Effects of Platelet-Rich Plasma on Pain and Muscle Strength in Patients With Knee Osteoarthritis

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Objective: No studies comparing the effects of platelet-rich plasma (PRP) injection and placebo injection in bilateral knee osteoarthritis in the same patient, or discussing muscle strength after PRP injection, have been published.

Design: Twenty patients with bilateral knee osteoarthritis were eligible, and 40 knees were randomized into two groups: PRP (knees [right or left by a coin toss] receiving a single intra-articular PRP injection) and saline group (the contralateral knee of the same patient, into which single 4-mL intra-articular injection of normal saline was administered). The primary outcome measure was Western Ontario and McMaster's Universities Osteoarthritis Index and the secondary included isokinetic test results. The evaluation was at baseline and at 2 wks, 1, 3, and 6 mos after injection.

Results: The PRP group showed a significant reduction in the Western Ontario and McMaster's Universities Osteoarthritis Index pain and total scores compared with normal saline group ($P < 0.05$). Although a significantly greater percentage of knee strength (extensor > flexor) was found in the PRP group during a longer follow-up period, PRP treatment resulted in insignificant differences in muscle strength compared with normal saline.

Conclusions: Platelet-rich plasma treatment significantly improves pain, stiffness, and disability in patients with knee osteoarthritis compared with normal saline treatment. Additional strength training is recommended to enhance muscle strength recovery.

Key Words: Platelet-Rich Plasma, Osteoarthritis, Knee

(*Am J Phys Med Rehabil* 2018;97:248–254)

Osteoarthritis (OA) of the knee is a chronic degenerative disorder characterized by progressive disintegration and softening of the articular cartilage in the synovial joints. It is often accompanied by osteophyte development, subchondral sclerosis, and cyst formation.[1] Elderly and obese adults are at the highest risk for developing knee OA. Therefore, this disease is one of the most common causes of disability.[2] The management of knee OA includes nonoperative therapy, such as analgesic drugs and physiotherapy, and operative treatment including osteotomy and knee arthroplasty.[1] Moreover, the risk of falls increases in patients with knee OA because mechanical receptors around the knee joint may be vulnerable because of anatomical changes caused by OA. Hence, impaired sensory input results in the inability to perform normal knee movement and is accompanied by a decline in muscle strength,[3] joint proprioception,[4] and balance.[5] Furthermore, some studies have demonstrated that muscle strength, joint proprioception, and balance could be improved in patients with knee OA after proper intervention.[6,7]

Platelet-rich plasma (PRP) is an autologous product that mainly contains concentrated platelets and growth factors. It is known to enhance tissue healing at injury sites through modification of the biological microenvironment.[8] Given its biochemical and biological nature, PRP treatment has received much attention for its use in the treatment of knee OA.[9,10] Recent studies have demonstrated that PRP exerts favorable effects on pain and knee joint function compared with placebo in early stages of the knee OA. However, the effectiveness of PRP in OA is still debatable because previous studies differed in the concentrations of leucocytes used for the preparation of PRP, dosage schedules, and so on.[11] Moreover, no study has investigated the effect of PRP in comparison with that of a placebo injection in the same patient with bilateral knee OA. It is of interest to examine the effect of PRP in the same patient with bilateral OA.

Isokinetic testing is frequently used as a diagnostic tool to measure muscle strength and dysbalance and to document therapeutic effect and disease progression in patients with joint or muscle disorders.[12] Only two previous studies have used isokinetic testing to evaluate the efficacy of the intra-articular injection of hyaluronic acid (HA) in patients with knee OA, Both studies showed positive results for muscle strength.[7,12]

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The study is supported by the Ministry of Science and Technology, Taiwan, Republic of China (Grant Number MOST 104-2314-B-016-050).

The research, article, or abstract was not presented in any form anywhere.

Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ajpmr.com).

ISSN: 0894-9115
DOI: 10.1097/PHM.0000000000000874

However, muscle strength after PRP injection has not been reported.

The goal of the present study was to conduct a prospective, randomized, double-blind, and placebo-controlled study to evaluate the effects of PRP on pain, functional activity, and isokinetic strength in patients with bilateral knee OA. We hypothesized that intra-articular injection of PRP would reduce pain, restore joint function, and increase muscle strength to a greater degree than a placebo injection with normal saline.

