Original Research

Efficacy of prophylactic platelet rich plasma (PRP) following open saphenous vein harvesting in cardiac surgery

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Abstract

Background: Wound infection represents a frequent trouble following open saphenous vein harvesting in cardiac surgery. Platelets' growth factors are crucial for the healing process. Prophylactic platelet rich plasma (PRP) application on leg wound might reduce the incidence of saphenous vein harvest site infections in patients undergoing coronary artery bypass graft surgery (CABG). **Methods**: Between January 2009 and December 2020, 987 consecutive patients underwent CABG using saphenous vein as conduit graft and were retrospectively divided into two groups. All patients had standard surgical leg wound closure and wound care, but treatment group received adjunctive topical application of PRP (no-PRP and PRP group, respectively). The primary outcome was wound infection. **Results**: Saphenous vein harvest site infection rate was similar between PRP (3.5%) and No-PRP (5.2%) group, $p = 0.215$. The ASEPSIS score was lower for the PRP group (PRP: 3.6 ± 9.1 vs. No-PRP: 5.3 ± 11.2; $p = 0.014$). Performing a subgroup analysis, the diabetic patients (PRP-DM) group had a lower rate of infection than control group (No-PRP DM) (2.6% vs. 7.7%, $p = 0.026$). PRP-DM patients had an inferior ASEPSIS score (PRP-DM: 2.7 ± 8.3 vs. No PRP-DM: 7.5 ± 13.2, $p < 0.001$). **Conclusions**: Topical application of autologous PRP on saphenoug vein harvest site might reduce the rate of surgical site infection, with particular benefit among diabetic patients.

Keywords: Platelet rich plasma; surgical wound infection; coronary artery bypass graft

1. Introduction

Coronary artery bypass grafting (CABG) surgery is the most appropriate revascularization strategy for patients with complex multivessel coronary artery disease and reduced left ventricular ejection fraction, improving prognosis and quality of life [1]. Despite the increased tendency of using arterial grafts considering their improved long term patency, the saphenous vein (SV) remain the most frequently used conduit in CABG especially in older patients [2]. The easy accessibility, possibility of simultaneous harvesting, and its length make the SV an almost-ideal conduit for CABG [2]. Unfortunately, SV grafts have two main limitations: high risk of graft failure (15%–20% within a year) and harvest-site complications [3,4]. The reported incidence of the saphenous vein harvest site infection (SVHI) ranges between 1% and 24% [5,6]. Although endoscopic SV graft harvesting reduces the rate of harvest-site complications, this technique has controversial impact on the graft patency [7,8]. It has been reported that SV graft patency has been consistently lower with endoscopic harvesting than with open SV harvesting, probably because of

mechanical factors during the procedure (e.g., overstretch injury) [8]. Therefore, some surgeons still prefer to perform a safe and gentle SV harvesting through a full open incision. Moreover, Diabetes Mellitus, that is associated with a 2 to 4-fold increased mortality risk from coronary artery disease, complicates the wound healing process in patient undergoing CABG. In this complex scenario, platelets growth factors play a pivotal role in tissue regeneration and healing. Autologous platelets are easily collected and concentrated by processing platelet-rich plasma (PRP). PRP contains at least 6 platelet growth factors, which have been associated with a beneficial wound healing [9–12]. Recently, much research focused on the effectiveness and safety of PRP in management of wound infection. So far, due to the novelty of PRP, few studies were published on its efficacy in human subjects. In view of the limited clarity of available data, the aim of our study was to examine the effects of the topical PRP use in leg wounds after SV harvesting.

Table 1. Baseline characteristics.

