Platelet-Rich Plasma Reduces Retear Rates After Arthroscopic Repair of Small- and Medium-Sized Rotator Cuff Tears but Is Not Cost-Effective
Patrick Vavken, Patrick Sadoghi, Matthew Palmer, Claudio Rosso, Andreas M. Mueller, Gregor Szoelloesy and Victor Valderrabano
DOI: 10.1177/0363546515572777

The online version of this article can be found at: http://ajs.sagepub.com/content/43/12/3071
Platelet-Rich Plasma Reduces Retear Rates After Arthroscopic Repair of Small- and Medium-Sized Rotator Cuff Tears but Is Not Cost-Effective

Patrick Vavken,*†§ MD, MSc, Patrick Sadoghi,‖ MD, Matthew Palmer,¶ MBA, Claudio Rosso,§# MD, Andreas M. Mueller,§ MD, Gregor Szoelloesy,§ MD, and Victor Valderrabano,§ MD, PhD

Investigation performed at Boston Children’s Hospital, Boston, Massachusetts, USA, and University Hospital Basel, Basel, Switzerland

Background: It has been suggested that platelet-rich plasma (PRP) improves healing after arthroscopic rotator cuff repair. The current literature provides ample but inconsistent data on this topic.

Purpose: To systematically review the current in vivo evidence for the use of platelet concentrates (PRP) in the arthroscopic treatment of rotator cuff tears to assess effectiveness, safety, and cost-effectiveness.

Study Design: Meta-analysis and cost-effectiveness analysis.

Methods: Published evidence from controlled, human trials of rotator cuff repair augmented with platelet concentrates was systematically gathered, and data on retear rates were extracted. Mathematical and clinical heterogeneity was evaluated, and fixed-effect meta-analysis was performed to calculate the risk ratio (RR) of retears and the number needed to treat (NNT). Subgroup analyses were made for small/medium tears (n = 404) and large/massive tears (n = 374). Cost-effectiveness was assessed using data from this meta-analysis and using cost data from the literature, including extensive sensitivity analyses, to calculate the incremental cost-effectiveness ratio (ICER).

Results: Thirteen studies published between 2010 and 2014 were identified for analysis. The RR for retear for all patients was 0.87 (95% CI, 0.67-1.12; \( P = .286 \)). For small- and medium-sized tears (<3 cm), the RR for retear was 0.60 (95% CI, 0.37-0.97), consistent with a significant difference in favor of PRP use (\( P = .038 \)). This translated into an NNT of 14 (95% CI, 7-125). However, at an ICER of US$127,893 per quality-adjusted life year gained, assuming a 5% revision rate, the use of PRP was not cost-effective for small- and medium-sized tears.

Conclusion: In large tears, even with double-row repair, the beneficial effects of PRP alone are insufficient to compensate the progressed tissue damage. The study data suggest that PRP may promote healing of small- and medium-sized tears to reduce retear rates. However, despite the substantial biological effect, at current cost, the use of PRP is not cost-effective in arthroscopic repair of small- and medium-sized tears.

Keywords: rotator cuff; platelet; PRP; evidence-based medicine; cost-effectiveness

It is currently estimated that roughly 250,000 cuff repairs are performed annually in the United States alone. However, despite the high incidence of both rotator cuff tears and repairs, and in contrast to the advances made in surgical technique, healing rates, or rather retear rates after rotator cuff repair, are still an issue. Even with double-row repair constructs, the high end of the range of retear rates is estimated to be as high as 30%, or 1 in 3 patients, for those with small- and medium-sized tears and up to 94% in large-sized tears.

The clinical importance of retears is unclear. Some prior literature quotes rates of up to 20% of symptomatic patients after retears; others report largely equivalent outcomes between structurally intact cuff repairs and retears. Also, the exact reasons for postoperative retears remain somewhat elusive. Tendon retears have been attributed to the same pathomechanism that had led to the initial tear, that is, degenerated tendon tissue succumbing to high mechanical stress, leading to retearing just medial to the repair site.

