Sports Med (2018) 48:971–989
https://doi.org/10.1007/s40279-018-0860-1

SYSTEMATIC REVIEW

Is Platelet-Rich Plasma (PRP) Effective in the Treatment of Acute Muscle Injuries? A Systematic Review and Meta-Analysis

Alberto Grassi[1] · Francesca Napoli[2] · Iacopo Romandini[3] · Kristian Samuelsson[4] · Stefano Zaffagnini[1] · Christian Candrian[2] · Giuseppe Filardo[3]

Published online: 23 January 2018
© Springer International Publishing AG, part of Springer Nature 2018

Abstract

Background Muscle lesions account for one-third of sport-related injuries, thus representing a substantial problem for both players and their teams. The use of platelet-rich plasma (PRP) injections is rapidly growing in clinical practice, prompted by an unmet clinical need with a large commercial market. However, after early reports of positive preliminary experience, higher quality studies recently questioned the real benefit provided by PRP injections to promote muscle healing and return to sport.

Objective To evaluate the effect of platelet-rich plasma (PRP) injections on outcomes following acute muscle injuries.

Design Meta-analysis of randomized, controlled trials (RCTs), Level I.

Data sources PubMed (MEDLINE), Cochrane (CENTRAL), Web of Science, clinicaltrials.gov, who.int, isrctn.com, greylit.org, opengrey.eu.

Eligibility criteria RCTs investigating the effect of PRP for the treatment of acute muscle injuries against at least one control group including patients treated with placebo injection or physical therapy. The outcomes evaluated were time to return to sport, re-injuries, complications, pain, muscle strength, range of motion (ROM)/flexibility, muscle function, and imaging.

Results Six studies, involving 374 patients, were included in the meta-analysis. The time to return to sport evaluated in all six studies was significantly shorter in patients treated with PRP (mean difference $= -7.17$ days). However, if only the double-blind studies ($n = 2$) or studies including only hamstring injuries ($n = 3$) were considered, non-significant differences were found. Re-injuries (relative risk $= -0.03$) and complications (relative risk $= 0.01$) were also similar between the two groups ($p > 0.05$), nor were any substantial differences found regarding pain, muscle strength, ROM/flexibility, muscle function, and imaging. The performance bias was high risk due to the lack of patient blinding in four studies. The quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was therefore low or very low.

Conclusions The promising biological rationale, the positive preclinical findings, and the successful early clinical experience of PRP injections are not confirmed by the recent high-level RCTs. Therefore any benefit in terms of

✉ Iacopo Romandini
iacoporoma@gmail.com

Alberto Grassi
alberto.grassi@ior.it

Francesca Napoli
Francesca.Napoli@eoc.ch

Kristian Samuelsson
kristian@samuelsson.cc

Stefano Zaffagnini
s.zaffagnini@biomec.ior.it

Christian Candrian
Christian.Candrian@eoc.ch

Giuseppe Filardo
g.filardo@biomec.ior.it

[1] II Clinic Rizzoli Orthopaedic Institute, Bologna, Italy

[2] EOC-Regional Hospital of Lugano, Lugano, Switzerland

[3] NABI Laboratory, Rizzoli Orthopaedic Institute, Bologna, Italy

[4] Department of Orthopaedics, Institute of Clinical Sciences, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

pain, function, return to sport, and recurrence using PRP injections for the treatment of acute muscle injuries is not supported. Due to the bias in the studies, the heterogeneity of the findings, and the limited sample size, the evidence should be considered to be of low or very low quality.

Key Points

Low to moderate quality randomized controlled trials show that PRP injections provide no superior, clinically relevant, effect on return to sport, recurrences, function, and pain for athletes with acute muscle injuries.

PRP treatment is a safe procedure with negligible adverse effects, but the large and indiscriminate use of PRP injections for the treatment of acute muscle injuries in clinical practice is not justified and PRP use should be limited to controlled trials until more positive evidence emerges and suggests otherwise.

1 Introduction

Muscle lesions account for one third of sport-related injuries and 92% of them affect the four major muscle groups of the lower limb: first and foremost hamstrings, followed by adductors, quadriceps, and calf muscles [1]. Taken as a whole, they are responsible for prolonged absence from sport, they may require long rehabilitation, and re-injury rates have been reported to be as high as 39% within the same season, thus representing a substantial problem for both players and their teams [1, 2].

Treatment goals are therefore to achieve the same functional level as prior to injury and to allow for the return to sports practice quickly and with minimal recurrence risk [3]. While PRICE (protection, rest, ice, compression, and elevation) is a commonly accepted overall approach to control the early inflammatory process, followed by rehabilitative exercises and gradual training therapy to recondition the injured structure, many other interventions are used to promote healing as well [4]. Among these, anti-inflammatory medications, electrotherapeutic modalities, hyperbaric oxygen therapies, photothermal therapy or injection strategies such as prolotherapy have been proposed. However, these treatments have no firm scientific basis and clinical evidence to support them is sparse, so they are mainly applied as empirical medicine due to the lack of indications from high-level trials [4–6].

The increasing knowledge of basic science related to muscle healing set the stage for the introduction of a novel biological approach to accelerate the healing of injured muscles. The early inflammatory phase is followed by repair and remodeling processes, where undifferentiated satellite cells proliferate and differentiate to restore the muscle structure, in response to several growth factors (GFs) [7]. Many of these bioactive molecules are stored in the platelet alpha granules, such as insulin-like GF (IGF-I), hepatocyte GF (HGF), fibroblast GF (FGF-2) and transforming GF (TGF-β1), which may be key regulators of muscle regeneration and myogenesis [8]. Therefore, platelet-rich plasma (PRP), which can be defined as a blood derivative with a higher platelet concentrate than whole blood, gained increasing interest to deliver a high concentration of autologous GFs and bioactive molecules in physiologic proportions, with low costs and in a minimally invasive way [9]. Under the acronym PRP, countless procedures have been developed, leading to heterogeneous concentrates in terms of absolute number of platelets, activation methods, presence or absence of white blood cells, etc., all factors that might influence the effect on the tissue target [10–13]. While some authors have attempted to introduce some order into this multifaceted field, the biological nature of this autologous approach makes standardization difficult. Classifications that endeavor to summarize procedures according to macro-categories (PRP with or without leukocytes, with or without fibrin, etc.) are useful whereas other more detailed classifications have proved more problematic in terms of practical applicability [12, 14]. Nonetheless, regardless of the heterogeneity and classifications limitations, preclinical evaluations suggested that the local delivery of PRP might reduce recovery time [8]. Thus, the application in clinical practice increased rapidly, prompted by an unmet clinical need with a large commercial market [15]. However, after early reports of positive preliminary experience, higher quality studies have recently questioned the real benefit provided by PRP injections to promote the healing process and return to sport.

The purpose of this meta-analysis was to evaluate whether PRP injections improve the outcomes of acute muscle injuries compared with standard rehabilitation, in terms of time of return to sport, as well as re-injuries, complications, pain, strength and flexibility recovery, functional scores, and imaging.

2 Methods

2.1 Search Strategy

A meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and

Meta-Analysis (PRISMA) guidelines [16]. A systematic electronic search was performed on 1 November 2017 in the following databases: PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science electronic databases. The search period was 1987–2017; articles included in the meta-analysis were published between 2013 and 2016. The grey literature databases *clinicaltrials.gov*, *who.int*, *greylit.org*, *opengrey.eu* and *isrctn.com*, were searched as well for unpublished studies.

The search string was built as follows: "(PRP OR platelet-rich plasma OR plasma rich in growth factors OR platelet derived growth factor OR platelet derived OR platelet gel OR platelet concentrate OR PRF OR platelet rich fibrin OR ACP OR autologous conditioned plasma OR PRGF OR platelet lysate) AND (muscle injury)". The electronic database search was supplemented by a manual search of the reference lists of included articles.

2.2 Article Selection

The eligibility of searched articles was assessed on the basis of prespecified inclusion criteria.

- Articles published in peer-reviewed journals, unpublished studies.
- Articles written in any language.
- Randomized, controlled trials (RCTs) and quasi-RCTs investigating the effect of PRP in the treatment of acute muscle injuries.
- At least one control group including patients treated with placebo injection or physical therapy.
- The treatment of acute muscle injuries including upper and lower limbs.

