The use of platelet-rich plasma for acute muscle tears: Systematic review and meta-analysis of current evidence

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ABSTRACT

Introduction: Acute muscle tear is the most common type of injury in sports activities. There is a present interest in the search of modalities that could shorten and improve healing time. The use of platelet-rich plasma (PRP) has increased over the past years, but such popularity does not count with sufficient scientific support to back up its effectiveness. The purpose of this study is to collect, analyze and summarize the available published data so as to clarify the effects of PRP use on muscle tears through a systematic review and meta-analysis. **Materials and Methods:** We conducted a systematic review of the literature on the use of PRP for the treatment of acute muscle injuries. A meta-analysis was conducted to evaluate the effects of PRP. **Results:** A total of 7 papers met the inclusion criteria for analysis: six randomized controlled trials and one cohort study. The overall time to return to play after PRP treatment was a mean of 29 days (range, 10 to 50.9 days), and in the control groups was a mean of 35.4 days (range, 22 to 52.8 days). The meta-analysis (5 of the 7 papers) showed a significant difference in earlier return to sports with the use of PRP when compared to conventional therapy (-7.80 days; P=0.007). No difference in the recurrence rate was reported. **Conclusions:** The meta-analysis demonstrated a favorable effect of PRP when compared to conventional therapy. However, our analysis demonstrated significant study heterogeneity. Thus, our findings should be interpreted with caution. We still cannot recommend the use of PRP for the treatment of muscle tears.

Key words: Platelet-rich plasma; growth factors; muscle injuries, regenerative medicine, biologics.

Level of Evidence: II

El uso de plasma rico en plaquetas para desgarros musculares agudos: revisión sistemática y metanálisis de la evidencia actual

RESUMEN

Introducción: El desgarro muscular agudo es el tipo de lesión más frecuente en actividades deportivas. El interés se ha centrado en buscar modalidades que reduzcan y mejoren el tiempo de curación. El uso de plasma rico en plaquetas ha crecido en los últimos años, pero no estuvo acompañado de suficiente respaldo científico sobre su eficacia. Este estudio intenta recabar, analizar y sintetizar la información publicada para esclarecer los efectos del uso de plasma rico en plaquetas en desgarros musculares agudos, mediante una revisión sistemática y un metanálisis. **Materiales y Métodos:** Se realizó una revisión bibliográfica sistemática sobre el uso de plasma rico en plaquetas para tratar lesiones musculares agudas. Se llevó a cabo un metanálisis para evaluar los efectos del plasma rico en plaquetas. **Resultados:** Siete artículos cumplieron los criterios de inclusión (6 ensayos controlados aleatorizados y 1 estudio de cohorte). La media del tiempo hasta el retorno al deporte en el grupo con plasma rico en plaquetas fue de 29 días (rango 10-50.9) y de 35.4 días (rango 22-52.8) en el grupo de control. Cinco de 7 artículos fueron incluidos en el metanálisis y se halló una diferencia significativa en el retorno deportivo con el uso de plasma rico en plaquetas comparado con la terapia convencional (-7.80 días; p = 0,007). No se informaron diferencias en la tasa de recurrencia. **Conclusiones:** El metaná-

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lisis mostró un efecto favorable del plasma rico en plaquetas en comparación con la terapia convencional. Sin embargo, nuestro análisis demostró una heterogeneidad significativa en el estudio. Los resultados deben interpretarse con cautela. Aún no podemos recomendar el plasma rico en plaquetas para tratar desgarros musculares agudos.
Palabras clave: Plasma rico en plaquetas; factores de crecimiento; lesiones musculares; medicina regenerativa; biológicos.
Nivel de Evidencia: II

INTRODUCTION

Acute muscle injuries constitute up to one-third of all sports injuries and are associated with a reinjury rate of up to 40% during the first year.[1,2] Standard treatment modalities include early muscle activation and stretching exercises with analgesic and anti-inflammatory therapy. The treatment for these injuries, despite being very common, has seen little progress and these modalities remain the gold standard for acute muscle injuries.

