Platelet-Rich Plasma on Ankle Sprains – Efficacy on Pain Reduction and Shorter Return to Play: A Systematic Review of Available Randomized Control Trials

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ABSTRACT

Background The role of platelet-rich plasma (PRP) has been widely studied, but only recently did trials emerge that probed into its potential role in ankle sprains. With the limited available literature, most of the trials results showed that it might have a role in faster healing and pain reduction.

Objectives The purpose of this review is to summarize available studies on ankle sprains in order to identify if there is good initial evidence of its role on return to play (RTP) among active individuals as well as pain reduction. It is also to identify if results were consistent among studies.

Methodology A systematic search of available literature in online databases was done to compare results about outcome measures on pain score and RTP. Included studies are those with a population of 18 years and above treated with PRP with or without post-procedural immobilization. Outcome scorings that assessed pain as a parameter was also included.

Results Three randomized controlled trials and two prospective studies were identified. Results showed an average of 8 weeks to RTP (p-value - 0.006) with decreased pain in ankle sprains treated with PRP and functional therapy.

Limitation Only one randomized controlled trial (RCT) compared PRP with a placebo and a small population of all studies made available. More comparable RCTs are needed to strengthen results of the studies.

Conclusion The use of PRP on ankle sprains may have a potential role in shorter time to RTP and pain reduction.

Key words Ankle Sprains, Lateral Ankle Sprains, Platelet-rich Plasma, PRP

INTRODUCTION

Among musculoskeletal injuries, ankle sprain is considered as one of the most common soft tissue injury accounting for approximately 15% to 20%.[1] It comprises about 80% of ankle injuries commonly seen.[2] The incidence is relatively high, especially among those with a high level of activities and sports.[3]

The role of conservative management in the treatment of ankle sprain is considered to be superior to surgical interventions. However, recovery time may

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take longer, especially with more severe injuries. Mean return to play (RTP) is approximately 45 days.[4,5] This length of period may affect the conditioning of athletes or at the very least, patients with active lifestyles.

Platelet-rich plasma (PRP) is progressively being studied in the field of sports and rehabilitation medicine. In recent years, clinical trials have been conducted to identify its role in different soft tissue injuries. Numerous reviews compiled the outcomes on different soft tissue conditions. At the forefront of these soft tissue injuries are lateral epicondylitis, Achilles tendon ruptures and rotator cuff pathologies. [6] Despite intensive literature on PRP, no reviews were made on its potential role on lateral ankle sprains.

With recent available studies of PRP on ankle sprains, the purpose of this systematic review is to identify if there is indeed a potential role of PRP in terms of RTP and pain reduction on lateral ankle sprains.

METHODOLOGY

The authors conducted a comprehensive literature search using the PubMed and Cochrane Library to identify peer reviewed articles about management of lateral ankle sprains with the use of PRP in accordance to the PRISMA statement.[7] Google Scholar was likewise used in order to assess any additional studies. References of the identified article that met the inclusion criteria were assessed for additional researches in line with the topic.

The search terms used as keywords were 1) Ankle Sprain, 2) Lateral Ankle Sprain 3) PRP and 4) Platelet-Rich Plasma. Articles in the last 20 years were included focusing on randomized controlled trials (RCTs) and prospective studies. Inclusion criteria must have had a population of 18 years old and above, treatment arm involved injection of PRP with or without post-procedural immobilization and outcome measure included pain score and/or RTP. Other functional scoring on top of the outcomes mentioned was noted in the result and discussion. No ligament injury was specified and studies involving high and low ankle sprains were included. References of article hits were then screened for relevant publications. The search included other languages if there were any. Only completed trials were included. Publications where the full text was not available were still incorporated. Articles including ankle fractures, medial ankle injuries and other non-ligamentous injuries were excluded. Likewise, case reports, case series and retrospective studies were removed.

