Annals of Surgery: International
Received: Feb 06, 2016, Accepted: Mar 23, 2016, Published: Mar 27, 2016
Ann Surg Int, Volume 2, Issue 2
http://crescopublications.org/pdf/asi/ASI-2-011.pdf
Article Number: ASI-2-011

Research Article Open Access

Autologous Platelet Rich Plasma and Concentrated Platelet Poor Plasma are Safe in Patients Requiring Lobectomies but do not reduce the Duration of Air Leak: A Randomized Controlled Trial

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Citation: Terry Zwiep, Robert Humphrey, Dalilah Fortin, Richard I. Inculet and Richard A. Malthaner (2016) Autologous Platelet Rich Plasma and Concentrated Platelet Poor Plasma are Safe in Patients Requiring Lobectomies but do not reduce the Duration of Air Leak: A Randomized Controlled Trial. Ann SurgInt 2: 011.

Abstract

Objective
To determine whether the administration of platelet rich plasma (PRP) and concentrated platelet poor plasma (cPPP) could reduce the duration of post-operative air leaks after lobectomy for lung tumours.

Methods
102 patients were randomized to receive PRP and cPPP, and 96 patients were randomized to the control arm after standard lobectomies. Data were analyzed on an intention-to-treat basis. The primary outcome was duration of air leak. Secondary outcomes included: incidence of air leak, prolonged air leak, total chest drainage at 48 hours post-operatively, time to removal of chest tubes, complications, length of hospital stay, and 30-day mortality.

Results
The median duration of air leak was not significantly different (86h vs. 84h, p=0.719) for PRP and cPPP vs. control. Prolonged air leak was similar with the percent stopped at 7 days (79% vs. 77%), 48h mean chest tube drainage was similar (1174mL vs. 1198mL, p=0.698), the median time to removal of chest tube was similar (117h vs. 120h, p=0.930), and complications were similar (36% vs. 37%, p=0.979) for the PRP and cPPP group vs. control, respectively. Length of hospital stay was less in the PRP and cPPP group (5.4d vs. 6.2d, p=0.275), but not statistically significant. Three mortalities occurred (1 in PRP and cPPP and 2 in the control group).

Conclusion
The application of autologous platelet rich plasma and concentrated platelet poor plasma is safe in patients requiring lobectomies but does not reduce the duration of air leak.

Keywords: Air leak; Fibrin sealant; Lobectomy; Lung surgery; Randomized trial

Abbreviations: FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; Q1 = First Quartile; Q3 = Third Quartile; SD = Standard Deviation

Background

Air-leaks are the most common complication after pulmonary resection [1]. The average duration of post-operative air leak (POAL) has been reported to be 78 hours, and prolonged air leaks (> 7 days) occur in 8% to 26% of cases [1 - 3]. POALs result in morbidity (e.g., empyema, prolonged need for chest drainage, and delayed hospital discharge), and rarely result in mortality [4]. POALs delay hospital discharge by 5 to 13 days [3]. Strategies to decrease the incidence and duration of these leaks include: chest drainage (water seal and/or suction); surgical sealants; pleural tenting; and, pneumoperitoneum [1].Repeat surgical intervention is required in cases of non-resolving air leaks despite conservative measures [1, 4].

Surgical sealant products have been developed to promote hemostasis and atraumatic tissue union. Human derived products and synthetic sealants have been shown to have clinical applications in Thoracic surgery [5]. A Cochrane systematic review of sixteen randomized controlled trials (1642 patients) was performed by Belda-Sanchisand colleagues to determine the effectiveness of surgical sealants post-lobectomy compared to standard chest closure alone [6]. The primary outcome measured was postoperative hospital stay. There were thirteen trials that showed a difference between treatment and control groups, with six trials showing significant differences. A significant time to chest tube removal was demonstrated in three trials, and three trials also showed a decrease in length of hospital stay. Persistent air leaks occurred significantly less in the treatment groups in two trials. The authors concluded that, "surgical sealants have some beneficial effect in reducing postoperative air leaks, but systematic use of surgical sealants in clinical practice cannot be recommended at the moment" [6]. Further, the review highlighted the need for more randomized controlled trials to better define the use of surgical sealants.