METHODS

Study Design

This study was conducted at the Tri-Service General Hospital, Taiwan. The study protocol was reviewed and approved by the institutional review board of the Tri-Service General Hospital (Number 2-103-05-075) and all eligible patients provided written informed consent before enrollment. The study conforms to all CONSORT guidelines and reports the required information accordingly (see Checklist, Supplemental Digital Content, http://links.lww.com/PHM/A534). This clinical study was registered at ClinicalTrials.gov (Registration Number NCT02239029). A total of 20 patients were eligible. Their knees (n = 40) were randomized into two groups: PRP group (treated with a single intra-articular PRP injection in the right or left knee via a coin toss) and saline group (the contralateral knee of the same patient, treated via a single 4-mL intra-articular injection of normal saline) (Fig. 1). The coin was tossed 20 times, with heads indicating the right (n = 8) and tails indicating the left (n = 12) knee. All participants were followed up for 6 mos after injection.

Participants

Patients with a radiological diagnosis of degenerative joint disease of both knees equivalent to Ahlback Stage I–II were recruited for this study. The stage of degeneration was interpreted by the same radiologist with 8 yrs of experience in orthopedic imaging.[13] Eligible participants met the following criteria: age of 50–75 yrs, pain in both knees lasting for a minimum of 6 mos, same OA grade in both knees, and bilateral pain level during walking of at least 4 on visual analog scale. The following exclusion criteria were applied: intra-articular injections (such as HA or steroids) in the knee joint 6 mos before the study, anti-inflammatory medication administered 1 wk before the study, intra-articular tumors, previous knee surgery, any other connective tissue disorder affecting the knee joint, use of anticoagulants, liver disease, cancer history, and inability to undergo muscle strength testing.

Platelet-Rich Plasma Preparation

Platelet-rich plasma was prepared as previously described.[14] Briefly, 10 ml of blood was withdrawn from the antecubital vein of each patient and centrifuged at 1500 × g (3400 rpm) for 15 mins at room temperature using the universal centrifuge Regen Lab to that provide 4 ml of PRP (RegenKit-THT-1, Regen Lab, Le Mont-sur-Lausanne, Switzerland), which is a leukocyte- and platelet-rich plasma according to the Dohan Ehrenfest et al. classification.[15]

Intra-articular Injection

The patient was seated with the knee flexed at 70 degrees. The needle was inserted into the intra-articular joint space of the knee 1 cm above the tibial plateau and 1 cm lateral to the patellar tendon toward the femoral notch. This has been demonstrated to be the most accurate injection site for ensuring intra-articular penetration of the drug (93% accuracy rate).[16] The physician, who had more than 10 yrs of experience in intra-articular injection of the knee joint, performed the injection in all patients. The injection syringe was covered to prevent patients from being able to identify the contents. In addition, patients turned their heads away from the direction of the syringe when the physician performed the injection. Patients received no analgesics or any other intra-articular injection during the study period. Other treatments, such as physical therapy and therapeutic exercises, were not prescribed. Only acetaminophen (500 mg, up to 4 g/d) was allowed as a rescue medication during the course of the study.

Outcome Measurements

The Western Ontario and McMaster's Universities Osteoarthritis Index (WOMAC) was considered the primary outcome measure. The WOMAC includes 3 subscales with 24 items (5 items for pain, 2 items for joint stiffness, and 17 items for physical function). All items ranged from 0 (mildest) to 10 points (most severe).[17] The WOMAC was evaluated at baseline and at 2 wks, 1 mo, 3 mos, and 6 mos after injection. The secondary outcome variable was muscle performance evaluated using isokinetic testing at baseline and at 2 wks, 1 mo, 3 mos, and 6 mos after injection. The evaluation of muscle strength of the knees in both groups was performed with a calibrated isokinetic testing machine (Biodex System 3 Pro, Biodex Corporation, Shirley, NY) according to standard procedures.[18] The reproducibility, reliability, and safety of this device and technique are well demonstrated.[18–20] The patient was seated with 90-degree hip flexion with the shoulder, wrist, thigh, and tested lower leg fixed with straps. The patient was instructed to perform concentric knee exercises, including flexion and extension, at angular velocities of 60 degree/sec and 180 degree/sec, respectively. A resting interval of 90 secs was allowed between the two velocity tests. Peak torque (Newton meter) was recognized as the maximal force produced by the tested musculature at different angular velocities. The average was calculated using the values obtained from three measurements. The same investigator, with 6 yrs' experience in isokinetic testing and who was blinded to the randomization, documented the clinical assessment and isokinetic testing results. The demographic data of patients were also collected.

