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Evidence analysis on the utilization of platelet-rich plasma as an adjuvant in the repair of rotator cuff tears

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Abstract

BACKGROUND

Systematic Review

AIM

We performed this systematic overview on the overlapping meta-analyses that analyzed autologous platelet-rich plasma (PRP) as an adjuvant in the repair of rotator cuff tears and identify the studies which provide the current best evidence on this subject and generate recommendations for the same.

METHODS

We conducted independent and duplicate electronic database searches in PubMed, Web of Science, Scopus, Embase, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects on September 8, 2021 to identify meta-analyses that analyzed the efficacy of PRP as an adjuvant in the repair of rotator cuff tears. Methodological quality assessment was made using Oxford Levels of Evidence, AMSTAR scoring and AMSTAR 2 grades. We then utilized the Jadad decision algorithm to identify the study with the highest quality to represent the current best evidence to generate the recommendation.

RESULTS

20 meta-analyses fulfilling the eligibility criteria were included. The AMSTAR scores of the included studies varied from 6-10 (mean:7.9). All the included studies had critically low reliability in their summary of results due to their methodological flaws according to AMSTAR 2 grades. Significant heterogeneity was observed in the reporting of VAS, function outcome scores (long-term UCLA score, ASES score, SST score), operative time and long-term re-tear rates. Recent meta-analyses are more supportive of the role of intra-operative administration of PRPs at the bone-tendon interface in improving the overall healing and re-tear rates, functional outcome and pain. The initial size of the tear and type of repair performed do not seem to affect the benefit of PRPs. Among the different preparations used, leucocyte poor (LP)-PRP possibly offers the greatest benefit as a biological augment in these situations.

CONCLUSION

Based on this systematic overview, we give a Level II recommendation that intra-operative use of PRPs at the bone-tendon interface can augment the healing rate, reduce re-tears, enhance functional outcome and mitigate pain in patients undergoing arthroscopic rotator cuff repair. LP-PRP possibly offers the greatest benefit in terms of healing rates, as compared with other platelet preparations.

INTRODUCTION

Despite substantial improvements and huge strides made in the surgical procedures and the fixation constructs employed in the repair of rotator cuff tears, high failure rates persist to remain a major cause for concern[1]. The reported failure rates of rotator cuff repairs vary between 8 and 94%[1–4]; and multitudinous factors including age, systemic comorbidities, smoking status, size of tear, degree of fatty infiltration and surgical approaches or techniques have been purported to determine the outcome in these patients[5].

With the understanding that there is still room for significant improvement, the need for employing additional modalities for ameliorating healing in this setting has been growingly acknowledged[6]. It has been well-demonstrated that degenerated rotator cuff tissue has substantially compromised microcirculation, as compared with normal, healthy tissue[7]. Moreover, the fibro-vascular scar at the region of bone-tendon interface following repair of the rotator cuff tear is of poorer quality, in comparison with the innate tissue[8]. Since these aforementioned biological factors have been postulated to be the potential underlying cause for impaired tendon healing capacity after surgical repair, a significant degree of promise has been recently placed on biological augmentation strategies for enhancing tissue healing after rotator cuff repair surgeries[1,9].

Platelet-rich plasma (PRP) is a platelet concentrate, which is prepared by centrifugation of autologous whole blood; and contains various growth factors including platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), transforming growth factor-β (TGF- β), epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF). Based on the preparations and constitution (leukocyte content and fibrin architecture), PRP have been classified as pure PRP, leucocyte and PRP (L-PRP), leucocyte and platelet-rich fibrin (L-PRF) and pure platelet-rich fibrin (P-PRF)[1-6]. Platelet-rich plasma (PRP) and platelet-rich fibrin matrix (PRFM) have been gaining popularity as agents for biological augmentation in diverse sub-specialties of orthopaedic surgery, either as the sole treatment modality or as an adjunct to surgical repair[8,9]. There is growing evidence from animal-based models on the positive effects of platelet-derived autologous growth factors on collagen production, cell proliferation, tissue revascularization and tendon regeneration in the setting of operative arthroscopic rotator cuff repair (ARCR)[10,11]. Nevertheless, there is substantial discrepancy in the results of the published meta-analyses; and the true efficacy and role of using PRP at the time of rotator cuff repair is still ambiguous[12–16].

