Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2024, 16(2), 34-50
https://ijbc.ir

Review Article

Optimizing Patient Blood Management in Cardiac Surgery: A Systematic Review

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Citation Alotaibi S G, Alnouri M A, Sulaiman R M, Abduljaleel A, Bogari A F, Mufti H N. Optimizing patient blood management in cardiac surgery: a systematic review. Iran J Blood Cancer. 2024 June 30;16(2):34-50.

doi 0

Article info:

Received: 2 Apr 2024
Accepted: 24 May 2024
Published: 30 June 2024

Abstract

Background: Heart diseases are typically treated with cardiac surgery, which often requires preoperative, intraoperative, and postoperative blood transfusion. However, blood transfusion is a risk factor for serious complications after cardiac surgery, including death. Patient Blood Management (PBM) programs were developed to mitigate the risks of blood transfusion by reducing its use in cardiac surgery.

Objective: This systematic review aims to study the currently published literature on PBM strategies that effectively reduce the rates of preoperative, intraoperative, and postoperative blood transfusion for cardiac surgery.

Methodology: This systematic review analyzed preoperative blood management strategies in cardiac surgery, focusing on studies published between 2018 and 2024 designed to reduce blood transfusion rates. The study utilized a modified 2022 protocol for systematic reviews and meta-analysis, grading evidence using a 2008 system, and selected 21 studies for a systematic review.

Results: The studies identified 12 PBM strategies, including iron therapy, Aminocaproic acid, Cardiopulmonary by-pass system, cell salvage, Perfusion Blood Collection, gel foam patches, Large-volume acute normovolemic hemodilution, Platelets Transfusion Therapy, Modified Ultrafiltration, TEM-based algorithms, and restrictive management of SVO2, which significantly reduced blood transfusion volumes and rates before, during, and after cardiac surgery.

Conclusion: The 12 PBM strategies identified are valuable additions to the current list, but further clinical evaluation is needed to improve their efficacy and safety in cardiac surgery.

Keywords:

Blood transfusion
Cardiac surgery
Patient blood management
Systematic review
Bleeding disorder

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[DOI: 10.61186/ijbc.16.2.34]

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1. INTRODUCTION

Cardiac surgery is a standard therapeutic intervention for an array of heart diseases (1, 2), from aneurysms and arrhythmia to heart failure and heart valve disease. However, it is frequently correlated with the high incidence of coagulopathy and blood loss (3, 4). Thus, cardiac surgery is commonly associated with the use of large volumes of blood products (3), Packed Red Blood Cells (PRBC), Cryoprecipitate, Platelet Concentrate (PC) and Fresh Frozen Plasma (FFP) (5). However, the rate of intraoperative deaths during cardiac surgery remains high, primarily due to single- or multiple-organ failure (6). Systemic Inflammatory Response Syndrome (SIRS) is a key mechanism that typically triggers organ injury and dysfunction after cardiac surgery. SIRS is a reactive outcome of injuries that occur during cardiac surgery, such as major surgical dissection (including cardiopulmonary bypass [CPB], ischemic reperfusion, and frequent blood transfusion (6). These injuries and SIRS increase the risk of cardiovascular, central nervous system, renal, and respiratory dysfunctions.

Significant bleeding during cardiac surgery, even after transfusion, increases the risk of morbidity and mortality (7). Intraoperative blood transfusion has a high risk for adverse postoperative outcomes, including short- and long-term mortality, thrombosis, stroke, and prolonged mechanical ventilation (3, 8). Intraoperative blood transfusion can trigger pro-inflammatory responses that develop into fully blown SIRS. Therefore, fewer blood transfusions are a better option for safer cardiac surgery (9). Comorbidities, such as infective endocarditis (10), also increase the risk of bleeding complications. Some blood transfusion products, such as cryoprecipitate (5), are not associated with in-hospital death. Patient Blood Management (PBM) programs were developed to address the abovementioned blood transfusion-related issues. PBM is an evidence-based, multidisciplinary, patient-focused method designed to improve patient outcomes by optimizing hemostasis, maintaining normal haemoglobin concentration, reducing bleeding, and improving physiological tolerance to anaemia (11). Its implementation follows three therapeutic pillars: preoperative patient evaluation, reduced intraoperative bleeding, and enhanced anaemia tolerance. Every hospital is expected to implement PBM as a patient-centred initiative.

Effective PBM is necessary for reducing the risk of adverse outcomes (1). PBM can also involve the use of a minimally invasive intervention methodology (3) and early re-exploration for postoperative bleeding (12). Traditional blood conservation techniques, including anti-fibrinolytic, preoperative anemia management, topical hemostatic agents, and reduction of transfusion triggers, are associated with hemodilution problems due to priming solution use (13). However, implementing PBM during cardiac surgery effectively reduces the rate of blood transfusions and their related complications, thus improving patient outcomes (9).

This systematic review aimed to study the currently published literature on PBM strategies that effectively reduce the rates of preoperative, intraoperative, and postoperative blood transfusion for cardiac surgery.

2. METHODOLOGY

2.1 Search strategy

To execute this systematic review & literature search, the most recent articles and abstracts that are accessible through paid databases, based on Optimizing patient blood management in cardiac surgery, were considered prioritized by the use of Google Scholar, Springer, PubMed, and Science Direct. The terms were carefully selected from the 2018-2024 studies in the literature search to obtain comprehensive results. These keywords include “Blood transfusion during cardiac surgery”, “Preoperative blood management”, “cardiac surgery”, “Postoperative” AND “transfusion reduction”, AND “cardiac surgery”, “Topical hemostatic agents” AND “transfusion reduction” AND "cardiac surgery", “Recombinant factor concentrates” AND “transfusion reduction AND "cardiac surgery", “Minimally invasive surgery” AND “transfusion reduction” AND “cardiac surgery”.

2.2 Selection Criteria

Studies of patients who underwent cardiac surgery and required blood transfusion during cardiopulmonary surgeries included identifying patient blood management strategy and reducing the rate of blood transfusion during surgery to decrease morbidities and pre, post, and intra-operative mortalities. These studies were selected by following the inclusion and exclusion selection criteria.

2.3 Inclusion Criteria

The additional criteria were used to purify the study's relevance.