Overall population	PRP (n = 452)	No PRP (n = 501)	*p* value
Age (years) (median; IQR)	67 (13)	67 (14)	0.588
Male gender (%, n)	77.9% (352)	76.0% (381)	0.504
BMI (kg/m^2) (mean ± SD)	27.51 ± 4.699	27.14 ± 4.509	0.211
COPD (%, n)	15.2% (69)	13% (65)	0.310
Diabetes Mellitus (%, n)	41.8% (189)	38.9% (195)	0.363
Diabetes Mellitus Type 2	164 (87%)	169 (86%)	0.976
Smoking (%, n)	35.6% (161)	30.53% (153)	0.096
Hypertension (%, n)	35.3% (160)	33.3% (167)	0.503
Dyslipidemia (%, n)	30.9% (140)	27.1% (136)	0.193
Creatinine (mg/dL) (mean ± SD)	1.02 ± 0.25	1.01 ± 0.25	0.467
Among patients with DM	DM with PRP (n = 189)	DM without PRP (n = 195)	*p* value
Age (years) (median; IQR)	67 (12)	68 (12)	0.873
Male gender (%, n)	73% (138)	70.2% (137)	0.549
BMI (kg/m^2) (mean ± SD)	27.62 ± 4.89	26.83 ± 4.40	0.096
COPD (%, n)	10% (19)	13.8% (27)	0.252
Smoking (%, n)	16.4% (31)	10.7% (21)	0.107
Hypertension (%, n)	12.6% (24)	12.3% (24)	0.908
Dyslipidemia (%, n)	12.6% (24)	16.9% (33)	0.244
Creatinine (mg/dL) (mean ± SD)	1.03 ± 0.25	1.02 ± 0.25	0.725

DM, Diabetes Mellitus; PRP, Platelet Rich Plasma; BMI, Body mass index; COPD, Chronic Obstructive Pulmonary Disease; IQR, interquartile range; SD, standard deviation.

2. Material and methods

The purpose of this study was to determine if the incidence of perioperative saphenous vein harvest site infection could be effectively reduced by topical PRP application during the wound closure.

2.1 Study design

We performed a retrospective observational single center non-randomized cohort study recruiting all patients undergoing cardiac surgery at the "Magna Graecia" University, Catanzaro, Italy. Patients were considered eligible if they were receiving an elective CABG using a saphenous vein graft with an open technique. Exclusion criteria included lower leg surgical intervention, severe peripheral vascular disease, emergent surgery, dialysis-dependent renal failure, chronic steroid administration, previous CABG, or preoperative anemia (Hb <9 g/dL). Patients undergoing saphenous vein harvesting through bridging and endoscopic technique were excluded. Between January 2009 and December 2020, 953 consecutive patients undergoing open cardiac surgery requiring a saphenous vein graft at a single cardiac surgical center were consented and were included in our database (University Magna Graecia of Catanzaro IRB approval ER.FE.2018.15.A). There were 452 consecutive patients who received standard of care leg wound closure plus PRP composed of autologous platelet rich plasma, calcium and thrombin applied to the subcutaneous tissue at the time of closure from February 2012 to December 2020 (PRP group). These patients were compared to the previous 501 consecutive patients who received standard of care leg wound closure, from January 2009 to January 2012 (No-PRP group). All data were prospectively collected and retrospectively analyzed.

Primary outcome was the incidence of lower extremities surgical site infections. This was determined through assessment of the ASEPSIS score [13]. Only the moderate and severe complaints were included for incidence analysis. The wound evaluation was performed daily during the hospitalization and at 1-month follow-up. Data were retrospectively analysed. The need for informed consent was waived due to the retrospective study design.

2.2 PRP preparation

Details of PRP preparation have been previously described [10]. Eighteen milliliters of whole blood were taken from the central line and processed to obtain a red-colored platelet gel, rich in growth factors released from the alpha granules in the activated platelets. About 8 mL of PRP was obtained out of 18 mL of blood. It was stored vertically at room temperature until its application. PRP was spread on the leg wound before the closure of subcutaneous tissue (Fig. 1). Care was taken not to remove any of the activated PRP with swabs during closure of the wound.