The overall purpose of the current study was to perform a detailed systematic review of the existing meta-analyses evaluating the role of PRP in patients undergoing rotator

cuff repair; and to specifically provide answers to the following research questions, namely: a. To evaluate the effect of this strategy on overall clinical outcome scores, b. To evaluate the reduction in re-tear or failure rates, c. To analyse the evolution and variations in the techniques of procurement and application of PRP across different studies, and d. To critically analyse and interpret the best currently available evidence and provide recommendations; and e. To discern the major gaps in the existing literature and identify the scope for future research on this subject.

MATERIALS AND METHODS

We present herewith a systematic overview of meta analyses, performed by duly cohering the guidelines of the Back Review Group of Cochrane Collaboration[17]; and aim to report the same based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18].

Search strategy

Two reviewers performed an independent literature search for systematic reviews with meta-analysis evaluating PRP therapy along with surgical repair for rotator cuff tear. The comprehensive search was performed on the Electronic databases including PubMed, Web of Science, Scopus, Embase, Cochrane Database of Systematic Reviews (CDSR), and the Database of Abstracts of Reviews of Effects (DARE) on September 8, 2021. Our search was neither restricted to any specific language nor confined to any particular period. The electronic search strategy was designed in accordance with the Peer Review of Electronic Search Strategy (PRESS) guidelines[19]. The keywords used for the search included: “Platelet-rich Plasma”, “PRP”, “rotator cuff repair”, “rotator cuff tear”, “clinical outcome”, “re-tear rate”, “failure rate”, “Systematic Review”, “Meta-analysis” together with Boolean operators such as “AND”, “OR” and “NOT”. A manual search of the key journals was made; and reference list of the selected articles was searched to identify studies not identified in the primary search. Additionally, a search was also made in the International prospective register of systematic reviews (PROSPERO) for any ongoing review which is nearing completion.

All the studies meeting the inclusion criteria were included and analyzed. Any discrepancy between the two reviewers was resolved through discussion until a consensus was achieved. The PRISMA flow chart for the study selection into systematic overview has been shown in Figure 1.

Inclusion Criteria

Review articles were included in our study if they satisfied the following criteria:

Systematic review with meta-analysis comparing surgical repair with and without PRP for rotator cuff tears.

Studies which analyzed at least one of the outcome measures like Visual Analog Scale (VAS) score, Disabilities of the Arm, Shoulder and Hand (DASH) score, Constant score, University of California Los Angeles (UCLA) score, American Shoulder and Elbow Surgeons (ASES) score, Simple Shoulder Test (SST) score, operating time, patient satisfaction, tendon healing and re-tear rates.

Exclusion criteria

Narrative reviews, systematic reviews without data pooling/ meta-analysis, systematic reviews with mixed intervention groups, correspondence articles, pre-clinical studies, studies on animal models and cadaveric studies were excluded.

Data extraction

Data was extracted from meta-analyses by two reviewers independently. Notably, data extracted from the studies included: first author details, date of last literature search performed, year and journal of publication, number, and nature of studies included, language restrictions, criteria for inclusion and exclusion for studies, databases used for literature search, software employed for analysis, subgroup/ sensitivity analysis, analysis of publication bias, conflict of interest, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary, and I^2 statistic value of variables in each meta-analysis. Disagreements were settled by consensus.

Assessment of Quality of Study Methodology

The methodological quality of included reviews was evaluated using Oxford Levels of Evidence[20]. Additionally, the Assessment of Multiple Systematic Reviews (AMSTAR)[21] and its updated grading tool AMSTAR 2[22] were also used to assess their methodological robustness with good validity and reliability[23]. Two reviewers independently assessed quality of methodology of the included studies. Disagreements were settled by consensus.

Heterogeneity assessment

I^2 test was used for the assessment of heterogeneity[24]. When $I^2 > 50\%$ and $p<0.1$, heterogeneity is deemed to exist among included trials; and the reviewers evaluated whether the studies utilized sensitivity or subgroup analyses to assess the reasons for heterogeneity and strengthen the robustness of pooled data.

Application of Jadad decision algorithm

Variability in the findings among included meta-analyses was interpreted with the help of Jadad decision algorithm. As per Jadad *et al*[25], possible reasons for discordance in the results among included studies include differences in study question, inclusion and exclusion criteria, quality assessment, data pooling/ extraction, and statistical analysis. Currently, this is the most commonly used algorithm for generating recommendations among meta-analyses with discordant results[26–29]. Two reviewers used this algorithm independently to arrive at a single meta-analysis representing the current best evidence in order to generate recommendations.