All the criteria had to be fulfilled for the article to be included. Biomechanical, in vitro studies, review articles, surgical techniques, case reports, letters to the editor, and editorials were excluded. When two or more papers evaluated the same patient cohorts, the relevant data were extracted from each study, but only the study with a longer follow-up was considered in order to avoid data duplication. Two authors independently reviewed the title and abstract of each article from the systematic literature search. The full text of the article was obtained and evaluated if eligibility could not be assessed from the first screening. Any disagreements were resolved via a consensus discussion between the two reviewers and the senior author was consulted if the disagreement could not be resolved.

2.3 Outcome Measurements

The outcomes extracted from the included studies were the time to return to sport, the re-injury and complication rate, pain, strength, flexibility, and range of motion (ROM) and, finally, the healing process evaluated with ultrasound or magnetic resonance imaging (MRI).

2.4 Data Extraction and Synthesis

An electronic piloted form for data extraction was created prior to the study. Patient demographic details, including sex, age, type of muscle injury, and level of activity, were extracted. Details of study design, such as level of evidence, inclusion and exclusion criteria, type of randomization, blinding of patients or outcome assessors, injection protocol, PRP characteristics, and rehabilitation details, were collected. For the outcome measurements, the time needed to return to unrestricted sport activity, according to the criteria reported in each study, and the number of patients who experienced a complication or a re-injury, were extracted. Information regarding pain measured with subjective scales, strength measured with an isokinetic machine, handheld dynamometry or manual testing, and ROM/flexibility measured through clinical evaluation were extracted as well.

2.5 Assessment of Risk of Bias and Quality of Evidence

The risk of bias was evaluated according to the standardized Cochrane Database questionnaire [17]. Selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias were rated as "high risk," "low risk," or "unclear risk." Each item for each study was reported in a table and a summary table reporting the percentage of studies with a specific bias risk was produced. The performance and detection bias were evaluated twice: both for outcomes that could have been affected by the patient's knowledge of the type of treatment (time to return to sport, pain and functional scores) and those that were considered independent from treatment knowledge (re-injuries, complications, strength, flexibility, and radiologic features). Reporting bias was assessed by checking the respective trial registrations, when available, to determine whether the outcomes reported in the trial protocol corresponded to the outcomes finally reported in the published paper. If trial registration protocols were not available, reporting bias was considered to be low risk if the final outcomes included key outcomes such as time to return to sport, complications and functional or pain evaluation; when this was not the case, a high risk of reporting bias was considered to be present. The purpose of the assessment of risk of bias was to provide a descriptive

summary of the main sources of potential bias in the included studies. Articles were not excluded on the basis of the assessment.

The overall quality of evidence for each outcome was graded as "high," "moderate," "low," or "very low," according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [18], based on study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on the GRADE guidelines [18], the quality of evidence of each outcome was downgraded from the highest level in the case of: high risk of bias, high statistical heterogeneity of the outcome or conflicting results among the various studies, use of surrogate measurements (e.g., score for muscle function) or heterogeneous definitions for the same outcome (e.g., muscle healing with MRI or US), and CIs overlapping the null value or a total sample size lower than the calculated optimal information size (obtained with post hoc sample analysis using https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html) [18].

2.6 Statistical Analysis

The meta-analysis was performed using RevMan V.5.0.18.33 (the Cochrane Collaboration, Copenhagen, Denmark). Continuous variables were extracted and analyzed as the mean ± standard deviation (SD) [19]. If the mean or SD were not reported, authors were contacted via e-mail in order to obtain raw data for the calculations. The mean difference (MD) and 95% confidence interval (CI) were calculated for the continuous variable of "time (days) to return to sport." The risk difference (RD) and 95% CI were calculated for the dichotomous variables of re-injuries and complications. We tested for heterogeneity using the χ^2 and Higgins' I^2 tests. Data were pooled using a Mantel–Haenszel random-effects model if the statistical heterogeneity was moderate to substantial (>40% at I^2 test) [19]; a fixed-effects model was used if the statistical heterogeneity was below 50% [20]. Publication bias was planned to be investigated with a funnel plot if more than ten studies were available for a specific outcome. A sensitivity analysis was performed separately analyzing studies with a single-blind or double-blind design and studies evaluating hamstring injuries or different injury location. Also, a meta regression evaluating sample size was performed in the case of more than 10 studies available. Due to extreme heterogeneity in the presentation of pain, strength, ROM/flexibility and imaging outcomes, a pure meta-analysis was not possible and the results of these outcomes were reported in a narrative manner. A p value of <0.05 was considered statistically significant in all analyses.

3 Results

3.1 Article Selection

The initial search resulted in a total of 2181 articles. After the removal of papers not relevant to the purpose of this study, 104 papers were considered eligible for inclusion in this meta-analysis. Another 93 papers were removed because they did not meet the inclusion criteria and 11 RCTs were therefore identified. Three of these RCTs, two found in *clinicaltrials.gov* and one study abstract were excluded because the final results had already been published in peer-reviewed journals. No further papers were found in the other grey literature databases *who.int*, *greylit.org*, *opengrey.eu*, *isrctn.com*.

Eight articles were therefore included for qualitative synthesis [6, 15, 21–26] (Fig. 1). However, two studies [6, 21] involved the same patient population: one paper was the study protocol and the other contained the study results, but both were included since they presented non-mutually exclusive information. Another two studies [15, 22] evaluated the same patient cohort: one study reported the time to return to sport outcome, while the other reported the re-injury rate and functional outcomes and both these studies were therefore included, but they were regarded as a single study in the data presentation and statistical analysis. Finally, six studies were included in the quantitative synthesis and meta-analysis.

3.2 Study Characteristics

All six included studies were RCTs. The exclusion criteria were similar, especially regarding injury onset, the presence of non-steroidal anti-inflammatory drugs (NSAIDs) and the assumption or use of other injected therapies. All but one of the studies had two arms comparing PRP injections with isolated conventional physical therapy ($n = 3$), physical therapy and hematoma aspiration ($n = 1$) or physical therapy and isotonic saline injection ($n = 1$). The study by Hamilton et al. [23] had three arms, comparing PRP, platelet-poor plasma (PPP), and no injections. In the latter case, only the no injection arm was used as control group and accounted in the analysis. All studies reported to blind outcome assessors, but only two studies were considered to be double-blind (Table 1).

3.3 Patient Characteristics

Overall, 374 patients were enrolled in the six studies, ranging from 28 to 90 patients per study. However, only 145 who received a PRP injection and 191 who were included in the control group were finally included in the

