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Synergistic activity of platelet rich plasma and high volume image guided injection for patellar tendinopathy

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Abstract

Purpose Platelet rich plasma and high volume image guided injections of saline have been used in the treatment of patellar tendinopathy with positive results. As the different mechanisms of action do not interfere each other, it can be hypothesized that they can be used in combination. Aim of this study was twofold: first, to evaluate the efficacy of these two treatments in the management of patellar tendinopathy; second, to verify whether the combination of these therapies could provide further advantages.

Methods Fifty-four patients suffering from patellar tendinopathy were enrolled. After clinical (VAS and VISA-P) and sonographic evaluation, two ultrasound guided injections (2 weeks apart) of platelet rich plasma, high-volume image-guided injections of saline, or both in association were performed. The VAS and VISA-P scores obtained from the three treatments groups (18 patients in each group) were compared across the different follow-up times (3 and 6 months).

Results In the short term both treatments showed comparable efficacy, whereas in the medium term the positive effects of high-volume image-guided injections gradually diminished and platelet rich plasma showed greater efficacy. Better results (reduced pain, improved function and increased number of subjects who exhibited optimal recovery [> 20 points in VISA-P score]) were observed when both procedures were associated.

Conclusions The contemporaneous administration of platelet rich plasma and high volume image guided injections of saline treatments, which influence tendon repair by means of different mechanisms, grants a greater improvement for patellar tendinopathy. This finding has clinical relevance, given that this condition has a substantial impact on sports and work performance.

Level of evidence III.

Keywords High volume image-guided injections · Patellar tendon · Platelet rich plasma · Tendinopathy

Introduction

Inferior pole patellar tendinopathy (PT, proximal insertional tendon attachment), also known as jumper's knee, is most common in athletes whose sports involve frequent jumping, such as basketball and volleyball [26, 29, 44]. The prevalence in elite athletes is estimated to be up to 14% at any given time, rising to 22% over a career [29], whereas non-elite athletes have an estimated prevalence of 8.5% [44]. Moreover, jumper's knee can be observed also in people who do not practice sport activities [26, 44].

Ultrasound (US) imaging of PT typically reveals decreased echogenicity, disorganized echotexture, cysts and intratendinous calcification [13, 26]; neovascular proliferation can be seen, using Colour Doppler (CD) US. According to authors, the pain intensity is grossly related to the number of new vessels [15], but this relationship is refuted by others [18].

The use of platelet rich plasma (PRP) seems to be a valuable treatment option for recalcitrant PT [20, 24, 30]. The beneficial effects have been demonstrated, both in open studies [23, 25, 43] and in comparative randomized trials, against external shock waves [42] or dry needling [21].

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Recently, high volume image guided injections (HVIGI) of saline at the interface between the surface of patellar tendon and the relative fat pad, associated to anesthetics and, in some studies, to corticosteroids or aprotinin, have been used in the treatment of PT with positive results [16, 31, 35]. A double blind randomized controlled trial is now in progress to validate these preliminary findings [10]. It is suggested that the disruption of neovessels and their accompanying nerves, and the breakage of adhesions, due to the high amount of saline solution, can explain the positive outcomes [16, 31, 35].

Given that the mechanisms of action of the PRP and HVIGI procedures are different (the first enhances healing providing amounts of growth factors by means of intratendinous injection, the second mechanically affecting the vascularization) and do not interfere each other, PRP can be administered in the case of HVIGI failure and viceversa. However, the effects of the contemporaneous administration, that could provide better clinical results by means of a synergicistic activity, at our knowledge, have never been evaluated.

Therefore, the aims of the present study were twofold: first, to evaluate and compare the efficacy of these two treatments in the management of PT; second, to verify whether the combination of these therapies could provide further advantages.

Materials and methods

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards; informed written consent for participation was obtained from each patient. Instutional ethics committee approval was not required for the nature of this study [27] because both procedures are safe and currently performed in the clinical practice as reported in previous published studies [10, 16, 20–25, 30, 31, 35, 42, 43].

Patients suffering from PT were enrolled. The diagnosis was made on the basis of history, clinical examination (pain, tenderness and functional limitation) and US-CD features of tendon damage (degenerative changes and neovessels proliferation).

