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ORIGINAL RESEARCH ARTICLE

Injection of Platelet-Rich Plasma in Patients with Primary and Secondary Knee Osteoarthritis

A Pilot Study

ABSTRACT

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Objective: To evaluate the clinical effects of intraarticular platelet-rich plasma (PRP) injections in a small group of patients with primary and secondary osteoarthritis. Most of the current treatments for osteoarthritis are palliative and attack the symptoms rather than influencing the biochemical environment of the joint. Autologous platelet-rich plasma has emerged as a treatment option for tendinopathies and chronic wounds. In addition to release of growth factors, platelet-rich plasma also promotes concentrated anti-inflammatory signals including interleukin-1ra, which has been a focus of emerging treatments for osteoarthritis.

Design: In this single-center, uncontrolled, prospective preliminary study, 14 patients with primary and secondary knee osteoarthritis who met the study criteria received three platelet-rich plasma injections in the affected knee at ~4-wk intervals. Outcome measures included the Brittberg-Peterson Visual Pain (Visual Analog Scale [VAS]), Activities, and Expectations score and the Knee Injury and Osteoarthritis Outcome Scores at preinjection visit at 2-, 5-, 11-, 18-, and 52-wk follow-up visits. Musculoskeletal ultrasound was used to measure cartilage thickness.

Results: There were no adverse events reported. The study demonstrated significant and almost linear improvements in Knee Injury and Osteoarthritis Outcome Scores, including pain and symptom relief. Brittberg-Peterson VAS showed many improvements including reduced pain after knee movement and at rest. Cartilage assessment was limited because of the small sample size. The majority of the patients expressed a favorable outcome at 12 mos after treatment.

Conclusions: The positive trends and safety profile demonstrated could potentially be used to inspire a larger, blinded, and randomized clinical trial to determine whether platelet-rich plasma is safe and effective for the treatment of knee osteoarthritis.

Key Words: Platelet-Rich Plasma, Knee, Osteoarthritis, Injection

There are >27 million Americans aged 25 yrs or older who suffer from osteoarthritis (OA).[1] By 2030, the demand for total knee arthroplasties will increase >670%.[2] This condition places a staggering burden on our current economy, with billions of dollars annually associated with pharmaceutical treatment for pain relief, rehabilitation, and joint replacements.

At present, there are few options for patients with mild to moderate arthritis. Most of the approaches are palliative and address the symptoms rather than influencing the biochemical environment of the joint or the disease process. Current opinion is that the disease progression results from an imbalance between proinflammatory cytokines (including interleukin [IL]-1a, IL-1β, and tumor necrosis factor-α) and anti-inflammatory cytokines (including IL-4, IL-10, and IL-1ra).[3] This cytokine imbalance is thought to activate proteolytic enzymes, leading to the destruction of cartilage.[4,5] The majority of recently proposed therapeutic modalities for OA has a foundation in attempting to address this cytokine imbalance.[6] In addition to cartilage loss, arthritis of the knee joint may adversely affect subchondral bone, synovium, ligaments, capsule, menisci, surrounding musculature, and perhaps the sensory nervous system.[7]

Weight loss and exercise are excellent treatment options for OA, yet are often associated with poor compliance. There is a distinct need for new procedures that are cost effective by reducing the need for pharmaceutical and surgical management, while targeting the biochemical process of OA. Some of the experimental ortho-biological treatments include platelet-rich plasma (PRP) injection graft therapy, high-concentrate PRP (HcPRP), autologous bone marrow aspirate concentration and adipose cells, IL-1 receptor antagonist, nerve growth factor inhibitor, and osteogenic protein-1among others.

Autologous PRP is a volume of plasma having a platelet concentration above normative baseline values.[8] Depending on the method used to process the PRP, it may also contain white blood cell concentrations above baseline values.[9] Platelets and white blood cells are sources of high concentrations of cytokines well documented to regulate a number of processes related to healing and tissue regeneration.[10] These processes include cell migration, cell proliferation, angiogenesis, inflammation mediation, and collagen synthesis.[9,11]

Originally, platelets were thought to act solely in the clotting process. However, in addition to local hemostasis at sites of vascular injury, platelets contain an abundance of growth factors and cytokines that are crucial in soft tissue healing and bone mineralization.[12] Furthermore, we have learned that platelets also discharge many bioactive proteins responsible for attracting macrophages, mesenchymal stem cells, and osteoblasts, which not only promote removal of necrotic tissue but also expedite tissue regeneration and healing.[13] Autologous PRP has emerged as a treatment for recalcitrant tendinopathies and chronic wounds.

