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Topical application of autologous blood products during surgical closure following a coronary artery bypass graft☆

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Abstract

Objective: Surgical site wound complications are associated with increased cost, morbidity, and mortality following cardiothoracic surgery. Recent publications have advocated the application of autologous blood components as an adjunctive tool to surgical closure during various surgical procedures. The current study was intended to assess the safety and efficacy of the application of autologous platelet rich and platelet poor plasma to the sternal closure and saphenous vein harvest site during closure following a coronary artery bypass graft. **Patients and methods:** A retrospective analysis was performed on 1446 consecutive coronary artery bypass grafting procedures from two surgeons. A patient group receiving topical application of platelet rich and platelet poor plasma during closure of their chest and leg surgical incisions was compared to a patient population receiving standard treatment of care. Forty covariates were collected for each patient included in the study. Propensity scoring was used to adjust for baseline imbalance. Asymptotic logistic regression and exact statistical methods were used to determine the effect of the autologous blood application on infection and drainage of the sternal and leg wounds. **Results:** One thousand, one hundred and twenty-eight patients had sufficient data to be included in the final analysis, with 571 of these patients receiving the treatment compared to 557 control patients. No treatment-related adverse events were noted and the application process did not significantly affect the operative time. **Conclusion:** This retrospective analysis of a consecutive series of patients receiving a coronary artery bypass grafting procedure concluded that application of platelet rich and platelet poor plasma significantly reduced occurrences of chest wound infection, chest drainage, and leg wound drainage. This novel therapy merits further investigation.

Keywords: CABG; Mediastinitis; Platelet rich plasma

1. Introduction

Postoperative wound disturbances following cardiothoracic surgery, most notably surgical site infection, are associated with increased morbidity, mortality, and costs [1—2]. Occurrence of sternal infection (mediastinitis) has been reported in up to 20% of cases, however most studies report an incidence rate of 1—2% [3]. There is an overall wound disturbance rate of 8—10% for the chest incision following cardiothoracic surgery [4,5]. The leg incision for saphenous vein harvest can also be the site of significant postoperative wound complications. The trend toward endoscopic harvest of the saphenous vein has decreased complication rates, however endoscopic harvest of the saphenous vein still has an infection rate of 2—4% and an overall wound complication rate of 6—8% [6—8]. The high morbidity, mortality and costs associated with these postoperative wound disturbances make advances that can reduce postoperative wound complications attractive to the cardiothoracic surgeon.

The topical application of platelet rich plasma (PRP) and platelet poor plasma (PPP) in conjunction with a clotting agent (typically bovine thrombin) has been advocated for numerous indications [9—11]. The aim of PRP application is to accelerate the healing cascade through the action of elevated cytokine concentrations released during platelet degranulation. Platelet derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor, and transforming growth factor beta (TGF-β) are examples of cytokines shown to be present in concentrated levels in PRP [12]. It is hypothesized that these elevated cytokine levels induce an accelerated healing response at the site of application. Produced as a by-product during the centrifugation process used to

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produce the platelet rich product, PPP has been advocated as a tissue sealant for topical hemostasis during surgical closure [11].

Two recent publications have reported improved post-operative outcomes following the topical application of PRP and PPP in combination with bovine thrombin to the chest incision and vein harvest site during surgical closure [13–15]. Englert et al. demonstrated a trend towards reduction in chest incision pain, leg incision pain, and measurable bruising in a randomized, blinded study with 30 total patients [13]. Trowbridge et al. compared 382 patients receiving platelet rich plasma to a 948 patient non-randomized concurrent control group and a 929 patient historical control group [14]. This analysis demonstrated a significant reduction in the rate of superficial and deep chest wound infections in the platelet rich plasma group compared to both the concurrent and historical controls. These studies support the adjunctive use of autologous blood components in cardiothoracic procedures and warrant further investigation into the safety and efficacy of this technique.

The following study is a retrospective analysis of 1446 consecutive coronary artery bypass graft (CABG) procedures. A population receiving topical application of autologous platelet rich and platelet poor plasma to the sternal closure and saphenous vein harvest site was compared to a control group. Forty operative measures were compared between the two groups to assess the safety of the treatment and identify associations between the treatment and various outcome measures. Propensity scoring techniques were used to address bias between the treatment and control groups, thereby increasing the conclusive value of this analysis.