RESULTS

Search results

A comprehensive search of the electronic database generated 796 articles, which were subjected to an initial screening for removing duplicate articles. This yielded 472 articles. Further screening of title and abstract resulted in the exclusion of 439 articles.

Therefore, 33 articles qualified for reviewing the full-text. Upon full-text review by both reviewers, 13 were excluded. Finally, 20 meta-analyses were included in this systematic review[30–46,1,47,48]. These overlapping meta-analyses were published in different journals between 2012 and 2021; and the number of studies included in them ranged between 5 and 19 (Table 1). The publication years of the included studies in these meta-analyses ranged between 2008 and 2020 as shown in Table 2.

Search methodology of the meta-analyses

Although the included meta-analyses made a comprehensive literature search, the search databases employed were not similar. Sixteen, 1 and 7 studies searched PubMed, Embase and Medline databases, respectively. While 2 of them searched the Cochrane library, one searched Web of Science. 18 searched Scopus, 16 Google Scholar, 3 Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, 2 China National Knowledge Infrastructure (CNKI) database, 1 Wan fang and 2 meta-analyses searched VIP database. Of the 20 studies, 4 included studies only in English[1,42,43,46] while 7 others mentioned no linguistic restriction in their search criteria[30,33,38,40,41,44,45]. Further details regarding the search methodology employed in the included meta-analyses has been presented in Table 3.

Methodological quality

Using Oxford Levels of Evidence, the quality of included studies was determined based on the nature of primary studies considered in the analysis. Of the 20 studies analyzed, 6 were of level-II evidence, one level-III and the rest of them were of level III evidence (table 4). Among the 20 studies, 12 used RevMan5.3, 4 used Stata software, 1 used open meta, 2 used R-foundation for data analyses; while in one study, the software employed was not mentioned (Table 4). Additionally, three studies utilized the GRADE system, 12 studies performed sensitivity analysis, and 16 conducted sub-group analysis

to explore the heterogeneity in their results. Eleven studies assessed for possible publication bias.

As shown in table 5, AMSTAR scores of included studies ranged between 6 and 10 (mean 7.8). Based on AMSTAR-2 grading, none of the studies were without any critical methodological flaw in the conduction of meta-analysis. Among all included studies, the meta-analysis by Zhang *et al*[30] was found to be of the highest quality with an AMSTAR score of 10/11 (Table 5). However, this study too suffered from critical methodological flaws of including status of publication (i.e grey literature) as a criterion for inclusion and not providing the list of (included and excluded) studies.

Assessment of heterogeneity

All the studies included used I^2 statistic for heterogeneity assessment. Mild heterogeneity was noted in short-term UCLA score, tendon healing rates and patient satisfaction. Heterogeneity in the reporting of DASH score, Constant score and short-term re-tear rate was moderate; while heterogeneity of VAS, long-term UCLA score, ASES score, SST score, operative time and long-term re-tear rates was significant (Table 6). It is of utmost importance to probe into source of discordance among included studies, as recommendations generated are put into clinical practice and for developing public health-care policies[49]. The heterogeneity of results among the meta-analyses was primarily due to variation in the nature of primary studies included (other than RCTs).

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Results of Jadad decision algorithm

The pooled results from each included meta-analysis are presented in Figure 2. To identify the study which provides the best possible evidence to generate treatment recommendations, Jadad decision algorithm was adopted. Two authors independently applied the decision algorithm to determine the meta-analysis with the highest quality to develop recommendation on the use of PRP in ARCR. Considering that all the 20

studies aimed to answer similar clinical questions despite analyzing a varied spectrum of primary studies, the study with the highest quality was selected on the basis of its methodological quality, restrictions involved (such as language or publication status), databases involved and analysis protocols adopted (Figure 3).

Based on this algorithm, the meta-analysis by Zhang *et al*[30] was determined to be the highest-quality study. This study observed no major benefits on overall clinical outcomes and re-tear rate following PRP administration in full-thickness rotator cuff tears; while a reduction in the rate of re-tears was demonstrated for small- and medium-sized tears. However, the selected study is also not free of critical methodological flaw based on AMSTAR 2 criteria. Hence, we analysed the rationale for the development of the succedent systematic reviews as in Table 7, and tried to understand the evolution, variation in the techniques of procurement, and application of PRP across different studies with due consideration to the high-quality evidence developed in the recent years and arrived at the following results.

