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Platelet-rich plasma in patients with tibiofemoral cartilage degeneration

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Abstract
Introduction Recently an articular cartilage repair has been given much attention in the orthopaedic field. Cartilage regeneration capacity is very limited. Optimal approach seems to be a delivery of natural growth factors. Autologous platelet-rich plasma (PRP) contains proliferative and chemoattractant growth factors. The objective of the present study was to determine if PRP can increase tibiofemoral cartilage regeneration and improve knee function.

Materials and methods Fifty consecutive and strictly selected patients, affected by Grade II or III chondromalatia, underwent 1 year treatment (9 injections) with autologous PRP in a liquid form with 2.0 to 2.5-fold platelets concentration. Outcome measures included the Lysholm, Tegner, IKDC, and Cincinnati scores. Magnetic resonance imaging was used to evaluate cartilage thickness and degree of degeneration.

Results The study demonstrated significant improvement in Lysholm ($p < 0.05$), Tegner ($p < 0.05$), IKDC ($p < 0.05$), and Cincinnati ($p < 0.05$) scores. Results improved at 12-month follow-up. Cartilage assessment revealed no significant cartilage regeneration ($p < 0.05$). There were no adverse events reported.

Conclusions PRP significantly reduced pain and improved quality of live in patients with low degree of cartilage degeneration. Magnetic resonance imaging did not confirmed any significant cartilage condition improvement.

Keywords Knee · Chondromalatia · Platelet-rich plasma

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Introduction

Articular cartilage is a specialised connective tissue that supports and distributes loads and ensures a low-friction motion in joints. Such unique characteristics are provided by a highly organised extracellular matrix composed of fibrillar collagen, hydrated proteoglycans, and hyaluronic acid. Chondrocytes, the living component in articular cartilage, are responsible for maintaining the extracellular matrix in balanced condition for which synthetic and catabolic responses have to be mounted. This demands chondrocytes to sense the chemical composition of the extracellular matrix and any changes that it may undergo, as well as

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to sense and interpret a variety of signals that can affect the matrix composition. These include mechanical forces and soluble mediators, namely hormones, growth factors and cytokines, produced by neighbouring or distant cells. Cartilage homeostasis involves a dynamic balance between all those factors, some favouring an anabolic programme and other stimulating catabolic responses required for matrix turnover and renewal. Any disturbance of this equilibrium can lead to quantitative and/or qualitative changes in the pattern of chondrocyte gene expression, bringing about alterations in the composition and structure of the articular cartilage that can compromise its function and integrity and ultimately lead to the development and progression of arthritis.

Platelet-rich plasma (PRP) is now widely used to treat several musculoskeletal soft-tissue lesions. Platelets contain many kinds of growth factors, such as platelet-derived growth factors (PDGF), transforming growth factors (TGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF). The use of these growth factors has been considered as a way to manipulate the host healing response at the site of injury or degeneration, to facilitate the repair and remodelling of the tissue [1].

Despite interesting and promising pre-clinical findings [2–4], the number of published clinical studies regarding PRP application is limited, with the majority of articles involving applications on tendons and ligaments [5–7]. Another common application of PRP is for the treatment of chondromalatia of the knee. The debate over PRP usage for knee degenerative conditions reaches far and wide, but there is a lack of clinical trials on this field. It is not clear up to now when PRP inject, how and how much to inject. It is necessary to define the proper application intervals, platelet concentration, volume and technique. We have conducted a pilot prospective randomised controlled trial comparing 50 patients treated with intraarticular PRP injections under strictly defined circumstances with 50 patients treated with 1 % mesocain to confirm the hypothesis that PRP improves knee condition.

Materials and methods

Study design

Between January and November 2009, all 50 patients who were included in the prospective study and received PRP treatment for tibiofemoral chondromalatia underwent purely diagnostic knee arthroscopy at our institution. In the control group the 1 % mesocain (5 ml) was applied intraarticularly in the same algorithm as the PRP in the treated group (control group selected at random). The study was determined to meet ethical standards and was approved by the Ethical Committee of the authors' institution. All these patients received an information, providing them with the risks and benefits of the procedure. Only the subjects who provided informed consent were enrolled in the study. Inclusion criteria were isolated Grade II or Grade III nontraumatic chondromalatia according to Outerbridge grading scale [8]. At arthroscopy, the findings of a cartilage condition on the tibia and/or femoral condyles were reported as follows: Grade 0—normal cartilage, Grade I—cartilage softening, Grade II—superficial changes (fibrilation), Grade III—deep changes (fissuring and fragmentation), but no bone exposed, Grade IV—full-thickness cartilage defects. All arthroscopies were performed by experienced surgeons (R.H., A.S.) during the first day following the magnetic resonance imaging. The knees were examined systematically with use of a probe. Under direct vision and with careful probing, special attention was paid to the degree of the tibiofemoral cartilage surface condition. More degenerated tibiofemoral compartment (medial or lateral) was considered and the condition of its cartilage was recorded.

