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Intra-articular and extra-articular platelet-rich plasma injections for knee osteoarthritis: A 26-week, single-arm, pilot feasibility study

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ABSTRACT

Aim: Platelet Rich Plasma (PRP) is an emerging therapy for knee osteoarthritis (KOA). Studies have evaluated the effectiveness of intra-articular PRP, which ignores extra-articular tissue dysfunction and may provide incomplete treatment of KOA. The study aimed to pilot test a leukocyte-rich (mononuclear cells) PRP injection protocol for primary KOA, which consisted of single intra-articular injection and extra-articular injections on the medial coronary and medial collateral ligaments.

Methods: A prospective 26-week single-arm uncontrolled feasibility pilot study. Patients (N = 12) with primary KOA as defined by the American Rheumatology Association, with moderate to severe medial knee pain which failed conservative management, were recruited in a university primary care clinic and received a single session of PRP injection in week 1. The primary outcome was the feasibility of the protocol at 26 weeks as defined by rates of recruitment, compliance, retention, dropout, side effects or adverse events; and treatment satisfaction. Secondary outcomes included the Western Ontario McMaster University Osteoarthritis Index, the Intermittent and Constant Osteoarthritis Pain total and subscales, objective physical function tests and EuroQol-5D.

Results: Twelve of 40 potential patients were recruited in 3 months period (recruitment rate 30%, x2 = 3.33, P = 0.068). All participants adhered to the protocol and completed the follow up assessment with no dropouts (dropout rate 0%, X2= 2.67, P = 0.103). Satisfaction was high; no related adverse events were reported. Most secondary outcomes showed statistically significant improvement.

Conclusions: Concomitant intra-articular and extra-articular PRP injections were feasible and produced preliminary favourable outcomes.

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1. Introduction

Knee osteoarthritis (KOA) is the most common form of arthritis and a major cause of pain and disability worldwide [1,2]. However, care options are limited. While exercise and weight reduction are effective in appropriate patients with KOA [3,4], factors such as fatigue, treatment access, and the degenerative nature of osteoarthritis are barriers to success [5]. A recent systematic review and meta-analyses confirmed that paracetamol provides minimal improvements in pain and function [6,7]; although non-steroidal anti-inflammatory drugs (NSAIDs) have been found to be effective, the safety profiles of these drugs remain a significant concern to physicians and patients [8]. Options such as physical therapy and complementary therapies, such as acupuncture and herbal treatments, have been shown to be marginally effective [9]. Other conservative measures, including intra-articular corticosteroid and hyaluronic acid injections, offer short-term benefits but have limitations based on safety; corticosteroids may even confer harm through effects on intra-articular cartilage volume [10]. Total knee replacement for advanced KOA is effective but is also costly and carries operative risk [11]. Therefore, identifying safe and effective non-surgical therapy remains a high priority in clinical practice and orthopaedic research [12].

Platelet-rich plasma (PRP) injection is an emerging minimally invasive treatment for KOA. It is a bioactive regenerative therapy that theoretically augments tissue healing through the natural healing cascade [13]. It is produced from autologous venous blood and is centrifuged to a concentrate with platelet count above baseline blood levels [14]. Growth factors are released from the alpha granules of platelets and induce chemotaxis, cell migration, angiogenesis, proliferation, differentiation, and matrix production through a complex myriad of cellular functions that promote healing and tissue repair [15–17]. Leukocyte-rich and leukocyte-poor PRP preparations are available; leukocyte-poor PRP is preferred because high leukocyte concentration has been shown to increase the expression of catabolic cascades and inflammatory markers, such as interleukin-1 and tumour necrosis factor-alpha, leading to possible cell death [18,19]. Several studies have assessed the outcomes of PRP in patient subgroups. Although most of the analyses had small sample sizes and high variability, and were thus inconclusive, the findings consistently indicated that PRP might have better outcomes in younger patients and those with less degenerative changes [20].