Table 1 Critical Domains

AMSTAR 2 critical domains
• Protocol registered before commencement of the review (item 2)
• Adequacy of the literature search (item 4)
• Justification for excluding individual studies (item 7)
• Risk of bias from individual studies being included in the review (item 9)
• Appropriateness of meta-analytical methods (item 11)
• Consideration of risk of bias when interpreting results of the review (item 13)
• Assessment of the presence and likely impact of publication bias (item 15)

Both authors independently scanned and reviewed the records obtained from the searches. In cases of disagreement between the two authors, discussion with the research adviser to resolve conflicts was done.

Identified articles were subjected to "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR) 2 appraisal tool.[8] This was designed as a practical critical appraisal tool to carry out rapid and reproducible assessments of the quality of conduct of systematic reviews of RCTs of interventions. It is a 16-item tool which allocates the confidence that we can give to the results of each RCT. A score of crucially low to high is given depending on the number of critical domains it has. Shown in Table 1 are the critical domains with corresponding item number and Table 2 shows the description of each grading. Each RCT was appraised to identify the quality of study.[9]

RESULTS

A total of 56 articles were identified and 51 did not meet the inclusion criteria. Only five studies were included. Three RCTs were identified. One was a prospective cohort study which compared the treatment group with historical control used in a previous study done by the same author. One RCT enrolled in Cochrane clinical trials was still ongoing and had to be removed. One prospective study was identified and published in Mexico in 2008. However, the full text of the latter was not available. Based on the AMSTAR 2 tool, the review may have a moderate rating since some items in the tool pertain to statistical analysis usually done in a meta-analysis and not in systematic review.

Three RCTs and two prospective studies were identified. A population of athletes was noted in one

Table 2 Overall Rating

Rating the overall confidence in results of the review
• **High** • No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of results of the available studies that addresses the question of interest
• **Moderate** • More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of results of available studies that were included in the review
• **Low** • One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of available studies that address the question of interest
• **Critically low** • More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of available studies

**Multiple* non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

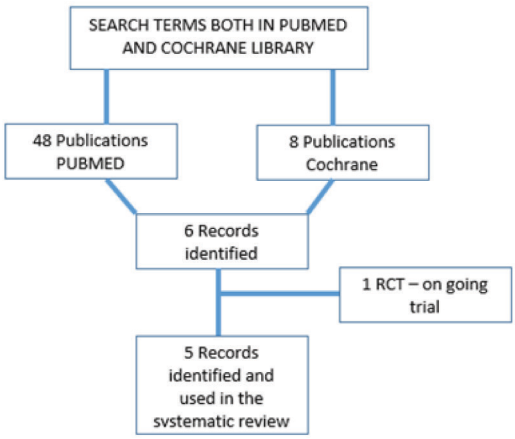

Figure 1 Search Strategy Diagram

RCT and prospective study. Two studies identified pain scoring before and after treatment. Two studies analyzed time of RTP, specifically in those studies involving athletes. A quality assessment of the RCT is summarized in Table 3. The included RCTs showed a relatively good quality output based on the presence of critical points. One paper however, did not mention any acquisition of consent, but included in their writing that it was approved by their ethical board (IRB). The abstract of the prospective study did not specify if the population consisted of athletes but made a mention that the outcome assessed was the ability to return to a previous sport at the time of follow-up. The details of individual studies are listed in Table 4 and 5.

Table 3 Quality Assessment of RCTs

	Laver, et al. 2014	**Rowden, et al. 2015**	**Blanco-Rivera, et al. 2019**
Purpose clearly stated	+	+	+
Literature review relevant	+	+	+
Appropriate study design	+	+	+
No bias present	+	+	+
Sample description in detail	+	+	+
Sample size justified	o	o	o
Informed consent	no mention	+	+
Validity of outcome measure used	+	+	+
Reliability of outcome measure used	+	+	+
Intervention described	+	+	+
Statistical reporting of results	+	+	+
Appropriate statistical analysis	+	+	+
Clinical importance reported	+	+	+
Appropriate conclusion	+	+	+
Limitation stated	+	+	+
Randomization	Block randomization	+	Online tool
Blinding	o	Patient and investigator	o

