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Original Article

The application of platelet-rich plasma in the treatment of knee osteoarthritis: A literature review

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ABSTRACT

Background: Primary knee osteoarthritis remains a difficult-to-control degenerative disease. With the rise in average life expectancy and the incidence of obesity, osteoarthritis has brought an increasing economic and physical burden on people. This article summarizes the latest understanding of platelet-rich plasma in the treatment of knee osteoarthritis, and reviews the economic issues of PRP.

Methods: The literatures in Pubmed, Embase, Cochrane library, Web-science and other databases were searched, and literature inclusion and exclusion criteria were formulated. According to the Cochrane systematic reviewer's manual, the included literatures were grouped, and qualitative descriptions and quantitative meta-analysis were performed. Continuous statistical methods were used to compare the effects and adverse effects of PRP before and after treatment, as well as between PRP and other conservative treatments.

Results: A total of 12 randomized controlled trials were included in this study. A total of 959 KOA patients (1070 knees) were enrolled and followed for 3–12 months. PRP total knee scores were significantly better than baseline at 1, 2, 3, 6 and 12 months after treatment (1 month: SMD = 0.60, P < 0.01; 2 months: SMD = 0.98, P < 0.01; 3 months: SMD = 1.16, P < 0.01; 6 months: SMD = 1.49, P < 0.01; 12 months: SMD = 1.47, P < 0.01). In terms of adverse reactions, PRP did not increase the risk of adverse events compared with HA (OR = 0.96, P = 0.85).

Conclusions: Compared with many other treatment methods, intra-articular injection of PRP has been proven to be safe and effective to improve the quality of life of patients with KOA.

1. Introduction

Knee osteoarthritis (KOA) is a joint degenerative disease with knee pain and limited function as the main clinical manifestations. The main pathological characteristics of this disease are destruction of articular cartilage, secondary subchondral osteoblastic hyperplasia, and synovial inflammation, and it will affect the entire joint and surrounding tissue. In China, the total prevalence of symptomatic KOA was as high as 8.1% [1] in 2012, which brought a huge medical economic burden to the whole society, so it has become a hot spot in clinical research. Its conservative treatment methods include functional exercise, physical therapy, non-steroidal anti-inflammatory drugs, and intra-articular injection of hyaluronic acid (HA). Although these methods have been used clinically for many years, there is currently no one method to achieve a true cure. With the rise of regenerative medicine, the use of biological agents to treat KOA has become a hot topic of research.

In 1993, Hood first proposed the concept of platelet-rich plasma (PRP), and found that PRP is rich in platelets, the number of which is more than three times that of whole blood. After platelet activation, it can release a variety of cell growth factors and inflammatory regulators, promote vascular reconstruction of damaged tissue, repair of damaged connective tissue, and proliferation and differentiation of mesenchymal stem cells into tissue-specific cell types. Based on the results of a large number of basic research and animal experiments, PRP has begun to be used in clinical treatment, and intra-articular injection is used to prevent the delay of OA progression. Although there have been many related clinical studies of intra-articular injection of PRP in the treatment of KOA at home and

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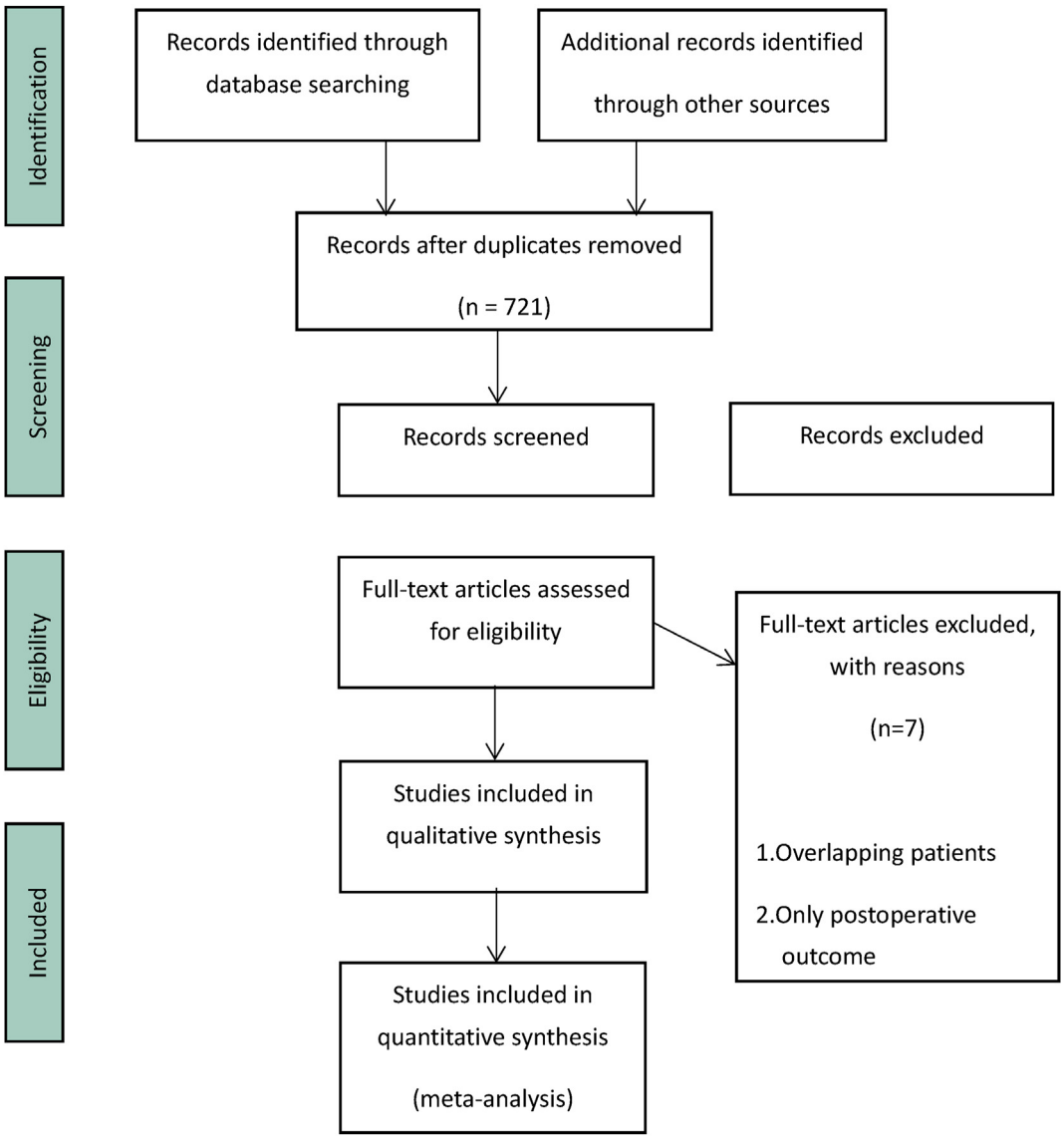