✓ Articles (preferably full-text articles) already published in peer-reviewed journals in the last four years (2018– 2024) were included in the analysis.

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✓Reviews on both cardiac and non-cardiac surgeries were only included.
✓Articles of clinical studies, clinical trials, non-systematic reviews, observational studies (e.g., cohort and cross-sectional studies), randomized controlled trials (RCTs), systematic reviews and meta-analyses on patients who underwent cardiac surgery or any other relevant procedure were considered for inclusion.
✓To increase the robustness and replicability of the results, the inclusion of studies of other designs, especially those commonly used for the analysis of PBM strategies for cardiac surgery, was allowed to ensure that PBM strategies that were analyzed in the last four years but not with any of the preferred study designs were covered.
✓Reviews were based on the ideal design, and it was preferred to use cohort studies or other study designs of lesser evidentiary strength instead of RCTs and clinical studies and trials.
✓To increase the review's scope, systematic review and meta-analysis articles were included to offer a broader overview of the empirical development of PBM strategies to date.
✓Abstracts were also considered for inclusion into this review because contrary to the typical recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol, experience in the beneficial use of abstracts allows for their inclusion for systematic review, provided that the relevant data (e.g., total sample population, group sample sizes, and treatment outcomes) needed for the analysis are indicated in the abstract.

2.4 Exclusion Criteria

✓Articles published in languages other than English were excluded from the identification step of the PRISMA process to avoid limitations caused by errors in the translation of the research findings.
✓Unclear reporting of information relevant to this study in an abstract led to the automatic exclusion of the article even if the appropriate information can be found in the article's title.
✓Any ambiguity in an abstract was grounds for excluding the article from selection.
✓Unpublished clinical studies were also excluded from the analysis.

2.5 Data Extraction

2.5.1 Type of Data Extracted

The results were extracted from published peer-reviewed articles. The primary data extracted included findings on the efficacy of PBM strategies implemented for patients who underwent cardiac surgery of any type, complications associated with these strategies, sample distribution into intervention and control groups, and relevant statistical data, such as effect size, confidence interval, and significance of the study.

The data identified from databases n=2750, after screening duplicate records were excluded n=401, and the records which were ineligible by automation tools were also excluded n=349, records removed because of other reasons n=657, n=1407 records were screened, from which 422 records excluded; as a result of 985 records assessed for eligibility, from which the studies which were not conducted in previous 6 years were excluded n=355, studies based on languages other than English were not included n=321, the studies which contained irrelevant data, were not reviewed n=285, the total number of studies which were included in this systematic review were 24 in numbers (from 2018-2024). Demographic data were considered important but not indispensable when choosing between access to critical efficacy information and the absence of sex or age data of the sample population, as shown in **Table 1**.

2.6 Data Extraction & Analysis

✓The 2020 edition of the PRISMA guidelines was used to identify, screen, assess, and include the articles reviewed in this study of PBM in cardiac surgery.
✓Some modifications were introduced to avoid omitting the results in articles that are not easily accessible in full text. These modifications included the inclusion of abstracts and the exclusion of other sources (e.g., registers, websites, and organizations with limitations). Nevertheless, reporting the PRISMA process was done per the detailed framework.
✓The information initially required for identifying potentially relevant articles for inclusion into this systematic review were the study title, first author, demographic data (if available but limited to biological data such as the sex and age of participants), intervention, inclusion of controls, outcomes of interest, and quality of evidence. Screening was done in two stages: titles and abstracts were reviewed first, and the full texts of the articles were reviewed. If an abstract did not include sufficient relevant information and the full text of the

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Table 1. Characteristics of the participants included in the reviewed studies.

Study	Sex (M/F)	Age (years)	Total Population	Diagnoses	Country	Reference
Ali et al.	344/214	40.5-84.3	558	NR	Korea, Switzerland	(14)
Cain et al.	NR	NR	12406	NR	USA	(15)
Elkhouly, Fouad	112/8	48-62	120	NR	Egypt	(16)
Hasan et al.	467/222	54-78.8	689	NR	USA	(17)
Hinton et al.	NR	NR	12043	NR	USA	(18)
Kelava et al.	NR	Adult	19111	NR	USA	(19)
Kloeser et al.	NR	NR	1927	Preoperative anemia	NR	(20)
Ledergerber et al.	384/113	68 (median)	497	NR	Switzerland	(21)
Liu et al.	NR	44-88	2286	NR	Canada, Egypt, Korea, Spain, Switzerland, UK	(22)
Matzek et al.	683/475*	54-76	1158	Myocardial infarction Congested heart failure Stroke	USA	(23)
Ming et al.	NR	NR	110	NR	China	(24)
Naguib et al.	42/26	Up to 134 days old	68	Congenital heart disease	USA	(25)
Navaratnam et al.	NR	Neonates	165	NR	USA	(26)
Senarslan et al.	NR	NR	50	Thoracic aortic aneurysm	Turkey	(27)
Shi et al.	1906/1173	52.8 (mean)	3079	NR	China	(28)
Smith et al.	61/39	66.8 ± 13.7	100	Excessive microvascular bleeding	USA	(29)
Sutherland et al.,	NR	NR	214	NR	USA	(30)
Yang et al.	302/160	51.75 ± 5.15	462	Rheumatic heart disease Congenital valvular disease Degenerative valvular disease	China	(13)
Zeroual et al.	NR	Adult	100	NR	USA	(31)
Zhou et al.	91/66	18-65	157	NR	China	(32)
Hinton, J.V., et al.,	NR	Adult	21, 449	Cardiac & Thoracic diseases Cerebrovascular disease Peripheral vascular disease Respiratory disease	Australia	(5)
S. Gunaydin et al.,	NR	Adult	80	Cardiac pulmonary disease	Turkey	(33)
Jia Shi et al.,	NR	Adult	10,591	CPB and patients in anti-coagulant therapy	NR	(34)
S Mishra et al.,	28/12	Adult	80	CABG	India	(35)

NR: Not reported.
*Computed proportionately with non-cardiac surgery samples.

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[DOI: 10.61186/ijbc.16.2.34]

article could not be accessed; the study was automatically excluded from the analysis.