2. Materials and methods

2.1. Surgical method

The procedures included in this analysis were performed by two surgeons at six different surgery centers. All of the patients received preoperative intravenous antibiotics 30–60 min prior to the procedure. Open surgical methods were used on all median sternotomies, with a standard wiring technique used for sternal closure. An endoscopic approach was used for the saphenous vein harvests.

In the treatment population, 55 cc of whole blood was drawn just prior to surgery and mixed with 5 cc of anticoagulant citrate dextrose formula A. For patients requiring a saphenous vein harvest, an additional 55 cc blood was drawn in the same manner. The anticoagulated blood was then processed using GPS^{TM} II platelet concentrate system (Biomet Biologics, Warsaw, IN). Following a 15 min centrifugation cycle, 5–7 cc of PRP and 25–30 cc of PPP were obtained per 60 cc disposable. Topical bovine thrombin was reconstituted with 10% calcium chloride at a concentration of 1000 U/ml and applied at a 1:10 ratio with the desired blood component using a dual sprayer device (Micromedics, Eagan, MN). PRP was sprayed onto the exposed sternal edges and subcutaneous tissue of the chest wound, with PPP applied to each tissue layer during closure. At the leg site, PRP was applied along the course of the graft harvest site using a 30 cm long dual cannula (Micromedics).

2.2. Statistical analysis

All patients undergoing a CABG between October 2000 and September 2005 were included in the study. Forty operative covariates and records of any procedure-related adverse events were collected for each patient. Cases with severe morbidities (multi-organ failure, cancer, etc.) outside the scope of the cardiothoracic procedure were excluded from the final analysis to provide a more heterogeneous patient population.

The association of the application of ABP and outcomes (chest infection and drainage, leg infection and drainage) was examined using Fisher's exact test. In addition, propensity scoring was used to adjust for potential baseline imbalance. Due to the fact that propensity scoring requires a full compliment of covariates, missing covariates were replaced with the overall mean for that variable. Although this data management method artificially decreases the variance of a propensity score, it does not affect the rank of the score, which is what is used in the final analysis. Following reduction of selection bias, propensity scores were created for outcome measures using the observed covariates. Asymptotic model-based parameter estimates were used to estimate parameters for binary outcomes [20]. Normality of count outcomes was tested using the Shapiro-Walk statistic. These variables were also examined for a fit to a Poisson distribution. In the cases where normality was rejected, assessment of count variables used a Poisson regression model.

3. Results

A total of 1128 patients were included in the analysis. Autologous blood products (ABP) were applied in 571 patients and 557 patients served as controls (no ABP application). Data was collected for the ABP patients between February 2002 and September 2005 and for the control patients between October 2000 and February 2005. Forty covariates were included in the final analysis (Table 1). Analysis of leg infection and drainage rates used the subset of patients that had saphenous vein harvest (n_{ABP} = 560, $n_{ccontrol}$ = 456).

The ABP group had one incidence of sternal infection (0.18%) compared to 11 cases (1.98%) in the control group. There were 3 cases (0.53%) of notable drainage from the sternum in the ABP compared to 30 cases (5.39%) in the control group. For the leg vein harvest site, the ABP group had no reported infections and 61 (10.89%) incidences of excessive drainage compared to 3 (0.66%) surgical site infections and 212 (48.4%) cases of excessive leg drainage in the control group (Table 2). Following propensity scoring, it could be concluded that ABP application reduced the odds of chest wound infection by 93%, chest drainage by 96%, and leg wound drainage by 88% (Table 3). There was no significant difference for leg infection between groups as there were no leg infections (zero) in the ABP group.

4. Discussion

This analysis adequately addresses the question of safety of autologous blood component application during surgical

Table 1
Variables that were included in the chest wound analysis are shown for the ABP and control groups

