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ORIGINAL ARTICLE

The influence of sample size and gender composition on the meta-analysis conclusion of platelet-rich plasma treatment for osteoarthritis

Kun Zhao [a,b,d,☆], Yan-shan Liu [a,b,f,☆], Liu-yan Nie [g], Lin-na Qian [a], Nan-fang Nie [a,b], Sebastian Leptihn [c], Varitsara Bunpetch [a,b], Jia-qi Xu [a,b], Xiao-hui Zou [a,b,f,**], Hongwei Ouyang [a,b,c,d,e,*]

[a] Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cells and Regenerative Medicine, Zhejiang University School of Medicine, Hangzhou, China
[b] Key Laboratory of Tissue Engineering and Regenerative Medicine of Zhejiang Province, Zhejiang University School of Medicine, Hangzhou, China
[c] Zhejiang University-University of Edinburgh Institute, Zhejiang University School of Medicine, Hangzhou, China
[d] Department of Sports Medicine, Zhejiang University School of Medicine, Hangzhou, China
[e] China Orthopedic Regenerative Medicine Group (CORMed), Hangzhou, China
[f] Clinical Research Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, PR China
[g] Department of Rheumatology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, PR China

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ABSTRACT

Objective: The magnitude of the therapeutic effects of intra-articular injection of platelet-rich plasma (PRP) on osteoarthritis (OA) is still under debate. The goal of this study that was a systematic review of randomised controlled trials of PRP injections for the treatment of OA was to elucidate the therapeutic efficacy of PRP.

Methods: Electronic databases of PubMed, CENTRAL, EMBASE, EBSCO, ClinicalTrials.gov, and International Clinical Trials Registry Platform were searched from inception to June 2018 for RCTs that compared PRP injections to controls in patients with OA. A random-effects approach was used to compile data and subgroups according to trial size (large trials versus small trials), patient profile (age and gender), and PRP preparation method was performed.

Results: Thirty trials met the inclusion criteria and were analysed. All results had unexplained statistical heterogeneity. Patients treated with PRP compared with control showed statistically relevant pain relief and function improvement at short term (standardised mean difference [SMD] = −0.62, 95% confidence interval [CI]: −0.98 to −0.27, $P = 0.0006$, SMD = −0.74, 95% CI: −1.11 to 0.36, $P = 0.0001$, respectively), medium term (SMD = −0.53, 95% CI: −0.83 to −0.23, $P = 0.0006$, SMD = −0.50, 95% CI: −0.75 to −0.25, $P = 0.0006$), and long term (SMD = −0.69, 95% CI: −1.08 to −0.30, $P = 0.0006$, SMD = −0.68, 95% CI: −0.1.09 to −0.27, $P = 0.001$, respectively). A subgroup analysis of the data from large trials and from trials composed of less than 50% female patients revealed that therapeutic effects of the treatment are insignificant.

Conclusions: According to the currently available data, PRP injections are beneficial for pain relief and function improvement in patients with OA. This meta-analysis, however, demonstrated that the efficacy of PRP is related to sample size and gender composition. Thus, more randomised controlled trials of high quality and larger patient size, also including gender aspects, are required to understand this phenomenon.

The translational potential of this article: The translation potential of this meta-analysis is that provided another perspective to analyse the treatment effect of PRP for OA. In future research, phenotypes subpopulation and gender difference of OA patient should be considered for PRP treatment.

Abbreviations: PRP, platelet-rich plasma; OA, osteoarthritis; RCTs, randomised controlled trials; ICTRP, International Clinical Trials Registry Platform; FDA, the U.S. Food and Drug Administration; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; IA, intra-articular; SMD, standardised mean difference; CI, confidence intervals; LP, leucocyte-poor; LR, Leucocyte-rich; CCTs, clinical controlled trials; HA, hyaluronic acid.

* Corresponding author. Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cells and Regenerative Medicine, Zhejiang University School of Medicine, Hangzhou, China.
** Corresponding author. Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cells and Regenerative Medicine, Zhejiang University School of Medicine, Hangzhou, China.
E-mail addresses: zouxiaohui@zju.edu.cn (X.-h. Zou), hwoy@zju.edu.cn (H. Ouyang).
☆ Contribute equally.