✓ For articles with accessible full texts, information missing in the abstract was verified using information in the main text and data tables.

✓ To obtain relevant studies, systematic reviews and meta-analyses on cardiac surgery and other cardiac surgical procedures, including coronary artery bypass grafting (CABG), coronary angioplasty, and heart valve surgery.

✓ This method of not excluding comprehensive literature reviews for being broad in scope increased access to more studies relevant to the present review. The only exceptions were reviews that included articles irrelevant to the present study.

2.7 Quality Assessment

The quality of the evidence reported in the included studies was graded using a modified form of the 2008 Grading of Recommendations Assessment, Development, and Evaluation (GRADE) System (36). However, to fit the context of this study, the GRADE system was restricted to assessing the quality of evidence without providing a report on the studies' strengths of recommendation; moreover, given that the GRADE system also covers the assessment of reporting bias, to evaluate the risks of bias in the included studies no other tool was used. Quality of evidence Grading was based on the original definitions given below in **Table 2**.

Table 2. Quality of evidence and definitions.

Grade	Definition
High quality	Further research is very unlikely to change our confidence in the estimated effect.
Moderate quality	Further research is likely to impact our confidence in the estimated effect and may change the estimate.
Low quality	Further research is likely to impact our confidence in the estimated effect and is expected to change the estimate.
Very low quality	The estimated effect is very uncertain.

Standard assumptions regarding the qualities of specific study designs (e.g., RCTs as high-quality studies or cohort studies as low-quality studies) may not be observed under the GRADE system. These assumptions may be downgraded or upgraded based on confidence in the evidence from several elements of each study, such as evidence indirectness, study limitations, impression and reporting bias, and inconsistency of results. The study characteristics that were prioritized in this study include study design, surgical techniques used in cardiac surgery, surgeries performed concomitantly with cardiac surgery, whether CABG or valve replacement, subgroup sizes, the PBM intervention used, and the GRADE assessment of the study's quality of evidence, as shown in **Table 3**.

All these data must be reported in the articles selected for review except for information on concomitant surgeries. However, articles that reported unspecified procedures were considered for inclusion, provided the methodology indicated that the study involved cardiac surgery.

3. RESULTS

3.1 Search Results

The 2750 articles were identified in PubMed and through Google Scholar. Only 24 research studies were included for review, as shown in **Figure 1**.

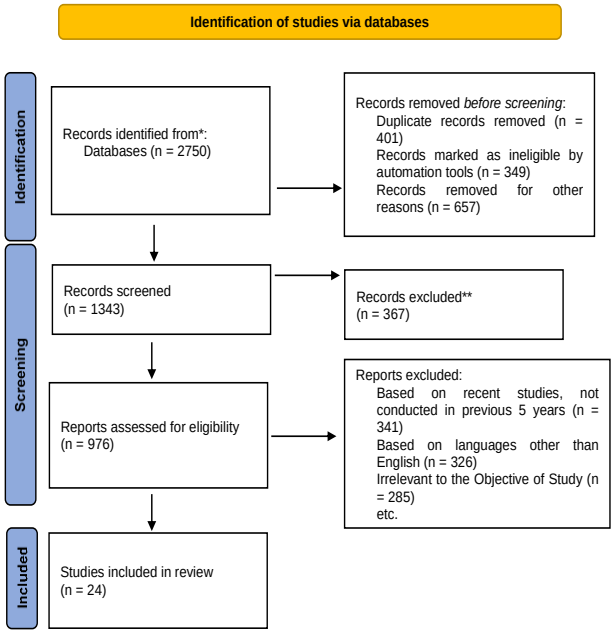

Figure 1. PRISMA Flow chart for article selection.

The articles included were reports of four RCTs, 2 prospective cohort studies, 12 retrospective cohort studies, 2 systematic reviews and meta-analyses, and one non-systematic review. Most of the studies (14 studies) were cohort studies, as shown in **Table 4**.

About 65% of all the studies reviewed in terms of quantity and sample size, the patients were generally divided into two groups:

1) Intervention or exposure group.
2) Control group.

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Table 3. Characteristics of the included studies.

Study	Year of publication	Design	Surgical Procedures	Concomitant Surgeries	Subgroup Size (Test/Control)	PBM Intervention	Quality grade	Reference
Ali et al.	2022	Systematic review and meta-analysis	TAVR CABG	-	280/278	Preoperative erythropoietin therapy	H	(14)
Cain et al.	2022	Retrospective cohort study	Single-vessel CPB	-	2688/9818	Minimally invasive Surgery (MIS)	M	(15)
Elkhouly, Fouad	2023	Prospective cohort study (randomized)	CPB Valve replacement	-	60/60	Gel foam patches	H	(16)
Hasan et al.	2022	Retrospective cohort study	CPB	-	311/378	TEG-based algorithm	M	(17)
Hinton et al.	2023	Retrospective cohort study (matched)	NR	-	195/743	Cryop transfusion	M	(18)
Kelava et al.	2022	Retrospective cohort study	CPB	-	NR	EACA MIS	M	(19)
Kloeser et al.	2023	Non-systematic review	Unspecified procedures	-	915/905/104	Preoperative iron therapy, erythropoietin therapy, combination	M	(20)
Ledergerber et al.	2023	Retrospective cohort study (unmatched + matched)	NR	-	289/450	VWFC	L	(21)
Liu et al.	2023	Systematic review and meta-analysis	CABG, TAVI, Valvular,	-	995/1331	Iron therapy	H	(22)
Matzek et al.	2022	Retrospective cohort study	Cardiovascular surgery, transplant	-	1158/3049*	Phlebotomy	VL	(23)
Ming et al.	2023	Prospective RCT	CPB	-	55/55	L-ANH	H	(24)
Naguib et al.	2023	Prospective cohort study	CPB	-	40/20	ROTEM®-based algorithm	L	(25)
Navaratnam et al.	2023	Retrospective cohort study (matched)	CPB	Sternotomy	79/86	PCC	M	(26)

