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Effectiveness of a Single High Dose of Platelet-Rich Plasma (PRP) Injection Over Corticosteroid and Hyaluronic Acid Injections on Osteoarthritis, Chronic Tendinitis and Tennis Elbow Treatment

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Abstract

Background: Corticosteroid, hyaluronic acid (HA) injections and Anti-inflammatory agents are considered as non-invasive treatments for knee osteoarthritis (OA), Chronic Tendinitis (CT) and Tennis elbow (TE) that are supposed to provide symptomatic relief and to help surgical delay intervention. Platelet rich plasma (PRP) is a biological component shown to be beneficial for different orthopedic dysfunctionalities treatment. The presence of GFs in PRPs such as transforming growth factor-β, insulin-like growth factor 1co-stimulate the mesenchymal stem cells and fibroblasts secretions and promotes the fibrin matrix formation which effectively drive the healing process, induces regenerative response and lead to the damage structure repair in orthopedics trauma. **Methods:** Three groups of a total of 30 patients presenting OA, CT and TE diagnosis, non-responding to corticosteroid, HA and non-steroid anti-inflammatory treatments were randomized to undergo one intra-articular injections of single high dose of PRP. The efficacy of Intra-articular PRP Injections was evaluated before the injection and one month

after. The efficiency assessment score was based on [1] Knee injury and Osteoarthritis Outcome Score, [2] Physical Function Short Form (KOOS-PS) Arabic (KSA) version LK 1.0, [3] HOOS-Physical Function Short form (HOOS-PS), and [4] Macdermid patient-rated Tennis Elbow. **Results:** A significant reduction of pain and a marked improvement in movements was observed in the 3 patient's groups, PRP-injected patients showed significantly higher values compared with baseline: ($p < 0.005$ vs baseline), improve functional status and reduce clearly the articular dysfunctions over the time. In our study, single High dose injection of PRP provided an overall superior clinical improvement compared with HA and corticosteroid treatments over the time and the different follow-up checkpoints of the study.

Keywords

Platelet Rich Plasma (PRP), Osteoarthritis, Chronic Tendinitis, Tennis Elbow, Corticosteroid, Hyaluronic Acid, Non-Steroid Anti-Inflammatory

1. Introduction

Platelet rich plasma (PRP) has been shown to be efficient for many orthopedic diseases like tendinopathies (*i.e.*, lateral epicondylitis [1], patellar tendinopathy [2], Achilles tendinopathy [3], shoulder impingement syndrome [4], rotator cuff tear [5], osteoarthritis knee [6], and avascular necrosis of femoral head [7]). The economic costs of orthopedic dysfunctions are high, including expenses related to treatment, MRI and radiographies, and those due to limited work productivity.

In the current study, we emphasized on, the Osteoarthritis, the Chronic tendinitis and the tennis elbow prevalent conditions of articular disabilities.

Knee osteoarthritis (KOA) affects 10% of the developed world population. Patients with KOA are at a higher lifetime risk compared to the general population by OA of 45% [8]. KOA is a joint disorder resulting from progressive articular damage affecting mostly the knees and the hips. Nowadays, there is no efficient treatment for KOA, non-indicative clinical data about the disease progression [9]. Anti-pain treatment and maintaining a healthy lifestyle are primordial and can be of benefit [8]. Surgery interventions to compensate or replace damaged tissue are also a treatment option [9]. Current guidelines recommend a combination of movement exercises and drug therapies such as non-steroid anti-inflammatory molecules (NSAID) [10]. However, this treatment generally has temporary benefits and moderate outcomes in KOA patients. Furthermore, patients with comorbidities are not illegible for NSAID treatment. Recent study discussed that repeated injections protocol of Intra-articular glucocorticoids is associated with a cartilage loss feature is generally recommended only for short-term pain relief and a [11] [12]. The use of Hyaluronic acid (HA) is controversial where guidelines offer restricted recommendations [12]. Despite these

non-curable treatment strategies for KOA, knee arthroplasty results as a definitive treatment associated to an expensive cost, and a high risk of post-surgical medical complications [13]. Thus, an alternative non-invasive and safe treatment for KOA is crucial.

