https://doi.org/10.31925/farmacia.2025.2.16 **ORIGINAL ARTICLE**

ENHANCING MICROFRACTURE TREATMENT FOR CHONDRAL LESIONS WITH PLATELET-RICH PLASMA: AN OBSERVATIONAL STUDY

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Abstract

Chondral lesions are more often found in patients with knee pain, either from normal wear and tear or due to traumatic events. The treatment for this condition is still debatable, depending on the type of the lesion, age, or other comorbidities. Microfractures alone or enhanced with other biological agents, like platelet-rich plasma (PRP) or bone marrow aspirate concentrate (BMAC), are a convenient solution, often used, with different results offered by other studies. We evaluated 24 patients presenting chondral lesions Outerbridge grades 3 and 4 who were treated with microfractures alone or enhanced by PRP using scores from the International Knee Documentation Committee (IKDC) and VAS (visual analogue score). Evaluation was performed at admission, at 3 months, 6 months, and 1 year. Results show improvement in time for both groups. Patients treated with microfractures and PRP have significantly higher IKDC scores at all three moments. This means the overall quality improved after the treatment with microfractures and PRP compared with the group that received only the microfractures. Patients treated only with microfractures had significantly higher VAS scores compared with the other group, meaning higher residual pain. Our results suggest that enhancing microfractures with PRP injections is better than microfractures alone.

Rezumat

Leziunile condrale sunt frecvent întâlnite la pacienții cu dureri de genunchi, fie ca urmare a uzurii normale, fie din cauza unor traumatisme. Tratamentul acestei afecțiuni este încă un subiect de dezbatere, fiind influențat de tipul leziunii, vârsta pacientului și prezența altor comorbidități. Microfracturile, utilizate fie ca atare, fie în combinație cu soluții biologice precum plasma bogată în trombocite (PRP) sau concentratul de aspirat medular (BMAC), reprezintă o opțiune frecvent aleasă, deși studiile existente raportează rezultate variabile. În acest studiu, am evaluat 24 de pacienți cu leziuni condrale de gradul 3 și 4 conform clasificării Outerbridge, tratați fie prin microfracturi simple, fie prin microfracturi combinate cu PRP. Evoluția pacienților a fost monitorizată utilizând scorurile IKDC (International Knee Documentation Committee) și VAS (Visual Analog Scale) la momentul internării, precum și la 3 luni, 6 luni și 1 an post-tratament. Rezultatele indică o îmbunătățire progresivă în ambele grupuri. Cu toate acestea, pacienții care au beneficiat de microfracturi asociate cu PRP au înregistrat scoruri IKDC semnificativ mai mari la toate momentele de evaluare, sugerând o recuperare mai bună comparativ cu cei care au primit doar microfracturi. În plus, pacienții tratați exclusiv prin microfracturi au raportat scoruri VAS mai ridicate, ceea ce indică o durere reziduală mai mare. În concluzie, adăugarea injecțiilor PRP la tratamentul cu microfracturi oferă rezultate superioare față de microfracturile singure, atât în ceea ce privește funcționalitatea genunchiului, cât și reducerea durerii.

Keywords: chondral lesion; microfractures; biological treatment; platelet-rich plasma

Introduction

The cartilage covers the ends of the bones in a joint, provides cushioning, and helps bones glide smoothly over each other. Articular cartilage lacks blood vessels, lymphatics, and nerves and exists in a challenging biomechanical environment. Most importantly, it has a limited ability for self-repair and regeneration [1]. Its structure consists of a dense extracellular matrix (ECM) with sparsely distributed chondrocytes, the highly specialised cells responsible for maintaining cartilage integrity. The ECM primarily comprises water, collagen, and proteoglycans, along with smaller amounts of non-collagenous proteins and glycoproteins [2]. These components are needed for water retention within the ECM, which is important for maintaining the mechanical properties of the cartilage.

Having even a minor lesion is sufficient for the patient to feel significant pain and to lead, in time, to the overall destruction of the joint. Lesions of the chondral surface can occur from either normal wear and tear or from traumatic falls, sports injuries or other injuries of the joint (for example, the ACL tear). Chondral defects are found in 34% to 62% of knee arthroscopies, while full-thickness focal lesions measuring at least 1 - 2 cm^2 are present in 4.2% to

6.2% of cases [3-5]. For example, in the US, 900,000 Americans have this type of lesion, which results in approximately 200,000 surgical procedures [6].