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Senarslan et al.	2022	Retrospective cohort study	TAA repair & dissection	-	25/25	Cell saving	M	(27)
Shi et al.	2022	RCT (double-blinded)	CPB	-	1525/1506	High-dose tranexamic acid regimen	H	(28)
Smith et al.	2022	Prospective RCT	CPB	Aortic replacement Sternotomy	51/49	PCC	H	(29)
Sutherland et al.,	2022	Retrospective cohort study	NR	-	82/73/59	Off-label recombinant Factor VIIA	M	(30)
Yang et al.	2023	Retrospective cohort study	Valve replacement (double, aortic, mitral)	Tricuspid valve repair left atrial plication	212/250	Modified CPB system	L	(13)
Zeroual et al.	2021	RCT (single-blinded)	NR	-	50/50	Restricted central venous oxygen saturation	H	(31)
Zhou et al.	2023	Retrospective cohort	Valvular (single, multiple)	CPB	78/79	Cell saving	M	(32)
Hinton, J.V., et al.,	2024	Retrospective cohort study	CABG CPB	-	15,360/6,189	PLTS Transfusion	M	(18)
S. Gunaydin et al.,	2018	Prospective study	Cardiac surgery CPB	-	40/40	Cell salvage therapy	M	(33)
Jia Shi et al.,	2019	Randomized controlled trial	CPB Cardiac surgeries	Coagulopathy	1573/4477	Tranexamic acid regimen	M	(34)
Satish Kumar Mishra et al.,	2020	Randomized Control trial	CABG CPB	Coagulopathy	40/40	Epsilon-Amino-Caproic acid therapy	M	(35)

CABG: coronary artery bypass grafting; **CPB:** cardiopulmonary bypass; **EACA:** E-aminocaproic acid; **HC:** historical control; **L-ANH:** large-volume acute normovolemic hemodilution; **MIS:** minimally invasive surgery; **NEE:** no effect estimate; **NR:** nonrandomized samples; **NS:** non-standardized; **PCC:** prothrombin complex concentrate; **RCT:** randomized controlled (or clinical) trial; **TAA:** thoracic aortic aneurysm; **TAVI:** transcatheter aortic valve implantation; **TAVR:** transcatheter aortic valve replacement; **TEG:** thromboelastographic; **VWFC:** Von Willebrand Factor Concentrate; **PLTS:** Platelets transfusion therapy.
* **Nonsurgical control group**

A total of **63,540** patients were included in this systematically reviewed study, as shown in **Figure 2**.

3.2 Transfusion Rates and Related Complications

Blood transfusion is a known risk factor in postoperative adverse events. Reduction in the blood transfusion and

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conservation of the patient's blood are the primary objectives of PBM. This review showed that the net transfusion rate, the difference between the test and control groups, varied across surgical stages and blood products, as shown in **Table 5**.

Table 4. Summary of the study designs and sample sizes.

Study design	Number of articles	Distribution (%)	Total sample size
Randomized controlled trial	6	30	14,012
Cohort study (Prospective)	3	15	260
Cohort study (Retrospective)	12	60	41,576
Systematic review and meta-analyses	2	10	2,884
Non-systematic review	1	5	4,808
TOTAL	**24**		**63,540**

3.3 Blood Management Strategies

The PBM strategies analyzed in the reviewed studies included Preoperative strategies such as iron therapy and iron + erythropoietin therapy, Platelets transfusion therapy; Intraoperative strategies such as Large-volume Acute Normovolemic Hemodilution (L-ANH), Post-Perfusion Blood Collection (PPBC), Cell Salvage/Cell Saver, Modified Ultrafiltration (MUF), and Thromboelastometry (TEM)-based algorithms; and Postoperative strategies such as iron therapy and restrictive SVO2 saturation level. Iron + CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; EACA, E-aminocaproic acid; HC, historical control; L-ANH, large-volume acute normovolemic hemodilution; MIS, minimally invasive surgery; NEE, no effect estimate; NR, nonrandomized samples; NS, non-standardized; PCC, prothrombin complex concentrate; RCT, randomized controlled (or clinical) trial; TAA, thoracic aortic aneurysm; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; TEG, thromboelastographic; VWFC: Von Willebrand Factor Concentrate; PLTS: Platelets transfusion therapy.

* Nonsurgical control group

erythropoietin therapy was the only preoperative PBM supplementation strategy that successfully reduced PRBC transfusion rates in the reviewed studies. Several intraoperative PBM transfusion reduction strategies, including L-ANH, PPBC, cell saver, and MUF, effectively reduced the blood transfusion rate. Regarding postoperative PBM, restrictive management of SVO_2 saturation level effectively reduced PRBC transfusion by 64%.

Antifibrinolytics, such as aminocaproic acid and tranexamic acid, reduce transfusion rates by managing coagulopathy mechanisms such that reduced PRBC transfusion becomes possible, especially using intraoperative cryoprecipitate, postoperative platelets, and postoperative FFP. However, these benefits were only observed with aminocaproic acid, not tranexamic acid, which only modestly reduced blood transfusion rates.

3.3.1 Platelets Transfusion Therapy

Thrombocytopenia is a commonly associated contraindication in surgeries due to excessive loss of blood. Platelet transfusion therapy (1 unit) before surgery is the better option to reduce the risk of bleeding by managing the loss of platelets and increased risk of bleeding. Fresh Frozen Plasma transfusion is also used in clinical practice. Still, the study conducted between 2005 and 2021 found that the relative effectiveness of PLTS Transfusion in cardiac surgery is safer than FPP transfusion because of the reduced operative mortality rate in ratio to FPP (18).

3.3.2 Hemostatic Agents

Among the topical hemostats reviewed in this study, including topical hemostats and Recombinant Factor Concentrates (RFCs), gel foam patches appeared more effective in significantly reducing transfusion rates than gelatinized thrombin preparations. The hemostatic effects of these agents play an important role in blood conservation. Recombinant factor VIIA concentrate was the only RFC that significantly reduced transfusion rates, but only when administered earlier and in low doses.

3.3.3 Blood Conservation Techniques

The blood conservation techniques evaluated in the reviewed studies included Minimally Invasive Surgery (MIS), Mechanical Circulatory Support, and Modified Cardiopulmonary Bypass System (CPBS). Modified CPBS was the only blood conservation PBM technique that seemed to have transfusion reduction benefits. MIS has yielded mixed results in the aspect of reducing transfusion rates. There has been no recent study on phlebotomy reduction strategies.

