The effect of platelet-rich plasma on sternal healing postmedian sternotomy in patients undergoing open heart surgery

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Background
Plasma is the fluid portion of blood which contains clotting factors, other proteins, and ions. Platelet-rich plasma (PRP) is defined as a volume of the plasma fraction of autologous blood with many more platelets than what is typically found in blood. The concentration of platelets and thereby the concentration of growth factors (GFs) can be 5 to 10 times greater (or richer) than usual. The aim of this study is to evaluate the effect of PRP on sternal healing post median sternotomy in patients undergoing cardiac surgery.

Patients and methods
A single-center, prospective, comparative study. We recruited 100 patients who were referred for open heart surgery, through median sternotomy, to our Cardiothoracic Surgery Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt between March 2020 and January 2022. Patients were divided into two equal groups; the study group where we applied topical autologous PRP to the sternal edges before sternal closure, and the control group who did not receive PRP.

Results
The two groups were similar in their demographics. We found no significant benefit in terms of sternal healing between the two groups assessed by measuring bone density. Superficial and deep wound infections were similar in both groups; however, we found a marked reduction in blood loss in patients who received PRP (group 1) compared with control group (group 2).

Conclusion
Applying PRP topically to the sternal edges following median sternotomy did not improve sternal healing of the incidence of superficial or deep sternal wound infection. It may be beneficial in reducing blood loss from the sternal edges and hence blood transfusion requirement following surgery.

Keywords:
open heart surgery, platelet rich plasma, sternal healing postmedian sternotomy

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Introduction

Successful healing of the sternum after open heart surgery is a complicated phenomenon because the natural body's ability may fail to efficiently repair the sternum following surgery.

Recent evidence-based data suggested new modalities to increase the quality and accelerate sternal healing in high-risk patients after open heart surgery who are vulnerable to early sternal dehiscence. Platelet-rich plasma (PRP) is considered an attractive alternative option in that manner. Marx and associates demonstrated the positive influence of PRP on bone regeneration and healing since 1998 [1].

Autologous PRP carries minimal risk of infectious disease transmission, immunologic reactions, and rejection. PRP with concentrations of 4 to 5 folds of the normal average platelets (1 100 000 platelets/μl) proved to have a remarkable increase in bone mineral density and regeneration. The market for PRP grew from $45 million in 2009 to more than $120 million by 2016 in the world with widespread usage in the fields of joint repair, Dermatology, and Oro dental surgery [2].

Multiple factors affect the PRP efficacy in the sternal bone healing and regeneration process. Platelet preparation before surgical application is an area of concern with PRP. For this issue, an appropriate anticoagulant must be used to prevent the early spontaneous activation of the platelets [3].

Several anticoagulants have been employed for PRP preparation including heparin, citrate, acid-citrate-

dextrose solution A or anticoagulant citrate dextrose-A, citrate-phosphate-dextrose, citrate-theophylline-adenosine-dipyridamole, and ethylene diamine tetra-acetic acid. Several manual or automated systems have been designed for preparing PRP including clinical laboratory methods and kits. PRP produced by single- or double-step centrifugation technology via platelet-pheresis (autologous selective filtration) and the cell separators. However, these methods are rarely used nowadays, due to several factors including high cost, large volume of peripheral blood should be withdrawn from the patients, and potentially damage to the platelet. Commercially available PRP kits and devices differ in the ease of use, one or two-step centrifugation protocols, centrifugation speed, final PRP volume, platelet count and activation, platelet and growth factor (GF) concentrations, and final red blood cells (RBCs') and white blood cells (WBCs') count [4]. Nevertheless, the cost of the commercial kits for PRP processing is still a challenge [5].

The aim of this study is to evaluate the effect of PRP on sternal healing postmedian sternotomy in patients undergoing cardiac surgery.

Patients and methods

This is a prospective comparative study. We recruited 100 patients referred to our Cardiothoracic department, Faculty of Medicine, Ain Shams University and Ain Shams Specialized Hospital to perform open heart surgery who fulfill our inclusion criteria. The study has been performed between March 2020 and January 2022.