Sample Size

To reduce the type II error and increase the power of the study, a preliminary power analysis using G*power 3.1.9.2 statistical software (University of Düsseldorf, Düsseldorf, Germany), based on a power (1-β) of 0.8, α of 0.05, and effect size of 0.45 was performed, indicating that a total sample of 17 patients was necessary in each group.

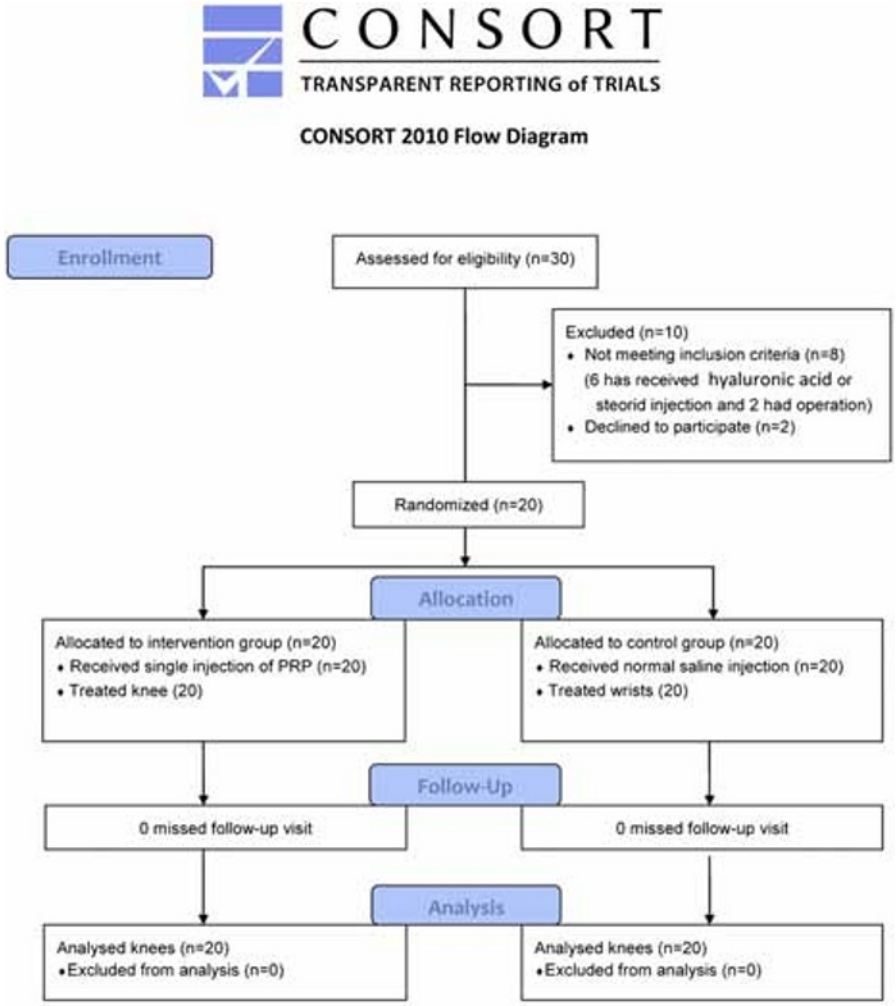

FIGURE 1. Study flow diagram.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Version 22 (Asia Analytics Taiwan Ltd, Taipei, Taiwan). Demographic data were analyzed using the Mann-Whitney *U* test for continuous data and the χ^2 test for categorical data. The differences within the groups were investigated using repeated-measures analysis of variance (ANOVA), followed by post-hoc tests, whereas the difference between the groups was investigated with the Mann-Whitney *U* test. Statistical significance was set at a *P* value of less than 0.05.

RESULTS

All 20 participants (5 men and 15 women; mean [SD] age = 63.25[6.84]yrs) completed the study. Their clinical and demographic characteristics are presented in Table 1. The dominant foot of all patients was on the right foot. Fourteen of 20 knees (70%) were documented as having Ahlback Stage I, and six of 20 knees (30%) as having Ahlback Stage II in both groups. The injection sites for PRP were the left knee in 12 and the right knee in 8 patients. No statistically significant difference in Ahlback Stage, injection site, and duration between the two groups was observed.

