PLATELET-RICH PLASMAPHERESIS IN CARDIAC SURGERY: A META-ANALYSIS OF THE EFFECT ON TRANSFUSION REQUIREMENTS

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Objective: **Our purpose was to determine whether intraoperative platelet-rich plasmapheresis in cardiac surgery is effective in reducing the proportion of patients exposed to allogeneic red cell transfusions.** ***Methods:*** **A systematic search for prospective, randomized trials of platelet-rich plasmapheresis in cardiac surgery, using MEDLINE, HEALTHSTAR, *Current Contents*, "Biological Abstracts," and EMBASE/Excerpta Medica up to August 1997, was completed. Trials were included if they reported either the proportion of patients exposed to allogeneic red cells or the units of allogeneic red cells transfused. Trials were abstracted by 2 independent investigators and the quality of trial design was assessed with the use of a validated scale.** ***Results:*** **Seventeen references met the inclusion criteria (1369 patients [675 control: 694 platelet-rich plasmapheresis]). Platelet-rich plasmapheresis reduced the likelihood of exposure to allogeneic red cells in cardiac surgery (odds ratio 0.44; 95% confidence interval 0.27, 0.72, *P* = .001). Platelet-rich plasmapheresis had a small but statistically significant effect on both the volume of blood lost in the first 24 hours (weighted mean difference –102 mL; 95% confidence interval –148, –55 mL, *P* < .0001) and the mean units transfused (weighted mean difference –0.33 units; 95% confidence interval –0.43, –0.23, *P* < .0001). However, platelet-rich plasmapheresis was only marginally effective (odds ratio 0.83, 95% confidence interval 0.34, 2.01, *P* = .68) for "good" quality trials, whereas it appeared very effective in trials with poor methodologic quality (odds ratio 0.33, 95% confidence interval 0.17, 0.62, *P* = .0007).** ***Conclusions:*** **Although platelet-rich plasmapheresis appeared effective in decreasing the proportion of patients receiving transfusions after cardiac operations, the quality of most of the supporting trials was low and the benefit was small in trials of good quality. Further clinical trials should be completed. (J Thorac Cardiovasc Surg 1998;116:641-7)**

Concern about the side-effects of allogeneic blood transfusion, especially the transmission of viral infections, has led to the development of a variety of methods intended to minimize perioperative transfusion in cardiac surgery. These include technologies such as preoperative autologous donation, pharmaceuticals, acute normovolemic hemodilution, cell salvage, and intraoperative platelet-rich plasmapheresis. This last technique involves the prebypass preparation of platelet-rich plasma (PRP) from whole blood. Whereas the separated red cells are readministered to the patient before bypass, the PRP is given after the administration of protamine. With some of the devices used for this technology, the platelets may be concentrated further, thus also allowing for retransfusion of platelet-poor plasma before bypass. Both of these approaches spare the platelets the potential detrimental effects of exposure to the bypass circuit,[1] which include a decrease in the number of circulating platelets of up to 50% and abnormal function in the remaining platelets.[1]

The primary objective of this meta-analysis was to determine whether platelet-rich plasmapheresis in car-

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Table I. *Trial characteristics*

First author	*Date*	*Type of operation*	*Procedure*	*ASA preop*	*Postop transfusion threshold*	*Jadad score*
Boldt[17]	1990	Primary	CABG	No patients	Yes	1
Jones[18]	1990	Primary	CABG	Some patients	Yes	1
Boey[14]	1993	Primary	CABG	No patients	Yes	2
Tobe[15]	1993	Primary	CABG	Some patients	No	5
Boldt[16]	1993	Primary	CABG	No patients	Yes	2
Ereth[20]	1993	Redo	Valve	Some patients	Yes	3
Stammers[21]	1993	Primary and redo	CABG and valve	Some patients	Yes	1
Wong[13]	1994	Primary	CABG and valve	Some patients	Yes	2
Quigley[10]	1995	Primary	CABG and valve	Some patients	Yes	1
Shore- Lesserson[11]	1995	Redo	CABG and valve	Some patients	Yes	3
Armellin[22]	1995	Primary and redo	CABG and valve	No patients	Yes	2
Triulzi[12]	1995	Primary and redo	CABG and valve	Some patients	Yes	2
Christenson[8]	1996	Redo	CABG	Some patients	Yes	1
Menges[9]	1996	Primary	CABG	No patients	Yes	1
Stover[5]	1996	Primary and redo	CABG and valve	Data not given	No	1
Armellin[7]	1997	Primary and redo	CABG and valve	Some patients	Yes	3
Menges[19]	1997	Primary	CABG	No patients	Yes	1