A recent meta-analysis identified thirteen trials in which glues, patches, or buttresses were used to prevent prolonged POALs [7].The buttresses used were made from bovine pericardium. Overall, the length of prolonged POALs was decreased by 7 days in the groups which received the glues, patches, or buttresses. This was a significant difference, however, there was a publication bias identified by this meta-analysis [7].

From the published studies, it can be seen that mixed results have been obtained with the use of surgical sealants following pulmonary resection. Most of the products are based on fibrin or synthetic sealants. A thrombin-fibrinogen patch has also been developed. These include Vivostat®, CoSeal®, ProGel®, and TachoSil®, among others [8-11].Results from the trials which have studied these products, have shown reductions in duration of air leak and length of hospital stay with some of the sealants. The uses of two products which have a theoretical benefit to improve tissue healing and union were studied in the current trial.

The critical role of platelets in hemostasis and tissue healing provides the rationale for platelet rich plasma (PRP) [12, 13]. Concentrated platelet-poor plasma (cPPP) on the other hand, contains concentrates of fibrin and growth factors and has been shown to function as a fibrin sealant [12, 13]. When used together, PRP and cPPP result in an increased rate of hard and soft tissue wound healing, and a decrease in pain, blood loss and infection rate [12, 13]. Preparation requires 65mL of autologous blood which is centrifuged and concentrated to yield 6mL of PRP and 15mL of cPPP [12, 13]. Since PRP and cPPP are derived from the patient's own blood, there is no risk of infectious disease transmission or immune reaction [14]. Further, no increase in infection rate at the site of application has been found [14]. The objective of this study was to determine whether the administration of platelet-rich and concentrated platelet-poor plasma could reduce the duration of post-operative air leak after lobectomy for lung tumours.

Methods

Patients

This prospective, randomized, double-blinded controlled trial was conducted between January 2008 and August 2010. A total of 206 patients were enrolled. Adult patients undergoing lobectomy for lung tumours at London Health Sciences Centre (LHSC) were eligible for enrollment. The trial was registered with ClinicalTrials.gov with the identifier: NCT00665912.

Ethics approval was obtained through the Health Sciences Research Ethics Board (HSREB) at the Western University, Ontario, Canada. Consent was obtained by the operating surgeon or his/her delegate prior to lobectomy. Lobectomy via thoracotomy or video assisted thoracoscopy requiring conversion was eligible for inclusion. Lobectomies that incorporated a wedge of adjacent lobe(s) were also eligible. Exclusion criteria included the need for pneumonectomy, sleeve lobectomy, determination of unresectability (prior to the initiation of lobectomy), completed VATS lobectomy, and wedge resection alone.

Randomization

Patients were randomized to undergo standard lobectomy (control group), or standard lobectomy plus administration of PRP and cPPP (intervention group). Randomization was concealed and occurred via a computerized random number generator using sequentially numbered, pre-sealed opaque envelopes. For patients satisfying inclusion criteria, randomization occurred by opening the next sequentially numbered envelope, at the time of operation, once the tumour had been deemed resectable. The advantage of this approach is that it limited the number of patients included that were deemed unresectable at the time of operation. All patients were analyzed using the intention-to-treat principle.

Surgical Technique

The surgical technique was driven by the consulting surgeon. Individual pulmonary vessels were isolated, then either stapled, ligated, or clipped depending on the size. The bronchi were transected and then closed with sutures. Incomplete fissures were dissected until the interlobar artery was isolated and then divided using staplers. Any air leaks detected after the lung was removed were sutured at the discretion of the attending surgeon prior to the administration of any PRP and cPPP.

PRP and cPPP Preparation and Administration

A blood sample (65ml) was drawn only from patients randomized to the intervention group. Blood samples were drawn by the anesthesia team and concealed in an opaque container. In order to maintain blinding of the surgical team, the anesthesia team pretended to draw blood from patients in the control group, and placed the empty syringe into the same opaque container.