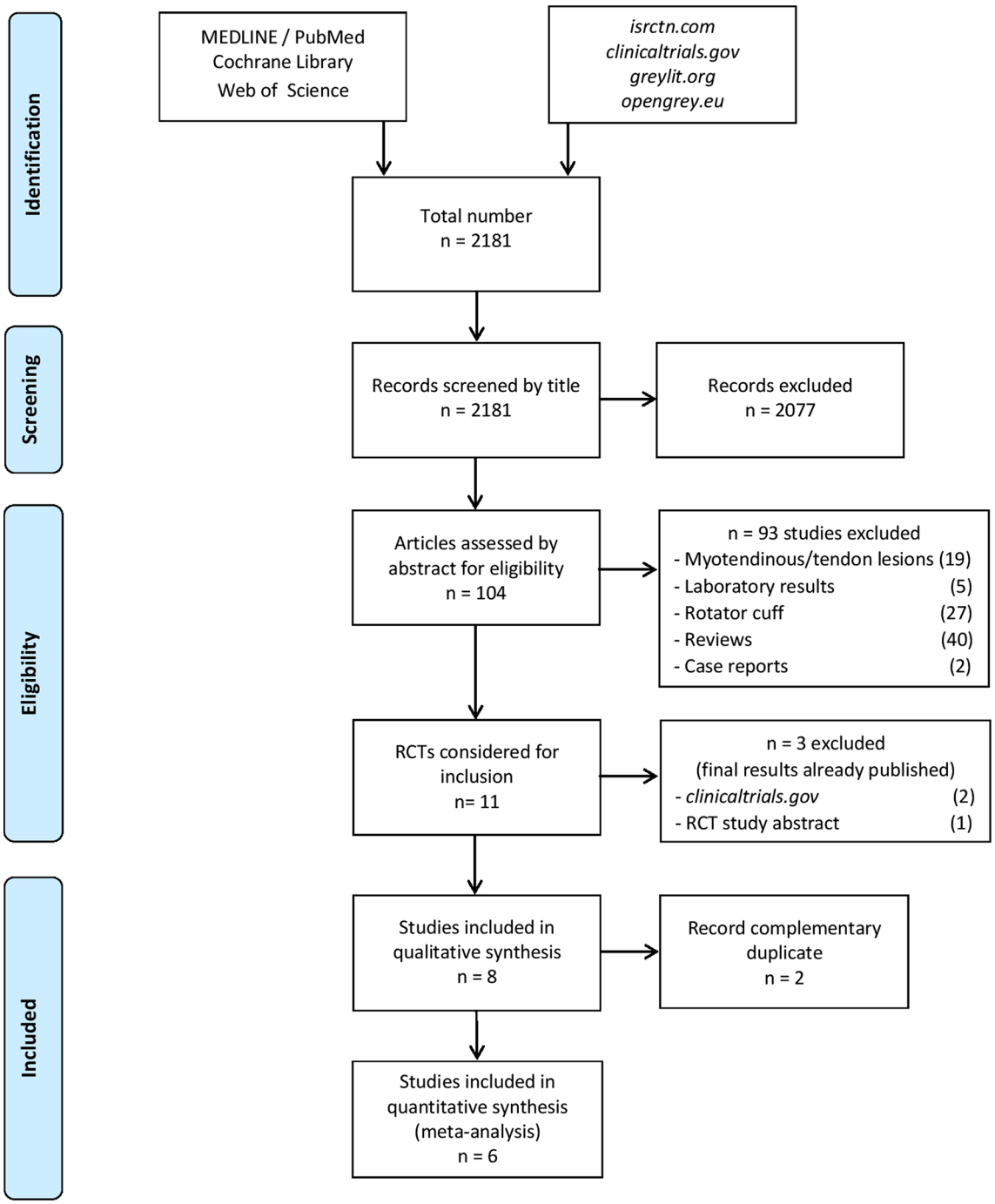

Fig. 1 PRISMA flow chart for study inclusion. *RCTs* randomized controlled trials

meta-analysis, due to a 0–14% rate of lost to follow-up. Patients were predominantly professional male athletes, with a mean age of under 30 years, except for Martinez-Zapata et al. [25] (45 years). Three studies exclusively comprised hamstring injuries [6, 15, 23], while the remaining three included several injury locations such as hamstrings, rectus femoris, quadriceps, gastrocnemius, thigh, foot and ankle, and shoulder. For the four studies that measured the injury dimension with ultrasound or MRI, no differences were reported between those treated with PRP and those in the control group at the baseline evaluation (Table 2).

Table 1 Methodological characteristics of the included studies

Study	Journal	Inclusion criteria	Exclusion criteria	Study type	Arms	Randomization	Control group treatment	Blinding of patients	Blinding of assessors
Rossi et al. [26]	KSSTA	Age 18–40 years	NSAIDs 1 week before randomization	RCT	2	Opaque envelopes	None	No	Yes
		< 7 days since injury	Unable to comply rehabilitation program						
		All muscle injuries classified by US as grade II	Previous surgeries or pathologies of the involved muscle						
			Any form of injection						
Martinez-Zapata et al. [25]	Blood Transfusion	Age ≥ 18 years	NSAIDs, corticosteroids, ASA, one week before randomization	RCT	2	Computer	Hematoma evacuation	Yes	Yes
		Evacuable haematoma at the gastrocnemius muscle or the lower portion of the rectus femoral muscle	Unable to attend follow-ups						
		Surgery not recommended	Bleeding disorders						
Reurink et al. [15]	BJSM	MRI ≤ 5 days since injury	No macroscopic tissue damage	RCT	2	Computer	Isotonic saline injection	Yes	Yes
		Positive MRI	Negative MRI						
		Not complete muscle lesion (grade I–II)	Complete muscle lesion (grade III)						
			Tendon avulsion						
Hamilton et al. [23]	BJSM	Male gender	Contraindication MRI and injection	RCT	3	Computer	None or PPP injection	No	Yes
		Age 18–50 years	Concurrent other injury inhibiting rehabilitation						
		MRI ≤ 5 days since injury	Unwilling to comply follow-up						
		MRI confirmed grade I or II hamstring lesion	Re-injury or chronic hamstring injury						
		Available for follow-up, able to perform physiotherapy 5 session/week	Skin infection, diabetes, bleeding risk						

Table 1 continued

Study	Journal	Inclusion criteria	Exclusion criteria	Study type	Arms	Randomization	Control group treatment	Blinding of patients	Blinding of assessors
A Hamid et al. [6]	AJSM	Age $\geq$ 18 years <7 days since injury Able to understand and follow the study protocol	NSAIDs one week before randomization Any form of injection Previous muscle surgery Unable to fulfill weekly follow-up appointments and comply rehabilitation program Cardiovascular, renal or hepatic disease; malignancy; anemia	RCT	2	Computer	None	No	Yes
Bubnov et al. [24]	Medical Ultrasonography	NR	NR	RCT	2	NR	None	No	NR

NR not reported, *AJSM* American Journal of Sports Medicine, *BJSM* British Journal of Sports Medicine, *KSSTA* Knee Surgery, Sports Traumatology, Arthroscopy, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ASA* acetylsalicylic acid, *MRI* magnetic resonance imaging, *PPP* platelet poor plasma, *RCT* randomized controlled trial, *US* ultrasound

3.4 PRP Injection and Rehabilitation Protocols

The description of PRP type used was presented in detail in five of the six studies, while in the work by Bubnov et al. [24], no information was given to enable the possible replication of their PRP preparation. The injection was usually intralesional, under ultrasound guidance and within 5–7 days of injuries in four studies; one study reported a mean time interval of 14 days, while two studies did not report this detail. Only two studies performed hematoma aspiration, one of them used this practice to blind the patients to PRP or no injection treatment. The rehabilitation protocol was described or referenced satisfactorily in all studies, apart from the one by Bubnov et al. [24] (Table 3).

3.5 Outcomes of PRP versus Control

3.5.1 Return to Sport

A clear definition of return to sport was reported in all six studies. The mean time to return to sport ranged from 10 to 42 days in the PRP group and from 22 to 42 days in the control group. Three studies reported a significantly shorter time to return to sport in patients treated with PRP and three studies reported no differences. A random-effect meta-analysis ($I^2 = 95\%$; $p < 0.00001$) revealed a significant mean difference of -7.17 (95% CI -12.26 to -2.08; $p = 0.006$) in favor of PRP (Fig. 2).

However, considering only the two double-blind studies, the mean difference between PRP and the control group obtained with a fixed-effect meta-analysis ($I^2 = 0\%$; $p = 0.71$) was not significant (-5.65, 95% CI -12.14 to 0.84; $p = 0.09$) (Fig. 3a). A similar finding was also reported in the random-effect meta-analysis ($I^2 = 44\%$; $p = 0.17$) of the three studies evaluating only hamstring injuries (-5.95, 95% CI -12.48 to 0.57, $p = 0.07$) (Fig. 3b). On the other hand, a significant mean difference in favor of PRP was reported when considering the four single-blind studies or the three studies with heterogeneous muscle involvement (Table 4).

3.5.2 Re-injuries

A clear definition of re-injury was reported in four studies. The re-injury rate ranged from 0 to 27% in the PRP group and from 0 to 30% in the control group. The fixed-effect meta-analysis ($I^2 = 0\%$; $p = 0.87$) revealed a non-significant risk difference of -0.03 (95% CI -0.10 to 0.05; $p = 0.50$) (Fig. 4a).

