1</div><div>Platelet-rich plasmapheresis: n = 24; M/F = 16/8; mean (+/-SD) age = 59 (13) years.</div></div> <div><div>2</div><div>Intraoperative hemodilution: n = 18; M/F = 15/3; mean (+/-SD) = 58 (11) years.</div></div> <div><div>3</div><div>Control group: n = 28; M/F = 23/5; mean (+/-SD) age = 62 (11) years</div></div>	
Interventions	<div><div>1</div><div>Platelet-rich plasmapheresis (PRP) harvesting 20% plasma volume was performed after the induction of anesthesia using the Haemonetics Plasma Saver®. The volume of PRP targeted for collection was 20% of the patients plasma volume.</div></div> <div><div>2</div><div>Intraoperative hemodilution (IH) was performed after the induction ofanesthesia. The volume of whole blood targeted for removal was 17+/-2% of the circulating blood volume.</div></div> <div><div>3</div><div>Control group were managed without PRP or IH.</div></div> NB: All groups were exposed to intra- and post-operative cell salvage	
Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Length of stay in hospital (days). Length of stay in ICU (days). Hours on ventilator.	
Notes	Quality assessment score (Schulz criteria): 3/7 Transfusion protocol used.	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Wajon 2001

Methods	Patients were randomised to treatment or control by using a random number table. Method of concealing treatment allocation was not described	
Participants	<p>90 patients undergoing repeat coronary artery bypass graft surgery were randomly assigned to one of two groups:</p> <ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis group: n= 40; M/F = 36/4; mean (+/-SD) age = 66 (8) years 2 Control group: n = 44; M/F =37/7; mean (+/-SD) age = 65 (9) years <p>NB: One patient from the control group and five patients from the PRP group were excluded from the final analysis</p>	
Interventions	<ol style="list-style-type: none"> 1 Platelet-rich plasmapheresis was commenced after the induction of anaesthesia by use of the Electromedics AT 1000 cell saver. Blood was 	

separated into three components by using the direct draw modified buffycoat method of plateletpheresis. Blood was initially withdrawn from the patient at 100 ml/min into a 225-ml bowl at 5600 rpm and the platelet-poor plasma (PPP) separated. The centrifuge was then slowed to 2400 rpm and the draw rate reduced to 50 ml/min, allowing the PRP in the buffy coat and upper red cell layer to be collected. Between 2500-3000 ml of blood was processed in 3-6 passes, each taking approximately 10 minutes. The majority of the PPP and red cells were returned to the patient immediately. Approximately 50 ml of PRP was reserved to produce platelet gel. This was applied to suture lines, raw areas, and sternal edges

2 Control were managed without PRP or platelet gel.

NB: Before CPB all patients received IV EACA 10 g.

Outcomes	Number of patients transfused allogeneic blood (n). Units of allogeneic blood transfused. Blood loss (mls). Haematological levels. Coagulation levels. Hospital length of stay (days).	
Notes	Quality assessment score (Schulz criteria): 2/7 Transfusion protocol used.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Wong 1994

Methods	Method of randomisation and allocation concealment was not described. Two patients were withdrawn from the final analysis	
Participants	40 cardiac surgery patients were randomised to one of two groups: <div><div>1</div><div>Platelet-rich plasmapheresis group: n = 20; M/F = 15/5; mean (+/-SD) age = 58 (16) years.</div></div> <div><div>2</div><div>Control group: n = 20; M/F = 12/8; mean (+/-SD) = 67 (8) years</div></div>	
Interventions	<div><div>1</div><div>Platelet-rich plasmapheresis (PRP) was performed immediately after the induction of anaesthesia using the Haemonetics Plasma Saving System. Approximately 30% of the estimated plasma volume to a maximum of 1 litre of PRP was harvested from each patient. Blood was withdrawn into a 225 ml bowl and centrifuged at 3500 rpm for 10-20 min. The PRP was collected along with the first 25 ml of red blood cells. The remaining red blood cells were returned to the patient immediately. The cycle was repeated until the calculated PRP volume had been harvested. Harvesting took approximately 30 minutes.</div></div> <div><div>2</div><div>Control group were managed without PRP.</div></div> NB: Patients in both groups received cell salvage.	
Outcomes	No. of patients exposed to allogeneic blood (n). Units of allogeneic blood transfused. Haematological levels. Coagulation levels.	
Notes	Quality assessment score (Schulz criteria): 1/7 Transfusion protocol used.	
Risk of bias		

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not described
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Control group received standard treatment (no PRP)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Reich 1991	Insufficient data.
Stover 1996	Duplicate article.
Stover 1997	Duplicate article.
Tobe 1993	Both intervention and control groups received PRP. The control group received PRP before heparinisation and the intervention group received PRP after heparin reversal
Triulzi 1992	Duplicate article.