Blood drawn from patients in the intervention group was prepared outside of the operating room. The surgical team remained blinded while the sample was being prepared. All 3 surgeons employed a standardized approach to administration of the PRP and cPPP samples. After removing the lobe, the chest cavity was filled with warmed normal saline and the remaining lung tissue was inflated to a minimum pressure of $+30cmH_2O$ in order to detect an intra-operative air leak. The fluid was then suctioned off and the lung was partially deflated. The surgeon remained blinded to the allocation arm until it was time to apply the PRP. At this point if the patient was randomized to the intervention arm, a standard amount of PRP prepared using the GPS® System followed by cPPP using the Plasmax® Plasma Concentrator was then administered to sites of parenchymal dissection [15,16]. Ventilation was suspended for a period of time to allow the product to set, followed by standard chest closure. Each patient in the experimental arm received the same amount of PRP solution. Those in the control group underwent standard closure alone without the application of any vehicle. All patients had two chest tubes inserted in the operating room, connected to a water seal drainage system, and placed at $-20cm\ H_20$ of suction for a minimum of 24 hours. The grading of the degree of air leak in the operating room was considered subjective and therefore not recorded. Patients received routine post-operative chest tube care. The discontinuance of pleural suction was done at the discretion of the consulting surgeon. The tubes were removed in the morning after the air leak ceased.

Primary and Secondary Outcomes

The primary outcome of the study was duration of air leak. Air leak was defined as bubbling in the chest drainage canister after 2 forced coughs followed by a forced expiratory effort. Secondary outcomes included: incidence of air leak; prolonged air leak; total chest drainage at 48 hours post-operatively; time to removal of chest tubes; complications (specifically incidence of infection and hemorrhage requiring transfusion); length of hospital stay (days); and 30-day mortality.

Air leak was chosen as the primary outcome for a number of reasons. Air leaks are easily identifiable and thus were readily assessed by study nurses. The detection of air leak was minimally dependent on patient effort. Duration of air leaks is correlated with duration of chest tube drainage, which results in pain and risk of empyema (chest cavity infection). Air leaks also prolong hospital stay, and may require re-operation if closure does not occur. It was therefore hypothesized that reducing the duration of air leaks, through the use of PRP and cPPP, would have multiple benefits including: sooner chest tube removal; reduced post-operative pain; fewer empyemas; and, reduced hospital stay.

Outcome Assessment

Trained and blinded assessors assessed each patient. The nurses on the Thoracic Surgical Ward were trained as air leak assessors via an information session. Each nurse had the opportunity to practice air leak assessment prior to commencing the study. Air leaks and other outcomes were recorded by these nurses in the usual way on the patient's post-operative flow sheet. As well, the principle investigators assessed chest radiographs to detect pneumothorax (indicative of air leak). Patients were assessed at the following time periods: every four hours for the duration of post-operative hospital stay, at the first post-operative visit (4-6 weeks post-operation), and for patients discharged with a prolonged air leak, assessments occurred weekly until the cessation of the leak.

There were no additional visits or assessments for the purpose of this study. Apart from the PRP and cPPP, both groups received the same care.

Sample Size

The last 51 consecutive lobectomies performed at London Health Sciences Centre were retrospectively reviewed to determine the air leak duration at this institution. The median duration of air leaks was 71.0 hours with a standard deviation of 144.5 hours. The current study was powered to show a reduction of 24 hours in air leak duration. Twenty four hours was chosen as the minimal clinically significant change as this would enable the majority of patients to have chest tubes removed and be discharged from hospital one day earlier. Assuming exponential air leak duration and that the primary comparison will be made using a log-rank test, 93 patients per group were required to detect a reduction of 24 hours in the median air leak duration at the 0.05 level of significance with 80% power. A conservative estimate of 10% loss to follow-up was assumed. Therefore, 102 subjects per group were required, for a total of 204.

