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ORIGINAL ARTICLE

Platelet-rich plasma inside the sternotomy wound reduces the incidence of sternal wound infections

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Abstract

Despite the large choice of wide-spectrum antibiotic therapy, deep sternal wound infection (DSWI) following cardiac surgery is a life-threatening complication worldwide. This study evaluated that the use of platelet-rich plasma (PRP) applied inside the sternotomy wound would reduce the effect of sternal wound infections, both superficial and deep. Between January 2007 and January 2012, 1093 consecutive patients underwent cardiac surgery through median sternotomy. Patients were divided into two groups. Group B, the study group, included those who received the PRP applied inside the sternotomy wound before closure. Group A, the control group, included patients who received a median sternotomy but without the application of PRP. Antibiotic prophylaxis remained unchanged across the study and between the two groups. Occurrence of DSWI was significantly higher in group A than in group B [10 of 671 (1·5%) versus 1 of 422 (0·20%), $P = 0{\cdot}043$]. Also, superficial sternal wound infections (SSWIs) were significantly higher in group A than in group B [19 of 671 (2·8%) versus 2 of 422 (0·5%), $P = 0{\cdot}006$]. The use of PRP can significantly reduce the occurrence of DSWI and SSWI in cardiac surgery.

Introduction

Deep sternal wound infection (DSWI) is a life-threatening complication after cardiac surgery. Although the advent of new strategies and the improvement of antibiotic treatment, DSWI still carries a high mortality rate (5–50%) and morbidity after cardiac surgery, leading to a prolonged hospital stay and increasing use of hospital resources (1). The incidence of post-sternotomy mediastinitis ranges between 0·2% and 8% (1). Many risk factors predisposing to DSWI have been identified (2,3). However, several risk factors are patient-related (such as age, gender, diabetes mellitus, chronic obstructive pulmonary disease, obesity and chronic kidney failure), whereas others are factors related to the surgical procedure or the hospital environment (such as prolonged preoperative stay, duration of surgery, use of bilateral internal mammary artery and resternotomy for bleeding) (2). Contemporary cardiac surgery population is generally older with multiple risk factors for DSWI than used to be in the past (4). Therapeutic approaches for the treatment of DSWI have changed several times over the last few years and the best treatment has not yet been clearly identified. Early surgical debridement, continuous specific antibiotic irrigation, vacuum-assisted closure

Key Messages

- platelet-rich plasma (PRP) promotes early and effective wound healing and reduces wound infections
- the negative pressure of chest cavities might aspirate germs from the skin site of infections to the bone, sutures and to vascular and cardiac structures, leading to catastrophic outcomes
- PRP could significantly reduce the incidence of both deep sternal wound infections and superficial sternal wound infections without any adverse reaction
- the cost of a preventive treatment with PRP is definitely lower than 1-day hospital stay

(VAC) therapy and reconstructive procedure have considerably reduced mortality in patients with DSWI (5–7). Nevertheless, preventive strategies to reduce the occurrence of DSWI can play an important role to reduce hospital costs and improve patient recovery. Platelet-rich plasma (PRP) has been proposed in the treatment of post-surgical infections to promote earlier wound healing (8). Topical application of autologous PRP is nowadays employed in several surgical specialities (such as plastic surgery, maxillofacial surgery and orthopaedic surgery) (8,9). There are reports of PRP application to successfully treat DSWI refractory to the conventional surgical treatment (10). However, results have been controversial and so far there are no clear evidences about the role of PRP in the prevention of DSWI (11–13). The aim of this study was to evaluate retrospectively whether the PRP application inside the sternotomy wound after sternal closure can prevent sternal wound infections after cardiac surgery, both deep (DSWI) and superficial (SSWI).

Patients and methods

Patients

Between January 2007 and January 2012, 1093 consecutive patients who underwent cardiac surgery through a full median sternotomy were enrolled in the study. From January 2007 to January 2010, 671 patients (group A) received standard closure, whereas from January 2010 to January 2012, 422 patients (group B) were technically closed in the same way except for the application of autologous PRP over the sternal closed edges before closure of subcutaneous tissue. The study protocol was approved by the Institution's Ethical Committee/Institutional Review Board. Informed consent was obtained from each patient enrolled in the study.

