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Research Article

Platelet-Rich Plasma in the Treatment of Hand, Foot, and Ankle Osteoarthritis: A Systematic Review

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Abstract

Platelet-rich plasma (PRP) administration has been considered an ideal approach for the management of symptomatic joint disorders when other conservative treatments fail to reduce the symptoms. In this systematic review, we aim to discuss the effectiveness of PRP in the management of hand, foot and ankle osteoarthritis as reported by previous studies. For that, we conducted a systematic electronic database search for suitable studies from inception till 22nd October 2020 in nine databases. We included original studies with no restrictions on study design, country, language or publication date. Finally, 13 studies were included in the current study. The current literture shows that PRP injection into the ankle was effective in reducing the pain and enhancing the mobility of this joint 24 weeks after the injection measured by the VAS, Japanese Society for Surgery of the Foot (JSSF), and the self-administered foot evaluation questionnaire (SAFE-Q) scales. For the foot, PRP injection significantly improved the pain and movememnt when compared to the hyaloronic acid (HA) injection; nevertheless, the PRP results were comparable to prolotherapy. For the hand, the patient was able to pursue his daily activities with improved functions, better VAS, DASH scores, and SAFE-Q scores, with a reported high satisfaction from the patient about this treatment modality and its efficacy compared to steroids or lidocaine. However, HA was significantly better at longer outcomes than PRP modality which failed to have a maintained efficacy. In conclusion, among the majority of the studies included, PRP showed a significant improvement in patients receiving for the management of osteoarthritis in small joints involving the hands and feet.

Keywords: *Platelet-Rich Plasma; PRP; Arthritis; Hand; Ankle, Feet; Hyaluronic Acid*

Introduction

Disorders causing pain in the musculoskeletal system is a frequent condition that affects many people. It has been estimated that almost one-fifth of the older patients suffer from pains in the ankle and foot [1]. Among the various degenerative joint diseases, osteoarthritis has been ranked as the commonest pathology, and the leading disorder that can easily causes disabilities in elderly patients [2,3]. It is well-known that some joints experience osteoarthritis as patients get older with no underlying etiology, however, osteoarthritis involving the ankle and foot joints mostly occurs due to trauma which exposes the subchondral bones [4,5]. The problem with osteoarthritis is that it induces a state of stiffness, pain, and affection of the joint mobility as a result of breaking down the joint cartilages.

This will affect patients' movements and their abilities to perform their daily activities [6,7]. Additionally, it can easily lead to the development of other morbidities, and complications together with the subsequent high costs [2,3,8]. Accordingly, many approaches have been made based on the economic and prognostic burdens of these events. The management of this disorder is usually conservative where topical capsaicin, thermal modalities, non-steroidal anti-inflammatory drugs (NSAIDs), and steroid intra-articular injections are usually applied [9]. However, once the pathology has been discovered, no treatment has been described as effective in curing the lesion. Therefore, the management of osteoarthritis has been almost exclusively surgical [10-12]. However, such procedures are hard to be conducted on delicate joints that require more careful approaches to avoid unnecessary complications [13,14]. Recent modalities are direct to induce tissue growth and regeneration [15]. Among these, platelet-rich plasma (PRP), has been effectively used to reduce pain and induce the affected chondrocyte growth and regeneration which will reduce the morbidity of joints and improve the outcomes [16,17].

The application of PRP was first introduced in the 1980s and is defined as increased amounts of plasma platelets than what is normally found in the average peripheral blood [18]. Its initial administration was prescribed in the field of hematology, however, it has been frequently used in other fields as surgeries including oral-maxillofacial, plastic and cardiac surgeries in addition to the field of dermatology, ophthalmology, gynecology, and urology [19]. Besides, PRP has been also used in the field of orthopedics for the management of many acute and chronic disorders involving the musculoskeletal system. In addition to reducing the need to perform invasive surgery, PRP administration has been considered an ideal approach for the management of symptomatic joint disorders when other conservative treatments fail to reduce the symptoms. It has been also effectively used in the management of both big and small joints which indicates the effectiveness and viability of this modality [16,17,20].