The microfracture technique was developed by Steadman and is based on the body's own capability of healing [7]. Microfractures are performed arthroscopically and represent a bone marrow stimulation (BMS) procedure used for the repair of small osteochondral lesions by stimulating the formation of fibrocartilaginous tissue [8]. In this minimally invasive procedure, we aim to stimulate mesenchymal stem cells (MSCs) by penetrating the subchondral bone plate with an awl, promoting the formation of fibrous cartilage tissue for lesion repair.

One way to enhance the microfracture clot biologically by incorporating growth factors, thereby improving the quality and quantity of the regenerated tissue, is to add different biological adjuvants. Different options are available, like adipose tissue-derived stem cells (ADSCs), bone marrow aspirate concentrate (BMAC) or autologous platelet-rich plasma (PRP).

Autologous platelet-rich plasma (PRP) is a biologically active therapy with regenerative capacity. It was defined as the volume of plasma containing above the limit number of thrombocytes. PRP induces chondrogenic differentiation of progenitor cells [9]. The platelets have alpha granules that contain growth factors like the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which are released in the joint and change the joint homeostasis. TGF-β is an important protein that stimulates fibroblast proliferation and promotes the synthesis of type I collagen and fibronectin. PRP also includes insulin-like growth factor, osteocalcin, fibrinogen, fibronectin, osteonectin, thrombospondin-1, and vitronectin. Insulin-like growth factor-1 (IGF-1) attracts fibroblasts and enhances protein production. A study performed by Akeda *et al*. [10] revealed that PRP decreases the catabolism and also improves the metabolism, promoting chondral remodelling. Also, a higher level of collagen type 2 and prostaglandin synthesis has been documented. Even though there is no consensus about the number of PRP administrations, some studies have revealed good results in reducing inflammation and decreasing pain [11, 12].

Given the positive results of biological therapies with PRP in treating chondral lesions, we aimed to determine whether, when combined with arthroscopic treatment - specifically microfractures - we could achieve positive outcomes in symptom relief and knee functionality.

Materials and Methods

Study design and ethics

We have performed an observational study starting from October 2022 until October 2024, on 24 patients presenting chondral lesions in the knee, who were treated with arthroscopically microfractures, either alone or enhanced with PRP, in order to determine if there is any improvement after injecting PRP. All the study participants signed an informed consent for inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Clinical Emergency Hospital, Bucharest.

Patient selection

We aimed to control all variables that could affect our final results, thus we selected patients who fulfilled our criteria. Patients selected for the study were aged 18 to 60 years, with chondral lesions in the medial compartment, classified as Outerbridge grades 3 and 4, limited to 2-3 cm^2.

Given that obesity leads to an unfavourable outcome, we excluded those with a BMI above 30. We also excluded patients who had other associated joint lesions, such as meniscal tears, ligamentous ruptures, or malalignment. Patients who presented with other comorbidities that can influence the final results, such as inflammatory arthritis, local or systemic infections, or metabolic diseases, were also excluded.

All the patients had an MRI evaluation of the affected knee prior to the surgical intervention, performed with 3T or 1.5T scanners, to properly assess the joint and exclude other pathologies. MRI assessment of **cartilage lesions** in terms of size, location, and depth primarily relies on spin echo (SE) and gradient echo (GRE) sequences, along with their variations. Standard SE or fast SE sequences include T1-weighted, T2-weighted, and proton density (PD)-weighted images.

Outerbridge classification is an arthroscopic grading system of articular cartilage defects (Table I) [13].

Table I

Outerbridge classification

Outerbridge Classification	Description
0	Intact cartilage
1	Superficial lesions
2	Lesions extending down to < 50% of cartilage depth
3	Defects extending down > 50% of cartilage depth
4	Complete cartilage loss with a defect through the chondral bone

Group description

The therapeutic approach for Outerbridge grade 3 and 4 chondral lesions measuring up to 2 - 3 cm^2, depending on the specific characteristics of each case, consists of arthroscopic microfracture surgery. In addition to the primary surgical treatment, the attending physician may choose adjuvant therapies based on current studies, such as PRP administration. The patients we analysed were treated either with microfractures alone or with microfractures followed by PRP administration, depending on the physician's choice.