Currently, most studies on PRP therapy are anecdotal, nonrandomized, or involve insufficient sample sizes and are underpowered.[13] Recently, there is emerging literature on the beneficial effects of PRP for chronic, nonhealing tendon injuries including lateral epicondylitis and plantar fasciitis.[13–15] However, at present, there are limited studies documenting the safety and efficacy of a nonsurgical PRP injectable for intraarticular use in knee OA.

PRP therapy provides delivery of a highly concentrated cocktail of growth factors to accelerate healing. Transforming growth factor-β, present in PRP, has been associated with chondrogenesis in cartilage repair.[13,16] Data presented at the 2007 International Cartilage Repair Society meeting in Warsaw indicated PRP amplification of chondrocyte proliferation with convincing clinical effects on degenerative knee cartilage.[13,17,18] It was recently demonstrated that PRP increased hyaluronic acid concentration, stabilizing angiogenesis in ten patients with osteoarthritic knees.[13,19] Furthermore, it was documented that PRP encouraged chondrogenesis as an injectable scaffold while seeded with chondrocytes in rabbit ears. Hard knobbles were found and seen on magnetic resonance imaging, as well as histologic investigation and staining, which confirmed cartilage cultivation.[13,20]

A retrospective study demonstrated that intraoperative administration of PRP to a reconstructed joint was associated with fewer transfusions, shorter hospitalization, greater knee range of motion, no infections, and decreased narcotic requirements.[13,21] Multiple studies have reproduced similar findings with PRP used intraoperatively during total knee arthroplasties.[22,23]

We hypothesized that intraarticular administration of PRP would improve function and decrease pain in patients suffering with knee OA. It is unknown whether PRP is capable of inducing cartilage synthesis.

The aim of this study was to evaluate the potential treatment of OA symptoms with PRP. Fourteen patients who failed numerous conservative treatments for OA received a series of three PRP injections into a symptomatic knee during a 12-wk time period. These patients were then followed up for a year.

METHODS

Setting

The study was performed in an outpatient orthopedic clinic in Santa Monica, CA.

Subjects

Patients with a history of primary or secondary knee OA >3 mos were considered for this prospective, nonrandomized, open-enrollment pilot study. All patients were 18 yrs of age or older and spoke fluent English. The study was determined to meet ethical standards and was approved by the Quorum Institutional Review Board, Seattle, WA. The patients received an information packet, providing them with the risks and benefits of the procedure and were given ample time to ask any questions. The subjects who provided informed consent were enrolled in the study. Potential subjects completed questionnaires in the office and had the opportunity to have any concerns addressed by the principal investigator.

Patients meeting all of the following criteria were considered for the study: damage to articular cartilage seen during arthroscopy or on weight-bearing radiographs, a visual analog pain score (VAS) of >60 on a 100-mm scale, discontinued use of nonsteroidal anti-inflammatory drugs for at least 1 mo after the treatment, completed informed consent, and pain that was unresponsive to at least two conventional therapies (local steroid injections, viscosupplementation, nonsteroidal anti-inflammatory drugs, physical therapy, acupuncture, bracing, assistive devices, and lifestyle modification).

Patients were excluded from the study if they had any of the following criteria: pregnancy or breastfeeding, younger than 18 yrs, participating or planning to participate in a worker's compensation program, had pending or planned legal action pertaining to knee pain, were intolerant to acetaminophen or vicodin, had a history of drug abuse, cortisone injection within 6 wks, use of a nonsteroidal anti-inflammatory medication <1-wk before, had a history of anemia, bleeding disorders, rheumatoid arthritis, knee surgery within 3 mos of treatment, infection of the knee joint within 6 mos, had active infection or had any active malignancy.

Procedures

Three injections were performed in the affected knee at ~4-wk intervals. PRP was obtained using the GPS III Platelet Concentration System (Biomet Biologics, Warsaw, IN) per the instructions for use. Fifty-four milliliter of the patient's blood was obtained via venipuncture and mixed with 6 ml of anticoagulant citrate dextrose formula A. The 60 ml of anticoagulated blood was put into a specially designed disposable and centrifuged for 15 mins at 1700*g* in a dedicated centrifuge (Model 755VES, The Drucker Company, Philipsburg, PA). After centrifugation, ~6 ml of PRP was obtained from the disposable. The 6 ml of PRP was injected in combination with 0.6 ml of a 1000 U/ml bovine thrombin suspension in 10% calcium chloride solution.