Other 98 patients were excluded to get the cohort of 50 study cases. Exclusion criteria were very strict: Grade I (only softening) or Grade IV (exposed subchondral bone) tibiofemoral chondromalatia (15 cases); patellofemoral chondral damage (7 cases); associated intraarticular lesions confirmed during arthroscopy (menisci, ligaments, osteochondral defects) (18 cases); associated extraarticular lesions confirmed by magnetic resonance imaging (ligaments, tendons, bursae) (3 cases); lower limb axial deviation confirmed by whole leg weight-bearing radiograph ($\geq 3°$) (21 cases); knee trauma in patients history (3 cases); body mass index (BMI) higher than 35 (8 cases); hyaluronic acid intraarticular injection 6 months prior to the arthroscopy and up to last follow-up control (3 cases); steroids intraarticular injection 3 months prior to the arthroscopy and up to last follow-up control (3 cases); symptomatic slow acting drugs for osteoarthritis (SYSADOA) and/or non-steroidal anti-inflammatory drugs (NSAID) administration during the PRP treatment (6 cases); systemic autoimmune rheumatic and/or polyarticular disease (2 cases); gout, pseudogout and hyperuricaemia (2 cases). Other exclusion criteria included: non-informed consent (1 case); treated knee injury during the PRP therapy (1 patient with lesion of the medial meniscus); PRP injection cycle not completed (1 patient moved to another part of the country); blood disease and/or immunosuppressant treatment and/or dicoumarol therapy (1 case); immunosuppressant and/or neoplastic and/or infectious diseases (1 case).

After patients' inclusion into the study, the preoperative magnetic resonance imaging (1.5 Tesla scanner) was reevaluated with emphasis on cartilage condition at both tibiofemoral compartments in the PRP group. A standard knee

coil and a field of view of 10–16 cm was used. The slice thickness was 3 mm, with a 0.5 mm intersection gap. Sagittal T1 and T2-weighted images, axial three-dimensional T1 weighted fast spoiled gradient-recalled images with fat suppression, and coronal proton density images with fat suppression were evaluated. An experienced musculoskeletal radiologist (M.P.) blinded to subsequent arthroscopy findings reassessed all images. The magnetic resonance images were recorded as showing either normal cartilage thickness or a loss of cartilage (in tenths of mm). Grading of chondromalatia was based on the system described by Outerbridge [8] as follows: Grade 0—normal cartilage condition, Grade I—high signal intensity and swelling of the cartilage, Grade II—superficial fibrillation and/or fissuring, Grade III—deep fissuring and fragmentation, Grade IV—total loss of cartilage (exposed bone). More degenerated tibiofemoral compartment (medial or lateral) was considered and the condition of its cartilage was recorded. The radiologist evaluation differed from the orthopaedic surgeon (performing the arthroscopy) interpretation only in two cases, and these two magnetic resonance descriptions were corrected by consensus. Second magnetic resonance imaging with the same cartilage evaluation protocol was performed 12 months after the end of the PRP treatment in all cases. In control group no magnetic resonance imaging study was conducted not to increase project expenses.

Patients' characteristics

There were 50 patients (28 right and 22 left knees) in the PRP group, 29 men (58 %) and 21 women (42 %), with a mean age at the time of the arthroscopy of 58.1 years (range 31–75 years). Arthroscopy and preoperative magnetic resonance imaging confirmed most degenerated cartilage condition on the medial femoral condyle in 22 cases (44 %), medially on the tibia in 11 cases (22 %), on the lateral femoral condyle in 11 cases (22 %), and laterally on the tibia in 6 cases (12 %). 21 knees (42 %) revealed in most degenerated location signs of chondromalacia of the Grade II and 29 knees (58 %) of the Grade III. The average body mass index was 28.1 kg/m^2 (range 20.1–33.7 kg/m^2). In the control group the demographic data were very similar. There were 25 patients (14 right and 11 left knees), 13 men (52 %) and 12 women (48 %), with a mean age at the time of the arthroscopy of 58.4 years (range 36–74 years). Arthroscopy confirmed most degenerated cartilage condition on the medial femoral condyle in 9 cases (36 %), medially on the tibia in 6 cases (24 %), on the lateral femoral condyle in 7 cases (28 %), and laterally on the tibia in 3 cases (12 %). 9 knees (36 %) revealed in most degenerated location signs of chondromalacia of the Grade II and 16 knees (64 %) of the Grade III. The average body mass index was 27.8 kg/m^2 (range 19.6 to 34.7 kg/m^2).