Fig. 1. Study flow diagram.

abroad, many research conclusions on the efficacy and safety of PRP are not completely consistent.

The purpose of this study is therefore:

(1) Review the application status of evidence-based information and cell therapy in the treatment of KOA;
(2) Review some economic issues in these options for treating KOA.

2. Materials and methods

2.1. Study design and search strategy

A review was conducted using the Web of Science database in February 2020, following the PRISMA guidelines. From 1949 to 2020, these searches were performed on the PubMed, Ovid MEDLINE, and Web of Science databases. The query words used in this study are (knee, osteoarthritis or gonarthrosis, platelet-rich or PRP, randomized controlled trials are arbitrary words, and the connection word is "and") for our search.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) study type: randomized controlled trial; (2) study object: patients with confirmed KOA; (3) intervention measures: PRP is used for intra-knee injection.

Exclusion criteria: (1) non-randomized controlled trials; (2) PRP combined with oral medicine, Chinese medicine or surgery; (3) letters, edited materials, unpublished abstracts, and manuscripts published in open access journals; (4) Republished literature (such as early and final papers for the same clinical trial).

2.3. Literature quality evaluation

According to the Cochrane bias risk assessment criteria [2], two researchers read the title and abstract of the literature from the retrieval strategy, and independently extracted the literature

Table 1
General research on 12 RCTs.

Author Reference	Published year	Number of cases	Number of knees	Drug treatment in the control group	Curative effect	Number of cases with adverse reactions	Jadad score
Ahmad [25]	2018	89	89	HA Once every 2 weeks 3 times in total	PRP > HA	PRP group (3) Control group (2)	3
Cole BJ [26]	2017	99	99	HA Once a week 5 times in total	PRP > HA	PRP group (2) Control group (4)	7
Di martino [8]	2019	167	167	HA Once a week 3 times in total	PRP > HA	PRP group (6) Control group (5)	7
Duymus TM [21]	2016	102	102	HA 1 time 4 times ozone	PRP > HA PRP > ozone	PRP group (3) HA group (2) Ozone group (2)	4
Huang Y [22]	2019	120	120	HA Once a week 3 times in total corticosteroids Once every 3 weeks 3 times in total	PRP > HA PRP > corticosteroids	PRP group (1) HA group (2) corticosteroids group (2)	3
Lin KY [3]	2019	53	87	HA normal saline (NS)	PRP > HA PRP > NS	PRP group (1) HA group (2) NS group (1)	4
Lisi [27]	2019	47	50	HA Once every 4 weeks 3 times in total	PRP > HA	PRP group (0) Control group (0)	3
Patel [4]	2013	74	148	NS 1 time	PRP > NS	PRP group (6) Control group (5)	4
Paterson [5]	2016	19	19	HA Once a week 3 times in total	PRP=HA	PRP group (0) Control group (0)	7
Rahimzade [28]	2018	42	42	25% glucose	PRP>25% glucose	PRP group (0) Control group (1)	4
Simental [14]	2016	65	65	acetaminophen Once a day 6 times in total	PRP > acetaminophen	PRP group (1) Control group (2)	3
Su, Ke [29]	2018	82	82	HA Once a week 5 times in total	PRP > HA	PRP group 1) Control group (0)	5

Note: RCTs - randomized controlled trial; PRP - platelet-rich plasma; HA - hyaluronic acid; NS - normal saline.

according to predetermined inclusion and exclusion criteria. The final inclusion was determined by three researchers.

2.4. Data extraction and analysis

Based on the knee function scores of each study treatment group and control group, a standardized mean difference(SMD) and a 95% confidence interval (CI) were calculated and used as a summary of the effect size. If multiple knee joint function scores are used in the study, when the data are complete, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), knee injury and osteoarthritis outcome score (KOOS), and The International Knee Documentation Committee score (IKDC) is selected for priority calculation.At the same time, the adverse reactions of various studies were collated and analyzed, and the relative risk was calculated. If there are multiple treatment groups in the study, the one with better effect is selected for quantitative analysis. The data extraction, transformation and analysis methods used refer to the Cochrane Handbook for Systematic Reviews of Interventions [2].

2.5. Statistical analysis

Meta-analysis was performed using Review manager 5. 3 software provided by Cochrane Collaboration Network, supplemented by Graphpad Prism 5.1 software for calculation and mapping. Sensitivity analysis was performed by removing a study, and funnel plots were made to assess publication bias. $P < 0.05$ was considered statistically significant.