Table 4 Summary of RCTs

Publication	Randomization/ Blinding	Intervention	Outcome Measure	Result	Conclusion
Laver, et al. 2014	+ block randomization No blinding	Control (8) immobilization and rehab Treatment (8) PRP, immobilization and rehab	Primary: Return to play Residual pain Secondary: Dynamic stability via ultrasound	"All patients presented with a tear to the AITFL with dynamic syndesmosis instability in dorsiflexion–external rotation, and larger neutral tibia–fibula distance on ultrasound. Early diagnosis and treatment lead to shorter RTP, with 40.8 (±8.9) and 59.6 (±12.0) days for the PRP and control groups, respectively (p = 0.006). Significantly less residual pain upon return to activity was found in the PRP group; five patients (62.5%) in the control group returned to play with minor discomfort versus one patient in the treatment group (12.5%). One patient in the control group had continuous pain and disability and subsequently underwent syndesmosis reconstruction"	"Athletes suffering from high ankle sprains benefit from ultrasound-guided PRP injections with a shorter RTP, re-stabilization of the syndesmosis joint and less long-term residual pain."
Rowden, et al. 2015	+ + patient and investigator	Control (15) placebo injection and initial immobilization Treatment (18) PRP and initial immobilization	VAS and LEFS	"There was no statistically significant difference in VAS and LEFS scores between groups"	"In this small study, PRP did not provide benefit in either pain control or function over placebo "
Blanco-Rivera, et al. 2019	+ online tool No blinding	Control (10) Immobilization and rehab Treatment (11) PRP, immobilization and rehab	Primary: VAS Secondary: AOFAS FADI	"The experimental group presented the highest reduction in pain and better functional scores than the control group at 8 weeks. At the end of follow-up period, the results of both groups were similar."	"We can conclude that the use of PRP therapy as an adjuvant for the treatment of lateral ankle sprains allows the patient to report less pain during his recovery time and better functionality outcome when compared with immobilization only. A larger study, including a placebo group would be necessary to confirm these findings."

AITFL – Anterior Inferior Tibiofibular Ligament

Table 5 Summary of Prospective Studies

Publication	Randomization/ Blinding	Intervention	Outcome Measure	Result	Conclusion
Samra, et al. 2015	n/a	Control (11) Immobilization Treatment (10) With one dropout PRP and immobilization	Primary: Return to play Secondary: Pain Functional outcome testing	"Time to return to play was significantly less in the intervention group (p=0.048)."	"A single autologous PRP injection may accelerate safe and successful return to Rugby Union, with improved functional capacity and reduced fear avoidance. It demonstrates the feasibility of a randomized controlled trial to further assess this therapy."
Frei, et al. 2008	+ + patient and investigator	n-11 PRP, immobilization and rehab	Tibiotalar space stability assessment tests and functional radiograph	"The average time of healing was 5.18 weeks. Five patients showed no signs of instability at 4 weeks after therapy and could return to their previous sports activities. At 6 weeks after therapy, 90.9% of the patients resumed their full sports activities."	"The use of bio-inductive properties of growth factors is one of the options for treating injuries to the ligamentous complex of the ankle. It can be used alternatively to conventional surgery or as an adjunct accelerating and improving the healing of traumatic lesions and postoperative conditions.'

Laver, et al. in 2014 compared the time of RTP and dynamic ultrasound assessment of syndesmosis between PRP administered to the anteroinferior talofibular ligament injury followed by immobilization in a walking boot to those with immobilization alone. This was conducted among elite athletes who met their inclusion criteria. Both groups underwent the same rehabilitation program. Results showed significant mean RTP in the PRP group. Six out of the eight participants allocated in the treatment arm were able to return to their respective sports before the 6-week follow-up. The actual mean difference in days was 18.8 days, approximately 3 weeks earlier than the control group.

Rowden, et al. (2015) compared the Visual Analog Scale (VAS) and Lower Extremity Functional Scale (LEFS) among the enrolled participants (n=37) randomized to control placebo group and treatment PRP group. Four participants did not proceed to the study, the reason of which was not stated. There were 18 patients allocated to the control arm, while 15 were randomized to the treatment arm. A physical follow-up was conducted at 2-3 days and 7-8 days. Last follow-up was conducted through a telephone interview on the 30th day post administration. Results showed that there was a significant improvement of outcome measures for both groups in terms of pre- and post-intervention analysis. However when compared with each other, it failed to show significant difference.

