Biologic Augmentation Reduces the Failure Rate of Meniscal Repair

A Systematic Review and Meta-analysis

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Background: Clinical results after isolated meniscal repair are not always satisfactory, with an overall failure rate of around 25%. To improve the success rate of meniscal repair, different biologic augmentation techniques have been introduced in clinical practice, but their real efficacy is still controversial.

Purpose/Hypothesis: To evaluate the safety, clinical results, and failure rate of biologic augmentation techniques for meniscal repair. The hypothesis was that biologic augmentation would improve the results of meniscal repair.

Study Design: Systematic review and meta-analysis of comparative studies.

Methods: A systematic review of the literature was performed in March 2020 of 3 electronic databases (PubMed, Scopus, and the Cochrane Library) regarding meniscal repair combined with biologic augmentation techniques. Articles combining biologic augmentation with other surgical procedures besides meniscal suture were excluded. The quality of the included studies was assessed using a modified Coleman Methodology Score, and the risk of bias was evaluated using the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) and the RoB 2.0 (Revised Tool for Risk of Bias in Randomized Trials) for nonrandomized and randomized controlled trials, respectively.

Results: A total of 11 studies were included in the qualitative analysis: platelet-rich plasma (PRP) augmentation in 6 comparatives studies, fibrin clot augmentation in 2 case series, and mesenchymal stem cells augmentation in 2 case series and 1 case report. One severe adverse event of septic arthritis was reported for PRP 1 month after surgery. The quality of evidence evaluated with the modified Coleman Methodology Score was low overall. Five studies reporting on 286 patients (111 PRP augmentation, 175 control) were included in the quantitative synthesis. A significantly lower risk of failure was documented in the PRP augmentation group as compared with the control group: 9.9% (4.5%-19.1%) versus 25.7% (12.7%-38.7%) ($P < .0005$).

Conclusion: The literature on biologic meniscal augmentation is recent and scarce. Only a few comparative trials are available, all focusing on the potential of PRP. The meta-analysis documented that PRP is safe and useful in improving the survival rate, with a 9.9% rate of failure versus 25.7% for the control group. Further high-level studies are needed to confirm these findings and identify the most effective biologic augmentation strategy to improve the outcome of meniscal repair.

Keywords: meniscal repair; meniscal suture; biologic augmentation; fibrin clot; PRP; MSC

Meniscal lesions represent one of the most frequent orthopaedic injuries, resulting in an estimated 61 meniscectomies per 100,000 inhabitants.[23,27,47] The loss of meniscal tissue in an injured and postmeniscectomy (partial or total) meniscus can alter joint biomechanics and the biologic environment, promoting the development of early osteoarthritis (OA) with consequent joint pain, decreased function, and impairment of quality of life.[43] Accordingly, especially in young patients, meniscal tissue should be preserved as much as possible to prevent OA development.[21] In this light, meniscal repair techniques gained increasing interest to address tears, especially in areas with adequate blood supply.[18,44] Meniscal sutures allow one to stabilize the tear, favoring the physiological meniscal repair processes through the proliferation of cells involved in tissue repair processes, their adhesion, and, finally, the healing of the meniscal lesion.[2,13] Nevertheless, clinical results after isolated meniscal repair are not always satisfactory, with an overall failure rate of around 25%.[1,41,48,51]

In the past few decades, different approaches have been studied to improve the success rate of meniscal repairs, with a focus on biologic augmentation. Preclinical studies showed that different biologic augmentation techniques could increase meniscal cell activity and promote meniscal

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tissue repair.[6,61] In particular, platelet-rich plasma (PRP) has been used to harness anabolic potential through the release of growth factors and bioactive molecules, showing positive effects in terms of cell proliferation and matrix production.[6] Also the application of fibrin clot can provide chemotactic and mitogenic stimuli for reparative cells and scaffold properties to guide the reparative process.[3] Finally, the healing improvement described in the literature when meniscal repair was associated with anterior cruciate ligament reconstruction (ACLR),[12,59] as attributed to the release of mesenchymal stem cells (MSCs) from the tibial tunnel and supported the benefit of using biologic factors to improve meniscal healing. Accordingly, biologic augmentation techniques have been introduced in clinical practice, but their real efficacy is still controversial.[25]

The aim of this systematic review and meta-analysis was to evaluate the safety, clinical results, and failure rate of biologic augmentation techniques for meniscal repair. The hypothesis was that biologic augmentation would improve the results of meniscal repair.

METHODS

Search Strategy and Article Selection

A systematic review of the literature was performed to select all articles dealing with biologic augmentation techniques for meniscal repair. The search was conducted on March 20, 2020, of 3 medical electronic databases (PubMed, Scopus, and the Cochrane Library) using the following parameters:

> ((Meniscus) OR (meniscal)) AND ((repair) OR (suture)) AND ((growth factors) OR (PRP) OR (platelet-rich plasma) OR (plasma rich in growth factors) OR (platelet derived growth factor) OR (platelet derived) OR (platelet gel) OR (platelet concentrate) OR (PRF) OR (platelet rich fibrin) OR (platelet rich membrane) OR (ACP) OR (autologous conditioned plasma) OR (PRGF) OR (platelet lysate) OR (stem cells) OR (mesenchymal stem cells) OR (stromal cells) OR (fibrin clot)).