Inclusion criteria

Patients planned for open heart surgery through median sternotomy with one or more of the following criteria; patients with BMI greater than 30, diabetic (DM) patients, patients with history of chest wall irradiation, patients planned for bilateral internal mammary artery harvesting and finally patients with age above 70 years old.

Exclusion criteria

Patients with previous open-heart surgery (redo sternotomy), anemic patients with preoperative HB level less than 11, all patients who underwent emergency cardiac surgery.

Study tools

PRP plus centrifugal machine.

Preparation technique

Ultra-centrifuge technique.

A 50 ml of venous autologous whole-blood were collected from each patient, following insertion of the central venous line by the anesthetist during induction of anesthesia, into 5 tubes (each containing 10 ml) with trisodium citrate as anticoagulant. The tubes were sent for Centrifugation using 800D Centrifuge at 112 g units (3500 rpm) for 10 min at room temperature to separate the red blood cells at the bottom of the tube, the buffy coat (containing the white blood cells) in the middle and the plasma above. The portion of plasma was taken and activated using Calcium gluconate (1 : 9) and collected in a single tube.

Study procedures

Patient data were collected preoperatively and intraoperatively. Patients were distributed into two equal groups. Demographic data were collected such as age, sex, weight, Body mass index (BMI), DM, history of radiation exposure and the use of bilateral Internal mammary artery (BIMA) during coronary artery bypass grafts surgery.

Intraoperative

We applied topically the prepared PRP on the sternal edge of only one group of them before sternal closure at the end of surgery.

Postoperative

The patients were followed till being discharged from hospital and for the first 3 months after surgery. Sternal stability and absence of dehiscence was the primary outcome. Secondary outcome was incidence of superficial and deep sternal wound infection in both groups. After 3 months all patients had computed tomography (CT) chest with three-dimensional bone reconstruction to assess sternal healing and the value of bone density was measured.

Statistical analysis

Data were statistically analyzed using statistical package of social science (SPSS). Using the arithmetic mean, standard deviation using hypothesis student's '*t*' tests for quantitative data analysis, while qualitative data (ordinal, categorical) will be analyzed using Chi-square test (χ^2) (Fisher's Exact Test). For all statistical comparisons, a P value of less than 0.05 is considered significant and a P value of less than 0.01 is considered highly significant.

Results

Table 1 shows that mean age of the PRP injected group was 62 years (±6.74) compared with 58.90 years (±5.88)

Table 1 Comparison between characteristics of platelet-rich plasma injected group and control groups

			Test of significance	
	PRP injected group (*n*=50) No. (%)	Control group (*n*=50) No. (%)	χ^2	*P*-value
Age (Mean±SD) years	62±6.743	58.90±5.881	**T-test** 0.569	0.235
DM			0.071	0.790
Yes	42 (84%)	41 (82%)		
No	8 (16%)	9 (18%)		
Sex			1.268	0.437
Male	27 (54%)	25 (50%)		
Female	23 (46%)	25(50%)		
BMI Categories			2.837	0.092
Overweight (25-29.9)	5 (10%)	1 (2%)		
Obese (≥30)	45 (90%)	49 (98%)		
Type of operation			4.548	0.128
CABG	26 (52%)	30 (60%)		
MVR	7 (14%)	0		
AVR	7 (14%)	7 (14%)		
DVR	5 (10%)	4 (8%)		
MVR+TVR	4 (8%)	7 (14%)		
TVR	1 (2%)	2 (4%)		
Ejection fraction before (Mean±SD)	53.40±1.81	52.84±1.49	**T-test** 1.685	0.095

DVR, double valve replacement; MVR, mitral valve replacement; TVR, tricuspid valve replacemen.

in the control group. PRP injected group included 54% males and 46% females, while the control group had equal number of both genders. Regarding BMI, 45% of the participants of PRP injected group were obese and 10% were overweight compared with 98% and 2% in the control group, respectively. A total of 42% of the DM participants were in the PRP injected group, while 41% were in the control group. Most of the participants in the PRP injected group (52%) underwent Coronary artery bypass graft (CABG). The Mean ejection fraction (EF) before surgery in the PRR injected group was 53.40 (±1.81) compared with 52.84 (±1.49) in the control group. There was no statistically significant difference in the characteristics between participants of the two groups with *P* value (≥0.05).