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Introduction

Osteoarthritis (OA) is the most prevalent degenerative joint disorder characterised by pain, stiffness, limitation of movement, and disability [1], affecting approximately 18% of women and 10% of men older than 60 years of age [2]. Despite intensive laboratory and clinical investigations, unambiguously effective therapies targeting the underlying causes have not yet been developed [2]. Blood-derived products as a safe treatment could modify the biological microenvironment at different points in the disease process and might provide an opportunity to interfere with self-perpetuating mechanisms in OA [3]. One of the strategies to relieve symptoms of OA is the injection of platelet-rich plasma (PRP) into affected joints because it is safe, simple to use, and acceptable [3]. PRP is an autologous concentrate of human platelets isolated through centrifugation of the patient's blood, containing numerous components including growth factors, cytokines, and many other mediators. PRP injections have been shown to be able to promote healing of injured tendons, ligaments, muscles, and joints and can also be applied when various musculoskeletal problems occur [4]. Although intra-articular (IA) injections of PRP are legally available and offered in the United States to patients with OA in the clinic [5], meta-analysis published to date have not reached consistent conclusions and the American Academy of Orthopaedic Surgeons (AAOS) guideline mentions "we are unable to recommend for or against growth factor injections and/or PRP for patients with symptomatic OA of the knee" [5–9]. New randomised controlled trials have been conducted after the most recently published meta-analysis on PRP [10–13]. In this study, we identified all randomised trials published to date and analysed all of which fulfilled the required quality standard to provide a statistically supported and updated insight into the efficacy of PRP in treating OA.

Methods

This meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [14] and presented based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [15]. The protocol for this meta-analysis is available in International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018100067).

Data sources and searches

We identified studies that evaluated the efficacy of PRP for patients with OA by searching PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, ClinicalTrials.gov, and International Clinical Trials Registry Platform databases from inception to June 12, 2018. The search terms used were "platelet rich plasma", "platelet rich fibrin", "PRP" combined with "osteoarthritis" and "osteoarthrosis"; Table S1 shows the search strategy details. We also extracted relevant articles that met the inclusion criteria for randomised trials which were included in previous systematic reviews or meta-analysis.

Eligibility criteria

Types of studies

Randomised controlled trials available as full-text articles were potentially eligible for inclusion.

Types of participants

Adult patients who were clinically diagnosed with OA based on the criteria described by the American College of Rheumatology or clinical and radiological information.

Types of interventions

Studies of interest were patients who received IA injections with PRP or closely related platelet-containing products [i.e., autologous blood, platelet–leucocyte gel, platelet concentrate, platelet gel, or plasma rich in growth factors (PRGF-Endoret)], which were compared with control treatments including saline, or no treatment, or another active treatment (e.g. nonsteroidal anti inflammatory drugs, hyaluronic acid [HA], or physical therapy). Further inclusion criteria were that platelet-rich therapy was the only treatment given or was delivered in addition to a standard of care treatment applied to all trial participants, which includes operative or nonoperative measures.

Types of outcomes

Studies reporting one or both of the following outcome measures were eligible for inclusion: (1) pain and (2) physical function, measured with standard medical instruments.

Data extraction

Two authors independently extracted the following information: authors, the year of publication, country, age distribution, gender proportion, study design, intervention condition, intervention period, and outcome measures. If there were disagreements between the two reviewers, a third author was consulted to decide for inclusion or exclusion of the study for the meta-analysis. If the trials permitted multiple comparisons, only the information and data of interest reported in the original articles were extracted. In case the necessary information on any data was unavailable but important for the study, the authors responsible for the published report were contacted and the data were obtained.

Risk of bias assessment

Studies that met the inclusion criteria were evaluated for methodological quality to assess the risk of bias using the Cochrane Collaboration's risk of bias tool as described in the Cochrane Handbook for Systematic Reviews of Interventions; each quality item was graded into three categories: low risk, high risk, or unclear risk [14]. The quality assessment covered the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Review Manager 5.3 (Nordic Cochrane Centre) was used to present the results graphically. This assessment was performed independently by two reviewers and in the event of disagreements regarding the assessment of studies, a third reviewer was consulted.

Data synthesis and analysis

We used a prespecified cutoff of 50 randomly assigned patients per arm to distinguish between small-scale and large-scale trials and grouped the outcomes into three time points of assessment: short term ($\leq$3 months), medium term (>3 months but $\leq$6 months), and long term (12 months).