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used.[50] A flowchart of the study selection for qualitative and quantitative data synthesis is reported in Figure 1. The screening processes and analysis were performed by 2 independent observers (A.P. and D.R.), with disagreement solved by consensus with a third author (L.A.).

Data Extraction and Qualitative Synthesis

In the first step, the articles were screened by title and abstract according to the following inclusion criteria: clinical reports of any level of evidence, including case reports, written exclusively in English about meniscal repair combined with biologic augmentation techniques. Exclusion criteria were articles written in other languages, preclinical studies or reviews, and articles combining biologic augmentation to surgical procedures other than meniscal suture. In the second step, the full texts were analyzed and screened, with exclusions according to the previously described criteria. Moreover, studies reporting only the results of meniscal suture combined with ACLR were excluded to avoid the bias effect from the demonstrated improvement of meniscal healing after ACLR.[59] Reference lists of the selected articles as well as from the systematic reviews found with the first and second rounds were also screened. Relevant data—article, study type, number of patients, mean age, sex, follow-up, type of meniscal lesions, biologic augmentation procedure, adverse events, and results—were extracted and collected in a database with the consensus of the 2 observers to be analyzed for the aim of the present article.

Assessment of Quality of Evidence and Risk of Bias

The quality of the studies was assessed independently by 2 observers (A.P. and D.R.) with disagreements resolved by consensus with a third author (L.A.), using the subscales of a Coleman Methodology Score modified by Kon et al[37] to better suit the studies about knee surgical procedures and as already applied to analyze meniscal literature.[21] Bias within each study was evaluated using ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) and RoB 2.0 (Revised Tool for Risk of Bias in Randomized Trials), as approved by the Cochrane Collaboration for nonrandomized and randomized controlled trials (RCTs), respectively.[53,54]

Quantitative Synthesis and Statistical Analysis

A meta-analysis was performed to analyze the failure rates of meniscal repair with biologic augmentation (treatment group) versus meniscal repair alone (control group), including only comparative articles reporting the number of

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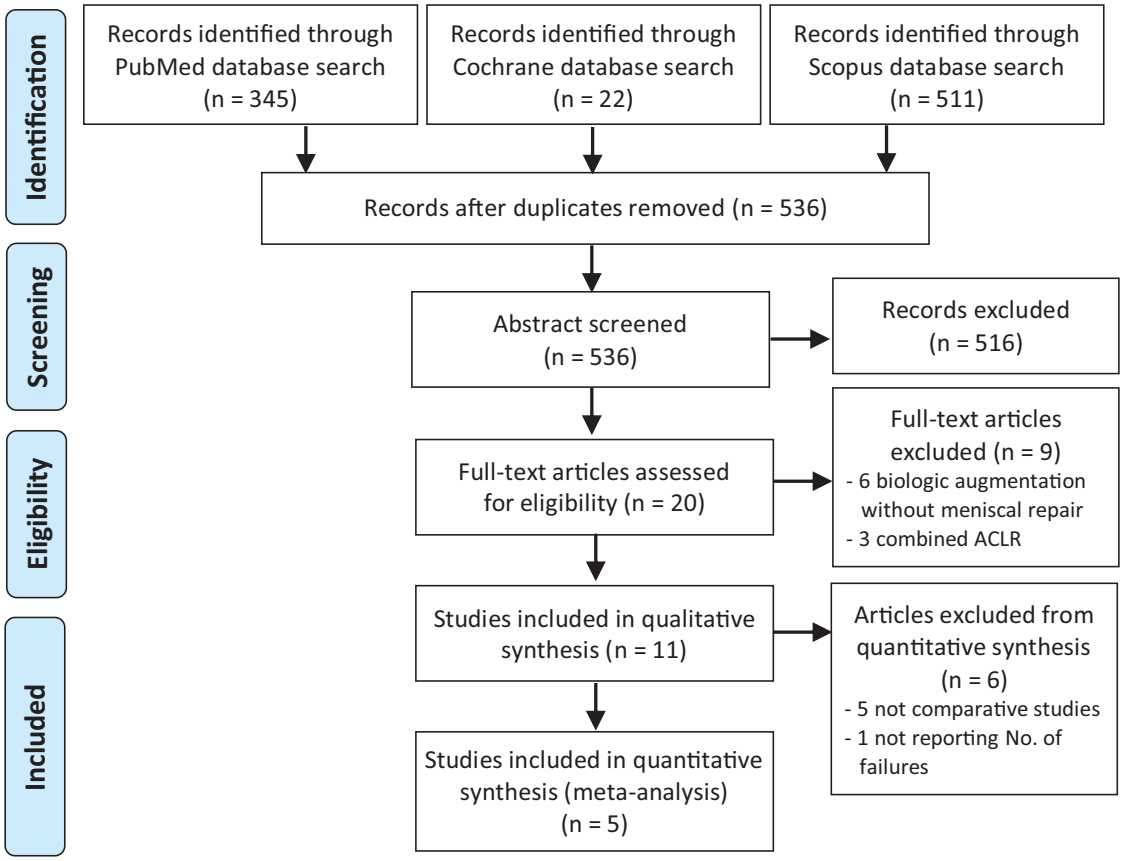

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the study selection process. ACLR, anterior cruciate ligament reconstruction.