Table 2 Patient characteristics of the included studies

Study	Patients							Age (years)	
	Total	M/F	Professional athletes (Y/N)	PRP (included)	PRP (at FU)	Control (included)	Control (at FU)	PRP	Control
Rossi et al. [26]	75	58/17	46/29	35	34	40	38	22.9 ± 3.5	21.8 ± 3.2
Martinez-Zapata et al. [25]	71	58/13	18/53	28	27	32	30	45.9 ± 10.3	45.3 ± 9.8
Reurink et al. [15]	80	76/4	59/21	41	41	39	39	28.0 ± 7.0	30.0 ± 8.0
Hamilton et al. [23]	90	90/0	87/3	30	28	30	27	26.6 ± 5.9	25.5 ± 5.7
A Hamid et al. [6]	28	24/4	19/9	14	12	14	12	20.0 ± 6.5	21.0 ± 8.8
Bubnov et al. [24]	30	30/0	30/0	15	15	15	15	24	24

Study	Lesion site				Lesion size					
	Diagnosis	Grade	PRP	Control	PRP			Control		
Rossi et al. [26]	US	II	Hamstring (16), quadriceps (7), gastrocnemius (12)	Hamstring (18), quadriceps (8), gastrocnemius (11)	15.9 ± 5.9 mm (W)	23.4 ± 10.2 mm (L)	NR	16.7 ± 5.1 (W)	24.5 ± 8.7 (L)	NR
Martinez-Zapata et al. [25]	US	NR	Gastrocnemius (32), rectus femoralis (1)	Gastrocnemius (36), rectus femoralis (2)	6.1 ± 6.3 cm (W)	11.4 ± 5.7 cm (L)	19.27 ± 25.35 mm^2 (Vol)	7.5 ± 9.7 cm (W)	13.0 ± 14.6 cm (L)	22.52 ± 27.83 mm^2 (Vol)
Reurink et al. [15]	MRI	I and II	Hamstring	Hamstring	NR	11.1 ± 6.0 cm (L)	NR	NR	12.7 ± 6.0 cm (L)	NR
Hamilton et al. [23]	MRI	I and II	Hamstring	Hamstring	2.4 ± 1.3 cm (W)	15.8 ± 8.2 cm (L)	NR	2.3 ± 1.3 (W)	15.5 ± 6.1 (L)	NR
A Hamid et al. [6]	US	II	Hamstring	Hamstring	NR	3.4 ± 1.1 cm (L)	15.3 ± 34.2 cm3 (Vol)	NR	2.3 ± 1.0 cm (L)	15.3 ± 34.2 cm^3 (Vol)
Bubnov et al. [24]	US	NR	Thigh (10), foot and ankle (5), shoulder (2)	Thigh (8), foot and ankle (5), shoulder (4)	NR	NR	NR	NR	NR	NR

Data are n or mean ± SD

NR not reported, *M* male, *F* female, *US* ultrasound, *MRI* magnetic resonance imaging, *PRP* platelet-rich plasma, *W* width, *L* length, *Vol* volume, *Y* Yes, *N* No, *FU* follow-up

Table 3 Characteristics of the PRP preparations and injection protocols of the included studies

Study		PRP characteristics				Injection						Concomitant treatments	
	Follow-up	Commercial name	Centrifugation	Activating agent	Cells	Timing after injury (days)	Number	PRP volume	Location	Hematoma aspiration	Ultrasound guidance	Additional treatments	Rehabilitation
Rossi et al. [26]	2, 12, 24 months	NR	1400 rpm × 3 min 3000 rpm × 4 min	No	NR	2.3 (1–4)	1	Proportional to injury	Intralesional	NR	Yes	NR	Supervised protocol with agility and trunk stabilization exercises Four phases with progression based on pain and ROM Three times/week
Martinez-Zapata et al. [25]	1–8 weeks 6, 12 months	MCS +, Hemonetics	4800 rpm	Calcium chloride	Platelets $1381 \pm .430 \times 10^9$/L Leukocytes $0.11 \pm 0.06 \times 10^9$/L Erythrocytes $0.00004 \pm 0.04\ 10^9$/L	14.2 ± 9.1	1	4–8 ml	NR	Yes	Yes	Rest, ice compression analgesic	Recovery protocol for calf/rectus femoralis injuries
Reurink et al. [15]	1, 4, 10, 26 weeks 12 months	ACP, Arthrex	NR	NR	Platelets $433 \pm 128 \times 10^9$/L Leukocytes $1.9 \pm 2.1 \times 10^9$/L	3 (2–5)	2	3 ml	Intralesional	NR	Yes	Ice	Daily home lengthening, resistance, cycling, stepping, isometric and core-stability exercises Twice a week supervised training sessions
Hamilton et al. [23]	2, 6 months	GPS III, Biomet	3200 rpm × 15 min	No	Platelets $765.8 \pm 423.6 \times 10^9$/L Leukocytes $26.1 \pm 13.7 \times 10^9$/L Erythrocytes $1.0 \pm 0.9 \times 10^9$/L	NR	1	3 ml	Intralesional	NR	No	NR	ROM, progressive strengthening, core stability, agility exercises Sports-specific functional field testing Five times/week

Table 3 continued

Study		PRP characteristics				Injection					Concomitant treatments	
	Follow-up	Commercial name	Centrifugation	Activating agent	Cells	Timing after injury (days)	Number	PRP volume	Location	Hematoma aspiration	Ultrasound guidance	Additional treatments	Rehabilitation
A Hamid et al. [6]	NR	GPS III, Biomet	NR	No	Platelets 1297 × 10^9/L Leukocytes 38.3 × 10^9/L	4.6 ± 1.9	1	3 ml	Intralesional	NR	Yes	Bromelain	Daily home progressive agility and trunk stabilization exercises Booklet and video Once a week rehabilitation session
Bubnov et al. [24]	1, 2, 3, 4 weeks	NR	NR	NR	NR	NR	1	5 ml	NR	Yes	Yes	Anti-inflammatory	General physical therapy

Data are n, range or mean ± SD

NR not reported, *rpm* repetitions per minutes, *min* minutes, *ROM* range of motion, PRP platelet rich plasma

3.5.3 Complications

Only two studies reported at least one complication due to treatment (discomfort at the injection site, hematoma or hyperesthesia in the posterior thigh). The fixed-effect meta-analysis ($I^2 = 0\%$; $p = 1.00$) revealed a non-significant risk difference of 0.01 (95% CI −0.05 to 0.06; $p = 0.84$) (Fig. 4b).

3.5.4 Pain

Five studies evaluated pain during rehabilitation. Two studies reported no differences, while three studies reported significantly better outcomes ($p < 0.05$) in patients treated with PRP, especially in the first 3 weeks (Table 5).

3.5.5 Strength

All four studies that evaluated muscle strength reported no differences between PRP and the control group at the final follow-up. Only Bubnov et al. [24] reported higher strength in patients treated with PRP but only during the first 2 weeks.

3.5.6 ROM/Flexibility

Only two studies evaluated ROM or flexibility. Reurink et al. [15] reported no differences, while Bubnov et al. [24] reported a higher ROM in patients treated with PRP at all the considered time points (1–4 weeks).

3.5.7 Functional Scores

Only Reurink et al. [15] used a subjective score (the Hamstring Outcome Score and Satisfaction) to assess muscle function, reporting no significant differences between patients treated with PRP or isotonic saline injection.

3.5.8 Imaging

No differences in muscle healing were reported both in the two studies that evaluated muscle edema reduction at MRI and in the two studies that evaluated ultrasonographic appearance (Table 5).

3.6 Study Quality and Risk of Bias

Since most of the studies described randomization and allocation concealment correctly, "selection bias" was considered as low risk. "Performance bias" was high risk for the time to return to sport, pain and functional scores, since three studies did not blind the patients to treatment.

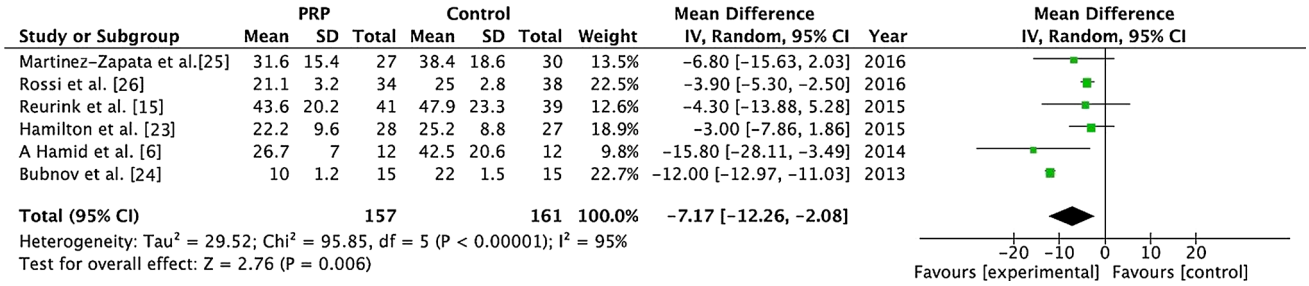

Fig. 2 Pooled mean difference for return to sport for PRP and control interventions. Square size indicates the size of the population investigated in each study; diamond is the estimated pooled effect: width indicates the 95% CI. Data using PPP as control were excluded from the analysis. *PRP* platelet rich plasma, *CI* confidence intervals, *PPP* platelet poor plasma, *IV* inverse variance, *SD* standard deviation