Exclusion criteria were the following: history of patellar tendon surgery or tendon tears; recent knee trauma and/or recent onset of symptomatology (less than 3 months); intra-articular injections with steroids, hyaluronic acid and/or PRP of the involved district, physical therapies (e.g. laser, extra-corporeal shock wave, ultrasound), eccentric training, within the previous 3 months; rheumatic pathologies (rheumatoid, psoriatic and reactive arthritis, arthritis associated with inflammatory bowel diseases, and spondiloarthritis), severe systemic diseases (renal, hepatic, cardiac, infections, endocrinopathies, malignancies), immunodepression, anticoagulants or antiaggregants therapy, Hb values < 11 g/dl, and/or platelet values < 150.000/mm^3.

At baseline, demographic and anthropometric data were collected. In each subject, height and weight were measured and BMI was then calculated. Clinical and functional measures included pain during the previous week both at rest and during activities (registered by means of a 0–10 cm visual analogue scale [VAS]), Victorian Institute of Sport Assessment-Patellar (VISA-P) questionnaire (adapted to the Italian language) [32]. The VISA-P provides a subjective functional evaluation of patellar tendon, and consists in 8 questions which measure the domains of pain and function in daily living and sporting activity. Results range from 0 to 100, where 100 means any or little functional limitation. NSAIDs use (number of patients) was also evaluated.

US and CD evaluation of the affected tendon was performed using a high-resolution, multi-frequency (6–15 MHz) linear array transducer (*ProSound ALPHA10, Aloka, Japan*). According to standard protocol, both longitudinal and transverse scans were taken [1, 2, 40]. PT was diagnosed when diffuse/focal tendon thickening, abnormal tendon echotexture (dishomogeneous hypo- or hyperechoic areas, associated with loss of the normal fibrillar pattern and/or irregularity of the tendon margins), enthesophytes (step up bony prominence of the normal bone contour) and bone erosions (cortical breakage with a step down contour defect) were observed. On the basis of these structural abnormalities, tendons were then stratified for severity as "mild" (one area of disorganized echotexture), "moderate" (some areas of disorganized echotexture), and "severe" (disorganized echotexture and diffuse hypo- or hyperechoic areas and/or calcifications) [1, 2]. Presence of neovascularization was investigated by means of CD and graded as (0), (1+), (2+), (3+) according to a semi quantitative estimate of the number of vessels [5, 37]. To avoid artifacts, sensitivity was optimized for low flow, and the gain was set just below the noise level.

The therapeutic procedures were performed in sterile conditions and under US-guidance.

HVIGI First, a 21G needle was inserted immediately at the interface between the tendon/paratenon and the fat pad (Hoffa body), immediately adjacent to the area of neovascularization, and, once verified its correct placement, 10 mL of mepivacaine 2% were injected; thereafter, 30 mL of normal saline was introduced by means of luer-lock syringes, using 10 mL syringes one after another to maintain high pressure. The procedure was repeated after 2 weeks.

PRP After peritendineous anesthesia with 10 mL of mepivacaine 2% (as for HVIGI), the needle (21G) was inserted into the degenerated tendon and small autologous pure PRP depots were left at the site of most damaged areas, and then

proximal and distal (peppering technique), for a total amount of 4–5 mL. PRP was prepared using the Regen Lab A-PRP Kit (*Regenlab, Switzerland*). In detail, 8 mL of autologous blood was harvested from the cubital vein and collected into a tube containing a citrate *anti-coagulant* in addition to the thixotropic cell-separation gel. Then, the tube was carefully turn upside down several times (5×) to homogenize the blood with the anti-coagulant. After centrifugation (single spin, Force [RCF]: 1500 g, 3400 rpm for 5 min), the blood was fractionated, with the red blood cells trapped under the gel, and the cellular sediment, including the platelets, settled on the surface of the gel. Therefore, by gently inverting the tube several time, the sediment was mixed with the plasma supernatant, and PRP (1.6 × native platelet concentration, > 80% platelet recovery, no leukocytes, red blood cell remnant < 0.3%, as mean) was obtained. A second injection of PRP was repeated with the same technique after 2 weeks.

HVIGI + PRP Both administrations of saline and PRP were performed with the same modalities in an unique session, delivering first 10 mL of mepivacaine 2% (peritendineous anesthesia), thereafter 30 mL of saline solution (at the interface between the tendon/paratenon and the fat pad), and finally PRP, moving the needle into the degenerated tendon. As previously, the procedure was repeated after 2 weeks.