failures of the treatment and control groups. Collected but nonreported data were asked to the corresponding authors of the studies. The statistical analysis and forest plot were carried out according to Neyeloff et al[42] using Microsoft Excel. The Mantel-Haenszel method was used to provide a pooled odds ratio across the studies. Statistical heterogeneity among the groups was evaluated by the Q test, and the I^2 method was used to quantify the heterogeneity. Statistical tests for heterogeneity were used to determine whether repair failure rates were the same in all studies. The results from the Cochran Q test rejected the null hypothesis, revealing that there was low heterogeneity across the studies ($Q = 4.77$). Furthermore, the I^2 statistic revealed that a low percentage of the total variation observed across studies was due to heterogeneity instead of chance ($I^2 = 16.12\%$). These findings justified the choice of using a fixed effects model for conducting the analysis (Mantel-Haenszel, Robins-Breslow-Greenland method). $P = .05$ was considered statistically significant.

RESULTS

Literature Search Results

The database search identified 536 records. Abstracts were screened and selected according to the inclusion/exclusion criteria, and 20 full-text articles were obtained and assessed for eligibility (Figure 1). Nine articles were excluded: In 6 studies, biologic augmentation was combined with other meniscal treatments,[7,9,34,56,58,63] and in 3 studies, meniscal suture was combined with ACLR.[28,46,57] Thus, 11 studies were included in the qualitative analysis (a detailed study description is reported in Appendix Table A1). All articles were published from 2014 onward. Six were comparative studies: 1 RCT, 3 prospective comparative studies, and 2 retrospective comparative studies. The other studies were 4 prospective case series and 1 case report. Among the 11 studies in the qualitative synthesis, 5 noncomparative studies[31,32,40,49,60] and 1 comparative study did not report the number of failures for biologic meniscal augmentation and control[36] and were excluded, leaving 5 comparative studies (all on PRP) for quantitative synthesis on the failure rate of meniscal repair.

Quality of Evidence and Risk of Bias

As evaluated with the modified Coleman Methodology Score, the quality of evidence was low overall for the studies. In fact, 4 studies had a score >60 (with 1 score >70); 3 studies, between 50 and 59; 3 studies, between 40 and 49; and 1 study, <40 (Appendix Table A1). As evaluated with RoB 2.0, an overall low risk of bias was assessed for the only

TABLE 1
Assessment of Risk of Bias for the RCT Using the RoB 2.0[a]

Lead Author (Year)	Randomization Process	Deviations From Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk
Kaminski[33] (2018)	Low	Low	Low	Low	Low	Low

[a]RCT, randomized controlled trial; RoB 2.0, Revised Tool for Risk of Bias in Randomized Trials.

TABLE 2
Assessment of Risk of Bias for Non-RCTs Using the ROBINS-I[a]

	Bias[b]							
Lead Author (Year)	1: Confounding	2: Participants	3: Interventions	4: Intended Interventions	5: Missing Data	6: Outcomes Measurement	7: Reported Result	Overall Risk
Pujol[45] (2015)	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Griffin[24] (2015)	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Kemmochi[36] (2018)	Moderate	Serious	Serious	Low	Low	Low	Moderate	Serious
Dai[10] (2019)	Moderate	Serious	Low	Low	Moderate	Low	Serious	Serious
Everhart[17] (2019)	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate

[a]RCT, randomized controlled trial; ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions.
[b](1) Bias attributed to confounding. (2) Bias in selection of participants. (3) Bias in classification of interventions. (4) Bias attributed to deviations from intended interventions. (5) Bias attributed to missing data. (6) Bias in measurement of outcomes. (7) Bias in selection of the reported result.

RCT[33] (Table 1). The evaluation with ROBINS-I for comparative nonrandomized studies showed a moderate risk of bias for 3 articles[17,24,45] and a serious risk for the remaining 2 articles (Table 2).[10,36]

Qualitative Synthesis

The studies evaluated in the qualitative synthesis included 353 patients treated with meniscal repair procedures. The sample was 69.8% male and 30.2% female (data were available for 202 patients in 10 studies); the mean age was 33.2 years (data were available for 202 patients in 10 studies); and patients were evaluated at a mean 35.7 months of follow-up (data were available for 353 patients in 11 studies). The repaired meniscal lesions formed a heterogeneous group, including radial, longitudinal, horizontal, root, and complex meniscal injuries located in medial or lateral menisci (including lateral discoid meniscus). Biologic augmentation procedures were performed in 173 cases. In all studies, biologic augmentation was directly applied at the site of the meniscal lesion before or after meniscal suturing. As reported in Appendix Table A1, patients were evaluated with heterogeneous clinical scores, and magnetic resonance imaging (MRI) and second-look arthroscopy evaluations were performed in 4 and 2 studies, respectively.

The biologic augmentation techniques reported in the 11 studies were PRP augmentation in 6 comparatives studies,[10,17,24,33,36,45] fibrin clot augmentation in 2 case series,[32,40] and MSC augmentation in 2 case series[49,60] and 1 case report.[31]

PRP Augmentation. PRP was the most frequently studied biologic augmentation for meniscal repair, with 6 comparative studies on 128 patients treated with PRP as compared with 180 controls treated by only meniscal suture. In all the studies that specified the administration route, PRP was directly administered in situ at the time of the meniscal repair, which was performed using different suture techniques (see Appendix Table A1 for details).