3. Result

3.1. Study inclusion and paper quality

Through English database and manual search, a total of 326 articles were obtained. After screening, 12 RCTs were finally included for qualitative and quantitative analysis (Fig. 1). The general conditions of the included studies are shown in Table 1. A total of 957 KOA patients (1070 knees) were included. The follow-up period was from 1 month to 5 years after treatment (Table 1). According to the improved Jadad score, 9 of the 12 RCTs studies scored 4 to 7 points, which were high-quality studies; 3 of which scored 2 to 3 points, were low-quality studies. According to the Cochrane bias risk assessment criteria, there are 5 low-level biases, 3 moderate biases, and the remaining 3 are highly biased (Fig. 2). The funnel plot obtained from each analysis was basically symmetrical with a small bias, as shown in the funnel plot of knee score 12 months after PRP treatment of KOA compared with baseline (Fig. 3).

3.2. The therapeutic effect of PRP on KOA

After intra-articular injection of PRP, the knee function scores of the patients were significantly improved compared with before treatment: 1 month after treatment [SMD = 0.60, 95% CI (0.45,

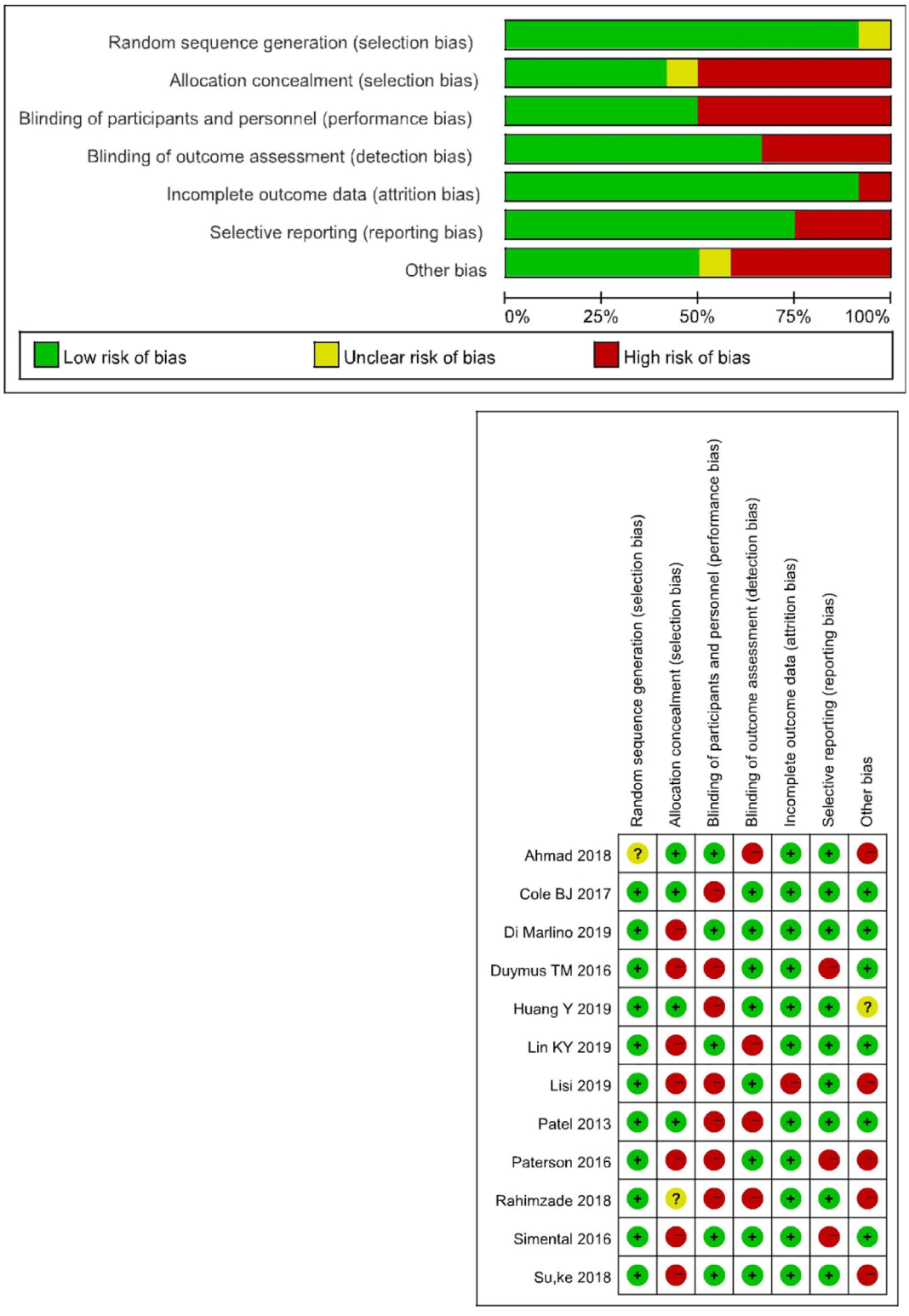

Fig. 2. (A) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (B) Risk of bias graph: review authors' judgements about each risk of bias item for each included study.

0.75), P < 0.01], 2 months [SMD = 0.98, 95% CI (0.73, 1.24), P < 0. 01], 3 months [SMD = 1.16, 95% CI (0.99, 1.33), P < 0. 01], 6 months [SMD = 1.49, 95% CI (1.34, 1.65), P < 0.01], 12 months [SMD = 1.47, 95% CI (1.29, 1.65), P < 0.01], the differences are statistically significant, and The removal of either study did not significantly affect the final results. Knee scores were improved after PRP treatment, and with the increase of follow-up time, the results of knee improvement were more significant, and the difference was the largest at 6 months of follow-up after treatment, and the scores stabilized at 12 months after treatment (Fig. 4).

