

The Effect of Hemoperfusion on Bleeding after CABG in Patients on Preoperative Plavix: A Pilot Study

Alireza Jahangirifard¹, Mandana Hossein Zadeh², Seyed Bashir Mirtajani³, Hamid Jamali Taraei⁴, Farzad Salari⁴, Mohammad Hossein Mandegar^{5*}

¹Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

²Masih Deveshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

³Lung transplant Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

⁴Bank Melli Hospital, Tehran, Iran.

⁵Department of Cardiac Surgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Article history:

Received 18 November 2023

Revised 12 December 2023

Accepted 27 December 2023

Keywords:

CABG;

Hemoperfusion;

Plavix;

Postoperative bleeding

ABSTRACT

Background: Bleeding management during and after urgent heart surgery is always challenging in patients who are taken anticoagulants especially antiplatelet ones. The present study was conducted with the aim of investigating the role of intraoperative hemoperfusion in the active removal of Plavix in patients undergoing on-pump CABG surgery.

Methods: The present study recruited patients on Plavix who underwent urgent CABG surgery. All patients have discontinued consuming Plavix less than 36 hours before surgery. During cardiopulmonary bypass, hemoperfusion set was added to the circuit and the surgery was done according to the standard open heart surgery protocols. The patients were transferred to the intensive care unit at the end of surgery and amount of bleeding was recorded in the ICU sheet hourly and calculated after 24 hours.

Results: In our study, the average age of participating patients was 73.625 years. 5 patients out of 8 (62.5%) were male and 3 (37.5%) were female. Hypertension and blood type O were the most prevalent among the patients. The average amount of bleeding was 425 in the first day after surgery and the average units of transfused blood for patients was 0.125, which is acceptable and less than the values reported in other studies that do not use the hemoperfusion.

Conclusion: The use of hemoperfusion during urgent CABG surgery, can reduce the postoperative bleeding and blood products consumption in patients on preoperative Plavix.

Introduction

Acute coronary syndrome (ACS) is one of the cardiovascular diseases with a relatively high prevalence all over the world [1], which requires

treatment by coronary artery bypass grafting (CABG) in 10% of cases. In addition, antithrombotic therapy can also play a significant role in the treatment of ACS. The use of this treatment method in patients who face the risk of severe bleeding in the postoperative period and may need

The authors declare no conflicts of interest.

*Corresponding author.

E-mail address: acamed.gr@gmail.com

Copyright © 2024 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences.



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (<https://creativecommons.org/licenses/by-nc/4.0/>). Noncommercial uses of the work are permitted, provided the original work is properly cited.

surgical revascularization is associated with limitations [2-3].

Clopidogrel (Plavix) is one of the oral drugs offered for the treatment of ACS, which depends on CYP2C19 activation in the liver and plays its role by inhibiting the P2Y₁₂ component in the ADP receptor located in the platelet membrane. Therefore, it can be said that clopidogrel is an oral thienopyridine antiplatelet drug [4]. Studies have shown that clopidogrel is not effective in people with ACS who have a different allele of CYP2C19, and for this reason, more cardiovascular complications are observed in these patients [5].

The use of clopidogrel can be associated with side effects such as bleeding, which is aggravated by the use of anticoagulants such as ASA. The use of this drug has been approved in cases such as ST elevation MI and non-ST elevation MI, stable ischemic diseases, peripheral vascular disease, ischemic stroke, and unstable angina [6-9].

In cases where the patient experiences non-surgical bleeding in the post-operative period, supportive treatments such as the use of blood products including red blood cells, coagulation factors and platelets are usually included in the treatment line. The performance of these blood products in the management of the patient's clinical condition has not yet been properly determined, however, this approach seems to play an important role in reducing the complications and costs of the patient's stay in the intensive care unit, as well as reducing the length of hospitalization [10].