In the first published article, a prospective case-control study of 2015, Pujol et al[45] treated 34 patients affected by horizontal meniscal tears: 17 with a mini-arthrotomic meniscal suture and 17 with PRP-augmented meniscal repair. At 24-month follow-up, significantly higher clinical and MRI scores were reported for PRP group, with 1 subsequent meniscectomy considered a failure versus 2 in the control group. In a retrospective comparative study of the same year, Griffin et al[24] analyzed 35 patients treated with arthroscopic meniscal repair, of which the suture was augmented with PRP in 15 patients: at the final 4-year follow-up, no significant differences were found in terms of clinical outcomes and failure rate.

In the RCT, Kaminski et al[33] compared the results of 20 patients treated with all-inside meniscal suture augmented with PRP with 17 treated via meniscal repair and placebo. At midterm follow-up, patients in the PRP group demonstrated a significant superior healing rate (as assessed with second-look arthroscopy or MRI) as compared with the

control group (85% vs 47%), although with no significant differences in clinical scores. In 2018, Kemmochi et al[36] published a comparative study including 22 patients who had undergone meniscal repair, 17 with PRP augmentation. At a short-term follow-up of 6 months, a significant improvement in clinical scores was reported in the treatment and control groups. In a retrospective comparative study in 2019, Dai et al[10] analyzed 29 patients with discoid lateral meniscal tears: 15 patients underwent saucerization of discoid meniscus and arthroscopic meniscal suture, while the same treatment was augmented with a local injection of PRP in 14 patients. At 2 years, a clinical improvement was observed in both groups, with better results for younger patients and without significant differences between groups in terms of clinical scores and failures.

Finally, Everhart et al[17] analyzed 550 patients in a 4-group cohort study: 106 isolated meniscal repairs, 45 meniscal repairs augmented with PRP, 241 meniscal repairs combined with ACLR, and 158 meniscal repairs augmented with PRP combined with ACLR. At 3 years of follow-up, PRP augmentation did not provide any improvement in terms of meniscal survival when combined with ACLR. Conversely, by taking into account only the patients with meniscal repair procedures and without combined ACLR, according to the inclusion criteria of the present review, PRP was independently associated with a lower risk of failure at the final follow-up.

Fibrin Clot Augmentation. Two studies on 34 patients overall were included in which an autologous blood clot was applied. The first study, published in 2014 by Kamimura and Kimura,[32] analyzed the outcome of 10 patients with degenerative horizontal tears treated with fibrin clot–augmented meniscal repair. At midterm follow-up, all patients showed significant clinical improvement, but 7 patients showed complete healing at second-look arthroscopy performed at 6-month follow-up. More recently, Nakayama et al[40] published a prospective study including 24 patients affected by symptomatic degenerative meniscal lesions and treated with meniscal suture augmented with fibrin clot. At midterm follow-up, a significant improvement of the subjective scores was reported, while 6 of 24 meniscal repairs were considered clinical failures for a 75% success rate.

MSC Augmentation. Three articles, including 2 small case series and 1 case report, described the results of different types of MSCs as augmentation for meniscal repair in 11 patients overall. In the case report by James et al,[31] a 29-year-old man with a symptomatic complete radial tear of the medial meniscus underwent a crisscross transtibial suture augmented with an autologous injection of PRP and bone marrow aspirate concentrate in the repair site. A second-look arthroscopy performed after 6 months revealed complete meniscal healing, and the patient reported significant clinical improvement at 1 year. A clinical study on meniscal repair augmented with expanded bone marrow–derived MSCs delivered through a collagen scaffold was described by Whitehouse et al[60] in 2017. Analyzing 5 isolated meniscal lesions at short-term follow-up, they reported clinical improvement in 3 patients over the first 12 months and stable results between 12 and 24 months, while the other 2 patients underwent meniscectomy for incomplete healing. Finally, Sekiya et al[49] augmented the meniscal repair with expanded autologous synovial MSCs in 5 patients presenting complex degenerative meniscal lesions. All patients showed significant improvement in the majority of the clinical scores evaluated at 2-year follow-up, without failures.

Safety and Complications. The only severe adverse events reported in the studies included a case of septic arthritis in the PRP group 1 month after surgery, which resolved after joint washing combined with 45 days of oral antibiotics, and a local hematoma requiring surgical drainage in a patient in the control group, both described by Pujol et al.[45] For mild adverse events, Kamimura and Kimura[32] reported 1 case of asymptomatic fast-fix suture displacement, which was removed during an arthroscopic postoperative evaluation. Sekiya et al[49] described 39 mild adverse events, most represented by knee pain or joint effusion, although 3 cases were possibly related to MSC transplantation: a C-reactive protein increase in 1 case, which resolved after 2 weeks, and 2 cases of localized warmth and knee effusion, which occurred at 14 days after cell transplantation and completely resolved within 24 weeks. Four studies reported no occurrence of complications,[31,33,36,60] while 4 studies did not report about complications.[10,17,24,40]

Quantitative Synthesis and Meta-analysis on Failure Rates

According to the inclusion criteria, 5 studies[10,17,24,33,45] reporting on 286 patients were included in the quantitative synthesis: 111 in the biologic augmentation group and 175 in the control group. The 1 RCT and 4 comparative studies analyzed the outcome and failure rate at a mean ± SD follow-up of 38 ± 13 months. Because of data heterogeneity, meta-analysis was possible on only the failure rates.