The Chronic Tendinitis (CT) disorder implicates serious complications and some treatment protocols with very poor curative effects, with high probabilities of relapse [14]. The root of the disease is a long-term excessive physical exercise, which causes an overstretch of the tissue surrounding the tendon. Inflammatory modifications occur and rub the tendon and the periorbital tissue [14] [15]. Then, chronic inflammation conducts the degeneration of the hyaline and fatty tissues of the tendon [16] and the spontaneous rupture of the Achilles tendon. Although, the treatment for Chronic tendinitis varies on the severity of the injury, it mainly engages, nonsurgical methods, basically steroid hormone-blocking therapy [17], oral NSAID [18], and low-frequency ultrasound stimulation [19]. Steroids and lidocaine apply strong anti-inflammatory and analgesic effects and are widely used for CT treatment in clinical practice [17] [19]. To date, the clinical application of these anti-pain medications in the treatment of CT is largely controversial.

The tennis elbow (TE) or lateral epicondylitisis one of the most common overuse syndromes related to excessive wrist extension [20]. TE is associated to angio-fibroblastic degeneration and collagen disarray [21]. On histological level, sections reveal fibroblasts and blood vessels consistent with neoangiogenic process [22]. TE pain can be reduced using physiotherapy tools [23], NSAID, and cortisone (steroid) injections [24]. Recent studies described that cortisone injections reduce inflammation over few months, where the healing process is always long to handle since the cortisone infiltration can destroy healthy tendon cells and increase the severity of the TE context for some patients [24].

Biological components have been recently studied for KOA, CT and TE treatment such as MSCs and PRP. PRP is as autologous blood product enriched in platelets concentration [25] [26] [27]. Platelets are the natural healing cells recruited into the tissue injury [28]; in addition PRPs include antibacterial and fungicidal proteins, numerous growth factors (GFs) such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I), fibroblastic growth factor (FGF) and hepatocyte growth factor (HGF) [29] [30]. The liberation of these GFs is supposed to be allied to the PRP efficacy in wound healing [29]. Several clinical trials have shown that PRP may be promising for KOA, CT and TE treatment [31]. GFs are the effectors that improve the healing of tendon injuries treated by PRP injections. The use of PRP is rarely associated to medical complications and less invasive than other therapeutic options indicated for some patients, such as surgery [32] [33]. The PRP components especially the GFs and the fibrin matrix represent a potential biological tool for the healing process in orthopedics trauma after PRP treatment.

The aim of this study is to determine whether a single high dose of PRP and plasma injection improve validated outcomes in patients with symptomatic KOA, CT and TE. Herein, we highlight the effect of PRP as a first treatment line for inflammatory joint problems and tendinopathies.

2. Materials and Methods

2.1. Study Design and Patient Selection

This is a retrospective, experimental study. Thirty patients with Osteoarthritis, Chronic Tendinitis and Tennis Elbow were divided into 3 groups: Group A (n = 10), Group B (n = 10) and Group C (n = 10), respectively. The Injection of the single high dose of PRP treatment took place on an outpatient clinic without the need for hospital admission. One session was performed per patient. All participants were aged between 26 and 58 years old (median age 42 years old) and were refractory to the usual conservative corticosteroids or hyaluronic acid treatments. There were no exclusion criteria; all patients with OA, CT, and TE were included.

All procedures run during the study were carried out in compliance with institutional ethical standards. Reviva Regenerative Medicine Center and the Middle East Institute of Health—University Hospital Ethics Review Boards approved the collection and processing of venous blood (Approval Reference Number Reviva-IRB-MEIH-005-21) and all patients were asked to read, approve, and sign an informed consent form prior to any participation.

Patient evaluation and pain score: To evaluate disease progression and examine the regenerative power of the PRP, we used the Knee injury and Osteoarthritis Outcome Score—Physical Function Short Form (KOOS-PS) Arabic (KSA) version LK 1.0 for group A patient (Annex 1), HOOS-Physical Function Short form (HOOS-PS) for group B patients in (Annex 2), and Macdermid patient-rated Tennis Elbow Evaluation in group C patients (Annex 3).

Adverse effects: patients with mild transient adverse events. Pain, rigidity and synovitis were the most common complaints. There were no lasting adverse effects to any participants.

