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Interest of platelet rich plasma in Achilles tendon rupture management: a systematic review

Running title: Platelet rich plasma in Achilles Tendon Rupture management

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Abstract

Objectives: Acute Achilles tendon rupture (ATR) is a disabling sport-related injury. Its management involves conservative treatment with early weight-bearing or surgical treatment. Platelet-rich plasma (PRP) has raised interest as an adjuvant for treatment, given its properties on tendon repair and its anti-inflammatory effect. We aimed to assess clinical impact of PRP use in surgical or non-surgical treatment of acute ATR: range of motion, muscle strength, function, return to sport and adverse events.

Method: A systematic literature research was performed using PubMed, ScienceDirect, and Google Scholar databases to collect studies reporting clinical outcomes after acute ATR treated with PRP.

Results: Eight studies were eligible and included 543 acute ATR. Four were randomized comparative studies. A total of 128 patients were treated surgically and 415 were treated conservatively, 271 received PRP injection. Five studies described the type of PRP used, which was variable. Only one study including 12 patients found significant outcomes in favor of the PRP group, with a 4-week earlier recovery of a normal range of motion and a 7-week earlier return to running. No difference in clinical or morphological evaluations, strength measurement, and functional outcomes was found in other studies both at short and long-term. PRP did not seem to modify the frequency of adverse events.

Conclusions: Data are not clearly in favour of a significant effect of the PRP use for treatment of ATR. There might be a slight effect on evolution during the first months. Its interest should be assessed in future studies with strong methodology.

Keywords: Achilles tendon rupture; Achilles tendon tear; Platelet-rich plasma; Platelet-rich product.

Introduction

Achilles tendon rupture (ATR) is a common injury, occurring in 65 to 78.5% of cases during sport practice [1,2]. It mainly concerns males from 54 to 95% of the injured athletes with a mean age around 40 [1–3]. Its incidence increases with age due to tendon tissue aging, especially in case of participation in high-demanding sport practice, such as basketball, soccer, racket sports [1–4]. ATR is a disabling injury that prevents 24% of professional athletes to return to sport at their previous level one year after injury [5]. ATR management can either be surgical or non-surgical and remains controversial [6–8]. Platelet rich plasma (PRP) is an autologous, whole blood product developed in the 1970s. It provides a supra-physiological concentration of platelets, leukocytes, growth factors, and other bioactive proteins such as cytokines and chemokines for delivery to an injury site. In vitro and in vivo studies showed that growth factors present in PRP and PRP-products, exert biological effects on tendon repair, with proliferative [9,10], anti-inflammatory [10] and biomechanical properties [11,12]. Therefore, its interest has been suggested in the management of bone, cartilage, tendon and muscle injuries [13]. Recent studies have enhanced the interest of PRP in tendon and ligament pathologies, especially in partial rotator cuff tear [14]. However, no benefit has been clearly shown in chronic Achilles tendinopathy [15]. In a systematic review, Filardo et al [16] assessed the use of PRP in tendon-related disorders and more specifically Achilles tendon rupture. They concluded in the absence of interest of PRP as an adjuvant of surgical repair. Yet, several recent studies suggested a benefit of the PRP use in ATR with operative or non-operative treatment [17–21].

In this systematic review we aimed to assess functional outcomes, especially return to sport after the use of PRP and PRP products in operative and non-operative management of patients with ATR.

Material and methods

Literature search

We searched articles in the medical databases: PubMed, ScienceDirect and Google Scholar in February 2021. We also searched articles in Embase and Cochrane libraries in June 2021.

Article research extended from January 2000 to December 2020. Only comparative studies in English language including 2 or more cases on humans were selected. Due to the demographics of ATR, inclusion was limited to adults. Multiple searches were carried out using the following MeSH: (« Achilles tendon rupture» OR« Achilles tendon tear”) AND (« PRP » OR “Platelet-rich plasma” OR “platelet-rich fibrin”). The search was performed independently by 2 assessors (PD, AFC) to assess titles and abstracts of potentially relevant articles, and then the full-text articles were retrieved. In case of doubt, a third assessor’s advice was asked (MD). All relevant articles were read independently in full text by the two researchers (PD, AFC) to assess if the articles met the inclusion criteria. After identification of key articles, their references and citation lists were also hand searched for further information sources. Reviews and meta-analysis were also analyzed, in order to broaden the search for studies that might have been missed through the electronic search.