CABG, Coronary artery bypass grafting; *redo,* reoperative surgery.

diac surgery is effective in reducing the proportion of patients exposed to allogeneic red cells in the perioperative period. The secondary objectives were to determine whether platelet-rich plasmapheresis is effective in reducing the number of units of allogeneic red cells transfused and the amount of blood lost during the first 24 hours after the operation. The impact of trial methodology on efficacy was also assessed by means of a validated quality assessment scale.[2]

Methods and materials

Literature search and study selection. Systematic searches of MEDLINE (1966–July 1997), HEALTHSTAR (1995–July 1997), *Current Contents* (week 1–week 29, 1997), "Biological Abstracts" (1990–March 1997), and EMBASE/Excerpta Medica (1980-1997) were conducted in August 1997 to identify prospective randomized controlled trials. The search strategy was first developed on MEDLINE and then adapted to the controlled vocabulary of each of the other databases.[3] All titles and abstracts of the identified articles were reviewed by 2 investigators to determine potential eligibility for analysis. Any trial comparing intraoperative platelet-rich plasmapheresis to an appropriate control group, regardless of language or medium of publication, was retrieved for further examination. Platelet-rich plasmapheresis was defined as the process of preparation of autologous platelets from whole blood by means of centrifugation. If insufficient detail was provided in the abstract to determine eligibility, the article was retrieved for further review. Medtronic Inc of Canada (Mississaugua, Ontario) was asked to contribute all articles or reports on this subject from their records. Bibliographies of all identified trials and review articles were hand searched for additional publications.

Authors of trials not reporting either the number of subjects exposed to at least 1 unit of allogeneic red cells or the volume of allogeneic red cells transfused were contacted in an attempt to retrieve the necessary information. Duplicate publications, studies in children, and trials in which the patients were pseudo-randomized were excluded.

Data extraction. Data from each of the studies were independently abstracted onto study data forms by 2 individuals (F.D.R., P.S.W.). Disagreements were resolved by consensus. Non–English language trials were abstracted by 1 of the investigators with the assistance of a translator. No attempt was made to conceal the identity of the author or the medium of the publication. When necessary, authors were contacted in an attempt to clarify results or to provide missing data.

Data abstracted included the proportion of subjects exposed to at least 1 unit of allogeneic red cells in the perioperative period, the type of operation (eg, primary versus reoperative, valve versus coronary artery bypass grafting), the mean units of packed red cells, platelets, and fresh frozen plasma transfused per patient randomized, the mean blood loss within 24 hours of the operation, whether a perioperative transfusion protocol was reported, the preoperative use of aspirin, the preoperative and discharge hematocrit values, and the volume of PRP prepared. In those studies in which this latter volume was recorded as a percentage of the total plasma volume, a conversion factor of 45 mL/kg body weight was used to estimate the total PRP collected.[4] In 1 trial[5] the volume collected was recorded in units of platelets. This was converted to volume of PRP collected by means of a factor of 55 mL/unit (*Clinical Guide to Transfusion;* Canadian Red Cross Society, 1987). The methodologic quality of the trials was determined with the use of the scale developed by Jadad and associates.[2] This scale rates trial design from 0 to 5 depending on subject and investigator blinding, the method of randomization, and the reporting of subject withdrawals. A

score of 3 or more is considered good quality and a score of less than 3 is considered poor quality.[2]

Analysis. The proportion of patients receiving a transfusion was analyzed with Meta-Analyst (Meta-Analyst[0.988]; Lau J, Chalmers TC, 1995) using Der Simonian and Laird's random effects model.[6] Results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). An OR of 1.0 suggests that there was no difference between treatment and control, an OR less than 1.0 indicates that fewer patients in the treatment group (PRP) received allogeneic red cell transfusion, and an OR of greater than 1.0 indicates that more patients in the treatment group received allogeneic red cell transfusion. Tests for heterogeneity were performed for each meta-analysis. If positive, the studies that appeared to be the major contributors to the heterogeneity were evaluated in an attempt to discover the possible reasons. Subgroup analyses based on the type of procedure, volume of blood withdrawn before the operation, transfusion protocol, and pretreatment with aspirin were proposed a priori.