Aim of the Study

In this systematic review, we aim to discuss the effectiveness of PRP in the management of hand, foot and ankle osteoarthritis as reported by previous studies.

Methods

Search strategy and study selection

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic review and meta-analysis where registration of the protocol is not mandated [21]. We conducted a systematic electronic database search for suitable studies from inception till 22th October 2020 in nine databases including Google Scholar, System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), Clinical trials.gov, metaRegister of Controlled Trials (mRCT) and The WHO International Clinical Trials Registry Platform (ICTRP) databases using the following search term: (platelet-rich plasma OR platelet rich fibrin OR platelet-rich fibrin OR platelet gel OR autologous conditioned plasma OR pure platelet-rich-plasma OR platelets OR platelet concentrate OR prp OR prgf OR acp) AND (arthritis OR osteoarthritis OR OA) AND (ankle OR talus OR foot OR hand OR carpal OR trapezio* OR metacarpal OR radio-carpal OR thumb OR talus OR osteochondral). We included original studies

reporting the effectiveness of PRP in the management of hand, foot and ankle osteoarthritis. There were no restrictions on study design, country, language or publication date. Papers were excluded if there were one of the following exclusion criteria: 1) Non-original studies 2) *in vitro* or animal studies; 4) data duplication, overlapping or unreliably extracted or incomplete data; 5) abstract only articles, reviews, thesis, books, conference papers or articles without available full texts (conferences, editorials, author response, letters, and comments. Three independent reviewers screened titles and abstracts for selecting eligible papers. The further full-text screening was performed to ensure the inclusion of relevant papers in our systematic review. Any disagreement was done by discussion and consulting the senior member when necessary.

Data extraction

The data extraction form was developed by two authors, using a Microsoft Excel file. Three reviewers independently extracted data from included studies using the excel sheet. Data checking was performed through a fourth reviewer. All the disagreements and discrepancies were resolved by discussion and consultation with a senior member when necessary.

Quality assessment

Three independent reviewers evaluated the risk of bias in included studies. For randomized controlled trials (RCTs), the Cochrane's revised quality assessment tool (RoB 2) was used to assess the quality of each included study [22]. For non-randomized designs, the risk of bias in non-randomized studies - of interventions tool (ROBINS-I) was used [23]. Any discrepancy between the reviewers was solved by discussion.

Results

Search results

Systematic search resulted in 2,747 records; of these 2,426 records were screened using title and abstract after exclusion of duplicates. Title and abstract screening yielded 71 papers eligible for full-text screening. Out of these, we included ten studies, in addition to another three studies from manual search (Figure 1).

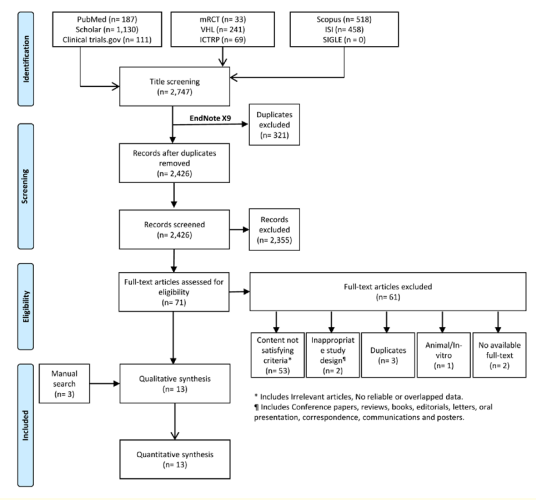


Figure 1: *PRISMA flow diagram showing the process of the review.*

Characteristics and bias of the included studies

Only three of the included studies [24-26] were RCTs while the others were either non-randomized trials, cohorts, case series, or case reports. Sample sizes of the included studies were highly variable ranging from only one patient [27] to 125 pateints [28]. The mean ages of the pateints in the included studies ranged from 39.5 years [24] and up to 62.9 years [29]. Moreover, the patients' mean follow up duration ranged from 8 weeks [28] and up to 40 months [30]. The detailed chractersitics of the included studies are summarized in table 1.

