Original Article

Platelet-Rich Plasmapheresis: A Meta-Analysis of Clinical Outcomes and Costs

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Keywords: platelet-rich plasmapheresis, sequestration, cardiopulmonary bypass, outcomes, economics, meta-analysis

Presented at the American Society of Extra-Corporeal Technology 35th International Conference, April 3-6, 1997, Phoenix, Arizona

ABSTRACT

Platelet-rich plasmapheresis (PRP) just prior to cardiopulmonary bypass (CPB) surgery is used to improve post CPB hemostasis and to minimize the risks associated with exposure to allogeneic blood and its components.

Meta-analysis examines evidence of PRP's impact on clinical outcomes by integrating the results across published research studies. Data on clinical outcomes was collected from 20 published studies. These outcomes, DRG payment rates, and current national average costs were used to examine the impact of PRP on costs.

This study provides evidence that the use of PRP results in improved clinical outcomes when compared to the identical control groups not receiving PRP. These improved clinical outcomes result in subsequent lower costs per patient in the PRP groups. All clinical outcomes analyzed were improved: blood product usage, length of stay, intensive care stay, time to extubation, incidence of cardiovascular accident, and incidence of reoperation. The most striking differences occur in use of all blood products, particularly packed red blood cells.

This study provides an example of how initial expenditure on technology used during CPB results in overall cost savings. Estimated cost savings range from $2,505.00 to $4,209.00. More importantly, patients benefit from improved clinical outcomes.

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INTRODUCTION

The current healthcare climate has evolved to include unprecedented pressure directed at clinicians to limit resource utilization and to eliminate as much waste as possible (1). This pressure has, in part, caused healthcare providers to examine outcomes of treatment where cost savings might be generated. Health benefits that patients receive must also be considered when examining these outcomes and the cost savings that can be generated in these areas.

The rapid evolution in available technologies has occurred simultaneously with changes in clinical environments, patients' demands, administrative systems, and the health insurance industry. New health technologies often gain widespread use without the benefit of systematic evaluation of their costs and benefits (2). The clinical outcomes and costs of alternative technological interventions are both necessary for effective clinical decision making today. When alternative technological devices are available for treatment of the same condition in the same patient, the differences in clinical outcomes and costs are more critical. Healthcare reform must result in treatment choices that cost control without jeopardizing the quality of patient care.

Coronary artery bypass is one of the most common surgeries performed in the United States today. Ten billion dollars was spent on open heart procedures in 1992 in the United States (3). The American Heart Association (4) reports that in 1993 over 485,000 CPB procedures were performed in the United States. Estimates for the costs of cardiovascular disease for 1996 are expected to reach 151.1 billion dollars (4).

Blood management is an integral part of CPB, with post CPB hemostasis a focus of concern. Healthcare providers attempt to minimize the patient's exposure to allogeneic blood or its components. While the appearance of HIV in the allogenic blood supply has caused healthcare providers to be more vigilant in their approach to blood conservation, numerous other problems may occur with allogenic transfusion. Some other adverse clinical outcomes that must be considered are transfusion reactions and transmission of diseases in addition to HIV. In addition, platelet demand has increased dramatically while donation of blood has decreased. Platelet dysfunction is an important factor in postoperative bleeding after CPB. Harvesting a high yield of concentrated platelet- and leukocyte-rich plasma was developed with the goal of attenuating some of the deleterious effects of cardiopulmonary bypass (5). Protection of platelets and leukocytes through plasmapheresis results in reduced postoperative bleeding (5).

OUTCOMES AND COSTS

Outcomes management has been described as a way to help patients, payers, and providers make rational medical care-related choices based on better insight into the effect of these choices on the patient's life (6). It is important that outcomes examined are actually clinical endpoints and not intermediate, or process, variables. These outcomes become more critical when comparing alternative interventions.

Comparing the effect of one intervention to an alternative intervention has long been considered the classic estimation problem in the health field. Costs to the individual as well as the healthcare system are the result of clinical outcomes and the way they relate to the length and quality of life (7). All healthcare decisions affect the total costs of healthcare and adverse health outcomes resulting from these decisions negatively affect the length and quality of life.