In the past few years, a growing body of evidence has supported PRP as a treatment option for KOA. Numerous studies of intra-articular PRP have been shown to be effective and safe to reduce pain and improve function in patients with KOA [21]. Extra-articular PRP injections on soft tissue attachment are also commonly used in clinical practice with beneficial effects [22]. Injection of PRP into isolated knee structures has been studied; this has included the augmentation of tissue healing in anterior cruciate ligament reconstruction and patella tendon grafts, with variable degrees of success [23,24]. The application of PRP on the medial collateral ligament has been studied in animal models with positive results [25–27]. The use of PRP on meniscus repair remains controversial [28,29]. Given that KOA is a complex disease associated with degenerative intra-articular cartilage, bone, synovium and extra-articular knee structures, such as ligament tear and laxity [30], a concomitant intra-articular and extra-articular injection approach may provide added value compared with intra-articular injection alone.

To prepare for a future trial assessing multiple approaches, a novel PRP injection protocol for KOA was pilot tested, consisting of both intra-articular joint injection and extra-articular injections into medial coronary and medial collateral ligaments. Feasibility of the protocol was evaluated, and the preliminary clinical effectiveness was studied using validated and guideline-recommended patient-orientated outcomes. It was hypothesised that the combined injection approach is feasible, safe, and potentially effective in reducing pain and improving function in patients with KOA.

2. Materials and methods

2.1. Study design

The Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee approved this study. All patients provided written informed consent. The study was a 26-week, single-arm, uncontrolled feasibility study. The study was registered in the clinical trial registry ChiCTR-OIC-17010625.

2.2. Participants and settings

Patients were recruited from seven general outpatient clinics. The study site was a university affiliated primary care clinic. Inclusion criteria were: being aged 45–75 years; having a diagnosis of primary KOA based on clinical and radiological criteria as defined by the American Rheumatology Association; having moderate-to-severe medial knee pain for at least three months, defined as a score of ≥3 (0–6 ordinal response scale) for the question ‘What is the average level of your left/right knee pain in the past 3 months?’; and failure to achieve pain reduction to a score <3 (0–6 ordinal response scale) after six months of usual care, which included weight reduction as needed, exercise, physical therapy and pharmacological treatment. Exclusion criteria included: patients on anticoagulation, immunosuppressive or daily opioid therapy; a history of collagen tissue or other autoimmune disorders; pregnancy; haematological diseases; severe cardiovascular diseases; prior or planned total knee replacement of the affected knee; allergy or intolerance to acetaminophen or xylocaine; body mass index (BMI) ≥35 kg/m^2; interim knee joint infectious arthritis or trauma; haemoglobin level <11 g/dl; platelet concentration <150,000/mm^3; clinical examination suggesting that the patient was not appropriate due to comorbid medical conditions; and patients who could not understand, read or write Chinese.

