EVALUATION OF PLATELET RICH PLASMA IN REDUCING STERNAL WOUND COMPLICATIONS IN CABG SURGERY WITH MEDIAN STERNOTOMY

SYNOPSIS

By

Dr. Sangeen Khan Wazir

Principal Investigator:
Dr. Sangeen Khan Wazir, MBBS
Pakistan Institute of Medical Sciences (PIMS)
Ibn-e-Sina Road, G-8/3, Islamabad, Pakistan

Phone: +92-334 -8123491
Email: sangeenkhanwazir@outlook.com

Purpose of Document:
This document contains the full study protocol for the interventional clinical trial evaluating the use of autologous platelet-rich plasma (PRP) for improving sternal wound healing after coronary artery bypass surgery. It includes background, methods, discussion, keywords, rationale, research question, population, intervention, comparison, outcomes, study objectives, operational definitions, hypothesis, study design, study setting, duration, sample selection (inclusion and exclusion criteria), sample size, sampling technique, data collection procedure, data analysis, ethical considerations and references.

TABLE OF CONTENTS

ABSTRACT

Background

Deep and superficial wound infections following cardiac surgery increases morbidity, mortality and cost. Autologous platelet rich plasma PRP derived from patients own blood has been used in other surgical settings to promote successful wound healing. The goal of this study is to analyze the effect of PRP during sternal closure in addition to standard wound care for reducing the frequency of postoperative complications.

Methods

Over a period of six months, all consecutive consenting patients undergoing on pump coronary bypass grafting surgery requiring sternotomy will be enrolled. The patients will be randomized into two groups. The control group will receive standard of care sternal closure. The study group will receive standard of care sternal closure plus PRP applied to the sternum and the surrounding tissue at the time of closure. Participants and outcome assessors are blinded to group assignment, while surgeons performing the procedure are aware of the intervention. The patients will be followed up for a period of 30 days post-surgery. Wound healing, deep and superficial infection including mediastinitis, and readmissions within 30 days will be documented as primary outcomes. Secondary outcome will be the overall cost burden for the 30-days post-surgery period. Other outcomes will be ICU stay (days), blood transfusions more than 4 units and platelets transfusions more than 4 units.

Discussion

Wound dehiscence and infection in post cardiac surgery period are a significant source of morbidity and mortality. Treatment of these complications may cause prolonged hospitalization, prolonged antibiotic therapy, and revisions of operative procedures. In addition to burden on physical health, the complications associated with cardiac surgery can portend a high financial cost to the patient. The PRP has been shown to decrease the incidence of sternal wound complications following cardiac surgery and routine use of platelet rich plasma has been advocated for all patients undergoing sternotomy for cardiac surgical procedures.

Keywords

Sternal wound infection, Superficial sternal wound infection, Deep sternal wound infection, Surgical site infection, Delayed wound healing, Median sternotomy, Cardiac surgery, Postoperative wound complications, Hospital length of stay, Cost analysis, Platelet rich plasma, coronary artery bypass grafting, wound healing, CABG, readmission rate

INTRODUCTION

Median sternotomy in cardiac surgery is considered to be the gold standard incisional approach for the majority of cardiac operative procedures resulting in a low failure rate and excellent long-term outcomes [1].

Although the incidence of sternal complications after cardiac operations through median sternotomy is relatively low, ranging from 0.4% to 8%, it is associated with a comparatively high mortality rate of up to 47% if left undetected. Indicative of this, the 4-year survival rate of patients diagnosed with sternal complications is 65% compared with 85% in patients who heal without such complications [2]. Median sternotomy can have many complications like wound dehiscence and infection in 0.2 to 8 % of the patients [3, 4]. Some of the serious complications of sternotomy include Deep sternal wound problems DSWP following cardiac surgery, ranging from 0.4–3% in unselected patients [5]. DSWP are rare, but can have serious complications, as it is associated with prolonged hospital stays, long-term antibiotic therapy, multiple surgical procedures, higher mortality and morbidity, and increased patient suffering and costs [6]. This complication can be avoided by using protein rich plasma PRP, since platelets upon activation will excrete growth factors and attractants for tissue stem cells, thus promoting tissue healing [5].