DATA AND ANALYSES

Comparison 1 Platelet-rich plasmapheresis versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. exposed to allogeneic RBC transfusion (All Studies)	22	1589	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.90]
2 No. exposed to allogeneic RBC transfusion (Type of surgery)	22	1589	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.90]
2.1 Cardiac surgery	20	1539	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.55, 0.88]
2.2 Vascular surgery	2	50	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.76, 1.32]
3 No. exposed to allogeneic RBC transfusion (Post-operative or trial transfusion trigger)	18	1429	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.56, 0.90]
3.1 Hb < 6.6-7.0 g/dL	4	315	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.18, 0.62]
3.2 Hb < 8.0-8.5 g/dL	7	363	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.25]
3.3 Hb < 9.0 g/dL	4	591	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
3.4 Hb < 10.0 g/dL	3	160	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.59, 2.07]
4 No. exposed to allogeneic RBC transfusion (Intra-operative cell salvage)	22	1589	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Intra-operative cell salvage	16	1033	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.93]
4.2 No intra-operative cell salvage	6	556	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.11]
5 No. exposed to allogeneic RBC transfusion (Post-operative cell salvage)	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Post-operative cell salvage	3	196	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.70]
5.2 No post-operative cell salvage	19	1393	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.55, 0.89]
6 No. exposed to allogeneic RBC transfusion (Mean PRP volume collected)	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 200-300 ml	1	40	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.03, 1.56]
6.2 301-500 ml	4	184	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.15, 1.20]
6.3 501-700 ml	5	362	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.54, 1.10]
6.4 >700 ml	3	82	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.44, 2.12]
7 No. exposed to allogeneic RBC transfusion (Mean platelet yield $\times 10(11)/L$)	10	758	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
7.1 <1.8	4	409	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.40]
7.2 2.5-2.9	2	140	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.32, 0.73]
7.3 3.0-3.5	4	209	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.05, 2.02]
8 No. exposed to allogeneic RBC transfusion (Mean platelet count of PRP)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 <250 $\times 10(3)/uL$	2	80	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.67]
8.2 250-350 $\times 10(3)/uL$	2	54	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.31]
8.3 550-600 $\times 10(3)/uL$	2	139	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.25]
8.4 700-870 $\times 10(3)/uL$	2	100	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.29]
9 Units of allogeneic RBC transfused (All Studies)	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Total (Intra-operative / Post-operative)	8	376	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.93, 0.56]
9.2 Intra-operative	3	561	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.30, -0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Post-operative	3	615	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.65, -0.22]
10 No. exposed to allogeneic platelet transfusion (All Studies)	10	516	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.85]
11 Units of allogeneic platelets transfused (All Studies)	5	321	Mean Difference (IV, Random, 95% CI)	-0.96 [-1.56, -0.37]
12 No. exposed to fresh frozen plasma transfusion (All Studies)	9	484	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.17, 1.12]
13 Units of FFP transfused (All Studies)	11	1027	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.79, -0.20]
13.1 Transfusion protocol	10	1007	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.79, -0.20]
13.2 No transfusion protocol	1	20	Mean Difference (IV, Random, 95% CI)	Not estimable
14 No. exposed to cryoprecipitate transfusion (All Studies)	3	152	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.20, 2.61]
15 Units of cryoprecipitate transfused (All Studies)	3	223	Mean Difference (IV, Random, 95% CI)	-0.76 [-2.18, 0.66]
16 Blood loss (All Studies)	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Intra-operative blood loss	5	210	Mean Difference (IV, Random, 95% CI)	-127.54 [-402.05, 146.98]
16.2 Post-operative blood loss - 0-12 hours	4	654	Mean Difference (IV, Random, 95% CI)	-43.70 [-89.76, 2.37]
16.3 Post-operative blood loss - 0-24 hours	9	371	Mean Difference (IV, Random, 95% CI)	-247.17 [-396.45, -97.90]
16.4 Post-operative blood loss - 0-48 hours	2	58	Mean Difference (IV, Random, 95% CI)	-284.49 [-348.75, -220.24]
16.5 Total post-operative blood loss	7	787	Mean Difference (IV, Random, 95% CI)	-230.10 [-374.42, -85.79]

Comparison 2

Adverse events and other outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5	488	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.11, 9.23]
2 Re-operation for bleeding	5	529	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.15, 2.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Length of hospital stay (LOS) - days	5	351	Mean Difference (IV, Random, 95% CI)	-1.04 [-2.25, 0.18]

WHAT'S NEW

Last assessed as up-to-date: 24 March 2009.