2.2. Preparation of Autologous PRP

After obtaining patients' consent and in order to prepare 30 different samples of PRP, venous blood was collected from patients using a sterile 20 ml syringe containing ACD solution. Under a laminar flow hood, the blood was transferred to a 50 ml centrifuge tube. The PRP preparation procedure consisted of two centrifugation steps. The initial centrifugation low speed for 15 min at room temperature separates the whole blood into three layers: an upper layer containing mostly platelets and WBC (White Blood Cells), an intermediate thin layer identified as the buffy coat rich in WBC, and a bottom layer that consists mostly of RBCs (Red Blood Cells). Most of the red blood cells were eliminated and the upper layer and buffy coat are transferred to an empty sterile tube and centri-

fuged at higher speed for 8 min for Platelet concentration and PRP collection.

2.3. PRP Analysis

VEGF, PDGF and Platelet Assay

VEGF and PDGF were measured by ELISA. The supernatant and the antibody (monoclonal biotinyle) form a complex after the interaction of biotin and streptavidin during incubation for 60 min. The excess was eliminated by washing and an enzyme-antibody complex is added. The complex antibody-enzyme formed the final sandwich complex. After incubation, the excess was washed again. Afterwards, sulfuric acid was added to stop the reaction and the solution's color transformed from blue to yellow. The color intensity was directly correlated to the concentration at 450 nm. The total leukocyte count was <2 in our PRP analysis. The PDGF concentration in the PRP ranged from 50,230 to 74,948 pg/ml (63,668 ± 12,968 pg/ml) and VEGF from 1368 to 2429 pg/ml (1788 ± 1245 pg/ml).

All blood samples were drawn in ACDA-anticoagulated blood and run on a Sysmex SE 9500 in the main Laboratory within 15 min of phlebotomy. The baseline platelet count ranged from 1.89 to 2.90 × 105 platelet/µl (mean 2.0 × 105 platelet/µl). The PRP concentrate had a platelet count ranging from 12.55 to 15.8 × 105 platelet/µl (mean 13.88 ± 1.76 × 105 platelet/µl) with a recovery of 90% (87.4% - 92.6%). The total platelet count injected ranged from 10.14 to 10.83 billion (10.45 ± 0.46) in a total volume of 3 mlg.

2.4. Injection Procedure

After the collection of blood and PRP preparation (described above), the area where the PRP will be injected was cleaned with Povidone Iodine (Betadine®) swab to be disinfected.

For the injection in the Knee, many approaches can be adopted starting from either above the knee going to the side (superolateral injection), as well as from the above going to the middle (superomedial). Furthermore, another injection method could be going from the front toward the middle (anteromedial) or the side (anterolateral). In this study, for knee injection, supero-lateral approach had been adopted because it provides a better access and is less difficult than the others.

The superolateral injection starts by drawing a line from the apex of the Patella laterally to the Lateral Pole and another line to the medial pole with the upper border of the Patella being the base of the triangle. The needle can then be inserted into the half point of the lateral line directed toward the intra-articular space of the knee.

For tennis elbow injection, a 25 G needle is inserted over the center of Lateral Epicondyle either at 45 or 90 degrees of the skin with a 0.6 - 1.6 cm depth.

For tendinitis injection, needles used depend on the weights of patients, where the goal is to reach the greater trochanteric bursa where the PRP will be injected.

2.5. Statistical Analysis

Subgroup analysis included (single vs bilateral) and duration of symptom (≤median vs > median duration). The median duration of symptoms was determined by the baseline data. We performed an omnibus (likelihood ratio χ^2) test for treatment-subgroup interaction in a model for the primary outcome. *P* value of less than 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc).

3. Results

KOOPS-PS, HOOPS-PS and the Patient-rated Tennis Elbow Evaluation questionnaires were used to calculate specific scores for each activity. These scores were used to evaluate and compare the pre- and post-injection status for the knee, hip and tennis elbow, respectively. Concerning the knee injections, seven criteria were used to evaluate the efficacy of the injections: rising from bed, putting on socks, rising from sitting, bending to floor, twisting/pivoting on the injured knee, kneeling and squatting. The difficulties in the execution of each of the above-mentioned tasks diminished after the injections, mainly from Severe/Extreme before the injection to Moderate/Mild after injections. The average and median values of the scores are represented in Table 1. *Significant improvement from baseline at one month the decrease observed in the calculated scores is statistically significant ($p < 0.05$).