The literature has identified a range of preoperative, perioperative, and postoperative risk factors that are suggested to contribute to the development of sternal complications [2] . Risk factors known for postoperative complications in patients going through cardiac surgery include obesity, bilateral harvesting of the internal mammary artery, unilateral LIMA harvesting, diabetes, steroid therapy, history of active smoking, osteoporosis, and chronic lung diseases [2, 7, 8, 9]. Two studies listed the postoperative requirement for blood products as an independent risk factor for sternal infection [2] . The replacement of blood products may lead to host immunosuppression and increase the risk of sternal infection [2] . Insulin-dependent diabetes mellitus is considered the most serious predisposing factor for deep infections [4]. Given that the IMA is a major blood supply to the sternum, some studies report mobilization of these arteries may lead to sternal hypoperfusion and increase the risk of sternal infection [2].

Complications in the post-surgery period are a significant source of mortality. Treatment of these complications may cause prolonged hospitalization, prolonged antibiotic therapy, and

revisions of operative procedures [10]. Centrifugal-based platelet concentration methods have been developed separating whole blood in a red blood cell (RBC) layer, a platelet rich plasma (PRP) layer and a platelet poor plasma (PPP) layer. The PRP layer also contains a high concentration of leukocytes, which might provide additional protection against infection. Numerous growth factors and chemoattractants are excreted from activated platelets, in sufficient amounts to stimulate vascular proliferation and attract tissue stem cells and in addition platelets also appear to have antimicrobial properties [5]. During the inflammatory phase of wound healing, PRP stimulates the release of growth factors such vascular endothelial growth factor and transforming growth factor beta, which are believed to stimulate cell proliferation, migration, differentiation, and matrix synthesis. These same growth factors can positively affect chondrocyte metabolism, increase chondrogenesis, and improve bone healing and regeneration. PRP wound irrigation was found to be safe and cost-effective, improving healing and leading to a lower incidence of sternal infections [6]. Nowadays, PRP is being used in many specialties to promote speed-up tissue healing and hence less complications . Furthermore, PRP inhibits in vitro the growth of Staphylococcus aureus, the most common bacteria responsible for DSWI, and Escherichia coli, whereas it was ineffective against Pseudomonas aeruginosa, Enterococcus faecalis and Klebsiella pneumoniae [9]. PRP can be injected in the LIMA bed, hence increasing neovascularization, speeding up the healing process, as a result can avoid deep sternal wound infection, sternal dehiscence and reoperation secondary to postoperative complications.

The PRP has found multiple uses in many fields, including oral, maxillofacial, and plastic surgery [8,10]. In cardiac surgery patients, PRP has been shown to decrease the incidence of sternal wound complications [10]. Although it is not used routinely, some authors suggest regular use of PRP based on preliminary results from studies on reducing complications in patients undergoing cardiac surgery with median sternotomy [8].

Rationale

Postoperative complications cause significant morbidity in post cardiac surgery patients. The PRP has been proposed in clinical trials to reduce the frequency of complications in patients undergoing median sternotomy for cardiac operative procedures. The purpose of our study is to evaluate whether there is any beneficial effect of use of PRP in addition to standard care after on pump CABG, cardiac surgery.

Research Question

Does application of PRP after CABG, cardiac surgery reduce the frequency of sternal wound complications?

Objective

To compare the complication rates of application of PRP in addition to standard sternal wound closure versus standard sternal wound closure alone.

Population

All consecutive patients of age 45 to 72, undergoing CABG, cardiac surgery with median sternotomy will be included in the study.

Intervention

Application of 6 mL of autologous PRP to sternum and soft tissue during sternal closure.

