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Research Article

JOURNAL OF ORTHOPAEDICS AND SPORTS MEDICINE

ISSN: 2688-5115

Platelet Rich Fibrin Combined with Hyaluronic Acid in the Treatment of Meniscal injuries: A Retrospective 1-Year Follow-Up Study

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Abstract

Introduction: Meniscal injuries represent a significant clinical challenge, given the crucial role of the meniscus in maintaining knee joint stability, load distribution, and overall joint health. These injuries are prevalent among athletes and the general population, with their management often dependent on the location and severity of the tear. Current treatment modalities range from conservative management, including physical therapy, to surgical interventions like partial meniscectomy and meniscal repair.

Biological therapies aim to exploit the body's inherent healing potential by introducing bioactive agents that can modulate the local environment of the injury site. Among these, Platelet-Rich Fibrin (PRF) and Hyaluronic Acid (HA) have emerged as promising candidates due to their synergistic effects on tissue regeneration.

Methods: This is a retrospective database cohort study. The clinic database was searched for patients that had undergone PRF combined with HA and ALB-PRF treatment for Meniscal injuries between January 2018 and November 2023. 78 patients were included in the study. The data analyzed were 1-year follow-up NRS scores of multiple clinical tests and sonographic pictures before the treatment, 1 month after, 3 months after and 12 months after the treatment.

Results: Statistically significant positive NRS score changes (p = 0,0001) were presented for all measured clinical outcomes. Sonographic positive changes were also presented; a mean decrease in structural changes of 5 mm (p = 0,0001) was seen.

Conclusion: In conclusion, PRF combined with HA and ALB-PRF is an effective treatment for clinically diagnosed meniscal injuries. Significantly lowered NRS pain scores in clinical and orthopedic tests as well as significant positive changes in sonographic pictures 3 months after the treatment combined with 1 year-follow-up data indicates significant long-term effects.

Keywords: PRF; ALB-PRF; Meniscus injury; Sonography; Regenerative medicine; HA

Abbreviations: PRF: Platelet Rich Fibrin; HA: Hyaluronic Acid; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; PRP: Platelet Rich Plasma; TGF-β: Transforming Growth Factor Beta; PDGF: Platelet-Derived Growth Factor; VEGF: Vascular Endothelial Growth Factor; EGF: Epidermal Growth Factor; PPP: Platelet-Poor Plasma; ALB-PRF: Heat Coagulated Albumin PRF; L-PRF: Liquid PRF; C-PRF: Concentrated PRF; SD: Standard Deviation; NRS: Numerical Rating Scale

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Citation: Torbjörn Ogéus. Platelet Rich Fibrin Combined with Hyaluronic Acid in the Treatment of Meniscal injuries: A Retrospective 1-Year Follow-Up Study. Journal of Orthopedics and Sports Medicine. 7 (2025): 88-95.

Received: January 30, 2025
Accepted: February 19, 2025
Published: March 05, 2025

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DOI:10.26502/josm.511500184

Introduction

Meniscal injuries represent a significant clinical challenge, given the crucial role of the meniscus in maintaining knee joint stability, load distribution, and overall joint health. These injuries are prevalent among athletes and the general population, with their management often dependent on the location and severity of the tear. Current treatment modalities range from conservative management, including physical therapy, to surgical interventions like partial meniscectomy and meniscal repair [1]. However, the limitations of these approaches including incomplete healing, long recovery times, and increased risk of osteoarthritis after meniscectomies have driven interest in biological therapies to enhance tissue regeneration and repair.

Meniscal surgeries, particularly partial meniscectomy, are commonly performed for irreparable tears or symptomatic relief. While these procedures often provide short-term benefits, they are associated with significant long-term drawbacks. Partial meniscectomy, for example, alters the biomechanics of the knee joint, leading to increased stress on articular cartilage and accelerated joint degeneration [2]. Consequently, patients undergoing meniscal surgeries face an elevated risk of developing osteoarthritis over time. Meniscal repair, although preferable to meniscectomy in preserving meniscal function, has variable success rates depending on the tear's location, size, and the vascularity of the affected zone [3]. Moreover, surgical procedures often require extensive rehabilitation periods and may not fully restore the meniscus's native functionality.