After each session, patients were kept under observation for approximately 30 min (monitoring early side effects) and then discharged from the Unit. At home, patients were advised to restrict from strenuous activities for at least 3–4 days; ice packs and acetaminophen (but not NSAIDs) were allowed. Moreover, patients were asked to register possible adverse events (pain, swelling, heat, functional limitations) and acetaminophen consumption during the following days after the injection. A rehabilitation program, based on eccentric training and stretching, was recommended daily (3 sets × 15 repetitions) for at least 3 months [33], during which a gradual return to sport activities (when practiced) was encouraged.

The clinical and US assessments were repeated at 3 and 6 months after the last injection.

Statistical analysis

Data are reported as mean ± standard deviation for continuous variables, whereas categorical and dichotomous variables are reported as frequencies and percentage. The significance level was determined at $p < 0.05$. The two-sample Student's *t* test was used to compare continuous variables, when the distribution of data was normal; the Wilcoxon's rank sum test was used otherwise. The χ^2 test was used to evaluate associations between categorical data.

The results obtained from the three treatments groups were compared (intra- and infra-group comparison) across the different follow-up times. The means of VAS and VISA-P scores registered at 3 and 6 months were compared with baseline values. Moreover, the patients were divided in sub-groups according to the increase of VISA-P score observed in each subject: an increase < 10 was considered unsatisfactory, from 10 to 19 intermediate and 20 or more satisfactory. The scores of US lesions and of neovascularisation were also evaluated and, therefore, a comparison was made across the different follow-up times.

Results

Out of 73 patients evaluated in the Unit for PT (from January 2013 to July 2016), 54 met the inclusion criteria. Eighteen patients were randomly included in PRP, HVIGI and HVIGI + PRP groups, and completed the 6 months follow-up.

At baseline, the participants did not differ significantly for demographic and anthropometric characteristics, and symptoms duration (Table 1). Only the number of subjects practicing sport (at amateur level) was slightly higher in HVIGI + PRP group in comparison to PRP group ($p = 0.04$). The VAS scores for pain at rest and during activities, VISA-P scores and NSAID consumption did not show significant difference, as well as the sonographic features of tendon degeneration and neovascularization.

Table 1 Patients' characteristics at baseline

	HVIGI	PRP	HVIGI + PRP
Age	37 ± 11.9	38.6 ± 12.4	39.4 ± 13.1
M:F	10:8	7:11	9:9
BMI	24.5 ± 2.9	25 ± 3.3	25.5 ± 3.3
Symptom duration	10.3 ± 3.1	10.9 ± 3.1	12.1 ± 2.6
Sport			
Yes	12	7	13
No	6	11	5
VAS rest	2.6 ± 0.8	2.4 ± 1.2	2.7 ± 1
VAS activities	5.4 ± 0.9	5.2 ± 1.4	5.1 ± 1.1
NSAIDs consumption			
No. of patients	14	13	11
VISA-P	52.8 ± 9.1	53.2 ± 11.1	51.9 ± 8.5
US			
Mild	5	7	4
Moderate	7	5	6
Severe	6	6	8
CD			
0	0	0	0
1+	4	3	3
2+	7	10	7
3+	7	5	8

In comparison to baseline values, at 3 months, pain decreased and VISA-P score increased in all groups (Tables 2, 3, 4); at 6 months a further improvement was observed in PRP and HVIGI + PRP groups, but not in HVIGI group. However, the therapeutic response was different in each single subject and, therefore, the percentage of subjects with unsatisfactory, intermediate and satisfactory outcomes varied in the 3 treatment groups. Indeed, at 3 months, 3, 3 and 8 subjects showed a satisfactory result (VISA-P increase > 20 points) in HVIGI (Table 2), PRP (Table 3) and HVIGI + PRP (Table 4) groups, respectively; at 6 months the number of subjects with satisfactory results was 2, 7 and 13 in the PRP, HVIGI and HVIGI + PRP groups, respectively (Tables 2, 3, 4). At 3 months, no vessels or minimal neovascularization (+ 1) were