Comparison

The control group will undergo midline sternotomy with a sternal saw blade. The sternum will be closed with a simple interrupted or figure of eight stainless steel wire. The wounds will be closed in a layered manner with absorbable suture and dressed with Steri-Strips, gauze and paper tape. The study group will additionally receive 6 mL of autologous PRP applied to sternum and soft tissue during sternal closure.

Outcome

(i) Primary Outcome;

Primary outcome will be measured as frequency of sternal wound complications in terms of delayed healing, superficial infection, deep infections, and readmission rate including mediastinitis in 30-days period post-surgery.

(ii) Secondary outcome;

Secondary outcome will be the overall cost burden for the 30-days post-surgery period.

(iii) Other outcomes;

Other outcomes will be ICU stay (days), blood transfusions more than 4 units and platelets transfusions more than 4 units within 30 days.

OPERATIONAL DEFINITIONS

1-Cardiac Surgery: Cardiac surgery, also called heart surgery, involves surgical operations performed on the heart to correct life-threatening conditions. The surgery can be either open-heart surgery or minimally invasive surgery depending on the condition to be corrected.

2-PRP: Platelet-rich plasma (PRP) is defined as a portion of the plasma fraction of autologous blood having a platelet concentration above baseline.

3-Study Outcome

Study Outcome will be measured as frequency of sternal wound complications in terms of delayed healing, superficial infection, deep infections, and readmission rate including mediastinitis in 30-days period post-surgery. Secondary outcome will be the overall cost burden for the 30-days post-surgery period. Other outcomes will be ICU stay (days), blood transfusions more than 4 units and platelets transfusions more than 4 units within 30 days.

4- DSWI: DSWI diagnosis will be made, based on the guidelines of the CDC, in patients who developed one or more of the following: [1] positive culture of mediastinal tissue or fluid; [2] clinical evidence of mediastinitis during sternal reoperation; or [3] chest pain, sternal instability, purulent discharge from the mediastinum associated with a positive blood culture. DSWI presenting in the first 30 days after operation will be included in the study.

5- SWI: All the infections will be considered positive that will involve skin and subcutaneous tissue within the first 30 postoperative days, not reaching the sternum, requiring local surgical intervention with regular wound care, accompanied by antibiotic therapy and/or Vacuum Assisted Closure (VAC) therapy.

6- Delayed Healing: Healing is a complex biochemical process of tissue repair after it has been damaged. It has three stages which are inflammation, proliferation and remodelling. Delay in the specific time period or in the biochemical process is called delayed healing. Skin,

subcutaneous tissue or sternum which is unable to heal within two weeks of surgery will be considered delayed wound healing.

7- Readmission: It is defined as any hospital readmission within 30 days of discharge related to the index surgery.

8- ICU stay: Stay that refers to the duration, in days, spent in the intensive care unit, within 30 days postoperatively.

9- Blood transfusion: It is defined as the requirement of more than 4 units of packed red blood cells (PRBC) or platelets within 30 days postoperatively.

Hypothesis

Administration of platelet rich plasma during sternal wound closure reduces the frequency of complications in the 30-days post-surgery period.

MATERIAL AND METHODS

Study Design

Randomized control trial

Study Setting

The Department of Cardiac Surgery, Cardiac Center, Pakistan Institute of
Medical Sciences (PIMS), Islamabad.

Duration

06 months after acceptance of synopsis

Sample selection;

Inclusion criteria

Patients from 45 to 72 years of age, undergoing on pump CABG,

cardiac surgery with median sternotomy.

Patients who provide consent.

Exclusion criteria

- BMI less than **18.5** or more than **24.9**

- Bilateral harvesting of the internal mammary artery,

- Steroid therapy,

- Known Diabetic,

- Active smoker,

- Osteoporosis,

- Chronic lung disease,

- CPB time more than 72.5 minutes

- Platelet Rich Plasma cannot be obtained.
- Patients who are not candidates for blood bank donations.