Date	Event	Description
11 February 2011	New citation changed required but conclusions have not	The editorial group is aware that a clinical trial by Prof. Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews which include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author (Boldt 1990, Boldt 1993, Menges 1996, Menges 1997) on the conclusions of the review.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 2, 2003

Date	Event	Description
12 May 2009	New search has been performed	The search has been updated. Four new trials are included in the review. The Results and Conclusions sections have been amended
27 March 2008	Amended	Converted to new review format.

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- * Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Does platelet-rich plasmapheresis (PRP) reduce the need for donor blood

Platelet-rich plasmapheresis is a technique that involves a patient's own blood (autologous whole blood) being withdrawn via an intravenous catheter into a device that separates the blood by centrifugation into red blood cells (RBC), plasma, and a highly concentrated platelet solution. This concentrated autologous platelet solution is returned to the patient at the end of the operation to optimise blood clotting and minimise bleeding. The review of trials found that while PRP can reduce post-operative blood loss and the need for blood transfusion, other techniques may be more effective.

	Adequate sequence generation?	Allocation concealment?	Blinding?
Armellin 1995	?	?	+
Armellin 1997	?	?	+
Boey 1993	?	?	+
Boldt 1990	?	?	+
Boldt 1993	?	?	+
Christenson 1996/a	?	?	+
Christenson 1996/b	?	?	+
DelRossi 1990	?	?	+
Ereth 1993	?	?	+
Farouk 2003	?	?	+
Ferraris 1993	?	?	+
Ford 2002	+	?	+
Godet 1995	?	?	?
Jones 1990	?	?	+
Klein 2001	?	?	+
Liu 1998	?	?	+
Menges 1996	?	?	+
Menges 1997	?	?	+
Quigley 1995	?	?	+
Safwat 2002	+	+	+
Shore-Lesserson 1995	+	?	+
Stammers 1993	?	?	+
Stover 2000	?	?	+
Triulzi 1995	+	?	+
Wajon 2001	+	?	+
Wong 1994	?	?	+

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

Figure 3. Funnel plot of comparison: 1 Platelet-rich plasmapheresis versus control, outcome: 1.1 No. exposed to allogeneic RBC transfusion (All Studies)

Table 1
Quantity of platelet-rich plasma collected

Study	Year	PRP ml/kg	PRP volume collected (mean+/-sd)	Platelet count of PRP (mean+/-sd)	PRP platelet yield $\times 10^{11}/L$ (mean+/-sd)
Armellin	1995	10	NR	NR	NR
Armellin	1997	10	NR	NR	1.7+/-0.3
Boey	1993	10	NR	$310 \pm 99 \times 10^9/L$	NR
Boldt	1990	10	NR	$301 \pm 44 \times 10^3/ml$	NR
Boldt	1993	10	780 ± 80	$250 \pm 30 \times 10^9/L$	NR
Christenson	1996/a	NR	348 ± 95	$864 \pm 139 \times 10^3/\mu L$	3.0 ± 0.6
Christenson	1996/b	NR	433 ± 34	$747 \pm 157 \times 10^3/\mu L$	3.4 ± 0.6
DelRossi	1990	NR	220 ± 61	NR	NR
Ereth	1993	NR	690 (499, 863) *	NR	2.7 (1.7, 3.0) units *
Farouk	2003	NR	NR	NR	NR
Ferraris	1993	8-10	740 ± 69	$150-250 \times 10^3/\mu L$	NR
Ford	2002	NR	321 ± 64	$3.38 \pm 1.06 \times 10^{11}$	$29 \pm 8.8\%$ of circulating platelet mass
Godet	1995	10	739 ± 351	$62 \pm 31 g/L$	NR
Jones	1990	NR	NR	NR	2.5 ± 0.35
Klein	2001	NR	233	NR	2.93
Lui	1998	10	NR	NR	NR
Menges	1996	10	NR	$245 \pm 36 \times 10^9/L$	NR
Menges	1997	10	NR	$239 \pm 33 \times 10^9/L$	NR
Quigley	1995	NR	NR	$66 \pm 32 \times 10^9/L$	NR
Safwat	2002	NR	333 ± 134	NR	NR
Shore-Lesserson	1995	15	NR	NR	1.2
Stammers	1993	NR	600 ± 100	NR	NR
Stover	2000	NR	567 ± 169	$560 \pm 189 \times 10^3/\mu L$	3.1
Triulzi	1995	NR	650 ± 124	NR	1.42 ± 0.74
Wajon	2001	NR	628 ± 126	$586 \pm 213 \times 10^3/\mu L$	$30 \pm 7\%$ of circulating platelet mass
Wong	1994	NR	892 ± 150	$140 \pm 27 \times 10^9/L$	1.40 ± 0.27