The risk of post-surgical osteoarthritis underscores the need for alternative strategies that prioritize tissue regeneration over resection or repair alone. Osteoarthritis is a progressive joint disease characterized by cartilage degradation, subchondral bone remodeling, and chronic inflammation. Once initiated, it poses a significant challenge to effective management, further emphasizing the importance of preserving the meniscus' structural and functional integrity [4]. These concerns have catalyzed the exploration of biologically driven treatments aimed at enhancing intrinsic healing mechanisms while minimizing surgical interventions.

Biological therapies aim to exploit the body's inherent healing potential by introducing bioactive agents that can modulate the local environment of the injury site. Among these, Platelet-Rich Fibrin (PRF) and Hyaluronic Acid (HA) have emerged as promising candidates due to their synergistic effects on tissue regeneration. PRF, a second-generation platelet concentrate, is an autologous material rich in growth factors and cytokines that can stimulate cellular proliferation, angiogenesis, and extracellular matrix synthesis [5]. On the other hand, HA is a naturally occurring glycosaminoglycan that plays a vital role in maintaining joint homeostasis by modulating inflammation, enhancing lubrication, and promoting cellular migration and proliferation [6].

The combination of PRF and HA has been hypothesized to offer enhanced regenerative outcomes compared to either therapy alone. PRF provides a scaffold and sustained release of bioactive molecules, while HA complements these effects by improving the viscoelastic properties of the joint environment and facilitating cell-matrix interactions [7]. Preliminary studies have demonstrated the potential of this combination in the management of other orthopedic conditions, such as osteoarthritis and cartilage defects [8,9]. However, its application in meniscal injuries remains underexplored, and there is a need for robust clinical evidence to establish its efficacy and safety.

Meniscal injuries can be broadly classified into vascular and avascular zones, with the former exhibiting higher healing potential due to better blood supply. The avascular zone, by contrast, poses a greater challenge for tissue repair due to limited nutrient and oxygen delivery [10]. The unique properties of PRF and HA make them particularly suitable for addressing these challenges. PRF's ability to release growth factors over time can stimulate angiogenesis and matrix remodeling in poorly vascularized areas, while HA's anti-inflammatory and lubricative properties can mitigate joint degeneration and facilitate cellular activities crucial for tissue repair [11].

The retrospective nature of this study allows for the analysis of real-world clinical data to evaluate the outcomes of combining PRF and HA in the treatment of meniscal injuries. By examining a cohort of patients treated with this novel combination, the study seeks to assess its impact on pain relief, functional recovery, and imaging-based parameters of tissue repair. The findings could provide valuable insights into the potential of PRF and HA as a synergistic biological therapy for meniscal regeneration.

The significance of this study lies in its potential to contribute to the growing body of evidence supporting biologically driven approaches to meniscal repair. By integrating the strengths of PRF and HA, this combination therapy may offer a minimally invasive, effective alternative to conventional treatments, with the promise of improving long-term joint health and patient quality of life.

Materials and Methods

Different mixtures of autologous platelet concentration protocols have been studied and used clinically to treat tendon and other collagen injuries. Some studies have indicated a positive effect on pain and other symptoms. However, many different versions of injections with autologous blood products have been used clinically and no standard protocols exist [12]. In numerous studies recently, a way of extending

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DOI:10.26502/josm.511500184

the effect of the injected platelets by heating a liquid platelet-poor plasma (PPP) layer have been used and studied, this technique enhances the resorption properties of albumin, by creating an albumin gel, which extends the resorption properties from 2 weeks to greater than 4 months (ALB-PRF) [13].

PRF's therapeutic potential in meniscal repair lies in its ability to enhance the natural healing process of collagen structures, which is often impaired in meniscal injuries. The fibrin matrix formed during PRF preparation and ALB-PRF addition acts as a scaffold, supporting cell migration and proliferation while gradually releasing growth factors over time. This scaffold provides a favorable microenvironment for meniscal healing by facilitating the recruitment of fibroblasts and other reparative cells to the site of injury [14]. These cells play a crucial role in synthesizing new collagen fibers, which are essential for restoring the meniscal integrity. Combining these properties with the properties of hyaluronic acid gives the injected PRF an enhanced scaffold matrix as well as an increased cell proliferation compared to a PRF injection without the HA [15].