All 5 studies exclusively analyzed PRP augmentation. As reported in Appendix Table A1, they described meniscal repair performed in different patterns of tears (vertical, horizontal, radial, and root) through arthroscopic or arthrotomic suture techniques and by applying different types of PRP. The mean sample size of the studies in the quantitative analysis was 57, with means of 22 and 35 in the meniscal augmentation and control groups, respectively. Failures were defined differently, as subsequent reoperation (meniscectomy or iterative repair of the same meniscus),[10,17,24,45] joint line symptoms (pain and/or locking or swelling),[10] or healing failure at MRI or second-look arthroscopy with subsequent meniscectomy.[33]

In the studies, 11 failures in the meniscal augmentation groups and 45 failures in the control groups occurred, for overall failure rates of 9.9% (95% CI, 4.52%-19.1%) and 25.7% (95% CI, 12.7%-38.7%), respectively. The comparison of odds ratios for failure between the groups demonstrated a significant lower risk of failure in the meniscal augmentation group as compared with the control group (odds ratio, 0.31; 95% CI, 0.14-0.69; $P < .0005$) (Figure 2).

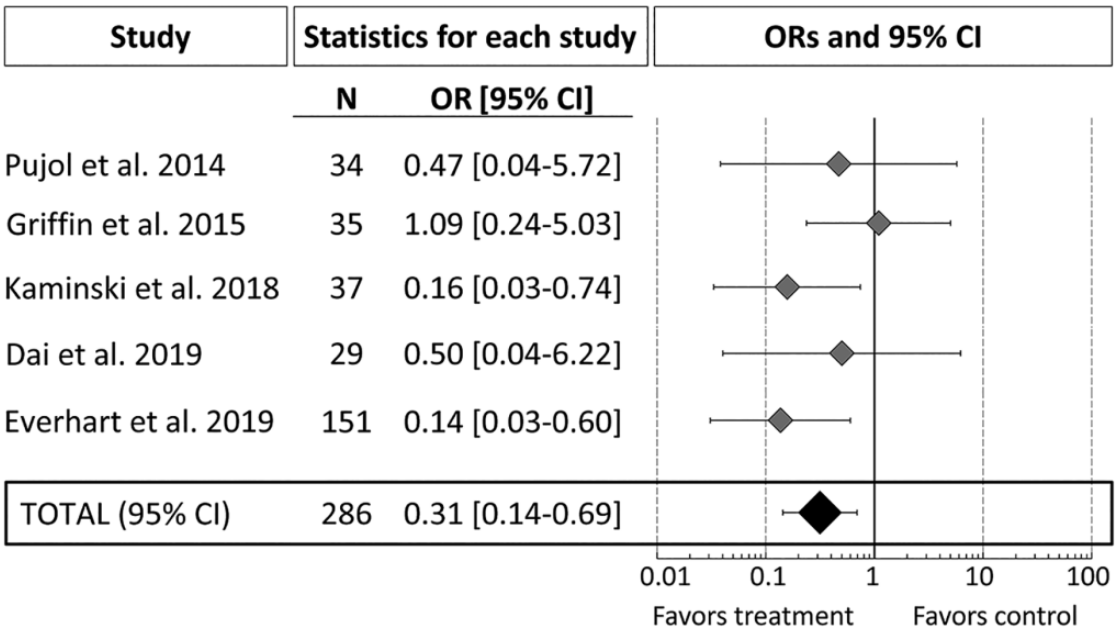

Figure 2. Forest plot of the 5 studies comparing failure rates between meniscal repair with platelet-rich plasma augmentation and isolated meniscal repair. The gray diamonds represent the point estimates of the weighted odds ratios (ORs) for each study, and the horizontal bars represent the 95% CIs. The black diamond represents the summary odds ratio.

DISCUSSION

The main finding of this study was that meniscal repair combined with biologic PRP augmentation presents a reduced failure risk as compared with isolated meniscal repair. Other biologic augmentation procedures have been reported in the literature, ranging from fibrin clot to MSCs, with a low number of adverse events but still poor evidence supporting its use in clinical practice.

The concept of meniscal repair dates back a long time,[14] and in the past few decades, it has gained more support to preserve meniscal structure and function.[26,35] At the same time, there is an increasing awareness about the nonnegligible failure rate in isolated meniscal repairs. The reason lies in the well-known low healing potential of the meniscal structure, which can be attributed to a biologic impairment related to the poor vascularity and cellularity of meniscal tissue.[2] In this light, the first attempts to add biologic products as meniscal repair augmentation started in the 1990s with the use of fibrin clot.[28] This is a biologic blood-derived product containing chemotactic factors, similar to PDGF (platelet-derived growth factor) and fibronectin, which may stimulate local cell activity within the meniscus and attract synovial cells to favor the meniscal healing process.[3,28] After positive preclinical results,[3] Henning et al[28] and van Trommel et al[57] studied the clinical effectiveness of arthroscopic meniscal sutures augmented with fibrin clot in patients with concomitant ACLR. Both studies reported promising results, with a lower failure rate in the menisci treated with the fibrin clot than in those treated with an isolated meniscal repair (8% vs 41%).[28] More recently, Ra et al[46] confirmed these results in a series of 12 patients affected by meniscal radial tears, with complete healing found in 11 cases. Nevertheless, the aforementioned studies included mainly patients undergoing concomitant ACLR, thus impairing the possibility of isolating the real effect of meniscal fibrin clot augmentation. The 2 case series reporting isolated meniscal repair augmented with fibrin clot in the current review[32,40] showed doubtful benefits in terms of clinical results, with a success rate of 70% to 75%, and were supported by a low level of evidence. Moreover, several potential contraindications have been underlined for fibrin clots, such as the additional time required to prepare a clot, the lack of a standardized technique, and the risk of contamination related to the preparation in the operating room of the exogenous fibrin clot.[11]