Significant heterogeneity was observed in the reporting of VAS, function outcome scores (long-term UCLA score, ASES score, SST score), operative time and long-term re-tear rates. Recent meta-analyses are more supportive of the role of intra-operative administration of PRPs at the bone-tendon interface in improving the overall healing and re-tear rates, functional outcome and pain. The initial size of the tear and type of repair performed do not seem to affect the benefit of PRPs. Among the different preparations used, leucocyte poor (LP)-PRP possibly offers the greatest benefit as a biological augment in these situations.

Major conclusions from the individual studies

Different studies employed specific criteria to include studies, with an aim to provide more useful and relevant information as compared to the previously-published literature. Chen *et al* (2019), Hurley *et al* (2020), Zhao *et al* (2021), Ryan *et al* (2021) and Li *et al* (2021) compared the effects of PRP preparations on the basis of their relative leucocyte concentrations[1,42,44,46,47].

The initial studies by Chahal *et al* (2012), Moraes (2013), Zhang *et al* (2013), Li *et al* (2014), Zhao *et al* (2014) and Xiao *et al* (2016) did not reveal any benefit following PRP application[31–34,37]. Warth *et al* (2014), Hurley *et al* (2018) and Xu *et al* (2021) observed that PRP was more helpful in enhancing the healing rates of large-sized tears[44,48]. Vavken *et al* (2015) and Cai *et al* (2015) reported better outcome following PRP application in small- to medium-sized tears[36,38]. The recent studies published by Han *et al* (2019), Wang *et al* (2019), Chen *et al* (2019), Yang *et al* (2020) and Cavendish *et al* (2020) concluded that intraoperative PRP application significantly enhanced the short- and long-term clinical outcome and mitigated the re-tear rates after RC repair[39,41–43,45]. The recently-published literature [Hurley (2020), Zhao (2021), Ryan (2021), Li (2021) and Xu (2021)] also seemed to demonstrate better outcome (functional scores and re-tear rates) with LP-PRP, as compared with LR-PRP[1,33,44,46,48]. The individual data of the included studies are presented in Table 7.

DISCUSSION

Till date, numerous RCTs have analyzed the efficacy of adjuvant PRP therapy in patients undergoing surgical repair of RC tears[6,30,39]. Although theoretically, biological augmentation with PRP can potentially enhance healing and mitigate failure rates after arthroscopic rotator cuff repair , our understanding of the exact role of PRP therapy in this scenario is still ambiguous[9,33]. Limited sample sizes, heterogeneity in the treatment protocols, PRP preparations and techniques employed; and the paucity of long term results have been their major limitations of the currently published studies on this subject[1,6].

To further strengthen the results, multiple meta-analyses have been conducted to consolidate the findings of more recent RCTs, so as to provide the higher level of evidence on the effectiveness of the intervention in operatively-treated RC tears[6]. However, the spectra of primary studies included in these recent analysis and the databases utilized for study inclusion are still discordant[1,37,48]. Hence, a systematic overview of these overlapping meta-analyses was planned in order to identify the

highest quality study among the available studies; as well as to formulate and generate recommendations regarding the use of adjuvant PRP in such situations.

Platelets are a source of high concentrations of different growth factors (like platelet-derived growth factor, transforming growth factor-beta, fibroblast growth factor, vascular endothelial growth factor and epidermal growth factor), which can potentially stimulate cell proliferation. They form a temporary matrix which can fill the defects and thereby provide a scaffold for cell migration and tissue remodelling[34]. The earliest meta-analysis on this subject was published by Chahal *et al*[32] in 2013. Although they observed marginal benefits in small and moderate sized tears, there was no major improvement in the overall re-tear rates or shoulder-specific outcomes after ARCR in larger or at-risk tears. Following this, in a Cochrane review, Moraes *et al*[31] reviewed studies involving intra-operative application of PRP; and concluded marginal benefits of PRP administration, especially with respect to improvements in short-term VAS and short-term re-tears. There has been a recent surge in the number of meta-analyses published on this subject since 2020[1,34,47,48]. While a majority of the older meta-analyses failed to show any major benefit of PRP therapy in this cohort of patients, more recent studies seem to re-iterate the potential benefits of adjuvant PRP treatment as evident from Figure 2. Older age, number of tendons involved, large tear size, duration of pre-operative symptoms and degree of pre-operative fatty degeneration have been postulated as some of the major factors predictive of high post-operative re-tear rates[32]. Table 7 discusses in detail the observations of each of these meta-analyses and enlists the reasons put forth by authors on the need for performing an additional meta-analysis in the presence of multiple pre-existing studies in the literature.