Variable	ABP (N = 571)	Control (N = 557)	p-value
Patient age	62.37 ± 10.92	61.40 ± 11.17	NS
Smoker (yes)	308 (53.9%)	310 (55.7%)	NS
Preoperative creatine (μmol/l)	0.98 ± 0.45	0.96 ± 0.28	NS
Preoperative left ventricular ejection fraction	53.04 ± 10.02	54.53 ± 9.94	<0.05
Reoperation (yes)	9 (1.6%)	11 (2.0%)	NS
Prior sternal irradiation (yes)	8 (1.4%)	13 (2.3%)	NS
Diabetes			
Type I	139 (24.3%)	126 (22.6%)	NS
Type II	193 (33.8%)	202 (36.35)	NS
Preoperative dialysis (yes)	4 (0.7%)	6 (1.1%)	NS
History COPD (yes)	72 (12.7%)	79 (14.2%)	NS
Preoperative stay (days)	1.05 ± 1.48	1.23 ± 1.35	<0.05
History of hypertension	558 (97.7%)	533 (95.7%)	NS
Preoperative antibiotic (levaquin)	571 (100.0%)	546 (98.0%)	<0.05
Operative status			
Elective	71 (12.4%)	10 (1.8%)	<0.001
Urgent	459 (80.4%)	520 (93.4%)	
Emergent	26 (4.6%)	31 (5.6)	
Desperate	1 (0.2%)	0 (0.0%)	
Not recorded	0 (0.0%)	10 (1.8%)	
Operating surgeon (RSK)	431 (75.5%)	523 (93.9%)	<0.001
Procedure time (min)	203 ± 66.9	205.5 ± 85.0	NS
Bypass use (yes)	25 (4.4%)	160 (28.7%)	<0.001
Saphenous vein harvest (yes)	560 (98.0%)	456 (81.9%)	<0.001
Saphenous vein quantity (cm)	39.57 ± 19.20	39.58 ± 17.38	NS
Mammary vein harvest (yes)	552 (96.6%)	463 (83.1%)	<0.001
Intraoperative transfusion (units)			
Whole blood	1.26 ± 1.18	0.81 ± 0.67	<0.001
Packed red blood cells	0.38 ± 0.69	0.26 ± 0.49	<0.01
Plasma	0.07 ± 0.29	0.11 ± 0.36	NS
Other	0.03 ± 0.19	0.0	<0.05
Postoperative stay (days)	5.98 ± 1.28	6.42 ± 2.00	<0.001
ICU stay (days)	2.15 ± 0.51	2.34 ± 1.33	<0.05
Postoperative ventilation (yes)	168 (29.4%)	491 (88.2%)	<0.001
Postoperative dialysis (yes)	14 (2.5%)	23 (4.1%)	NS
Postoperative wound care protocol (normal care)	570 (99.8%)	552 (99.1%)	NS
Postoperative antibiotics (days)	3.47 ± 1.24	4.27 ± 2.70	<0.001
Postoperative antibiotics (levaquin)	560 (98.0%)	529 (95.0%)	<0.01
Postoperative transfusion (units)			
Whole blood	0.01 ± 0.14	0.01 ± 0.07	NS
Packed red blood cells	0.35 ± 0.71	0.30 ± 0.72	NS
Plasma	0.09 ± 0.42	0.06 ± 0.35	NS
Other	0.0053 ± 0.07	0.0054 ± 0.13	NS
Hematocrit (%)			
Preoperative	40.46 ± 3.79	41.37 ± 2.06	<0.001
Postoperative	35.21 ± 3.21	35.96 ± 2.74	<0.001
Day 1	35.06 ± 3.24	36.16 ± 2.88	<0.001
Hemoglobin (g%)			
Preoperative	13.95 ± 1.12	14.55 ± 0.88	<0.001
Postoperative	12.31 ± 1.17	12.35 ± 1.22	NS
Day 1	12.25 ± 1.05	12.52 ± 1.26	<0.001

For continuous variables, the mean and standard deviations are shown. For categorical variables, the number of observations and percentage of the total group affected are shown. A p-value less than 0.05 was considered significant.

closure following a CABG procedure. Similar to previous reports, there were no treatment-related adverse events reported in the data collected. In addition, the application of ABP did not significantly alter the average length of the procedure. The initial analysis performed on this data using Fisher's exact test demonstrated a significant effect for ABP application on chest infection rate, chest drainage rate and leg drainage rate when ABP application was implemented during surgical closure (Table 2). The strength of these conclusions was limited by a number of differences observed between the two groups. Even considering that some differences between groups can be expected in observational studies such as the current one due to a lack of controlled enrollment and randomization [16], there were notable differences in the two patient populations. Although the dates of procedure for the two groups overlapped, the

Table 2
Analysis of outcome variables prior to adjustment for selection bias

Variable	ABP	Control	*p*-value (Fisher's exact)	*p*-value (logistic regression)
Chest infection (yes)	1 (0.18%)	11 (1.98%)	<0.001	<0.01
Chest drainage (yes)	3 (0.53%)	30 (5.39%)	<0.001	<0.001
Leg infection (yes)[a]	0 (0%)	3 (0.66%)	NS	NS
Leg drainage (yes)[a]	61 (10.89%)	212 (46.49%)	<0.001	<0.001