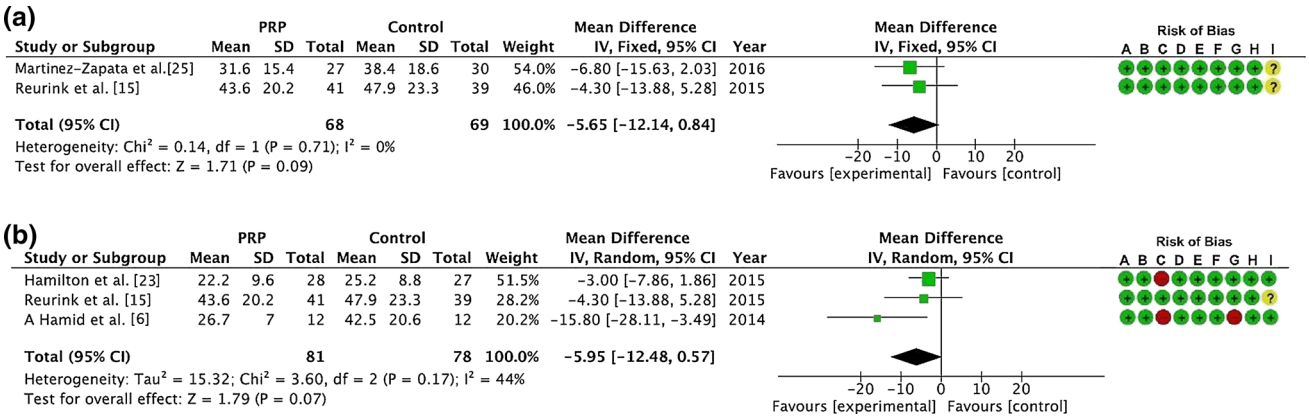

Fig. 3 Sensitivity analysis, the mean difference for return to sport for PRP and control based on double-blind studies only (**a**) and studies including only hamstring injuries (**b**). Square size indicates the size of the population investigated in each study; diamond is the estimated pooled effect: width indicates the 95% CI. Data using PPP as control were excluded from the analysis. Risk of bias: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel for subjective outcomes or (D) objective outcomes (performance bias); (E) blinding of outcome assessment for subjective outcomes or (F) objective outcomes (detection bias); (G) Incomplete outcome data (attrition bias); (H) Selective reporting (reporting bias) and (I) Other bias. *SD* standard deviation, *IV* inverse variance, *CI* confidence intervals, *PRP* platelet rich plasma, *PPP* platelet poor plasma, *RCT* randomized controlled trials

Table 4 Sensitivity analysis according to study patient blinding, muscle involved and control groups

Variable	Time to return to sport				Heterogeneity	
	n	MD	95% CI	*p* value	I^2 (%)	*p* value
Double-blind	2	− 5.65	− 12.14 to 0.84	0.09	0	0.71
Single-blind	4	− 7.75	− 13.82 to − 1.69	0.01*	97	0.00001
Hamstrings	3	− 5.95	− 12.48 to 0.57	0.07	44	0.17
Various locations	3	− 7.69	− 14.51 to − 0.87	0.03*	98	0.00001

MD mean difference, *n* number of studies, *CI* confidence interval

*Statistical significance ($p < 0.05$)

Conversely, performance bias was considered low risk when evaluating re-injury, complications, strength, flexibility, and radiologic features, since these outcomes were not likely affected by the knowledge of the treatment by the patients. Blinding of outcome assessors was reported in all except one study (in which blinding was unclear), resulting in an overall low risk of "detection bias" for all the outcomes. Both "attrition bias" and "reporting bias" were considered low risk due to the limited number of patients lost to follow-up and to the adherence of outcome reporting to study protocols (Fig. 5). Only Hamid et al. [6] reported a drop-out rate of 14% in both groups. Finally, a high risk of other bias was present in the study by Bubnov et al. [24], due to the inadequate comparison of patient populations and imprecise descriptions of PRP preparation, while the risk was unclear in the study by Martinez-Zapata et al. [25], due to the late PRP injection (mean 14 days) (Fig. 6).

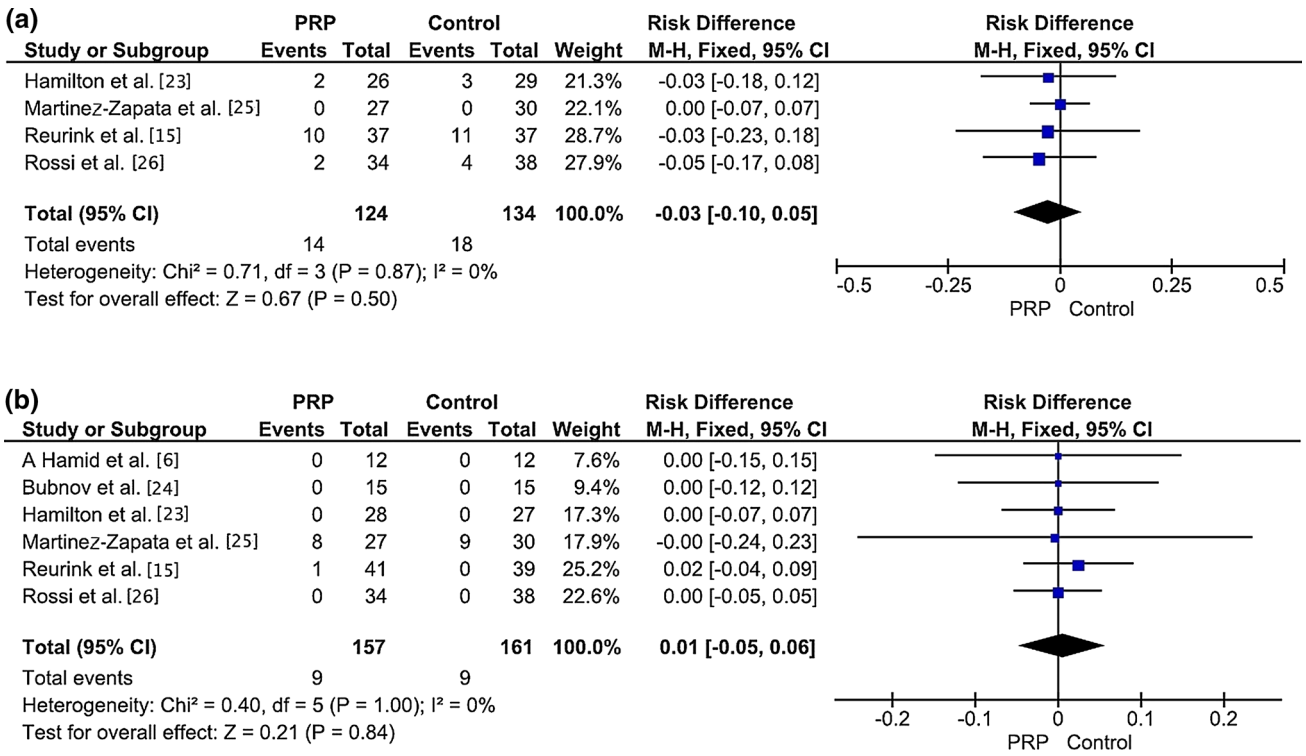

Fig. 4 Pooled risk difference for re-injury (a) and complications (b) for PRP and control interventions. Square size indicates the size of the population investigated in each study; diamond is the estimated pooled effect: width indicates the 95% CI. Data using PPP as control were excluded from the analysis. *PRP* platelet rich plasma, *PPP* platelet poor plasma, *M-H* Mantel–Haenszel, *CI* confidence intervals

Due to the presence of these biases and the limited number of studies and patients for most outcomes, the overall quality of evidence according to the GRADE guidelines for time to return to sport, pain, strength, flexibility, muscle function and muscle healing (through radiologic outcomes) was rated as low or very low (Fig. 7). Other issues that contributed to the lack of high evidence quality were the high statistical heterogeneity or the conflicting results in the studies and the indirect evaluation of muscle healing. However, if considering only double-blind studies, the evidence for the lack of significant difference in the time to return to sport could be considered of moderate quality, due to the lack of performance bias, and limited heterogeneity. Finally, due to the low risk of performance bias for re-injury and complication outcomes, the evidence of similar outcomes between PRP and control could be considered moderate as well.

4 Discussion

The main finding of this meta-analysis is that the current evidence from the available studies with the highest quality does not support the hypothesis that the use of PRP injections promotes muscle healing and return to sport, due to the moderate quality of evidence of no significant differences between PRP and control group. Conversely, considering all the six RCTs included in the review, the time to return to sport was significantly shorter after PRP application. However, due to the bias in these studies analyzed overall, the heterogeneity of the findings and the limited sample size, the evidence of this finding should be regarded as very low quality according to the GRADE guidelines.