Eligibility criteria

The inclusion criteria were: controlled study of more than 2 cases of isolated and complete Achilles tendon rupture, with operative or non-operative treatment, associated with PRP or PRP-products, in patients over 18 years old. Studies had to compare at least two groups of injured patients. Exclusion criteria were partial ATR or major leg injury. All types of PRP

were considered, and all types of management of ATR, surgical or non-surgical treatment, were considered.

Data extraction

All the included studies were analyzed, and data were extracted and summarized in tables using Microsoft Excel (version 2013, Microsoft Corporation, Redmond, WA, USA): study design, year of publication, type of treatment and reported outcomes. Data were extracted independently by two authors subsequently after all the eligible studies were recruited.

Quality analysis

We used PRISMA guidelines for this review [22]. The included studies were critically appraised using GRADE approach, in order to evaluate the study quality of evidence [23]. This approach classifies the quality of evidence in one of four levels: high, moderate, low and very low. Evidence based on randomized controlled trials begins as “high quality” evidence, but the strength of our confidence in the evidence might decrease due to study limitation, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. On the opposite, observational studies start with a “low quality” rating, grading upwards if the effect is very large, if there is evidence of a dose-response relationship or if all plausible biases decrease the magnitude of an apparent treatment effect.

Results

Study selection

Our research found 788 results. Out of these records, we retained 49 articles by title. After removing duplicates and reading abstracts, 8 articles were assessed for full-text reading. We excluded one of them [24] because it studied the interest of PRP injection in chronic Achilles tendon tear with no control group. One relevant article was included via another source [21]. We finally included 8 original articles representing 543 patients [18–21,25–28]. PRISMA flowchart summarizes the search strategy for this systematic review (fig 1). The articles were all series of cases with sample sizes from 12 to 230 patients with unilateral acute ATR. All studies were monocentric, except that of Keene et al. [19] which included patients from 19 distinct hospitals. Alviti et al. [21] studied three groups: patients who underwent surgery with adjuvant treatment with platelet-rich fibrin (PRF), patients who underwent surgery without PRF, and healthy controls. In our study we excluded the group of healthy subjects.

Demographic data

Finally, our review assessed 543 patients (table 1). Mean age ranged from 29 to 46 years. Eighty-two percent were males. All of them had unilateral ATR. Ruptures occurred from 58 to 100% of cases during sport practice [21,25]. In two studies including 30 and 20 patients, the percentage of sport-related ruptures was not specified [21,25].

Quality analysis of the included studies is reported in table 2.

Diagnosis and treatment

Diagnosis can easily be made on clinical findings with a palpable gap and a positive Thompson test. Yet, some authors proposed a systematic imaging assessment with MRI or ultrasound to confirm the diagnosis [18,25,27].

Treatment was initiated after acute ruptures. Two-hundred-seventy-one patients received at least one PRP injection. Treatment was operative in 5 studies including 128 patients, in which 64 received PRP [20,21,25,27,28], and non-operative in 3 studies including 415 patients, in which 207 received PRP [18,19,26]. The number of PRP administrations ranged from one to four [18,19]. The type of PRP products was variable. Only five studies described its composition [19,20,26–28], which ranged from 2 to 6 times higher platelet concentration than in blood [19,20,26,27], to even 17 times higher than blood for Schepull et al[28]. Alvit and Sanchez used platelet-rich-fibrin, the middle-layer during centrifugation, after being activated, was mixed with jellifying agents, an enzyme that cleaves fibrin peptide, to induce polymerization [21,27]. The final product has the density of the fibrin matrix and is applied over the suture site as fibrin glue. De Carli et al. used both liquid and jellified PRP [25]. Boesen describes an ultrasound-guided injection [18].

