Platelet-rich plasma versus oral paracetamol for treatment of early knee osteoarthritis. Preliminary study

ABSTRACT

Background: In the treatment of early osteoarthritis, analgesics and nonsteroidal anti-inflammatory drugs are frequently used to relieve pain. Currently, platelet-rich plasma is used as an alternative treatment for osteoarthritis. The aim of this study was to evaluate the effect of platelet-rich plasma compared to paracetamol as treatment for patients with grade I knee osteoarthritis.

Methods: We evaluated 42 patients who were randomized into two groups. Group one was treated with 5 ml of platelet-rich plasma in two applications, whereas group two was treated with 1 g of oral paracetamol every 8 h for 30 days. Both patient groups received supervised physical rehabilitation during the 6-month observation period. Peripheral blood samples were taken to measure plasma IL-1β, TNF-α and TGF-β1 levels at day 0 and at 6 months post-treatment. Clinical evaluation was conducted using the Knee injury and Osteoarthritis Outcome Score (KOOS) at the start of the study and for every subsequent month during the study period.

Results: The KOOS for group one at treatment initiation was measured at 30.1 points, whereas at the end it was measured at 48.2 points, showing 60% clinical improvement. There were no statistically significant differences in IL-1β and TNF-α levels between groups treated either with platelet-rich plasma or paracetamol.

Conclusions: Patients treated with platelet-rich plasma showed a statistically significant increase in serum levels of TGF-β1, which was associated with an improvement in the clinical evaluation used (KOOS).

Key words: Knee osteoarthritis, platelet-rich plasma, KOOS, growth factors.

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BACKGROUND

Osteoarthritis is a degenerative joint disease of multifactorial origin with a prevalence of 4-30% depending on age, gender and definition of the disease. Risk factors include obesity, prior joint injury, intense physical activity, osteoarthritis of the hand and family history of the disease. Although it is not an acute inflammatory disease, the tendency is to be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics. The risk of suffering symptomatic osteoarthritis in adult patients is 44.7%. Its incidence increases when it is associated with obesity. In fact, intense exercise has been linked as a triggering factor.

Patients with osteoarthritis may have chronic latent inflammation with elevated serum concentrations of inflammatory cytokines such as interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) as the result of tissue damage. Wassilew et al. evaluated the expression of metalloproteases (MMPs) of the extracellular matrix and proinflammatory cytokines in the synovium of knees with history of trauma and non-traumatic osteoarthritis. They found no differences in their study in the metalloprotease expression of the extracellular matrix, IL-1β or TNF-α in the synovial tissues of patients in both groups. TNF-α concentration in the synovial tissue was correlated with the age of the injury and chondral damage in patients with traumatic knee disorders such that quantification of TNF-α could serve to evaluate the individual risk factor for osteoarthritis.

Multiple treatments have been described for patients with osteoarthritis such as hyaluronic acid, chondroitin sulfate, and nonsteroidal anti-inflammatory drugs. Currently, intraarticular platelet-rich plasma has been used with good results for treatment of osteochondral defects.

The objective of the study was to compare the efficacy of intra-articular platelet-rich plasma vs. oral acetaminophen for treatment of early osteoarthritis (grade I) through valuation using the clinical scale of Knee injury and Osteoarthritis Outcome Score (KOOS) and to measure the serum concentrations of TGF-β1 growth factor and proinflammatory cytokines (IL-1β and TNF-α).

METHODS

We included patients > 40 years of age without gender distinction. Patients had knee pain of 3 months duration without prior treatment. X-rays revealed primary grade I osteoarthritis according to the Kellgren and Lawrence classification. We excluded patients with osteoarthritis grades III and IV, morbid obesity, angular deformities > 15º in varo-valgus, joint instability, history of septic knee arthritis, autoimmune diseases, cerebrovascular or malignant diseases, active infections, hemoglobin 11.0 g/dl, coagulation defects, anticoagulation therapy, systemic corticosteroids administered 3 months prior to the initial visit, major surgery or blood transfusion in the 2 prior months, or history of alcohol or drug abuse. The study was approved by the Ethics Committee of our hospital. All patients were informed of the procedure and signed an informed consent for admission into the study.

Patients were randomly assigned to two groups distributed with the help of the Alea T-7/33 program. Group 1 (experimental) received platelet-rich plasma and group 2 (control) was treated with 1 g/8 h of oral paracetamol. In addition, both groups received education about their disease. They were sent to physical therapy for stretching exercises and muscular strengthening of the lower extremities supervised by a therapist. During the initial visit a clinical history, KOOS evaluation, and knee x-rays in two projections (anteroposterior and lateral) were done.

Group I patients were given an intraarticular injection of platelet-rich plasma on two occasions, with 15 days in between injections. During
each visit, a 60-cc blood sample was taken from the basilic or antecubital vein of the upper extremity which was processed with the GPS® III Platelet Concentrate Separation Kit with ACD-A system (Biomet®, USA). After the samples were processed, intraarticular injection of 5 ml of platelet-rich plasma was given after asepsis of the region of the knee and under sterile conditions on the superolateral corner of the knee. The patients remained at relative rest for 24 h. At the end of the 24 h they reinitiated their daily activities as tolerated after the rehabilitation exercises indicated. Group 2 received 1 g of paracetamol every 8 h orally. The rehabilitation was started in a manner similar to Group 1. Physical therapy was carried out with isometric and isotonic exercises of the femur, which were supervised by a therapist.