Treatment

PRP was obtained using self-developed controlled technique in the PRP group. 30 ml of the patient's blood was drawn from a forearm vein into three 10-ml test tubes and mixed with 1 ml of anticoagulant, 0.9 % citrate dextrose solution (Sarstedt, Nümbrecht, Germany). Another 3 ml test tube of blood with 0.3 ml of anticoagulant EDTA K (Sarstedt, Nümbrecht, Germany) was used for the whole blood count control. Blood was then immediately brought to the laboratory and centrifuged for 10 min at 1,200 rpm with relative centrifugal force 150 g in a dedicated centrifuge (Jouan B4i, Jouan, Saint-Herblain, France) at 20 °C. The blood in test tubes was separated into plasma and hemocyte (erythrocyte and leukocyte) fractions. This centrifuge regimen provides the PRP directly. Isolated PRP was obtained from centrifuge tubes by an experienced physician—haematologist (P.J.) with a sterile pipette in volume of 3 ml from each tube. 6 ml of PRP from two test tubes were transferred to a sterile syringe and applied to the patient. 3 ml of PRP from one test tube was used for cell (platelet) count control.

Concentration of platelets was counted in a haematological analyzer (AcT DIFF, Beckman-Coulter, London, UK). The approximate 2.0 to 2.5-fold platelet concentration (taking into consideration the mean human blood platelet count of 200,000/μl) was achieved in all specimens. Mean platelet concentration in PRP was 459,000/μl (range 407,000/μl to 513,000/μl).

The injection of 6 ml of PRP without any additive was made by orthopaedic surgeons (A.S., M.K.) immediately after its obtaining by haematologist under the sterile condition into the suprapatellar bursa communicating with the affected knee articular cavity using musculoskeletal ultrasound (SS Sonic, Fukuda, Tokyo, Japan) with a 7–10 MHz linear transducer to ensure proper needle placement. Active flexion and extension of the knee was recommended after the PRP injection. The patient was observed in a supine position for 10–15 min afterwards, and was then discharged home without further special recommendations or limitations.

First PRP injection was performed 6 weeks after the primary diagnostic arthroscopy which included patients into the study. Next five PRP injections were applied at 1-week intervals (like in competing injection techniques such as hyaluronic acid). This first part of the treatment protocol then included six injections and lasted 6 weeks. Treatment interruption for 3 months came after these first six PRP injections. Afterwards, three PRP injections were performed at 3-month intervals for maintenance. All patients received altogether nine PRP injections during 1 year after the primary arthroscopy. In the control group the 1 % mesocain (5 ml) was applied intraarticularly in the same algorithm as the PRP in the treated group.

Clinical evaluation

Assessment questionnaires were retrospectively completed during the first day following the arthroscopy and patients inclusion into the study. To carefully assess the subjective and objective clinical outcomes, these questionnaires were used: Lysholm score [9], Tegner activity score [10], IKDC scores [11], and Cincinnati score [12]. All these scores were recompleted 12 months after the end of the PRP treatment. Evaluations were performed by uninvolved orthopaedic surgeon (M.K.) and experienced psychologist (P.H.). Combination of the used scores minimises according to the psychiatrist (P.H.) the placebo effect of undergoing surgery and having multiple intraarticular injections.

Statistical analysis

The description of subjective and objective clinical parameters and thickness and structure of the cartilage shown by magnetic resonance imaging included mean, mode, median, standard deviation and range for continuous variables. For statistical evaluation of the mean values, the paired Student *t* test was used. Because of great range of values, the conclusion created by paired Student *t* test was controlled by nonparametric Mann–Whitney tests. All data were statistically treated by STATISTICA 9.0 software. A p value <0.05 was considered statistically significant.

To create a valid result for IKDC objective score, where alphabetic scale is used (A–D), the mode and median obtained before first PRP injection were compared with data obtained after treatment.

Results

No patient from 100 evaluated was lost for follow-up. Preoperative and postoperative data concerning clinical scores are shown in Table 1. The data included in Lysholm score shown the decrease of the pain, swelling, star-climbing and loping; instability, loping and squatting was observed. Similar results were found in the IKDC subjective score and Cincinnati score, where pain intensity, swelling, stairs and walking were improved. Giving way, jumping, running activity and overall activity level was not improved. This condition was confirmed by the Tegner score of activity on development in remaining categories. Only this scoring scale revealed the activity before and after the application of the PRP injections on the same level. The IKDC objective score, which was the only objective clinical score in this research, shown the stagnation of the objective clinical condition of the knee joints investigated by orthopaedist surgeons (A.S, M.K).