Continuous outcomes were used for statistical efficacy analysis using Hedge's standardised mean difference (SMD) with 95% confidence intervals (CIs) with the random effects model for pooling estimates for each analysis. The significance of the pooled effects was evaluated by a Z-test, and a P value of less than 0.05 was considered significant. I^2 statistic was used to examine overall heterogeneity between studies, and values higher than 50% were defined to have high heterogeneity [16].

Subgroup analyses were carried out according to trial size (large trials versus small trials), patient characteristics (age and gender), and PRP preparation method (PRP category, spinning approach, and activator).

All statistical analyses were performed using Review Manager 5.3 and Stata software (version 15.1; StataCorp, USA).

Results

Study identification and characteristics

From the database search, 1455 potentially eligible records and two

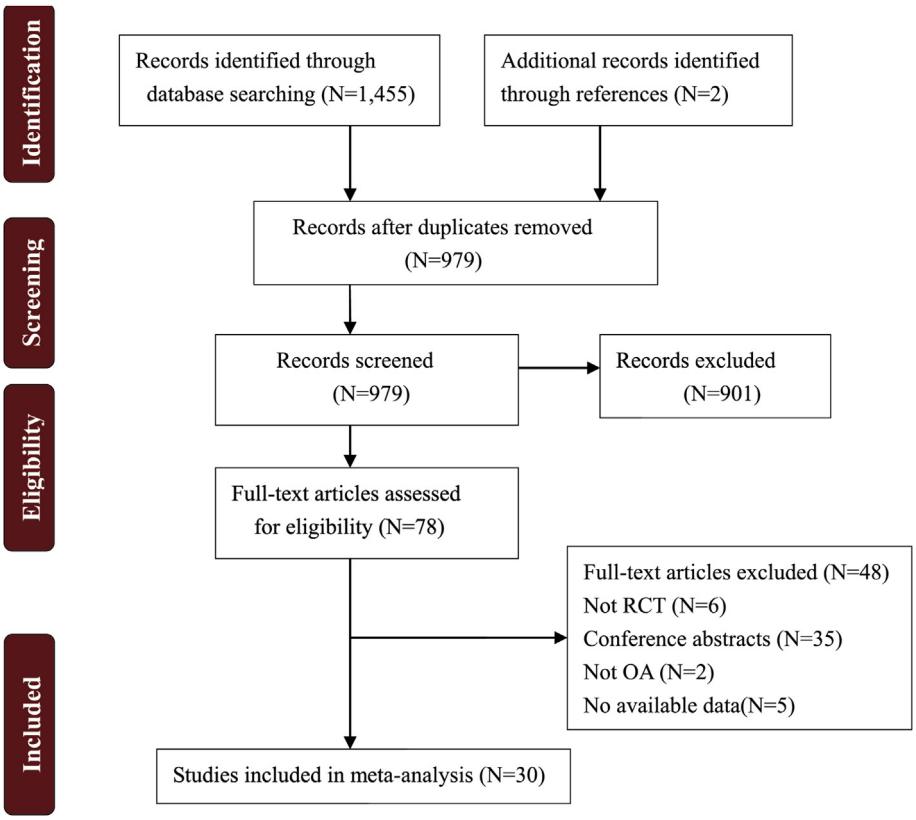

Figure 1. Diagram of the study selection process for the systematic review and meta-analysis.

previously published meta-studies [17,18] were identified, from which 478 articles were duplicates. After a review of the abstract, 901 studies did not meet our inclusion criteria and were excluded. The remaining 78 full-text documents were analysed, however, only 30 randomised controlled trials (RCTs) [10,12,13,17–43] were ultimately included in this meta-analysis (Figure 1).

All studies were randomised and 12 were double-blind trials; 20 trials described an adequate random sequence generation process. The risk of bias of included studies is shown in Figure S1. The characteristics of the included data are summarised in Table 1. The 30 included trials were published between 2012 and 2018, with sample sizes ranging from 31 to 183 patients and a total of 2178 patients. The mean participant age ranged from 32.3 to 71.4 years.

Outcome of meta-analysis

Detailed scale data that were included in the meta-analysis are summarised in Table S2.