A recent study was conducted by Blanco-Rivera, et al. in 2019 which randomized 21 patients to the treatment and control group. Patients included had age ranging from 18 to 60 years old. Randomization was done through an online tool which selected 10 patients in the control arm and the remaining in the experimental arm. No mention of blinding the assessor was stated. Experimental arm included administration of 5 ml PRP to the identified anterior tibiofibular ligament sprain. This was followed by rigid immobilization using a short below knee plaster cast with the ankle in neutral position. The same immobilization was placed in the control arm. Infiltration of placebo to the control group was not mentioned. Follow-up was done at 3, 5, 8 and 24th week with assessment of VAS, American Orthopaedic

Foot and Ankle Score (AOFAS) and Foot and Ankle Disability Index (FADI). There was significant reduction in the aforementioned outcomes at the start and during the duration of follow-up. Towards the end of the study, no significant difference was noted.

One prospective controlled cohort study was identified. This was conducted by Samra, et al. in 2015. Results of this clinical trial showed a significant reduction of pain score at 3, 5 and 8 weeks compared to immobilization alone. However, results were comparable in terms of pain score and functional testing.

A prospective study conducted by Frei, et al. in 2008 on 11 patients with acute lateral ankle sprain was given one dose of PRP post injury. Radiographs were observed pre- and post-PRP injection to identify improvement Time to return to sports was also noted. Average time of healing was at 5.18 weeks. Forty five percent (5/11) did present with a stable ankle at 4 weeks and were able to return to previous sports activities. There was narrowing of previously widened tibiotalar space on radiographs at the 4th and 6th week assessment. At 6 weeks post treatment, 10 of the 11 participants were able to resume their full sports activities. Since the abstract was the only reference for this study, there was no mention of the outcome of the remaining patient who was not able to return to sports at 6 weeks.

DISCUSSION

In current literature, strong evidence suggests that conservative management still plays a major role in treating ankle sprains. An earlier systematic review by Petersen, et al. (2013) concluded that ankle sprains, regardless of grade, may be treated conservatively. [1] Among the two RCTs, no significant difference in terms of functional and pain scores were noted when surgical and non-surgical treatment was compared.[1,3,10] There was however, a higher incidence of instability in ankle sprains treated by functional therapy alone in the study conducted by Takao, et al. [1,11] The authors of the systematic review stated that the decision for surgery should be individualized.[1] In a recent systematic review and meta-analysis conducted by Doherty, et al. (2016), pooled RCTs showed strong evidence supporting external supports and exercise therapy. Although there is high level of heterogenous data from the latter, the generated forest plot from 23 high quality (AMSTAR score of >7) RCTs still favor exercise therapy.[3] Despite the extensive review done by both authors, there was no mention of PRP as the management for ankle sprains.

Studies on PRP have been conducted as early as the 70's. PRP is an example of an autologous product which promotes healing ina variety of soft tissues. This eventually led to numerous trials that looked into its potential role as a biological stimulus to enhance healing.[12] Because of its potential benefit on bone, tendon and ligament healing, it has been widely studied in the field of orthopaedics.

The preparation of PRP involves drawing the patient's own blood. The extracted whole blood is subjected to centrifugation. This process separates red blood cells (RBCs) from plasma and the "buffy coat," which contains the concentrated platelets and leukocytes.[13] Basically, the platelets contain varying amounts of growth factors and mediators which can augment the healing process.

The initial use of PRP in orthopaedic sports was limited to tendinopathies, joint injuries and muscle tears in an early review conducted.[14] With some studies showing promising results, more researches were conducted to identify the efficacy of this treatment and its possible role in semi-conservative management or to augment surgical repair.