We divided the patients into two groups based on their treatment. In the first group, Group A, we included those treated with micro fractures performed arthroscopically and PRP injections. In the second group, Group B, we selected the ones who received only the microfractures in the same manner, but without further PRP injections.

Surgical technique

During arthroscopy of the knee, all the lesions were first inspected, and then with a curet, vertical walls were created around the cartilage defect. The debridement of the base of the lesion has been done, removing the calcified cartilage for better clot adherence and to provide chondral nutrition. With a surgical awl, multiple holes were created in the subchondral bone, starting from the periphery towards the centre of the lesion. All the holes were placed 3 to 4mm apart (a shorter distance can make the subchondral bone more vulnerable) [14]. After all the holes were drilled, the arthroscopic pump was stopped in order to visualise blood and fat droplets coming from the holes. No drains were used.

PRP preparation and administration

We used the Arthrex ACP® double syringe kit to isolate platelets and growth factors within a plasma layer separate from the red and white blood cells in the blood. A maximum of 16 cc of blood is drawn from a peripheral vein. The blood is spun at a rate of 1500 rpm for 5 minutes. Once the centrifugation is complete, the double syringe is removed from the bucket, taking care not to tip or agitate the separated layers. The yellow plasma layer is then removed and injected in less than 30 minutes into the knee through an anterolateral approach. Studies showed, for this PRP kit, an increase of platelets of 2-3 times compared to baseline, PDGF-AB 26.259 ± 3.061 pg/mL and P-Selectin 421 ± 52 ng/mL [15].

Group A received PRP infiltrations: the first one after the first week after the surgery, and the next two every three weeks. All the patients were instructed to be well hydrated, so we recommended that they drink 2 to 3 litres of water every day, three days before the infiltration. No anti-inflammatory pills were allowed five days before and one week after the infiltration.

Postoperative rehabilitation

After the surgery none of the patients received immobilization devices. We used the same protocols of rehabilitation for both groups: they were encouraged to have passive and active motion right from the beginning, but they were not allowed to apply loading on the affected limb for 4 weeks. After that, they start loading gradually until they gained full weight bearing at 6 weeks. In case of pain, they were allowed to take acetaminophen or tramadol.

Outcome measures

All the patients were evaluated initially and then at 3 months, 6 months and 1 year, using IKDC (International Knee Documentation Committee) score and VAS (Visual Analogue Scale).

The International Knee Documentation Committee (IKDC) Score is a standardised evaluation tool used to assess knee function, symptoms, and activity levels in patients with knee injuries or conditions. This assessment is purely subjective, assigning patients an overall functional score. The questionnaire focuses on three main categories: symptoms, athletic activity, and knee function. Scores range from 0 (indicating the lowest or most severe symptoms) to 100 (representing the best function and minimal symptoms). The score is calculated using the formula:

$$\text{IKDC} = (sum\ of\ items \div maximum\ possible\ score) \times 100.$$

VAS is a numerical pain rating scale from 0 (no pain) to 10 (worst pain). Patients were asked to rate their pain at the moment of evaluation, on this scale, from 1 to 10.

Statistical analysis

All the information we collected was analysed using IBM SPSS Statistics for Windows version 29.0. Continuous variables were examined to verify whether they met the normality condition of the distribution and were expressed through mean value, standard deviation, minimum, and maximum. The independent samples t-test was used to compare the means based on the dichotomous variables in the study. The repeated measures ANOVA method is used to analyse variability within the same observation unit, aiming to compare multiple conditions or observations over time, typically in studies that involve changes in a dependent variable. A p-value < 0.05 was considered statistically significant.

Results and Discussion

Age and sex distribution

The first group included patients with a mean age of 40.42 years, and the second group included patients with a mean age of 41.92 years. Both groups have a similar standard deviation, ranging between 10.55 and 10.67, which suggests a wide age distribution in both groups. Both groups have a similar age range, varying between 28 and 59/60 years, indicating a diversity of ages within each group. Groups A and B

have a similar age distribution, with minor differences in the mean age and comparable variability between the two groups (Figure 1). These data suggest that age is not a significant difference between the groups (Table II), and further analysis could examine other relevant variables.

Group A consisted of 5 females and 7 men, while Group B included 4 females and eight men (Figures 2 and 3).