Continuous data, such as the total number of units of allogeneic red cells transfused and the mean blood loss during the first 24 hours after the operation, were analyzed by means of RevMan 1.04b (RevMan 1.04b, *The Cochrane Review Manager,* 1994), which uses a fixed effects model. Summary results of continuous data are expressed as weighted mean differences (WMD) with 95% CI.

Table II. *Devices for collection of platelet-rich plasma*

First author	*Device**
Boldt[16]	Haemonetics Plasma Collecting System V50
Jones[18]	Haemonetics Model 5000
Boey[14]	Haemonetics Plasma Collecting System
Tobe[15]	Haemonetics Plasma Saver Autologous Plasma Collection System
Boldt[17]	Haemonetics Plasma Collecting System V50
Ereth[20]	Haemonetics Plasma Saver
Stammers[21]	Haemonetics Plasma Saver
Wong[13]	Haemonetics Plasma Saver
Quigley[10]	Haemonetics Cell Saver IV
Shore-Lesserson[11]	Haemonetics Plasma Saver
Armellin[7]	Haemonetics Ultralite
Triulzi[12]	Haemonetics Plasma Saver
Christenson[8]	Electromedics Elmd—500 Autotransfusion/ Platelet Sequestration Device
Menges[9]	Haemonetics Plasma Collecting System V250
Stover[5]	Electromedics AT 1000
Armellin[22]	Haemonetics Ultralite
Menges[19]	Haemonetics

*Haemonetics Corporation, Braintree, Massachusetts. Electromedics Inc, Parker, Colorado.

Results

The systematic literature searches yielded 1072 references in total. After review of all references, the bibliographies of trials and reviews, and industry literature searches, a total of 19 prospective randomized trials were eligible for analysis. Of the 19 randomized controlled trials, 1 was identified by industry[5] and 18 were identified by the systematic literature search. Whereas 17 met the inclusion criteria,[5,7-22] information on outcomes for 2 trials could not be obtained from either the publication or communication with the authors.[23,24] The trials included in this meta-analysis included a total of 1369 patients (675 control patients; 694 patients subjected to platelet-rich plasmapheresis). The characteristics of the trials are summarized in Tables I and II.

Of the 17 included trials, 16 trials reported the proportion of patients exposed to at least 1 unit of allogeneic red cells and 15 documented the total number of units of allogeneic red cells transfused. The median sample size of the 17 trials was 44 (range 24-284). The mean volume of PRP collected was 730 mL (15 trials reporting, range 306-1050 mL) and the mean 24-hour blood loss was 821 mL in the platelet-rich plasmapheresis arm (12 trials reporting, range 481-1514 mL) and 909 mL in the control arm (range 525-1304 mL).

The effectiveness of platelet-rich plasmapheresis on the proportion of patients receiving allogeneic red cells is shown in Fig 1. When all eligible trials were considered, platelet-rich plasmapheresis significantly reduced the likelihood of exposure to at least 1 unit of allogeneic red cells (OR 0.44; 95% CI 0.27, 0.72; P = .0012). Platelet-rich plasmapheresis reduced the number of units of allogeneic red cells transfused (WMD –0.33 units; 95% CI –0.43, –0.23). Twelve of the studies provided sufficient information for the determination of the total 24-hour blood loss from the mediastinal tubes. Platelet-rich plasmapheresis had a small but statistically significant effect on the volume of blood lost in the first 24 hours of the perioperative period (WMD –102 mL; 95% CI –148, –55 mL; P = .00002).

Marked heterogeneity was found in the primary outcome analysis of the proportion of patients receiving allogeneic red cells (χ^2 47.1; 15 degrees of freedom; P < .001), as well as the secondary outcomes, 24-hour blood loss (χ^2 33.0; 11 degrees of freedom; P < .001), and mean units transfused (χ^2 61.2; 10 degrees of freedom; P < .001).* Subgroups were analyzed to better clarify the potential causes of this heterogeneity. The variables examined in the subgroups were defined a priori and included the surgical procedure, the proportion of patients receiving acetylsalicylic acid, the transfusion threshold, the amount of platelet plasma volume collected, and the methodologic quality of the trials (Fig 2).

*A χ^2 for mean units could not be calculated for the 15 studies because 4 studies had standard deviations of 0. Therefore a χ^2 for homogeneity was calculated for 11 studies.