Pain relief

Short-term follow-up

Data of nineteen trials (1326 patients) contributed to the meta-analysis of pain relief at short-term. Unexplained statistical heterogeneity was excessive (I^2 = 89%), and we could not identify a particular trial causing this excess variability (Figure 2A). Data pooling when such a high degree of heterogeneity of unknown cause exists is not advisable [44]. If the data were pooled, a significant effect of PRP treatment on pain was observed (SMD = −0.62, 95% CI: −0.98 to −0.27, P = 0.0006). In contrast to this, pooling large trials showed no significant effect of the treatment on pain levels (SMD = −0.13, 95% CI: −0.57 to 0.30, P = 0.55), but both results were heterogeneous (I^2 = 79%) (Figure 2A).

Medium-term follow-up

Twenty-one trials reported pain reduction in the treatment group (n = 859) relative to the control group (n = 838) at medium-term follow-up. Pooling showed that PRP injection had a benefit on pain reduction when compared with all controls (SMD = −0.53, 95% CI: −0.83 to −0.23, P = 0.0006) with an excessive degree of unexplained statistical heterogeneity (I^2 = 89%) (Figure 2B). When pooling large trials comparing PRP with all controls (SMD = −0.46, 95% CI: −1.08 to 0.15, P = 0.14) (Figure 2B), results were inconclusive. One trial [30] was only followed for 4 months, in contrast to other studies, which were followed for 6 months. The exclusion of the 4-month trial did not statistically change the magnitude or direction of the overall obtained observations.

Long-term follow-up

Thirteen studies were available for analysis (510 intervention patients and 498 control patients). To ensure the consistency of results, data from a 12-month follow-up period were used instead of 18-month follow-up [12]. Pooling these studies showed a significant overall effect of PRP treatment being beneficial (SMD = −0.69, 95% CI: −1.08 to −0.30, P = 0.0006). However, no significant effect is observed when pooling large trials (SMD = −0.26, 95% CI: −0.89 to 0.36, P = 0.41) (Figure 2C).

Physical function improvement

Seventeen trials reported a measure of joint function assessed after a short-term period (547 intervention patients and 551 control patients). Because different measurement systems were used in these trials, we calculated the standardised effect. Only two large trials were available [20,26], which showed no significant effect favouring PRP treatment for joint function improvement when their data were pooled (SMD = 0.04, 95% CI: −0.20 to 0.27, P = 0.76), and heterogeneity was acceptable (I^2 = 0%) (Figure 3A). At medium-term and long-term follow-up, meta-analysis of both large trials could not demonstrate a significant effect of