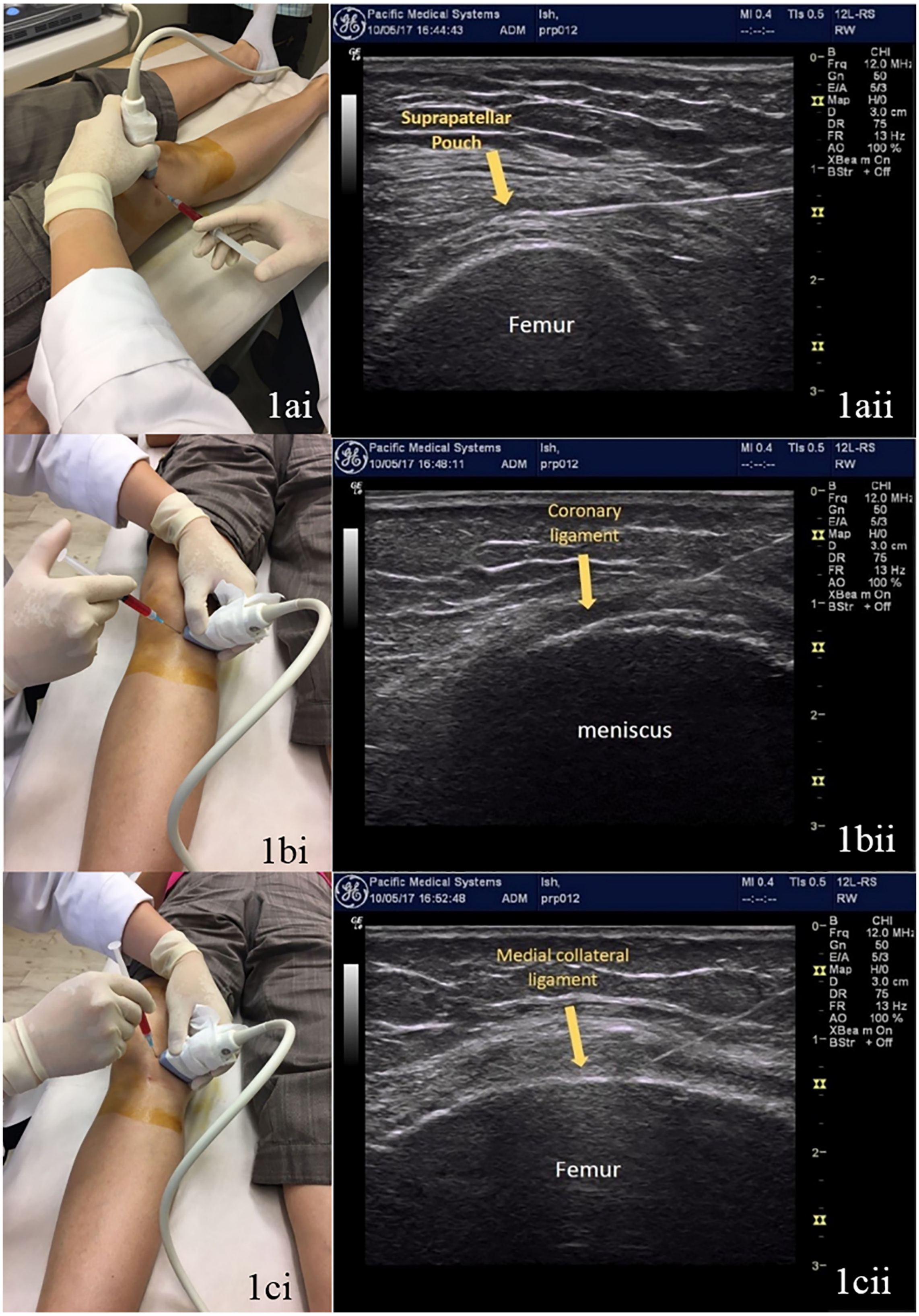

Figure 1. ai and aii show intra-articular injection through the suprapatellar pouch; bi and bii show extra-articular injection into the medial coronary ligament; ci and cii show extra-articular injection into the proximal end of the medial collateral ligament.

2.3. Intervention

The PRP injectate (SmartPRep System, Harvest Terumo) was a leukocyte-rich concentrate composed of mainly mononuclear cells (lymphocytes and monocytes) and reduced granulocytes (by 60%) compared with whole blood, with limited proinflammatory effect [31]. A volume of 54 ml of autologous venous blood was drawn under aseptic technique and mixed with eight millilitres of Anticoagulant Citrate Dextrose solution. The blood was transferred into a two-chamber device, which was then put into a bench-top centrifuge. Spinning procedures were followed according to the manufacturer, which consisted of a K-spin (three minutes at 2500 ± 150 rpm), followed by standard two-cycle spinning. The first cycle also took three minutes at 2500 ± 150 rpm and the second cycle took nine minutes at 2300 ± 140 rpm; seven millilitres of PRP was produced. Of the seven millilitre PRP, one millilitre was sent to the laboratory to validate the platelet concentration; the remaining six millilitres was mixed with one millilitre of one percent xylocaine to make a total of seven millilitres for injections.

The injections were conducted by a trained physician at the study site. If patients had bilateral knee pain, the more painful knee was injected. Each treated knee received one PRP injection session after enrolment. All injections were conducted under ultrasound guidance (GE Logiq e BT11) and strict aseptic technique. Local anaesthetic wheals with one percent xylocaine were placed at the injection sites. After that, three millilitres of PRP was injected into the knee joint through the suprapatellar pouch, two millilitres over the medial coronary ligament, and two millilitres over the proximal medial collateral ligament (MCL) (Figure 1). Although anterior cruciate ligament injuries are commonly reported to be dysfunctional in KOA, it is technically difficult to inject this ligament under ultrasound guidance. Therefore, the medial coronary and medial collateral ligaments were chosen in this protocol, and the physician palpated the major tender site at the ligaments' insertions. The MCL has an important role in knee joint stability, and its injuries are associated with KOA [32]. The role of PRP on MCL has been confirmed in animal studies [25–27]. In the current study, MCL injury was confirmed by the ultrasound finding of thickened and heterogeneously hypoechoic appearance of the ligament at the proximal end of its attachment at the femoral condyle [33]. The medial coronary ligament is in close proximity to the medial meniscus, and its integrity prevents meniscal extrusion, which is associated with progression of KOA [34,35]. Evidence of injury in the current study was defined as ultrasound finding of a swollen rim around the medial tibial condyle.