Miller et al presented data suggesting that early retears (within 3 months) are...
associated with mechanical failure of the surgical fixation. Cummins and Murrell, in a prospective analysis of 342 rotator cuff repairs, cited tendon pulling through sutures due to poor tendon quality as the most common type of failure, followed by new tears through the damaged tissue, followed by anchor failure. Lannotti et al. analyzed the time to failure after cuff repair in a longitudinal study of 113 cases and showed that most had occurred at 19 weeks. Le et al. analyzed risk factors for retears in 1000 consecutive rotator cuff repairs but were only able to state that retears are a multifactorial process and associated with tear size.

One suggested answer to this problem is augmentation of rotator cuff repairs with matrices or other similar devices to protect the rotator cuff repair. However, the results of such augmentation have not been overwhelming. Flury, of Zurich, reported on the use of an extracellular matrix patch in ruptured rotator cuffs, observing a rerupture rate of roughly 40% at 5 months but some improvement in clinical scores. Iannotti et al. in 2006, published a randomized controlled trial of the use of porcine small intestine submucosa (SIS) in chronic cuff tears, but did not find improved healing rates or clinical scores compared with standard repair. Barber et al. used an acellular human dermal matrix and did find a reduction in retears with augmentation. Apart from clinical outcomes, the level of technical complexity of patch-augmented rotator cuff repair can be considered a shortcoming as well.

An alternative approach that has received much attention is the use of autologous platelet concentrates, for example, platelet-rich plasma (PRP). Building on basic science, animal models, and data from other orthopaedic procedures, it is hoped that platelet concentrates will improve rotator cuff healing by supporting regeneration of the degenerated tendon tissue and by stimulating the differentiation of the scar tissue at the repair site. Of note, platelet concentrates are not meant to improve biomechanical strength of a repair directly, as an adhesive would, but may be used to reduce retear rates.

In this study, we wanted to systematically gather and analyze the in vivo, human data for the use of platelet concentrates in rotator cuff repair. First, we wanted to know if the addition of PRP to arthroscopic rotator cuff repair would lead to a statistically relevant effect. In this context, we were interested in the clinical endpoints, with or without clarification of retear rates, expressed as the number needed to treat (NNT). Second, we were interested in comparing the PRP treatment with the arthroscopic rotator cuff repair. Third, we wanted to assess if any potentially beneficial effect of PRP on retear rates would be cost-effective. This was estimated with the use of the incremental cost-effectiveness ratio (ICER), or the amount of additional clinical effect afforded per additional dollar spent. Last, but not least, since this was a meta-analysis of prior data, we also wanted to assess the quality of the included primary data that this analysis was built upon.

METHODS

This systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.

Systematic Search and Strategy

The online databases PubMed, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR) were searched. All dates and languages were included. The last search was performed on August 1, 2014. The search algorithm was “rotator AND platelet” and was replicated using the keywords as MeSH (Medical Subject Headings) terms as well. All searches were unlimited to language and publication date. In addition, the bibliographies of the included studies were reviewed by hand to identify further publications.

Studies were included if they reported on the use of platelets in rotator cuff repairs in human, controlled trials. Both title and abstracts from all search results were screened for eligibility in duplicate. Studies were excluded if title and/or abstract clearly invalidated eligibility. Full-text articles or abstracts allowing extraction of all relevant endpoints were obtained for all studies matching the inclusion criteria or with unclear eligibility, and the full-text papers were reviewed in duplicate. All study selections were cross-referenced. Disagreement was resolved by consensus or with the help of an in-house shoulder expert.

Extraction of Relevant Data

We extracted data on the study design characteristics and on the type of treatment(s) used for descriptive purposes. The main endpoints for the analysis were retear rates and complications. All data were extracted in duplicate and entered into a predefined datasheet. Data consistency was checked independently after extraction. Disagreement was resolved by consensus.

Address correspondence to Patrick Vavken, MD, MSc, Division of Sports Medicine, Boston Children’s Hospital, Harvard Medical School, 316 Longwood Avenue, Boston, MA 02115, USA (email: patrick.vavken@childrens.harvard.edu).
Division of Sports Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, Massachusetts, USA.
Department of Orthopaedic Surgery, University Hospital Basel, Basel, Switzerland.
Department of Orthopaedic Surgery, Medical University Graz, Graz, Austria.
Harvard Business School, Cambridge, Massachusetts, USA.
ALTIIUS Swiss Sportsmed Center, Basel, Switzerland.