2.3 Preoperative and intraoperative management

Preoperative shaving and bath with povidone-iodine soap solution before surgery were performed for all patients. Considering saphenous vein harvesting, skin was incised with scalpel and electrocautery was never used. Full
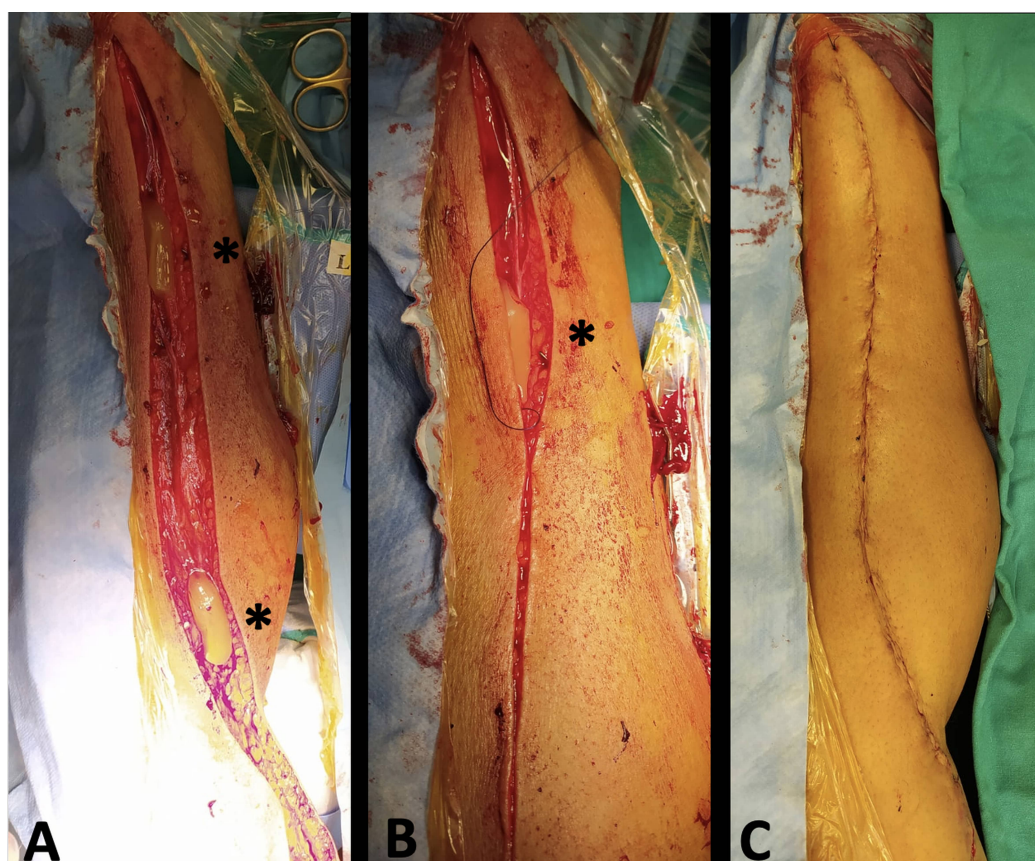
Fig. 1. Saphenous vein is harvested to be used for coronary artery bypass graft. (A) During leg closure, platelet rich plasma ("yellow gel" pointed by the *) is applied to enhance wound healing and prevent saphenous vein harvesting site infection. (B) The leg wound is closed keeping the platelet rich plasma ("yellow gel" pointed by the *) in the subcutaneous tissue. (C) The leg wound is closed.

open technique was used in all patients. Leg closure was always achieved before heparin administration. The harvest wound was closed with intracutaneous poliglecaprone 3/0 according to our routine. In the treatment group, a plenty amount of PRP was spread on the wound immediately before closure. The leg was then wrapped with sterile elastic bandages. Cardiopulmonary bypass and surgical techniques were standardized and similar throughout the study period.