Leukocyte concentration in PRP remains an active debate. Some studies suggested leukocyte-rich PRP to be of better efficacy [29,30], while others highlighted the pro-inflammatory and catabolic effect on tendons exerted by white blood cells [10,31]. However, most studies used leukocyte-rich PRP [18–21,25,26]. Two studies described its concentration, ranging from 2 to 4 times higher than leukocytes concentration in plasma [19,20], while Sánchez et al. used a leukocyte-free PRP product [27]. The volume of PRP injected also varied from 3 to 10 ml, as described in table 3.

Various centrifuges were used in the studies: Keene et al. [19] used a Magellan Autologous platelet separator (Arteriocyte medical systems, MA), while Zou et al. [20] used a WEGO platelet rich plasma preparation kits (WEGO Ltd., Shandong, China), De Carli et al. used a MyCells® Autologous Platelet Preparation System (Kaylight LTD, Ramat-Hasharon, Israel) [25], Sánchez et al used a PRGF System II (BTI, Vitoria-Gazteiz, Spain) [27], Kaniki et al. used a Rotafix 32A centrifuge (Hettich, Tuttlingen, Germany)[26]. Some studies did not

report the centrifuge used [18,21,28] . In their studies, Schepull et al. [28] had to store their PRP overnight before injection, which may have led to less efficacy. Protocols for centrifugation also differed, as reported in Table 3.

After ATR diagnosis and surgical or non-surgical management, the non-bearing duration was not consensually proposed. Boesen et al. [18] and Schepull et al. [28] considered early weight-bearing according to the patients' tolerance. Zou et al. [20] proposed a 6-week non-bearing period while other authors advocated for 2 or 3 weeks of non-bearing [19,26,27]. Whether they had early weight-bearing or initial non-bearing, patients were all immobilized in a removable cast, for a duration that extended up to 9 weeks [20]. Total immobilization time is summarized in table 3. Keene et al. [19] promoted an immobilization of not more than 6 weeks and two other studies left the immobilization at therapist's discretion [26,27].

Clinical evaluation

The ankle range of motion (ROM) was assessed in 5 studies [18,20,26–28]. Only Sánchez et al. [27] found a significant difference between groups: athletes who received PRP recovered earlier full ankle ROM (7.0 +/- 2.0 weeks versus 11.0 +/- 3.0 weeks, $P=0.03$). The other studies found no statistical difference concerning ankle ROM between the PRP groups and the control groups [18,20,26,28].

The calf circumference had been assessed by Boesen et al., who found a decrease of the amyotrophy in both groups over time, with no difference between those groups [18]. At one year, both groups still had significant asymmetrical calf circumferences compared to healthy sides. Other studies found similar results with evaluations extending to two years post rupture

[20,26,28]. However, the relation between calf circumference and muscle strength is weak after ATR [32].

Strength assessment

Boesen et al [18], Keene et al [19], and Schepull et al [28], used the heel-rise-test, a strength test which is commonly used to evaluate muscle function in ATR [33]. All the patients had improved their results with time and no difference was seen between the PRP and the control groups in the measures related to the heel rise endurance test.

In their surgical series, Zou et al. [20] performed isokinetic measurement to assess strength recovery after ATR. They found a significant superior limb symmetry index in PRP group for plantar flexion strength and dorsiflexion strength at 60, 120 and 240°/s 3 months after surgery. The limb symmetry index for the plantar flexion was measured at 68.8% +/- 3.3 vs 64.2 % +/- 7.0 at 60°/s ($p=0.022$), 66.1% +/- 2.9 vs 62.8% +/- 5.5 at 120°/s ($p=0.043$), and 67.8% +/- 5.5 vs 61.4% +/- 9.2 at 240°/s ($p=0.021$), for the PRP group and the control group, respectively. The limb symmetry index for the dorsiflexion strength at 3 months was measured at 69.7% +/- 4.0 vs 65.6 % +/- 6.6 at 60°/s ($p=0.035$), 67.9% +/- 4.4 vs 63.0% +/- 5.3 at 120°/s ($p=0.006$), and 67.9% +/- 4.1 vs 61.4 % +/- 3.2 at 240°/s ($p<0.001$), for the PRP group and the control group, respectively. However, one of the limits in their study is that they used different surgical techniques depending on the groups. In the control group the ruptured tendon was debrided before end-to-end repair whereas in the PRP group no debridement was performed in order to maintain tendon length. There was also a lack of power, with only 36 patients included. At 6-month follow-up both groups were similar.