In addition to promoting tissue regeneration, PRF may also modulate inflammation in collagen injuries. Chronic tendinopathies as well as meniscal injuries are often associated with low-grade, persistent inflammation, which contributes to pain and tissue degeneration. The leukocytes in the PRF mixture release anti-inflammatory cytokines, which can help reduce this chronic inflammation and promote a shift towards tissue repair. Furthermore, PRF has been shown to increase the expression of genes involved in tissue repair and collagen production, further supporting its role in enhancing meniscal regeneration [16].

Preparation of PRF and ALB-PRF

All patients that underwent PRF, ALB-PRF and HA treatment of meniscal injuries at the clinic during the reported time frame received the same treatment protocol:

20ml blood was collected from the patients before each of the PRF injections. Two 10ml Plastic, round-bottomed vacuum tubes (Liquid PRF tubes) were used to collect the blood, after collection, the tubes were spun on a horizontal swing-out bucket rotors centrifuge system. Two different PRF protocols were utilized in the treatments, the first injection consisted of a combination of Liquid-PRF (L-PRF) and Concentrated-PRF (C-PRF) protocol where two separate centrifugations, the first 300xg for 5 min where one of the tubes were removed and a second centrifugation consisted of a modified C-PRF where the last three tubes were spun at 2000xg for 4 min. After the second spin the two different protocols were combined in a mixture of L-PRF and a modified C-PRF for the first injection. The second injection consisted of a Heat-Coagulated Albumin Gel -PRF (ALB-PRF) protocol of 2000xg for 8 min followed by a heating and cooling down process before the injection was performed. The two protocols were utilized following international guidelines for PRF preparation published by Miron et al. in 2019 [17] (except for the modified C-PRF protocol).

The PRF injection consisted of a mixture of L-PRF and a modified C-PRF [18] injection of 3ml, centrifuged at 300xg for 5 min and 2000xg for 4 min combined with 2ml HA. The ALB-PRF injection that was given was 3ml ALB-PRF, 2000xg for 8 min on a horizontal centrifuge, the albumin layer was heated according to the ALB-PRF protocol; 75 degrees for 10 min [19]. In the last step, the heat- coagulated albumin gel was cooled down to room temperature and mixed with the remaining C-PRF to create ALB-PRF. The centrifuge utilized in all PRF treatments was the Bio-PRF horizontal centrifuge (Bio-PRF, USA).

Administration of PRF and ALB-PRF

The patients underwent two injections, one L-PRF combined with modified C-PRF and Hyaluronic acid, Hyalur ® (Arthrex GmbH, Munich, Germany) and one ALB-PRF injection. In the first week one injection of L-PRF combined with modified C-PRF and HA. In the following week one ALB-PRF injection was performed. All injections to the meniscal injuries were performed with ultrasound guidance to ensure needle placement in the injured area.

5 days after the last injection, all patients received a simple rehabilitation program consisting of intervals on a stationary bicycle and strength training consisting of squats and straight leg deadlift with a slow progression of resistance.

Study design

This is a retrospective database cohort study. The clinic database was searched for patients that had undergone PRF combined with HA and ALB-PRF treatment for meniscal injuries between January 2018 and November 2023.

According to the Ethics Commission of Stockholm, Sweden, retrospective database-based studies do not require ethical approval and patient informed consent whenever the data were acquired, saved and treated anonymously. This applies to the present study.

Subjects

84 patients (36 female and 48 male) underwent PRF combined with HA and ALB-PRF treatment for meniscal injuries at the clinic during the above-referred period.

On the first day of treatment, patients were informed about the data collection that routinely takes place in the clinic and were asked to give written consent for data collection. With patient's consent, all patients were asked to report their perceived pain during the clinical tests, before the treatment

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DOI:10.26502/josm.511500184

started, after 1 month, 3 months and after 1 year. Sonographic pictures were taken on all treated joints before the treatment after 1 month and after 3 months.