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Table 5. Transfusion rates and related complications.

Study	Year	PBM Intervention	Transfusion Rate (Net)	Effect Size	Complications (Morbidity)	Complications (Mortality)	Ref.
Ali et al.	2022	Preoperative erythropoietin therapy	*Intraoperative* PRBC, 23.3%, <1.0-4.2 packs *Postoperative* PRBC, 28.5%, <1.0-5.5 packs	RR .33 - .99 95% CI (0.01 – 7.93)	*Intraoperative* Thrombosis, 2 events *Postoperative* Thrombosis, 6 events	90-day, n=15, 2.7%(SI)	**(14)**
Cain et al.	2023	Minimally invasive surgery	*Postoperative* AR -7.7%	OR 0.52	*Postoperative* Adverse cardiac events (SI) Graft occlusion (SI)	In-hospital, AR -0.91% (OR 0.32) 30-day, AR 0.88% (OR 0.77)	**(15)**
Elkhouly, Fouad	2023	Gel foam patch	*Intraoperative* -1.98 packs	~	*Postoperative* Re-exploration, -66.6% Mediastinitis, -33.3%	NR	**(16)**
Hasan et al.	2022	TEG-based algorithm	*Intraoperative* Blood products, -13.5% FFP, -64.3% Platelets, -43.1% FFP volume, -50% *Postoperative* No change	~	Reoperation for bleeding, -3% (SI) Graft occlusion re-intervention (SI) Mechanical ventilation (SI)	+1.0% (SI)	**(17)**
Hinton et al.	2023	Cryoprecipitate transfusion	*Postoperative* 2.35%, median dose of 5.83 units	~	*Postoperative* Infection (SI) AKI (SI)	In-hospital (SI) OR 1.10 66% CI (.43-2.84)	**(18)**
Kelava et al.	2022	EACA MIS	*Intraoperative v. postoperative* EACA, fewer PRBC transfusions MIS, no significant difference	~	Unspecified outcomes, no significant difference	NR	**(19)**
Kloeser et al.	2023	Preoperative iron therapy, erythropoietin therapy, combination	*Intraoperative* PRBC, no difference (iron, erythropoietin) *Postoperative* PRBC, no diff (iron, erythropoietin) PRBC, reduced patient proportion and need (iron + erythropoietin)	~	*Postoperative* Acute kidney injury, less or no difference	NR	**(20)**
Ledergerber et al.	2024	VWFC	*Intraoperative* FFP(d1), +400 mL Fibrinogen, + 1 g *Postoperative* Platelet count, +2 G/L (SI)	~	*Intraoperative* Blood loss (SI) *Postoperative* N.A.	SI	**(21)**
Liu et al.	2023	Preoperative iron therapy	*Overall (intra- and post-operative)* 55.1%	RR .91 95% CI (.81-1.03)	*Overall (SI)* Renal adverse events, -4.3%	-1.00% RR .58	**(22)**

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[DOI: 10.61186/ijbc.16.2.34]

			units transfused (SI)		Cardiac adverse events, -3.8% Cerebral adverse events, +1.4%	(95% CI, .36-.95)	
Matzek et al.	2022	Phlebotomy	*Postoperative* Daily blood draws, +1.2 (Equiv. increase per 100 mL PRBC transfused)	95% CI (1.14-1.17)	NR	NR	**(23)**
Ming et al.	2023	L-ANH	*Intraoperative* RBV, +491 mL PRBC, -18.2% (RD =.182, 95%CI = .007-.343)	OR 0.43 95% CI (.19-.98)	Postoperative excessive bleeding, -14.6% (RD = .146, 95%CI, .19-.98)	0%	**(24)**
Naguib et al.	2023	ROTEM®-based algorithm	*Intraoperative* PRBC, -6 mL/kg Platelets, -7 mL/kg Cryop, -7 mL/kg CBPP, +9 mL/kg TP, 0 mL/kg *Postoperative* PRBC, -16 mL/kg Platelets, +2 ml/kg Cryop, -9 ml/kg FFP, -8 ml/kg	~	*Postoperative* (0-60 days) thrombosis: IVC (8 days, no difference) RSFAV (+20 days) LPA (+8-11 days) RCFEIV (-40 days)	0%	**(25)**
Navaratnam et al.	2023	Activated 4-factor PCC	*Intraoperative* -15.3 mL/kg *Postoperative*	~	*Postoperative* (7, 30-day) Thrombosis, AKI (SI)	30-day (SI)	**(26)**
Senarslan et al.	2022	Cell saving	*Postoperative* PRBC reduced the total volume Total blood products reduced	~	*Postoperative* Unspecified morbidity	-0% difference with control	**(27)**
Shi et al.	2022	Tranexamic acid	*Postoperative* PRBC transfusion, 21.8% v. 26.0%	RR .84 97.55%CI (up to .96)	*Postoperative* Seizure, thrombosis, & kidney dysfunction, 17.67% v. 16.8%	0% difference with control	**(28)**
Smith et al.	2022	PCC	*Intraoperative* PRBC, -16.9% Total (SI) *Postoperative* PRCB (SI)		*Intraoperative* Bleeding rate (SI)	30-day, -2.1% (SI)	**(29)**
L. Sutherland, et al.,	2021	Off-label recombinant factor VIIA	High dose of recombinant factor, given in three divided groups of patients 18.02 µg/kg *v* 12.16 µg/kg and 14.08 µg/kg	-	Prolong prothrombin time	-	**(30)**
Yang et al.	2023	Modified CPB system	*Intraoperative* PRBC, -150 mL PRBC, -7.3% FFP, -3.79%	~	Cerebrovascular events, 0.94% (SI) Postoperative bleeding, 0.47% (SI)	0%	**(13)**