The injection was made into the suprapatellar bursa of the affected knee using musculoskeletal ultrasound (SonoSite Micromaxx, Bothell, WA) with a 7.6–13.0 MHz linear transducer to ensure proper needle placement. This large bursa was chosen because it communicates freely with the articular cavity and is easily visualized on ultrasound (Fig. 1). Immediately after the injection, passive flexion and extension of the affected knee was performed three times, followed by 10 mins of resting supine. Patients were given acetaminophen and hydrocodone for pain and instructed to limit the use of their affected knee for 24 hrs postinjection, after which normal activities could resume. No standardized physical therapy protocol was used during the treatment and postinjection phases.

Outcome Measures

The Brittberg-Peterson Visual Analog Pain, Activities, and Expectations Score including 10-mm Visual Analog Scale (VAS) with resting, walking, and with the knee in a bent position and the five subscale Knee Injury and Osteoarthritis Outcome Score (KOOS) were completed at a preinjection visit and at 2-, 5-, 11-, 18-, and 52-wk follow-up visits. These well known outcome measures have been previously validated for assessing knee pain and function and are endorsed by the International

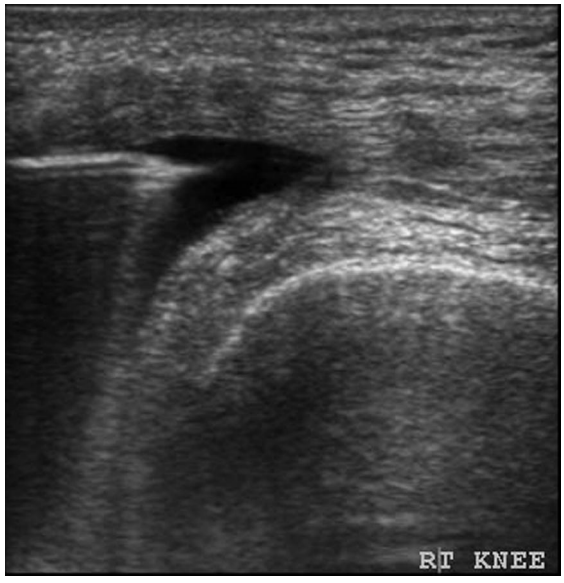

FIGURE 1 *Ultrasound-guided platelet-rich plasma injection of the suprapatellar recess.*

TABLE 1 Knee Injury and Osteoarthritis Outcome Scores

	Pain Relief		Symptom Relief		Activities of Daily Living		Sports		Quality-of-Life	
Week	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Baseline	35.3	4.96	31.6	4.84	44.8	5.24	9.6	6.83	1.0	6.68
2 wks	38.0	4.96	35.71	4.84	47.3	5.44	11.8	6.83	5.4	6.18
5 wks	41.7	4.96	34.4	4.84	51.6	5.66	9.6	6.83	7.6	6.18
11 wks	44.1	4.78	39.8	4.84	48.4	5.66	14.2	7.09	8.9	6.18
18 wks	45.7	4.96	40.7	5.03	55.7	5.44	20.0	7.09	13.0	6.18
52 wks	48.1	4.96	43.9	4.84	54.3	5.44	20.0	7.38	13.4	6.18
Trend *P* value	0.0295		0.0437		0.1136		0.1667		0.1048	

While all five scores increased, the increases in pain and symptom relief over time were statistically significant ($P = 0.0295$ for pain relief; $P = 0.0437$ for symptom relief).

Cartilage Repair Society. At the 1-yr follow-up, patients also filled out a questionnaire intended to assess patient satisfaction with the treatment. The 1-yr follow-up was conducted via telephone and mail, with the other patient visits taking place at the physician's office.