The patients were included if they were treated with PRF, HA and ALB-PRF treatment of their meniscus and the follow-up data was available. The patients were excluded in case all pain assessment data was not available or if they failed to follow the instructions of rehabilitation or missed their follow-up visits.

The inclusion criteria were met by 78 patients (33 female and 45 male) that were treated for meniscal injuries with PRF, HA and ALB-PRF.

Sonographic database

During the treatment protocol, sonographic (ultrasound) pictures of the affected meniscus were taken before the treatment, 1 month after, 3 months after the treatment and 12 months after the treatment. The focal area of the meniscus and specifically the portion of the meniscus extruding beyond the tibial margin structure were measured digitally in millimeter (mm) and compared on the before and after pictures and later added to the data file for each corresponding patient for easy database access. The most common finding in a patient with meniscal injuries on ultrasound is extrusion of the meniscus above the tibial margin [20].

The instruments

The Numerical Rating Scale (NRS) evaluates perceived pain on a segmented numerical scale with 11 points ranging from 0 to 10 [21] and can be used in combination with orthopedic tests for more exact measurements.

McMurray's test is a standardized orthopedic test to assess meniscal injuries clinically. It is performed in supine position where a full flexion in the knee is combined with an internal- and external rotation in separate movements while extending the knee gradually. This movement sweeps the meniscus between the tibial plateau and femoral condyles, potentially eliciting pain or a click if a tear is present [22].

The Apley Compression Test, also known as Apley's Test, is another clinical maneuver used to evaluate meniscal injuries in the knee. It involves both compression and distraction forces while rotating the lower leg and is performed while the patient is in a prone position, with the knee bent to a 90-degree angle, pain while compression indicates a meniscal injury [23].

Both tests show a high specificity of 80% or more but a lower sensitivity and should always be combined with diagnostic imaging such as magnetic resonance imaging or ultrasound to confirm meniscal injury and the extent thereof [24,25].

Statistical analysis

Mean and standard deviation (SD) or frequencies (percentage) were used to characterize the sample. The normal distribution of the data was tested with the use of T-test and ANOVA tests. Demographic data comparisons between the groups medial and lateral meniscus were performed based on data gathered before the treatment series with the use of t-tests for independent samples.

To investigate whether there were significant differences in the mean NRS scores of patient's multiple comparisons between the pairs of means were performed with t-tests and ANOVA for independent samples.

All statistical tests were performed with Prism 10 for Windows (Microsoft, USA). For all statistical tests, the 0.05 level of probability was set as the criterion for statistical significance.

Results

The data of the 78 patients that met the inclusion criteria were analyzed (Table 1). The patients in the sample were on average 42.73 ± 4.18 years old. There were no significant differences between the patients in the different test groups (medial and lateral meniscal injuries) concerning their mean age ($p = 0,38$). The distribution of male and female patients was not significantly different ($p = 0.81$) however the group of

Table 1

Demographic data of the patients in the sample.

	Lateral	Medial	p-value
n	33	45	
Age (years)	43,3 ± 4,25	42,17 ± 4,11	p = 0.38
Gender (%) Male	18 (54,5)	27 (60,0)	p = 0.81
Female	15 (45,4)	18 (40,0)	

Figure 1: Demographic data of the patients in the sample.

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DOI:10.26502/josm.511500184

male patients with medial meniscal injuries was considerably larger than the other groups (the demographic data can be seen in Figure1).

McMurray's test scores

The treated patients (n=78) were analyzed using an ANOVA test and showed a significant improvement in NRS score (p = 0,0001) with a mean change from 6.1 on the baseline measurement, 2.5 on the 1-month follow-up, 0.6 on the 3-month follow-up and 0.2 on the 1-year follow-up (96,7% decrease in total).