Table 2 showed that mean value of HU after surgery in the PRP injected group and control group was 369.72 ±(53.79) and 360.64 (±50.79), respectively, showing no statistically significant difference between the two groups. The Mean EF after surgery in the PRR injected group was 58.56 (±2.11) compared with 57.14 (±5.16) in the control group. This showed no statistically significant difference between the two groups with *P* value 0.076. None of the participants in the PRP injected group experienced postoperative bleeding compared with 10% of the participants in the control group. This showed statistically significant difference between the two groups regarding postoperative bleeding with *P* value 0.007. Superficial wound infection was detected in 4% and 10% of the participants in PRP injected group and

Table 2 Comparison between platelet-rich plasma injected group and control groups regarding the outcome

			Test of significance	
	PRP injected group (*n*=50) No. (%)	Control group (*n*=50) No. (%)	χ^2	*P*-value
Hounsfield Unit After (Mean±SD)	369.72±53.79	360.64±50.79	**T-test** 0.860	0.606
Postoperative Bleeding			5.263	0.007
Yes	0	5 (10%)		
No	50 (100%)	45(90%)		
Superficial wound infection			1.382	0.240
Yes	2 (4%)	5 (10%)		
No	48 (96%)	45 (90%)		
Deep wound infection			2.041	0.093
Yes	0	2 (4%)		
Sternal Dehiscence			0.344	0.554
Yes	1 (2%)	2 (4%)		

control group, respectively. There was not statistically significant difference between the two groups regarding Superficial wound infection with *P* value 0.240. None of the participants in the PRP injected group experienced deep wound infection compared with 4% in the control group, however, this was statistically insignificant *P* value 0.093. One participant from the PRP injected group had sternal dehiscence compared with 2 participants from the control group with *P* value 0.554.

Discussion

PRP, an autologous source of platelet-derived GFs, may play a role in regeneration.

There are numerous proposed mechanisms of regeneration by PRP, including the increased proliferation of human dermal fibroblasts, increased expression of Matrix Metalloproteinase (MMP-1 and MMP-3), increased production of procollagen type 1 peptide, and expression of collagen type1-alpha 1, leading to the synthesis of new collagen [6].

Due to its ability to regenerate, it has multiple medical applications, such as in orthopedics, where it is injected into joints to promote cartilaginous proliferation.

In our study, there was no difference in the sternum healing or the Hounsfield ratio. We followed our patients for three months after surgery; each patient had a CT chest with a three-dimensional reconstruction of the sternal bone. The Hounsfield unit was measured for the sternal bone, but there was no effect on healing because the measurements were similar. Similar results were reported by Yao *et al.* [7], who conducted a meta-analysis on sternal wound healing after cardiac surgery and the benefits of PRP application. Insufficient evidence of sufficient quality exists in the literature regarding the efficacy of PRP in the treatment of sternal wounds following cardiac surgery. The Retro spective cohort study (RSC) subgroup analysis revealed that the use of PRP significantly reduces Superficial wound infection (SWI) and deep sternal wound infection (DSWI). The combined results in the subgroup of rondomized control trials (RCTs) indicate no statistically significant difference. However, the studies using the Medtronic Magellan Autologous Platelet Separator to obtain PRP have revealed that PRP tends to prevent SWI and DSWI. In conclusion, PRP may be a promising treatment to prevent SWI in the future, which is safe, cost-effective, simple, and reliable. Insufficient evidence suggests that neither PRP treatment nor conventional treatment reduces post operative bleeding (PBL). Therefore, high-quality RCTs are needed to evaluate the efficacy of PRP on SWI, DSWI, and PBL, as well as its cost-effectiveness.