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			Platelets, SI TPV, -850 mL				
Zeroual et al.	2021	Restricted central venous oxygen saturation	*Postoperative (ICU)* PRBC, -32% Total PRBC, -29 units *Discharge* 8 patients, untransfused	OR 0.031 95%CI (0-0.153)	NR	NR	**(31)**
Zhou et al.	2023	Cell saving	*Intraoperative (SI)* PRBC, -12.0%, -0.5 U TP, -15.7%, -150 mL Cryop, +1.6% Platelet, -2.5% *Postoperative* PRBC, -22.1%, 0.0 U(SI) TP, -11.5%(SI), -200 Ml Cryop, -11.3%(SI) Platelet, 0.0%(SI)	OR 0.31 95% CI (.15-.63)	Re-exploration, +2.6%(SI) ALI, +2.7%(SI) Renal injury, +2.9%(SI) Liver injury, +6.6%(SI) Stroke, +1.3%(SI)	30-day, -1.2%(SI)	**(32)**
Hinton, J.V., et al.,	2024	PLTS Transfusion	Preoperative PLTS (8.79%) dose: 1 unit pooled platelets.	R. R 1.63 Cl 95% (1.40-1.91) P-value <0.001	Bleeding Complications 1826 (11.9) Cardiac Complication 9742 (63.4) Fluid Balance Complication 552 (3.6)	Operative mortality 455 (3.0) n= 15,360, up to 30 days postoperatively.	**(18)**
S. Gunaydin et al.,	2018	Cell salvage therapy	Post-operative RBC Transfusion	-	Thrombocytopenia because it is not very effective in platelet preservation.	NR	**(33)**
Jia Shi et al.,	2019	Tranexamic acid administration	Perioperative Tranexamic acid administration. TXA dose: <50 mg/kg, low dose bolus injection	RR 0.71, 95% CI 0.65 to 0.78, P<0.00001	Seizure attack RR 3.21, 95% CI 1.04 to 9.90, *P* = 0.04	Not associated with a high risk of mortality.	**(34)**
Satish Kumar Mishra et al.,	2020	Epsilon-Amino-Caproic acid therapy	Dose IV: 100 mg/kg over 20 minutes and in CPB 5-10 mg/kg prime followed by 10 mg/kg/hour infusion during surgery.	p=0.0022	Thrombotic events	Mortality in low and intermediate risks.	**(35)**

ALI: Acute Lung Injury; **AR:** Absolute Reduction; **CBPP:** CBP plasma; Cryop, cryoprecipitate; **FFP:** Fresh Frozen Plasma; **SI:** Statistically Insignificant; **IVC:** Inferior Vena Cava; **L-ANH:** Large-Volume Acute Normovolemic Hemodilution (12–15 ml /kg); **LPA:** Left Pulmonary Artery; **OR:** Odds Ratio; **PRBC:** Packed RBC; **RD:** Rate Difference; **RCFEIV:** Right Common Femoral and External Iliac Veins; **RR:** Risk Ratio; **RSFAV:** Right Superior Femoral Artery and Vein; **TP:** Total Plasma; **TPV:** Total Priming Volume; **VWFC:** Willebrand Factor Concentrate. All statistical results are significant unless otherwise stated.

3.4 Morbidity & Mortality

PBM strategies, such as preoperative erythropoietin therapy, are significantly associated with intraoperative and postoperative morbidities, including acute kidney injury, acute and non-acute liver injury, infection, kidney dysfunction, mediastinitis, seizure, stroke, thrombotic events, unspecified cardiac, cerebral, and renal adverse events, and re-intervention and re-exploration procedures. Although reduced, statistically significant mortality rates are associated with cryoprecipitate transfusion, platelets

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transfusion, erythropoietin therapy, iron therapy, MIS, PCC, and von Willebrand factor concentrates.

3.5 Summary of Clinical Outcomes

In the studies analyzed in this review, implementation of PBM reduced mortality rates by -0.90% (in-hospital) for MIS and -1.00% (in-hospital) for preoperative iron therapy, indicating a slight reduction in death outcomes even after implementation of empirically efficacious PBM strategies. Platelet transfusion instead of Fresh Frozen Plasma reduces the mortality rate in respect of sample, 8.79% (n= 15, 360, number of patients tested) and reported postoperative mortality rate of 3.0% (n=455) at 30 days. However, some strategies were associated with increased mortality at 90 days postoperatively (2.7% for preoperative erythropoietin therapy), 30 days postoperatively (0.88% for MIS), and during admission (1.0% for TEG-based algorithms). Morbidity complications that significantly declined after the implementation of some of the PBM strategies reviewed in this study included acute kidney injury (activated 4-factor PCC), excessive postoperative bleeding (L-ANH), mediastinitis (gel foam patches), re-exploration of surgical areas (gel foam patches), and thromboses (activated 4-factor PCC). The rates of other postoperative complications were not statistically significant. We did not retrieve any study that involved the evaluation of patient-reported outcomes.

4. DISCUSSION

4.1 Evidence-Based Strategies for Blood Management: Preoperative, Intraoperative, and Postoperative Management

4.1.1 Pre-operative Management

Anemia of any cause is a key target in preoperative PBM. Preoperative anemia is common in patients scheduled for surgery (14), including cardiac surgery (37). The current PBM strategies against preoperative anemia include vitamin supplementation, iron therapy, erythropoietin therapy, and, when necessary, allogenic transfusion (14).

4.1.2 Iron Therapy

In the non-systematic literature review of five relevant RCTs, Kloeser et al. (20) reported no relative differences in PRBC transfusion between the intervention and control groups, both the positive control group (reduced iron dose) and the negative control group (placebo). In an updated systematic review and meta-analysis, Liu et al. (22) confirmed a lack of reduction in transfusion requirements for preoperative administration of iron therapy.

4.1.3 Iron + Erythropoietin Therapy

In a systematic review and meta-analysis of two studies (N = 558), Ali et al. (14) observed low intraoperative and postoperative transfusion rates of 23.3% (n = 130) and 28.5% (n = 159), respectively, even after only a single dose of erythropoietin was administered preoperatively. The intervention included erythropoietin therapy (40,000 IU, injected) and iron supplementation. Lower PRBC transfusions were associated with a low 90-day mortality rate (3.1% vs. 11.0%) combined with erythropoietin therapy and iron supplementation.

