CHAPTER VII

THE USE OF HOMOLOGOUS PLATELET-RICH PLASMA FOR THE TREATMENT OF KNEE OSTEOARTHRITIS

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1.Introduction

Osteoarthritis is the common form of arthritis and a major cause of morbidity, activity limitation, physical disabilities, excess healthcare utilization, reduced health-related quality of life, and excess mortality, especially in people aged 45 years and above (1).The goals of osteoarthritis treatment include the alleviation of pain and improvement of functional status (2). Today, the majority of treatment modalities are palliative, including oral or topical nonsteroidal anti-inflammatory drugs. However, lifestyle modifications, particularly exercise and weight loss, are also effective (3,4). Recent research has focused on new methods for replacing or stimulating the repair of the damaged cartilage. Platelet-rich plasma (PRP) is a key source of the growth factors that are involved in tissue repair and regeneration.

Growth factors include platelet-derived growth factor (PDGF-AA, -BB, and -AB isomers), transforming growth factor (TGF-β1 and -β2 isomers), platelet factor 4 (PF4), interleukin-1 (IL-1), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), osteocalcin (Oc), osteonectin (On), fibrinogen (Fg), vitronectin (Vn), fibronectin (Fn), and thrombospondin-1 (TSP-1) (5).

These products deliver collections of bioactive molecules with important roles in fundamental processes, including inflammation, angiogenesis, cell migration, and metabolism, in pathological conditions. PRP is not only crucial in the repair of damaged structures but also in creating biological models that encourage tissue regeneration by improving the metabolic functions of those structures (6).

Recent papers have investigated the effects of PRP on cartilage repair. For instance, Kütük et al examined the action of PRP on cartilage repair in temporomandibularjoint osteoarthritis in rabbits (7). Using scanning electron microscopy, the researchers found thick and disorganized collagen fibrils in the control group and thin, well-organized collagen fibers in the PRP group. Histologically, the regeneration of the fibrocartilage and hyaline cartilage was higher in the PRP group.

Although the molecular in vivo effects of PRP must be investigated further, clinically, autologous intra-articular injection for the treatment of knee osteoarthritis is widely accepted and increasingly used to treat patients.

Autologous PRP is derived from a patient's own peripheral blood, which is then centrifuged to achieve a high concentration of platelets within a small volume of plasma. It is then reinjected at the injury site or inserted as a gel or other biomaterial during surgery. Various blood separation devices require differing preparation steps, essentially accomplishing similar goals. About 30–60 ml of venous blood is drawn by an aseptic technique from the antecubital vein. The use of an 18- or 19-g butterfly needle is advised to avoid irritation and trauma to the platelets, which are in a resting state. The blood is then placed in an FDA-approved device and centrifuged for 15 min at 3,200 rpm. Afterward, the blood is separated into platelet-poor plasma (PPP), red blood cells (RBCs), and PRP. Next, the PPP is extracted through a special port and discarded. While the PRP is in a vacuumed space, the device is shaken for 30 s to resuspend the platelets. The PRP is then withdrawn. Depending on the initial blood draw, there will be approximately 3–6 cc of PRP available (8).

PRP can also be prepared as random donor platelet concentrates from whole-blood-derived platelets or as apheresis platelets from a single donor (9).

In the whole blood (WB) harvesting method, 500 ml of blood is collected and stored in a citrate preservative at room temperature. Within 8 h, the blood is centrifuged at a slow spin, and the PRP is separated into an attached empty satellite bag. The PRP is centrifuged again at a fast spin and separated into 1 unit of platelet concentrate. Each unit of platelets contains 5.5 × 1010 platelets in 50–70 mL of plasma. Alternatively, platelets can be isolated from WB from the buffy coat layer by centrifugation of the WB in bags designed to remove RBCs and plasma through a tubing at the bottom and top of the bag. The platelet-enriched buffy coat is further processed (through centrifugation and/or leukoreduction filters) to eliminate white blood cells (WBCs) and any remaining RBCs. This method is employed in Europe and Canada. It

permits the storage of WB at room temperature for up to 24 h prior to platelet harvesting and provides some other advantages.

Apheresis platelets or single-donor platelets are obtained by performing apheresis on volunteer donors. During this procedure, large volumes of WB are processed in an extracorporeal circuit and centrifuged to separate the components. The RBCs and a certain percentage of the plasma are returned to the donor. A single donor on apheresis donates an equivalent of >3.0 × 1011 (6 units) of WB-derived platelets suspended in a volume of 200–400 mL of plasma. Single-donor apheresis-derived platelets minimize the number of donor exposures to which the transfusion recipient is exposed and have become the primary source of platelets in the United States (10).