Abbreviations: NR = not reported

* Median (IQR)

Table 2
Summary of co-interventions

Study	Year	CS	ANH	EACA	TXA	Aprotinin	PAD
Armellin	1995	No	NR	NR	NR	Yes	NR
Armellin	1997	Yes	NR	NR	NR	NR	NR
Boey	1993	No	NR	NR	NR	NR	NR
Boldt	1990	Yes	NR	NR	NR	NR	NR
Boldt	1993	Yes	NR	NR	NR	NR	NR
Christenson	1996/a	Yes	NR	No	No	No	NR
Christenson	1996/b	Yes	NR	NR	NR	NR	NR
DelRossi	1990	NR	NR	NR	NR	NR	NR
Ereth	1993	Yes	NR	NR	NR	NR	NR
Farouk	2003	NR	NR	NR	NR	NR	NR
Ferraris	1993	NR	NR	NR	NR	NR	NR
Ford	2002	Yes	NR	NR	Yes	NR	NR
Godet	1995	Yes	Yes	NR	NR	NR	Yes
Jones	1990	Yes	Yes	NR	NR	NR	NR
Klein	2001	NR	NR	NR	NR	NR	NR
Liu	1998	NR	NR	Yes	NR	NR	NR
Menges	1996	NR	NR	NR	NR	NR	NR
Menges	1997	Yes	NR	NR	NR	NR	NR
Quigley	1995	Yes	NR	NR	NR	NR	NR
Safwat	2002	Yes	NR	NR	NR	NR	NR
Shore-Lesserson	1995	Yes	NR	NR	NR	NR	NR
Stammers	1993	Yes	NR	NR	NR	NR	NR
Stover	2000	Yes	NR	Yes	NR	NR	NR
Triulzi	1995	Yes	NR	NR	NR	NR	NR
Wajon	2001	No	NR	Yes	NR	NR	NR
Wong	1994	Yes	NR	NR	NR	NR	NR

Abbreviations: NR= not reported; CS = cell salvage; ANH = acute normovolaemic haemodilution; EACA = epsilon aminocaproic acid; TXA = tranexamic acid; PAD = pre-operative autologous blood donation