The *p*-values were calculated using Fisher's exact and logistic regression ($\alpha = 0.05$). The *p*-values are not significant for leg infection as there were no leg infections (zero) in the ABP group.
[a] Analyzed using leg wound subset.

majority of the control population preceded the treatment population. Adjustments to the surgical procedure exclusive of the application of ABP are evident during this time period. Specific examples from this analysis are a significant increase in the number of intraoperative blood transfusions and a significant reduction in the rate of bypass usage over the study period. The potential effect to outcome measures of these other treatment differences reduces the ability to make conclusions regarding the application of ABP. For this reason, propensity scoring was implemented in the analysis. Propensity analysis is a statistical technique used to resolve treatment differences between groups in observational studies [17]. Propensity scoring successfully resolved the treatment differences in the current analysis and allows the current work to provide for more reliable conclusions related to the application of ABP. It was determined that ABP application reduced the odds of chest infection by 93%, chest drainage by 96% and leg wound drainage by 88% (Table 3).

The theoretical rational for applying ABP, in particular PRP, is an expedited healing response at the site of application. This theory has been supported with two recent publications showing an enhanced healing response in healthy individuals when PRP was applied to biopsy sites at the inner thigh [18] and oral mucosa [19]. It is a reasonable proposition that for surgical wounds, an expedited healing response could result in a reduction in the chance of postoperative wound complications [14]. An expedited healing response could be the underlying reason that the current work, similar to previous reports of the clinical application of PRP in cardiovascular surgical closure, noted a reduction in postoperative wound complications [13,14].

The effect of PRP application on chest infection rates seen in the current analysis is of particular interest as infection is a considerably more traumatic complication than wound drainage. The device used to produce the autologous blood products in this study produces a 8-fold increase in platelet concentration as well as a 5.4-fold increase in white blood cell in the PRP compared to the patient's whole blood [12]. Activated platelet concentrate has been promoted as a potential mode of regulating the immune response, with platelet α-granules known to contain a family of cationic peptides that play a substantial role in antimicrobial host defense [20,21]. A recent publication investigated the antibacterial effect of PRP using the Kirby-Bauer disc-diffusion method, a standard *in vitro* assay for antimicrobial activity. In this study, PRP produced using the same system as the current study demonstrated antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* [22]. The potential for PRP as a prophylactic tool to reduce postoperative wound complications, in particular the risk of surgical site infection, warrants further study.

This study has several advantages over prior publications investigating the application of ABP during cardiothoracic procedures. Although prospective in design, the Englert et al. study was underpowered to determine any treatment effects due to the fact that only 30 patients were enrolled. Similar to the current study, Trowbridge et al. compared a treatment group to a retrospective control and in addition compared the treatment group to a non-randomized concurrent group. In this work, several devices and techniques were used to produce the ABP that was applied. Prior work has demonstrated that using different methods to produce PRP will result in outputs with significantly different compositions [23]. Including several different methods of producing PRP in a clinical study will result in an inconsistent treatment in the study population. In the current study a single device, that has been demonstrated to produce a consistent PRP output [12], was used for all of the cases included in the study population. Although prospective randomized studies remain the gold standard for clinical investigations, the use of propensity scoring raises the reliability of the conclusions made with the current analysis [24]. These preliminary findings should be confirmed with prospective randomized clinical trials. For the 1128 patients that were included in the current study, the use of ABP application during surgical closure following CABG was seen to be a safe technique that significantly reduced the chances for postoperative infection of the sternum and postoperative wound drainage of the chest and leg incisions.

Table 3
Analysis of outcome variables following adjustment for treatment bias

Variable	Adjusted parameter estimates (95% CI)	*p*-value
Chest infection (yes)[a]	0.0743 (0.0032–1.7535)	<0.05
Chest drainage (yes)[a]	0.0424 (0.0085–0.2104)	<0.001
Leg infection (yes)[a,b]	ne	ne
Leg drainage (yes)[a,b]	0.1196 (0.0714–0.2004)	<0.001

Adjusted parameter estimates (exponentiated odds ratios) and the respective 95% CI intervals are shown as well as the adjusted *p*-values ($\alpha = 0.05$). ne: non-estimable due to sparcity.
[a] Asymptotic model-based parameter estimates, parameter estimates and 95% confidence intervals are shown; odds ratios are the exponentiation of these parameter estimates.
[b] Analyzed using leg wound subset.

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