4.1.4 Platelets (PLTS) Therapy

In the retrospective cohort study, a comparative analysis between PLTS and FPP was observed in cardiac surgery preoperatively, and 8.79% (n= 15, 360) received Platelet therapy (1-unit dose). In comparison, 3.54% (n=6,189) received FFP therapy (2-unit dose), post-operative PLTS mortality rate was found to be 3.0% (n=455). Still, FPP was associated with increased postoperative mortality rate, i.e., 4.8% (300), re-admission to ICU and AKI complications; it was concluded that platelet therapy is more effective in cardiac surgery than FPP (18).

4.2 Intra-operative Management

Large-Volume Acute Normovolemic Hemodilution (L-ANH)

Ming et al. (24) conducted a prospective RCT to compare moderate-volume acute normovolemic hemodilution (M-ANH). It was found that L-ANH was associated with a significantly reduced incidence of transfusion, excessive postoperative bleeding, and the risk of perioperative (intraoperative) transfusion of RBC units. However, ANH improved oxygen delivery to tissues during cardiac surgery. Re-transfusion of whole blood postoperatively restores the coagulative capacity of the body with the restoration of coagulation factors.

4.3 Post-Perfusion Blood Collection (PPBC)

Balcioglu et al. (38) found that PPBC is “the most appropriate option” for blood conservation in cardiovascular surgery, outranking modified ultrafiltration (MUF) (with preoperative autologous donation as the least ranked) in a multi-criteria assessment. These criteria included salvaged and processed volumes, post-process haemoglobin levels, end-process residual heparin, citrate toxicity, trained specialist requirements, allergic-immunologic reactions, and special patient use.

4.4 Cell Salvage/Cell Saver

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Vieira et al. (39) and Zhou et al. (32) found that cell salvage in pediatric surgery could reduce blood transfusion rates by 22%–25% while improving outcomes (40). Couch et al. (41) confirmed the successful use of cell savers in 97% of cardiac surgery cases. Senarslan et al. (27) observed a significant reduction in the total volume of PRBC and total blood products used in a group of patients managed using a cell saver compared to those who underwent surgery without a cell saver, but similar postoperative morbidity and mortality rates between both groups. S. Gunaydin et al., stated that cell saver is not much effective technique to preserve platelets, associated with complications of thrombocytopenia (33).

4.5 Modified Ultrafiltration (MUF)

In a systematic review and meta-analysis of RCTs, Hensley et al. (42) found that MUF is significantly associated with reduced intraoperative rate of RBC transfusions. This technique avoids the risk of acute kidney injury using large volumes of conventional ultra-filtered blood products.

4.6 Thromboelastometry-Based Algorithms

In a retrospective cohort study conducted using a rotational thromboelastometry (*ROTEM®*)-based algorithm, Naguib et al. (25) found that the use of a ROTEM-guided algorithm can effectively reduce intraoperative transfusion of cryoprecipitate and platelet fractions during cardiac surgery for neonates and infants. Hasan et al. (17) also observed a significant and absolute reduction (-13.5%) in intraoperative blood products. In addition, the FFP and platelet counts of the patients declined by 64.3% and 43.1%, respectively. The volume of FFP used was reduced by 50%.

4.7 Post-operative Management

4.7.1 Iron Therapy

Kloeser et al. (20) reported no difference in RBC transfusion rate after iron supplementation was administered postoperatively and even after the doses were administered preoperatively. The postoperative periods the authors studied were three days and up to four weeks after surgery. Doses ranging from 100 mg to 20 mg per kg are administered intravenously.

4.7.2 Restrictive SVO2 Saturation Level

Zeroual et al. (31) used a restrictive regimen for SVO2 saturation level (≤ 65%) as a trigger guideline for administering PRBC transfusion to postoperative patients in the intensive care unit. The intervention resulted in a 68% transfusion rate; 65 PRBC units were transfused, but the patients remained non-transfused after discharge. The discharge transfusion rate in the intervention group was 48.4% lower than in the control group (96 units vs. 126 units).

4.8 Intervention and Adults

4.8.1 Antifibrinolytics

Coagulopathy management typically involves the use of one of the two standard medications. Aminocaproic acid is commonly used in the United States, whereas tranexamic acid is frequently used in Canada (43).

4.8.2 Aminocaproic Acid

Kelava et al. (19) reported consistently reduced rates of PRBC transfusions for patients who received aminocaproic acid during and after cardiac surgery. This reduction in intraoperative and postoperative blood transfusion, even in a Minimally Invasive (MIS) procedure, involved using blood products, such as postoperative platelets, intraoperative cryoprecipitate, and postoperative FFP. S. Mishra et al. stated that Aminocaproic acid administration further required transfusion of PRBCs to reduce the bleeding rate intra-operatively, compared with Tranexamic acid (35).

4.8.3 Tranexamic Acid

In a double-blind RCT, Shi et al. (28) observed a modest, dose-dependent, but statistically significant reduction in the proportion of patients who received PRBC intraoperatively, with no significant difference in the reduction of postoperative complications, such as morbidity (e.g., seizure, kidney dysfunction, and thromboses) and 30-day mortality. The overall transfusion rates were 21.8% for the high-dose (30 mg/kg bolus, 16-mg/kg/h maintenance, and 2-mg/kg prime: intervention) group and 26.0% for the low-dose (10-mg/kg bolus, 2-mg/kg/h maintenance, and 2-mg/kg prime: positive control) group. J. Guo et al. stated that Tranexamic acid administration controls the incidence of bleeding by reducing the blood transfusion rate. Still, it was associated with an increased risk of Seizure attack (34).

4.9 Hemostatic Agents

4.9.1 Hemostatic Agents and Their Relevance

Hemostatic agents are important adjuncts that complement cardiac surgical techniques (25). This section focuses only on recent studies on topical hemostats and Recombinant Factor Concentrates (RFCs). Topical hemostats can be used for the management of bleeding of different grades, from

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mild capillary oozing (passive topical hemostats) to deep lesions (active topical hemostats) (41, 44). Topical sealants function as active topical hemostats to resolve deeper-seated bleeding.

4.9.2 Topical Agents

In a prospective cohort study conducted in Egypt, Elkhouly et al. (16) observed a significant reduction in the use of blood components (decline of 1.96 units) in the test group (gel foam patches). In another prospective cohort study, Danker et al. (45) found no significant differences in blood transfusion rates when using two different gelatinized thrombin-based flow-able topical hemostats.