Clinical decisions require accurate and complete outcomes and costs data. Limited resources make this information even more crucial. Adverse health outcomes and their costs must be included when examining long-term costs following technological intervention. Costs of cardiac surgery provide an example. Although the perfusion circuit and perfusion services account for roughly 10% of the total cost of coronary surgery (8), they have an remarkable impact on the remaining 90% of the costs. Using technology with the greatest impact on adverse outcomes that contibute significantly to total costs will effectively contain costs.

METHODS

META-ANALYSIS

One of the problems with estimating cost differences is a lack of aggregated outcome information, across studies (populations), on the treatment effects of interventions. Meta-analysis pools data from multiple trials that examine outcomes of a similar intervention. No published quantitative analysis has combined research findings to compare the effect on either the probability or magnitude of clinical outcomes following use of PRP prior to CPB.

Individual trials frequently lack sufficient statistical power to provide conclusive evidence about clinical outcomes or effectiveness due to small sample size or experimental design rather than true clinical significance. Meta-analysis combines results from many smaller studies to estimate the overall result (true population parameter) across studies. This information can then be optimally used by rational decision makers (9). "In the 10 years or so since meta-analysis began to have an impact on the medical literature, dramatic progress has been made in the use of this technique, and the usefulness of the method is generally accepted now" (10).

The rapidly increasing volume of research on PRP provides somewhat discrepant findings. Meta-analysis integrates these research findings, providing a sounder basis for generalizations. Statistical comparisons between approaches are needed to discern relevant differences because most new treatments are only marginally better than existing ones (7). The two basic quantitative questions posed in this study follow:

1. What is the direction of the difference in outcomes between PRP and non-PRP groups across studies?
2. Is the magnitude of the difference across studies significant?

ARTICLE IDENTIFICATION AND INCLUSION CRITERIA

Several search strategies were utilized. Standard medical online searches as well as the Cochrane Collaborations "optimal MEDLINE search strategy" using appropriate keywords were used to identify studies. Manual library and appropriate topic journal searches were also carried out. Bibliographic abstracts were searched under PRP, sequestration, cost and economic analysis for CPB, as well as trade names. Reference sections and bibliographies of all retrieved articles were carefully examined for additional studies. Refereed proceedings were also examined for appropriate abstracts providing data.

Inclusion criteria were as follows: 1) published, or abstracted with data results, in the English language between 1990 and 1996; 2) compare either treatment with PRP to no treatment or compare different levels of PRP 3) provide at least one clinical outcome marker; 4) patient popupation could not be solely redo surgeries. All data available on the following clinical markers was pulled from articles: red blood cell use, platelet use, fresh frozen plasma use, probability of transfusion, postop myocardial infarctions, postop cardiovascular accidents, reoperation, hours to extubation, hours in intensive care unit, and hospital length of stay.

Examination of 135 research studies (5,12-139,) on PRP reveals that only 20 of them provide data on clinical outcomes from which outcomes can directly be calculated to compare costs. Twenty studies (5,12-30) examine clinical outcomes resulting from the use of PRP. Statistically significant differences between the PRP and control group in clinical markers is reported in several studies (5,14,17,18,21,24-27). Sequestering less than 20% to 30% of circulating platelet volume does not result in significant differences in outcomes (13,19,28-30). This level is the "therapeutic dose" that has been established in the literature (5,15,17). All studies, even those that did not sequester the "therapeutic dose", were included in this meta-analysis.

The majority of these studies do not present information comparing the costs resulting from clinical outcomes of using PRP. There are no currently published clinical outcome and cost comparisons of trials where PRP is used against a control group of no treatment that include length of stay, hours in intensive care, hours intubated, use of blood products, and incidence of myocardial infarction (MI) and cerebral vascular accident (CVA). The majority of studies cannot be included in the meta-analysis because they include no clinical markers that can be assigned economic values. These studies (5,12-30) included 1068 PRP patients and 652 non-PRP patients. Data was entered and analyzed in FASTPRO version 1.8[a].

RANDOM EFFECTS MODEL

Different experimental settings and different investigators observed different levels of health outcomes. This is expected since randomness alone results in differences in outcomes among settings. Clinicians' interest in applying these meta-analysis results to patients in settings that will most likely differ from those of the experiments analyzed suggests use of the random effects model. A random effects model can be used in estimating the outcomes that might be observed in settings not identical to those the original research was performed in.