One of the new methods used to reduce bleeding during surgery is the use of a sorbent-filled hemoperfusion cartridge (DrugSorb-ATR system, CytoSorbents Corporation, Princeton, NJ, USA), which is based on the removal of medicinal substances through blood absorption and reducing the circulating drug level. This method is not able to absorb large molecules such as heparin, but molecules up to 60 kDa, such as small hydrophobic molecules, will be removed. In the past years, the effectiveness of this method in eliminating antithrombotic drugs, postoperative bleeding, and other clinical outcomes of patients in Europe and regions of the Middle East has been investigated [11-13].

Most of the previous studies have focused on investigating the effect of hemoperfusion on Ticagrelor removal, while in this pilot study we tried to understand the effectiveness of this method on reducing bleeding risk in patients who are taking Plavix as anti-platelet drug.

Methods

Patients

The present study was conducted as a pilot study with the aim of investigating the Plavix-removal capability of the mentioned device.

After initial evaluations, 8 patients participated in the study and the information obtained from them was recorded in pre-prepared forms. Patient selection criteria were based on the antiplatelet treatment line with Plavix administration, symptoms of unstable angina, and patients who are candidates for urgent CABG surgery based on angiographic data.

Inclusion criteria included age over 18 years, signing the consent form to participate in the research plan, on-pump CABG, taking Plavix, and surgery within 24 hours of stopping Plavix. Patients with liver failure or acute kidney diseases requiring kidney transplantation, left ventricular ejection fraction less than 30%, observation of coagulopathy before surgery, and patients taking immunosuppressive drugs except corticosteroids were excluded from the study. This study was carried out considering the Declaration of Helsinki and with the approval of the ethics committee in biomedical research of Shahid Beheshti University of Medical Sciences with the code (IR.SBMU.NRITLD.REC.1402.246). All patients signed a written informed consent form to participate in this research before entering the study.

All patients received fentanyl and midazolam as premedication after arrival to operating room. They were anesthetized with fentanyl, etomidate and rocuronium and we used fentanyl, propofol and cis-atracurium for maintaining anesthesia. The surgery was done by a team and according to the standard on pump CABG surgery protocols. After separation from CPB, heparin was reversed by protamine sulfate and activated clotting time (ACT) was kept in the normal range. Intubated patients were transferred to the intensive care unit and then they were weaned from the ventilator following the required standards. The bleeding was recorded in the ICU sheet hourly and calculated after 24 hours. The demographic data, required lab tests and the number of consumed blood products was registered on the day 1 after surgery, too.

Device

During surgery, the device was integrated as a bypass parallel circuit between oxygenator and reservoir. Cytosorb blood flow was maintained from the beginning of bypass until weaning, with a rate between 150 and 250 mL/min. Heparin was applied as anticoagulation with a target activated clotting times (ACT) more than 400 s, observed every 15 to 25 minutes. Cytosorb device is CE approved under the Medical Devices Directive and the safety of installation and handling was guaranteed by employing the trained and expert staff. No any device-related adverse effects was observed prior- or post-Cytosorb application.

Results

Based on the results in (Table 1), the average age of the patients in the study was 73,625 years. 5 patients out of 8 (62.5%) were male and 3 (37.5%) were female. Hypertension was the most underlying disease and blood

type O was prevalent among the patients. Based on the results in (Table 1), the average age of the patients in the study was 73,625 years. 5 patients out of 8 (62.5%) were male and 3 (37.5%) were female. Hypertension was the most underlying disease and blood type O was prevalent among the patients. The average bleeding in the first 24 hours after surgery in the patients was 425 ml, while in

general only 1 unit of blood (on average 0.125 units) was transfused.

Based on what can be seen in (Table 2), hematocrit (P=0.041), hemoglobin (P=0.047) and platelet (P=0.042) indices decreased significantly after surgery, while PTT (P=0.032) was associated with a significant increase.