4.9.3 Recombinant Factor Concentrates

Smith et al. (29) observed a significant reduction (16.9%) in intraoperative PRBC transfusions using an RFC. Navaratnam et al. (26) reported a significant decrease in intraoperative PRBC transfusions using a prothrombin complex concentrate. In a retrospective cohort study, Sutherland et al. (30) observed the lowest dose-dependent transfusion of blood products among cardiac surgery patients who received an early but low recombinant factor VIIA concentrate (18.02 μg/kg). In another retrospective cohort study, Ledergerber et al. (21) found that additional administration of von Willebrand factor concentrates to patients receiving platelet concentrates resulted in a significant increase in FFP transfusion rates within 24 hours postoperatively because of a 200 mL increase in blood loss.

4.10 Blood Conservation Techniques

4.10.1 Minimally Invasive Surgical Techniques

MIS is a key element in the reduction of postoperative morbidity and mortality rates. In a retrospective cohort study, Kelava et al. (19) found no significant differences in intraoperative and postoperative PRBC transfusion rates between patients who underwent MIS and the overall cohort of cardiac surgery patients. In another retrospective cohort study, Cain et al. (15) observed a significant reduction in postoperative transfusions among patients who underwent MIS compared with those who underwent conventional CPB.

4.10.2 The Role of Mechanical Circulatory Support

Yang et al. (13) found that a modified Cardio-Pulmonary Bypass System (CPBS) for neonates and infants effectively reduced the volume and rate of PRBC transfusions. This system also reduced FFP transfusion rates and volumes for primers (crystalloids and colloids) and ultrafiltration solutions.

4.10.3 Strategies for reducing phlebotomy

Phlebotomy is associated with iatrogenic blood loss even in critically ill patients, including those who have undergone cardiac surgery. Matzek et al. (23) observed that the highest frequency of requests for phlebotomy draws from laboratories was for cardiac surgery patients in the ICU. However, no recent studies on PBM programs include phlebotomy reduction strategies for patients scheduled for cardiac surgery.

4.10.4 Summary of Key Findings

Most of the PBM strategies reviewed in this study reduced PRBC transfusion volume and rates. These strategies included the use of aminocaproic acid, cell salvage, gel foam patches, iron + erythropoietin therapy, L-ANH, modified CPBS, MUF, PPBC, recombinant factor VIIA concentrates, restrictive management of SVO_2 saturation level, and TEM-based algorithms and Platelet transfusion therapy. MIS yielded mixed results, whereas hemostatic agents appeared to be more useful for conserving blood than reducing transfusion rates.

4.11 Focus on Recent Literature

4.11.1 Increasing use of algorithm-based PBM strategies

It was observed that a growing body of literature on anaemia screening and blood transfusion algorithms in cardiac surgery. One notable type of these algorithms is the TEG-based algorithms that use general and trademarked protocols (17, 25). Recent literature on this PBM strategy also mentions strategies such as algorithms based on platelet function analyses (46)or preemptive agreements between surgeons and anesthesiologists regarding a verbal haemoglobin-based trigger for PRBC administration (47).

4.11.2 Development of Non-Synthetic Materials

Most of the materials and active agents used in PBM strategies are synthetic materials, including some antifibrinolytics and hemostatic agents. The literature search revealed isolated indications of research interest in developing products based on non-synthetic sources. For instance, Kirali et al. (48) tested a polysaccharide algal hemostatic agent in patients who underwent coronary artery bypass graft surgery.

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4.12 Clinical implications

4.12.1 Continued Safety of Cryoprecipitate in Postoperative Transfusion

Busack et al. (49) found that among all blood products used in cardiac surgery, including PRBC, cryoprecipitate is the only blood product not associated with the statistically significant adverse outcomes observed using other blood products. These adverse outcomes include the need for increased mechanical ventilation, mortality, stroke, and thrombosis. Ibrahim Sultan MD et al. stated that patients who underwent cardiac surgery required blood transfusion without Packed Red Blood Cells (pRBC) have long-term survival rates and similar post-operative results to patients who did not require blood transfusion (50).

4.13 Limitations of reviewed studies

4.13.1 Susceptibility to Biases Inherent in Observational Studies

The articles analyzed in this review were predominantly articles of observational studies (65%), particularly retrospective cohort studies. This predominance of observational studies is expected because of the key advantages of the study design:

(1) a temporal framework capable of evaluating causality between "disease" (i.e., PBM strategies) and outcomes (i.e., reduction in PRBC transfusion);

(2) ability to examine rare exposures (e.g., cardiac surgery); and

(3) the potential to generate "the strongest scientific evidence" (51). However, observational studies are highly susceptible to biases, such as attrition (51, 52), selection (52), and comparable (53) biases.

5. CONCLUSION

This systematic review identified key PBM strategies that demonstrated clinical efficacy in reducing the rate of blood transfusions, specifically PRBC transfusions (54). These strategies include administration of aminocaproic acid, cell salvage, use of gel foam patches, iron + erythropoietin therapy, L-ANH, modified CPBS, MUF, PPBC, use of recombinant factor VIIA concentrates, restrictive management of SVO_2 saturation levels, TEM-based algorithms & Platelets transfusion therapy. The clinical value of these PBM strategies should be explored further to provide evidence that establishes their safety and efficacy and enhances their clinical effectiveness and safety in cardiac surgery.

5.1 Recommendations for future research

Program-Level Assessment of PBM for the Reduction of Blood Utilization

✓This systematic review was conducted to determine the efficacy of PBM-related strategies reported in literature published over the last three years.

✓ However, the synergistic implications of determining the efficacy of PBM as a comprehensive program for reducing transfusion before, during, and after cardiac surgery were not analyzed.

✓A few studies on this assessment paradigm have been conducted, including a retrospective matched cohort study by Zhang et al. in China (55).

✓Conducting more studies in different contexts or subgroups in various countries is an exciting direction for future PBM studies.

Acknowledgment

The authors thank King Fahad Armed Forces Hospital for continued support throughout the research.

Conflict of interest

The authors declare no conflict of interest.

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[DOI: 10.61186/ijbc.16.2.34]