The development of new biologic options, PRP in particular, led to an acceleration in the use of augmentation techniques for meniscal repair in the past years. PRP has already been applied in different orthopaedic fields. Its autologous origin, easy preparation, and possible release of a high local concentration of growth factors—including PDGF, transforming growth factor beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1)—make PRP an attractive solution with plausible application in meniscal-repair procedures, with potentially higher effects than those of fibrin clot. The rationale for this application of PRP was confirmed by the current literature, with comparative studies[10,17,24,33,36,45] demonstrating its safety and positive effects on meniscal healing. Nevertheless, the low number of recently published studies underlines that the field of meniscal-repair augmentation is still in its infancy and is experiencing a rapid development. In fact, to date, results are still very controversial, and 2 recent systematic reviews concluded that patients undergoing meniscal repair with PRP augmentation

experience clinical outcomes similar to those of conventional meniscal repair[4] and that the available evidence is insufficient to support the efficacy of PRP augmentation.[25] In particular, the second of these reviews[25] was a study that did not report failure rates and was therefore not included in our meta-analysis.[36] These results were partially confirmed by the qualitative analysis of the current article, with the description of a few low-quality studies reporting controversial clinical results about the efficacy of PRP, and these conclusions were extended to different biologic augmentation procedures for meniscal repair, such as fibrin clot and MSCs. Nevertheless, a different scenario was described through the meta-analysis of failures reported in comparative studies about PRP.

It is worth noting that in meniscal repair procedures, the crucial aspect to be improved regards the survival of the meniscal repair, more than the clinical outcomes of the procedure to avoid the detrimental effect of meniscal tissue loss. In the current study, this aspect was analyzed with stricter selection criteria with respect to the previous literature—specifically, by including the largest study of PRP augmentation with data on isolated meniscal repair[17] and excluding patients with concomitant ACLR, which is a well-known confounding factor. This led to a different conclusion than that seen in previous analyses: This meta-analysis demonstrated that meniscal repair augmented with PRP presents a significantly higher survival rate than that of the isolated meniscal suture. The present analysis including >350 patients documented a failure rate of 25.7% in the control group, in line with the literature evidence about meniscal sutures.[1,41,48,51] Conversely, PRP-augmented repair presented a significantly lower risk of failure when compared with controls, with a failure rate of 9.9%. These results support the potential of platelet concentrates to deliver growth factors and bioactive molecules.[15]

Preclinical studies showed the positive effects of growth factors on meniscal cells. Among these, Izal et al[29] conducted a study on sheep affected by meniscal injuries and showed an important role of TGF-β1 and IGF-1 to promote meniscal cell interaction and proliferation, respectively. PRP also contains VEGF, an important angiogenic factor whose role in preclinical studies led to an increased proliferation of rat meniscal cells in vitro and an enhanced vascularization of menisci in vivo.[19] Moreover, PDGF showed a significant effect on proteoglycan stimulation and increased meniscal cellularity in the porcine meniscus.[38] Overall, the theoretical effects underlined for these growth factors in preclinical models might explain the benefit documented for the clinical application of PRP as a biologic augmentation procedure for meniscal repair.

Nevertheless, these findings have to be interpreted in light of the several limitations presented by the available literature, including the low number of studies and the heterogeneity of patient cohorts and treatment approaches. Different types of meniscal lesions, types of PRP for the meniscal-repair augmentation, and surgical PRP application methods and postoperative rehabilitation protocols were evaluated, making subanalysis not possible. Different lesions may respond differently to the biologic augmentation, and the application of PRP in a fibrin form or a more fluid form may present varying efficacies. However, in the comparative studies in the meta-analysis, it was not possible to investigate different PRP application modalities, and treatment failures were not stratified by meniscal tear zone and type, making it impossible to shed some light about these aspects. Moreover, there is an increasing awareness on the complexity of PRP itself in light of its heterogeneity according to the preparation and application modalities, and the most suitable protocol to exploit PRP potential by concentrating the most effective cluster of growth factors to help meniscal healing remains to be defined.[8,39] Thus, the oversimplified nature of the current meta-analysis has to be recognized, and future studies need to better investigate what kind of augmentation could provide the best results and how to deliver it to the lesions. This will eventually lead to obtaining a standardization of meniscal repair augmentation procedures.