Due to inconclusive results from various clinical trials, numerous reviews were conducted, a recent one which was from Le, et al. in 2018. Use of PRP is supported by large clinical studies on lateral epicondylitis.[13] A statistically significant outcome of pain reduction and decreased percentage of residual elbow tenderness was documented. With high-quality evidence supporting efficacious results, it is suggested that PRP can be the treatment of choice. [13-15] Other clinical uses of PRP were studied on patellar, Achilles and rotator cuff tendinopathies. [13,14] Although significant improvement of pain was noted at short-term follow-up of PRP on chronic refractory patellar tendinopathies, comparable results were noted at subsequent assessments indicating that the role of PRP on pain reduction was limited to immediate improvement. The use of PRP on Achilles tendinopathies is still not routinely recommended by current literature.[13] Comparison between steroid and PRP injection for rotator cuff tear showed significant improvement of pain and functional outcome scorings.[14,16,17] Although

limited studies are still available, results might direct PRP as an alternative to steroids, especially with the latter sometimes leading to tendon ruptures. The role of PRP on surgical augmentation is more on rotator cuff than Achilles tendon repairs. Although pre-clinical trials were promising for PRP on Achilles tendon repair and some prospective studies showed good outcomes, but available literature does not show significant benefit of PRP as an adjunct.[13,14] In contrast to the review of Le, et al., a recent meta-analysis of Lorenzo, et al. in 2017 showed that PRP may be beneficial in decreasing the re-tear rate of rotator cuff repair.[16] The mention of PRP in ankle sprain was documented and also included in this review. Both studies by Laver, et al. and Rowden, et al. were cited; however, outcome measures were not comparable and probably the reason why it was not expounded in the review.

A systematic review conducted by Vannini, et al. in 2014, thoroughly discussed the use of PRP on foot and ankle pathologies, but failed to mention its role on ankle sprains. From our literature search, only one prospective study by Frei, et al. in 2008 and no published RCTs were available during that study period.

It was only recently that trials on lateral ankle sprains were conducted. In 2014, a case report by Lai, et al. investigated the potential role of PRP on lateral ankle complex injuries. They reported a case of a 39-year-old runner who had an MRI confirmed rupture of the ATFL after having an acute ankle sprain. PRP was administered followed by 4 weeks of immobilization. At 8 weeks, the patient was able to tolerate simple jogging with no pain and instability. On last follow-up at 6 months, the patient was able to run an hour a day with no complaints of residual pain, weakness and instability. MRI confirmed thickening and continuity of previously absent fibers of the ATFL. This return to sport was consistent with the study of Laver, et al. where the treatment arm of PRP, immobilization and rehab, was able to RTP 3 weeks earlier than those treated conventionally with immobilization and rehab.

Although studies are limited, available trials yield consistent results. An earlier abstract of a prospective study by Frei, et al. documented that 45% of test subjects were able to return to sports at 4 weeks and almost 100% return to previous sporting activity. Consistently, RTP was documented to be significantly shortened in the study of Samra, et al. Functional superiority of the treatment group was documented in RTP testing. Although the comparator was a historical group, no significant difference was seen when demographics were assessed at the start of their study. Both agility and vertical jump tests were significantly improved in the treatment arm. This may be attributed to more stable ankle mechanics secondary to improved tissue healing with augmentation of PRP consistent with the study of Laver, et al. It is important to take note that the population of both studies focused on athletes. These results, although not conclusive, may pave the way for more high quality trials that would further compare PRP with a placebo in order to yield statistically significant results.

Pain reduction is one of the primary goals of ankle sprain treatment. Consistent among the three identified studies that measured pain, no significant difference was seen towards the end of the follow-ups. The RCT by Blanco-Rivera however, did show a statistically significant result in all parameters tested including VAS score during the duration of the follow-ups. Although results were comparable, actual values were relatively better with the PRP group and good outcomes were seen on short-term assessment highlighting its role in faster recovery and RTP.

LIMITATION

Current available studies are very few to conclude any recommendations regarding use of PRP. The study is limited by the number of populations available in each study. No statistical analysis can be done with the available literature since the outcome measures and follow-ups are not comparable.

CONCLUSION

Among the available literature, PRP has shown beneficial effects in majority of the studies. Although limited by the number of studies as well as outcome measure in each, it still consistently showed shorter RTP and improved pain reduction. This may potentially be the basis for further RCTs to compare its efficacy with conventional treatment to have more statistically significant results.

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