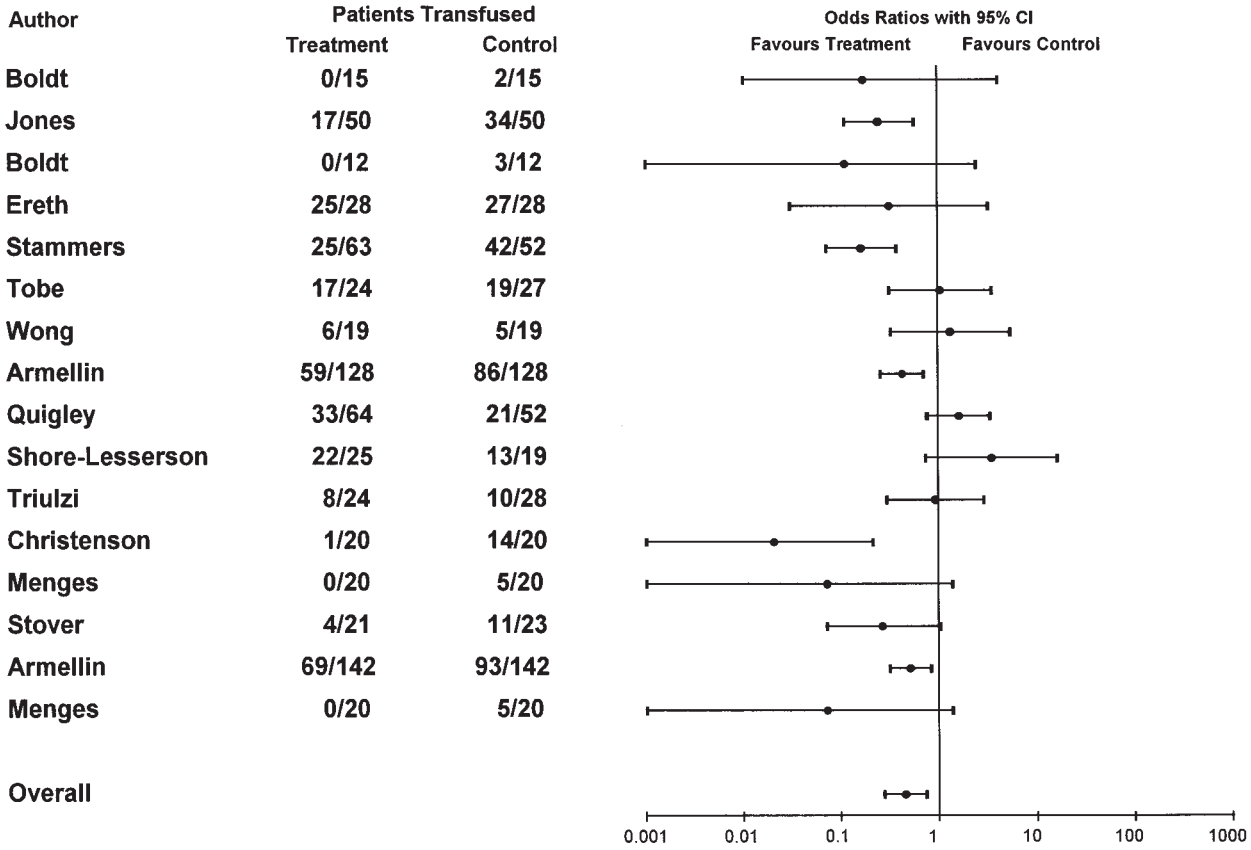

Fig 1. Platelet-rich plasmapheresis in cardiac surgery: Proportion of patients receiving transfusions of allogeneic red cells. *CI,* Confidence interval.

For the primary outcome of the proportion of patients receiving a transfusion of allogeneic red cells, there was no evidence of a difference in efficacy among the subgroups (Fig 2). There was a nonsignificant trend for trials with poor methodology to yield larger effect sizes. Additionally, there was a nonsignificant trend toward trials with higher postoperative transfusion thresholds and higher collected platelet plasma volumes to demonstrate a smaller treatment effect. Subgroup analysis was performed for mean units transfused and the blood loss within 24 hours of the operation, and no differences were found that would explain the heterogeneity (results not shown).

The rate of transfusion in the control group ranged between 13% and 96% in patients undergoing cardiac operations. Little correlation was observed between the proportion of patients receiving an allogeneic transfusion in the control group and the absolute risk reduction caused by platelet-rich plasmapheresis ($R2 = 0.0214$).