Patients were discouraged from using NSAIDs for two days after the injections, which might theoretically offset the effect of PRP. After that, they had no restriction on the use of analgesics. Patients were contacted by the study coordinator on day 2 and followed up on day 14 after the injections to assess for side effects or adverse events. Patients were given diaries to document any discomfort after the injections; they were advised to call to the study coordinator if they were uncertain whether the discomfort was related to the injections. Patients were discouraged from starting new therapies during the six-month study period.

2.4. Outcome measures

The primary outcome was to assess the feasibility of the protocol. Assessment included the rates of recruitment, compliance, retention, and dropout. Success criteria for this pilot study were set with a pre-specific threshold of a 50% recruitment rate, defined as the proportion of those who were screened to be eligible and enrolled in the study, and a <20% dropout rate. Satisfaction was measured by the proportion of patients who were satisfied with the treatment in response to the question ‘Would you recommend the therapy to others with KOA like yours? (yes/no)’. Serious adverse events or side effects were collected at each visit.

Secondary outcomes evaluated the treatment effect at 16 weeks and 26 weeks. These included the validated Chinese Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Intermittent and Constant Osteoarthritis Pain (ICOAP) score, objectively assessed physical function measures (30-second chair stand performance test, 40-m fast-paced walk test, Timed Up and Go Test (TUGT), and The EuroQuol-5D questionnaire (EQ-5D)). A seven-day recall diary was used to record the number of patients taking analgesic medications in the past week. All the questionnaires and tests were conducted in face-to-face interviews by the research assistants.

Demographics, body weight and height, duration of knee pain, and the number of co-morbidities were collected. The baseline physical activity status was assessed by the International Physical Activity Questionnaire (IPAQ). The Kellgren–Lawrence (KL) classification system was used to grade KOA severity on knee radiographs. Blood platelet and PRP platelet concentrations were recorded.

2.5. Sample size

The suggestion by Belle and Julious for a ‘rule of 12’ to optimise sample size efficiency for pilot studies was followed. Including at least 12 participants limited the spread of confidence intervals for mean response, whereas sample sizes >12 participants did not, prompting a recommendation of 12 participants for pilot studies with the primary focus of estimating average values and variability for planning larger subsequent studies [36].

2.6. Statistical analysis

The Chi-square (χ^2) test was used to assess recruitment and dropout rates against the pre-specified thresholds. To investigate significant changes over time following the intention-to-treat principle, a linear mixed model analysis was conducted for the secondary outcomes. In the linear mixed models, secondary outcomes were treated as the dependent variables, with time and baseline characteristics treated as covariates. Time was tested as a categorical variable. Age, gender, BMI, weekly physical activity level, knee pain duration, number of diagnosed chronic diseases, and the respective baseline outcome were entered to the models for adjustment. Unstructured covariance structure and fixed effect parameters were applied. The statistical package Stata version 12.0 was employed for data analysis.