Study design and endpoints

Data were collected prospectively and analysed retrospectively. Primary endpoint was the occurrence of DSWI. The occurrence of SSWI was considered as secondary endpoint.

Exclusion criteria

Two hundred and twenty-seven patients admitted at our institution during the same time period were excluded from the study because of the following criteria: bleeding disorders, emergency/salvage surgery and off pump coronary artery bypass grafting (CABG). In 50 patients, it was not possible to provide any autologous gel preparation because of primary or drug-related severe clotting abnormalities.

Definitions

The diagnosis of DSWI is based on the guidelines of the Centers for Disease Control and Prevention (14) when patients developed one or more of the following criteria: (i) an organism is isolated from the culture of mediastinal tissue or fluid; (ii) evidence of mediastinitis is seen during sternal reoperation and (iii) one of the following: chest pain, sternal instability, temperature more than 38°C is present and there is either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of drainage of the mediastinal area (14). SSWI are all the infections involving skin and subcutaneous tissue, not reaching sternum, requiring local surgical intervention with regular wound care, accompanied by antibiotic therapy and/or VAC and/or wire removal (14).

PRP preparation

Eighteen millilitres of whole blood was taken from the patient's central line in the operating room during the induction of anaesthesia and injected into two tubes (RegenKit; RegenLab, Le Montsur-Lausanne, Switzerland). The tubes were centrifuged (Regen PRP system; RegenLab) at 3500 *g* for 8 minutes, according to the manufacturer's recommendations, to obtain whole blood separation into three layers: red blood cells, the buffy coat and the plasma supernatant. About 2 ml of plasma supernatant was removed with a syringe, leaving an amount of plasma equal to the desired final volume of the material (usually 2 ml or less) above the buffy coat. The volume extracted was transferred under a laminar flow hood into a Vacutainer blood test tube (without anticoagulants) and 0·5 ml of calcium chloride or calcium gluconate was added. The solution was then left to rest horizontally for about 10 minutes in order to activate the coagulation cascade and platelet. In the mean time, the initial tube was gently agitated to mix the buffy coat with the remaining supernatant. The mixture was removed with a long-needled syringe and transferred into a sterile Petri dish. The activated plasma from the other tube was added gradually into the culture plate. After gentle mixing, a red-coloured platelet gel was obtained (red because of the presence of erythrocytes in the buffy coat), reach in growth factors released from the alpha granules in the activated platelets. Platelet gel alone appears white because it is composed of platelets and plasma without the buffy coat. The whole procedure of PRP application was performed under a laminar flow hood in sterile conditions. PRP was applied on the sternum before the closure of subcutaneous tissue.

Preoperative and intraoperative management

All patients were shaved and had a preoperative bath with povidone-iodine soap solution on the night before or on the morning of the operation. The operative field was prepped with povidone-iodine solution. The patients were draped in a standard fashion. The skin was covered with an adhesive plastic sheet. All patients received full median sternotomy and a cardiac surgery procedure with extracorporeal circulation. Skin was incised with scalpel and electrocautery was used to open only presternal layers and pericardium. Bone wax (Braun Aesculap AG, Tuttlingen, Germany) was applied to seal sternal edges. Internal mammary artery was harvested as pedicled in situ grafts, using an electrocautery in coronary cases. Cardiopulmonary bypass and surgical techniques were standardised and did not change during the study period

among the groups. The same three senior surgeons performed the surgery in all cases. Heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of over 480 seconds. Systemic temperature was kept between 32°C and 34°C. Myocardial protection was always achieved with intermittent antigrade and retrograde hyperkalemic blood cardioplegia. After the respective cardiac procedure was performed, patients were rewarmed (37°C) and weaned from CBP. Protamine was administered at the end of the operation to fully reverse heparin. Sternal closure was achieved with eight stainless steel wires. Pre-sternal space was closed with two layers of reabsorbable sutures, and the skin was closed with intradermic 3/0 sutures in a standard fashion.