The PRPs derived from other donations are routinely used for intravenous transfusion to patients with neoplastic or gastrointestinal diseases or diseases of the blood-forming organs in an effort to prevent or treat bleeding due to thrombocytopenia (11). It is also known that the administration of ABO-specific platelets is not strictly required because platelet concentrates contain few RBCs. In additional, platelets derived from Rh-positive donors are often transfused to Rh-negative patients.

Therefore, the uncomplicated attainability of homologous platelet suspensions in addition to the high concentration of platelets within small (50–70 cc) suspensions and the very low antigenic potential suggest that intra-articular injection of homologous PRP (H-PRP) might be effective in the treatment of degenerative osteoarthritis. Thus, in this preliminary study, the effects of H-PRP in the treatment of degenerative knee osteoarthritis were evaluated by performing intra-articular H-PRP injections in 52 patients with 6-month follow-ups.

2. Material and Methods

This study was approved by our institutional ethics committee (Clinical Research Ethics Committee of Necmettin Erbakan University, Meram School of Medicine). The diagnosis of osteoarthritis was based on the American College of Rheumatology (ACR) criteria (12) and the Ahlbach's radiological classification system based on AP weight bearing and lateral views of knees was used for staging of the disease.

The patients have chronic pain (at least 3 months) with no benefit from previous analgesic treatments or physiotherapy and the presence of grade 3–4 osteoarthritis according to the Ahlbach's classification system were included in current study.

Exclusion criteria were visco supplement or corticosteroid injections into the affected knee, previous knee surgery, previous knee trauma, presence of knee joint infection, systemic disorders such as diabetes and

rheumatoid arthritis, and patients undergoing therapy with anticoagulants or antiaggregants.

There were 25 men and 27 women, and their mean age was 58.77 (range: 47–70) years. The average body mass index was 34.74. All the patients were informed about the results of the process before the application of H-PRP injection. The injection was performed on those patients who were willing to undergo the procedure and signed the consent forms. The injection was performed bilaterally in 9 patients and unilaterally in 43 patients; a total of 61 knees were injected (Table 1).

2.1. Homologous PRP preparation

WB donations (450 mL) from subjects with the same blood groups as those of the patients were collected into quadruple blood bag systems after ABO- and RhD-compliance was confirmed for all patients. The H-PRP was collected by the buffy coat method. The WB was centrifuged at high speed with subsequent collection of the buffy coat. The buffy coat was then centrifuged at low speed to concentrate the platelets and remove RBCs and WBCs. The WB was then centrifuged at 3000 × g for 23 min. The supernatant plasma from the top of the container and the RBCs from the bottom of the container were removed using an automated instrument. Next, the obtained buffy coat was recentrifuged for 5 min at 400 × g (low speed), and approximately 50 mL of PRP was transferred into a platelet storage bag by an automated instrument.

2.2. Injection technique

All injections were carried out in an outpatient setting.The homologous material was evaluated the presence of any infectious diseases prior to administration in all cases. The injection was performed at the affected knee with a classical approach to the upper pole of the patella using a 22-g needle. No ultrasound guidance was employed. After cleaning the skin with an antiseptic solution, 5 ml of H-PRP was injected into each affected knee. After injection, passive flexion and extension was performed several times, and the patient rested in the supine position for 5–10 min. Patients were allowed to use paracetamol as required (maximum 2 g/day) if they felt pain, but they were asked not to use any analgesic within 24 h before evaluation and avoid intense physical activity.

2.3. Follow-up

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores were used to investigate the clinical effects of the treatment. The WOMAC is a proprietary set of standardized questionnaires widely used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. The WOMAC have five items for pain,

two items for stiffness, and 17 items for functional limitation. Physical functioning questions cover daily activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties (13). The scores were evaluated before and after the injection at months 1 and 6. Complications and adverse effects were also evaluated.

2.4. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows® software program version 18.0. Intergroup comparisons were made using the analysis of variance for repeated measures. To determine the statistically different groups, the Bonferroni-corrected paired t-test was used. A Pvalue of <0.05 was statistically significant.