In their surgical series, De Carli et al. found no difference between the group with PRP and the group without, six months after surgery, at both 60°/s and 120°/s of angular speed for the

peak torque and peak torque/weight [25]. Kaniki et al. [26] reported no significant difference at 1 and 2 years after non-surgical management at 30, 60 and 240°/s for plantar flexion strength.

Functional evaluation

Squat jump (SJ) and Countermovement jump (CMJ) are important parameters for the evaluation of sport-active patients, used as a predictor of maximal running velocity [34]. However, De Carli et al. [25] showed no difference in jumping bipodal and monopodal SJ and CMJ. Alviti and al. [21], in their surgical series, appraised gait analysis, and found no difference in mean walking speed, cadence and swing speed in PRP and non-treated PRP patients after ATR at six months.

Tendon trophicity

Tendon length after an acute ATR is correlated to strength and power [35]. Boesen et al. [18] evaluated tendon length with ultrasonography at 8 weeks (at the end of immobilization) and 12 months. In both groups, there was a significant decrease of the tendon length from 8 weeks to 12 months, without significant difference between groups.

Schepull et al [28] used Roentgen stereophotogrammetric analysis with simultaneous mechanical loading to describe the mechanical properties of a healing Achilles tendon. An estimate of e-modulus was then performed to describe elastic properties. These values, while having an unclear clinical significance, were not significantly different between groups.

Return to sport

Sánchez et al. [27] found earlier return to sport with PRP for surgically treated patients.

Athletes receiving PRP were permitted by their surgeon to return to running earlier than patients treated without PRP, 11.0 +/- 1.0 weeks vs 18.0 +/- 3.0 weeks, respectively ($p=0.04$), and to start training activities earlier, 14.0 +/- 0.8 weeks vs 21.0 +/- 3.0 weeks ($p<0.01$), respectively. However, there were methodological issues in this study, as their control group was operated between 1997 and 2001 and their group that benefited of PRP was included between 2002 and 2004. Moreover, their patients were not comparable in terms of previous sport activities. Only one patient out of the 6 controls was an elite athlete versus 2 out of 6 in the PRP group. Their practice also was different in terms of sports, with 4 soccer players and 2 basketball players in the PRP group versus 1 soccer player, 2 basketball players, 1 volleyball player and 2 racket sports players in the control group. Therefore, it might have interfered with the evaluation of their primary outcome.

In the study of Boesen et al. [18], the mean time to return to running was 21 weeks in the PRP group and 23 weeks in the placebo group. In the PRP group, 6 patients out of 19 returned to their previous level of sport during the 12-month follow-up, and 5 out of 19 in the placebo group. No statistical analysis was made on these values. The other studies did not report this parameter. We performed a statistical analysis, showing no significant difference between these two groups, with a Fischer's test finding a p-value of 0.99.

Functional scores

The Achilles Tendon Rupture score (ATRS) ranges from 0 (minimum) to 100 (maximum). It is a patient-reported instrument with high reliability, validity, and sensitivity for measuring

outcomes after treatment in patients with a total ATR [36]. It comprises 10 items that evaluate strength, endurance, stiffness, and function in daily living and physical activities. Its value at 3 months is strongly correlated with a patient's ability to return to sport at 1 year [37].

This score was used in 3 studies [18,19,28] and did not show any significant difference, but a tendency to a lower ATRS for PRP-treated patients. Yet, Schepull et al. [28] in their surgical series showed a significant negative effect at 12 months of PRP use, with a median Swedish version of the ATRS at 78 (percentiles 75 to 85) in the PRP group vs 89 (percentiles 83 to 92) in the control group ($p=0.014$). Boesen et al. [18] in their non-surgical series, showed a tendency to a higher ATRS in its Danish version at 12 months with a mean ATRS at 90.1 (SD 1.2) in the PRP group vs 88.8 (SD1.7) in the control group. Yet, this difference should not be considered as clinically significant because of the minimal detectable change depending on cultural ATRS version.