2.4 Postoperative management

All patients received gradient compression stockings for 30 postoperative days. Wound dressing was performed daily. In case of signs of wound infections, microbiologic analysis was performed immediately. In both groups, antibiotic prophylaxis consisted of intraoperative administration of 2 g of Cefazolin. Post-operatively, antibiotic prophylaxis continued with administration of cefazolin 2 g twice a day, unless dose adjustment were required for impaired kidney function. In the case positive cultures or clinical signs of infection, the antibiotic treatment was modified according to antibiogram. After discharge, patients were admitted in a physical rehabilitation center for at least 15 days. Professional nurses took care of the wounds. Any complications in wound healing were reported to our department for readmission of the patients. After, patients were visited for a 30-day follow-up at our outpatient clinic, where wounds were evaluated by a cardiac surgeon.

2.5 Statistical analysis

Statistical analysis was performed by the SPSS program for Mac, version 25.0 (IBM SPSS Statistics for Macintosh., Armonk, NY). Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). Categorical variables are presented as absolute numbers and percentages. Data were checked for normality before statistical analysis with the Shapiro-Wilk test. Normal distributed continuous variables were compared using the *student-t* test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were expressed as frequency with percentages and were analyzed by Pearson's χ^2. Logistic regression was used to assess whether there was an association between pre-operative risk factors and SVHI. A *p*-value < 0.05 was considered as criterion of statistical significance.

3. Results

A total of 953 consecutive patients underwent CABG using the great saphenous vein as conduit were considered eligible. Patients submitted to saphenous vein harvesting with bridging or endoscopic technique (235) in the same study period were not included into the study. Thirty-four patients were excluded because of previous CABG (10), lower leg surgical intervention (2), severe peripheral vascular disease (9), dialysis-dependent renal failure (9). Autologous PRP was not obtained in 4 patients because of primary or drugs related severe clotting abnormalities. PRP was spread on venous harvesting site before the closure of subcutaneous tissue of 452 patients. The control group of 501 patients (No PRP group) received a standard closure of the great saphenous vein harvest site. No treatment-related adverse events were observed. Every patient was submitted to CABG, however, 136 patients (30.1%) of the PRP group and 161 (32.1%) cases of the control group underwent to combined procedures (CABG and surgery of the aortic valve, CABG and surgery of the mitral valve, CABG and surgery for left ventricular aneurysm, CABG and surgery for aortic aneurysm) ($p = 0.173$). The groups were homogeneous for preoperative risk factors considering both the overall cohort and the subgroup of diabetic patients (Table 1). Mean length of the saphenectomy incisions was 43.8 ± 6.8 cm in the PRP group versus 43.4 ± 7.8 cm in the control group ($p = 0.088$). All the patients survived, and the follow-up was 100% complete. Sixteen (3.5%) in PRP group developed harvest site infection, whereas SVHI occurred in 26 patients (5.2%) in No-PRP group ($p = 0.215$). In PRP group microbiology cultures were positive in 15 patients versus 24 patients in No-PRP group. Single pathogen was implicated in 8 (53%) instances in PRP group versus 14 (58%) cases in the control group. Staphylococcus aureus was the most frequently isolated pathogen (PRP: 5 (33%) vs No-PRP: 7 (29%): methicillin-susceptible Staphylococcus aureus (MSSA) was found in 1 PRP cases and 2 events in No-PRP patients; methicillin resistant Staphylococcus aureus (MRSA) was identified in 4 PRP patients and in 5 cases in No-PRP group. Pseudomonas aeruginosa was identified in No-PRP group in 3 cases (12.5%). A polymicrobial infection was identified in 7 PRP patients (46.6%) and in 10 No-PRP patients (41.6%). Klebsiella pneumoniae, Enterobacter cloacae, Acinetobacter baumanii, Escherichia coli, Serratia marcescens and Proteus mirabilis were the most encountered pathogens in polymicrobial contaminations. A prior microbiological identification was not found in the other remaining cases for both groups (Table 2). The groups showed no significant difference for the major complication of the wound healing process (Table 3). However, assessing the ASEPSIS score, the PRP group showed a lower ASEPSIS score compared to the control group (PRP: 3.6 ± 9.1 vs. No-PRP: 5.3 ± 11.2; $p = 0.014$). In PRP group, infections were diagnosed on the same surgical admission (10, 62.5%), on readmission (3, 18.7%), and on post-discharge surveillance (3, 18.7%). Concerning the control group, in 11 patients (42.3%) the infection was diagnosed during the hospitalization period; 9 patients (34.6%) were admitted again for SVHI and in the remaining 6 patients (23%), the infection was assessed on post-discharge surveillance.