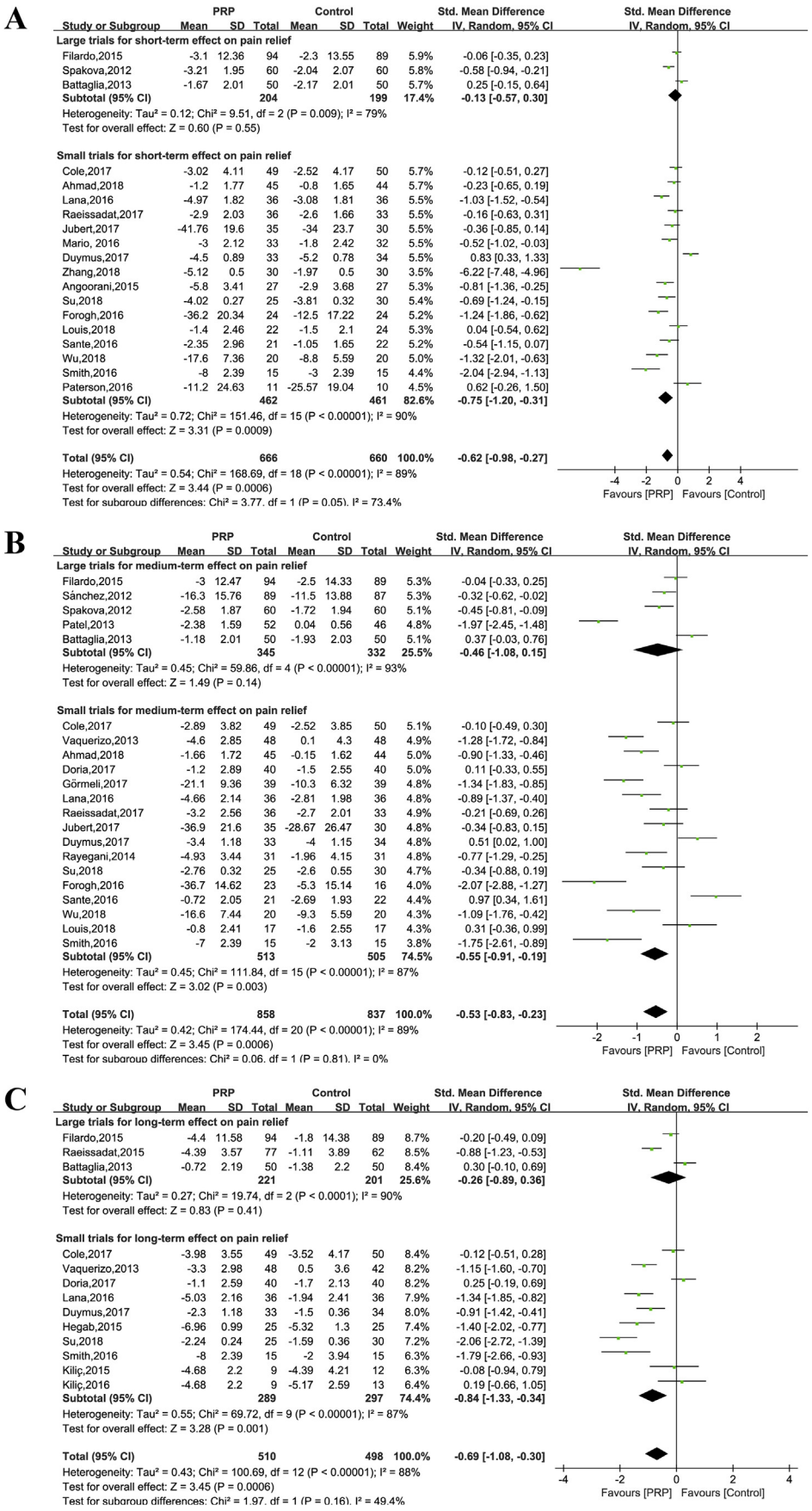

Figure 2. Forest plot for effectiveness of PRP compared with controls for pain relief. (A). At short-term follow-up; (B) at medium-term follow-up (C) at long-term follow-up.