During the past decade, the use of platelet-rich plasma (PRP) for muscle tear has increased on the basis of the potential immunomodulation effect of growth factors (GFs) on the stimulation and acceleration of tissue regeneration.[3] *In vitro* studies have revealed that the use of PRP on muscle cells may result in the enhancement of cellular proliferation, the differentiation of satellite cells and the synthesis of antiangiogenic factors.[4] In addition, animal studies have reported better muscle repair with the use of GFs.[5-7]

Several comparative prospective studies have examined the clinical outcomes obtained after the PRP was included in more conventional treatments for muscle injuries; however, to date their results have been contradictory. In light of the controversy surrounding the clinical effectiveness of PRP injections in the treatment of muscle injuries, the purpose of this study was to conduct a systematic review and meta-analysis on the use of PRP in the treatment of acute muscle injuries. Our specific objectives were to study the use of PRP in relation to: 1) the time to return to play (TTRTP); 2) the pain during rehabilitation; 3) the reinjury rates; and 4) the complications associated with the procedure.

MATERIALS AND METHODS

Identification and selection of papers

The study was performed in accordance with the PRISMA 2009 (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement.[8] We conducted a systematic review of the published literature on the use of PRP in the treatment of acute muscle injuries, using PubMed, Medline and the Cochrane Database of Systematic Reviews. The search took place on March 2017, as did the registration in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: 42017065393).

Searches in MEDLINE/PubMed. Search 1: "Platelet-Rich Plasma"[Mesh] AND "Muscles"[Mesh]. Search 2: ("platelet-rich plasma"[MeSH Terms] OR ("platelet-rich"[All Fields] AND "plasma"[All Fields]) OR "platelet-rich plasma"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields]) AND (("muscles"[MeSH Terms] OR "muscles"[All Fields] OR "muscle"[All Fields]) AND ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "injury"[All Fields]).

Inclusion and exclusion criteria

Paper inclusion criteria included: 1) human clinical trials (level I or II); 2) English-language literature; 3) acute muscle injuries diagnosed using ultrasound or MRI. Paper exclusion criteria included: case series, basic science papers, editorial articles, surveys, special topics, letters to the editor, personal correspondence, review articles, and nonorthopaedic studies.

Three members of the research team (AMR, LAR, NSP) independently reviewed the titles and abstracts of all the papers produced by our established queries. When necessary, the complete paper was reviewed to apply the inclusion/exclusion criteria. The literature references from the scientific papers were also reviewed to minimize the risk of missing any relevant paper.

Data collection

Data were recorded into a custom-made information extraction table. We collected data on the protocol used for the preparation of the PRP, the initial whole blood volume, anticoagulant used, processing machine, disposable equipment, method of separation and its characteristics (centrifugation or platelet-pheresis), platelet activation method, nomenclature, platelet count, final platelet concentration, GF analysis, final volume, and clinical use.

Statistical analysis

Patients were divided into two groups: those who underwent PRP therapy and those who underwent conventional therapy for acute muscle injury. Studies that did not report the group means and standard deviations were excluded from the analysis. Both group mean TTRTP (days) was extracted together with their standard deviations, in order to assess the weighted mean effect sizes and its standard error. The study heterogeneity was assessed using the Cochran's Q statistic and the I^2 statistic test. We used the z-test to determine the clinical significance with a statistical significance level set at $P<0.05$. All statistical analyses were performed using the software Stata 5.3.

RESULTS

Identification and selection of papers

Figure 1 shows the paper selection process. The search strategy identified 251 papers. Application of inclusion and exclusion criteria eliminated 239 studies, leaving 12 papers for full-text review. After a comprehensive review of these papers, 7 met the inclusion criteria for analysis (Table 1); 6 randomized controlled trials (level of evidence I) and 1 cohort study (level of evidence II).