Among all the initial meta-analyses, the study with an excellent quality of methodology with a larger sample size and minimal heterogeneity was published by Zhang *et al*[30] in 2013. This study also concluded that adjuvant PRPs could reduce the re-tear rates in small and medium-sized rotator cuff tears, but not in massive or full-thickness tears. The meta-analyses by Li *et al* (2014) and Zhao *et al* (2014) incorporated a

few more later-published RCTs. Both these studies did not reveal any major benefits of PRPs in terms of both clinical outcome scores and re-tear rates.

Warth *et al*[35] (2014) conducted a meta-regression analysis to evaluate the effect of 6 different co-variates (level of studies included, tear size, single- *vs* double-row repairs, types of PRP preparation, manual *vs* commercially available PRP preparations; and method of application of PRP) on overall clinical and structural outcome. They concluded that Constant scores were significantly improved when the PRPs were applied over the tendon-bone interface; and re-tears were significantly reduced in tears larger than 3 cm which were repaired using double-row technique. In contrast, both the meta-analysis [Vavken *et al*[36]; Cai *et al*[38] (which included only RCTs)] published following this study revealed no benefit in large, full-thickness tears. In both these studies, PRPs enhanced healing rates only in small- to moderate-sized tears. Additionally, Vavken *et al*[36] concluded that despite its biological effectiveness; at the present costs, the use of PRPs is not a cost-effective strategy in arthroscopic repair of small- to moderate-sized RC tears. Another meta-analysis by Xiao *et al*[37](2016) tried to enhance the power of the analysis by including both level I and II studies. Nevertheless, they too failed to reveal any major benefit in terms of both clinical outcome and re-tear rates. By being less selective in including studies for analysis, the quality of the meta-analysis also significantly deteriorated, as compared to previous studies.

Between 2016 and 2018, many new RCTs were performed; and 4 new meta-analyses were published in 2018 and 2019, which included these recent studies too. Hurley *et al*[40] (2018; involving 18 studies) compared PRP and platelet-rich fibrin (PRF) in ARCR. They concluded that PRPs improved pain score (short-term and long-term), Constant score and re-tear rates in RC tears of all sizes. Another similar study by Han *et al*[39] (involving 13 RCTs) too reported reduced re-tear rate and meliorated clinical outcome with PRP therapy in ARCR. Wang *et al*[41] (2019; included only 8 RCTs) observed good outcome with PRPs when administered in ARCRs with single-row technique. Chen *et al*[42] (2019) performed another higher quality meta-analysis (involving 18 Level 1 studies); and concluded that long-term re-tear rates were

significantly improved with PRP therapy. Additionally, the functional outcome scores (Constant score, UCLA score – at long- and short-terms) and VAS scores also were better in the PRP-treated group. They also performed detailed sub-group analysis in 3 different categories and concluded that: a. Functional outcome measures were more significantly improved when multiple tendons were torn or ruptured, b. Leukocyte-rich PRP (LR-PRP) group had much better improvement in Constant scores as compared with LP-PRP, and c. Patients receiving gel-preparations of PRP had significantly greater Constant scores than their respective comparison groups. They also assessed the minimal clinically important differences (MCID) for these patient-related outcome (PRO) measures. It was concluded that although significant improvements were observed in multiple functional outcome measures in the PRP-treated patient group, none reached their respective MCID. They opined that despite a reasonable number of publications on this subject, limited data availability, substantial study heterogeneity and poor methodological quality hampered our ability to reach firm conclusions regarding PRPs.