As shown in Table 2, no significant differences in baseline WOMAC scores were found between the two groups. The results revealed that both the PRP and placebo groups exhibited improved WOMAC subscales and total scores at all follow-up assessments ($P < 0.05$). Significant differences in WOMAC pain and total score improvements were found between the two groups at all follow-up assessments ($P < 0.05$). Interestingly, PRP treatment resulted in significantly lower WOMAC stiffness scores than saline injection at weeks 2 and 4, whereas significant differences in WOMAC function were observed at the third month. A tendency toward decreased differences between groups during a longer follow-up period was observed (Fig. 2).

Next, we determined the effects of PRP on muscle strength in patients with knee OA. As shown in Table 3, both groups exhibited significant improvements in knee strength at each time point compared with baseline ($P < 0.05$), whereas changes in extensors at angular velocities of 180 degrees/sec were insignificant at each time point compared with baseline ($P > 0.05$) in the placebo knees. The data also indicated a greater percentage of knee strength improvement (extensor > flexor) and the strength differences between the two knees became more obvious when the follow-up period was longer. Unexpectedly, PRP treatment

TABLE 1. Clinical characteristics of study participants and injected knees

	PRP Group (n = 20)	Saline Group (n = 20)	P^a
Sex, n			
Male/female	5/15		
Age, mean (SD), yr	63.25(6.84)		
BH, mean (SD), cm	153.7(25.77)		
BW, mean (SD), kg	60.95(8.75)		
BMI, mean (SD)	24.14(2.93)		
Hypertension	9		
DM	3		
OA knee, dominant foot R/L, n (%)	20:0	20:0	1
OA knee, n (%)			1
Stage I	14 (70)	14 (70)	
Stage II	6 (30)	6 (30)	
Injection site, n (%)			0.652
Left knee	12 (60.00)	8 (40.00)	
Right knee	8 (40.00)	12 (60.00)	
Duration, mean (SD), mo	65.35 (58.32)	60.10 (54.61)	0.78

[a]Mann-Whitney U test or χ^2 test.

BH, body height; BMI, body mass index; BW, body weight; DM, diabetes mellitus.

resulted in insignificant differences in muscle strength compared with saline, whereas the only significant improvements in flexor at angular velocities of 60 degrees/sec were observed at the sixth month (P = 0.04). Neither obvious complications nor adverse effects related to the injections were observed during the treatment and follow-up period in both groups.

DISCUSSION

We conducted a prospective, randomized, double-blind, and placebo-controlled study to simultaneously evaluate the effects of intra-articular PRP on pain, functional activity, and isokinetic strength in the same patient with bilateral knee OA. We found that intra-articular injections of PRP or normal saline improved pain, stiffness, disability, and knee strength in patients with mild to moderate knee OA. We showed that PRP treatment resulted in significantly better improvement in pain, stiffness, and disability than normal saline.

Increasing evidence has highlighted the efficacy of intra-articular injections of PRP for OA with promising clinical outcomes. Montañez-Heredia et al.[21] reported a double-blind randomized controlled trial to assess the efficacy of PRP versus HA in knee OA with three intra-articular injections at 15-day intervals. Pain and functional improvements were evaluated before and after treatment (3- and 6-mo follow-up) using visual analog scale, the Knee and Osteoarthritis Outcome System scale, and the European Quality of Life scale. The authors concluded that PRP treatment effectively improved pain at 3 mos after injection compared with HA in patients with early OA grades.[21] Kavadar et al.[22] reported 102 patients with grade 3 OA knee randomized into three groups and who received PRP injected with once, twice, or three times. Each injection was separated by a 2-wk interval. The result was recorded before treatment and at 1, 3 and 6 mos after the treatment via the visual analog scale, WOMAC, and Timed Up and Go test. The authors concluded that PRP is