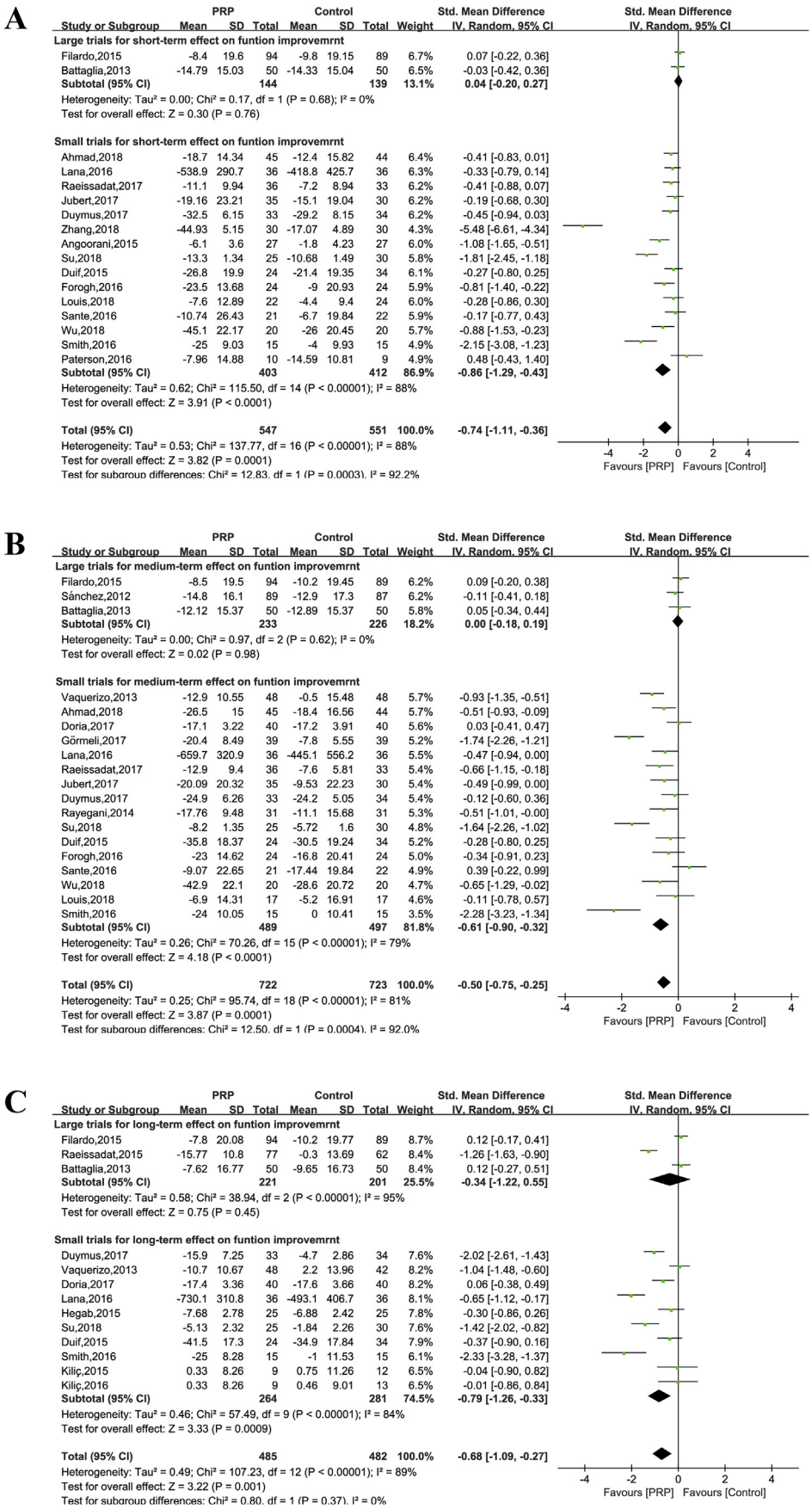

Figure 3. Forest plot for effectiveness of PRP compared with controls for function improvement. (A) At short-term follow-up; (B) at medium-term follow-up; (C) at long-term follow-up.

Table 1
Characteristics of included studies.