Postoperative management

All patients received a chest corset for 1 month postoperatively. Wound dressing was performed daily. In case of signs of wound infections, samples were promptly sent to microbiology. In both groups, postoperative antibiotic prophylaxis consisted of 400 mg/die i.v. Teicoplanin and 2×400 mg/die i.v. Ciprofloxacin until postoperative day 5. In patients with chronic kidney failure, antibiotic treatment was adjusted according to creatinine clearance. Whenever antibiotic therapy was continued over 1 week, Fluconazole (2×250 mg/die) was empirically added. In the case of isolation of germs or clinical signs of infection, the antibiotic treatment was modified based on its antibiogram. All patients were followed up at 1 week, 1 month and 6 and 12 months postoperatively in the outpatient clinic.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS Inc., Chicago, IL). Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as absolute numbers or percentages. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired *t*-test, whereas the Mann–Whitney *U*-test was used for those variables that were not normally distributed. Comparisons were considered significant if $P < 0{\cdot}05$.

Results

The two groups were homogeneous for preoperative and intraoperative risk factors (Tables 1 and 2).

In group B, only one (0·2%) patient developed DSWI compared with ten (1·5%) patients in control group A ($P = 0{\cdot}043$). Occurrence of SSWI was significantly lower in group A than in group B [19 of 671 (2·8%) versus 2 of 422 (0·5%), $P = 0{\cdot}006$). No adverse reactions were recorded in patients undergoing PRP treatment.

Discussion

Although the advent of minimally invasive techniques, median sternotomy is still the preferred access in cardiac surgery (15). However, DSWI remains a potentially life-threatening complication: the negative pressure of chest cavities might aspirate germs from the skin site of infections to the bone, sutures and to vascular and cardiac structures, leading to catastrophic outcomes.

Table 1 Preoperative risk factors

Risk factors	Group A 671 patients	Group B 422 patients	*P* value
Age > 70 years	378 (56·3%)	242 (57·5%)	0·742
Male sex	422 (62·8%)	272 (64·5%)	0·601
Smoking	65 (9·7%)	54 (12·8%)	0·108
Diabetes mellitus	263 (39·1%)	186 (44·1%)	0·110
Obesity (BMI > 30)	249 (37·1%)	164 (38·9%)	0·561
COPD	190 (28·3%)	130 (30·8%)	0·379
Chronic renal insufficiency	35 (5·2%)	16 (3·8%)	0·277
Corticosteroids	7 (1·0%)	6 (1·4%)	0·574
NYHA III and IV	288 (42·9%)	197 (46·7%)	0·223
Endocarditis	20 (3·0%)	8 (1·9%)	0·269
Antibiotic therapy up to operation	217 (32·3%)	124 (29·4%)	0·305
Pulmonary vascular disease	93 (13·9%)	71 (16·8%)	0·182
Cerebrovascular accident	65 (9·7%)	28 (6·6%)	0·078

CABG, coronary artery bypass graft; IMA, internal mammary artery; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Several risk factors, both patient-related and operation-related, have been identified in the setting of DSWI. However, factors linked to the patient's preoperative condition and to the complexity of the surgical procedure might not be eliminated (2,3).

Many efforts have been made over the last decade to find more effective strategies to treat DSWI and its associated complications. Several studies reported controversial results regarding the best approach to treat DSWI, including surgical debridement, continuous specific antibiotic irrigation, flap closure and the modern VAC therapy (5–7). Improvements in antibiotic therapies, biomedical technologies and reconstructive plastic surgery have significantly reduced mortality in patients with DSWI in the last decade (16–19).

In the early 1990s, the autologous PRP was proposed in the treatment of DSWI with good clinical results (8). During the inflammatory phase of tissue healing, activated platelet releases specific growth factors (GFs). Those include platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor and epithelial growth factor. Platelet GFs – together with other GF and cytokines – regulate the early migration of cells to the injury site, cell mitosis, angiogenesis, granulation tissue formation and bone regeneration (8).