Before the creation of the ATRS, other scores were widely used in literature to assess function in Achilles tendon rupture: The American orthopedic foot and Ankle Society Score (AOFAS) and the Achilles Victorian institute for Sports Assessment (VISA-A). The AOFAS ankle-hindfoot scale is a widely used tool in Achilles tendon rupture. It is region-specific and comprises items for pain, function, and alignment. However, it is not a patient-reporting score, De Carli et al. [25] did not show any difference between groups at 1, 3, 6 and 24 months. The VISA-A questionnaire was designed for Achilles tendinopathy. It consists of eight questions measuring pain, function in daily living and sporting activity. It is both used in clinical rating and quantitative research. De Carli et al.[25] did not show any difference between groups, too.

The Leppilahti score used by Kaniki and al. [26], and Zou et al. [20], comports subjective factors (pain, stiffness, muscle weakness, footwear restrictions and subjective outcomes) and objective factors (range of active motion and isokinetic calf muscle strength). It is not a

validated outcome measure for Achilles tendon rupture. In both studies, no significant difference was found at 2 years between groups.

The SF36 questionnaire used by Zou et al. [20], is a non-specific score evaluating the quality of life with both physical and psychological evaluation. In their trial, there were significant higher scores in the PRP group at six months, but not at 12 and 24 months. These findings must be tempered by the fact that they performed a slightly different surgery between PRP group and control group (the rupture ends of the tendon were removed in the control group, whereas on PRP group only blood clots were removed to maintain the Achilles tendon length), and therefore adding a potential confusion bias.

Adverse events

The common complications after acute ATR include infection and re-rupture. In surgery-treated patients, cohorts describe a rate of 4% of infections in open surgeries and 3.4% of re-rupture [38]. Non-operative treatment with early active movement and weight-bearing with a cast does not increase the risk of re-rupture compared with surgery and is associated to less frequent infections [6]. A total of 19 re-ruptures occurred on the 523 patients included in this review (3.6%): 9 in the non-operative PRP group, 8 in the conservative group without PRP, 1 in the surgically treated patients without PRP and 1 in the operated patients with PRP. We did not include patients from Alviti et al. [21] because no mention of the adverse events was found in their study. Studies described 11 infections, 6 in the non-operative control group, 4 in the surgically treated patients, and 1 in the surgery associated to PRP group, on a total of 471 patients (3.1%). Two surgically-treated patients with no PRP had presented a deep infection that needed surgical debridement. These results are consistent with previous studies [1,2,7,8,38]. Keene et al. described the development of a deep vein thrombosis in 6 patients

conservatively treated with PRP, and in 5 non-operative controls without PRP. One patient had a serious adverse event with myocardial infarction that occurred 2.5 hours after PRP injection, but was deemed unrelated [19]. Adverse events are presented in table 4.

Discussion

ATR is a common injury with an increasing incidence, especially in ageing adults, resulting in work incapacity and several months off sports [1–4]. Therefore, it has a major impact on athletes and there is a need for an accelerated and performant healing strategy. PRP is gaining increasing attention as an adjuvant for tendon healing and its safety has been established [10,12,14–16,24,29,39]. It is emerging for its use in ATR and in other pathologies such as epicondylitis and rotator cuff injuries [12,14,29–31,40].

In recent literature, Achilles tendon rupture occurs on 54 to 95% of men, with a mean age around 40 years[1–4], which is consistent with our findings. Historically, most of these injuries occurred in young men (aged 25 to 35 years), and it has been observed that the average age of ATR has increased with time, as has the proportion of women[3,4,41].