Table 3
Cell salvage techniques

Study	Year	Cell salvage technique
Armellin	1995	Shed mediastinal blood was not collected and reinfused during the post-operative period
Armellin	1997	After separation from CPB, the residual blood in the circuit was salvaged and concentrated using a Cell Saver® (Dideco SpA, Mirandola, Italy). This autologous blood was retransfused until the end of the operation. Shed mediastinal chest tube blood (SMCTB) was not collected and retransfused during the post-operative period
Boey	1993	Cell saver techniques were not employed.
Boldt	1990	Within 20 mins after the start of ECC, blood was concentrated using a cell saving system (Cell Saver® IV, Haemonetics®, Munich, FRG; 2 cycles standardised). After termination of ECC, the residual blood of the circuit was concentrated by the use of the cell saver system, and washed erythrocytes and the preoperatively removed autologous plasma were retransfused before the end of the operation. SMCTB was not collected and retransfused during the post-operative period
Boldt	1993	All fluids (cardioplegic solution, cooling, suction) were returned to the CPB circuit. Within 20 minutes after the start of CPB, blood in the circuit was concentrated using a hemofiltration device (HF-80, Fresenius, Bad Homburg, Germany). After separation from CPB, the residual blood of the circuit was salvaged and concentrated with the help of the hemofiltration device. This autologous hemofiltered blood was retransfused until the end of the operation. SMCTB was not collected and retransfused during the post-operative period
Christenson	1996	Autotransfusion with the Elmd 500 (Metronic Inc, Parker, Co, USA) was employed and ultrafiltration was included when deemed necessary by the perfusionist
Christenson	1996/a	As above.
DelRossi	1990	Use of cell salvage was not reported.
Ereth	1993	Salvaged blood from the surgical field was processed by the rapid cell salvage machine. <i>No specific details were provided.</i>
Farouk	2003	Use of cell salvage was not reported.
Ferraris	1993	Use of cell salvage was not reported.
Ford	2002	Intra-operative cell salvage was used for all patients. <i>No specific details were provided.</i>
Godet	1995	Cell Saver IV (Haemonetics) was used to concentrate and wash blood during the intra-operative period. The centrifugation part of the kit was only assembled when blood loss was equal to or exceeded 1000ml for economic reasons. [Translation]
Jones	1990	Intra-operative blood salvage was used for all patients. <i>No specific details were provided.</i> Reinfusion of shed mediastinal blood for the first 4 hours was used for all patients
Liu	1998	Use of cell salvage was not reported.
Menges	1996	After disconnection from CPB, the remaining blood of the extracorporeal bypass system was collected and concentrated using the haemofiltration technique. This autologous haemofiltered blood was re-transfused until the end of surgery. Shed mediastinal blood was not collected and retransfused during the post-operative period
Menges	1997	A haemofiltration technique (HF-80, Fresenius, Bad Homburg, Germany) was used to salvage all blood and all fluids (cardioplegic solution, intrathoracic cooling solution) from the surgical field during CPB. All blood remaining in the bypass circuit was concentrated with the haemofiltration technique and the haemofiltered autologous blood was returned to the patient at this time. During the post-operative period SMCTB was neither collected nor retransfused
Quigley	1995	Use of cell salvage was not reported.
Safwat	2002	An autotransfusion device was used to collect and re-infuse autologous RBC during the course of the operation in both groups
Shore-Lesserson	1995	A haematocrit (Hct) on CPB below 20% was treated by hemofiltration if oxygenator volume was adequate or with RBC. Intra-operative Cell Saver® 4 (Haemonetics®, Braintree, MA) was used for all patients. Shed mediastinal chest tube blood was collected and retransfused during the post-operative period
Stammers	1993	Autotransfusion with a cell washing system (Cell Saver® 4, Haemonetics®, Inc, Braintree, MA) was employed and ultrafiltration was included when deemed necessary by the perfusionist
Stover	2000	All patients in the study received intraoperative red cell salvage with the AT1000 (Medtronic Elec-tromedics, Inc). Salvaged red blood cells were returned to the patients before departing the operating room

Study	Year	Cell salvage technique
Triulzi	1995	Intra-operative salvage and bypass blood from the bypass pump were routinely returned to patients when available. Autologous blood not transfused in the operating room was transfused immediately after the operation. SMCTB was routinely used when available
Wajon	2001	Cell salvage was not used after the onset of CPB.
Wong	1994	A Cell Saver® system (Haemonetics®) was used to salvage all blood suctioned from the surgical field before and after CPB. All blood remaining in the bypass circuit was also processed through the Cell Saver® at the end of surgery and the autologous cell saver blood was returned to the patient at this time