3. Results

No severe adverse events or complications related to the injections were observed during the treatment or follow-up period. All patients were satisfied with the H-PRP treatment, especially regarding pain relapse, and no patients underwent knee surgery due to pain or functional limitations of the knees. A statistically significant improvement in all WOMAC scores was observed at months 1 and 6 compared to the preinjection values ($P = 0.00$). The positive effect on pain continued up to 6 months. However, at month 1, it was significantly better than that at month 6 ($P \leq 0.05$). Between months 1 and 6, the knee joint stiffness showed no statistically significant difference ($P \geq 0.05$), as it was stable at the 6-month follow up. However, both of them were better than the preinjection values. Similar to the pain scores, the physical function showed further improvement at the 6-month follow-up ($P \leq 0.05$). There was no statistically significant difference between months 1 and 6 in social functioning ($P \geq 0.05$). Emotional functioning was also improved during the follow-up periods ($P \leq 0.05$) (Table 2, 3).

4. Discussion

Intra-articular injections of autologous PRP have been widely accepted for the treatment of knee osteoarthritis. In addition to the treatment of chronic osteoarthritis, autologous PRP is also commonly used in sports medicine to treat injuries of the tendons, ligaments, and muscles (14,15,16).

Recently, the efficacy of autologous PRP for treating degenerative osteoarthritis has also been investigated in several studies (17,18,19). Clinical improvement, especially in terms of pain after knee movement and at rest, was reported.

In this study, we applied H-PRP derived from WB donations to treat chronic degenerative osteoarthritis using a method different from the standard autologous PRP. No complications or adverse effects due to H-PRP injections were observed. After the treatment, all the patients reported a significant reduction of pain at rest and movement. Moreover, all the patients reported a significant increase in the quality of their lives at the 6-month follow-up with only one H-PRP injection.

Crovetti et al reported about topical H-PRP application to treat chronic ulcers, including diabetic, venous, and neuropathic ulcers. They observed no adverse effects but faster promotion of granulation tissue and decreased pain in all cases (20).

However, the use of intra-articular injections of H-PRP has not been reported previously. The present study showed that intra-articular injections of H-PRP could be used safely and also exert positive effects similar to those of autologous PRP in the treatment of degenerative osteoarthritis.

All the donated blood samples are carefully tested for transfusion-transmissible infections (TTIs), including HIV, hepatitis B, hepatitis C, and syphilis. The H-PRP, like other blood transfusions, has achieved a high degree of safety regarding the transmission of viral diseases. The homologous material was tested for the presence of any infectious diseases prior to administration in all our cases.

Based on our study results, the advantages of homologous PRP versus the autologous PRP are as follows:

H-PRP can be easily obtained from blood centers and prepared from the blood of healthy donors without contact with the outside environment; therefore, the risk of infection is minimal.

Due to the interaction with autologous PRP in the preparation phase of the external environment, we believe that there might bea higher risk of contamination.

H-PRP application is completed with a single injection. However, two injections are performed in autologous PRP treatment. The patient's own blood is collected for the first injection to prepare autologous PRP. It is then injected into the joint. Therefore, autologous PRP application is more painful and uncomfortable than H-PRP application for the patient.

Autologous PRP application requires 30–35 min. First, the blood is collected from the patient, followed by in vivo autologous PRP preparation and then intra-articular injection. However, a single intra-articular injection of H-PRP into the joint requires a maximum of 5 min. Therefore, it is faster and more practical than autologous PRP.

To obtain 5 ml of PRP, approximately 50 ml of blood must be collected from each patient, and a minimum of 80–100 ml of blood is required for both knees. This process can intensify anemia in anemic patients, but H-PRP does not carry such a risk.

In addition, there is a possibility that growth factors released from the platelets of H-PRP might have stronger regenerating effects because they are obtained from healthy donors. In this regard, the superiority of H-PRP must be tested in more comprehensive, long-term studies.

Despite the high number of patients evaluated, the absence of a control group and the lack of testing of H-PRP samples to confirm the contents and standardization are limiting factors in this study. Although the WOMAC score is a highly valuable instrument, the score can depend on the patients' condition on the day they completed the questionnaire. In future studies, the evaluation should be performed using a more objective measurement as well as radiological images. In addition, despite the low risk, obtaining written consents from the patients could be difficult in some scenarios; our patients were fearful and anxious about potential prosthesis surgery of the knee joint, and therefore, they accepted the H-PRP treatment as a new treatment modality.

In conclusion, this preliminary study showed that intra-articular injections of H-PRP could be safely used without complications or adverse effects. It also has positive effects on the degree of pain and the level of physical and social activities in the treatment of chronic knee osteoarthritis like autologous PRP. Therefore, it could be used as an alternative method to autologous PRP in suitable cases.

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