Comparisons between studies are challenging owing to differences in the composition of PRP, number of injections, associated treatment, control groups, and evaluation criteria. Moreover, rehabilitation protocols were different in each study. For these reasons it is difficult to highlight the effect of PRP. In 2007, Sánchez et al. [27] showed a benefit of PRP for ATR, with an earlier return to sport for patients treated with PRP compared to surgery only in their pilot study. Yet, their study had multiple biases because of the lack of objective criterias for return to running, the comparison with historical controls, the difference in terms

of previous sport activities and level. The results they had with 12 patients do not seem consistent with later studies.

In surgical management of ATR, De Carli et al. [25] found no effect of PRP on strength and functional scores. Zou et al. [20] corroborated these findings with no long-term difference, even though they reported temporary greater calf strength (at 6 months) with PRP. Alviti et al. [21], using platelet-rich-fibrin, did not evidence any difference in gait analysis for surgically-treated patients.

Regarding non-operative treatment of ATR, Schepull et al. [28] showed that PRP had no statistically significant effect on improving recovery in terms of elasticity, strength and functional score. Kaniki et al. [26] conducted the first large cohort in 2014, with 145 patients, finding no significant difference in terms of functional score, elasticity and isokinetic strength in non-surgically treated patients. Recently, in a large multicentric randomized placebo-controlled trial with good methodology, Keene et al. [19] confirmed previous findings, with no statistical difference in terms of strength and function for non-operative management of ATR. Boesen et al. [18] found no difference either on function, elasticity and strength between PRP and placebo.

The PRP-product preparation is often poorly described and not standardized between trials, leading to heterogeneity. All studies used different centrifuges and different protocols to obtain PRP or PRP-product, which enhances the lack of consensus on the best process to use. What is called PRP or PRP-product in fact comprises products that are hardly comparable. In a large review, Padilla et al. [39] recently explained these differences in outcomes with heterogeneity of PRP and PRP-products. It remains unclear whether leukocytes should be kept in PRP and PRP-products. With PRP-products containing 17 times more platelets than in plasma [28], the relative absence of growth factors and fibrin as well as fibrinogen could also

be detrimental, because of potential exposure of growth factors to proteolysis. The optimal composition of PRP remains unclear as well as the total number of injections, which may play a positive or negative role on healing. All the included studies had different administration protocols, and none of them showed a higher benefit upon the others, with comparable results regardless of the number or the volume of injections. Our review cannot advocate for a choice of a particular protocol concerning the administration of PRP.

Only two studies evaluated return to sport [18,27], the others studies considered indirect criteria. Even return to sport remains an ambiguous notion, and there are no objective return-to-sport criteria clearly defined in the literature. Its evaluation appears of interest due to the high frequency of ATR in athletes. Until recently there was no functional score for patients with ATR. Since the creation of ATRS, which is a validated measure with a predictive value for return to sport [36,37], there tends to be a wide use of this score as an outcome. Yet, ATRS shows a tendency to be worse for PRP-treated patients in all studies in the first six months [18,19,28]. ATRS versions used in these series were English, Swedish and Danish versions [18,19,28]. However, given the high heterogeneity of the ATRS minimal detectable change depending on the version used, ranging from 6.75 (for its English version) to 18.5 (for its Danish version), comparisons between two different translations cannot be reliable [42,43].

It seems that the clinical outcomes after six months do not differ with or without PRP use, in surgical and non-surgical treatment. Outcomes in the first six months after ATR are more difficult to interpret, data are not univocal concerning a possible effect of PRP, and whether this effect would be beneficial [27] or detrimental [28]. All data indicating a possible significant effect of PRP were not confirmed with later studies. However, we must be cautious, and we cannot exclude that larger studies with a choice of specific outcomes could prove an effect of PRP in this indication. Yet, due to the little clinical effect currently confirmed with the data available we cannot recommend its use in ATR management.