Table 1- Demographic and surgical information of patients

Patients	Gender	Age	Weight	Height	Underlying disease	Blood group	EF (%)	CPB (min)	Clamp time (min)	ACT after surgery	Drainage during first 24 hours	The number of PCS after first 24 hours
1	M	58	80	170	-	A+	50	62	36	118	750	-
2	M	74	76	174	HTN	O+	60	51	29	124	450	1
3	M	60	75	155	DM	B-	35	70	38	120	450	-
4	M	67	72	173	HTN, DM	O+	50	64	30	112	350	-
5	F	50	65	165	HTN	O+	50	57	35	128	250	-
6	M	62	78	176	HTN-DM	B-	45	48	31	127	300	-
7	F	67	68	161	HTN	O-	55	43	30	116	450	-
8	F	75	59	163	HTN	B	50	56	33	123	400	-
Mean	-	73.6	71.58	167.1	-	-	49.3	56.3	32.75	121.00	425.00	-
		2		2			7	7				

Table 2- Comparison of bleeding indices of patients before and after hemoperfusion

Patients	Before	After	P value
PT	13.562±2.972	13.287±2.237	0.120
PTT	29.870±8.231	51.125±12.091	0.032*
INR	1.175±0.307	1.175±0.335	0.938
HB	12.887±2.093	10.77±1.801	0.047*
HCT	37.787±8.319	31.625±5.998	0.041*
PLT	201.750±45.672	169.000±39.877	0.042*

Discussion

The present study was conducted with the aim of investigating the role of hemoperfusion in reducing postoperative bleeding in patients treated with Plavix and requiring urgent on-pump CABG.

Our results showed that intraoperative hemoperfusion can reduce bleeding during the first day after surgery in these patients, while the use of blood products was also very low.

Our studies have shown that this is the first in vivo study that evaluated the performance of hemoperfusion in reducing postoperative bleeding in patients treated with Plavix. In previous research, hemoperfusion in patients undergoing heart surgery on ticagrelor or rivaroxaban has been associated with positive results [14-16].

In some studies, it has been shown that the concentration of apixaban, ticagrelor, and rivaroxaban drugs is significantly reduced by hemoperfusion in less than 60 minutes and reaches below the therapeutic range [17-19]. In all these cases, the use of this filter has been reported without serious side effects.

Based on the results obtained from previous studies, the administration of Plavix before CABG causes an increase in bleeding after the operation and an increase in the units of blood products transfused to the patient, especially when taken together with aspirin [20].

Although these data were first reported in limited studies, they were also confirmed in larger-scale observational studies that were conducted later. Kapetanakis et al, by examining 2359 patients, showed that patients who had received Plavix for 7 days or more before CABG had a lot of bleeding and a higher need for red blood cell transfusion (OR 4.9, 95% CI 2.63–8.97 & OR 2.2, 95% CI 1.70–2.84 respectively) [21].

The results obtained from the largest survey conducted to date indicate that despite evaluating the role of confounding factors such as the use of anti-thrombin and anti-platelet drugs and performing this procedure by a surgeon, there was no significant relationship between the administration of Plavix for 5 days or less before CABG and the need for reoperation due to bleeding [22]. Meanwhile, 68% of the patients examined in this study needed to receive red blood cells after surgery, which is similar to the CRUSADE registry data (67%). These results in our pilot study were lower than this value (12.5%).

Data obtained from the study by Kang et al showed that patients undergoing CABG who took Plavix up to three days before surgery required an average of 5.8 cell units pack in the postoperative period. The results of Englberger's study also indicated an increase in bleeding and the need for fresh frozen plasma and platelets in patients who received Plavix surgery three days before. In this study, patients' need for blood products after surgery was 4.6 units [23]. In our study, one patient received one unit of blood products equivalent to an average of 0.125 units, and other patients did not need blood products transfusion.