Ultrasound assessment of cartilage thickness, a method previously demonstrated to be reproducible, was used to measure the thickness of the femoral articular cartilage.[24] The same ultrasound device used to guide the PRP injections was used for the cartilage measurements (SonoSite Micromaxx, 7.6–13.0 Mhz linear transducer). With the knee in flexion, cartilage thickness was measured at the lateral condyle, medial condyle, and intercondylar notch. Measurements were taken at the preinjection and 6-mo follow-up visits. Each measurement (baseline *vs.* 6-mo postinjection) was recorded by a different investigator, unaware of the previous measurements to ensure a blinded status. It was only technologically possible to obtain accurate

TABLE 2 Brittberg-Peterson VAS

Week	Minimum	Median	Mean	Maximum	*P* (Friedman)
Pain—resting					
Baseline	0	2	2.5	6	Reference
2 wks	0	2	2.5	6	0.3523
5 wks	0	2	1.8	6	0.5490
11 wks	0	2	1.9	5	0.4248
18 wks	0	1	1.1	3	**0.0135**
52 wks	0	0	0.8	3	**0.0011**
					Overall = **0.0005**
Pain—moving					
Baseline	1	5	4.6	9	Reference
2 wks	1	4	4.2	7	0.8978
5 wks	0	3	3.8	8	0.1434
11 wks	0	3	3.8	8	**0.0323**
18 wks	0	3	2.5	6	**0.0006**
52 wks	0	2	2.5	7	**0.0003**
					Overall = **0.0004**
Pain—bent knee					
Baseline	0	2	2.8	6	Reference
2 wks	0	3	2.3	5	0.8981
5 wks	0	2	2.2	8	0.6088
11 wks	0	2	2.2	5	0.3715
18 wks	0	2	1.6	4	0.1131
52 wks	0	0	1.3	7	**0.0037**
					Overall = **0.0349**

There was significant reduction in moving pain compared with baseline at 11, 18, and 52 wks, significant reduction in resting pain at 18 and 52 wks and significant reduction in bent knee pain at 52 wks. The trend across time was significant for all three pain measures.

TABLE 3 Ultrasound measured cartilage thickness

Cartilage Thickness in mm (n = 13)	Mean	Median	SD	SEM	P
Lateral					
Pre	2.50	2.45	0.97	0.28	—
6 mos post	2.73	2.65	0.81	0.23	—
Post–pre	0.23	0.10	0.61	0.18	**0.2292**
Central					
Pre	3.32	3.40	1.00	0.29	—
6 mos post	3.38	3.35	1.06	0.31	—
Post–pre	0.07	0.10	0.31	0.09	**0.4698**
Medial					
Pre	2.53	2.75	0.64	0.18	—
6 mos post	2.53	2.55	0.95	0.28	—
Post–pre	0.00	0.05	0.73	0.21	**1.0000**

Although there was some thickening in the lateral and central locations, none of the post minus pre changes were statistically significant. However, the sample size of n = 13 is inadequate for confirming small changes beyond chance.
SEM, standard error of the mean.

measurements at the time of follow-up rather than retrospectively obtaining pre- and post-treatment cartilage measurements.

Data Analysis

Statistical Methods

The distribution of each outcome (KOOS scales, Brittberg-Peterson VAS, cartilage thickness) was examined on a normal quantile (Q-Q) plot as well as a histogram to determine whether the data were well approximated by a normal (Guassian) distribution. For data that were well approximated by a normal distribution, the trend over time was summarized by means and standard deviations, and means were compared across time using repeated-measures analysis of variance methods. The corresponding Tukey–Fisher criterion was used under this analysis of variance model for all pairwise mean comparisons between any two times. In addition, an overall test for trend over time was carried out under this analysis of variance model.

Data that did not follow the normal distribution were summarized with medians and ranges over time as well as means and standard deviations. Medians were compared across time overall using the nonparametric Friedman repeated-measure model, and P values for trends and for pairwise median comparisons between any two times were computed under this model using the within-block ranks and the nonparametric Tukey contrasts.[25]