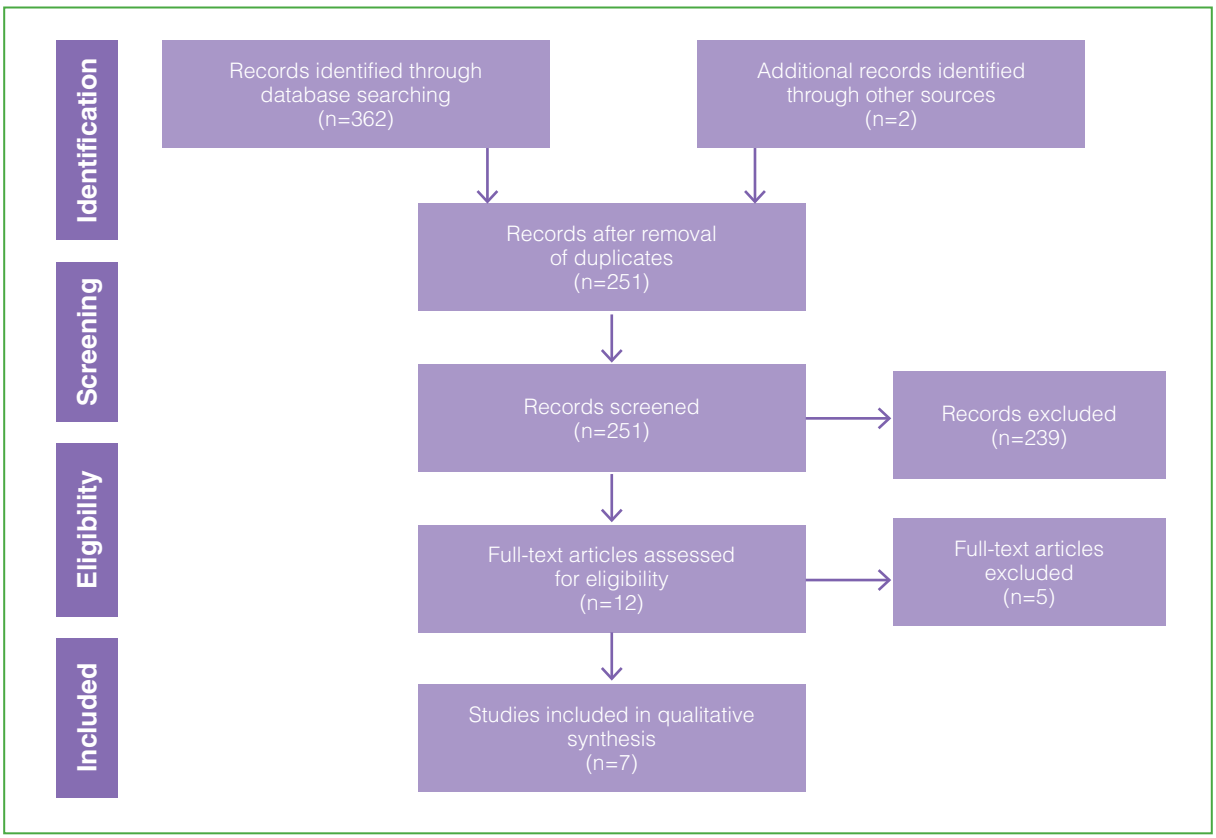

Figure 1. Flow diagram presenting the systematic review process used in this study (PRISMA)