Table 2 HVIGI: intragroup differences during the whole length of the study

	Baseline	3 months	*p* value	6 months	*p* value
VAS rest	2.6 ± 0.8	1.8 ± 0.6	0.0001	1.7 ± 1.1	0.003
VAS activities	5.4 ± 0.9	3.7 ± 0.9	0.0001	3.2 ± 1.2	0.0001
NSAIDs consumption					
No. of patients	14	6	0.007	5	0.002
VISA-P	52.8 ± 9.1	65.7 ± 11.5	0.0001	63.4 ± 9.8	0.002
US					
Mild	5	6	n.s	7	n.s
Moderate	7	7	n.s	7	n.s
Severe	6	5	n.s	4	n.s
CD					
0	0*	4^	n.s	6§	0.04
1 +	4*	5^	n.s	4§	–
2 +	7	6	n.s	4	n.s
3 +	7	3	n.s	4	n.s
Results					
Unsatisfactory (< 10)		6	n.s	7	n.s
Intermediate (10–19)		9	n.s	9	n.s
Satisfactory (> 20)		3	n.s	2	n.s

*^§The sum of these numbers was used for statistical analysis

Table 3 PRP: intragroup differences during the whole length of the study

	Baseline	3 months	*p* value	6 months	*p* value
VAS rest	2.4 ± 1.2	1.6 ± 0.9	0.0001	1 ± 0.6	0.0001
VAS activities	5.2 ± 1.4	3.9 ± 0.8	0.0001	2.6 ± 0.8	0.0001
NSAIDs consumption					
No. of patients	13	6	0.01	4	0.002
VISA-P	53.2 ± 11.1	66.2 ± 12.3	0.0001	71.2 ± 12.3	0.0001
US					
Mild	7	7	n.s	6	n.s
Moderate	5	7	n.s	7	n.s
Severe	6	4	n.s	5	n.s
CD					
0	0*	2^	n.s	6§	n.s
1 +	3*	2^	n.s	4§	–
2 +	10	11	n.s	4	0.04
3 +	5	3	n.s	4	n.s
Results					
Unsatisfactory (< 10)		6	n.s	6	n.s
Intermediate (10–19)		9	n.s	5	n.s
Satisfactory (> 20)		3	n.s	7	n.s

*^§The sum of these numbers was used for statistical analysis

Table 4 PRP + HVIGI: intragroup differences during the whole length of the study

	Baseline	3 months	*p* value	6 months	*p* value
VAS rest	2.7 ± 1	1.5 ± 0.5	0.0001	0.7 ± 0.6	0.0001
VAS activities	5.1 ± 1.1	3.7 ± 0.7	0.0001	1.8 ± 1.7	0.0001
NSAIDs consumption					
No. of patients	11	5	0.04	2	0.001
VISA-P	51.9 ± 8.5	72.2 ± 14.3	0.0001	79.1 ± 10.3	0.0001
US					
Mild	4	5	n.s	5	n.s
Moderate	6	5	n.s	6	n.s
Severe	8	8	n.s	7	n.s
CD					
0	0*	5^	n.s	4§	0.01
1 +	3*	3^	n.s	6§	–
2 +	7	8	n.s	6	n.s
3 +	8	2	n.s	2	n.s
Results					
Unsatisfactory (< 10)		4	n.s	3	n.s
Intermediate (10–19)		6	n.s	2	n.s
Satisfactory (> 20)		8	n.s	13	n.s

*^§The sum of these numbers was used for statistical analysis

observed in 9 and in 8 subjects in HVIGI and HVIGI + PRP groups, respectively, and in 4 subjects in PRP group. At 6 months the decrease of neovascularization was of the same magnitude in all groups. The degree of US lesions did not show significant differences at all follow-up times.

The intra-group comparison showed, at 3 months, an equivalence of pain and VISA-P scores among the groups (no significant difference). At 6 months HVIGI + PRP group was better than PRP (VISA-P: 79.1 ± 10.3 versus 71.2 ± 12.3, $p = 0.04$) and HVIGI (VISA-P: 79.1 ± 10.3 versus 63.4 ± 9.8, $p = 0001$), and PRP was better than HVIGI (VISA-P: 71.2 ± 12.3 versus 63.4 ± 9.8, $p = 0.03$). In comparison to HVIGI group the highest percentage of satisfactory responses was found in HVIGI + PRP group at 3 months (8 versus 3, n.s.) and reached statistical significance at 6 months (13 versus 2, $p = 0.0002$). The percentage found in PRP group at 6 months was intermediate, inferior to HVIGI + PRP (8 versus 13, n.s.) and superior to HVIGI (8 versus 2, $p = 0.02$).