Apley's test scores

The treated patients (n=78) were also analyzed using an ANOVA test and showed a similar positive change in in NRS score (p = 0,0001) with a mean change from 5.3 on the baseline measurement, 2.5 on the 1-month follow-up, 0.3 on the 3-month follow-up and 0.1 on the 1-year follow-up (98,1% decrease in total) (changes can be seen in Figure 2. Mean values of NRS scores on the treated knees with SD marked.

There were no statistically significant differences between the genders in any of the tests analyzed. A final analysis of the combined NRS data of the different pain tests was performed to determine the total combined changes in all the treated patients. A combined statistically significant (p = 0,0001) improvement of 98,2% was seen (with a mean change from 5.6 to 0.1 at the 12-month follow-up) (changes can be seen in Figure 3).

Sonographic data

The sonographic data of the 78 patients that met the inclusion criteria were analyzed with a two-tailed unpaired T-test and compared, before- treatment after one month, after 3 months and 12 months after the treatment.

The patients showed a statistically significant decrease in the portion of the meniscus extruding beyond the tibial margin structure from an average of 5mm extrusion to an average of near zero visibility of extrusion according to sonographic picture analysis (p = 0,0001) (changes can be seen in Figure 4).

Examples of the described sonographic changes, such as reduction in extruding meniscus and reduction of visible ruptures, as well as reduced fluid/inflammation can be seen in Figure 5.

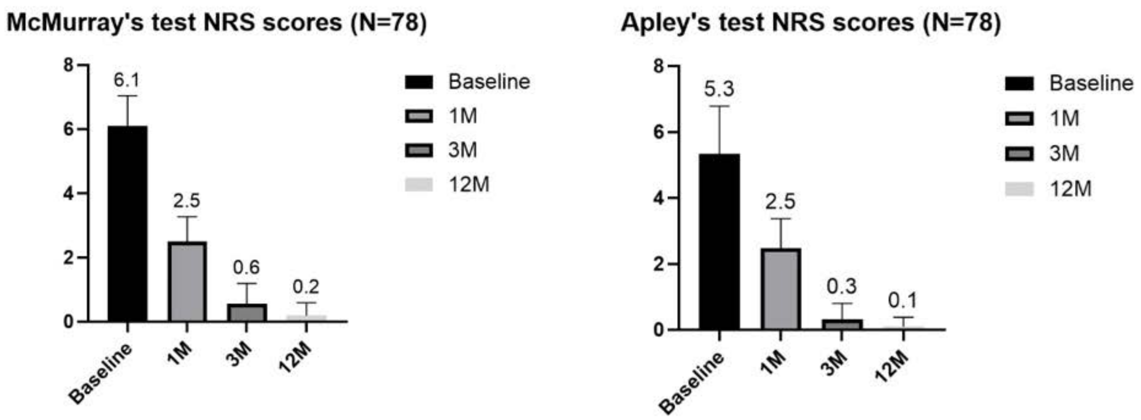

Figure 2: Mean values of NRS scores on the treated knees with SD marked.

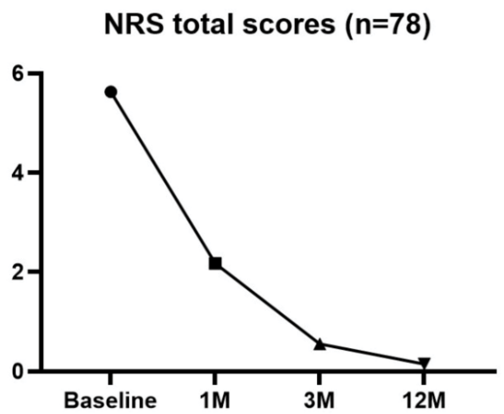

Figure 3: Change of mean values of the combined total NRS scores on the treated knees in a line graph.

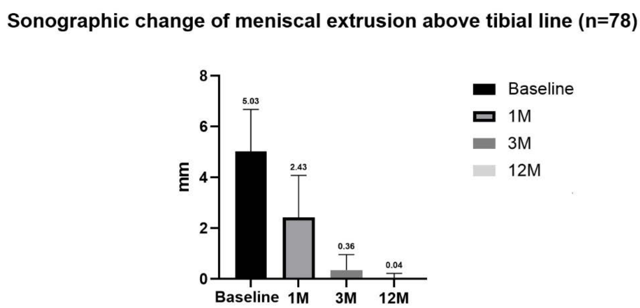

Figure 4: Change of mean values of the combined measurements on meniscal extrusion above the tibial border on ultrasound.