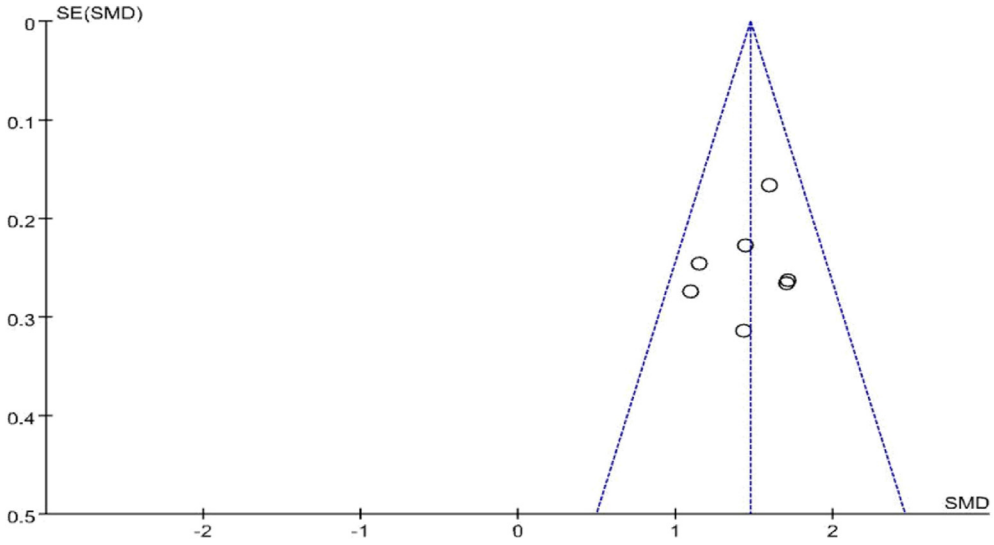

Fig. 3. A funnel plot of the knee score 12 months after PRP treatment of KOA compared with baseline.

3.3. Comparison of efficacy and safety between PRP and placebo

A total of 2 RCTs were enrolled in 156 knees with normal saline (NS) as a placebo to study the efficacy of PRP for KOA. Both studies were double-blind, high-quality studies. In terms of the efficacy of PRP, a summary and quantitative analysis of 2 studies was conducted, and the results showed that the WOMAC score of the PRP group was significantly better than that of the placebo group at 6–12 months after treatment [SMD = 1. 18, 95% CI (0.73, 1.24)], and the difference was statistically significant (P < 0.01). In terms of adverse reactions, one patient in the PRP group and one in the NS group had tachycardia in the Lin KY [3] study; while in the Patel [4] study, 6 patients in the PRP group and 5 patients in the NS group had adverse reactions of different degrees Symptoms include dizziness, headache, nausea, stomach pain, sweating, and tachycardia, but there were no serious consequences, and they resolved on their own within a few days. In spite of this, those patients could still complete treatment and follow-up. After using the random effects model for meta-analysis, the difference between the PRP group and the normal saline group was not statistically significant [RR = 1.03, 95% CI (0.37, 2.90), P = 0.96] (Fig. 5).

3.4. Comparison of efficacy and safety between PRP and HA

A total of 9 RCTs compared the efficacy of intra-articular injection of PRP with HA for KOA. A total of 713 patients were included, of which 5 were high-quality studies with double-blind controls. Eight of the nine RCTs concluded that the efficacy of PRP was superior to HA, and the difference was statistically significant. Paterson's [5] study concluded that the difference between the two was not statistically significant. Quantitative analysis of these studies found that after 1 month after treatment [SMD = 0.21, 95% CI (0.04, 0.39), P = 0.02], 2 months [SMD = 0.27, 95% CI (0.01, 0.54), P = 0. 04], 3 months [SMD = 0.35, 95% CI (0.17, 0.54), P < 0. 01], 6 months [SMD = 0.87, 95% CI (0.71, 1.03), P < 0.01], 12 months [SMD = 0.78, 95% CI (0.60, 0.96), P < 0. 01], functional scores were higher in the PRP group than in the HA group, especially at 6 months after treatment. The differences are statistically significant, and none of them are excluded will have a significant impact on the end result(Fig. 6.).

3.5. PRP treatment costs

Most PRP-related randomized controlled clinical studies did not mention PRP treatment costs. According to Akhundov K [6], the cost of preparing PRP kits in the North American market varies widely. Equipment prices range from $ 3.62 to $ 1550. At present, many scholars or manufacturers have begun to study safe, effective and low-cost PRP preparation technology. Machado ES [7] explored 4 ways to prepare PRP, and finally described a simple and safe method to obtain PRP using low cost, the total cost of disposable materials used is less than $ 10.

4. Discussion

4.1. Possible mechanism of PRP for KOA

KOA is more common in middle-aged and elderly patients, mainly manifested as joint pain and dysfunction, and is the main cause of pain and disability worldwide [8]. Its pathogenesis is not clear, and it is believed to be related to articular cartilage degeneration and synovial inflammation. The most significant effect is the serious degradation of articular cartilage during the development of the disease [9]. PRP is rich in a variety of growth factors and inflammation regulators. A large number of in vivo and in vitro experiments have confirmed that PRP can protect cartilage cells, promote cartilage healing, and reduce inflammation in joints [10]. At present, one of the molecular mechanisms is believed to contain interleukin IL-1b in the joint microenvironment of OA patients, which can activate the nuclear factor NF-kB [11] and then inhibit the synthesis of cartilage matrix. And PRP contains high concentration of growth factors, which can delay the development of osteoarthritis by inhibiting the activation of the NF-kB target gene. In addition, PRP can promote the synthesis of proteoglycan and collagen [12], and indirectly relieve the clinical symptoms of KOA.