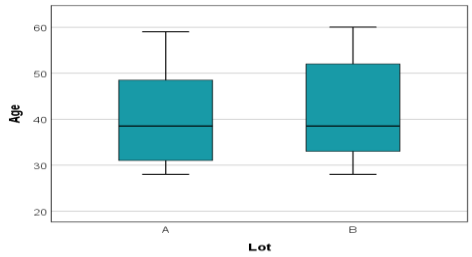

Figure 1.
Age distribution

Table II
Age statistics for admission

		Group	
		A	**B**
N	Valid	12	12
	Missing	0	0
Mean ± Std. Deviation		40.42 ± 10.553	41.92 ± 10.672
Minimum		28	28
Maximum		59	60

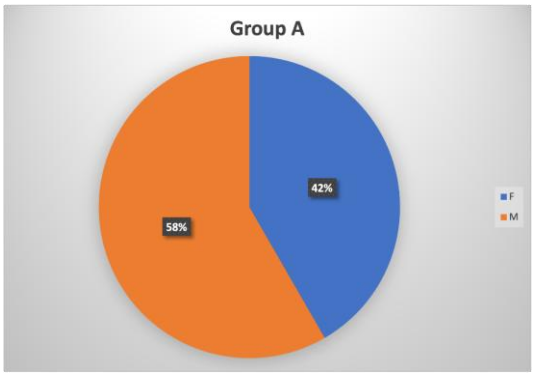

Figure 2.
Sex distribution in Group A

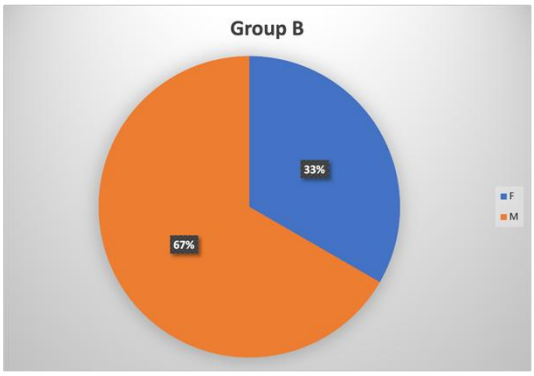

Figure 3.
Sex distribution in Group B

IKDC score

The IKDC score at admission for Group A shows a greater variety of scores, with significant dispersion (high standard deviation), suggesting that the studied group presents a wide range of conditions or performances on this test. The VAS score at admission for Group A shows a more concentrated distribution, with similar scores among participants, indicating less variability in this case (Table III). The IKDC score for Group B at admission has a higher standard deviation (4.4270), suggesting a wider dispersion of scores around the mean. The VAS score at admission for Group B has a more concentrated distribution, with scores closer among participants, indicating less variability in this case (Table IV).

Table III
IKDC and VAS score for admission (Group A)

		IKDC score (admission)	**VAS score (admission)**
N	Valid	12	12
	Missing	0	0
Mean ± Std. Deviation		36.008 ± 5.7293	7.08 ± 1.165
Minimum		26.4	5
Maximum		43.7	9

Table IV
IKDC and VAS score for admission (Group B)

		IKDC score (admission)	**VAS score (addmision)**
N	Valid	12	12
	Missing	0	0
Mean ± Std. Deviation		28.300 ± 4.4270	8.42 ± 0.900
Minimum		23.0	7
Maximum		36.8	10

Group A has significantly higher IKDC scores at all three moments (3 months, 6 months and 1 year), which means the overall quality improved after the treatment with microfractures and PRP compared with the group that received only the microfractures (Table V and Figure 4). The score differences between the groups are statistically significant at each time interval ($p < 0.05$). These results suggest that Group A performed better than Group B in terms of IKDC measurements throughout the three study phases. The results can be explained by a better local cartilage healing process, similar to other studies reported [16].

Table V

IKDC evaluation at 3m, 6m, 1y

	Lot	N	Mean ± Std. Deviation
IKDC 3m	A	12	43.300 ± 2.557
	B	12	40.042 ± 3.684
IKDC 6m	A	12	65.250 ± 3.833
	B	12	61.417 ± 2.230
IKDC 1y	A	12	71.467 ± 4.410
	B	12	65.525 ± 4.879