Limits

In our review, we have chosen to evaluate only the potential effect of PRP and PRP products in surgical or non-surgical treatment of ATR. We decided not to evaluate surgery versus non-surgical management of ATR, a subject that has been long debated and remains still controversial [6–8]. Recent findings tend to show better outcomes in terms of strength and patient-reported functional outcomes with early functional rehabilitation including weight-bearing and active exercises [44]. We included both surgically and non-surgically treated patients. That leads to more heterogeneity, but it may enhance a potential specific PRP-effect, regardless of the treatment used. The publication bias is minimal in our study, given that we have included mainly studies with negative results. Yet, there could be more unpublished studies with negative findings, leading to an under-estimation of the absence of effect of PRP. We did not conduct a meta-analysis in order to avoid misleading because of the heterogeneity of the methods, the diversity of outcomes, and the limited quality of several studies. As we were dealing with different treatments evaluated differently, we chose to consider them separately.

Conclusion

The current data available are not in favour of a clinically significant effect of the PRP use as an adjuvant for surgical or non-surgical treatment of ATR. There might be a slight effect on evolution during the first six months, but current evidence suggests that evolution in terms of function, strength, elasticity, is comparable after one year between PRP and non-PRP treated patients, with or without surgical management. Return to sport should be evaluated in larger

cohorts, but with the data currently available, it did not seem to be earlier with PRP use.

These results must be confirmed in future studies with strong methodology as well as standardized PRP products and validated outcomes.

Conflict of interest

None to report.

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None to report

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Legends

Figure 1: Flow chart of the included studies

Table 1: Demographic data of the included studies

Table 2: Evaluation of the level of evidence using GRADE approach

Table 3: Type of Platelet rich plasma used and Achilles tendon rupture management

Table 4: Adverse events

Table 1: Demographic data of the included studies.

Studies	Total patients (n) (PRP+controls)	Mean age (years)	Gender (M/F)	Injury during sport (%)	Diagnostic criteria	Delay of treatment
Keene et al. (2019)	230 (114+116)	46	173/57	157 (58%)	Clinical +/- US	<12 days
Boesen et al. (2020)	40 (20+20)	40	40/0	40 (100%)	Clinical + US	<3 days
Schepull et al. (2010)	30 (16+14)	39	24/6	30 (100%)	Not mentioned	<3 days
Zou et al. (2016)	36 (16+20)	29	35/1	34 (94%)	Not mentioned	<21 days
De Carli et al. (2015)	30 (15+15)	32	24/6	Not mentioned	Clinical + US	Not mentioned
Kaniki et al. (2014)	145 (73+72)	41	118/27	119 (82%)	Clinical +/- imaging	<14 days
Sanchez et al. (2007)	12 (6+6)	36,2	12/0	10 (83%)	Clinical + imaging (MRI or US)	<14 days
Alviti et al. (2017)	20 (11+9)	33	20/0	Not mentioned	Not mentioned	Not mentioned

Abbreviations: M: male. F: female. MRI: magnetic resonance imaging. US: ultrasound

Table 2: Evaluation of the level of evidence using GRADE approach

(++ = *important bias*, + = *bias*, - = *no bias*)

	Design	Level of evidence	GRADE approach	Limitations in study design or execution	Inconsistency of results	Indirectness of evidence	Imprecision	Quality of evidence
Sanchez et al. (2007)	Case-control study	III		++	+	-	+	Very low
Kaniki et al. (2014)	Retrospective comparative trial	III		++	-	+	-	Very low
De Carli et al. (2015)	Non-RCT	IV		++	-	+	-	Low
Zou et al. (2016)	RCT not blinded	II		+	-	+	-	Moderate
Schepull et al. (2010)	RCT double-blind	II		++	-	-	-	Moderate
Boesen et al. (2020)	RCT simple-blind	II		+	-	-	-	Moderate
Keene et al. (2019)	RCT double-blind	I		-	-	-	-	Strong
Alviti et al. (2017)	Retrospective comparative trial	IV		++	-	+	+	Very low