A logistic regression revealed a positive association between infection and COPD ($p = 0.038$), smoking habit ($p = 0.002$), and diabetes mellitus ($p = 0.002$) (Table 4). We observed that comparing the diabetic patients in PRP group (PRP-DM) with the diabetic patients in the control group (No PRP-DM) the rate of the SVHI was lower in the treated one with statistically significance (PRP-DM: 2.6% vs No-PRP-DM: 7.7%, $p = 0.026$). Likewise, in the diabetic patients, fewer major complication of the wound healing process occurred in the treated group (Table 5). Furthermore, the PRP-DM group showed a lower ASEPSIS score than the control group (PRP-DM: 2.7 ± 8.3 vs. No PRP-DM: 7.5 ± 13.2, $p < 0.001$).

4. Discussion

Leg wound healing after SV harvesting is an underestimated source of patient morbidity after cardiac surgery. The incidence of complications depends on the definition of wound infection and the follow-up frequency. The traditional open technique of SV harvesting provides an established and rapid way, with an optimal visualization of the

Table 2. Details of microbiological culture in PRP and No-PRP groups.

	PRP	No-PRP
Single pathogen infection	8	14
Staphylococcus aureus	5	7
MSSA	1	2
MRSA	4	5
Pseudomonas aeruginosa	2	3
Serratia marcescens	1	3
Acinetobacter baumanii	0	1
Polymicrobial infection	7	10
2 pathogens	5	4
3 pathogens	2	5
4 pathogens	0	1

MSSA, Methicillin-sensitive Staphylococcus aureus; MRSA, Methicillin-resistant Staphylococcus aureus.

Table 3. Major complication of the wound healing process.

Complications	PRP (n = 452)	No PRP (n = 501)	p value
Pain	100 (22.1%)	122 (24.3%)	0.417
Serous Exudate	67 (14.8%)	98 (19.5%)	0.054
Erythema	66 (14.6%)	71 (14.1%)	0.850
Purulent Exudate	11 (2.4%)	23 (4.5%)	0.073
Dehiscence	13 (2.8%)	24 (4.7%)	0.127
Infection	16 (3.5%)	26 (5.2%)	0.215

PRP, Platelet Rich Plasma.

Table 4. Logistic regression, details.

Model	Deviance	AIC	BIC	df	X²	p	McFadden R²	Nagelkerke R²	Tjur R²	Cox & Snell R²
H₀	344.365	346.365	351.224	952						
H₁	303.007	321.007	364.743	944	41.358	<0.001	0.120	0.140	0.066	0.042

Coefficients					Wald test			
	Estimate	Standard Error	Odds Ratio	z	Wald Statistic	df	p
(Intercept)	−3.169	1.699	0.042	−1.866	3.480	1	0.062
Age	−0.002	0.019	0.998	−0.114	0.013	1	0.909
Sex	0.074	0.385	1.077	0.192	0.037	1	0.848
BMI	−0.059	0.040	0.943	−1.484	2.202	1	0.138
COPD	0.769	0.370	2.157	2.080	4.325	1	0.038
Smoke	1.545	0.487	4.689	3.173	10.069	1	0.002
Hypertension	0.160	0.432	1.174	0.371	0.138	1	0.711
Dyslipidemia	0.463	0.388	1.589	1.194	1.426	1	0.232
Diabetes	1.159	0.381	3.188	3.040	9.239	1	0.002

BMI, Body mass index; COPD, Chronic Obstructive Pulmonary Disease; DM, diabetes mellitus.