TABLE 2. The measured WOMAC parameters before and after treatment

	PRP Group (n = 20)			Placebo Group (n = 20)			
	Mean(SE)	Improved, %	P^a	Mean(SE)	Improved, %	P^a	P^b
WOMAC (pain)	23.1(1.9)			19.1(1.4)			0.080
2nd wk	12.4(2.0)	−50.0	<0.001	15.0(1.2)	−20.1	<0.001	<0.001
1st mo	10.8(1.9)	−56.5	<0.001	12.5(1.2)	−32.2	<0.001	0.002
3rd mo	5.5(1.0)	−74.0	<0.001	10.3(1.0)	−44.0	<0.001	<0.001
6th mo	6.5(1.2)	−69.8	<0.001	9.8(1.0)	−46.3	<0.001	0.008
WOMAC (stiffness)	8.3(0.8)			6.7(0.5)			0.175
2nd wk	4.7(0.8)	−44.4	<0.001	5.4(0.5)	−17.6	0.084	0.008
1st mo	3.7(0.7)	−55.1	<0.001	4.4(0.6)	−31.8	0.010	0.047
3rd mo	1.8(0.4)	−75.7	<0.001	3.2(0.6)	−50.0	0.001	0.133
6th mo	2.4(0.5)	−69.6	<0.001	3.1(0.6)	−51.0	<0.001	0.311
WOMAC (function)	57.6(5.7)			46.1(5.28)			0.120
2nd wk	33.1(4.7)	−44.8	<0.001	32.1(4.2)	−29.9	0.004	0.155
1st mo	26.3(3.9)	−54.0	<0.001	27.3(3.6)	−38.0	0.004	0.194
3rd mo	12.5(2.4)	−75.6	<0.001	20.1(2.6)	−50.5	<0.001	0.004
6th mo	14.7(3.1)	−69.6	<0.001	17.5(1.9)	−54.9	<0.001	0.064
WOMAC (total)	89.6(8.1)			72.0(6.6)			0.102
2nd wk	50.2(7.2)	−47.0	<0.001	52.8(5.3)	−24.9	0.003	0.003
1st mo	40.8(6.2)	−55.7	<0.001	44.7(4.5)	−35.0	0.001	0.016
3rd mo	19.9(3.4)	−75.4	<0.001	34.1(3.4)	−48.0	<0.001	<0.001
6th mo	23.6(4.4)	−69.9	<0.001	30.5(2.3)	−52.1	<0.001	0.027

[a]Repeated-measures ANOVA followed by post-hoc tests.

[b]Mann-Whitney U test.