Author, year	Country	Design	Sample size	Age: mean (SD)	Male (%)	Follow-up	Assessment	Intervention	Control	Aim	Conclusion
Abdelfattah, 2020 (27)	Egypt	Prospective interventional	30	52.77 (±6 8.59)	-	12 weeks	Joint Palpation for tenderness with grading from IIV, Provocative tests (Grind test and Lever test), VAS for pain, AUSCAN score, grip and pinch strength	PRP	HA	To compare the effectiveness of PRP versus hyaluronic acid injection in osteoarthritis of thumb carpometacarpal joint based on clinical and functional outcome measures	We observed clinical improvement in both groups of carpometacarpal osteoarthritis (CMC OA) treated either with single dose of HA or PRP at 4 and 12 weeks follow up. However, HA provide a superior improvement with respect to PRP at 12 weeks follow up regarding VAS for pain, joint tenderness, AUSCAN hand function score, grip and pinch strength. So we support the use of a single hyaluronic acid injection as therapy for thumb CMC OA in preference to PRP injection.
Akpancar, 2019 (28)	Turkey	Cohort	49	56.08 (±11.30)	28.6	360 day	VAS, AOFAS, and AOS	PRP	PrT	To compare PRP and PrT injections for the management of OLT	Both PRP and PrT are efficient and safe methods in treatment of OLT. PrT offers advantages of less cost and minimal invasiveness.

Angthong, 2013 (29)	Thailand	Cohort	12	49.27 (±15.35)	25	Men 15.38 (SD: ±6.9) Months	visual analog scale foot and ankle [VAS-FA]) and health-related quality of life scores (Medical Outcomes Study, short-form, 36-item survey [SF-36])	PRP	NA	To determine the outcomes and quality of life after platelet-rich plasma therapy in patients with chronic recalcitrant diseases of the hindfoot and ankle and to identify the crucial clinical variables	Platelet-rich plasma injection might be an option but might not be a mainstay of non-operative treatment of problematic conditions of the hindfoot and ankle.
Fukawa, 2017 (30)	Japan	Cohort	20	59.3 (± 11.4)	25	24 weeks	VAS, JSSF ankle/hindfoot scale, and SAFE-Q scale	PRP	NA	To assess the safety and efficacy of an intra-articular injection of PRP in patients with ankle osteoarthritis.	Intra-articular injections of PRP resulted in no serious adverse effects and significantly reduced pain in the patients with ankle osteoarthritis. PRP treatment can be safe and effective and may be an option in the treatment of ankle osteoarthritis.
Görmeli, 2015 (24)	Turkey	RCT	40	39.54 (±8.85)	52.5	Mean 15.3 months (range,11-25 months)	AOFAS and VAS	PRP	HA group and placebo group	To compare the effects of HA and PRP as adjunct therapies after arthroscopic microfracture in OLT.	Both PRP and HA injections improved the clinical outcomes of patients who underwent operation for talar OCLs in the midterm period and can be used as adjunct therapies for these patients. Because a single dose of PRP provided better results, we recommend PRP as the primary adjunct treatment option in OLT postoperative period.