The random effects model assumes that each of the studies that are combined is a random sample from the distribution of true values in the entire population of interest (7). Support for this assumption is derived from the fact that these studies cover a broad spectrum of clinical settings, physician training and specialties, patient groups, and geographical areas. The assumption basic to the random effects model is existence of an underlying distribution for the "true" values in different settings. Specific equations and functional forms used in producing the parameter estimates are discussed in Appendix 1.

ECONOMIC EVALUATION

Cost comparisons derived from aggregate outcomes provide a systematic base of information useful for decision making purposes, particularly when health care resources are not unlimited. Interpretation of these results should, as always, proceed with care even though meta-analysis provides more consistent findings with less bias than any one individual study. Clinical benefits rather than intrinsic cost savings, regardless of incentives, should be the main rationale for the choice (141) of technology.

Adverse outcomes following the use of PRP v non-PRP are used to compare costs. Differences in probability of occurrence for each of the different health outcomes can be found in Table 1. Probability of occurrence is presented.

Value is assigned to these consequences based on (MEDPAR) diagnosis related groups (DRG) relative weighting scheme, where appropriate. Other costs are derived from national averages provided by numerous healthcare organizations and the government (142-146). Comparison of costs can be found in Table 2. Costs savings are calculated using an estimated cost for each health outcome and multiplying it by the effect size for that particular health outcome. Notice that costs from any system can be utilized; the probability of occurrence is multiplied by the desired cost basis (147).

An example for DRG 108, used to calculate costs for reoperation, follows. The charged amount for DRG 108 is multiplied by 80% to reflect estimated costs:

- Cost of Care: 0.80 X $23,782.00 = $19,025.60
  where: 0.8000 = assumption that costs are 80% of charges
- Overall Cost Savings due to Reoperation
  PRP: 0.0323 X $19,025.60 = $612.29
  where: 0.0323 = decrease in reoperation rates for PRP group and $19,025.60 = Cost of reoperation (DRG #108)
  non-PRP: 0.0446 X $19,025.60 = $847.59
  where: 0.0446 = reoperation rates for non-PRP group and $19,025.60 = Cost of reoperation (DRG #108)

a FASTPRO, Boston Academic Press, Boston, MA

Table 1: Clinical Outcomes: PRP vs. Control

Clinical outcome	PRP	Non PRP	p-value for difference	N Per outcome
RBC units	0.2296 (0.0135)	2.392 (0.0673)	0.00000	1593
FFP units	0.8601 (0.0307)	2.482 (0.0852)	0.00000	891
PLT units	0.2551 (0.0169)	1.887 (0.0885)	0.00000	942
Transfused [total units]	1.3448 (0.0187)	6.761 (0.0771)	0.00000	818
REOP/bleed [probability]	0.03234 (0.0125)	0.04455 (0.0204)	0.00000	118
MI [probability]	0.02475 (0.0154)	0.02475 (0.0154)	0.50000	418
CVA [probability]	0.00746 (0.0061)	0.03465 (0.0181)	0.00000	300
Extube [hours]	12.74 (0.567)	13.13 (0.938)	0.00018	405
SICU [hours]	67.46 (9.115)	80.4 (14.55)	0.00000	300
LOS [days]	9.223 (0.202)	10.88 (0.37)	0.00000	484
N	1068	652		

ALL differences in effect sizes between non-PRP & PRP significant @ $p<0.05$. (standard deviations)
RBC = red blood cells; MI = myocardial infarction; FFP = fresh frozen plasma; CVA = cerebral vascular accident; PLT = platelets; SICU = surgical intensive care unit; REOP = re-operation for bleeding; LOS = length of stay; N = number of patients; Effect size = difference between treatment (PRP) group and control (non-PRP) group

Table 1B: Clinical Outcomes: PRP vs. control: studies that sequestered "therapeutic" dose

Clinical outcome	PRP	Non PRP	p-value for difference
RBC units	0.2091 (0.0136)	2.541 (0.0741)	0.00000
FFP units	0.8530 (0.0310)	2.671 (0.0886)	0.00000
PLT units	0.2493 (0.0171)	2.033 (0.0947)	0.00000
Transfused [total units]	1.311 (0.0148)	7.245 (0.0812)	0.00000

Subsequent expenditures required for treatment of different health outcomes are then summed over each alternative.