No statistically significant superiority for PRP in any of the other evaluated outcomes could be proven by this meta-analysis. Nonetheless, several aspects, which may influence the study results, still deserve to be discussed. The first is the quality of the studies themselves. In fact, among the selected RCTs, high quality variability could be detected. This is not of secondary importance, since a direct correlation between low meta-analysis quality and positive results has been demonstrated in the literature [27], as confirmed by this study. In fact, when considering all the RCTs, return to sport was statistically faster with PRP, but this result was not confirmed when the analysis excluded unblinded studies (Fig. 3). These findings do not currently justify the use of PRP, but they should still be interpreted as a demonstration of the need for a larger number of high-quality trials, rather than a definitive demonstration of lack of potential for the PRP strategy. In fact, despite the lack of significance for both blinded studies and studies evaluating

Table 5 Results of the different outcomes of each included study

Study	Return to sport				Re-injury			Complications		Other outcomes				
	Definition	Return to sport	PRP (days) [mean ± SD]	Control (days) [mean ± SD]	Definition	PRP	Control	PRP	Control	Pain	Strength	Flexibility/ ROM	Functional scores	Imaging
Rossi et al. [26]	Unrestricted sporting activities once full ROM, strength and functional abilities can be performed without complaints of pain or stiffness	Shorter with PRP	21.1 ± 3.2	25.0 ± 2.8	Strain with clinical symptoms in a previously injured muscle as tenderness to palpation within the muscle–tendon unit, pain with resisted motion, or limitation of daily/sports activity	2/34	4/38	0	0	Lower pain at rest and resisted motion with PRP (all time points)	NR	NR	NR	NR
Martinez-Zapata et al. [25]	Return to usual pre-injury activities with absence of pain when walking, jumping or practicing sports	No differences	31.6 ± 15.4	38.4 ± 18.6	Relapse of symptoms (pain, functional disability) and confirmation of a change in the previously injured area by US	0/27	0/30	6 discomfort 1 hematoma	1 discomfort 7 hematoma	No differences (all time points)	NR	NR	NR	No difference in US parameters
Reurink et al. [15]	Return to unrestricted sports activity in training and/or match play	No differences	43.6 ± 20.2	47.9 ± 23.3	Acute onset of posterior thigh pain that occurred on the same side as the initial injury and caused absence from sport	10/37	11/37	1 hyperesthesia posterior thigh	0	No differences (all time points)	No differences	No differences	No difference (hamstring outcome score and satisfaction)	No difference in MRI edema at return to sport

Table 5 continued

Study	Return to sport				Re-injury			Complications		Other outcomes				
	Definition	Return to sport	PRP (days) [mean ± SD]	Control (days) [mean ± SD]	Definition	PRP	Control	PRP	Control	Pain	Strength	Flexibility/ ROM	Functional scores	Imaging
Hamilton et al. [23]	Completion of the full rehabilitation program (no symptoms, isokinetic evaluation, clinical evaluation)	No differences	22.2 ± 9.6	25.2 ± 8.8	Acute hamstring strain injuries at the same site, occurring within either two or 6 months from return to sport	2/26	3/29	0	0	NR	No differences	NR	NR	No differences in MRI edema decrease
A Hamid et al. [6]	Return to sport based on clinical sports medicine recommendations (pain- free, symmetrical ROM, concentric strength > 90% of healthy side)	Shorter with PRP	26.7 ± 7.0	42.5 ± 20.6	NR	NR	NR	0	0	Less pain with PRP (all time points)	No differences	NR	NR	NR
Bubnov et al. [24]	Physical recovery, movement volume and the ability to practice sport	Shorter with PRP	10 ± 1.2	22 ± 1.5	NR	NR	NR	0	0	Greater pain relief with PRP at one to 3 weeks. No differences at 4 weeks	Greater strength with PRP at one to 2 weeks. No differences at 4 weeks	Higher ROM with PRP at 1–4 weeks.	NR	Improved US healing with PRP at 2 weeks. No differences at 3–4 weeks

NR not reported, *SD* standard deviation, *ROM* range of motion, *PRP* platelet rich plasma, *PPP* platelet poor plasma, *MRI* magnetic resonance imaging, *US* ultrasound, *Inj* injection

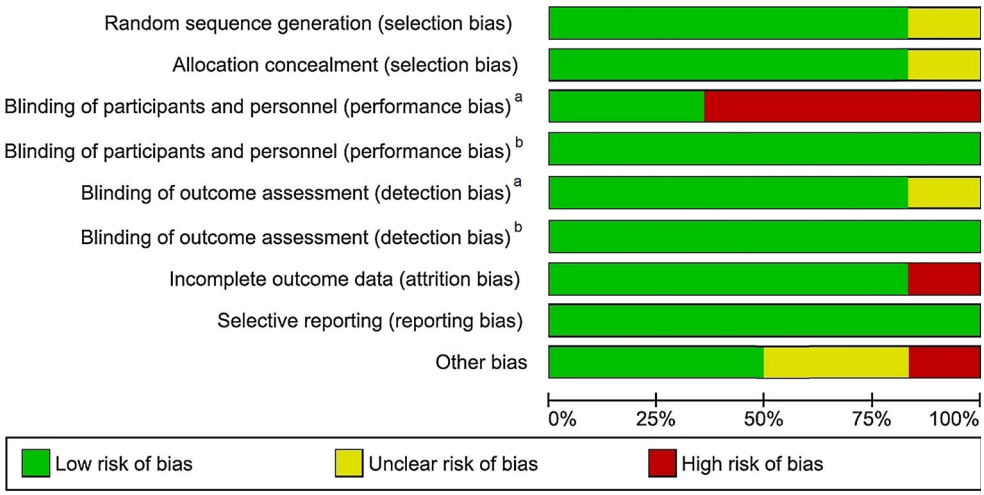

Fig. 5 Risk of bias summary table, with red as high risk of bias, green as low risk of bias and yellow as unclear risk of bias. [a]Bias referred to outcomes that could have been affected by the patient's knowledge of the type of treatment (time to return to sport, pain and functional scores). [b]Bias referred to outcomes that were reputed independent from treatment knowledge of the type of treatment (time to return to sport, pain and functional scores outcomes)

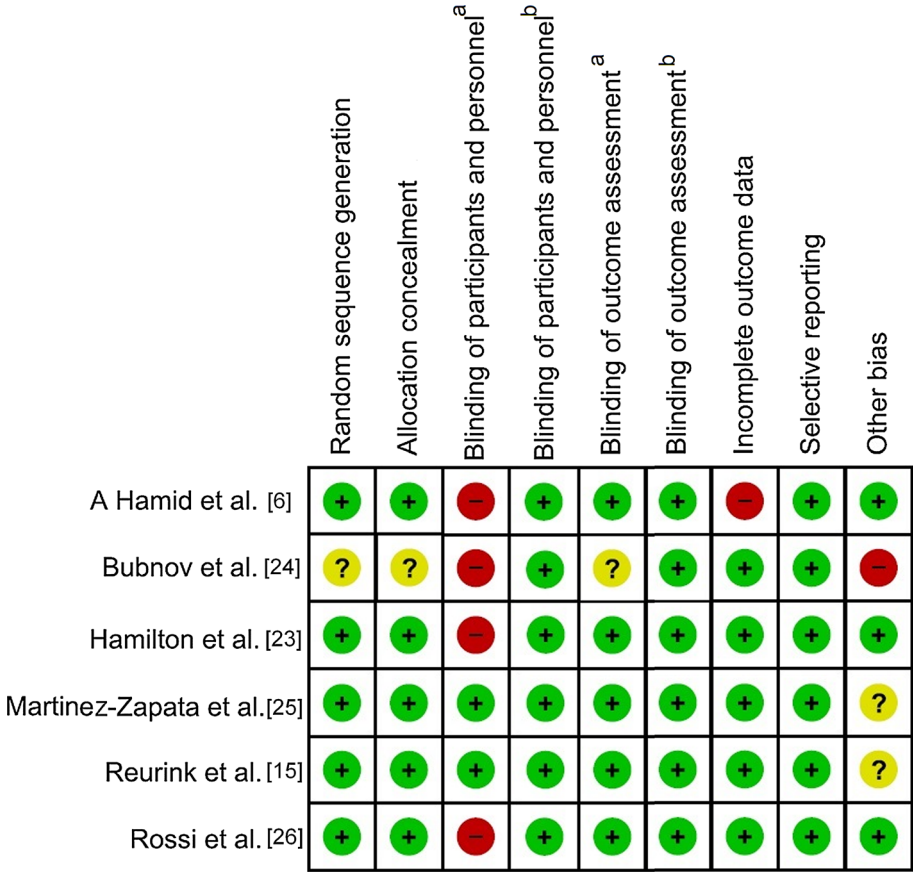

Fig. 6 Risk of bias in each study, considered as high (red), low (green) or unclear (yellow). [a]Bias referred to outcomes that could have been affected by the patient's knowledge of the type of treatment (time to return to sport, pain and functional scores). [b]Bias referred to outcomes that were reputed independent from treatment knowledge of the type of treatment (time to return to sport, pain and functional scores outcomes)