Guney, 2015 (31)	Turkey	Cohort	54	40.1 (± 14.7)	59.26	40.34 (±14.89) months	AOFAS, VAS, and FAAM	Microfracture plus PRP	Microfracture group and Mosaicplasty group	To compare medium-term functional effects of three different treatment modalities in patients with OLT.	All the three treatment modalities resulted in good medium-term functional results. However, mosaicplasty procedure seems to be a promising option and it might be preferred particularly in patients where pain control is important.
Mayoly, 2019 (32)	France	CT	3	62 (±3)	33.33	12 months	VAS, DASH and PRWE scores	Platelet-Rich Plasma Mixed-Microfat	NA	To describe the Platelet-Rich Plasma (PRP) mixed-microfat biological characteristics of an experimental Advanced Therapy Medicinal Product (ATMP) needed for clinical trial authorization	Microfat-PRP ATMP presented a good safety profile after an injection in wrist OA.
Loibl, 2016 (33)	Germany	CT	10	56.1 (±9.9)	20	6 months	DASH questionnaire, VAS MayoWrist score, The grip strength, and pinch strength	PRP	NA	To evaluate PRP injection into the trapeziometacarpal (TMC) joint.	PRP injection for symptomatic TMC osteoarthritis is a reasonable therapeutic option in early stages TMC osteoarthritis and can be performed with little to no morbidity.

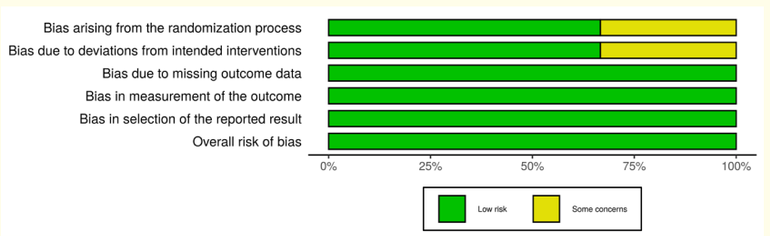
Malahias, 2018 (34)	Greece	RCT	32	62.9 (±11.03)	18.75	12 months	DASH-Q score and VAS	PRP	Steroid and local anesthetic	To investigate the superiority of ultrasound-guided intra-articular platelet-rich plasma (IA-PRP) injections compared with corticosteroid injections for the treatment of symptomatic trapeziometacarpal joint arthritis.	Corticosteroids offer short-term relief of symptoms, but IA-PRP might achieve a lasting effect of up to 12 months in the treatment of early to moderate symptomatic TMJ arthritis
Mei-Dan, 2012 (35)	Israel	RCT	30	39.65 (±16.73)	76.66	28 weeks	AHFS and VAS	PRP	hyaluronic acid	To evaluate the short-term efficacy and safety of platelet-rich plasma (PRP) compared with hyaluronic acid (HA) in reducing pain and disability caused by OCLs of the ankle.	Osteochondral lesions of the ankle treated with intra-articular injections of PRP and HA resulted in a decrease in pain scores and an increase in function for at least 6 months, with minimal adverse events. Platelet-rich plasma treatment led to a significantly better outcome than HA
Repetto, 2017 (36)	Italy	Case Series	20	57.5 (± 7.9)	60	17.7 (±6.4) months	VAS and FADI	PRP	NA	To assess the clinical effectiveness and feasibility of PRP injections in post-traumatic medium to advanced ankle OA to improve symptoms and delay the necessity for invasive surgical procedures.	the use of platelet-rich plasma injection is a valid and safe alternative to postpone the need for surgery

Medi-naPorqu-eres, 2019 (37)	Ger-many	Case report	1	59	100	12 months	VAS, grip and pinch strength, and the Quick-DASH-Q	PRP	NA	To draw atten-tion of healthcare providers deal-ing with Thumb CMC OA to PRP as a safe, beneficial therapy for this condi-tion which needs further as-sessment in ran-domized controlled trials	Our findings corroborate initial evi-dence for PRP injections for treatment of pain and im-pairment as-sociated with Thumb CMC-OA. How-ever, larger controlled, well-designed studies are needed to better guide future PRP treatment guidelines and consoli-date it as a safe and effective alternative in Thumb CMC-OA patients.
Sampson, 2016 (38)	USA	Case Series	125	57	NA	8 weeks	VAS, a global patient satis-faction survey, and The patient satisfaction survey	PRP	NA	Evaluate intra-articular injection of bone mar-row con-centrate (BMC), fol-lowed by platelet-rich plas-ma (PRP) injection at 8 weeks follow-up in moder-ate/severe osteoar-thritis.	Intra-artic-ular injec-tion of BMC, followed by a PRP injection, can provide short-term benefits in moderate-to-severe osteo-arthritis.