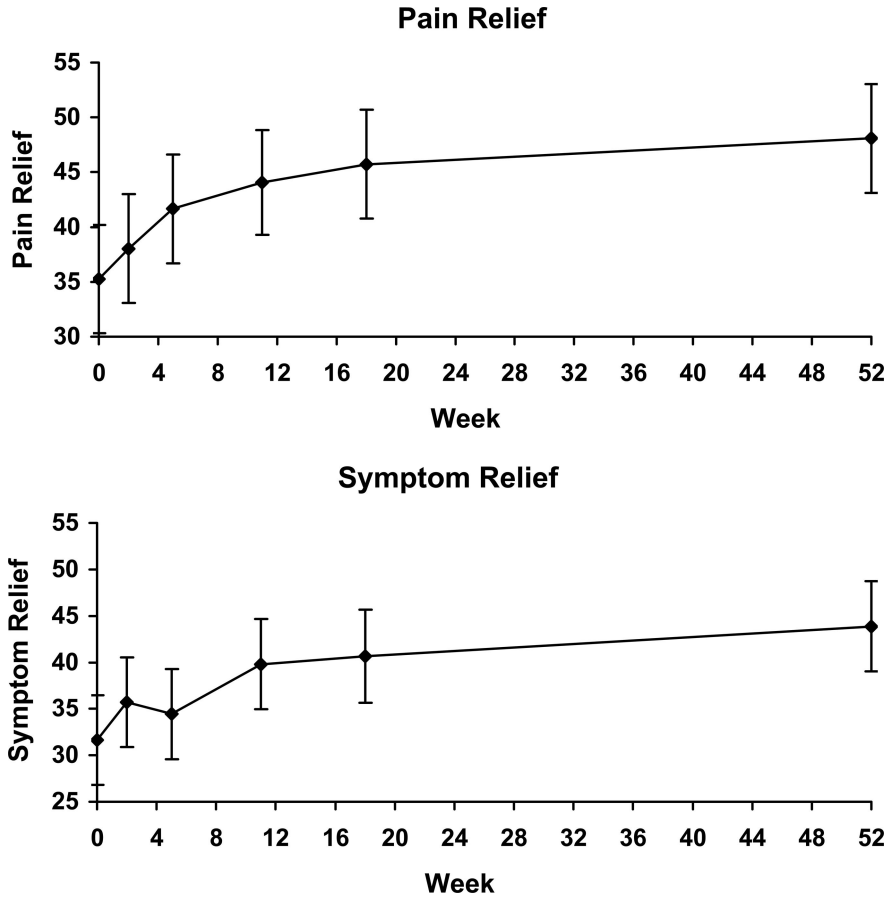

FIGURE 2 *Knee Injury and Osteoarthritis Outcome Score results.*

No power calculation was made before the study, as this is a pilot study. A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Fourteen patients with primary or secondary OA were enrolled in the study. The age range of the enrolled patients at the preinjection visit was 18–87 yrs, with a median of 51.8 yrs. Twelve of the 14 patients were men. Seven of the 14 patients had treatment on their right knee. The average (standard deviation) body mass index for participants was 25.0 kg/m^2, with a range of 20.9–32.5 kg/m^2. One patient was missing data for the Brittberg-Peterson VAS and cartilage outcomes.

KOOS-residual error histograms and normal quartile plots (not shown) confirm that the five KOOS subscales were well represented by a normal distribution. Table 1 shows the mean and standard errors over time for the five KOOS subscale, whereas Table 2 shows results of Brittberg-Paterson VAS at preinjection baseline, 2, 5, 11, 18, and 52 wks (Tables 2, 3; Figs. 2, 3).