Abbreviation: RCT = randomized controlled trial

Table 3: Type of Platelet rich plasma used, ATR management and main outcomes

Studies	ATR treatment	Control group	Centrifugation procedure : revolutions per minute (n) x time (min)	PRP: volume (mL) x no of injections	Activator	Non-bearing (week)	Total immobilization (week)	Maximum follow-up duration (week)	Main outcomes
Keene et al. (2019)	Non-surgical	Needle insertion, no injection	Not mentioned	4 x 1	No	3	< 6	24	Limb symmetry index in heel endurance test
Boesen et al. (2020)	Non-surgical	Needle insertion, <0.5mL isotonic saline	1500 x 5	4 x 4	No	0	8	52	ATRS, heel-rise raise and work, ROM, tendon elongation, calf circumference
Schepull et al. (2010)	Open surgery	No injection	Not mentioned	10 x 1	Not mentioned	0	7	52	Elasticity modulus, heel raise index
Zou et al. (2016)	Open surgery	No injection	2000 x 10, twice	3-4 x 1	No	6	9	104	Leppilahti score
De Carli et al. (2015)	Mini open surgery	No injection	Not mentioned	4 x 2	Thrombin-calcium gluconate	3	5	104	VAS, FAOS, VISA-A scales
Kaniki et al. (2014)	Non-surgical	No injection	1500 x 5	3-4 x 2	No	2	At therapist's discretion	104	Isokinetic plantar flexion strength
Sanchez et al. (2007)	Open surgery	No injection	8 minutes at 460g	4 x 2	Trisodium calcium tubes, activated by calcium chloride	2-3	At therapist's discretion	52	Range of motion, return to running, return to previous activity
Alviti et al. (2017)	Open surgery	No injection	3000 x 10	Not specified	Sodium citrate and jellifying agents as calcium gluconate	3	8	24	Gait analysis

Abbreviations: PRP: Platelet rich plasma; ATR: Achilles tendon rupture; VISA-A: Victorian Institute of Sports Assessment-Achilles; VAS: visual analog scale; ATRS: Achilles Tendon Rupture Score ; ROM : range of motion.

Table 4: Adverse events

	Follow up (week)	Number of patients	Complications
Keene et al. (2019)	4, 7, 13, 24	219, 215, 208, 216	<u>PRP</u> : 1 ST elevation myocardial infarction, 22 mild discomfort or minor bleeding, 6 deep vein thrombosis, 6 re-ruptures, 13 wound complications, 6 severe pain >10days after injection, 0 infection, 5 discomfort at injection site. <u>Placebo</u> : 8 mild discomfort or minor bleeding, 5 deep vein thrombosis, 4 re-ruptures, 13 wound complications, 6 severe pain >10 days after injection, 6 discomfort at injection site, 3 infections at injection site, 3 infections at non-injection site.
Boesen et al. (2020)	8, 52	40, 28	<u>PRP</u> : 1 re-rupture <10 weeks <u>Placebo</u> : 1 re-rupture <10 weeks
Schepull et al. (2010)	7, 19, 52	30, 28, 26	<u>PRP + surgery</u> : 1 re-rupture at 2 months, 1 infection treated with antibiotics, 1 deep vein thrombosis <u>Surgery</u> : 1 deep vein thrombosis
Zou et al. (2016)	3, 12, 27, 52, 104	36	<u>PRP + surgery</u> : no adverse events <u>Surgery</u> : 2 superficial infections, 1 deep infection because of allergic reaction, 2 wound healing delay, 1 re-rupture
De Carli et al. (2005)	3, 12, 27, 104	30, 30, 30, 30	<u>PRP + surgery</u> : 1 wound healing delay, 5 mild pain in the operated ankle after a long workout, 6 feelings of weakness after prolonged training <u>Surgery</u> : 2 wound healing delay, 4 mild pain in the operated ankle after a long workout, 6 feeling of weakness after prolonged training
Kaniki et al. (2014)	6, 52, 104	145, 93, 100	<u>PRP</u> : 2 ruptures <u>Non-operative</u> : 3 ruptures
Sánchez et al. (2007)	2, 4, 10, 16, 22, 28, 39, 52	12	<u>PRP + surgery</u> : no adverse events <u>Surgery</u> : 1 infection requiring surgical debridement
Alviti et al. (2017)	24	20	No mention

Abbreviations: PRP = platelet-rich plasma