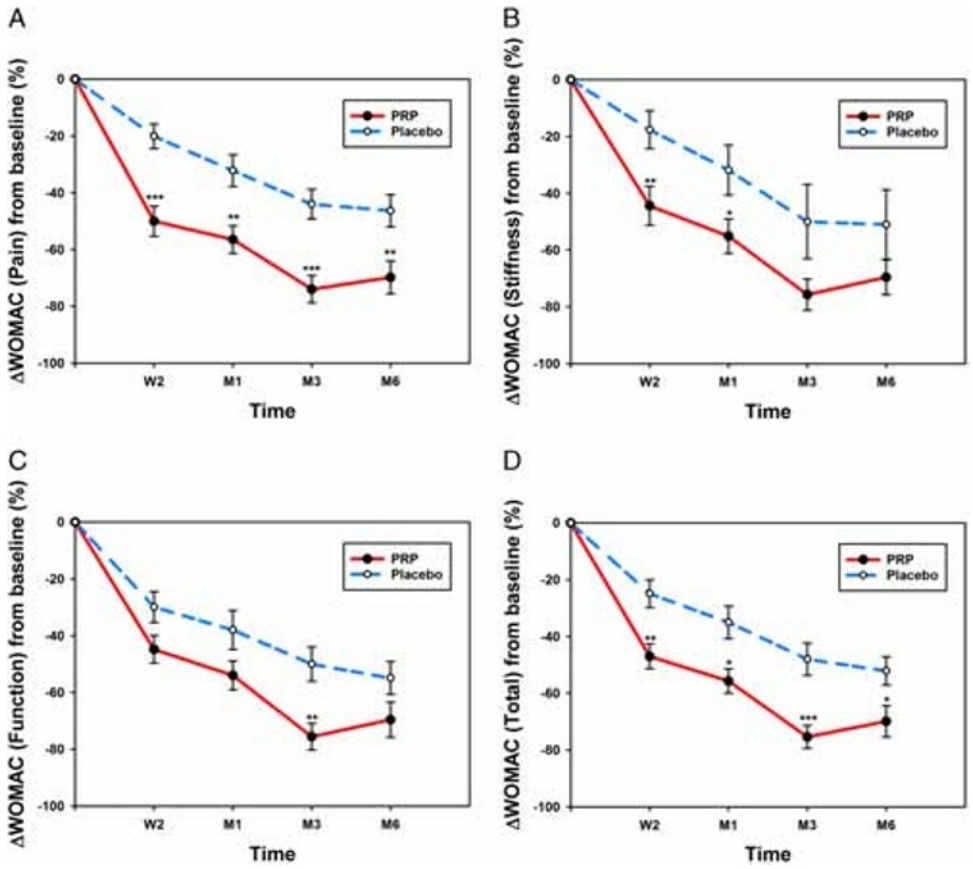

FIGURE 2. Pain, stiffness, function, and total WOMAC scores versus time for the PRP and saline placebo treatment groups. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. M, month; W, week.

effective for the treatment of pain and functional status in moderate knee OA.[22] A recent study revealed that intra-articular PRP significantly decreased symptoms compared with HA or placebo in patients with knee OA.[23] However, a recent trial with a large number of 192 patients reported that the efficacy of PRP was comparable with that of HA treatment.[24] It was suggested that the study design can have a crucial influence on outcome measurements, with a faulty design leading to the misinterpretation of results.

Few studies with placebo-controlled, double-blind, and randomized designs have been published.[25,26] In these studies, patients with bilateral knee OA received either PRP or placebo injection in one knee; the injection of a placebo might interfere with the results because patients may tend to feel improvement in the injected knee. It was suggested that the intra-articular injection of PRP and a placebo in the same patient is a relatively ideal study model as long as the grade of OA is the same in both knees (as per the inclusion criteria of the current study). Besides, previous studies established that PRP injection into only one OA knee instead of both knees could also be measured by WOMAC individually.[27] Although a crossover study would also be a suitable design, we did not consider it because such studies require long follow-up periods. The same grade of OA in both knees of the same patient also diminished the impact of model selection in this study. In the present study, we found that concurrent intra-articular injection with PRP and normal saline in the same patient could significantly improve pain, stiffness, strength, and disability. Furthermore, obvious differences between the two knees were observed during initial follow-up and progressively declined over time, suggesting that PRP has immediate effects comparable with those of saline alone. We found a tendency toward decreased differences between the knees with a longer follow-up period. A possible explanation is that saline is associated with a placebo effect, leading to improvement in symptoms. In addition, it was postulated that the pain relief effect of PRP on one knee with OA might contribute to improving pain in the other knee injected with normal saline through a compensatory mechanism, because both limbs were constantly used during the course of the study.

Pain and low muscle strength are associated with limited knee function in patients with knee OA. It has been suggested that patients with chronic pain exhibit pain avoidance behavior leading to muscle wasting. A recent study has demonstrated that the reduction of pain is associated with improved joint and muscle strength in patients with OA receiving intra-articular injections of HA.[11] Isokinetic muscle strength has been shown to improve in response to the injection of HA in patients with OA.[7] In those two studies, the effect of HA on the muscle strength of the knee was determined 5 wks after injection. In the present study, we reported the long-term follow-up of muscle strength after intra-articular injection of PRP and saline in patients with knee OA, showing improvements in the maximum peak torque in extension and flexion