Citation: Torbjörn Ogéus. Platelet Rich Fibrin Combined with Hyaluronic Acid in the Treatment of Meniscal injuries: A Retrospective 1-Year Follow-Up Study. Journal of Orthopedics and Sports Medicine. 7 (2025): 88-95.

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DOI:10.26502/josm.511500184

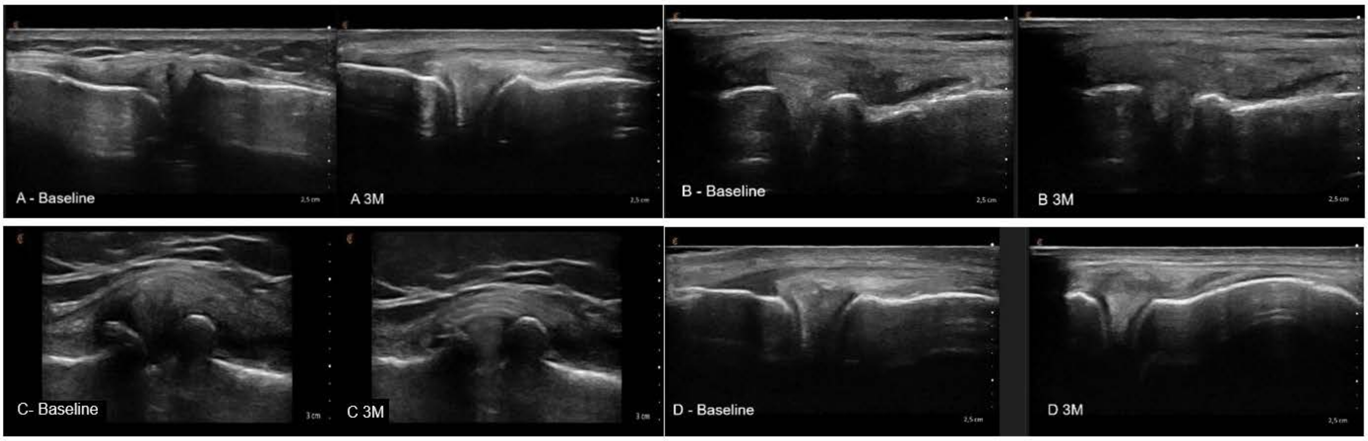

Figure 5: Sonographic pictures of treated meniscal injuries, before, and 3 Months after the PRF/HA and ALB-PRF treatment. A, A clear central rupture in the outer portion of the meniscus completely healed and a reduction of 5 mm extrusion. B, Mean change of meniscal extrusion of 4 mm. C, Osteoarthritic knee with typical osteophytes and a clear 6mm extrusion of meniscus in the before picture, a near complete reduction after 3 months. D, Medial meniscal extrusion of 3,5 mm above the tibial margin reduced to a normal position after 3 months.

Discussion

The use of PRF and HA as a combination therapy offers a compelling alternative to conventional treatments for meniscal injuries, including arthroscopy and physiotherapy. This section discusses the advantages and disadvantages of this novel approach compared to established methods. Patients that presented at the clinic with major meniscal injuries (such as larger bucket-handle tears) were referred to surgery and therefore form a small sub-group not included in the study that is worth mentioning where the PRF and HA treatment might not be suitable.

The retrospective nature of this study allows for the analysis of real-world clinical data to evaluate the outcomes of combining PRF and HA in the treatment of meniscal injuries. However, larger placebo-controlled studies with longer follow-up time are warranted and further studies replicating the results from this study are needed to further strengthen the evidence for this novel treatment combination.