The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.
Assessment of Internal Validity/Risk of Bias

We assessed the risk of bias in the included studies by using a modified Jadad scale. This score assesses randomization, concealment of allocation, attrition, and power with 1 point each, thus resulting in a score between 0 (worst result; high risk of bias) and 4 (best result; low risk of bias). In addition, we categorized all included studies by level of evidence.

Quantitative Data Synthesis

Publication bias among the included studies was assessed graphically using funnel plots and mathematically using the Egger weighted regression.\textsuperscript{13} The presence of between-study heterogeneity was qualified by the Cochrane Q test, using a $P$ value of 10% to adjust for the low power of this test in small samples, and quantified using the $I^2$ index.\textsuperscript{19,20} Data were synthesized to create cumulative risk ratios (RRs) and risk differences (RDs). The RDs were used to calculate the number needed to treat (ie, the number of patients who have to be treated with PRP to result in 1 less retear; NNT = 1/RD). All analyses were also performed for 2 subgroups, small/medium and large/massive tears, based on the Cofield classification system.\textsuperscript{7}

All calculations were performed using Intercooled STATA 10 (StataCorp LP). The level of significance for pooled estimates was set at 5%.

Cost-Effectiveness Analysis

All costs are given in 2013 US dollars. We used a decision-analytic tree model to calculate cost-effectiveness for the use of PRP in arthroscopic rotator cuff repair. Cost-effectiveness was calculated only for those scenarios that showed a significant improvement with the use of PRP. The model was structured to follow a typical rotator cuff patient for 2 years postoperatively, which we considered a frequently used duration of follow-up by a shoulder surgeon. The model parameters were obtained from the literature and our own analysis. Data on retear rates were obtained from our meta-analysis. For revision rates after retears, there were only very limited data, but we used a base rate of 5% as well as a sensitivity analysis in the range of 1% to 90%.\textsuperscript{10,17,23} Data on cost for rotator cuff repairs were obtained from published cost-effectiveness studies. Since the cost of PRP varies considerably, we used a range of costs from $450 to $2500. This included the PRP set as well as the venipuncture ($34) and 5 minutes in the operating room (OR) time ($5 \times $70 = $350) to apply the PRP. The amount of OR time was based on own data for 50 of our clinical cases, in which we used and timed the application of PRP. For our base case, we used the total cost for the PRP set, venipuncture, and additional time in the OR: $450 + $34 + $350 = $834. The utilities of 3 different postoperative states were extracted from the literature: (1) healed rotator cuff repair at 0.851, (2) revised retear at 0.820, and (3) untreated retear at 0.803.\textsuperscript{17,26} To calculate quality-adjusted life years (QALYs), we multiplied these utilities by the follow-up period (ie, 2 years). For revision rotator cuff repair after retears, we assumed the revision to take place 3 months after the initial surgery, with the patient spending the remaining 21 months in a “healed state” in terms of utility. The model was used to calculate the ICER for the rotator cuff repair with and without PRP. The published threshold of $100,000 per gained QALY was used.\textsuperscript{11}

RESULTS

Study Selection

Our search produced 276 studies in total. Of these, 13 publications were obtained and included based on the criteria described above. No additional studies were identified by bibliographic cross-reference (Figure 1). All included articles were published in English between 2010 and 2014.

Characteristics of the Included Studies

Among the 13 included studies, the mean age for those patients receiving PRP was 60.7 years, compared with 60.6 years for the controls. The percentage of females was 48% for PRP and 51% for controls. Six studies used a single-row repair, 4 a double-row repair, and 3 a repair as seen fit at the time of surgery. Nine studies used an interposition technique of a PRP pellet, and 4 applied PRP as a liquid spray/injection. Retears were assessed using magnetic resonance imaging (MRI) in 11 studies.
and ultrasound in 2 studies. The Sugaya scale was used to quantify retears in 7 studies.33

Retear Rates

There was no evidence of statistical heterogeneity for retear rates ($P = .295$, $I^2 = 15.2\%$) for repairs of tears all sizes. There was no evidence of publication bias for retear rates ($P = .172$). The cumulative risk ratio for a retear across all studies was 0.87 (95% CI, 0.67-1.12). This reduction of retear risk by 13% was not statistically significant ($P = .286$) since there might be any result between a 33% reduction and 12% increase in risk.