Table 1. Characteristics of the selected studies

Study	Level of Evidence	Follow-up (months)	Number of patients	Mean age (years)	Inclusion criteria	Intervention	Control group	Outcome measure
Martinez-Zapata *et al.* (2016)	I	12	57	45.6	Grade 2 gastrocnemius muscle or quadriceps muscle (classified by ultrasound examination)	A 4-8ml PRP injection guided by ultrasound + rehabilitation	Rehabilitation	Primary: time to healing (weeks) Secondary: recurrence, VAS pain score, quality of the regenerated area (ultrasound), adverse events
Rossi *et al.* (2016)	I	24	75	22.3	Grade 2 gastrocnemius muscle, quadriceps muscle or hamstring muscle (classified by ultrasound examination)	A PRP injection guided by ultrasound + rehabilitation	Rehabilitation	Primary: TTRTP (days) Secondary: recurrence, VAS pain score
Guillodo *et al.* (2016)	II	4	34	26.3	Grade 2 hamstring muscle (classified by ultrasound examination)	A 3ml PRP injection guided by ultrasound + rehabilitation	Rehabilitation	Primary: TTRTP (days)
Hamilton *et al.* (2015)	I	6	90	26.6	Grade I or II hamstring muscle (classified by ultrasound examination)	PRP group: three 1ml injections administered adjacent to the injured area (confirmed with palpation) + rehabilitation	Platelet-poor plasma group: three 1ml injections administered adjacent to the injured area (confirmed with palpation) + rehabilitation No injection group: rehabilitation	Primary: TTRTP (days) Secondary: recurrence
Reurink *et al.* (2015)	I	12	80	29.0	Grade I or II hamstring muscle (classified by ultrasound examination)	Two 3ml PRP injections (at days 5 and 10-12) guided by ultrasound + rehabilitation	A 3ml NS injection (at days 5 and 10-12) guided by ultrasound + rehabilitation	Primary: TTRTP Secondary: recurrence
A Hamid *et al.* (2014)	I	10	28	21.0	Grade II hamstring muscle (classified by ultrasound examination)	A 3ml PRP injection guided by ultrasound + rehabilitation	Rehabilitation	Primary: TTRTP (days) Secondary: pain
Bubnov *et al.* (2013)	I	1	30	24.0	Grade I or II muscle injury in thigh, foot or ankle (classified by ultrasound examination)	A 5 ml PRP injection guided by ultrasound + rehabilitation	Rehabilitation	Primary: VAS pain score Secondary: strength, range of motion, subjective global function, ultrasound result, TTRTP (days)

NS: normal saline; PRP: platelet-rich plasma; TTRTP: time to return to play; VAS: visual analog scale.

PRP preparation and application protocol

The used PRP protocol varied among studies, there is a detail of their characteristics in Table 2 (when available). Only four studies reported the PRP platelet concentration before its application.[1,5,9,10] A Hamid *et al*.[11], in particular, reported the median levels for the transforming GF-β1 and for the fibroblast GF of the final product. The remaining studies did not report GF values. Six out of the seven analyzed studies described the use of ultrasound for the muscle injury localization and ultrasound-guided PRP injections.[1,8-12]

Table 2. PRP therapy characteristics of the selected studies

Authors	Anticoagulant	Processing machine	Separation system	Method	RPM	Time (min)	Spin 2	RPM	Time (min)	Activating agent	Platelet count (x 109/l)	Platelet concentration	Final injected volume (ml)
Martinez-Zapata *et al.*	NR	*Multicomponent cell separator*	MCS+, Haemonetics, Braintree, MA, USA	Density separation	4800	10-15	No	No	No	0.05 cc of CaCl2	289.32 ± 126.85	4.89 ± 0.87	According to the volume of the injured area
Guillodo *et al.*	NR	NR	Ortho. Pras 20 kit	Density separation	NR	NR	No	No	No	NR	NR	NR	NR
Hamilton *et al.*	ACD-A	*GPS III centrifuge separation system*	Biomet Recover, GPS III Platelet Separation System	Density separation	3200	15	No	No	No	No	237.2 ± 50.2	3.2 (765.8 ± 423.6)	3
A Hamid *et al.*	NR	*The Biomet Gravitational Platelet Separation System*	(GPS III; Biomet, Warsaw, Indiana, USA)	Density separation	NR	NR	NR	NR	NR	No	234	1297	3
Reurink *et al.*	EDTA	*Arthrex ACP double-syringe system*	Arthrex Medizinische Instrumente GmbH, Garching, Germany	Density separation	-	-	-	-	-	NR	232	1.9 (433 ± 128)	3
Bubnov *et al.*	NR	NR	NR	Density separation	NR	NR	No	No	No	NR	NR	NR	2
Rossi *et al.*	EDTA	NR	NR	Density separation	1400	3	Yes	3000	4 min	No	NR	NR	According to the volume of the injured area