In the study of clopidogrel in unstable angina, researchers found that the risk of extensive bleeding is higher in patients who received Plavix for 5 days after surgery compared to other patients with more than 5 days [24]. Leong also showed in his study that the amount of bleeding in patients undergoing CABG surgery using Plavix was 573 (1,365-140) ml, while the average amount of bleeding in our patients was 425 ml, which is similar to the bleeding in patients who did not use Plavix in the Leong, s study (405 ml) [25].

According to the results obtained from investigating the anti-platelet properties of Plavix in healthy volunteers, the anti-platelet property improves 7 days after stopping this drug [26]. The College of Cardiology and the American Heart Association have also recommended reducing the time of drug exposure before surgery. According to these guidelines, "if the patient's clinical condition allows, the use of Plavix should be stopped five days before the patient undergoes CABG" [24].

In patients who cannot postpone surgery, platelet injection is recommended [27], but the implementation method proposed by us can be considered as a safe alternative to platelet injection.

The single-centered and observational nature of our study has limitations. Most importantly, the sample size available to us was very small. On the other hand, since our study was a single center, it may not be possible to generalize these results to other medical centers. The single-centered and observational nature of our study has limitations. Most importantly, the sample size available to us was very small. On the other hand, since our study

was a single center, it may not be possible to generalize these results to other medical centers.

Conclusion

Based on the results of the present study, it can be said that the use of hemoperfusion during urgent CABG surgery in patients on preoperative Plavix, can decrease the amount of postoperative bleeding and reduce the injection of blood products. Therefore, the hemoperfusion can be suggested as an efficient method to control bleeding after on pump CABG surgery in patients treated with Plavix.

References

- [1] Capodanno D, Angiolillo DJ. Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation*. 2013; 128(25):2785-98.
- [2] Savonitto S, Caracciolo M, Cattaneo M, De Servi S. Management of patients with recently implanted coronary stents on dual antiplatelet therapy who need to undergo major surgery. *J Thromb Haemost*. 2011; 9(11):2133-42.
- [3] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016;134(10):e123-55.
- [4] Ghantous AE, Ferneini EM. Aspirin, plavix, and other antiplatelet medications: what the oral and maxillofacial surgeon needs to know. *Oral Maxillofac Surg Clin North Am*. 2016; 28(4):497-506.
- [5] Brackbill ML, Kidd RS, Abdo AD, Warner JG, Harralson AF. Frequency of CYP3A4, CYP3A5, CYP2C9, and CYP2C19 variant alleles in patients receiving clopidogrel that experience repeat acute coronary syndrome. *Heart Vessels*. 2009; 24:73-8.
- [6] Braunwald E. Unstable angina and non-ST elevation myocardial infarction. *Am J Respir Crit*