Note: INFECTION level 'Si' coded as class 1.

Table 5. Major complication of the wound healing process in the diabetic and not diabetic patients.

Complications	PRP-DM (n = 189)	No PRP-DM (n = 195)	p value	PRP-No-DM (n = 263)	No-PRP- No-DM (n = 308)	p value
Pain	39 (20.6%)	57 (29.2%)	0.052	61 (23.1%)	65 (21.1%)	0.576
Serous exudate	24 (12.6%)	53 (27.1%)	<0.001	43 (16.3%)	45 (14.6%)	0.589
Erythema	16 (8.4%)	30 (15.3%)	0.037	50 (19%)	41 (13.3%)	0.069
Purulent Exudate	3 (1.58%)	13 (6.6%)	0.013	8 (3%)	10 (3.2%)	0.878
Dehiscence	5 (2.6%)	15 (7.7%)	0.026	8 (3%)	9 (2.9%)	0.944
Infection	5 (2.6%)	15 (7.7%)	0.026	11 (4.2%)	11 (3.5%)	0.717

PRP, Platelet Rich Plasma; DM, Diabetes Mellitus.

vein. Unfortunately, this approach is associated with a large scar formation, unsatisfactory cosmetic result, and a considerable risk of wound infection. In 2005 Fowler reported a major infection of the saphenous harvest site that occurred in 32.6% of a population of 11,636 patients, after CABG [14]. Our total incidence of wound infection is 4.4%. Besides their role in hemostasis, platelets have been shown to be crucial in wound healing and immunomodulation. It is thus thought that autologous platelets at the site of tissue damage might enhance the healing process and thereby protect against infection [15]. Moreover, during the inflammatory phase of tissue healing, activated platelet releases specific growth factors which regulate the early migration of cells to the injury site, cell mitosis, angiogenesis, granulation tissue formation [16]. Because of these features, PRP, or platelet concentrate, has emerged as a possible adjuvant therapy to aid in the healing of surgical wounds and injuries. The benefit of autologous PRP application has been already appreciated to prevent the sternal wounds infections and for the treatment of left ventricular assist device driveline infections [10–12].

Englert and colleagues in their study included 30 patients and found a decreased wound bruising in PRP group [17]. Vang performed a study with 36 patients observing that PRP-treated patients experienced less postoperative pain, reduced blood loss, and reduced symptoms [18]. In 2008, a retrospective analysis of CABG patients having endoscopic vein harvesting [19] concluded that PRP significantly reduced occurrences of chest wound infection, chest and leg wound drainage, concluding that the PRP therapy merits further investigation. Recently, Almdhal and co-workers prospectively enrolled 140 patients concluding that the topical application of autologous platelet-rich plasma on vein harvest wounds did not reduce the rate of surgical site infection [20]. This randomized controlled trial enrolled a small number of patients, with low incidence of complications and so underpowered. Our findings suggest that the topical use of autologous PRP reduced the incidence of vein harvest wound infection following CABG. Moreover, the No-PRP group had a higher rate of microbiological isolation compared to the PRP group (No-PRP: 24 vs. PRP: 15, Table 2). As already mentioned by other studies, PRP could reduce the development of infections through the antimicrobial effect of white blood cells and platelets [12]. *In vitro* analyses showed different degrees of a potential antimicrobical action of PRP against several germs common in wounds such as Stapilococcus aureus (MRSA, MSSA), Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Enterobacter cloacae, Proteus mirabilis, Acinetobacter baumanii, and Staphilococcus epidermidis. According to Farghali and colleagues, PRP has a bacteriostatic and bactericidal effect [21]. As like as antibiotics, PRP could counteract invading pathogens with a different spectrum of action. A minimum inhibitory concentration (MIC) should

be reached also for PRP in order to overcome and stop the bacterial growth [22]. In the present paper, PRP could have both promoted the healing process and counteracted the potential strains of bacteria in the treated group, resulting in low wound infections and healing complications (Tables 2 and 3).