In our study, we also investigated the effect of injection of PRP on sternal deep and superficial wound infection. We found no statistical difference between the two groups regarding infection in the same conditions, which approximately the same bypass time, weight, and DM. In addition, the effect of PRP on infection was not considered significant as it is a sterile blood product at all steps of preparation and application. Therefore, there is no risk of infection. Serraino *et al.* [8] investigated the impact of PRP on postoperative wound infection. a PRP-based preventative treatment is demonstrably less expensive than a one-day hospital stay. A patient with mediastinitis may require a minimum of seven days of hospitalization and the use of multiple wound dressing devices (vaccum [VAC] therapy, expensive antibiotic therapy, and advanced wound dressings). Therefore, the prevention of sternal wound infection with PRP is advantageous both in terms of cost analysis and in terms of reducing the patient's discomfort.

Regarding age, group [1] had a mean age of ~62 years, while group [2] had a mean age of ~58 years, as we sought to eliminate age as a factor in the healing process.

Concerning healing, we followed our patients for three months with CT chest with three-dimensional reconstruction for the 50 patients who received PRP on the edge of the sternum prior to closure and compared them to the control group [2]. Using the solid value of the Hounsfield unit, we determined that there is no significant effect of PRP usage on sternal healing. This finding may be due to the short follow-up period and small sample size.

Consistent with our findings, an earlier study was conducted on a larger cohort of 150 patients with 6-monthly follow-up. There were three treatment arms: activated PRP (infiltration every 21 days), single dose high molecular weight hyaluronic acid (HMWHA), and low molecular weight hyaluronic acid (LMWHA). Outcome measures used were a visual analog scale, quality of life related to health status (EQ-VAS), and knee function using the International Knee Documentation Committee index (IKDC). The authors reported better response rates in PRP-treated patients than in any treated with hyaluronic

acid ($P<0.005$). The response was better in all groups in younger patients and those with recent onset osteoarthritis [9].

In our study, five patients with excessive blood loss after surgery were investigated for bleeding. None of the patients had a surgical cause for the blood loss; they all belonged to the Group [2] control group. In addition, none of the patients who received PRP lost more than 300 ml of blood in the first 24 h; as a result, the use of PRP was found to be superior in terms of reducing blood loss and hand blood requirements.

Therefore, we believe it may have a positive local effect on hemostasis. Patients who underwent minimally invasive cardiac surgery or cardiac surgery without sternotomy may have a low risk of bleeding. Hence, we believe that significant medical bleeding originates from the sternum and fat tissue. The effect of introducing PRP to the surgical field can be immediately observed following injection.

The cell membrane of platelets consists of a phospholipid bilayer embedded with cholesterol, glycoproteins, and glycolipids. Platelet membranes are asymmetrically organized. Negatively charged phospholipids in resting platelets are preferentially present on the inner leaflet, most notably phosphatidylserine. The platelet membrane is rich in various glycoproteins (GPs) that bind agonists to activate platelets and serve primarily adhesive functions. Therefore, we attempted to identify the mechanism of the local effect of PRP that enhances coagulation and aids in the prevention of surgical bleeding [10].

Study limitations

This is not a randomized controlled study, further randomized control study are needed for better assessment of the effect of PRP on sternal healing, also the small number of patients in our study and finally, the short period of follow-up (3 months) is another limitation, longer follow-up period is needed to assess the effect of PRP application on the long term.

Conclusion

The application of PRP on the median sternotomy wound did not improve sternal healing compared with control group, as well as the incidence of superficial or deep sternal wound infection, however, it may reduce the incidence of postoperative bleeding. Further randomized control trials are needed to evaluate the value of its usage (Fig. 1).

Figure 1

Introduction of the platelet-rich plasma to the sternal edge.

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Conflicts of interest

There are no conflicts of interest.

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