Preoperative and postoperative data concerning magnetic resonance imaging findings are shown in Table 2. The thickness of the cartilage increased in 3 cases (6 %), remained equal in 47 cases (94 %) and decreased in no cases. The thickness increase was measured in all 3 cases only in tenths of mm, in no case 1 mm increase was exceeded. Cartilage structure improved only in 1 case.

No significant adverse events related to the use of PRP were observed in the present study. Mild pain caused by the injection was reported after 17 of all 450 applications. In no case the pain persisted more than 5 days (nobody was reluctant to continue with therapy and finish it).

Discussion

There are only scant data available on PRP cartilage treatment in the literature. Many orthopaedic surgeons now rush to implement this therapy before they have valid evidence-based data from pre-clinical and/or prospective blinded clinical trials, without any specific knowledge on what the active components are in PRP. For both medical professionals and patients, there is often the most important fact influencing the decision for PRP treatment that it is a treatment using the patient's own blood.

There are a few basic science and animal studies available on PRP and cartilage. Akeda et al. [3] proved on porcine model that proteoglycan and collagen syntheses by the PRP-treated chondrocytes were markedly higher than those by chondrocytes treated by fetal bovine serum or platelet-poor plasma. They revealed by biochemical analyses that PRP growth factors did not markedly affect the types of proteoglycans and collagens produced by porcine chondrocytes, suggesting that the cells remained phenotypically stable in the presence of PRP. Mishra et al. [4] proved on a cell culture experiment that PRP enhances mesenchymal stem cells proliferation and causes chondrogenic differentiation of mesenchymal stem cells in vitro. Most of other animal studies were conducted on rabbit knee models. Sun et al. [13] reported on a rabbit model that macroscopic examination, micro-computer tomography and histological evaluation of the newly formed cartilage and bone in the defect differ significantly between the PRP-treated and the untreated groups. Stimulatory effect of PRP on osteochondral formation was observed. Saito et al. [14] investigated the therapeutic potential of administration of gelatin hydrogel microspheres containing PRP by examining its effects on progression of osteoarthritis in a rabbit knee model. They concluded that PRP significantly stimulates chondrocyte glycosaminoglycan synthesis and suppresses progression of osteoarthritis in rabbits. Qi et al. [15] made full-thickness cartilage defects in rabbit knees and found out that autologous PRP had stimulated the formation of

Table 1 Presents results in all clinical scores in study and control group comparing preoperative condition and outcomes at last follow-up control

	Clinical scores (points)				
	Lysholm	Tegner	Cincinnati	IKDC sub.	IKDC ob.
Study group (50 patients)					
Preoperative					
Mean	**58.1**	**6.2**	**53.7**	**51.2**	**B**
Range	6–97	3–10	8–94	12.6–95.4	A–D
SD	25.7	2.1	22.3	8.6	x
Median	62.5	6.5	56	45.6	B
Modus	39	8	66	34.4	B
Postoperative (last follow up)					
Mean	**83.1**	**6.8**	**80.1**	**63.8**	**B**
Range	35–100	3–10	29–100	13.8–95.4	A–C
SD	18.1	2.1	21.1	23.2	x
Median	87	8	86.5	63.6	B
Modus	100	8	100	95.4	B
p value	**0.0001**	**0.3204**	**0.000016**	**0.015814**	**B**
Control group (50 patients)					
Preoperative					
Mean	**62.3**	**5.9**	**55.2**	**55.8**	**B**
Range	6–100	2–9	8–100	13.8–95.4	A–D
SD	23.5	2.3	23.1	10.6	x
Median	59.5	6.6	48	49.2	B
Modus	41	8	58	34.8	B
Postoperative (last follow up)					
Mean	**65.1**	**6.3**	**52.7**	**57.1**	**B**
Range	35–100	1–10	8–94	12.6–95.4	A–D
SD	21.3	2.4	18.1	21.2	x
Median	63.6	7	46	56.4	B
Modus	43	8	60	52.2	B
p value	**0.45019**	**0.4104**	**0.470192**	**0.392107**	**B**

Table 2 Presents results of magnetic resonance imaging

	Cartilage magnetic resonance imaging		
	mm	Grade II	Grade III
Preoperative			
Mean	**2.15**	**21**	**29**
Range	1.00–4.30		
SD	0.75		
Median	2.05		
Modus	1.5		
Postoperative			
Mean	**2.22**	**22**	**28**
Range	0.50–4.30		
SD	0.93		
Median	2.01		
Modus	1.5		
p value	**0.238581**		

cartilage tissue. The only negative indirect influence of PRP on cartilage healing was reported by Kon et al. [16] in a sheep model.