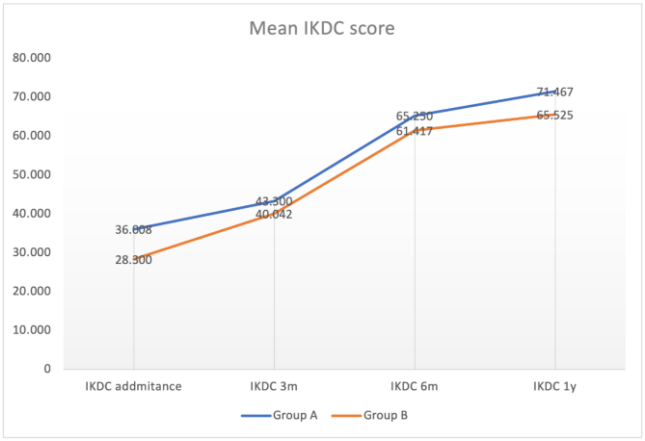

Figure 4.
Mean IKDC score evolution in time

VAS score

Group B has significantly higher scores than Group A at all three measurement points (3 months, 6 months, and 1 year) for the VAS score (Table VI and Figure 5). The score differences between the groups are statistically significant at each time interval ($p < 0.05$). These results suggest that Group B had a higher score compared to Group A in terms of VAS measurements throughout the three stages of the study. A higher VAS score means higher residual pain.

Table VI

VAS at 3m, 6m, 1y

	Lot	N	Mean ± Std. Deviation
VAS 3m	A	12	4.00 ± 0.73
	B	12	5.08 ± 0.99
VAS 6m	A	12	1.33 ± 1.07
	B	12	2.25 ± 0.62
VAS 1y	A	12	0.92 ± 0.66
	B	12	1.58 ± 0.51

Our results showed an improvement for patients treated with microfractures and PRP administration in terms of functionality and pain. The study published by Hayashi *et al*. showed no noticeable difference in cartilage response between day 0 and day 3, but a significant improvement was evident from day 7 to day 56, and most holes disappeared by day 28 [8], so it might be a good option for mid or long-term.

PRP promote cellular anabolism and the release of cytokines that have anti-inflammatory and analgesic effects. Growth factors like hepatocyte growth factor (HGF), IL-4 (interleukin 4) and TNF-α are implicated in reducing the levels of COX-1, COX-2 and prostaglandin E2, which act like proinflammatory mediators [17]. This can explain the pain improvement, expressed by lower VAS levels, and fewer episodes of knee swelling. PRP has the ability to reduce the production of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which plays a crucial role in soft tissue inflammation [18].

The improvement of chondral lesion healing, leading to an improvement of knee functionality, can be explained by the multitude of factors that are released by the platelets. VEGF promotes angiogenesis, increases vascular permeability and stimulates endothelial cell proliferation. IGF-1 and IGF-2 act as chemotactic agents for fibroblasts. Platelet factor 4

(PF4) also acts in attracting fibroblasts. A significant role is played by TGF-β, which stimulates the proliferation of undifferentiated mesenchymal cells, regulates collagen synthesis and collagenase secretion and modulates mitogenesis in endothelial cells, fibroblasts, and osteoblasts [19]. PDGF plays a key role in angiogenesis, macrophage activation, fibroblast chemotaxis, fibroblast proliferation, and collagen synthesis. Additionally, it contributes to bone metabolism by stimulating osteoblast replication and facilitating bone collagen degradation. PDGF is found in three isoforms - αα, ββ, and αβ. While their precise function remains unclear, one theory suggests that they bind selectively to different receptors. This suggests that platelet-derived growth factor may have a dual effect, serving as both a stimulator and regulator of bone and soft tissue repair [20]. Due to the fact that people nowadays are involved in more and more sports activities, they are at risk of developing chondral lesions. It's important to discover all the chondral defects as soon as possible and to approach them with the right treatment; otherwise, they can lead to osteoarthritis in time.