Table 4
Transfusion threshold

Study	Year	Red blood cells (RBC)	Fresh frozen plasma (FFP)	Platelets
Armellin	1995	During CPB Hb=7.0 g/dL Post-operative Hb<9.0 g/dL if <70 years Hb<10.0 g/dL if >70 years	FFP was administered for a prothrombin time (PT) or a partial thromboplastin time (PTT) of greater than 150% of control values in the presence of bleeding (>100 ml/hr)	NR
Armellin	1997	During CPB Hct=20% Post-operative Hb<9.0 g/dL if <70 years Hb<10.0 g/dL if >70 years	As above.	Platelet concentrates were administered only for a platelet count of less than 50,000/ μ L ³
Boey	1993	During CPB Hb<7.0 g/dL or Hct<21% Post-operative Symptomatic anaemia Hb<10.0 g/dL or Hct<30%	FFP was administered in the presence of clinical bleeding if the PT or PTT was prolonged >120% of control	Platelets were administered if the platelet count was <100 $\times$ 10 ⁹ /L.
Boldt	1990	During CPB Hb<7.0 g/dL Post-operative Hb<9.0 g/dL	NR	NR
Boldt	1993	During CPB Hb<7.0 g/dL Post-operative Hb<9.0 g/dL	NR	NR
Christenson	1996/a	Hct<20%	Patients were transfused coagulation factors only when bleeding was uncontrollable FFP was transfused when the PTT>35 seconds.	Patients were transfused coagulation factors only when bleeding was uncontrollable Platelets were transfused when platelet count was less than 50, 000/ μ L
Christenson	1996/b	As above	As above	As above
DelRossi	1990	Hct<30%	FFP transfusion was based on activated partial thromboplastin time. No threshold value was reported	NR
Ereth	1993	Transfusion criteria were not used.	Transfusion criteria were not used.	Transfusion criteria were not used.
Farouk	2003	Transfused to maintain volume and red cell mass appropriate for the age and condition of the patient	FFP was transfused for a prothrombin time >20 seconds. Cryoprecipitate was transfused for a fibrinogen level of 100 mg/dL	Platelets were transfused for platelet counts <100,000 in patients with active bleeding
Ferraris	1993	Post-operative Hct<25% if <70 years <27% if >70 years NB: the responsible surgeon ultimately determined the need for transfusion based on clinical assessment	Post-operative FFP was transfused if PTT ratio was greater than 1.3.	Post-operative Platelets were transfused if platelet count <75,000/ μ L.
Ford	2002	During CPB Hb<6.0 g/dL Post-operative Hb=8.0 g/dL	Post-operative FFP was transfused if the prothrombin time was >1.5 times the control	Post-operative Platelets were transfused in the presence of excessive bleeding if the platelet count was <100 $\times$ 10 ⁹ /L or regardless of platelet count if the patient had taken aspirin up to the time of surgery
Godet	1995	Intra-operative Hb<8.0 g/dL Post-operative Hb<10.0 g/dL	NR	NR

Study	Year	Red blood cells (RBC)	Fresh frozen plasma (FFP)	Platelets
Jones	1990	Post-operative Hb<7.0 g/dL if <70 years Hb<8.0 g/dL if >70 years Hb<10.0 in two patients with respiratory failure.	NR	Post-operative Platelets were transfused if the platelet count was <100 × 10 ⁹ /L in patients with active bleeding.
Klein	2001	Post-operative Hb<9.0 g/dL or Hct<25%	NR	NR
Liu	1998	Hct<30%	FFP were transfused if the PT/APTT value was 150% higher than control value	Platelets were transfused if the platelet count was <100,000/ml with evidence of active bleeding
Menges	1996	During CPB Hb<7.0 g/dL Post-operative Hb<8.5 g/dL	NR	NR
Menges	1997	During CPB Hb<7.0 g/dL OR Hb<8.0 g/dL after all salvaged blood had been transfused.	FFP was transfused only if the patient was bleeding (>2 ml/kg/hr chest tube drainage) and the activated partial thromboplastin time >45 seconds	Platelets was transfused only if the patient was bleeding (>2 ml/kg/hr chest tube drainage) and the platelet count was <80 × 10 ⁹ /L.
Quigley	1995	Hct<30%	FFP was transfused if mediastinal drainage was more than 200 ml/hr for two consecutive hours. Threshold value was not reported	Platelets were transfused if mediastinal drainage was more than 200 ml/hr for two consecutive hours. Threshold value was not reported
Safwat	2002	Hb<9.0 g/dL	FFP was transfused when INR >1.4 in the presence of inadequate haemostasis	Platelets were transfused if platelet count was <100,000 mm ³ in the presence of inadequate haemostasis
Shore-Lesserson	1995	During CPB Hct<20% Post-operative Hct<25% in the presence of hypovolaemia.	FFP was transfused for a PT<150% of control. Cryoprecipitate was given for a fibrinogen count <150 mg/dL.	Platelets were transfused for a platelet count <100,000 mm ³ or if the thromboelastograph demonstrated an angle <40° and a maximum amplitude (MA) <40 mm
Stammers	1993	Peri-operative Hb<7.0 g/dL if <70 years Hb<8.0 g/dL if >70 years Post-operative Hct<21 % except in the case of incomplete revascularisation where RBC were given for a Hct<25%	Peri-operative FFP was transfused when bleeding was uncontrollable and when prothrombin times (PT) were >16 seconds Cryoprecipitate was transfused when fibrinogen levels were <100 mg/dL	Peri-operative Platelets were transfused when platelet counts were <100,000/μL
Stover	2000	Hct 24%	FFP was transfused in the setting of clinical bleeding for PT>150% of normal Cryoprecipitate was given if fibrinogen level <100 mg/dL.	Platelets were transfused in the setting of clinical bleeding for platelet counts <100,000 μL
Triulzi	1995	Intra-operative Hct<20% with signs of acute ischemia or uncontrolled major blood loss Post-operative Hct<24% or symptomatic anaemia.	Intra-operative FFP was given for diffuse bleeding not adequately controlled by surgical haemostasis or platelet transfusion Post-operative FFP was given for diffuse bleeding with laboratory evidence of a coagulopathy	Intra-operative Platelets were given for diffuse bleeding after bypass with adequate surgical haemostasis Post-operative Platelets were given for a platelet count <100 × 10 ⁹ /L with diffuse bleeding or diffuse bleeding within 24 hours of bypass regardless of platelet count
Wajon	2001	During CPB Hb<7.0 g/dL Post-operative Hb<8.0 g/dL	FFP was transfused if the patient was bleeding (>2 ml/kg/hr chest tube drainage) or if the patient was clinically coagulopathic and laboratory tests indicated the use of FFP (INR>1.5, activated partial thromboplastin time >45 seconds)	Platelets were transfused if the patient was bleeding (>2 ml/kg/hr chest tube drainage) or if the patient was clinically coagulopathic and laboratory tests indicated the use of platelets (platelet count <100 × 10 ⁹ /L).
Wong	1994	During CPB Hb<6.0 g/dL	FFP was transfused if the patient was bleeding (>2 ml/kg/hr chest	Platelets were transfused if the patient was bleeding (>2 ml/kg/hr chest tube