ACD-A: anticoagulant citrate dextrose solution A; EDTA: ethylenediaminetetraacetic acid; NR: not reported; RPM: revolutions per minute.

Time to return to play

The overall mean TTRTP in PRP treatment was 29 days (range, 10 to 50.9 days), and in the control groups was 35.4 days (range, 22 to 52.8 days). The patients of three studies[5,11,12] were professional athletes before injury, while the other studies included patients who engaged in competitive and recreational sports.

Five out of the seven studies were eligible for meta-analysis,[8-12] which together included 224 patients with data on the TTRTP after PRP therapy. The meta-analysis showed a significant difference in the TTRTP in PRP patients against conventional-treatment patients (-7.80 days; CI95%: -13.48 to -2.12; P=0.007), as well as considerable heterogeneity (I^2= 96%; P<0.00001) (Figure 2).

Table 3. Time to return to play, according to the selected studies

Authors	Year	Journal	Cohort 1 (PRP)/Cohort 2 (control)	Mean	Range	Statistical significance (P)
Martinez-Zapata *et al.*	2016	*Blood Transfus*	Cohort 1	4.51 weeks	SD: 0.42	0.261
			Cohort 2	5.49 weeks	SD: 0.48	0.261
Guillodo *et al.*	2016	*Muscles Ligaments Tendons J*	Cohort 1	50.9 days	± 10.7	NS
			Cohort 2	52.8 days	± 15.7	NS
Hamilton *et al.*	2015	*Br J Sports Med*	Cohort 1	21 days	CI95%: 17.9-24.1	0.004 PRP vs. PPP
			Cohort 2	27 days	CI95%: 20.6-33.4	0.13 PPP vs. no injection
			Cohort 3	25 days	CI95%: 21.5-28.5	0.15 PRP vs. no injection
A Hamid *et al.*	2014	*Am J Sports Med*	Cohort 1	26.7 days	± 7	0.006
			Cohort 2	42.5 days	± 20.6	0.006
Reurink *et al.*	2015	*Br J Sports Med*	Cohort 1	42 days	30-58	0.66
			Cohort 2	42 days	37-56	0.66
Bubnov *et al.*	2013	*Med Ultrason*	Cohort 1	10 days	± 1.2	NR
			Cohort 2	22 days	± 1.5	NR
Rossi *et al.*	2016	*Knee Surg Sports Traumatol Arthrosc*	Cohort 1	21.1 days	± 3.1	0.001
			Cohort 2	25 days	± 2.8	0.001

PPP: platelet-poor plasma; PRP: platelet-rich plasma; NR: not reported; NS: not significant.