4.2. Efficacy of PRP for KOA

This article analyzed the clinical effects of 421 patients (450 knees) with PRP injection in the knee joint. The judgment methods included WOMAC score, VAS score, and IKDC score. The knee function scores of patients at 1, 2, 3, 6 and 12 months after PRP treatment were better than before treatment, the difference was

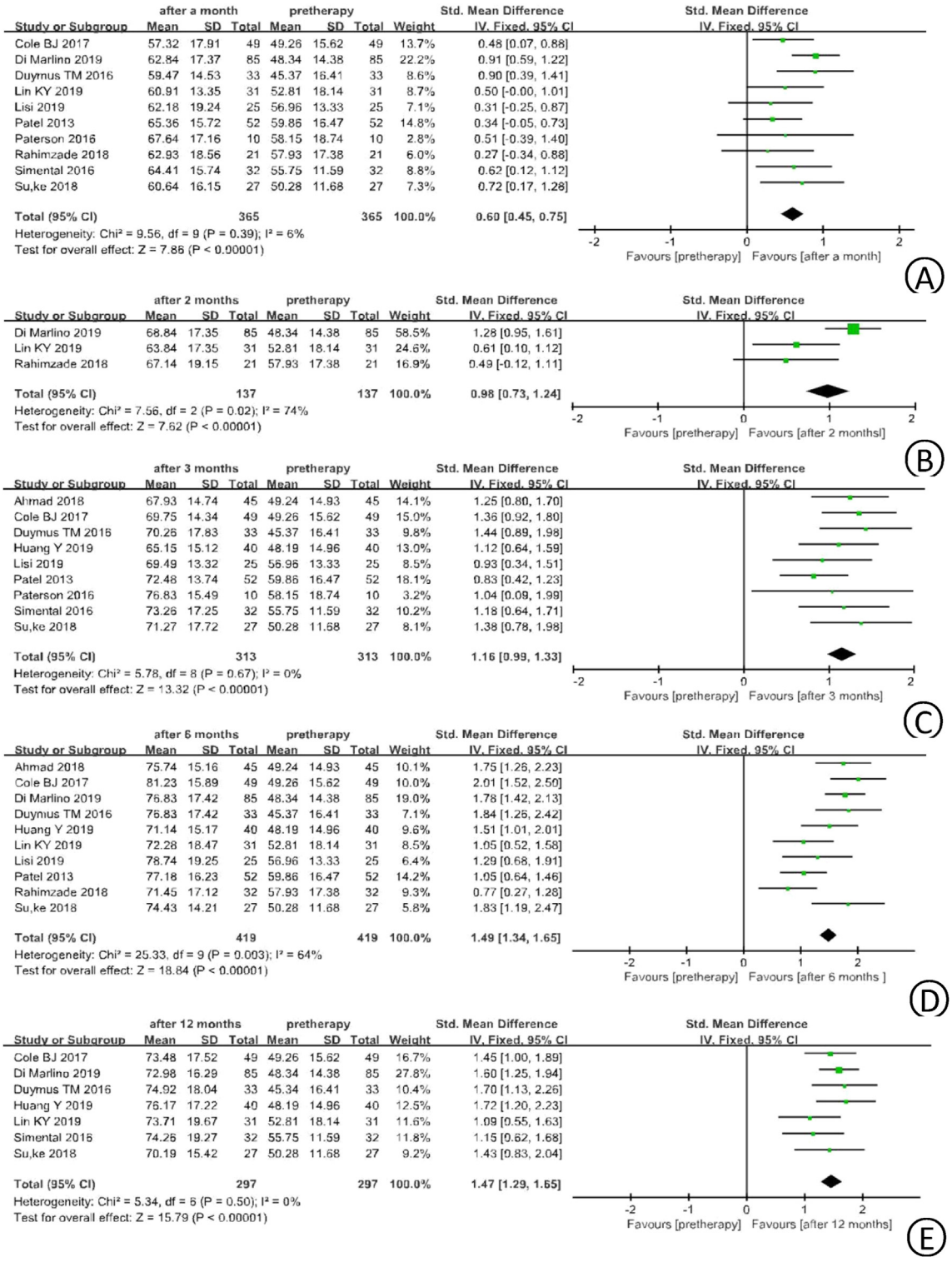

Fig. 4. Forest plot of comparison: Knee score before and after PRP treatment of KOA. A, 1 month after treatment; B, 2 months after treatment; C, 3 months after treatment; D, 4 months after treatment; E, 6 months after treatment; F, 12 months after treatment.

statistically significant, and no adverse reactions related to PRP occurred. In order to avoid the placebo effect in the treatment, the RCTs of Lin KY [3] and Patel [4] included in the study were set with normal saline as a control, and both studies were double-blind trials. The results also found that the effect of PRP on KOA was better than in the control group, the difference was statistically significant. This indicates that intra-articular injection of PRP can effectively improve knee function scores in patients with KOA.