Study	Year	Red blood cells (RBC)	Fresh frozen plasma (FFP)	Platelets
		OR Hb<8.0 g/dL after all cell saver blood had been transfused. Allo- geneic red blood cells were transfused for higher Hb levels only if judged absolutely vital to the patients well being by the attending surgeon and anaesthesiologist	tube drainage) and laboratory tests indicated the use of FFP	drainage) and laboratory tests indicated the use of platelets

Table 5
Duration of cardiopulmonary bypass (minutes) - mean (SD)

Study	Year	PRP (n)	PRP - duration of CPB	Control (n)	Control - duration of CPB
Menges	1997	20	73.0 (21.4)	20	72.2 (19.8)
Boey	1993	19	73.3 (20.9)	20	76.4 (16.3)
Menges	1996	20	76.3 (23.6)	20	80.5 (18.2)
Ford	2002	25	77.0 (59, 103) *	29	72.0 (60, 89) *
Boldt	1990	15	78.6 (4.5)	15	83.5 (17.0)
Christenson	1996/b	30	87.9 (34.8)	30	87.8 (29.0)
Boldt	1993	12	89.4 (21.1)	12	87.0 (20.7)
Farouk	2003	10	91.8 (21.9)	10	101.2 (23.9)
Christenson	1996/a	20	97.0 (37.0) **	20	97.0 (37.0) **
Jones	1990	50	102.0 (33.2)	50	106.0 (40.3)
Klein	2001	20	104.2 (21.1)	20	107.8 (24.8)
Armellin	1995	128	105.0 (36.0)	128	107.0 (38.0)
Triulzi	1995	24	106.0 (31.0)	28	102.0 (37.0)
Armellin	1997	142	106.5 (37.0)	142	109.7 (40.0)
Ereth	1993	28	113.0 (68, 170) *	28	108.0 (68, 148) *
Wajon	2001	40	114.0 (39.0)	44	108.0 (33.0)
Stammers	1993	63	121.2 (41.2)	52	114.6 (38.1)
Shore-Lesserson	1995	25	123.0 (45.0)	19	135.0 (39.0)
Stover	2000	26	125.0 (31.0)	29	136.0 (37.0)
Liu	1998	20	127.0 (24.0)	20	128.0 (25.0)
Wong	1994	20	140.0 (43.0)	20	132.0 (43.0)
Quigley	1995	64	143.0 (34.0)	52	141.0 (33.0)

* Median (IQR)

** Mean CPB time for both groups. Individual trial arm data were not reported.