Moreover, our results suggest that diabetic patients might benefit from the topical application of PRP on the wound site, preventing the incidence of complications. Diabetes Mellitus is one of the major risk factors for poor wound healing. The low capillary oxygen delivery leads to wound infections at the harvest site. Numerous *in vitro* and *in vivo* studies demonstrate the beneficial effects of PRP in diabetic ulcers [23,24]. Guo and colleagues observed the cutaneous healing process in chronic wounds treated with PRP in a diabetic rat model, providing evidence that platelet growth factor can effectively induce proliferation and migration of endothelial cells and fibroblasts to improve angiogenesis and re-epithelialization in chronic wounds [25]. Moreover, Chen and colleagues proved the antibacterial effect of autologous platelet-rich gel derived from subjects with diabetic dermal ulcers *in vitro* [26]. The application of platelet-rich gel was also found effective in enhancing healing of transmetatarsal amputations in diabetic dysvascular patients [27]. Massara and associates showed that the application of autologous platelet-rich plasma enhanced wound healing after lower limb revascularization [28]. Moreover, Ahmed and colleagues showed an increase in healing rate in PRP group vs. non-PRP group for the treatment of diabetic foot ulcers [29]. Our findings suggest that Staphylococcus aureus was the most common causal bacteria found in infected wounds, with a lower incidence in PRP group.

Despite close adherence to routine process of care measures, SVHI are an important source of morbidity in CABG patients. Although several risk factors (Diabetes Mellitus, smoking habit, obesity, etc.) can be identified, their impact on the rate of infection is not completely understood. A better understanding of patient risk factors, as well as the application of prevention strategies as like as PRP use, could guide future protocols of care.

Furthermore, the cost of the prophylactic application with PRP is certainly lower than that required for prolonged treatment of a SVHI (antibiotic administration, advanced wound dressing, vacuum-assisted closure therapy, in-hospital stay).

This study represents the largest retrospective comparison between PRP treated patients and control group for leg wound infections after cardiac surgery. The enrolled patients represent a standard CABG population. All baseline characteristics were well matched between the two groups. We exclude all the major confounding factors from our analysis as peripheral vascular disease, preoperative anemia, chronic renal failure. The overall care for patients was the same despite the PRP administration or the risk factors (including DM). Minor limitation is represented by the fact

that all data were collected from one institution. Moreover, the diabetic population was not further studied considering the severity of the DM itself and the antidiabetic treatment.

5. Conclusions

Although adherence to basic surgical principles and proper vein harvest site selection still remain the essential factors in preventing leg wound complications, Platelet-Rich Plasma treatment seems to reduce the surgical site infection in diabetic patients. To better investigate its role, larger prospectively RCTs are required. Moreover, PRP impact of the new less invasive techniques and the incidence of harvest site infection in high-risk patients should be investigated.

Abbreviations

CABG, Coronary artery bypass grafting; DM, Diabetes mellitus; GFs, growth factors; PRP, platelet-rich plasma; SV, saphenous vein; SVHI, saphenous vein harvest site infection.

Author contributions

FJ, RS, PM and GFS designed the research study. FJ, RS, AC, FV performed the research. MC and PM provided help and advice on methods. FJ, RS, AN analyzed the data. FJ, RS, AC, FV, PM, GFS wrote the manuscript. AN, FN, CC, MC revised the manuscript for significant intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

IRB approval: ER.FE.2018.15.A — 11th September 2018, University Magna Graecia of Catanzaro.

Conflict of interest

The authors declare no conflict of interest.

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