Regarding the hip injections, five criteria were tested: Descending stairs, getting in/out of the shower, sitting, running and twisting/pivoting on the loaded leg. The intensity of the difficulties in accomplishing the aforementioned tasks decreased significantly after injections, (the average and median in Table 2), except for "twisting/pivoting on the loaded leg" that showed similar results pre- and post-injection. *Significant improvement from baseline at one month the decrease observed in the calculated scores is statistically significant ($p < 0.05$).

As for the tennis elbow injections, four criteria were taken into consideration to evaluate the efficacy of the injections: Pain subscale, specific activities, usual

Table 1. Baseline clinical characteristics of patients with OA knee treated with PRP. *PRP* Platelet-rich plasma, Knee injury and Osteoarthritis Outcome Score—Physical Function Short Form (KOOS-PS) Arabic (KSA) version LK 1.0.

Study groups and time points		Koos-ps score						
		Rising from bed	Putting on socks/ stockings	Rising from sitting	Bending to floor	Twisting/pivoting on your injured knee	Kneeling	Squatting
Knee Injection	Before injection	2.9 (3)	2.81 (3)	2.9 (3)	2.77 (3)	2.72 (3)	2.4 (3.5)	3.36 (3)
	After injection	*1.45 (1)	*0.6 (0)	*1.45 (1)	*1.55 (1)	*1.54 (2)	*2.2 (2)	*1.45 (1)

Table 2. Baseline clinical characteristics of patients with CT shoulder treated with PRP. *PRP* Platelet-rich plasma, HOOS-Physical Function Short form (HOOS-PS).

Study groups and time points		Hoos-ps score				
		Descending stairs	Getting in/out of shower	Sitting	Running	Twisting/pivoting on your loaded leg
Hip injection	Before injection	2.5 (3)	2.25 (2.5)	2.75 (3)	2.75 (3)	1.75 (1.5)
	After injection	*2 (2)	*1.75 (1.5)	*2 (2)	*2 (2)	1.5 (1.5)

Table 3. Baseline clinical characteristics of patients with TE arms treated with PRP. *PRP* Platelet-rich plasma, Macdermid patient-rated tennis elbow evaluation.

Study groups and time points		Patient-rated tennis elbow evaluation				
		Pain subscale	Specific activities	Usual activities	Function subscale	Total score
Tennis Elbow Injection	Before injection	59.66 (60)	35.26 (36)	36.66 (31.63)	31.33 (22)	47.66 (46.75)
	After injection	*35.66 (36)				*35.75 (33.75)

activities and function subscale. The average amount of pain in the patients' arms decreased after injections only in the "pain subscale" section, the average and median in (Table 3). The other three criteria (specific activities, usual activities and function subscale) showed similar results before and after injections. *Significant improvement from baseline at one month the decrease observed in the calculated scores is statistically significant ($p < 0.05$).

4. Discussion

According to our study, in one month after injection, the patients of all three groups showed significantly lower scores KOOPS-PS, HOOPS-PS and Macdermid Lequesne, compared to their primary assessment before the injections (baseline levels). Based on the results, the HA and corticosteroid had significantly lower scores after one month of follow up post injection. It is clear that the corticosteroid and HA therapy in OA, CT and TA has some early beneficial but not long lasting effects. Our results demonstrated that 1-high dose injection of PRP seemed to have significant improvement. Compared to a meta-analysis conducted on a limited number of studies (n = 5) to evaluate the efficacy amongst different PRP injection therapies [34], our study, include more patients (n = 30) more specific clinical outcomes at different periods of follow-ups were compared; Our results could provide more information about the efficacy of high dose of PRP injection therapies especially for treating mild-moderate KOA, CT and TE.

Our results indicate that high dose of a single injection of PRP maintain pain relief after a one month of follow up compared to the HA and corticosteroid several injection treatments.