only hamstring muscles, in both cases the confidence intervals of the mean difference between the groups contained both the null value and a value of 7 days which could be considered of important clinical relevance, especially for athletes. Therefore, this allows the possibility of different results in the future, when more high-quality studies enable the evaluation of a larger number of patients. In addition to the small number of patients documented to date, the current literature also presents other important limitations, such as the heterogeneity of the studies in terms of patients enrolled, lesion degree and location, type of PRP and administration protocol, as well as treatment timing and associated rehabilitation protocol.

Patients were included according to different criteria, with the mean age ranging from 20 to 46 years and their activity level ranging from professional athletes to non-competitive sport. Only three studies selected a specific muscle group, while the others included different muscle

PRP vs Conventional Treatment for Acute Muscle Injuries

Bibliography:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional Treatment	Risk difference with PRP
Return to Sport (Double-blind studies) assessed with: See definitions	137 (2 RCTs)	⨁⨁⨁◯ MODERATE a	Not significant MD		
Return to sport (All studies) assessed with: See definitions	318 (6 RCTs)	⨁◯◯◯ VERY LOW b,c	Overall shorter return to sport in PRP group.		
Re-injury assessed with: See definitions	124 (4 RCTs)	⨁⨁⨁◯ MODERATE d	Not significant RR		
Complications\Adverse events assessed with: See definitions	318 (6 RCTs) a,d,e	⨁⨁⨁◯ MODERATE e	Not significant RR		
Pain assessed with: Subjective scale, clinical examination	263 (5 RCTs)	⨁◯◯◯ VERY LOW b,f,g,h	No differences of pain at final follow-up. Possible benefit of PRP during the first 3 weeks.		
Strength assessed with: Isokinetic machine, clinical evaluation	189 (4 RCTs)	⨁⨁◯◯ LOW g,h	No differences in strength at all follow-ups.		
Range of Motion\Flexibility assessed with: Clinical evaluation	110 (2 RCTs)	⨁◯◯◯ VERY LOW f,g,h	Possible increased ROM during the first 4 weeks.		
Subjective muscle function assessed with: Hamstring Outcome Score	80 (1 RCT)	⨁◯◯◯ VERY LOW i,j	No differences in muscle function.		
Muscle healing assessed with: Ultrasound or Magnetic Resonance	222 (4 RCTs)	⨁⨁◯◯ LOW g,h	No differences in muscle healing at imaging.		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Imprecision because Confidence Intervals included the null value
b. High risk of performance bias due to an outcome affected by unblinded patients
c. Very high statistical heterogeneity (I2>90%)
d. Imprecision because the Optimal Information Size for this outcome is not met (n = 4144)
e. Imprecision because the Optimal Information Size for this outcome is not met (n = 7492)
f. Studies with conflicting results
g. Different measurement methods for this outcome
h. Included studies underpowered for this outcome
i. Muscle function measured through a subjective score.
j. Only the study of Reurink et al. [15] considered for this outcome.

◀**Fig. 7** Summary of findings table, with quality of evidence rated according to the GRADE guidelines. *RCT* randomized controlled trial, *PRP* platelet rich plasma, *ROM* range of motion, *GRADE* Grading of Recommendations Assessment, Development and Evaluation

groups. Differences can also be found in lesion degree and chronicity, since the mean time from injury to PRP injection was up to 14 days. The latter is not a secondary consideration, since the timing of administration may dramatically change the effect of the applied GFs on the healing process. The muscle repair process involves two competing processes: the production of a connective tissue scar and the regeneration of disrupted muscle fibers [28]. Injury causes the disruption of muscle fibers and hemorrhage, followed by the extravasation of inflammatory cells leading to some degree of inflammation, which is required to remove necrotic muscle fibers and allow scar tissue to bridge the defect [29]. Activation of platelets also occurs early in the lesion area, where they help to orchestrate the healing process before the fibrosis phase begins. This occurs from 2 to 3 weeks after injury, when PRP could even be theoretically contraindicated, due to the presence of TGF-B, which may promote further fibrosis over regeneration [30]. Injections should therefore preferably be administered before this phase, as occurred in most but not all of the studies, although evidence that allows more accurate targeting of the window of benefit for PRP is still lacking. Analogously, the presence and amount of hematoma, its evacuation, the volume of PRP injected with respect to the damaged area due to its physical interaction with the disrupted fibers, as well as the containment of PRP in the injected area, are all factors that may jeopardize the local healing effect. In this context, activation of PRP is not always performed and some products rely on in situ, slow collagen-induced activation, which may influence molecular release and the biological effect on the one hand and the timing of gel formation on the other, which in turn may affect the physical interaction with the issue and the likelihood of confining GF secretion to the treated site [10].

One key element of heterogeneity, which is pivotal in PRP research in all fields, is the nature of the platelet concentrate itself. In fact, the abbreviation PRP is an umbrella for countless products, all differing in terms of a large number of variables, first and foremost cellularity and the number of platelets. A larger number of platelets may offer a higher concentration of GFs, which might help to recruit stem cells promoting a stronger healing response. On the other hand, the most locally effective dose of each GF and their combination is a long way from being understood and the scientific discussion relating to the optimal platelet concentration remains merely speculative. The same applies to leukocytes, monocytes, macrophages, and other cells that may be present in variable proportions according to the procedure used to obtain PRP. In particular, a great deal of attention is being focused on the possible negative effects of leukocytes, with in vitro studies showing deleterious effects in terms of inflammation and matrix molecule formation/degradation [11]. Nonetheless, in vitro studies may offer only a partial understanding of the role of these cells, especially in terms of muscle lesions, where some degree of inflammation is necessary in the early phase and where these cells may contribute to GF release and chemotaxis and, in the end, to the overall healing process [11, 29]. While the discussion relating to the best PRP formulation is still open, research efforts are focusing on a more targeted PRP use for muscle, such as the combined use of antifibrotic agents, where the rationale is to limit fibrosis in favor of the regeneration process, with preliminary promising findings [31].

Regardless of the PRP applied, the analysis of the available studies also revealed significant heterogeneity in terms of the mean time to return to sport between studies, which ranged from 10 to 42 days. This may be explained by the different patient populations that were treated, the different rehabilitation protocols applied, the involvement of a physical therapist and different criteria relating to the decision to return to unrestricted activities. Specific protocols have been shown to be able to influence the recovery time [32] and intensive rehabilitation remains a critical element for a successful RTS after muscle injury [23].

This study has some limitations. First of all, the limited number of studies and patients included in the meta-analysis clearly reduces the overall quality of its evidence and could possibly cause several outcomes not to reach statistical significance in the event of a true positive effect. However, the complex study design, with mandatory randomization and multiple blinding, only enables the performance of studies of this kind in high-volume selected centers in a multicentric fashion. Another important limitation that should be underlined, in addition to the heterogeneity of PRPs and populations, is the inhomogeneous reporting of the results. Even if we had been able to obtain missing mean and SD data from the authors through correspondence, use of a parametric test could be questioned due to the not-normal distribution of the time to return to sport. A meta-analysis of hazard ratios could have been more appropriate; however, it was not possible to obtain this outcome for all the studies or to extrapolate it from surrogate data. This could have introduced a bias in the statistical analysis that could have changed the significance of the results. Therefore, extreme care should be taken when interpreting the results of this meta-analysis, taking account of this statistical limitation. Moreover, the different methods that were used to investigate pain,

strength, flexibility and muscle imaging did not enable statistical pooling of these outcomes. Finally, a limitation is represented by the lack of pre-registration to systematic review databases such as PROSPERO. However, while we acknowledge that this practice should be encouraged in future works (especially for the adherence of results to the pre-determined study protocol), the sub-group and sensitivity analysis in the present work were planned a priori.