For purposes of simplicity, the assumption is made that all individuals experiencing the adverse health outcome will receive the same or a similar intervention. This assumption appears reasonable since there is nothing to indicate a difference in receiving interventions among any groups within a study. The differences in probability of incurring an adverse health outcome as a consequence of sequestration are derived from the above described meta-analysis procedures.

RESULTS

EFFECTIVENESS OF PRP

Outcomes: Table 1 contains the probability of occurrence of clinical outcomes for PRP and non-PRP groups. There are several striking results presented here. Firstly, all probabilities favor the PRP group patients. The difference between effect sizes for PRP v non-PRP groups are all significantly different than zero. The effect size is the difference between the treatment, in this study, the platelet-rich plasmapheresis group, and the control group in any specific outcome.

Patients in the platelet-rich plasmapheresis group use 90.4% fewer units (2 less units) of packed red blood cells, 65.3% fewer units (1.5 less units) of fresh frozen plasma, and 86.5% fewer units (1.5 less units) of platelets than patients in the control group. The patients in the PRP group spend 16.1% fewer (13 less) hours in intensive care and they spend 15.2% fewer, or 1 1/2 less, days in the hospital. Even though the difference in effect sizes is statistically significant for extubation, the difference is small in terms of clinical significance.

PRP appears to decrease the probability of developing certain adverse outcomes, as well. PRP patients are 27.4% less likely to need reoperation for bleeding and are 78.5% less likely to experience a cerebral vascular accident.

The studies (13,19,28-30) that sequestered less than the suggested therapeutic dose, i.e., less than 20% to 30%, make the result of use of PRP across studies smaller than if they are not included. Meta-analysis results without these five studies are presented in Table 1B. These studies included only use of blood products. Notice that the difference between the PRP group and the control group becomes greater when these studies that did not sequester at least 20 to 30% are removed from the analysis.

Use of platelet-rich plasmapheresis results in improved clinical outcomes for patients when compared to those on whom PRP is not used. These improved clinical outcomes result in 25.4% lower costs per patient on whom platelet-rich plasmapheresis is used.

The costs calculated for each separate outcome reflect the magnitude and significance of the outcomes themselves. Every category shows a greater cost for non-PRP patients when compared to PRP patients. The total cost savings are $4,203.03 given the cost assumptions presented in Table 3. Expected total costs for the outcomes considered for a patient not receiving PRP would be $16,532.46. Patients in the PRP group would expect a total of $12,329.44.

DISCUSSION

Limitations: This meta-analytic study provides aggregated quantitative results with the available data from the literature.

Numerous studies do not include clinical markers that can have an economic value calculated. Interpretation of these results as the best available from the data the field and the literature can currently provide is appropriate. This meta-analysis, like any other, can be updated as new studies become available.

Table 2: Costs: PRP vs. control

Clinical outcome	PRP	Non PRP
RBC units	$50.17	$522.65
FFP units	60.13	173.52
PLT units	13.87	102.62
Transfused	2.69	13.52
REOP/bleed	615.29	847.59
MI	126.17	126.17
CVA	358.22	1663.20
Extube hrs	509.60	525.20
SICU hrs	5059.50	6030.00
LOS days	5533.80	6528.00
Total cost	$12329.44	$16532.46

Table 3: Cost assumptions

Clinical outcome	Unit cost
RBC units	$218.50
FFP units	$69.91
PLT units	$54.38
Transfused (exposure)	$2.00
REOP/bleed	$19,025.60
MI	$5,097.60
CVA	$48,000.00
Extube hrs	$40.00
SICU hrs	$75.00
LOS days	$600.00

Further research with larger numbers of patients and more extensive collection of clinical outcomes would likely provide outcome and cost information with increased significance and accuracy. Trends are unlikely to change due to the number of studies and total number of patients. The data provided here furnish evidence that use of PRP in CPB results in an improvement in clinical outcomes. These improved outcomes provide cost savings for patients in the PRP group when compared to non-PRP patients.