In conformity with our study, a previous meta-analysis performed by Raeissadat *et al.* showed that the corticosteroid and HA effects were maintained of 4 - 6 months' post-injection [35]. EceUslu Guvendi *et al.* have also shown that, in comparison to PRP, patients treated with corticosteroid and HA have experienced earlier improvement in OA symptoms, however PRP had long anti-inflammatory effect compared to corticosteroid and HA therapy [32]. Gaballa *et al.* showed that corticosteroid and HA were able to reduce the score at the same level of PRP injections at the 1st month post-injection, unlikely three months post injections, patient who received corticosteroid and HA therapy showed higher scores than the PRP-injected patients [36]. Interestingly we found that a single high dose PRP injection has much long-term benefit effects compared to the study of Sara j *et al.* [36], in KOA mainly respond from severe/extreme before the injection to moderate/mild after injections, as for the TE the average amount of pain in the patients' arms decreased after injections, finally for the CT The intensity of the difficulties in accomplishing the aforementioned tasks decreased significantly after injections. Our study is close my consistent with the meta-analysis results of Jatupon Kongtharvonskul *et al.* where PRP was shown more benefit than autologous blood injection or steroid injections for patient with tennis elbow disease [37]. PRP injection and autologous blood injection display an improvement in disability scores and pressure pain threshold when compared with steroid injection. However, side effects are higher risks with autologous blood injection compared to PRP and steroid injections.

Several clinic trials revealed only short-term effects of corticosteroid injection within rotator cuff lesions. A recent clinical trial (Registration: ClinicalTrials.gov (Identifier: NCT02588872) showed that HA and PRP injections improve same pain score at any time point in the primary outcome measure. Interestingly, significant improvements were seen in other outcome measures, favoring PRP over HA. The study suggests that a decrease in 2 pro-inflammatory cytokines in the PRP injected patients, contribute to an improvement of symptoms [38].

Otherwise, corticosteroid and PRP were shown to reduce inflammation, however corticosteroid and HA don't belong to any biological regenerative mechanism impacting negatively their long-term anti-inflammation role. In our study, we demonstrated that single high dose PRP injection can be a rapid benefit for functional recovery and pain relief compared to corticosteroid and HA injection at both medium- and long-term follow-up. Significant improvement of PRP single high dose injection compared to baseline level was observed at one month of follow-up, the decrease in the outcomes score is statistically significant ($p < 0.05$) in OA, CT and TE patients.

PRP infiltrations have been widely used for the treatment of OA, CT and TE with many beneficial results. In our study, intra-articular PRP injections were well tolerated. We managed to reduce the mild synovitis within the first week after injection.

Treatment with single high dose of PRP injections was shown to be safe since no complications have been reported. We suggest that single high dose of PRP is

a safe non-invasive procedure with a very limited risk of infectious diseases transmission.

Based on the discussed evidence, comparing three active treatments for patients with OT, CT, and TE single high dose of PRP injection showed the best result on pain reducing after one month, whereas corticosteroid, HA injection and the NSAID showed the best score improving disabilities and pressure threshold.

5. Conclusion and Perspective

We found that PRP is a potential alternative option for KOA, CT and TE treatment. Our study attempts to provide additional information about the efficacy of the single high dose of PRP injection amongst various PRP, corticosteroids and HA injections therapies among patients with tendinopathies and arthritis; According to the current evidence, the single use of a high dose of PRP shows a significant improvement on pain and ROM scores. Considering the side effect of corticosteroids which are never indicated for some patients with a high risk of tendon rupture, we suggest the use of single high dose PRP instead of corticosteroid and HA injections among patients with OA, CT and TE.

However, the study design was not high-level evidence for long-term follow-up, so more studies should be further conducted to confirm these results.

The cost-effective analysis comparing PRP injections, corticosteroid and HA injections or the combination of physiotherapy should be evaluated on pain, disabilities, pressure pain threshold and risk of side effects outcomes. For the medium and long-term follow-up, high dose single PRP injection is in favor of long-lasting articular benefits and cartilage regeneration process. Additional studies with longer follow-up time points and larger sample sizes are a must to confirm our observations and to draw more refined conclusions about PRP-based therapy for KOA, Ct and TE patients.

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Author's Contributions

CK perform all the experiences, analyzing results and statistics and contribute in writing, DC contribute in experience design and interpretation of the results, RS assist in the experience, AC interpreted and analyzed the results, DC and AC and CK was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the

corresponding author on reasonable request.

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Competing Interests

The authors declare that they have no competing interests.

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