Statistical analysis

Descriptive between-group comparisons of demographic and baseline characteristics were size calculated. These characteristics included: age; sex; past medical history; side and type of surgery; size and type of tumour. Where there were clinically important between-group differences, covariate adjustment was considered for between-group comparisons of study endpoints.

Air leak duration for the two treatment groups was estimated using the Kaplan-Meier technique and between-group comparisons were made using the log-rank statistic. Time to removal of chest tubes and days to discharge were analyzed in a similar manner. Between-group comparisons of categorical secondary outcomes, including incidence of air leak, incidence of prolonged air leak, adverse events and 30-day mortality, were made using chi-square tests or, where expected cell sizes were less than five, Fisher's exact test. Between-group comparisons of continuous outcomes, including total chest drainage at 24 hours were made using unpaired t-tests. Skewed data such as length of hospital stay was analyzed using the non-parametric Mann Whitney U test.

A planned interim analysis was performed once data had been collected for one-half of the planned sample size (102 subjects). The primary outcome (air leak duration) was not significant at the 0.001 level, according to the Peto-Haybittle stopping rule [17]. All analyses were conducted using SAS 9.3 [SAS Institute Inc., Cary, NC, USA.]

Results

A total of 198 patients were included in the analysis: 102 (52%) in the PRP/cPPPgroup and 96 (48%) in the control group. The mean age was 65.9 (Standard Deviation (SD) 12.1, range 24-88) in the PRP/cPPP group, and 67.8 (SD 9.9, range 33-84) in the control group. The groups were similar with regards to demographics, pulmonary function tests, and procedures (Table 1). Most patients underwent a standard open lobectomy. Eight patients were excluded due to having an ineligible procedure, no intervention, or repeat procedure (Figure 1). Three patients died and were censored at the time of death.

Figure 1: Trial design flowchart.

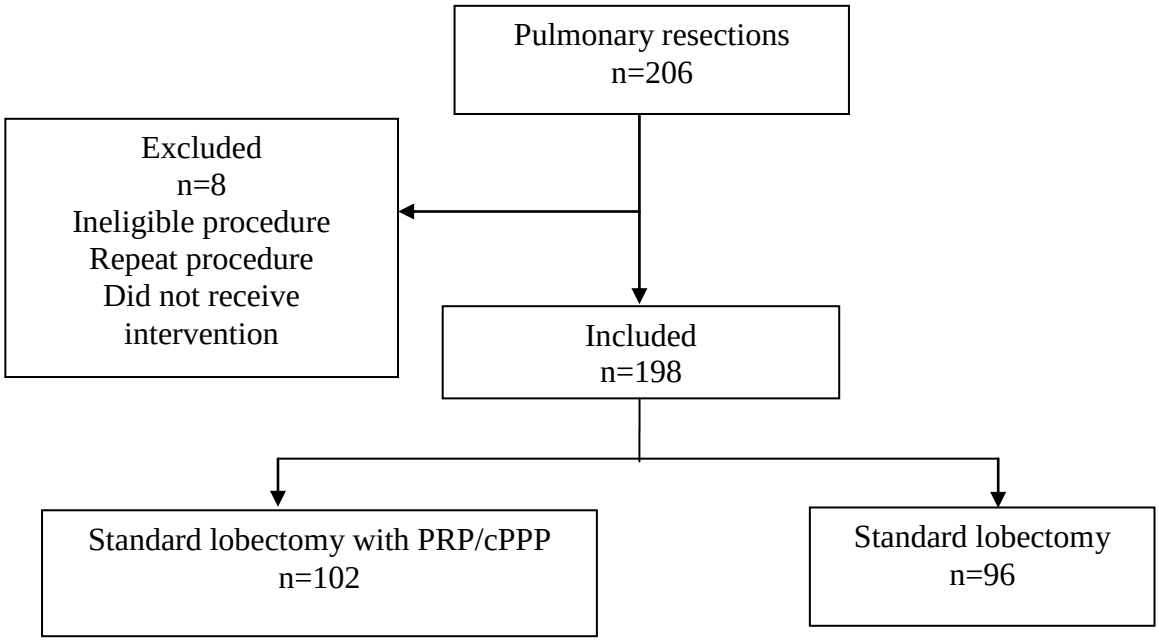

Table 1: Clinical and Demographic Characteristics of the Patients.