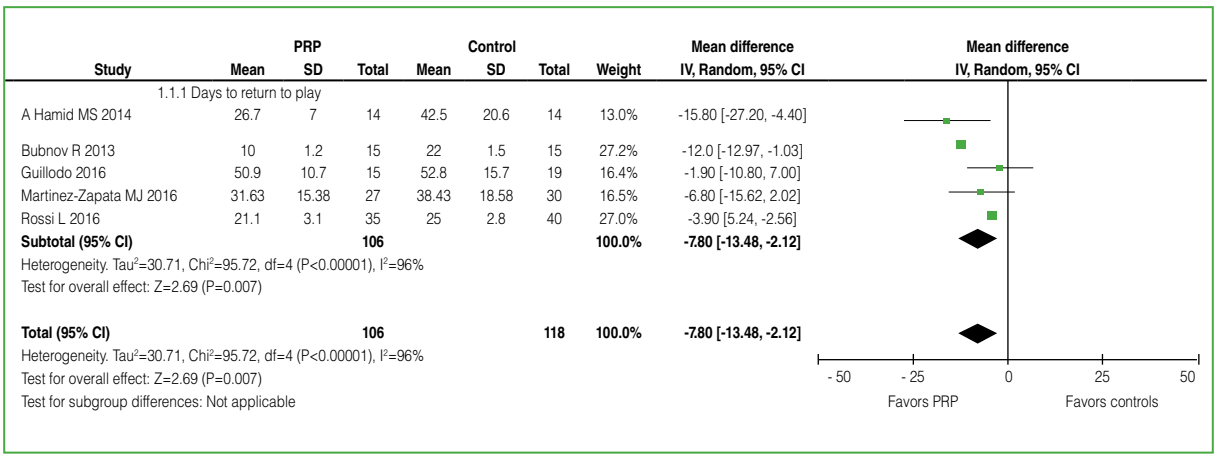

Figure 2. Forest plot of comparison: mean differences in the time to return to play after an acute muscle injury between both groups.

Five out of the seven studies reported that the TTRTP was significantly shortened in PRP patients.[2,9-11] In a randomized controlled trial, A Hamid *et al*.[11] compared 12 patients treated with PRP, in addition to rehabilitation, with 12 patients treated exclusively with rehabilitation. The PRP patients had a mean TTRTP of 26 days (range, 19-33) against 42 days (range, 22-62) in the control group (P=0.006). Bubnov *et al*.[9] reported less TTRTP for PRP patients (10±1.2 days) as compared to the control group (22±1.5 days). Rossi *et al*.[10] compared 35 patients treated with PRP therapy combined with a rehabilitation program and 40 patients with rehabilitation program only, and the mean TTRTP was 21.1±3.1 days and 25±2.8 days, respectively. Likewise, Hamilton *et al*.[3] reported 21 days for the PRP group and 25 for the control group.

The remaining three studies did not report statistically significant differences in the TTRTP between both groups.[8,12,13]

Pain

The assessment of pain progression after PRP injection was reported in five out of the seven studies. Reurink *et al*.[13] studied the pain using specific tests (Hamstring Outcome Score) at weeks 1 and 26, and found no significant differences between the PRP group and the control group. Four studies[9-12] evaluated pain as a variable and reported its progression at different follow-up time points. Martinez-Zapata *et al*.[12] studied the pain intensity (visual analogue scale) on a weekly basis for 8 weeks and then at 6 and 12 months. They reported similar pain intensities for both groups during follow-up. On the other hand, the other three studies[9-11] reported an average pain score significantly lower among the PRP patients during the healing process; however, these studies also failed to find any differences in the average pain score at the end of the follow-up period.

Recurrence

Four studies failed to find any differences in the reinjury rates between both groups (PRP and control). Martínez-Zapata *et al*.[12] had no reinjury cases (0/27 patients) in the PRP group and only one case in the control group (1/30). At 6-month follow-up, Hamilton *et al*.[2] reported a reinjury rate of 7.7% (2/30) in PRP patients and 10.3% (3/29) in the control group (P=0.905). Rossi *et al*.[10] reported a reinjury rate of 5.7% (2/34) for the PRP group and of 10% (4/48) for the control group (P not significant). Reurink *et al*.[13] reported the highest reinjury rates: 27% (10/37) for the PRP group and of 30% (11/37) for the control group (P=0.80).