Discussion

In this meta-analysis of patients undergoing cardiac surgery, intraoperative platelet-rich plasmapheresis was found to significantly decrease the proportion of patients receiving a transfusion in the perioperative period. Two secondary outcomes, mean units of allogeneic red cells transfused and mean blood loss within 24 hours of the operation, were also found to be significantly decreased in the experimental group compared with the control group.

However, a marked heterogeneity was observed in the results of the studies included in the meta-analysis. Numerous subgroup analyses performed for all 3 outcomes did not convincingly establish the reason for this heterogeneity (Fig 2). Because of the significant unexplained heterogeneity, caution must be exercised in recommending this technology without further large, high-quality randomized trials that clearly demonstrate benefit. Furthermore, the only trial in this meta-analysis that achieved a perfect methodologic score of 5 on the Jadad scale had an OR of 1.02 (95% CI 0.31, 3.42), which suggested that platelet-rich plasmapheresis was not effective.[15]

It was puzzling to find that the efficacy of platelet-rich plasmapheresis was inversely related to the volume of platelets collected (Fig 3). However, several other

Analysis	Patients Transfused		OR	95 % CI		p-value
	Treatment	*Control*		*LL*	*UL*	
Overall	286/675	390/655	**0.44**	0.27	0.72	0.0012
Type of Surgery						
Primary	73/224	94/215	**0.47**	0.19	1.15	0.098
Repeat	48/73	54/67	**0.31**	0.02	6.36	0.450
Primary or Repeat	165/378	242/373	**0.39**	0.24	0.62	<0.0001
Procedure						
CABG	35/161	82/164	**0.14**	0.03	0.61	0.001
CABG or Valve	226/486	281/463	**0.63**	0.35	1.12	0.120
ASA Use						
Some Pts on ASA	223/459	278/437	**0.55**	0.28	1.07	0.078
No Pts on ASA	59/195	101/195	**0.36**	0.22	0.58	<0.0001
Transfusion Threshold						
66 to 80 Hgb	51/169	103/162	**0.21**	0.08	0.53	0.001
80 to 90 Hgb	53/112	55/106	**0.54**	0.13	2.32	0.410
90 to 100 Hgb	161/349	202/337	**0.62**	0.32	1.19	0.150
Volume of Platelet Plasma Collected						
300-350 ml	5/41	25/43	**0.09**	0.01	0.95	0.045
650-800 ml	203/476	292/472	**0.39**	0.25	0.61	<0.0001
850-1050 ml	45/94	52/88	**0.92**	0.18	4.76	0.920
Quality						
Low Quality	153/456	238/439	**0.33**	0.17	0.62	0.001
High Quality	133/219	152/216	**0.83**	0.34	2.01	0.680

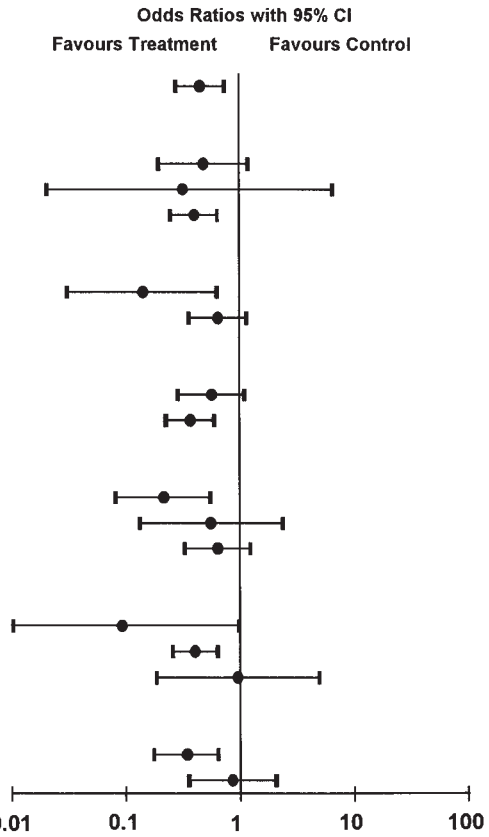

Fig 2. Proportion of patients receiving transfusions of allogeneic red cells: Subgroup analyses. *CABG,* Coronary artery bypass grafting. *ASA,* acetylsalicylic acid; *Hgb,* hemoglobin; *OR,* odds ratio; *CI,* confidence interval; *LL,* lower limit; *UL,* upper limit.