- Care Med. 2012; 185(9):924-32.
- [7] Basra SS, Virani SS, Paniagua D, Kar B, Jneid H. Acute Coronary Syndromes: Unstable Angina and Non-ST Elevation Myocardial Infarction. *Heart Fail Clin.* 2016; 12(1):31-48.
- [8] Nakata S, Yokoi Y, Matsumoto R, Shirai N, Otsuka R, Sugioka K, et al. Long-term cardiovascular outcomes following ischemic heart disease in patients with and without peripheral vascular disease. *Osaka City Med J.* 2008; 54(1):21-30.
- [9] Feehan J, Hariharan R, Buckenham T, Handley C, Bhatnagar A, Baba SP, et al. Carnosine as a potential therapeutic for the management of peripheral vascular disease. *Nutr Metab Cardiovasc Dis.* 2022; 32(10):2289-2296.
- [10] Besser MW. Post-operative of bleeding, haemolysis and coagulation in mechanical circulatory support patients. *Ann Transl Med.* 2020; 8(13):832.
- [11] Liu MH, Yu H, Zhou RH. Application of adsorptive blood purification techniques during cardiopulmonary bypass in cardiac surgery. *Oxidat Med Cell Longev.* 2022; 2022:6584631.
- [12] Mendes V, Colombier S, Verdy F, Bechtold X, Schlaepfer P, Scala E, et al. CytoSorb® hemoadsorption of apixaban during emergent cardio-pulmonary bypass: a case report. *Perfusion.* 2021; 36:873-5.
- [13] Hassan K, Kannmacher J, Wohlmuth P, Budde U, Schmoekel M, Geidel S. Cytosorb adsorption during emergency cardiac operations in patients at high risk of bleeding. *Ann Thorac Surg.* 2019; 108:45-51.
- [14] Gao F, Shen H, Wang ZJ, Yang SW, Liu XL, Zhou YJ. Rationale and design of the RT-AF study: combination of rivaroxaban and ticagrelor in patients with atrial fibrillation and coronary artery disease undergoing percutaneous coronary intervention. *Contemporary clinical trials.* 2015; 43:129-32.
- [15] Jackson R, Trus RM, El-Diasty M. Hemadsorption for removal of ticagrelor and direct oral anticoagulants in cardiac surgery. *Expert Rev Cardiovasc Ther.* 2022; 20(2):141-150.
- [16] Mair H, Jilek C, Haas B, Lamm P. Ticagrelor and rivaroxaban elimination with CytoSorb adsorber before urgent off-pump coronary bypass. *Ann Thorac Surg.* 2020; 110(5):e369-70.
- [17] Tripathi R, Morales J, Lee V, Gibson CM, Mack MJ, Schneider DJ, et al. Antithrombotic drug removal from whole blood using haemoadsorption with a porous polymer bead sorbent. *Eur Heart J Cardiovasc Pharmacother.* 2022; 8(8):847-56.
- [18] Hassan K, Geidel S, Zamvar V, Tanaka K, Knezevic-Woods Z, Wendt D, et al. Intraoperative ticagrelor removal via hemoadsorption during on-pump coronary artery bypass grafting. *JTCVS Open.* 2023; 15:190-196.
- [19] Jackson R, Trus RM, El-Diasty M. Hemadsorption for removal of ticagrelor and direct oral anticoagulants in cardiac surgery. *Expert Rev Cardiovasc Ther.* 2022; 20(2):141-150.
- [20] Straus S, Haxhibeqiri-Karabdic I, Grabovica SG, Granov N. A difference in bleeding and use of blood and blood products in patients who were preoperatively on aspirin or dual antiplatelet therapy before coronary artery bypass grafting. *Medical Archives.* 2018; 72(1):31.
- [21] Kapetanakis EI, Medlam DA, Boyce SW, Haile E, Hill PC, Dullum MK, et al. Clopidogrel administration prior to coronary artery bypass grafting surgery: the cardiologist's panacea or the surgeon's headache?. *Eur Heart J.* 2005; 26(6):576-83.
- [22] Kim JH, Newby LK, Clare RM, Shaw LK, Lodge AJ, Smith PK, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. *Am Heart J.* 2008; 156(5):886-92.
- [23] Kang W, Theman TE, Reed III JF, Stoltzfus J, Weger N. The effect of preoperative clopidogrel on bleeding after coronary artery bypass surgery. *J Surg Educ.* 2007; 64(2):88-92.
- [24] Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to update the 1999 guidelines for coronary artery bypass graft surgery). *Circulation.* 2004; 110(14):e340-437.
- [25] Leong JY, Baker RA, Shah PJ, Cherian VK, Knight JL. Clopidogrel and bleeding after coronary artery bypass graft surgery. *Ann Thorac Surg.* 2005; 80(3):928-33.
- [26] Li C, Hirsh J, Xie C, Johnston MA, Eikelboom JW. Reversal of the anti-platelet effects of aspirin and clopidogrel. *J Thromb Haemost.* 2012; 10(4):521-8.
- [27] Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J. Prophylactic platelet transfusions prior to surgery for people with a low platelet count. *Cochrane Database of Systematic Reviews.* 2018; 9(9):CD012779.