Complications

Four out of the seven cases report no complications associated with PRP.[5,8,10,11,14] Reurink *et al*.[13] reported one case of painful skin hyperesthesia at the PRP injection site, which extended the TTRTP. Martinez-Zapata *et al*.[12] reported complications, however, none were related to PRP therapy. Finally, Bubnov *et al*.[9] failed to assess complications.

Discussion

Over the past years, there has been a growing interest in the use of PRP to treat acute muscle injuries.[15] However, despite its growing popularity, evidence to support PRP use is lacking. Therefore, the objective of this review was to assess the published results on PRP therapy for acute muscle injuries. Overall, the studied results may suggest that PRP therapy reduces the TTRTP when compared to conventional treatment (-7.80 days; CI95%: -13.48 to -2.12; P=0.007). However, a thorough and critical evaluation of the measures taken in each published study is key to properly interpret the results and, thus, to prevent us from only relying on statistics or individual outcomes and taking them as absolute truths.

The limitations of this study include: the meta-analysis design, which, although it is considered the highest level of evidence, uses data from previously published studies (ideally, level of evidence I or II), and thus, may magnify or reduce any bias present in each individual study; in addition, our meta-analysis showed considerable heterogeneity in the studied data. Despite these limitations, this is one of the few reviews that study the use of PRP in patients who had sustained acute muscle tears, and as such a we consider it a potentially useful tool for clinical decision making.

In terms of pain, PRP therapy has been found useful to relieve pain in patients with knee osteoarthritis and epicondylitis.[8,16-18] In terms of pain associated with PRP in the treatment of acute muscle tear, the results suggest there is no difference between PRP patients and control patients at the end of the follow-up period, and most patients achieve full recovery. However, three studies[9-11] found a significant difference related to pain relief during treatment.

This relief during the rehabilitation period may in part account for most of the evaluated studies showing a shorter TTRTP in PRP patients. These outcomes may justify the use of this therapeutic option in the elite sport context while bearing in mind that pain relief may not be associated with an accelerated tissue repair.

As having a muscle injury history constitutes a significant risk factor for a new muscle tear,[19] treatment must prioritize achieving scar tissue formation with as less fibrous scarring as possible. Four studies[10,12-14] that analyzed recurrence rates found no differences between PRP patients and control patients. In our study, the recurrence rates were between 5.7% and 30%, not unlike the recurrence rates reported by Orchard *et al*.[15] However, due to the limited evidence available, the effects of PRP therapy on reinjuries remains an uncertainty. In other words, the stimulation of the myoblast differentiation and the ensuing tissue regeneration, as suggested by some *in vitro* studies, would result in better muscle tissue quality and a resultant decrease in the recurrence rate; however, such hypothesis is still to be proven by clinical trials.

The application of PRP therapy in the muscle tear treatment seems to be a safe option, as it has a low rate of reported complications. In the assessed studies, there were no serious adverse events, with the exception of a case of painful skin hyperesthesia at the injection site, reported by Reurink *et al*.[13]

Some *in vitro* and animal experimental studies have proven the PRP effectiveness for inducing myoblast regeneration.[4,6,7,20] However, these results have not yet been translated to the clinical practice. One reason for this discrepancy may be that the current formulation of PRP may not be appropriate to induce muscle regeneration. To date, leucocyte-rich PRP is the most widely used formulation in most clinical trials. However, the *in vitro* study of Dragoo *et al*.[4] has raised a number of new questions with its suggestion that platelet-poor plasma and leukocyte-poor PRP would stimulate myoblast differentiation, which is necessary for adequate muscle regeneration. All of these issues incite the rethinking of PRP greatest problem, all the enthusiasm related to its use and its application has not gone hand in hand with the understanding of its components, of the different actions, and of the time periods and points related to its application. Future clinical trials should include a thorough description of the PRP preparation protocols, which together with the qualitative and quantitative description of the used formulations are essential for an adequate interpretation of the results and a subsequent replication.

Conflict of interests: Authors claim they do not have any conflict of interest.

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