Recent meta-analyses and their observations:

Between 2020 and 2021, 7 new meta-analyses have been published on this topic. Owing to the availability of better quality, larger-scale RCTs over the recent years, these recent meta-analyses have been able to put forth stronger recommendations regarding the administration of PRPs. Cavendish *et al*[43] reported 16 RCTs and prospective trials (1045 participants), Hurley *et al*[44] included 13 RCTs (868 participants), Yang *et al*[45] analyzed 7 RCTs published between 2013 and 2018 (541 participants), Zhao *et al*[46] involved 10 RCTs (742 participants), Ryan *et al*[1] included 17 RCTs (1104 participants), Li *et al*[47] evaluated 23 RCTs (1440 patients) and Xu *et al*[48] studied 14 RCTs (923 patients). Hurley *et al*[44] analyzed RCTs comparing LP- or LR-PRP against controls, Zhao *et al*[46] evaluated studies involving LP-PRP, Ryan *et al*[1] evaluated 4 different types of PRPs (pure platelet-rich plasma [P-PRP], leukocyte and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte and platelet-rich fibrin); and Li *et al*[47] analyzed RCTs comparing PRP or PRF to controls in ARCR. The remaining 3 studies included all

RCTs evaluating the overall role of PRPs (with or without comparison to a control group)[43,45,48].

All the 7 recent meta-analyses support the role of PRPs in ARCR. Overall, based on their recommendations, PRPs are preferably delivered intra-operatively at the bone-tendon interface for the best possible outcome. Cavendish *et al*[43] reported that PRPs significantly reduce the failure rates after ARCR, irrespective of the size of tear. Xu *et al* demonstrated substantially improved re-tear rates following intra-operative use of PRP in large- or massive-sized tears[48]. Hurley *et al*[44] concluded that LP-PRP reduces re-tear, enhances healing potential and improves PRO, as compared with a control. Nevertheless, they could not make any strong recommendations regarding its superiority or inferiority as a biological augment, in comparison with LR-PRPs. Even in the meta-analysis by Zhao *et al*[46], LP-PRP was demonstrated to significantly reduce medium- and long-term post-operative re-tear rates in patients undergoing ARCR, irrespective of the size of tear and the technique of repair. Nevertheless, when defined in terms of MCID, the use of LP-PRP failed to reveal any clinically meaningful benefits in terms of post-operative VAS and PRO measures. Among the 4 different types of PRP employed, only P-PRP demonstrated statistically significant improvement in re-tear rate and Constant score. Theoretically, LP-PRP enhances the formation of normal collagen and mitigates the synthesis of inflammatory mediators. On the other hand, LR-PRP augments the cell catabolism and inflammatory response, both of which are not conducive for tendon healing. Therefore, in acute traumatic RC tears, use of LR-PRP may impair post-operative tissue healing. These recent meta-analyses also seem to indicate the superiority of LP-PRP (over LR-PRP) in ARCR[48]. Thus, despite multiple studies published on this topic, the literature is still unclear on whether the use of PRP is more beneficial in massive and full-thickness tears or smaller and partial thickness injuries[36,38,44,48]. A majority of the studies in the literature have also not clearly determined the correlation between the type of RC repair and the effect of PRP application[29-40,42-48]. However, two recent studies [Wang *et al* (2019) and Yang *et al* (2020)] have shown better outcome with PRP use following single-row RC repairs[6,41].

These recent studies have also cautioned regarding significant heterogeneity in the available preparations of PRPs, which leads to inconsistent outcome and difficulty in making strong recommendations in favour or against this treatment modality. Yang *et al*[45] demonstrated a significant decrease in re-tears, as well as a substantial improvement in short-term pain severity (VAS) and short-term functional outcome (Constant and UCLA scores). In a sub-group analysis, they also demonstrated meliorated outcome (in terms of VAS, functional scores and re-tear) in both single- and double-row repair groups. In a comparison study by Li *et al*[47] between PRP and PRF, PRP demonstrated significant improvement in pain, functional outcome and re-tears; while PRF only improved Constant score.

Directions for Future

Although PRP has been considered as a minimally-invasive effective non-operative treatment methodology for partial RC tears,[50] its utility as an adjuvant in the ARCR needs further refinement to preclude the heterogeneity in the results obtained and obtain consistent beneficial effects of the additive intervention performed. For example, role of repeat administration of PRP and utility of scaffolds as a medium of sustained delivery of the growth factors from the platelet concentrate may provide even more beneficial effects compared to the single direct use post-ARCR.[51] Although our systematic overview establishes the efficacy of PRP as an adjuvant to ARCR, there remains heterogeneity among the study results obtained due to the variability in the preparation and the utility of PRP. To clarify these aspects, blinded RCTs investigating the above-mentioned lacunae are required in the future.