Patients were evaluated using the KOOS scale, at the beginning of the treatment and monthly until the end of the study. This scale evaluates young patients with short- or long-term knee injuries. It is divided into five subscales: pain, other symptoms, sports and recreational activities, activities of daily life and quality of life.18

**RESULTS**

**Knee Injury and Osteoarthritis Outcome Score**

On initial evaluation of the patients there was no significant difference between groups. The average value of group I was 30.1 points (± 13.8) and for group 2 was 28.7 points (± 13.0). During the assessment of the second month, group I had an average value of 41.3 points (± 17.8) and group 2 of 36.3 points (± 11.4) (p= 0.03). The results obtained at the fourth month of treatment showed a significant difference between groups. The average value for group I was 51.2 points (± 15.4) and for group 2 was 42.2 points (± 14.7) (p= 0.008). The results at the end of the study showed significant differences in favor of group I, with values of 48.2 points (± 15.0) vs. 41.3 points (± 22.0) (p= 0.0008) of group 2.

**Serum concentrations of TGF-β, IL-1β and TNF-α**

At the beginning of the study the average value of TGF-β1 of the patients from group 1 (platelet rich plasma) was 13.9 pg/ml (± 12.7). In the control group the concentration was 27.9 pg/ml (± 10.3). During the evaluation at the end of the study the group who received platelet-rich plasma had a value of 29.3 pg/ml (± 7.5) (p= 0.003), whereas the control group had an average value of 29.1 pg/ml (± 6.3) (Table 1).

IL-1β values obtained before group 1 treatment were 1.54 pg/ml (± 2.4) and on completion 1.07 pg/ml (± 1.5). Group 2 had initial values of 0.96 pg/ml (± 1.2) and at completion 1.46 pg/ml (± 2.7). TNF-α values in group 1 were 3.21 pg/ml (± 0.8) and on completion 5.03 pg/ml (± 1.4); for group 2 the initial value was 3.53 pg/ml (± 1.3) and final value 5.83 pg/ml (± 1.7), without statistical significance (Table 1).

**Serum Detection of IL-1β, TNF-α and TGF-β**

For detection and quantitative analysis of the plasma proteins IL-1β, TNF-α and TGF-β, 20 ml of peripheral blood was taken. The system of suspension arrangements (Bio-Plex,® Bio-Rad Laboratories, Hercules, CA) was used, which consists of the combination of the ELISA technique and flow cytometry. In the former, a protein is trapped between two specific antibodies that are joined together in exclusive sites of the protein and, in the second, they separate and quantify the cells labeled with fluorochromes from a mixture. Statistical analysis was done with the Student t test and ANOVA. Data were analyzed with the STATA-IC-10-2008 program.
DISCUSSION

Platelet-rich plasma is the portion of a fraction of autologous plasma containing high concentrations of platelets and secretory proteins. In a pilot study by Sampson et al., the evaluation of 14 patients with primary or secondary osteoarthritis with application of three intra-articular injections of platelet rich plasma was reported. The researchers measured the KOOS scale for 1 year and did not find any adverse effects with this treatment. They also observed improvement in the median score values at rest and activities of movement and flexion of the knee. Our results for both groups followed a similar behavior in periods of improvement. At the end of the second month and subsequently at the fourth month, patients experienced an important decrease in symptoms when evaluated with the KOOS scale. At the end of the study both groups had better average scores than at the beginning.

The response to TGF-β appears to be related with age. A change in the signal of this growth factor could play a decisive role on age-related diseases. It appears to have a relationship with age and a change in the signal of this growth factor could play a decisive role on diseases related with age. Different reports indicate that cartilage chondrocytes with osteoarthritis also express anabolic factors such as TGF-β. It has been demonstrated that cartilaginous cells of young rats synthesize proteoglycans in response to TGF-β. Anitua et al., studied 63 patients to observe the relationship between growth factor concentrations and radiographic grade and found a direct and significant relationship between the concentrations of anabolic markers such as TGF-β with the degree of radiographic severity. Nelson et al., studied patients to determine if serum TGF-β predicts the incidence or progression of hip or knee osteoarthrosis. They carried out measurements in 330 patients > 45 years of age and found no relationship between the incidence and progression of radiographic osteoarthrosis, osteophytes and decrease of joint space with serum concentrations of TGF-β. In our study we found a meaningful increase in TGF-β expression in patients who received platelet-rich plasma as opposed to patients who were treated with oral paracetamol. The chondrocytes of cartilage damaged by osteoarthritis can be stimulated with catabolic cytokines to release products of degradation and cause severe joint damage. IL-1 is the main cytokine mediator of joint damage that intervenes in the inflammatory process in patients with osteoarthritis, which stimulates the chondrocytes to produce collagenases and breaks down the collagen fibers and aggregates. In addition to the fibrillated areas, the cartilage adjacent to the macroscopic lesions of osteoarthritis also express high IL-1 concentrations in comparison with normal cartilage chondrocytes such that the cartilaginous cells of patients with osteoarthritis are more sensitive to the action of IL-1. In this study there was no significant change in the IL-1β concentra-

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<td>TGF-β1</td>
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<td>13.9 (12.7)</td>
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<td>IL-1β</td>
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<td>TNF-α</td>
<td>(p= ns)</td>
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*Values are shown as pg/mL with standard deviation. PRP, platelet-rich plasma; TGF-β1, transforming growth factor-beta 1; IL-1β, interleukin 1beta; TNF-α, tumor necrosis factor-alpha; ns, nonsignificant.
In conclusion, patients treated with platelet-rich plasma had a significant increase in detection of TGF-β1 associated with improvement in the clinical scale of assessment (KOOS); there was no decrease found in the expression of inflammatory cytokines (IL-1β). Treatment with platelet-rich plasma is an option for patients with early knee osteoarthritis (stage 1), which should be done with low leukocyte concentration so as to avoid possible adverse effects and gene expression of pro-inflammatory cytokines. However, it is necessary to carry out studies that analyze the anabolic and catabolic biomarkers in the joint fluid.

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