Table 1: *Chracteristics of the included studies.*

SD: Standard Deviation; NA: Not Available; RCT: Randomized Controlled Trial; CT: Controlled Trial; OA: Osteoarthritis; VAS: Visual Analogue Scale; AUSCAN: Australian/Canadian Osteoarthritis Hand Index; PRP: Platelet-Rich Plasma; HA: Hyaluronic Acid; AOFAS: American Orthopedic Foot and Ankle Society Score; AOS: Ankle Osteoarthritis Scale; PrT: Prolotherapy; OLT: Osteochondral Lesions of Talus; SAFE-Q: Self-Administered Foot Evaluation Questionnaire; JSSF: Japanese Society for Surgery of the Foot; FAAM: Foot and Ankle Ability Measure; DASH-Q: Disabilities of the Arm and Shoulder Questionnaire; PRWE: Patient-Rated Wrist Evaluation; AHFS: Ankle-Hindfoot Scale; FADI: Foot and Ankle Disability Index.

Regarding the RCTs, the oveall risk of bias was low with no domains with high risk of bias. The domains with some concerns of bias were of the randomization process, and the deviation from the intended interventions. In contrast, there was a low risk of bias in domains of missing data, outcome measures, and selective reporting (Figure 2). For other study designs, about one-quarter of the studies showed a serious risk of bias, while ther others showed eithr a low risk or some concerns of bias.The domians of the most risk of bias were the deviation from the intended interventions, selective reporting of the results, cofounding bias, and missing data (Figure 3).



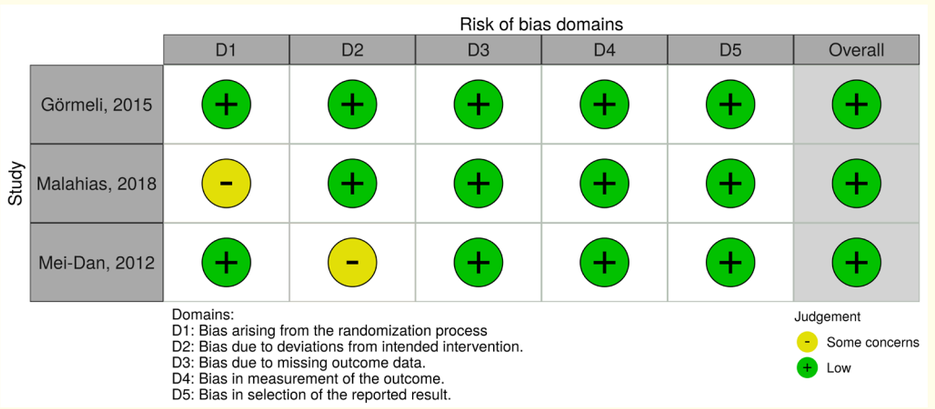
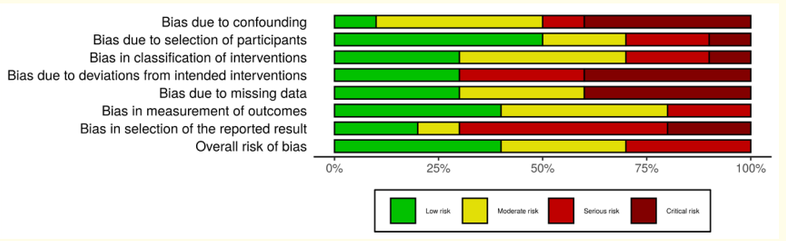


Figure 2: *Cochrane's revised quality assessment tool (RoB 2). A: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.*