Nowadays, PRP has been used in several surgical specialties (such as plastic surgery, maxillofacial surgery and orthopaedic surgery) to promote and speed-up tissue healing (8,9). Furthermore, Bielecki *et al.* showed that 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* (20). PRP application before wound closure in cardiac surgery has been proposed by several authors (21–24) with controversial results.

Table 2 Intraoperative risk factors

Risk factors	Group A 671 patients	Group B 422 patients	*P* value
Operation			
Isolated CABG	271 (40·4%)	187 (44·3%)	0·299
Single IMA	261	184	0·352
Double IMA	10	3	0·187
Isolated valvular operation	219 (32·6%)	111 (26·3%)	1·000
Other than isolated CABG isolated valvular operation	181 (27·0%)	124 (29·4%)	1·000
Operation time (incision to closure) > 300 minutes	101 (15·1%)	55 (13·0%)	0·353
Blood transfusion (number of patients)	305 (45·5%)	209 (49·5%)	0·189
Packed red blood cells (U)	2·74 ± 0·99	2·32 ± 1·09	0·094
Postoperative bleeding (ml)	630·42 ± 361·200	693·27 ± 333·802	0·721
Platelet ($n \times 10^3$ cells/mm^3) (48 hours postoperative)	125·32 ± 46·738	131·66 ± 49·738	0·153
Acute renal failure	21 (3·1%)	14 (3·3%)	0·864
Postoperative delirium	75 (11·2%)	52 (12·3%)	0·565
Respiratory failure (hypoxia)	22 (3·1%)	10 (2·4%)	0·386
Reopening	35 (5·2%)	15 (3·6%)	0·201
Hospital mortality	32 (4·8%)	16 (3·8%)	0·443

CABG, coronary artery bypass graft; IMA, internal mammary artery; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Some authors (21) studied the effects of PRP on the clinical outcome of patients undergoing CABG. The topical application of PRP on chest and leg wounds seemed to have a beneficial effect on pain, bruising and blood loss. Although prospective in design, both studies were underpowered to evaluate any treatment effects, because of the small number of patients enrolled. Conversely, Dörge *et al.* (22) concluded that the topical application of autologous PRP did not reduce the incidence of DSWI in cardiac surgery patients with high-risk profile. Similarly, Litmathe *et al.* (23) found no beneficial effect of PRP on wound healing in patients undergoing cardiac surgery. However, it can be argued that small number of patients enrolled in both trials might have influenced their conclusions. Khalafi *et al.* (24) in their retrospective analysis of a consecutive series of 1446 patients undergoing CABG found that the application of PRP significantly reduced the occurrence of chest and leg wound infection and discharge. However, this study included patients who had undergone endoscopic saphenous vein harvest with a relatively lower risk of mediastinal contamination from *Staphylococcus epidermidis*.

This study, although retrospective, proves that the routine use of PRP could significantly reduce the incidence of both DSWI and either SSWI without any adverse reaction to it. Moreover, the cost of a preventive treatment with PRP is definitely lower than that of 1-day hospital stay. Taking into account that one patient with mediastinitis may require at least 7 days of hospital stay and use of several devices for wound dressing (VAC therapy, antibiotic lavage, antibiotic instillation, costly antibiotic therapy and advanced wound dressings), the prevention of sternal wound infection with PRP is advantageous both in the cost analysis setting and to reduce further discomforts to the patient. In conclusion, regenerative medicine provided the surgeon a potential tool to help prevent dreadful complications such as sternal wound infections.

Limitations of the study

This study is a retrospective analysis with all the limitations of such observational studies. Moreover, it includes different frame times of surgical practice, although consecutively. However, over the years, surgeons, surgical techniques and surgical and clinical treatment protocols remain unchanged. Finally, excellent clinical results obtained with PRP application may raise ethical issues to perform a randomised trial.

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