TABLE 3. The measured isokinetic parameters before and after treatment

	PRP Group (n = 20)			Placebo Group (n = 20)			
	Mean(SE)	Improved, %	P^a	Mean(SE)	Improved, %	P^a	P^b
Knee (60/sec) ex, Nm							
Baseline	72.4(5.1)			80.8(5.8)			0.194
2nd wk	80.4(5.8)	11.6	0.002	85.1(6.2)	5.2	0.038	0.372
1st mo	82.3(5.8)	14.2	<0.001	88.5(6.0)	10.1	0.002	0.829
3rd mo	87.0(5.3)	22.1	<0.001	90.4(7.3)	10.9	0.001	0.062
6th mo	85.0(6.0)	17.8	<0.001	90.8(6.2)	13.1	<0.001	0.394
Knee (60/sec) flex, Nm							
Baseline	33.0(2.7)			34.0(2.6)			0.507
2nd wk	37.0(2.4)	17.1	0.028	38.9(2.3)	17.9	<0.001	0.402
1st mo	39.4(2.8)	23.0	0.002	40.6(2.4)	25.0	0.003	0.725
3rd mo	41.1(2.7)	28.9	<0.001	42.2(2.7)	28.3	<0.001	0.935
6th mo	43.4(3.2)	35.9	<0.001	39.4(2.7)	18.7	0.002	0.040
Knee (180/sec) ex, Nm							
Baseline	50.8(3.8)			54.1(4.0)			0.372
2nd wk	54.1(3.5)	8.1	0.004	56.5(3.5)	6.5	1.0	0.402
1st mo	55.3(3.7)	10.7	0.015	58.1(3.4)	9.9	0.881	0.787
3rd mo	58.9(3.4)	19.0	<0.001	58.4(3.5)	10.5	0.854	0.099
6th mo	58.6(3.6)	18.4	<0.001	58.8(3.6)	11.1	0.255	0.330
Knee (180/sec) flex, Nm							
Baseline	28.5(2.5)			28.6(2.5)			1.0
2nd wk	32.3(2.6)	17.0	0.007	32.5(2.5)	18.1	0.080	0.871
1st mo	33.2(2.7)	21.2	0.009	34.3(2.5)	24.7	0.021	0.516
3rd mo	35.5(2.6)	32.0	0.001	35.1(2.5)	31.1	0.005	0.646
6th mo	37.5(2.7)	40.2	<0.001	34.9(2.4)	29.7	0.003	0.417

[a]Repeated-measures ANOVA followed by post-hoc tests.

[b]Mann-Whitney U test.

Ex, extension; flex, flexion.

at both low (60 degree/sec) and high angular velocities (180 degree/sec) after the injections in both groups. The tendency toward increased differences between the knees at longer follow-up periods was observed in the PRP knees compared with the saline knees. This may have resulted from pain reduction (PRP > saline) as measured by WOMAC, which tends to make patients more willing to use their knee joints and ensures that muscle strength continues to improve. The muscles of the knee, the quadriceps, and hamstrings are known to work together to stabilize the knee joint. Quadriceps strength is important for the protection of the articular structures. Thus, decreased quadriceps strength might be a primary risk factor for knee OA.[28] It has been reported that elderly patients with pain related to knee OA usually have weak quadriceps muscles because of disuse atrophy. Disuse due to pain was defined as one of the major reasons for this muscle weakness.[13] The present results are in agreement with those of previous studies, showing greater percentages of improved knee strength in the extensors than in the flexors. However, none of the participants received additional strength exercises, and a follow-up duration of 6 mos is insufficient to observe the expected differences. The only significant improvements in the flexors at angular velocities of 60 degree/sec are observed at the sixth month ($P < 0.05$) (Table 3). This may due to the small size of the study population. Because most patients with chronic pain may avoid using the affected joints during daily activities and inactivity may cause muscle wasting, the failure of significant long-term maintenance of strength improvement may be predictable regardless of pain improvement. It has been suggested that these patients should be instructed to perform adequate concurrent strength exercises to augment their strength recovery. All types of strength exercise (isometric, isotonic, and isokinetic) have a similar important impact on knee OA. However, the optimal dosage (intensity, frequency, and duration) has not yet been established.[29] Further studies are necessary in the future.

The present study has some limitations. First, the size of the study population was relatively small. Second, concurrent injection with PRP and normal saline in the same patient may overestimate the impact of the placebo effect and further mask the differences between the groups. Further studies with a larger sample size, more conscientious design, and longer follow-up duration are required to elucidate the effects of PRP on isokinetic muscle strength. Third, because of cost and ethical issues, we used only a single injection of PRP or saline instead of multiple injections and were unable to measure PRP composition, including the concentrations of platelets, white blood cells, and growth factors. Most previous studies used one PRP injection in their study design. Moreover, Patel et al.[30] showed that a single dose of PRP is as effective as a double dose in early knee OA. This finding supports the validity of our study design and our aim was to design a placebo-controlled study

rather than a dose-dependent or concentration-dependent one. Further studies implementing these design elements may be necessary in the future.

In conclusion, this prospective, randomized, double-blind, placebo-controlled study revealed that both intra-articular PRP and normal saline injected into a patient with bilateral knee OA could improve long-term pain, functional activity, and knee strength. Furthermore, PRP treatment significantly improves pain, stiffness, and disability in patients with knee OA compared with normal saline treatment. Additional strengthening training is recommended to enhance muscle strength recovery.

ACKNOWLEDGMENTS

The authors thank Miss Jenifert Hsu who provided technical assistance for the completion of this study.

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