Variable		**PRP/cPPP Group (n=102)**	**Control Group (n=96)**
Age	Mean (SD)	65.9 (12.1)	67.8 (9.9)
	Min - Max	24 - 88	33 – 84
Gender	Mean (%)	48 (47.1%)	47 (49.0%)
Neoadjuvant Treatment	N (%)	8 (7.8%)	5 (5.2%)
FEV1	Mean (SD)	2.13 (0.73)	2.18 (0.79)
%Predicted FEV1	Mean (SD)	84.2 (20.2)	86.7 (20.7)
FVC	Mean (SD)	3.20 (0.91)	3.26 (1.02)
%Predicted FVC	Mean (SD)	100.6 (19.7)	100.1 (18.9)
FEV1/FVC	Mean (SD)	66.9 (12.2)	66.7 (12.2)
Procedure	Open Lobectomy	79 (77.5%)	80 (83.3%)
	Open Lobectomy + Wedge	11 (10.8%)	8 (8.3%)
	VATS to Open Lobectomy	11 (10.8%)	8 (8.3%)
	VATS to Open Lobectomy + Wedge	1 (1.0%)	0 (0.0%)

The primary outcome of the study was time to air leak cessation. The difference in air leak duration between the PRP/cPPP and the control group was not statistically significant (median (First Quartile (Q1), Third Quartile (Q3)) of 86 (50.5, 123.0) h vs. 84 (46.5, 146.5) h, p=0.719, Table 2). The groups had a similar percentage of patients who no longer had an air leak at 48, 96, and 168 hours. There were no late pneumothoraxes following chest tube removal.

None of the between-group differences for secondary outcomes were statistically significant (Table 2). For prolonged air leak the percent stopped at 7 days was 79.4% and. 76.8%, 48h mean chest tube drainage was1173.5 (SD 466.2) mL and 1198.1 (SD 422.2) mL (p=0.698), median (Q1, Q3) time to removal of chest tube was 117 (89, 156)h and 120 (89,184)h (p=0.930), and complications were 36.3% and 36.5% (p=0.979) in the for the PRP/cPPP group and control groups, respectively (Table 3). Median (Q1, Q3) length of hospital stay was less in the PRP/cPPP group (5.4 (4.3, 6.5) dvs. 6.2 (4.4, 8.4)d), but not statistically significant (p=0.275). Three mortalities occurred (1 in PRP/cPPP and 2 in the control group).

Table 2: Primary Outcome – Time to Air Leak Cessation

Outcome		**PRP/cPPP Group (n=102)**	**Control Group (n=96)**	**p value**
Time to Air Leak Cessation (hours)				
	Median (Q1, Q3)	86.0 (50.5, 123.0)	84.0 (46.5, 146.5)	0.719
	% stoppage at 48 hours	22.6	25.0	
	% stoppage at 96 hours	58.8	56.7	
	% stoppage at 168 hours	79.4	76.8	
48 Hour Drainage Mean (SD)		1173.5 (466.2)	1198.1 (422.2)	0.698
Chest tube removal (hours)				
	Median (Q1, Q3)	117.0 (89.0, 156.0)	120.0 (89.0, 184.0)	0.930
	% removed at 48 hours	1.0	0.0	>0.999
	% removed at 96 hours	37.3	33.7	0.601
	% removed at 168 hours	78.4	71.6	0.266
Discharge (days)				
	Median (Q1, Q3)	5.4 (4.3, 6.5)	6.2 (4.4, 8.4)	0.275
	Discharged at Day 5	43.1	34.7	0.277
	Discharged at Day 7	78.4	66.3	0.057
	Discharged at Day 10	82.4	82.1	0.964