Data from the studies that include clinical outcomes were combined using meta-analysis and offer the following evidence. All values are calculated on an average per patient basis. Examination of these outcomes provides unambiguous answers to the two questions posed earlier. The patients in the PRP group have improved incidence of adverse health outcomes. Non-PRP patients show higher total costs than patients in the PRP group. The direction of the difference is always negative; PRP patients perform better on all outcomes. The magnitude of the difference is always significant. These results demonstrate the existence of distinct patterns of significant differences in the impact across, as well as within, studies of treatment with PRP. Cost differences result from these improved clinical outcomes. All adverse clinical outcomes show a lower incidence of occurrence with use of PRP.

Quantitative synthesis of these data provide an overview of current information on use of PRP for CPB. When outcomes are combined to evaluate overall effectiveness, valuable information is provided for clinicians, patients, or policymakers use regarding the impact of PRP on outcomes and costs.

ACKNOWLEDGEMENT

This study was funded in part by Medtronic, Inc.

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APPENDIX 1

The methodology described here was used to analyze the data and arrive at the results presented from this meta-analysis. This methodology is that used by the analysis program, FASTPRO, which was used to perform the analyses. It is important that these formulas be specified in exactly the same manner the program uses to derive the parameter estimates, since all programs are slightly different and any questions regarding specification can be clearly addressed. The general model used is formulated as follows. Let $\Theta_k = \Theta_1, \Theta_2,...,\Theta_k$ be the basic parameters. There is no restriction that the basic parameters be independent; some or all of them can be multivariate. Let $\pi(\Theta_k)$ be the joint prior distribution for Θ_k. If all the basic parameters are independent, with prior distributions $\pi(\Theta_k)$, then

$$\pi(\Theta_k) = \prod_{i=1}^{k}(\Theta_i)$$

Functional parameters can be denoted as $\Theta_{k+1},...,\Theta_m$, with the order such that any particular functional parameter, Θ_l, can be written as a function of the basic parameters and other functional parameters that precede it in order. In general,

$$\Theta_l = f_l(\Theta_1, \Theta_2,...,\Theta_k,\Theta_{k+1},...,\Theta_{l-1})$$

A requirement of the general model is that this ordering be possible. This ordering implies that all functional parameters can, by successive substitutions, be written as functions only of basic parameters. Let Θ_m be the entire set of basic and functional parameters such that $\Theta_m = \Theta_1, \Theta_2,...,\Theta_m$. Data from the experiments can be represented by y_j, j = 1...*n* (variables representing the evidence), where j indexes the jth experiment. The general likelihood function for the jth experiment can be written as

$$Lj(y_j|\Theta_1, \Theta_2,...,\Theta_m)$$

The likelihood for this model can be represented by

$$\mathbf{L} = \prod_{j=1}^{n} L_j(\mathbf{y}j\,|\Theta_1,...,\Theta_m)$$

which is the product of the likelihood functions. Maximum likelihood estimates can be calculated using this model for parameters. The particular case for this analysis is a dichotomous outcomes model. The outcomes of interest are either success or failure. In this analysis, "success" is presence of an adverse health outcome. Then the outcome we observe is Θ, or the probability of developing the adverse health outcome ("success"). "Success," or presence of the ith adverse health outcome is denoted with $y_i = 1$ and $y_i = 0$ if the ith adverse health outcome is not present, or it is denoted as a failure. We can represent the number of successes with s, where

$$s = \sum_{i=1}^{n} y_i$$

and the number of failures with f, where

$$f = \sum_{i=1}^{n}(1-y_i).$$

Outcomes are assumed to be independent and identically distributed, and the likelihood function can then be derived from the binomial distribution, $L(\mathbf{y} \mid \Theta) \alpha \Theta^s (1 - \Theta)^f$. This assumes that all individuals are subject to the same probability of success.

The measure used here to compare health outcomes resulting from use of PRP is the actual probability. In all cases, given the data available, it is the actual probability of adverse health outcomes occurring. The actual difference in probabilities can be represented by: $\varepsilon_d = \Theta_s - \Theta_d$ The random effects or hierarchical model is used to perform the meta-analyses that combine information across studies. This model adjusts for existence of unknown biases that may impact experimental results. If the larger distribution from which all the experimental results are drawn is assumed normal, the specific form of the hierarchical distribution function is

$$P(\Theta_j \mid \mu, \tau^2) \propto 1/\tau\, e^{-(\Theta j-\mu)2/2\tau 2}$$

This is the functional form utilized in this analysis by the FASTPRO program.