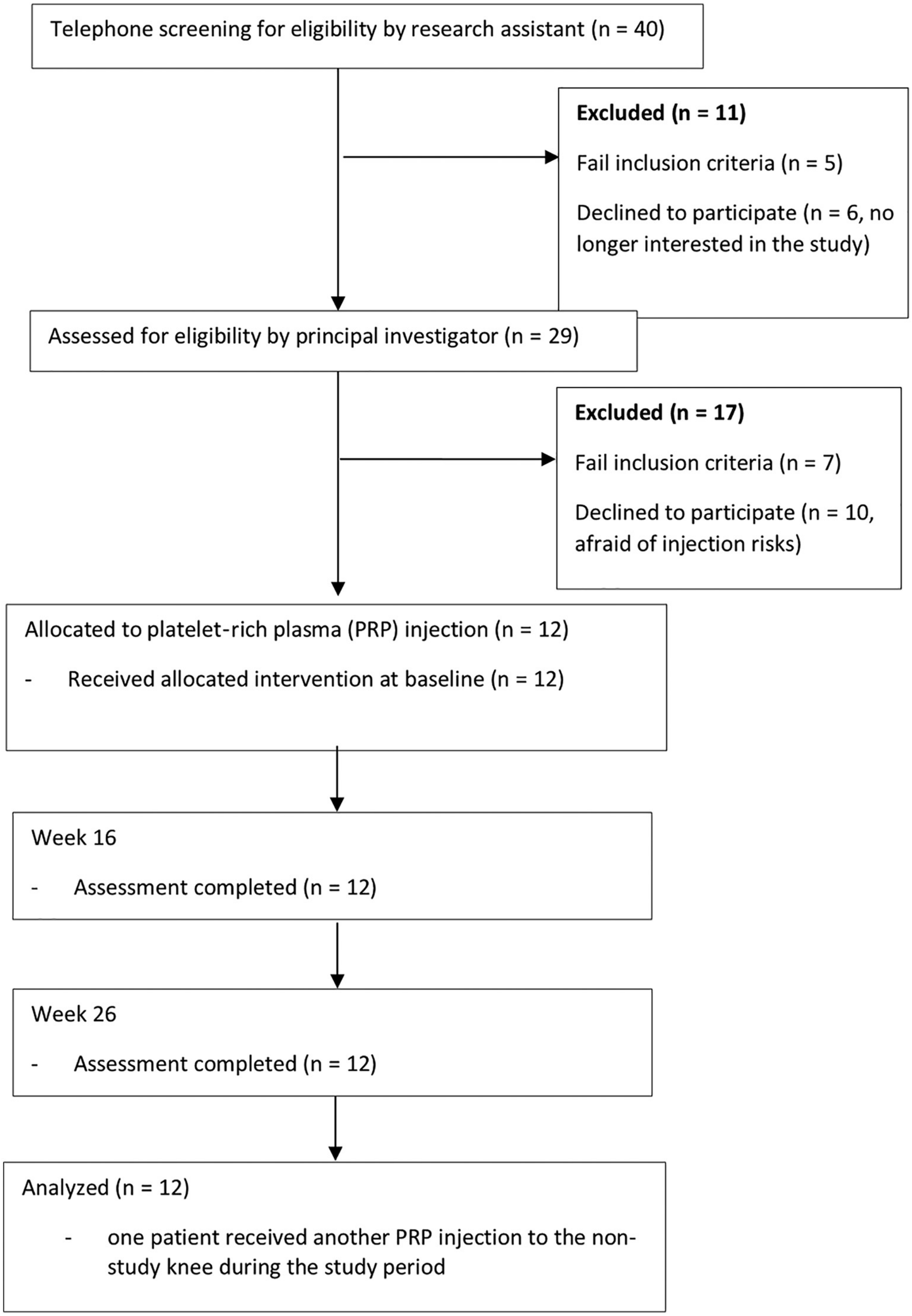

Figure 2. Study flow chart.

3. Results

Patients were recruited from 18 January to 08 April 2017. Of the 40 screened patients, 12 were eligible and enrolled into the study, and the overall recruitment rate was 30% ($\chi^2 = 3.33$, $P = 0.068$) (Figure 2). All 12 participants completed the baseline questionnaire and were included in the analysis.

The study sample (aged 61.7 ± 4.4 years, nine women) had a BMI of 25.0 ± 3.4 kg/m^2 and knee pain for 11.3 ± 9.24 years. Participants had KOA with a range of severity as assessed by KL grading. All were physically active. None were taking oral analgesics at baseline (Table 1). The PRP platelet concentration was 5.38 ± 1.07 times that of blood platelet concentration, meeting published criteria for PRP concentrations of at least three to five times above baseline [14]. All participants completed the follow-up outcome assessment and the dropout rate was 0% ($\chi^2 = 2.67$, $P = 0.103$). One patient was satisfied with the pain reduction and she went to another private doctor to receive another PRP injection to her non-study knee. The average time taken for the intervention was approximately one hour, including the preparation and injection time. All participants experienced self-limited post-injection pain but none of them took paracetamol or other analgesics for pain control. There were no other reported side effects. One serious adverse event of chest pain was reported during the study period and was determined to be unrelated to the study intervention. For treatment satisfaction, 10 participants (83.3%) would recommend the injection to others. Participants reported overall improvement in the WOMAC total score from baseline of −13.30 (95% confidence interval (CI) −20.72 to −5.88, $P < 0.001$); WOMAC pain score −11.62 (95% CI −20.83 to −2.41, $P = 0.013$); and WOMAC function score −13.74 (95% CI −21.78 to −5.69, $P = 0.001$). Other secondary outcomes also demonstrated statistically significant intra-group improvement. Results are summarised in Table 2.