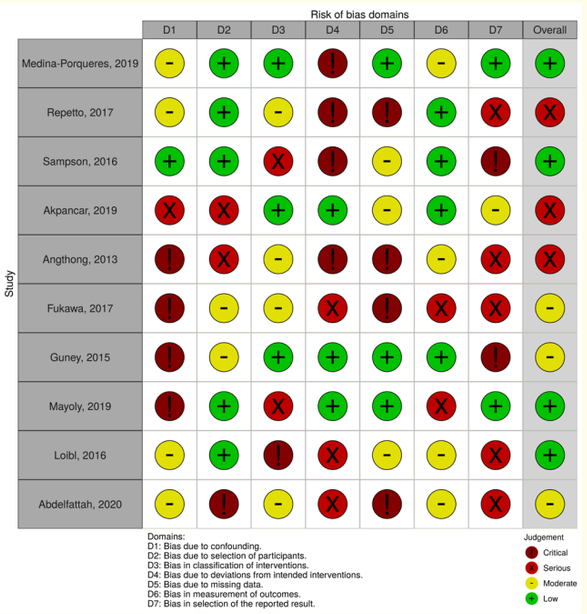


Figure 3: *Risk of bias in non-randomized studies - of interventions tool (ROBINS-I). A: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.*

Outcomes and Discussion

Efficacy of PRP on osteoarthritis of the ankle

Among the studies that were included in this review, only three of them [31-33] investigated the efficacy of PRP on osteoarthritis in the foot and ankle. Foot and leg lesions are harsh as control one's ability to move and perform their daily activities. Angthong., *et al*. [33] conducted a retrospective study of 12 patients suffering from chronic recalcitrant disorders involving the hindfoot and ankle. Patients were divided into satisfactory and non-satisfactory groups using the visual analog scale (VAS) foot and ankle scoring. Based on the results of the study, no satisfactory conclusion was reported by the authors as not all of the patients had satisfactory scores. However, the authors estimated that the mean visual score was significantly better after treatment than the pretreatment score and almost all of the score items were significantly higher in the satisfactory than the non-satisfactory groups. On the other hand, Fukawa., *et al*. [31] results showed that PRP injection into the ankle was effective in reducing the pain and enhancing the mobility of this joint 24 weeks after the injection measured by the VAS, Japanese Society for Surgery of the Foot (JSSF), and the self-administered foot evaluation questionnaire (SAFE-Q) scales. Similarly, Repetto., *et al*. [32] estimated that 80% of the patients were satisfied by the outcome of treatment as a significant decrease in the VAS score was estimated following a 4-week PRP course therapy. Therefore, it can be concluded that PRP is efficient in treating osteoarthritis in the ankle.

Efficacy of PRP on osteoarthritis of the foot

A total of included five studies investigated this outcome. Of these five studies, two of them [26,34], investigated PRP injection as the first line of treatment, while the other two investigated it secondary to treatment by surgeries, and only one [28] reported it following autologous bone marrow aspirate. Akpancar., *et al*. [34] conducted a retrospective cohort study of 49 patients with osteochondral lesions of the talus (OLT) where the effect of PRP was compared with prolotherapy (PrT) in managing OLT patients. The authors reported that both modalities showed great improvement in the pain and movement of the patietns with no significant difference between the two groups, and with 90.9% reporting satisfaction about PRP injections. Mei-Dan., *et al*. [26] compared between PRP and hyaloronic acid injection in their patients and found that PRP injection significantly improved the pain and movememnt after six months from the injection when compared to the other group. Guney., *et al*. [30] conducted a randomized controlled trial (RCT) of 35 patients to study the efficacy of PRP injection after surgery in terms of VAS and functional improvement after injection. Although baseline pain was more severe in PRP patients than the controls, a significant reduction in pain, and improved in VAS scores and joint functions were estimated in the PRP group after 16 months from the treatment. Similarly, an RCT of 40 patients by Gormeli., *et al*. [35] was conducted to compare between VAS and hyaluronic acid injections and found that PRP was significantly superior in terms of improved function and VAS scores at an average of 15 months of follow-up. Additionally, Sampson., *et al*. [28] reported the results of PRP injection following autologous bone marrow aspirate in 125 patients. The authors reported that the process was significant in reducing pain at 20 weeks of follow-up with a noticeable difference in this efficacy between weight-bearing joints and others that are not.