A total of 404 rotator cuff tears ≤3 cm were individually analyzed as a subgroup of small- to medium-sized tears according to Cofield.7 Again, there was no evidence for statistical heterogeneity ($P = .158$, $I^2 = 33.9\%$). There was no evidence for publication bias ($P = .154$). The cumulative risk ratio for retears was 0.60 (95% CI, 0.37-0.97). This reduction by 40% on average, or at least 3%, is consistent with a significant difference in favor of the use of PRP ($P = .038$). This translates into an NNT of 14 (95% CI, 7-125), or 1 less retear for every 14 patients treated with PRP instead of without PRP (Figure 2).

For the remaining 374 large and massive tears (>3 cm), there was no evidence of statistical heterogeneity ($P = .757$, $I^2 = 0.0\%$) or publication bias ($P = .469$). However, neither was there evidence of a beneficial effect (RR, 1.05; 95% CI, 0.79-1.39; $P = .744$).

Complications

There were no differences in complications between the PRP-augmented and the standard repairs, with a rate ratio of 1.04 (95% CI, 0.1-7.8) at a $P$ value of 0.480. In sum, 3 complications in each group were specifically mentioned. In the standard repair group, there were 2 stiff shoulders and 1 revision for a clinically relevant rotator cuff tendon repair failure. In the PRP group, there was 1 stiff shoulder and 2 cases of infection in the study by Bergeson et al.2

Cost-Effectiveness

Cost-effectiveness analysis was done only for small- and medium-sized tears, since they showed a significant effect of PRP. The difference in effectiveness between repair with and without PRP was 0.0059 QALYs. We assumed that the difference in cost between the 2 treatment options would consist only of the additional cost of PRP fabrication and use (PRP kit, venipuncture, extra OR time). Thus, we calculated a base case for an increased overall cost of $834 with the use of PRP divided by an incremental effectiveness of 0.0059 QALYs, corresponding to an ICER of $127,893 per QALY gained.

For our sensitivity analysis, we changed rates of retears as well as revisions to observe the resulting changes in ICER. This analysis showed that with increasing revision rates, the use of PRP became less cost-effective. Moving from a 5% to a 10% revision rate increased the ICER to $130,240, indicating that the more cases that resulted in a revision, the less important the reduction of retear rates became (Figure 3).

On the other hand, utility of PRP use and cost-effectiveness improved with increased retear rates. When moving from a 10% to 20% retear, the ICER decreased from $225,162 to $112,581, indicating that as the retear rates increased, the value of PRP became more valuable. To reach the cutoff for cost-effectiveness of $100,000 per QALY gained, the use of PRP, in our model, could not be more expensive than $652.11 in total cost (including OR time and venipuncture). Based on our own OR time and

Figure 2. Forest plot of the meta-analysis for small- and medium-sized tears (<3 cm). Given is the risk difference (RD), not risk ratio, which is used to calculate the number needed to treat, or NNT = 1/RD. The individual studies are given in the horizontal lines; the dotted vertical line is the sum effect. PRP, platelet-rich plasma; RCTR, rotator cuff tendon repair.

Figure 3. Sensitivity analysis on the incremental cost-effectiveness ratio (ICER) by cost of platelet-rich plasma (PRP) and revision rate. The ICER is given for 4 revision rates (5%/10%/20%/30%) over a range of PRP cost from US$500 to $1000. The dashed line represents the cost-effectiveness threshold of $100,000 (quality-adjusted life year) gained and corresponds to a PRP cost of $652.11 for the base case revision rate of 5%.
Risk of Bias in the Included Studies

The average Jadad score for the included studies was 3.1 ± 0.8 of a best possible outcome of 4 points. Eight studies were randomized, 12 were blinded, 13 studies reported on attrition, and 7 studies reported on a formal sample size calculation.