More recent and ambitious approaches are affected by even more limitations. This is the case of MSCs, which are gaining increasing interest as a biologic augmentation to improve the limited healing potential of meniscal tears. Different preclinical studies performed both in vitro and in animal models showed their potential for the repair of meniscal lesions by producing a meniscal-like tissue with abundant extracellular matrix around the cells and favoring meniscal healing.[16,30,52,55,62] However, alongside the promising preclinical results, very few clinical studies are available in the literature, as represented by case series or case reports involving a limited number of patients. Thus, the current few and low-level data on this approach make MSC meniscal augmentation repair an interesting anecdotal topic, which needs important investigation to confirm benefit and limitations to justify its application in clinical practice.

The literature analysis documented an increasing interest in new biologic options to increase tissue-healing potential, and it is likely that further evidence will provide key elements to understand the potential of the different approaches. Accordingly, this is a rapidly evolving field, and conclusions should be drawn with caution. Based on the available evidence, PRP seems to provide a useful augmentation to meniscal repair. Despite an overall lower number of failures, the use of different clinical scores hindered the possibility of performing a cumulative analysis of other aspects about the outcome of PRP augmentation. Since not all studies in this meta-analysis describe the principal PRP features in terms of platelets and leukocytes, future studies should give more attention to PRP characteristics to evaluate the best type of PRP for this specific application. Moreover, the definition of failure after meniscal repair varied among the studies. The importance of a shared definition of failure in orthopaedic studies has already been highlighted,[20] and future studies on meniscal repair should not only apply a commonly agreed definition but include surgical, clinical, and radiological criteria as well. Doing so would allow for better study comparison to understand the real efficacy of the available procedure and to investigate the potential of the new approaches to improve the survival of meniscal repair.

In spite of the limitations of the studies, this meta-analysis supported a significant effect of PRP augmentation on reducing the high risk of failures of meniscal repair techniques. In turn, this might translate into a higher survival of the meniscus, affecting joint homeostasis over time. Future studies should confirm these findings and determine the benefits in terms of clinical outcome and prevention of OA degeneration. Moreover, another aspect that needs to be investigated is the cost-effectiveness of these biologic procedures. In fact, for other application modalities, such as intra-articular injection for knee OA treatment, positive findings have been reported in terms of not only statistical differences but also clinically perceived benefit and cost-effectiveness versus other solutions.[5,22] Nevertheless, it remains to be clarified whether the same conclusions may be extended to other orthopaedic applications of PRP. Thus, future studies should explore these aspects and confirm if PRP can be considered a suitable and cost-effective augmentation procedure for meniscal repair.

CONCLUSION

The literature on biologic meniscal augmentation is recent and scarce, with different procedures documented, ranging from fibrin clot to MSCs. Only a few comparative trials are available, all focusing on the potential of PRP. The meta-analysis documented that PRP is safe and useful in improving the survival rate, with a 9.9% failure rate versus 25.7% for the control group. Further high-level studies are needed to confirm these findings and identify the most effective biologic augmentation strategy to improve the outcome of meniscal repair.

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APPENDIX

TABLE A1
Characteristics of the Included Studies[a]

Lead Author (Year)	Study Type; No. of Patients	Mean Age; No. of Male; Mean Follow-up	Type of Meniscal Lesion	Procedure	Adverse Events	Results	Coleman Score
PRP augmentation							
Pujol[45] (2015)	Prospective comparative study; 34 (17 TG vs 17 CG)	TG: 28 y, CG: 32 y; 13 vs 11 M; 34 mo	Horizontal meniscal lesions. TG: 9 lateral, 8 medial. CG: 6 lateral, 11 medial	TG: mini-arthrotomic meniscal repair + 5-mL LR-PRP (GPS III system) in situ. CG: isolated open meniscal repair	TG: 1 septic arthritis. CG: 1 local hematoma	Significant clinical (KOOS Pain and Sport) and MRI improvement in TG vs CG. No correlation between MRI and the clinical outcomes. Failures (secondary partial or subtotal meniscectomy): 2 CG and 1 TG	67
Griffin[24] (2015)	Retrospective comparative study; 35 (15 TG vs 20 CG)	TG: 26 y, CG: 35 y; 11 vs 17 M; 48 mo	TG: 7 lateral, 8 medial; 6 BH, 2 horizontal, 6 long, 1 vertical. CG: 14 lateral, 6 medial; 4 BH, 1 horizontal, 10 long, 3 vertical, 2 undersurface	TG: arthroscopic meniscus repair + PRP (Cascade) in situ. CG: isolated arthroscopic meniscus repair	NA	No differences in clinical outcome, failures, postoperative ROM, return to work or return to sport in TG vs CG. Failures (secondary partial meniscectomy or unicondylar knee arthroplasty): 5 CG and 4 TG	49
Kaminski[33] (2018)	Double-blind RCT; 37 menisci (20 TG vs 17 CG)	TG: 26 y, CG: 30 y; 16 vs 14 M; 54 mo	Unstable complete vertical longitudinal meniscal lesions	TG: arthroscopic meniscal repair + 8-mL LR-PRP in situ. CG: arhroscopic meniscal repair + 8-mL saline in situ	None	Superior healing rate of meniscal lesions in TG vs CG (85% vs 47%). Higher IKDC, WOMAC, and KOOS in TG vs CG. No significant differences in VAS score. Failures (MRI nonhealing or second-look arthroscopy): 9 CG and 3 TG	74
Kemmochi[36] (2018)	Prospective comparative study; 22 (17 TG vs 5 CG)	TG: 32 y, CG: 21 y; 9 vs 3 M; 6 mo	TG: 13 lateral, 6 medial. CG: 4 lateral, 1 medial	TG: arthroscopic meniscus repair + L-PRF and LR-PRP in situ. CG: isolated arthroscopic meniscal repair	None	Improvement in Lysholm and IKDC scores in all patients without significative differences in TG vs CG. No clear signs of healing at MRI. Failures: not specified	62