The number and interval of PRP injections have not been unified. Görmeli's [13] clinical randomized controlled study of 162 patients showed that multiple (3) PRP injections can help achieve better clinical results, which is consistent with the results of most

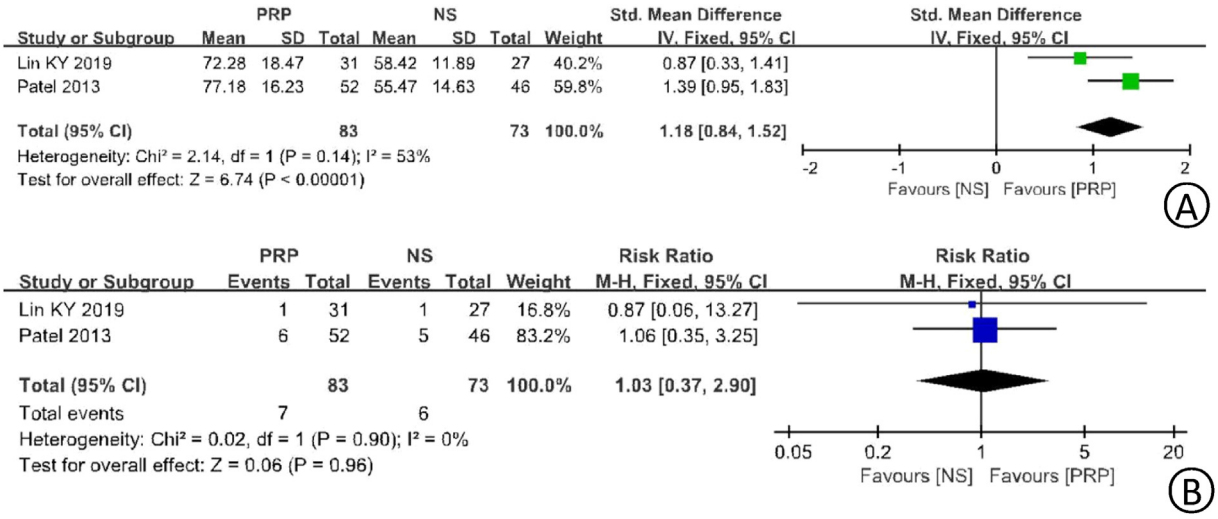

Fig. 5. Forest plot of comparison: WOMAC score and adverse reactions of PRP and placebo for knee OA. A, WOMAC score; B, adverse reaction.

scholars. However, the interval is applied from 1 week to 4 weeks. Due to the various preparation methods of PRP, there is still no relevant high-quality RCT to prove the impact of PRP injection interval on the treatment effect.

However, most of these RCTs only followed short-term and intermediate-term (6–12 months) clinical data, and only Simental [14] and Di martino [15] et al. followed up longer-term clinical data (2 and 5 years respectively). The results show that the long-term clinical effect of PRP treatment gradually decreases, but compared with other conservative treatments, the retreatment rate of patients treated with PRP is significantly reduced.

In addition, there is currently a lack of standardization in the preparation of PRP products, and there are differences in the types and concentrations of growth factors contained in PRP, leading to controversy over the clinical effectiveness of PRP in the treatment of KOA. In particular, there is much debate as to whether concentrated leukocytes should be retained in PRP. Based on analysis of Milants C's [16] basic experiments, the existence of leukocytes in PRP should be avoided to prevent inflammatory reactions. While Kenmochi [17] has demonstrated through clinical trials that leukocyte-rich PRP is still effective for KOA, and the occurrence of adverse reactions has no statistical significance with leukocyte-poor PRP. However, due to the various ways to prepare PRP, more high-quality RCTs are still needed to prove the effect of leukocytes in PRP.

4.3. Comparison of efficacy between PRP and other conservative treatment methods

At present, for early and mid-term KOA, clinically conservative treatment methods are preferred. Oral non-steroidal anti-inflammatory drugs are the most widely used in drug therapy. They have effective effects on the relief of clinical symptoms such as pain and swelling in early mild KOA patients. However, it requires long-term use and has more adverse reactions. Intra-articular injection of drug treatment can form high-concentration drugs locally in the diseased tissue, reduce systemic reactions, and do not require long-term use. Therefore, this has become the main method to stimulate cartilage regeneration.

Currently, the most commonly used intra-articular injection drug is HA, which is an important part of the synovial fluid in the knee joint. HA plays a key role in lubricating the articular surface, reducing stress on the load bearing surface, and transporting synovial cartilage nutrients. Navarro-Sarabia F [18] conducted a follow-up of 306 KOA patients in a randomized controlled trial of intra-articular injection of HA versus placebo for up to 40 months. The results showed that repeated intra-articular injections of HA could improve clinical symptoms in patients with KOA However, after prolonged treatment, it does not reflect whether there is a remission of KOA or just a change in the natural process of the disease. Most of the RCTs selected in this article use HA as a control group for PRP treatment. Their results show that both treatment methods have effectively improved the knee function and symptoms over time. Compared with HA, PRP not only provides better clinical improvement, but also has a lower retreatment rate [15] during long-term follow-up.

In addition, ozone and corticosteroids are also commonly used in knee joint injections. Babaei-Ghazani A [19] performed a follow-up of 62 patients in ultrasound-guided corticosteroid injection and oxygen-ozone injection on KOA for 3 months. The results showed that both corticosteroids and ozone injections were effective in patients with KOA, and patients in the ozone group had longer clinical symptoms. This is because of the strong oxidizing properties [20] of ozone, which has a strong anti-inflammatory and powerful analgesic effect. In this article, Duymus TM [21] and Huang Y [22] respectively used ozone and corticosteroids as the control group for PRP treatment. The results showed that the early efficacy of each group was similar, but the middle-term effect was significantly better in the PRP group, and ozone and corticosteroids had lost their effectiveness in the late stage. This is because ozone and corticosteroids have not improved the microenvironment of the cells in the joints, so they have good clinical effects only in the short term. Therefore, they cannot replace the role of HA and PRP in KOA treatment.

In addition to PRP, scholars are exploring other biologic therapies. Such as Amniotic Suspension Allograft (ASA), mesenchymal stem cells (MSCs), exosomes, botulinum toxin type A, etc [23]. However, due to lack of high-quality research and other reasons, their clinical application is currently limited.