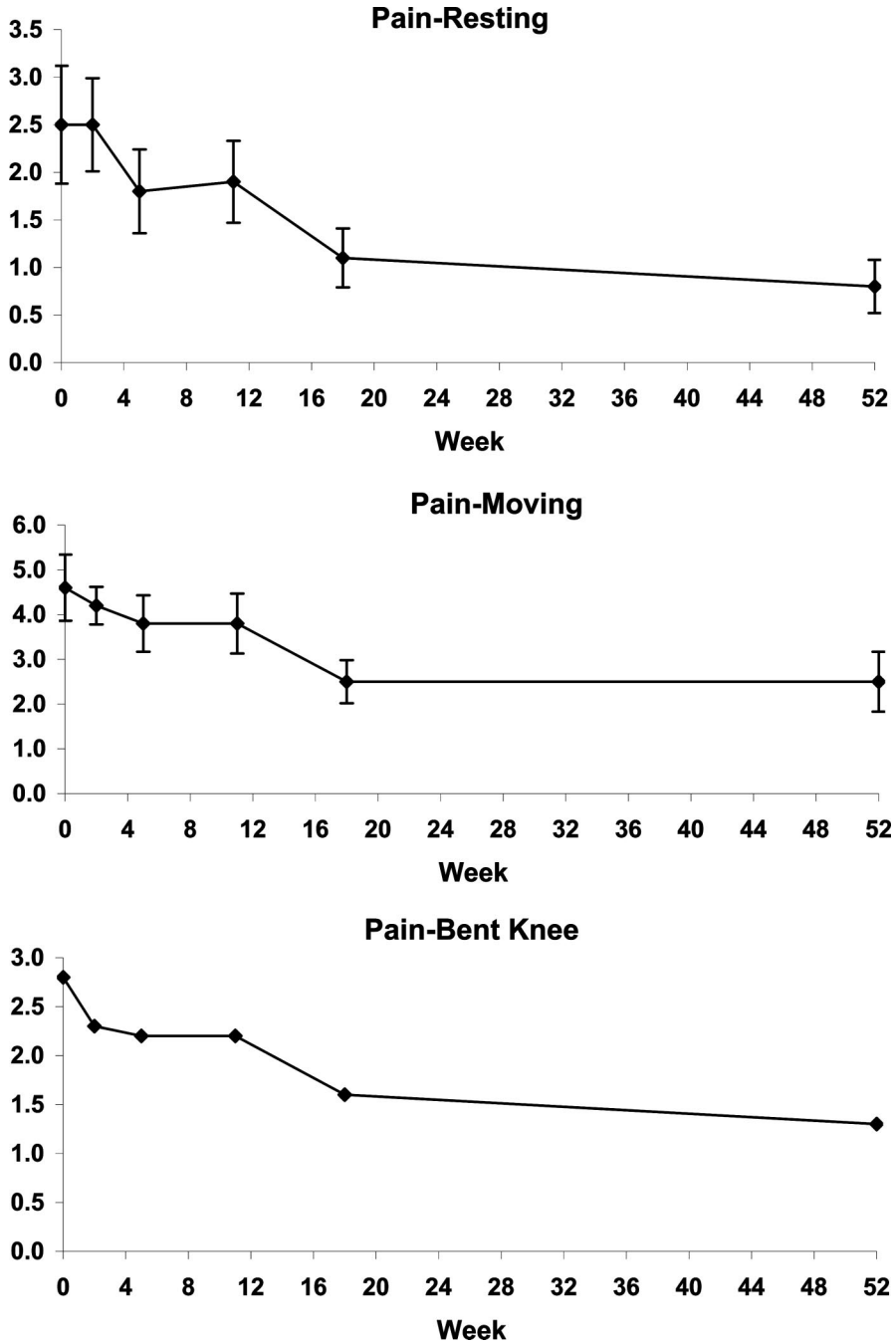

FIGURE 3 *Brittberg-Peterson Pain VAS results.*

Ultrasound measurement of the cartilage thickness was not significantly different during the first 6 mos; however, 6 of 13 patients demonstrated increased femoral articular cartilage on sonography at the lateral condyle, medial condyle, and intercondylar notch (Table 3). The oldest patient (an 87-yr-old man) demonstrated increased cartilage thickness at 6 mos compared with the preinjection measurements on the lateral (1.3 *vs.* 2.0 mm) and medial (2.4 *vs.* 2.5 mm) condyles, with no change at the intercondylar notch (1.5 mm at both time points) (Figs 4, 5). He also demonstrated improved Brittberg-Peterson VAS scores at the 1-year follow-up compared with preinjection values for the knee at rest (6 *vs.* 1), the knee while moving (9 *vs.* 2), and the knee while bent (6 *vs.* 1).

Patient satisfaction-A survey was filled out at the 1-year follow-up to assess patient satisfaction. Eight of the 13 patients indicated that they had achieved their individual goal with the injection. Eight of the 13 patients indicated that the injected knee had improved, 3 of the 13 patients indicated that the injected knee had stayed the same, and 2 of the 13 patients indicated that the injected knee had gotten worse, and the pain was no longer tolerable.

Adverse Events

Modest pain caused by the injection and persisting for the week following an injection was reported. The patients did not describe long-term complications related to the procedure and no serious adverse events attributable to the treatment. The majority of the patients expressed overall satisfaction at 12 mos after treatment.

DISCUSSION

The aim of this study was not to provide conclusive insight into the efficacy of PRP injections as a treatment for OA. Rather, this preliminary study was performed to provide potential outcome measures and provide data that could potentially be used to facilitate a blinded, randomized controlled clinical trial to determine whether PRP is safe and effective for knee OA. However, the data demonstrated significant and almost linear improvements in KOOS, including pain and symptom relief. Brittberg-Peterson VAS showed many improvements including pain after knee movement and at rest. Cartilage assessment was limited because of the small sample size. Overall, several patients were satisfied after treatment, in a population group that had significant OA with few treatment options. The findings suggest that patients who benefited from the injection series maintained those positive results for at least 12 mos without other medications or treatments.