All the treatments were well tolerated and no significant adverse reactions were registered, with the exception of slight discomfort after injection (pain, swelling) which lasted few hours.

Discussion

The most important finding of the present study was the observation of the synergistic activity of platelet rich plasma and high volume image guided injections, administered in the same therapeutic session. This finding is new, because in the past these treatments for PT have been performed separately and never in association. As shown by a recent meta-analysis PRP is provided of beneficial effects in PT [22], whereas preliminary results on the use of HVIGI are promising [16, 31, 35]. The present research shows that in the short term (3 months) HVIGI and PRP are provided of similar mild positive effects; however, at 6 months, the subjects submitted to the contemporaneous administration of PRP and HVIGI show better results (pain decrease, VISA-P score increase and number of satisfactory outcomes), both in comparison to PRP and HVIGI used separately.

The rationale of this synergistic activity relies on the assumption that these procedures exploit different mechanisms of action, which do not interfere and potentiate each other.

The efficacy of PRP in the short term is reported to the ability of several molecules (growth factors, chemokines, signaling proteins), stored inside the platelets, to modulate different aspects of tendon repair (inflammation, chemotaxis, angiogenesis, cell migration and proliferation) by activating intracellular signal-transduction pathways [3, 7–9, 17, 28, 39]. In the long term the efficacy is probably related to the activation of stem/progenitor cells (tendon SPCs, TSPCs) inside tendons and adjacent tissues, which maintain adequate tenocyte numbers throughout life and replenish them after injury [12, 41]. The final outcome is scar tissue formation and remodeling, which can partially restore tendon function.

On the other hand, the efficacy of HVIGI is explained by a different mechanism of action [16, 31, 35]. Indeed, the

high volume (30 mL) of normal saline injected in the interface between tendon/paratenon and fat pad can mechanically stress the neovessels around the symptomatic tendon; as consequence, their stretching, disruption and occlusion can damage the accompanying nerves by direct trauma or ischemia, therefore, decreasing pain [4, 5, 37]. However, this effect is short-lasting and the efficacy is temporarily limited.

The strengths of the present study are: first, the cohorts of patients were comparable for clinical and demographic characteristics, symptoms duration and severity, grading of echotexture damage and neovascularization at baseline. Second, the procedures were performed under US guidance by a trained operator and the same anestethic drug was used. Third, in the follow-up an eccentric exercise program was implemented in all groups, accordingly to Boesen et al. [14].

However, several limitations must be acknowledged. It is a retrospective observational trial including a limited number of patients with a short follow-up period (6 months). A blinded design, and a power analysis to evaluate a proper sample size to detect significant differences between groups, would be appropriate. However, in the specific situation, blindness was difficult to comply with (blood withdrawl in some patients, injection of fluids different in amount and colour) and the evaluation of a proper sample size was hindered by the high variability of outcomes observed in previous studies, which would require a very large number of participants. So, this can be considered as a pilot study, needing confirmation. No blinding process was involved when collected outcome data. A placebo effect, which usually ranges 15–30% [11], although similar in all groups, cannot be ruled out. The local anesthetic injected into the fat pad, which is very rich in pain receptors, can also decrease symptoms. The compliance to eccentric loading exercise program was not registered. Actually, it is very difficult to get reliable information on this issue, which is reported by the patient and cannot be objectively verified. This is a very important point because eccentric training may favour a better recovery. Indeed, during the eccentric movement, the blood flow in the ventral portion of the tendon is stopped, thus reducing the neoangiogenesis and disrupting accompanying nerves [34]. Moreover, tendons respond to eccentric mechanical forces by adapting their metabolism, altering gene expression, and activating TSPCs, so assuring the prosecution of the healing mechanism for several months afterwards [6, 33, 36, 38]. Therefore, we cannot exclude that difference in implementation of eccentric training could contribute to the final outcome of patients.

Conclusions

In the short term (3 months) HVIGI and PRP are provided of comparable efficacy, whereas at 6 months the positive effects of HVIGI are gradually reduced and PRP shows greater efficacy. The association of both procedures grants the best outcomes, as shown by the reduction of VAS scores for pain, the increase of VISA-P score and the number of subjects who exhibit optimal recovery. This means that these therapeutic options can be safely used in combination and reinforce mutually because exploiting different mechanisms of action. The finding has clinical relevance, given that patellar tendinopathy has a substantial impact on sports and work performance [19].

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Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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