Sample size

The sample size has been calculated by using WHO size calculator with the statistical assumptions as following:

(Level of significance = 5%), (Power of test = 80%), (Population standard deviation = 3.0)

(Anticipated population, rate of oedema and infiltration in prp group, P1= 18%)

Anticipated population, rate of oedema and infiltration in control group, P2= 44% Sample size comes out to be 49 cases in each study group and a total of 98 patients will be included in the study.

Sampling Technique

Participants will be recruited using non-probability consecutive sampling and randomly assigned to one of two groups.

Data Collection Procedure

The study protocol will be first submitted for approval to the hospital ethics committee and Advance Research committee. A written informed consent will be taken from all parents/ caretakers. The subjects fulfilling inclusion will be enrolled from Cardiac Center. Participants will be recruited using non-probability consecutive sampling and randomly assigned to one of two groups. The antibiotic prophylaxis will be given 60 min before incision. The preoperative antibiotics protocol and glycemic management protocol will be standard and will remain the same for all patients throughout the study. Patients will be given general anesthesia. This will ensure that they are asleep and pain free through the whole surgery. An incision of 8- to 10-inch will be made in the chest. A midline sternotomy with a sternal saw blade will be done. Bleeding sites will be secured followed by pericardiectomy. Once the heart is visible, cannulation will be done and the patient will be connected to a heart-lung bypass machine. The machine will move blood away from the heart so that the surgeon can operate. Surgery will be performed according to local guidelines. Patients will be heparinized using an initial dose of 300 IU/kg unfractionated heparin. During surgery the activated clotting time (ACT) will be maintained at least 480 s. All patients undergoing sternotomy will be included in the study including emergencies, reoperations, ventricular assist device implantations, heart transplants, aortic dissections and standard operations (i.e. coronary artery bypass grafting and valve repairs or replacements). Following sternotomy, the use of bone wax on the sternum will be avoided, as this might form an intrasternal barrier and interfere with PRP augmented healing. Targeted flow rates during cardiopulmonary bypass were 2.6 L/min/m2 , yielding a venous saturation of 70−80%. After heparin reversal is achieved with protamine, all the bleeding spots will be identified and stopped i.e. haemostasis will be secured. The control group will undergo midline sternotomy with a sternal saw blade. The sternum will be closed with a simple interrupted or figure of eight stainless steel wire. The wounds will be closed in a layered manner with absorbable suture and dressed with Steri-Strips, gauze and paper tape. The study group will additionally receive 6 mL of autologous PRP applied to sternum and soft

tissue during sternal closure. Participants and outcome assessors will be blinded to group assignment, while surgeons performing the procedure will be aware of the intervention

Primary outcome will be measured as frequency of sternal wound complications in terms of delayed healing, superficial infection, deep infections, and readmission rate including mediastinitis in 30-days period post-surgery. Secondary outcome will be the overall cost burden for the 30-days post-surgery period. Other outcomes will be ICU stay (days), red cell concentrate (RCC) more than 4 units and platelets transfusions more than 4 units.

All the information will be entered on the predesigned Performa by the researcher himself to comply with the study protocol attached as **Annexure-I.**

Data Analysis

Quantitative variables (age, hospital stay, ICU stay, cost) will be summarized as mean ± SD or median (IQR) and compared using t-test or Mann–Whitney U test. Categorical variables (superficial/deep wound infections, delayed healing, readmissions, transfusion requirements, residence (urban\rural), education status and socioeconomic background (low\middle) will be reported as counts and percentages and compared using chi-square or Fisher's exact test. A p-value <0.05 will be considered significant. Missing data will be handled using complete case analysis. All analyses will be performed using [SPSS/R].

Ethical Considerations

From ethical point of view:

- Those patients will be included in the study that will be willing to participate in the study.
- A written informed consent will be taken from the patients and they will be ensured that their confidentiality will not be breached.
- There will be no compromise on the standard care and treatment for study purposes.

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