DISCUSSION

Summary of Evidence

In this study, we aimed at assessing the value of adding platelet concentrates to arthroscopic rotator cuff repair. We found that PRP is an effective and safe way of reducing retear rates in the arthroscopic repair of small- and medium-sized rotator cuff tears. We did not find evidence to support the use of PRP in large and massive tears. Finally, with the current cost of PRP application, our model showed that the use of PRP after arthroscopic repair of small- and medium-sized rotator cuff tears is not cost-effective.

Assessing retear rates, we found no benefit of PRP on rotator cuff repair for defects of all sizes. However, focusing on a subgroup of tears sized 3 cm or less (ie, small- and medium-sized tears), we found a significant beneficial effect. In addition to statistical significance, there was also a sizable clinical effect, consistent with an NNT of 14. In other words, for every 14 patients with a small- or medium-sized tear treated with PRP, 1 retear can be avoided. Trying to explain the difference in effect between small/medium and large/召开 tears, we like to revisit the concept of the rotator cable described by Burkhart et al.4 This likens the cuff insertion to a “suspension bridge” where individual anchor points, rather than the whole cuff of tissue, are responsible for load transmission. With remaining intact cable, a small/medium tear is stable, whereas, by definition, a large/召开 tear will not allow for the cable to be intact and will therefore be unstable.28 The differential healing potential of PRP with stable and unstable tissue defects is consistent with other fields. For example, work done by Murray et al30,31 on the effect of PRP in ligament and tendon healing around the knee showed that not platelets alone, but only a stable collagen-platelet composite, promotes healing.14

We found no evidence for an increase or decrease in associated complications with the use of PRP. Interestingly, Bergeson et al2 found an increased rate of postoperative infection. We reviewed the literature for infection associated with PRP usage in humans but did not find any data suggesting an increase in risk, although it is known that PRP has pro- and anti-inflammatory effects. A potential problem of PRP is overstimulation of the healing tissue, resulting in a poorly differentiated scar, but without histological data and information on PRP concentrations, this issue cannot be assessed at this point.27,35

Of particular interest was if the found reduction in retear risk would translate into a clinically relevant effect. Recent publications have shown that there is hardly any difference in clinical outcome between those patients with intact rotator cuff repairs and those with retears.32 Others have reported that up to 20% of patients with retears are symptomatic, and 10% return for revisions.32 For this study, we did not want to commit to a single number but rather to assess the cost-effectiveness over a spectrum of revision rates from 1% to 90%. However, we built our base case on a 5% revision rate for return small- and medium-sized tears. Of note, cost-effectiveness assessment is not a cold, mathematical exercise, caring more for profits than patients, but includes both quality-of-life measurement and cost of care. We found, in our model, that the use of PRP is not cost-effective. An argument could be made that our base case is too expensive, with OR time at an academic institution of $70 per minute compared with ambulatory surgical centers where this cost might be $20 or $30 per minute. However, even in a best-case scenario, the total cost of preparing and applying PRP, including consumables and fixed cost, has to be below $652.11, which seems difficult with the current pricing of commercial PRP machines and kits.

Limitations

Our study has potential shortcomings. First, like any meta-analysis, our results build on and therefore are dependent on prior studies and their quality. We did assess study quality and found no indications of heterogeneity, publication bias, or lack of validity due to poor design. Second, there is considerable variety in cost of care for shoulder patients depending on geographic location and type of institution. However, we did include wide ranges of potential costs to offset this shortcoming. Third, our assumed time point for surgical revision (ie, 3 months postoperatively) is rather early. However, we wanted to err on the safe side, since a later revision would translate into a patient being in a poor state of health longer and, thus, an even wider gap in cost-effectiveness. Last, there is considerable disagreement if a retear after cuff repair is problematic or not. The most recent evidence suggested that structural integrity after rotator cuff repair does not affect clinical outcomes.32

CONCLUSION

In large tears, even with double-row repair, the beneficial effects of PRP alone are insufficient to compensate the progressed tissue damage. Our data suggest that PRP may promote healing of small- and medium-sized tears to reduce retear rates. However, despite the substantial biological effect, at current cost, the use of PRP is not cost-effective in arthroscopic repair of small- and medium-sized tears.
REFERENCES