Before trying to determine the effectiveness of PRP in human medicine its definition has to be determined. There are many preparation protocols, kits, centrifuges and methods to trigger platelet activation before use. The same is true for application techniques, including using injectable activated PRP liquid concentrate versus implanting a fibrin scaffold, optimal timing of injections and the specific volume to use. Medical professionals often use different compositions of PRP and obtain different clinical results. The general descriptions of PRP are very broad—it is defined as blood plasma that has been enriched with platelets or as a concentration of platelets above normal value of 200,000 in a small volume of plasma. Anitua et al. [17] clearly proved that maximum cell proliferation rate is obtained with twofold to fourfold platelet concentration. Similar results were

found by Graziani et al. [18]. They observed optimal outcomes at a 2.5-fold platelet concentration. Increased concentrations resulted in the reduction of cell proliferation and a suboptimal effect on cell function. Hence, higher platelet concentrations do not increase the "anabolic" effect of PRP. The PRP preparation technique should exclude maximum of leukocytes from the final product because of their "catabolic" effect on cell proliferation. They increase inflammatory reaction by release of interleukins, tumour necrosing factor and interferon. They contain and express matrix metalloproteases that contribute to extracellular matrix degradation. Leukocytes also make fibrin unstable by accelerating fibrinolysis [19].

There are probably a lot of serious clinical studies running nowadays but there is a small amount of really serious clinical studies for PRP articular cartilage treatment available now. If it would be clearly proven that PRP is good for instance for tendons, this does not mean that it is good for cartilage and osteoarthritis, too. Anitua et al. [20] examined the effect of a platelet-derived preparation rich in growth factors in osteoarthritic synovial cell biology. They isolated cells from osteoarthritic knees, exposed them to either a platelet-poor preparation or a platelet-derived preparation rich in growth factors and found that platelets enhance hyaluronic acid secretion. Kon et al. [21] published the first clinical study on cartilage in 2010. 115 knees (100 patients) affected by chronic degenerative condition were treated with PRP intraarticular injections. Three PRP units of 5 ml each were used. Patients were clinically prospectively evaluated up to 12 months postoperatively. A statistically significant improvement of clinical scores was obtained. The results remained stable from the end of the therapy to 6-month follow-up, whereas they became significantly worse at 12-month follow-up. The study provided evidence of the technique's safety and showed pain reduction and improved function. Only minor adverse events were detected, such as a mild pain reaction and effusion after the injections, which persisted for no more than 2 days. The same scientific group performed a subsequent evaluation of these knees at 2-year follow-up and confirmed the decreasing trend toward an overall worsening of the results [22]. The authors determined the median duration of the beneficial effect of their PRP preparation to be 9 months. Their findings indicate that treatment with PRP injections can reduce pain and improve knee function and quality of life with short-term efficacy. Third published prospective study on PRP in patients with knee osteoarthritis found in the literature was done by Sampson et al. [23]. They treated only 14 patients by PRP injections at 4-week intervals and demonstrated significant and almost linear improvement (up to 52 weeks) including pain and symptom relief.

Some limitations of present study require consideration. First, to prevent patients from further source of pain, we did not carry out second-look arthroscopies to evaluate the cartilage condition after the PRP therapy. We used only an indirect diagnostic tool—magnetic resonance imaging which is considered an accurate option for identification of more severe (Grade-II, III, or IV) cases of chondromalatia [24]. Second, a possible influence of PRP on synovial layer of the joint capsule and therefore on overall clinical result cannot be separated from its effect to the hyaline cartilage. Third, no definitive statements on presented PRP treatment protocol can be made regarding the duration of its beneficial effect and longer follow-up will be necessary to prove it. To blind such a study is technically difficult or unethical by pouring patient's blood down the drain. The strength of present study is given by strict patients inclusion criteria, precisely described treatment protocol and conscientious clinical as well as imaging evaluation of results.

In conclusion, the PRP treatment of tibiofemoral chondromalatia (Grade II and III) done with the described protocol has no significant influence on cartilage condition in the magnetic resonance imaging. Our findings indicate that this technique is safe and provide pain reduction and improved function. We confirmed the hypothesis that PRP improves knee condition and clinical outcomes.

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