Advantages of PRF + HA Therapy

Enhanced Tissue Regeneration: Unlike arthroscopy, which primarily addresses mechanical symptoms by removing damaged tissue, PRF and HA aim to stimulate intrinsic healing mechanisms. PRF's growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), promote cellular proliferation and extracellular matrix synthesis, crucial for meniscal repair [26]. HA, on the other hand, improves the viscoelastic properties of the synovial fluid, facilitating joint lubrication and reducing inflammation [27]. Additionally, HA enhances the uptake and retention of growth factors released by PRF, further amplifying regenerative processes [28].

Minimally Invasive Nature: Arthroscopy, while less invasive than open surgery, still requires anesthesia and carries risks such as infection and thrombosis. PRF and HA, delivered through injections, offer a less invasive option with minimal downtime and fewer complications [29].

Potential for Long-Term Benefits: Physiotherapy focuses on symptom management and functional restoration but does not directly address the structural damage to the meniscus. PRF and HA's regenerative capabilities provide the potential for lasting structural repair, potentially reducing the progression to osteoarthritis [30].

Reduced Rehabilitation Time: Surgical treatments often necessitate prolonged rehabilitation to regain joint function. PRF and HA therapies, with their non-surgical approach, may shorten recovery times, enabling patients to return to their normal activities sooner [31].

Disadvantages of PRF + HA Therapy

Variable Outcomes: The efficacy of PRF and HA is influenced by factors such as patient age, the chronicity of the injury, and the specific characteristics of the meniscal tear. This variability can make it challenging to predict outcomes reliably [32]. The results from this study indicate a good prognosis for most meniscal tears, however larger so-called Bucket-handle tears, or injuries with loose fragments might be difficult to heal, and surgery might be a better solution in such cases.

Limited Long-Term Data: While preliminary studies indicate promising results, there is a paucity of long-term data on the durability of PRF and HA's regenerative effects. This contrasts with the more extensive evidence base for arthroscopy and physiotherapy [33].

Cost Considerations: The preparation and application of PRF and HA can be costly, potentially limiting accessibility

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DOI:10.26502/josm.511500184

for some patients. In contrast, physiotherapy is often more affordable and widely available [34]. PRF and HA, however, are significantly more affordable than surgery.

Need for Multiple Treatments: Achieving optimal outcomes with PRF and HA may require multiple treatment sessions, which can be inconvenient for patients and increase overall costs [35]. If the results in this study can be replicated in larger studies a protocol with two injections and long-term effects can be suggested as an option to surgery or physiotherapy.

Comparative Perspective

Arthroscopy remains a widely used option for meniscal injuries, particularly in cases where mechanical symptoms like locking are present. However, its long-term implications, including the risk of osteoarthritis, highlight the need for regenerative alternatives. Physiotherapy, while non-invasive, primarily addresses functional outcomes and may not prevent long-term joint degeneration. PRF and HA offer a unique approach by addressing both symptom relief and structural repair, positioning them as a promising addition to the therapeutic arsenal for meniscal injuries.

Conclusion

In conclusion, PRF combined with HA is an effective treatment for clinically diagnosed meniscal injuries. Significantly lowered NRS-pain scores 1 year after the treatment, combined with a significant positive change on sonographic imaging were presented.

Declarations

Ethics Approval

According to the Ethics Commission of Stockholm, Sweden, retrospective database-based studies do not require ethical approval and patient informed consent whenever the data were acquired, saved and treated anonymously. This applies to the present study.

The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to Participate: Not applicable.

Consent for Publication

This manuscript does not contain any individual person's data. All data exposed in this manuscript was anonymized.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Acknowledgements

The author was the main and only contributor to the manuscript.

Competing Interests

The author declares that he has no competing interests.

Authors' contributions

All texts, design, literature review and drafting of this study were done by TO, responsible for the submitted manuscript.

Availability of Data and Materials

All data generated or analyzed during this study can be provided by the corresponding author upon reasonable request and is available for review by the Editor-in-Chief of this journal.

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Citation: Torbjörn Ogéus. Platelet Rich Fibrin Combined with Hyaluronic Acid in the Treatment of Meniscal injuries: A Retrospective 1-Year Follow-Up Study. Journal of Orthopedics and Sports Medicine. 7 (2025): 88-95.