The age, gender, and body mass index of participants in this study may not accurately reflect the general population. The study primarily involved men, despite a growing trend in women with OA. In addition, younger patients with chondropenia were included in the study after developing secondary OA. However, both women in the study reported a positive result from the study with continued pain relief at 12 mos. These findings suggest that a larger study should incorporate more women to address arthritis in this population. Moreover, the data imply that perhaps the degree of OA and chondropenia is more critical opposed to the patients' overall age and viable platelets. Although limited by small sample size and a lack of control, the findings suggest a trend that documents improvement in pain scores and function, with a favorable experience reported.

Longer follow-up would be beneficial to determine whether there is an endpoint of benefit from an injection series. Perhaps, an additional fourth injection or another series of injections would benefit those who did not receive a favorable outcome or

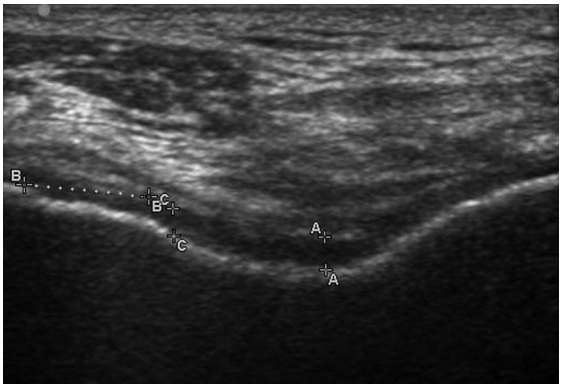

FIGURE 4 *Knee cartilage measurement with ultrasound preinjection in an 87-yr-old man.*

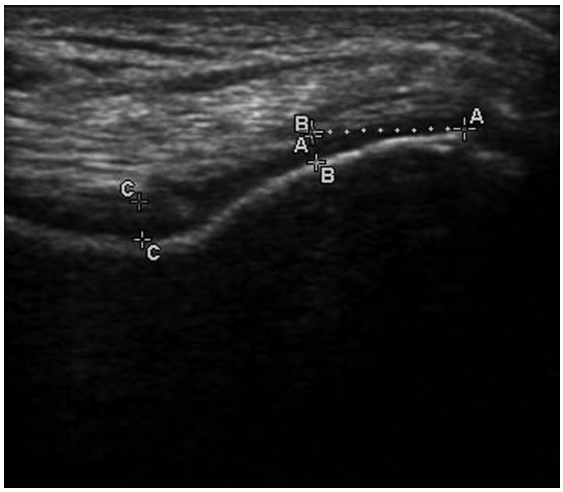

FIGURE 5 *Knee cartilage measurement with ultrasound 6-mos postinjection in an 87-yr-old man.*

reached a plateau with time. The study included a range of patients with varying degree of OA both anatomically and functionally, which could perhaps explain the variation of overall satisfaction. One of the patients experienced a slip and fall, spraining his medial collateral ligament on the treated knee. This new pain may have complicated the patient's recovery and response to the study treatment.

At present, there is limited published literature on PRP treatment for OA to compare our results and interpretations with. At the 2010 Annual American Academy of Orthopaedic Surgeons meeting, preliminary data were presented that demonstrated statistically significant superiority of PRP compared with viscosupplementation (hyaluronic acid) injections for treatment of OA.[26] The study found that PRP injections provided more symptomatic relief and prolonged efficacy than hyaluronic acid injections with reduction in pain and recovering articular function at 6-mo follow-up.[26] Another recent randomized controlled trial showed statistically significant improved pain and function after a PRP injection compared with cortisone for lateral epicondylitis.[27]

The conclusions made with this study are clearly limited by many factors, most notably, the limited sample size, nonrandomized study design, lack of a comparative control, and lack of patient blinding to the treatment. A sample size calculation was not performed before initiating the study, which may have hindered this work. The limited sample size severely limits the power and therefore the significance of statistical analysis. The lack of a control group does not allow one to see the comparative natural history without PRP intervention. There was no funding involved in this study, which limited the available resources. Current realms of research include exploring the potential benefits of combining PRP with viscosupplementation or autologous adult stem cells from marrow aspirate or adipose cells, as well as increasing the platelet concentration up to 23× baseline with highly concentrated PRP.[28]

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