4. Discussion

This study found a protocol of intra-articular and extra-articular PRP injections to be feasible. Recruitment was rapid, with a high adherence rate and no dropouts. The procedure was well tolerated, with minimal use of post-injection analgesic medication and high satisfaction. The procedure was feasible to be conducted by trained physicians, although the procedure time could be a concern for some busy clinics. The results also supported preliminary favourable outcomes in terms of pain reduction, improvement of function, and better pain experience and quality of life in participants with KOA. Despite the small sample size, the improvement in the WOMAC total score of 13.30 exceeded the effect of the control injection of intra-articular normal saline (11.34) [37], and exceeded the minimal clinically important difference of 12 points in rehabilitation intervention for KOA [38].

These data are unique in that this is the first protocol to assess the feasibility of concomitant intra-articular and extra-articular injections, and the first to assess the effects of such a protocol. In general, the outcomes surrounding both feasibility and self-reported measures mirror those of studies using intra-articular injections alone. The overall positive effects of PRP on chondrocyte proliferation and regeneration in focal and complex degenerative osteoarthritic joints have been supported in in vitro animal chondrocytes and in vivo preclinical studies [39]. The possible mechanisms of pain reduction include reduction of proinflammatory cytokines in the affected joint, which might otherwise stimulate the nociceptors [40], and augmentation of cannabinoid

Table 1
Baseline characteristics of participants, mean ± SD.

	Total (N = 12)
Age	61.67 ± 4.4
BMI	24.97 ± 3.4
Gender	
Male	3 (25%)
Female	9 (75%)
Number of chronic diseases	
1	3 (25%)
2	4 (33.3%)
3 or above	5 (41.7%)
Knee pain duration (years)	11.25 ± 9.24
PRP/blood platelet concentration	5.38 ± 1.07
PRP platelet concentration	1310.17 ± 454.71
Blood platelet concentration	246.58 ± 72.66
Kellgren–Lawrence Grading	
1 — Doubtful JSN and possible osteophytic lipping	3 (25%)
2 — Definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph	3 (25%)
3 — Multiple osteophytes, definite JSN, sclerosis, possible bony deformity	4 (33.3%)
4 — Large osteophytes, marked JSN, severe sclerosis and definite bony deformity	2 (16.7%)
IPAQ (MET), median (IQR)	2208 (1763)
Low	0
Moderate	8 (66.7%)
High	4 (33.3%)

BMI = body mass index, PRP = platelet rich plasma, JSN = joint space narrowing, IPAQ = International Physical Activity Questionnaire, MET = metabolic equivalent.

Table 2
Effect of treatment on different outcome measures (n = 12).