4.4. Safety of PRP for KOA

Currently, most of the PRP used in clinical practice is to obtain the product PRP by drawing the patient's own venous blood, adding biogel and centrifugation in vitro, so PRP does not cause immune rejection and has no risk of disease transmission. This is also confirmed [24] in the treatment of diseases other than KOA by PRP. In combination with the RCTs mentioned in this article, the adverse

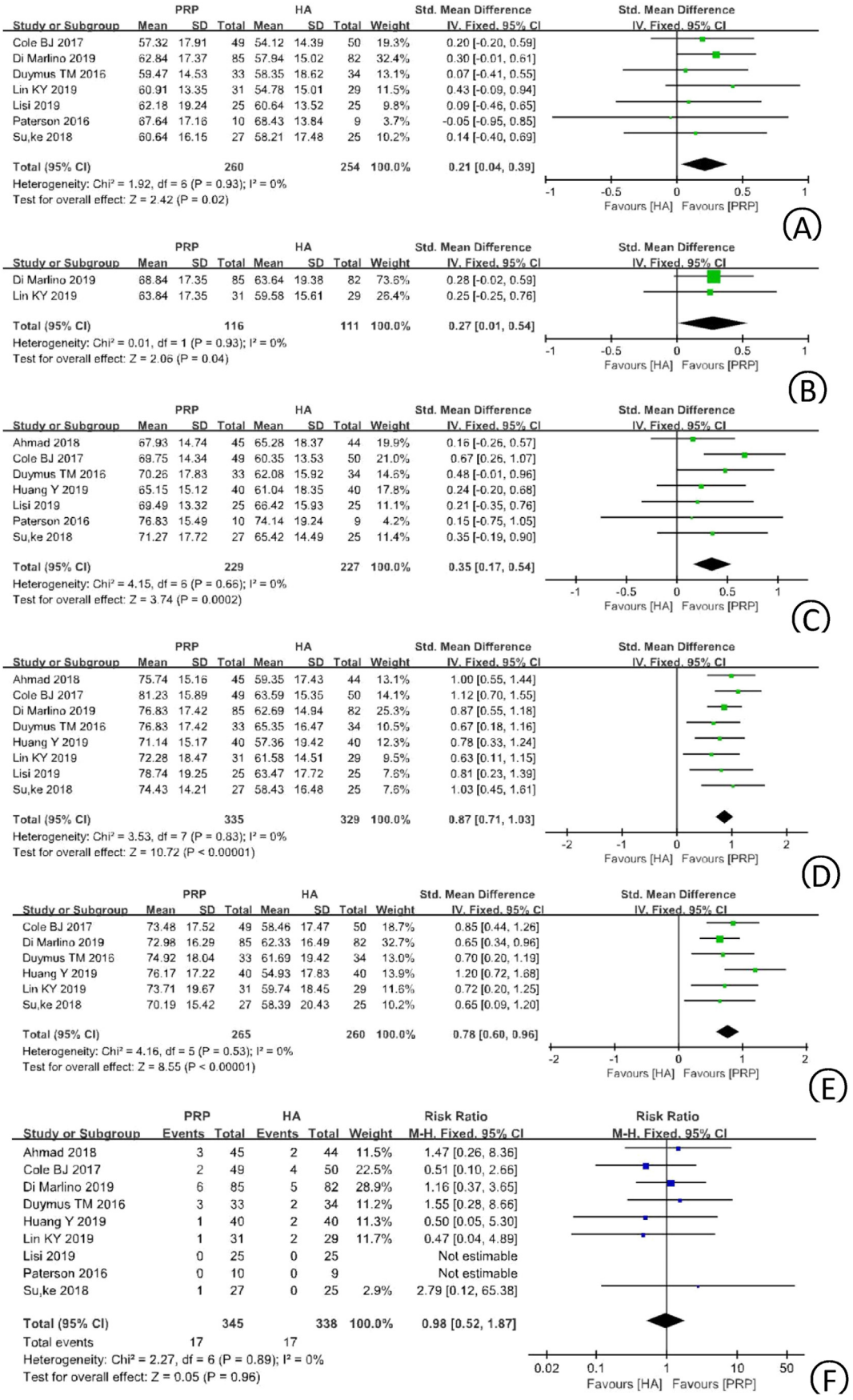

Fig. 6. Forest plot of comparison: The comparison of knee score between PRP and HA for KOA treatment. A, 1 month after treatment; B, 2 months after treatment; C, 3 months after treatment; D, 4 months after treatment; E, 6 months after treatment; F, 12 months after treatment.

reactions caused by PRP are non-specific, and most are related to the injection operation itself, and there is no statistical difference compared with the adverse reactions of the control group. Therefore, these adverse reactions usually resolve and resolve themselves within a few days.

4.5. Limitations and shortcomings of this study

Although clear inclusion and exclusion criteria were established in this study, significant heterogeneity was found between these RCTs in quantitative analysis. These heterogeneity may come from the degree of illness of KOA patients, or from the method, composition, content, injection method and frequency of PRP, and may be related to the scoring standards and methods used in these studies. Although this article conducted a subgroup analysis according to the treatment methods of each follow-up time point and the control group, and unifiedly summarized knee function scores, it still could not effectively reduce heterogeneity. This is in contrast to the situation encountered in previous systematic reviews. In addition, due to the limited patient information provided by the included RCTs, this study cannot classify the age and condition of the patients, making it difficult to discover which patients are most sensitive to the efficacy of PRP.