Efficacy of PRP on osteoarthritis of the hand

A total of five studies investigated the effect of PRP on the hand joints especially the thumb carpometacarpal joint osteoarthritis (TCMC-OA). For instance, Medina-Porqueres., *et al*. [27] reported a case of PRP three injections into the TCMC joint at a 1-week interval in a patient suffering from chronic pain in his thumb. After a 12-month follow-up period, the patient was able to pursue his daily activities with improved functions, high VAS, and SAFE-Q scores were obtained with a reported high satisfaction from the patient about this treatment modality and its efficacy [27]. Abdelfattah., *et al*. [36] conducted a prospective interventional study on 30 patients suffering from TCMC-OA to compare the efficacy of PRP and that of hyaluronic acid injections. Although significant improvement was recorded in both groups, hyaluronic acid was significantly better at longer outcomes than PRP modality which failed to have a maintained efficacy at 12 months, unlike the other group. On the other hand, Loibl., *et al*. [37] reported that after two PRP injections into the trapeziometa-

carpal (TMC) joint, significant improvements were estimated in the VAS and MAYO scores, but not the DASH scores after 6 months from the initiation of therapy. Although the DASH scores in this study were not significant, Mayoly., *et al*. [38] reported a case series of three patients and showed that all of them had improved DASH scores. However, PRP injections were combined with micro-fat preparation injections into the wrist. On the other hand, Malahias., *et al*. [25] conducted an RCT of 33 patients to compare between PRP and steroid and lidocaine injections in terms of their efficacy in managing OA of the TMC joint. At 12-months of follow-up, significant improvement in the VAS, Q-DASH, and patients' satisfaction was associated with the PRP group than the steroid and lidocaine ones. Moreover, steroids also relieved patients' pain early after injection, however, this improvement was not as significant as PRP at longer intervals. Therefore, although steroids are still being used as first drug modalities for the management of these events [39], physicians should consider PRP modality as a long-term effective measurement.

Based on these findings, PRP modality is an effective treatment in the management of all of the mentioned joints. This is consistent with the results of a meta-analysis of four RCTs conducted by Evans., *et al*. [40] which found that PRP was more significant than the used control modalities at long and short-term assessments. The same study also showed that PRP was effective in enhancing chondrocyte cell activity and regeneration. This has been reported by some of our included studies which have also suggested that multiple therapeutic modalities should be applied in the management of small joints [25,26,31,32,37]. Certain factors should be considered when judging the results of a certain study. These include the preparation of PRP and the frequency of centrifugation [40]. Moreover, although the findings in this review indicate the efficacy of PRP in both mild and severe osteoarthritis, previous studies demonstrated that PRP application has been effective in early osteoarthritis only [31,41,42], while other studies proved that it can be effective in the management of late osteoarthritis [25,43], however, there was no comparison conducted in the latter ones. Gormeli., *et al*. [41] reported that PRP with mild osteoarthritis are more likely to present with a good prognosis because they are more likely to have residual functioning cells that may contribute to the regeneration process.

Limitations to our study include the limited sample size in many of the included studies, in addition to the heterogeneity between the included study designs and the protocols of PRP preparation.

Conclusion

Osteoarthritis is one of the most common musculoskeletal disorders that affect many of the elderly population and can cause serious annoying and mobility-limiting complications. Although surgery has been proposed as an effective measurement for the management of this disorder, many side effects have been reported with surgeries on small joints. PRP has recently gained a good reputation for the management of pain, reducing inflammation, and inducing tissue regeneration. Among the studies that were included in this study, almost all of them reported a significant improvement in patients receiving PRP for the management of osteoarthritis in small joints involving the hands and feet.

Conflict of Interest

None.

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