(continued)

TABLE A1 (continued)

Lead Author (Year)	Study Type; No. of Patients	Mean Age; No. of Male; Mean Follow-up	Type of Meniscal Lesion	Procedure	Adverse Events	Results	Coleman Score
Dai[10] (2019)	Retrospective comparative study; 29 (14 TG vs 15 CG)	TG: 32 y, CG: 30 y; 6 vs 5 M; 21 mo	All DLM lesions: 11 long, 10 complex, 7 horizontal, 1 radial	TG: arthroscopic DLM saucerization + in-out suture + 4-mL LR-PRP in situ. CG: arthroscopic DLM saucerization + in-out suture	NA	Significant improvement in Lysholm score, Ikeuchi grade, and VAS pain in TG and CG without significative differences between groups. Failures (joint line symptoms or repeated arthroscopy): 2 CG and 1 TG	55
Everhart[17] (2019)	Prospective comparative study; 151 (45 TG vs 106 CG) (total: 550 including ACLR)	29 y[b]; 129 vs 219 M[b]; 36 mo	TG[b]: 60% medial, 26% lateral, 14% both. CG[b]: 62% medial, 27% lateral, 11% both	TG: arthroscopic meniscal repair + PRP (GPS III/ Angel system). CG: isolated arthroscopic meniscal repair	NA	PRP augmentation improved survival of isolated meniscal repairs but not meniscal repair with concomitant ACLR. Failures in isolated meniscal repair procedure (secondary meniscectomy, meniscal repair revision, total knee arthroplasty): 27 CG and 2 TG	56
Fibrin clot augmentation							
Kamimura[32] (2014)	Prospective case series; 10	36 y; 5 M; 40 mo	Horizontal meniscal lesions: 3 lateral, 4 medial, 3 DLM	Arthroscopic meniscal regolarization + all-inside suture + fibrin clot (autologous) in situ	1 displaced fast-fix arthroscopic removal	Significant improvement of Lysholm and IKDC scores in all patients, complete recovery for Tegner score in 6. At second-look arthroscopy, 7 complete and 3 incomplete healing. No failures reported	51

(continued)

TABLE A1 (continued)

Lead Author (Year)	Study Type; No. of Patients	Mean Age; No. of Male; Mean Follow-up	Type of Meniscal Lesion	Procedure	Adverse Events	Results	Coleman Score
Nakayama[40] (2020)	Prospective case series; 24	47 y; 21 M; 40 mo	Degenerative medial meniscal lesions	Arthroscopic meniscal repair + fibrin clot (autologous) in situ	NA	Significant improvement of Lysholm score; 6 repair failures, varus deformity was a risk factor; 6 failures (pain at joint line associated with catching/locking/ swelling, intrameniscal fluid in the repair site at MRI, second-look arthroscopy)	65
Mesenchymal stem cell augmentation							
James[31] (2015)	Case report; 1	29 y; 1 M; 12 mo	Complete radial medial meniscal lesions	Arthroscopic meniscal repair + PRP and autologous BMAC in situ	None	Complete recovery of ROM and preinjury activity level without pain or swelling; 6-mo second-look arthroscopy revealed a complete meniscal healing	40
Whitehouse[60] (2017)	Prospective case series; 5	37 y; 4 M; 24 mo	Medial meniscal lesions: 3 BH, 1 BH with radial extension, 1 vertical flap	Arthroscopic meniscal repair + expanded bone marrow MSC/ collagen-scaffold inserted into the lesion	None	Improvements in all clinical scores at 12 mo maintained up to 24 mo.; 3 cases of healing and 2 failures (pain, swelling, and locking with subsequent meniscectomy)	45
Sekiya[49] (2019)	Prospective case series; 5	48 y; 5 M; 24 mo	Complex degenerative medial meniscal tears	First step: arthroscopic meniscal repair + synovial suprapatellar harvest for culture. Second step: arthroscopic MSCs transplantation (after 14 d) in situ	No major, 39 mild, 3 MSC related: 1 CRP increase, 1 effusion, 1 localized warmth	Significant improvement of Lysholm and KOOS at 2 y, with resumption of Tegner level in all patients. Meniscal tears were indistinguishable at 2-y MRI. Failures not specified	33

[a]ACLR, anterior cruciate ligament reconstruction; BH, bucket-handle; BMAC, bone marrow aspirate concentrate; CG, control group; CRP, C-reactive protein; DLM, discoid lateral meniscus; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; L-PRF, leucocyte- and platelet-rich fibrin; LR-PRP, leucocyte- and platelet-rich plasma; M, male; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NA, not available; PRP, platelet-rich plasma; RCT, randomized controlled trial; ROM, range of motion; TG, treatment group; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[b]Data reported for the entire population, including combined ACLR.