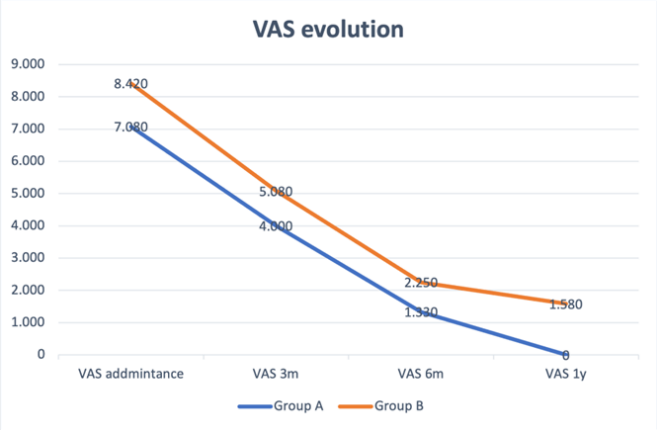

Figure 5.
VAS score evolution

From a pharmacotherapy perspective in osteoarthritis, the most commonly used treatments include topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), as well as regular intra-articular injections of corticosteroids or hyaluronic acid. The biological and regenerative approach using PRP comes with fewer side effects and long-term effects. PRP was chosen as the biological therapy due to its extensive use in regenerative medicine, its easy obtaining process, and its low risk profile [21].

The proper treatment for chondral lesions is still debatable. Studies revealed different results, varying from positive to negative ones [22, 23]. Even though the microfracture technique is not an innovative technique nowadays, it is still used in a lot of centres. We have to take into consideration that it is still a cheap intervention and doesn't require extremely high skills. By adding the PRP to microfractures, we offered the body supplementary help in healing the chondral defect. It is true that the new tissue that grows on the affected site is fibrocartilaginous, which cannot have the same properties as the natural cartilage. This type of tissue has a very dense matrix of collagen fibres. Compared with the hyaline cartilage, the fibrocartilaginous one consists primarily of type I collagen. The microfracture technique is what is called a cell-homing approach. Studies have revealed that in the case of a subchondral lesion, there is a higher rate of new cartilage formation. Mesenchymal stem cells (MSCs) that are present in the bone marrow are the precursors of chondrocytes. The problem is that their concentration is very low, 0.001% [24]. Microfractures facilitate the migration of mesenchymal stem cells, haematopoietic stem cells, and osteoblasts to the cartilage defect.

Another option for enhancing microfractures is autologous and micro-fragmented adipose tissue, adipose tissue-derived stem cells (ADSCs), because they are easy to harvest and handle, unaffected by aging, and have shown chondrogenic differentiation both in vitro and in vivo under optimal conditions. ADSCs express markers such as CD105+, CD73+, CD90+, and CD44+ and negative for HLA-DR, CD34, CD31 and CD45 [25].

Bone marrow aspirate concentrate (BMAC) is another option and is a widely used term that describes a combination of bone marrow elements and mesenchymal stem cells (MSCs) derived from bone marrow. Cassano *et al*. noticed that BMAC exhibited a 172.5-fold increase in VEGF, a 78-fold increase in IL-8, a 4.6-fold increase in IL-1β, a 3.4-fold increase in TGF-β2, and a 1.3-fold increase in PDGF [26]. The authors concluded that there was no significant difference in platelet counts between BMC-A and PRP, but leukocyte concentrations varied. TGF-β and PDGF levels were similar in both

BMC-A and PRP. However, interleukin-1 receptor antagonist concentrations were significantly higher in BMC-A compared to PRP [26]. IL1-RA is a protein and a natural inhibitor of the pro-inflammatory effect of IL1 [27].

The patients selected for this study were accepted after a rigorous evaluation. We chose the ones with similar lesions, with ages between 29 and 60 years old, with the mean age of 40.42 for the first group and 41.92 for the second one. We considered the variables that could influence the results, including BMI and systemic or local comorbidities. Therefore, the inclusion of patients was limited to 12 *per* group. We plan to conduct patient evaluations for a duration exceeding one year, as the tissue formed post-microfractures and PRP administration exhibits diminished resistance to compressive stresses, rendering it susceptible to injury over time and necessitating further interventions.

The quantity and timing of PRP treatment are also debatable [28]; however, we opted to proceed based on the literature and our prior clinical experience. In this observational analysis, we selected patients who underwent surgery by various orthopaedic surgeons, employing a consistent technique as outlined in the literature [29]. These findings corroborate previous studies on this subject [30-31].

Conclusions

Microfractures combined with biological therapy, PRP, are useful instruments for improving the quality of life in patients with chondral lesions. Microfractures performed arthroscopically combined with the administration of 3 doses of PRP led to improved knee function and less pain compared with simple microfractures, as demonstrated by the VAS and IKDC score measured at 3 months, 6 months, and 1 year. Our results align with other published studies, but further research is needed, especially for more extended evaluations over time.

Conflict of interest

The authors declare no conflict of interest.

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