Outcome	Week	Mean (SD)	Adjusted for baseline characteristics & baseline outcome measure	
			β coefficient (95% CI)	*P* value
WOMAC				
Pain	0	51.44 (23.77)		
	16	33.48 (15.82)	−17.97 (−27.18, −8.76)	<0.001*
	26	39.83 (15.82)	−11.62 (−20.83, −2.41)	0.013*
Stiffness	0	59.44 (24.24)		
	16	41.56 (27.95)	−17.88 (−27.58, −8.17)	<0.001*
	26	45.63 (27.32)	−13.81 (−23.52, −4.11)	0.005*
Function	0	54.76 (23.27)		
	16	33.52 (13.90)	−21.24 (−29.28, −13.20)	<0.001*
	26	41.02 (19.24)	−13.74 (−21.78, −5.69)	0.001*
Total	0	54.46 (23.03)		
	16	34.18 (14.03)	−20.28 (−27.70, −12.86)	<0.001*
	26	41.16 (18.05)	−13.30 (−20.72, −5.88)	<0.001*
ICOAP				
Constant	0	49.58 (19.36)		
	16	32.92 (17.38)	−16.67 (−25.69, −7.65)	<0.001*
	26	22.08 (18.76)	−27.5 (−36.52, −18.48)	<0.001*
Intermittent	0	55.56 (14.79)		
	16	40.28 (13.22)	−15.28 (−22.53, −8.03)	<0.001*
	26	40.28 (13.22)	−17.71 (−24.96, −10.46)	<0.001*
Total	0	52.84 (14.95)		
	16	36.93 (14.41)	−15.91 (−23.10, −8.72)	<0.001*
	26	30.68 (12.95)	−22.16 (−29.35, −14.97)	<0.001*
OARSI				
TUGT	0	11.67 (2.43)		
	16	11.58 (2.75)	−0.083 (−1.56, 1.40)	0.912
	26	10.83 (2.69)	−0.83 (−2.31, 0.65)	0.27
30 second chair stand test	0	7.83 (2.66)		
	16	8.50 (3.12)	0.67 (−0.49, 1.82)	0.258
	26	9.08 (2.71)	1.25 (0.10, 2.40)	0.034*
40 m fast paced walk	0	38.25 (4.79)		
	16	38.75 (8.06)	0.5 (−1.99, 2.99)	0.694
	26	37.83 (8.13)	−0.42 (−2.90, 2.07)	0.743
EQ5D index	0	0.50 (0.34)		
	16	0.65 (0.16)	0.16 (0.01, 0.30)	0.036*
	26	0.53 (0.27)	0.03 (−0.12, 0.18)	0.685
EQVS	0	71.25 (19.67)		
	16	77 (9.90)	5.75 (−1.53, 13.03)	0.122
	26	75 (15.08)	3.75 (−3.53, 11.03)	0.313

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, ICOAP = Intermittent and Constant Osteoarthritis Pain, OARSI = Osteoarthritis Research Society International, TUGT = Timed Up and Go Test, EQ5D = EuroQol-5D, EQVS = EuroQol-5D Visual Analogue Scale. All the models were adjusted for age, gender, BMI, weekly physical activity level, knee pain duration and number of diagnosed chronic diseases as well as the respective baseline outcome. Week is treated as categorical variable.

* $P < 0.05$.

receptors, which provide analgesic effects [41]. Although the precise effect of PRP on soft tissues remains unclear, its use remains popular among high-level athletes, participants with lateral epicondylitis, and in some surgical augmentation procedures [22]. The reservoir of growth factors is believed to stimulate tissue healing and repair, thus enhancing structural integrity [16]. Based on the current evidence of PRP on cartilage and soft tissues, this protocol may provide a minimally invasive therapy for KOA that is more comprehensive than intra-articular injections alone.

This pilot study had some limitations. First, it did not radiologically confirm the degeneration of medial collateral and medial coronary ligaments, which would have required magnetic resonance imaging (MRI); the most painful sites over the ligament insertions were palpated before injections, followed by ultrasonographic confirmation. Second, the exclusion criteria may have limited external validity. Third, the assessment of treatment satisfaction was indirect and subject to bias.

Larger-scale randomised controlled trials are needed to confirm the overall clinical effect of combined intra-articular and extra-articular PRP injections for KOA. The following are suggestions for future trial design. Inclusion criteria should recruit participants with MRI-confirmed soft tissue injury. Although intra-articular PRP is generally recommended for patients with lower degrees of degeneration, its use should not be declined in patients with severe KOA who are not surgical candidates. Therefore, a subgroup analysis among participants with all KOA severity will identify the best responding group. Finally, the choice of control groups should include an intra-articular-only group, extra-articular-only group, and a combined intra-articular and extra-articular group to elucidate relative effects of injection strategies.

5. Conclusion

This study found that a protocol involving intra-articular and extra-articular PRP injection is feasible and suggests a positive effect on self-reported outcomes. Future clinical trials with MRI-confirmed ligament injuries and which include comparison with active comparators will help determine its overall efficacy and facilitate its deployment in real-world practice.

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Contributions

RWSS was the principal investigator of the study and responsible for the trial operation, data interpretation and completion of the manuscript. RWKW was responsible for the design of the injection protocol, conducting the knee injections, and writing-up the manuscript. LSW, DR, KDR, AI and SYSW contributed to the conception and study design, data interpretation and writing-up the manuscript. DZ and BHKY were responsible for sample size calculation, statistical analysis and data interpretation.

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