Table 3: Complications

Complication	PRP/cPPP Group (n=102)	Control Group (n=96)	p value
Any	37 (36.3%)	35 (36.5%)	.979
Congestive heart failure	0 (0.0%)	1 (1.0%)	.485
Urinary tract infection	3 (2.9%)	1 (1.0%)	.622
Cardiac arrhythmia	12 (11.8%)	16 (16.7%)	.323
Cardiac ischemia	2 (2.0%)	2 (2.1%)	>.999
Confusion	4 (3.9%)	4 (4.2%)	>.999
Deceased	1 (1.0%)	2 (2.1%)	.612
Diabetes insipidus	1 (1.0%)	0 (0.0%)	>.999
Empyema	0 (0.0%)	2 (2.1%)	.234
Ischemic Bowel	1 (1.0%)	0 (0.0%)	>.999
Left Horner's Syndrome	0 (0.0%)	1 (1.0%)	.485
Pneumonia	2 (2.0%)	2 (2.1%)	>.999
Pneumothorax following chest tube removal	6 (5.9%)	4 (4.2%)	.749
Post-op atelectasis	1 (1.0%)	0 (0.0%)	>.999
Post-op bleed	5 (4.9%)	2 (2.1%)	.446
Renal Failure	2 (2.0%)	1 (1.0%)	>.999
Respiratory Failure	3 (2.9%)	4 (4.2%)	.715
Stroke	1 (1.0%)	0 (0.0%)	>.999
Thrombocytopenia	1 (1.0%)	0 (0.0%)	>.999
Urinary Retention	0 (0.0%)	1 (1.0%)	.485
Wound Infection	1 (1.0%)	1 (1.0%)	>.999

Discussion

Post-operative air leaks (POALs) are a common and significant complication following pulmonary resection [3]. POALs lead to further complications and longer hospital stays. Through the prevention of POALs, overall complications and costs should be reduced. Strategies to reduce the occurrence of POALs have been tried in the past and most commonly make use of fibrin sealants. As stated in the recent Cochrane Review, more studies need to be done to be able to recommend the use of surgical sealants in thoracic surgery [6].This study made use of both PRP and cPPP with the goal of reducing the duration of POALs.

The PRP component provides platelets which are beneficial in hemostasis and tissue healing. The cPPP contains fibrin and growth factors which has been shown to function effectively as a fibrin sealant. Together, it was hypothesized that they would be more effective than fibrin sealants alone. As these products are derived from the patient's own blood at the time of surgery, it was also thought that they would be safe to use with little risk of allergic reactions that can be seen with synthetic products. These autologous products also do not carry the same risk of blood-borne infections which other blood products may.

This randomized, prospective trial evaluated the use of PRP/cPPP in reducing the duration of air leaks following pulmonary resection. The trial was adequately powered, randomization was concealed, and the patients, surgeons (until the point of application), and assessors were blinded. This study did not identify a significant reduction in duration of POALs in patients treated with PRP/cPPP undergoing a standard lobectomy, versus those who had a standard lobectomy alone.The secondary endpoints of this study demonstrated that PRP/cPPP is safe to use, as complication rates were not different between the two groups. There was also a trend toward earlier hospital discharge in the PRP/cPPPgroup; however, this difference was not significant.

This study could have been improved by expanding the patient population to include multiple centers and including longer follow up to account for any late side effects that may occur from the use of PRP/cPPP.Another limitation of the study is the delay in publication. This was an unfunded trial that relied to the voluntary support of the surgeons, and our clinical and research staff. Ideally, we would have collected additional data such has a screening log of potential patients, the number of patients refusing enrollment, the degree of intraoperative air leaks, cost, and quality of life, but the numerous changes in personal and responsibilities prolonged the process. Never the less, this trial has added to the ongoing debate about the use of surgical sealants following pulmonary resection. The results would not favour the routine use of these products.

Conclusions

The findings from this study indicate that there is no advantage in the application of autologous platelet rich plasma and concentrated platelet poor plasma after pulmonary resection in the reduction of post-operative air leaks versus standard closure alone. PRP/cPPP does appear to be safe to use.

Acknowledgement:

Larry Stitt MSc from LW Stitt Statistical Services for support in the analysis of the data.

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