authors have already suggested that the most important factor contributing to efficacy is the absolute number of platelets collected, not their volume.[25,26] In 2 of the trials[5,8] reported in this meta-analysis, in which between 300 and 350 mL of PRP was collected (OR 0.09; 95% CI 0.01-0.9; P = .045), a 2-speed centrifugation technique was used (AT1000; Electromedics Inc, Parker, Colo), which is known to produce a platelet-rich concentrate equivalent to 6 units of platelets.[26] In 7 of the 17 trials, we were able to calculate, a posteriori, the number of platelets extracted. There appeared to be a correlation between efficacy and the number of platelets extracted, although this correlation was not tested statistically (Fig 3). This finding should be viewed with considerable caution because this was a post hoc subgroup analysis conducted on a small number of patients.[27]

Other factors may influence the efficacy of this technology. First, platelet function is significantly impaired after centrifugation, and the platelets may be refractory to stimulation for a period of 4 to 6 hours.[28] Second, although this technology decreased the volume of postoperative shed mediastinal blood compared with that of the control group (WMD –102 mL [–148, –55 mL]), it cannot limit the intraoperative blood loss that occurs during cardiopulmonary bypass. This loss is particularly important with reoperative surgery because of vascular adhesions and contributes to the increased transfusion requirements in this population.

In the 1 trial that recorded complications related to platelet-rich plasmapheresis,[11] some of the patients had hypotension and several had to be excluded from the study before the completion of PRP collection as a result of hemodynamic instability. This instability may have been related to inadequate fluid replacement during the withdrawal of whole blood, leading to hypovolemia.

Limitations of this meta-analyses must be addressed. Caution must be exercised when looking at the results of meta-analyses with small sample sizes. Meta-analyses of other interventions, such as magnesium and nitrates for patients with myocardial infarction, have reached false positive conclusions about efficacy when their results were compared with a subsequent "definitive" large trial.[29] Second, there was a large amount of heterogeneity between the trials analyzed, which was not explained by subgroup analyses. However, the lack of an explanation may have been related to the fact that

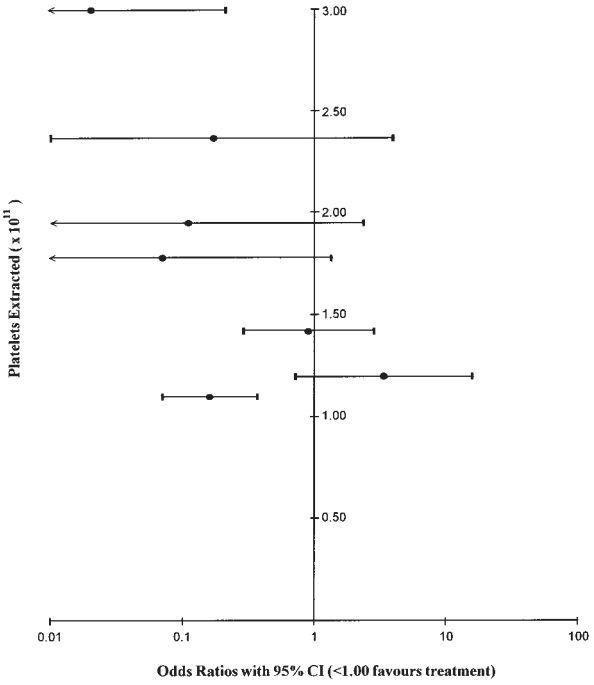

Fig 3. Effect size (proportion receiving allogeneic red cells) versus total platelets extracted. *CI*, Confidence interval.

the subgroups were too small to allow statistically significant answers to be found. Finally, not all studies reported both the primary and secondary outcomes; thus only a subset, albeit a majority of the identified trials, were included in the analysis. Similarly, only a handful of trials reported adverse events. This supports the recommendations that uniform and comprehensive standards are needed when reporting results of trials of blood conservation technologies.[30]

In conclusion, the overall OR found in this meta-analysis suggests that the proportion of patients receiving a transfusion was decreased in patients in whom platelet-rich plasmapheresis was used in cardiac surgery. This was associated with a decrease in the total volume of transfused allogeneic red cells and a small but statistically significant decrease in the total shed mediastinal blood. However, the poor methodologic quality of most of the trial reports and the marked heterogeneity of the results make it very difficult to determine the true efficacy of platelet-rich plasmapheresis. A large, double-blind, randomized, controlled trial is needed to further delineate the role of intraoperative platelet-rich plasmapheresis in cardiac surgery.

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