5. Conclusion

In summary, based on the analysis of the included RCTs, intra-articular injection of PRP is a safe and effective method for treating early and mid-term KOA, and it has better clinical effects than HA, ozone, and corticosteroids. However, these results need to be further verified by a large number of well-designed and less heterogeneous RCTs.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

We did the meta-analysis, and the retrieval and download of the paper could be obtained through the platform provided by the campus network of Southern Medical University. In this process, no economic interests were involved.

References

[1] Zhao M, Liang Y, Wang X. Chinese primary knee osteoarthritis progression cohort (CPKOPC) to evaluate the progression of knee osteoarthritis in the Beijing population: a prospective cohort study protocol. BMJ Open 2019 Aug;9(8):430–6.
[2] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for systematic reviews of interventions version 6.0 (updated july 2019). Cochrane; 2019 July. Available from: www.training.cochrane.org/handbook.
[3] Lin K, Yang C, Hsu C. Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: a randomized, double-blind, triple-parallel, placebo-controlled clinical trial. Arthroscopy 2019 Jan;35(1):106–17.
[4] Patel S, Dhillon MS, Aggarwal S. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 2013 Feb;41(2):356–64.
[5] Paterson KL, Nicholls M, Bennell KL. Intra-articular injection of photoactivated platelet-rich plasma in patients with knee osteoarthritis: a double-blind, randomized controlled pilot study. BMC Muscoskel Disord 2016 Feb;9(2):167–71.
[6] Akhundov K, Pietramaggiori G, Waselle L. Development of a cost-effective method for platelet-rich plasma (PRP) preparation for topical wound healing. Ann Burns Fire Disasters 2012 Dec;25(4):207–13.
[7] Machado ES, Leite R, Dos Santos CC. Turn down - turn up: a simple and low-cost protocol for preparing platelet-rich plasma. Clinics 2019 Oct;74(10):1132–7.
[8] Sakellariou G, Conaghan PG, Zhang W. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis 2017 Sep;76(9):1484–94.
[9] Abramoff B, Caldera FE. Osteoarthritis: pathology, diagnosis, and treatment options. Med Clin North Am 2020 Mar;104(2):161–7.
[10] Vilchez-Cavazos F, Millán-Alanís JM, Blázquez-Saldaña J. Comparison of the clinical effectiveness of single versus multiple injections of platelet-rich plasma in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Orthop J Sports Med 2019 Dec;7(12):1536–42.
[11] Mehranfar S, Abdi Rad I, Mostafavi E. The use of stromal vascular fraction (SVF), platelet-rich plasma (PRP) and stem cells in the treatment of osteoarthritis: an overview of clinical trials. Artif Cells Nanomed Biotechnol 2019 Dec;47(1):882–90.
[12] Gato-Calvo L, Magalhaes J, Ruiz-Romero C. Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Ther Adv Chronic Dis 2019 Oct;77(2):223–8.
[13] Görmeli G, Görmeli CA, Ataoglu B. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2017 Mar;25(3):958–65.
[14] Simental-Mendia M, Vilchez-Cavazos JF, Pena-Martinez VM. Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Arch Orthop Trauma Surg 2016 Dec;136(12):1723–32.
[15] Di Martino A, Di Matteo B, Papio T. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 Years of a double-blind, randomized controlled trial. Am J Sports Med 2019 Feb;47(2):347–54.
[16] Milants C, Bruyère O, Kaux JF. Responders to platelet-rich plasma in osteoarthritis: a technical analysis. BioMed Res Int 2017 Jan;20(1):1–11.
[17] Kenmochi M. Clinical outcomes following injections of leukocyte-rich platelet-rich plasma in osteoarthritis patients. J Orthop 2020 Jan;18(1):143–9.
[18] Navarro-Sarabia F, Coronel P, Collantes E. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011 Nov;70(11):1957–62.
[19] Babaei-Ghazani A, Najarzadeh S, Mansoori K. The effects of ultrasound-guided corticosteroid injection compared to oxygen–ozone (O2–O3) injection in patients with knee osteoarthritis: a randomized controlled trial. Clin Rheumatol 2018 Sep;37(9):2517–27.
[20] Lopes De Jesus CC, Dos Santos FC, de Jesus LMOB. Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: a randomized, double-blinded, placebo-controlled study. PloS One 2017 Feb;12(7):791–8.
[21] Duymus TM, Mutlu S, Dernek B. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc 2017 Feb;25(2):485–92.
[22] Huang Y, Liu X, Xu X. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis: a prospective randomized controlled study. Orthopade 2019 Mar;48(3):239–47.
[23] Bao X, Tan J, Flyzik M. Effect of therapeutic exercise on knee osteoarthritis after intra-articular injection of botulinum toxin type A, hyaluronate or saline: a randomized controlled trial. J Rehabil Med 2018 Jun 15;50(6):534–41.
[24] Ojea-Pérez AM, Acebes-Huerta A, Arias-Fernández T. Implementation of a closed platelet-rich-plasma preparation method using the local blood bank infrastructure at the Principality of Asturias (Spain): back to basic methodology and a demographics perspective after 1 year. Transfus Apher Sci 2019 Oct;58(5):701–4.
[25] Ahmad HS, Farrag SE, Okasha AE. Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. Int J Rheum Dis 2018 May;21(5):960–6.
[26] Cole BJ, Karas V, Hussey K. Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. Am J Sports Med 2017 Feb;45(2):960–6.
[27] Lisi C, Perotti C, Scudeller L. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clin Rehabil 2018 Mar;32(3):330–9.
[28] Rahimzadeh P, Imani F, Faiz SHR. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clin Interv Aging 2018 Jan;13(1):73–9.
[29] Su K, Bai Y, Wang J. Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis. Clin Rheumatol 2018 May;37(5):1341–50.