Limitations

This study has some limitations. The quality of the meta-analyses identified in our study were of Level I/II evidence due to the quality of the included primary studies in them. Hence, we were unable to provide a Level I recommendation on the utility of PRP in ARCR with the existing literature. This systematic overview may be influenced by the limitations and biases involved in the meta-analyses and their primary studies. Moreover, selecting the meta-analysis of highest quality based on Jadad algorithm

generates recommendations based on the results of the selected meta-analysis at the cost of studies missed from their primary search as highlighted in Table 2. Moreover, we identified many recent meta-analyses, apart from the meta-analysis selected through Jadad algorithm, which had the power of the recent RCTs on the subject. Hence, we resorted to give a collaborative evidence based on all the recent evidence though they lack the methodological robustness of the study identified by Jadad algorithm thereby making the final level of recommendation that was achieved out of this study to be Level II. Heterogeneity was noted across the studies in terms of their methods of preparation, use of activators, and method of application of PRP which could have accounted for the variability noted across the primary studies and the meta-analyses that included them into analysis.

CONCLUSION

Based on our systematic overview of the existing meta-analyses, we could observe that despite multiple publications on this subject over the past years, methodological quality of the included studies and heterogeneity in protocols employed across different individual trials continue to remain major impediments in clearly defining the role of PRPs in ARCR. Nevertheless, the recent meta-analysis published over the past 2 to 3 years seem to indicate a clear benefit of intra-operative use of PRPs at the bone-tendon interface in terms of post-operative pain, functional outcome and re-tear rates (irrespective of the type of repair performed). Although the older studies supported its role in only small to moderate tears, recent studies indicate a definite benefit in tears of all sizes (including massive ones). Among the different preparations used, LP-PRP possibly offers the greatest benefit as a biological augment in these situations.

ARTICLE HIGHLIGHTS

Research background

Platelet-rich plasma has been gaining popularity as an agent for biological augmentation either as the sole treatment modality or as an adjunct to surgical repair.

Research motivation

There is growing evidence on the positive effects of platelet-derived autologous growth factors on collagen production, cell proliferation, tissue revascularization and tendon regeneration thereby making them useful as an augment to arthroscopic rotator cuff repair.

Research objectives

The overall purpose of the current study was to perform a detailed systematic review of the existing meta-analyses evaluating the role of PRP in patients undergoing rotator cuff repair; and to specifically provide answers to the following research questions, namely: a. To evaluate the effect of this strategy on overall clinical outcome scores, b. To evaluate the reduction in re-tear or failure rates, c. To analyse the evolution and variations in the techniques of procurement and application of PRP across different studies, and d. To critically analyse and interpret the best currently available evidence and provide recommendations; and e. To discern the major gaps in the existing literature and identify the scope for future research on this subject.

Research methods

We then utilized the Jadad decision algorithm to identify the study with the highest quality to represent the current best evidence to generate the recommendation.

Research results

Recent meta-analyses are more supportive of the role of intra-operative administration of PRPs at the bone-tendon interface in improving the overall healing and re-tear rates, functional outcome and pain. The initial size of the tear and type of repair performed do not seem to affect the benefit of PRPs. Among the different preparations used, leucocyte

poor (LP)-PRP possibly offers the greatest benefit as a biological augment in these situations.

Research conclusions

Based on this systematic overview, we give a Level II recommendation that intra-operative use of PRPs at the bone-tendon interface can augment the healing rate, reduce re-tears, enhance functional outcome and mitigate pain in patients undergoing arthroscopic rotator cuff repair.

Research perspectives

LP-PRP possibly offers the greatest benefit in terms of healing rates, as compared with other platelet preparations.

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PRIMARY SOURCES

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3	Ryan J. Warth, Grant J. Dornan, Evan W. James, Marilee P. Horan, Peter J. Millett. "Clinical and Structural Outcomes After Arthroscopic Repair of Full-Thickness Rotator Cuff Tears With and Without Platelet-Rich Product Supplementation: A Meta-analysis and Meta-regression", Arthroscopy: The Journal of Arthroscopic & Related Surgery, 2015 Crossref	27 words — < 1%
4	Merkx, M.A.W.. "Reconstruction of the mandible using preshaped 2.3mm titanium plates, autogenous particulate cortico-cancellous bone grafts and platelet rich plasma: a report on eight patients", International Journal of Oral & Maxillofacial Surgery, 200412 Crossref	26 words — < 1%
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