Despite the aforementioned limitations, this meta-analysis still makes it possible to identify important findings. PRP treatment is a safe procedure, as the studies reported only negligible adverse effects, but, in terms of efficacy, the current literature does not support its use for muscle injuries. Its large and indiscriminate use in clinical practice is not justified and PRP injections should be reserved for controlled trials, until positive evidence emerges and suggests otherwise. Further studies are needed, both to strengthen the evaluation of the different PRPs and to investigate more appropriate delivery methods, as well as identifying the more responsive clinical targets. As shown for other PRP applications in the musculoskeletal system [33], PRP has a large placebo effect and future studies should ensure correct blinding procedures to understand its real potential. Homogeneous populations, satisfactory randomization, the precise description of PRP characteristics and the precise reporting of the results, possibly with several measurements of dispersion (standard deviation, standard error and confidence intervals), should be other mandatory features of future studies. Moreover, imaging evaluations of the repair tissue and clinical evaluations of patient symptoms and function should be documented both in the early stages, which are crucial for athletes aiming for a quick return to sport, and also in the long-term, to document whether tissue modifications may lead to a reduction in the recurrence of muscle injury.

5 Conclusion

Recent high-level trials with a moderate GRADE quality level of evidence do not confirm the promising biological rationale, the positive preclinical findings, and the successful early clinical experience with PRP injection. In fact, while the time to return to sport was significantly shorter after PRP application considering all the six RCTs included in the review with overall low-quality evidence, when considering only double-blind studies the evidence for the lack of significant difference could be considered of moderate quality. Therefore, any benefit in terms of clinical outcomes, return to sport, and recurrence using PRP injections for the treatment of acute muscle injuries is not supported by the available literature. PRP treatment showed negligible adverse effects, but its application in clinical practice is not justified, and PRP use should be limited to controlled trials until more positive evidence emerges and suggests otherwise.

Author Contributions Alberto Grassi, Francesca Napoli and Iacopo Romandini performed a database search, reviewed the articles and were responsible for data collection. Alberto Grassi performed an analysis of the results. Giuseppe Filardo and Alberto Grassi wrote the paper and critically evaluated the results. Kristian Samuelsson, Stefano Zaffagnini, and Christian Candrian critically reviewed and edited the manuscript.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this article.

Conflict of interest Alberto Grassi, Francesca Napoli, Iacopo Romandini, Kristian Samuelsson and Christian Candrian declare that they have no conflicts of interest relevant to the content of this review. Giuseppe Filardo has worked in the platelet-rich plasma field for the past 10 years with no sponsorship. Recently, his institution received support for studying injective agents in osteoarthritis (not in a muscle-related field). This author declares no personal conflicts of interest of direct relevance to the content of this review. Stefano Zaffagnini receives personal fees from Smith and Nephew and DePuy, outside this work, and declares no conflicts of interest relevant to the content of this review.

References

1. Ekstrand J, Hagglund M, Walden M. Epidemiology of muscle injuries in professional football (soccer). Am J Sports Med. 2011;39(6):1226–32.
2. Orchard J, Best TM, Verrall GM. Return to play following muscle strains. Clin J Sport Med. 2005;15(6):436–41.
3. Heiderscheit BC, Sherry MA, Silder A, et al. Hamstring strain injuries: recommendations for diagnosis, rehabilitation, and injury prevention. J Orthop Sports Phys Ther. 2010;40(2):67–81.
4. Ueblacker P, Haensel L, Mueller-Wohlfahrt HW. Treatment of muscle injuries in football. J Sports Sci. 2016;34(24):2329–37.
5. Assis L, Moretti AI, Abrahao TB, et al. Low-level laser therapy (808 nm) contributes to muscle regeneration and prevents fibrosis in rat tibialis anterior muscle after cryolesion. Lasers Med Sci. 2013;28(3):947–55.
6. Ms AH, Mohamed Ali MR, Yusof A, et al. Platelet-rich plasma injections for the treatment of hamstring injuries: a randomized controlled trial. Am J Sports Med. 2014;42(10):2410–8.
7. Creaney L, Hamilton B. Growth factor delivery methods in the management of sports injuries: the state of play. Br J Sports Med. 2008;42(5):314–20.
8. Cole BJ, Seroyer ST, Filardo G, et al. Platelet-rich plasma: where are we now and where are we going? Sports Health. 2010;2(3):203–10.
9. Filardo G, Kon E, Roffi A, et al. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. Knee Surg Sports Traumatol Arthrosc. 2015;23(9):2459–74.
10. Cavallo C, Roffi A, Grigolo B, et al. Platelet-rich plasma: the choice of activation method affects the release of bioactive molecules. Biomed Res Int. 2016;2016:6591717.

11. Filardo G, Di Matteo B, Kon E, et al. Platelet-rich plasma in tendon-related disorders: results and indications. Knee Surg Sports Traumatol Arthrosc. 2016. https://doi.org/10.1007/s00167-016-4261-4.
12. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthroscopy. 2012;28(7):998–1009.
13. Torricelli P, Fini M, Filardo G, et al. Regenerative medicine for the treatment of musculoskeletal overuse injuries in competition horses. Int Orthop. 2011;35(10):1569–76.
14. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27(3):158–67.
15. Reurink G, Goudswaard GJ, Moen MH, et al. Rationale, secondary outcome scores and 1-year follow-up of a randomised trial of platelet-rich plasma injections in acute hamstring muscle injury: the Dutch Hamstring Injection Therapy study. Br J Sports Med. 2015;49(18):1206–12.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
17. Higgins JPTAD, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). London: The Cochrane Collaboration; 2011.
18. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
19. Higgins JPTDJ, Altman DG. Special topics in statistics. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. London: The Cochrane Collaboration; 2011.
20. Deeks JJHJ, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). London: The Cochrane Collaboration; 2011.
21. Ms AH, Mohamed Ali MR, Yusof A, et al. Platelet-rich plasma (PRP): an adjuvant to hasten hamstring muscle recovery. A randomized controlled trial protocol (ISCRTN66528592). BMC Musculoskelet Disord. 2012;13:138.
22. Reurink G, Goudswaard GJ, Moen MH, et al. Platelet-rich plasma injections in acute muscle injury. N Engl J Med. 2014;370(26):2546–7.
23. Hamilton B, Tol JL, Almusa E, et al. Platelet-rich plasma does not enhance return to play in hamstring injuries: a randomised controlled trial. Br J Sports Med. 2015;49(14):943–50.
24. Bubnov R, Yevseenko V, Semeniv I. Ultrasound guided injections of platelets rich plasma for muscle injury in professional athletes. Comparative study. Med Ultrason. 2013;15(2):101–5.
25. Martinez-Zapata MJ, Orozco L, Balius R, et al. Efficacy of autologous platelet-rich plasma for the treatment of muscle rupture with haematoma: a multicentre, randomised, double-blind, placebo-controlled clinical trial. Blood Transfus. 2016;14(2):245–54.
26. Rossi LA, Molina Romoli AR, Bertona Altieri BA, et al. Does platelet-rich plasma decrease time to return to sports in acute muscle tear? A randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2016. https://doi.org/10.1007/s00167-016-4129-7.
27. Serner A, van Eijck CH, Beumer BR, et al. Study quality on groin injury management remains low: a systematic review on treatment of groin pain in athletes. Br J Sports Med. 2015;49(12):813.
28. Drezner JA. Practical management: hamstring muscle injuries. Clin J Sport Med. 2003;13(1):48–52.
29. Almekinders LC, Gilbert JA. Healing of experimental muscle strains and the effects of nonsteroidal antiinflammatory medication. Am J Sports Med. 1986;14(4):303–8.
30. Huard J, Li Y, Fu FH. Muscle injuries and repair: current trends in research. J Bone Joint Surg Am. 2002;84(5):822–32.
31. Li H, Hicks JJ, Wang L, et al. Customized platelet-rich plasma with transforming growth factor beta1 neutralization antibody to reduce fibrosis in skeletal muscle. Biomaterials. 2016;87:147–56.
32. Sherry MA, Best TM. A comparison of 2 rehabilitation programs in the treatment of acute hamstring strains. J Orthop Sports Phys Ther. 2004;34(3):116–25.
33. Filardo G, Kon E. PRP: product Rich in Placebo? Knee Surg Sports Traumatol Arthrosc. 2016;24(12):3702–3.