Study	Country	PRP group						Control group				Outcome	Measurement time point (month)
		Sample size	Age (year)	Female (%)	Category	Spinning approach	Activator	Sample size	Age (year)	Female (%)	Intervention		
Sánchez, 2012 [17]	Spain	89	60.5 ± 7.9	52	LP	Single	$CaCl_2$	87	58.9 ± 8.2	52	HA	WOMAC pain, stiffness, physical function, and adverse event	6
Spakova, 2012 [19]	Slovakia	60	52.8 ± 12.4	45	LP	Treble	NR	60	53.2 ± 14.5	48	HA	NRS and adverse event	3 and 6
Battaglia, 2013 [20]	Italy	50	51.0 ± 12.0	40	LR	Double	$CaCl_2$	50	56.0 ± 12.0	34	HA	VAS, HHS, and adverse event	1, 3, 6, and 12
Patel, 2013 [21]	India	27	53.1 ± 11.6	59	LP	Single	$CaCl_2$	23	53.7 ± 8.2	74	Saline	VAS	6
Vaquerizo, 2013 [18]	Spain	48	62.4 ± 6.6	67	LP	Single	$CaCl_2$	48	64.8 ± 7.7	54	HA	WOMAC pain, stiffness, physical function, and adverse event	6 and 12
Rayegani, 2014 [22]	Iran	31	58.1 ± 9.0	94	LR	Double	NR	31	54.7 ± 10.8	94	Unclear	WOMAC pain, stiffness, and physical function	6
Angoorani, 2015 [23]	Iran	27	62.2 ± 12.1	82	LR	Double	$CaCl_2$	27	61.6 ± 8.1	93	TENS+exercise	KOOS and adverse event	1 and 2
Duif, 2015 [25]	Germany	24	64.1 ± 9.0	42	LP	Single	NR	34	64.3 ± 9.0	65	Blank	Lysholm	1.5, 6, and 12
Filardo, 2015 [26]	Italy	94	53.3 ± 13.2	36	LR	Double	$CaCl_2$	89	57.6 ± 11.8	42	HA	KOOS, EQ-VAS, IKDC, and adverse event	2, 6, and 12
Hegab, 2015 [27]	Egypt	25	39.0 ± 5.0	64	LP	Single	NR	25	38.2 ± 4.4	56	HA	VAS, MMO, and adverse event	12
Kiliç, 2015 [24]	Turkey	18	32.2 ± 14.3	88	LR	Single	NR	12	35.1 ± 14.8	93	Blank	VAS, MMO, adverse event	12
Raeissadat, 2015 [28]	Iran	77	56.9 ± 9.1	90	LR	Double	NR	62	61.1 ± 7.5	76	HA	WOMAC pain, stiffness, and physical function	12
Forogh, 2016 [31]	Iran	24	59.1 ± 7.0	71	LR	Double	$CaCl_2$	24	61.1 ± 6.7	63	corticosteroid	VAS and KOOS	2 and 6
Kiliç, 2016 [29]	Turkey	18	32.2 ± 14.3	89	LR	Single	NR	13	28.1 ± 11.1	77	HA	VAS, MMO, and adverse event	12
Lana, 2016 [32]	USA	36	60.9 ± 7.0	81	LR	Double	thrombin	36	60.0 ± 6.6	92	HA	VAS, WOMAC pain, stiffness, and physical function	1, 3, 6, and 12
Mario, 2016 [34]	Mexico	33	57.2 ± 8.1	67	LP	Double	$CaCl_2$	32	55.6 ± 11.4	62	acetaminophen	VAS	3
Paterson, 2016 [33]	Australia	11	49.9 ± 13.7	27	LR	Double	Ultraviolet light	10	52.7 ± 10.3	30	HA	VAS, KOOS, and adverse event	1 and 3
Sante, 2016 [30]	Italy	21	71.4 ± 6.0	48	LP	Double	NR	22	73.6 ± 7.9	59	HA	VAS, WOMAC pain, stiffness, and physical function	1 and 4
Smith, 2016 [35]	USA	15	53.5 ± 8.2	67	LP	Single	NR	15	46.6 ± 9.3	60	Saline	WOMAC pain, stiffness, physical function, and adverse event	0.25, 0.5, 2, 3, 6, and 12
Cole, 2017 [36]	USA	49	56.0 ± 10.4	43	LP	Single	NR	50	56.9 ± 10.5	60	HA	WOMAC pain	3, 6, and 12
Doria, 2017 [37]	Italy	40	67.3 ± 5.8	Unclear	LR	Double	thrombin	40	68.0 ± 4.6	unclear	HA	VAS, WOMAC pain, stiffness, physical function, HHS, and adverse events	6 and 12
Duymus, 2017 [38]	Turkey	33	60.4 ± 5.1	97	LR	Single	NR	34	60.3 ± 9.1	97	HA	WOMAC pain, stiffness, and physical function	1, 3, 6, and 12
Görmeli, 2017 [39]	Turkey	39	53.7 ± 13.1	59	LR	Double	$CaCl_2$	39	53.5 ± 14.0	56	HA	IKDC and EQ-VAS	6
Jubert, 2017 [40]	Spain	35	65.6 ± 8.6	66	LP	Double	NR	30	68.0 ± 7.2	80	corticosteroid	VAS and KOOS	1, 3, and 6
Raeissadat, 2017 [41]	Iran	36	57.0 ± 7.2	81	LR	Trible	$CaCl_2$	33	59.5 ± 7.5	82	HA	VAS, WOMAC pain, stiffness, and physical function	2 and 6

(*continued on next page*)

Table 1 (*continued*)

Study	Country	PRP group						Control group				Outcome	Measurement time point (month)
		Sample size	Age (year)	Female (%)	Category	Spinning approach	Activator	Sample size	Age (year)	Female (%)	Intervention		
Ahmad, 2018 [10]	Egypt	45	56.2 ± 6.8	69	LR	Single	NR	44	56.8 ± 7.4	68	HA	IKDC, NRS and VAS	3 and 6
Louis, 2018 [11]	France	24	53.2 ± 11.7	42	LP	Double	$CaCl_2$	24	48.5 ± 11.5	54	HA	VAS, WOMAC pain, stiffness, physical function, and adverse events	1, 3, and 6
Su, 2018 [12]	China	25	54.2 ± 6.6	56	LR	Double	$CaCl_2$	30	53.1 ± 6.4	60	HA	VAS, WOMAC pain, stiffness, physical function, and adverse events	1, 3, 6, 12, and 18
Wu, 2018 [42]	China	20	63.3 ± 6.8	75	LR	Single	NR	20	63.3 ± 6.8	75	Saline	WOMAC pain, stiffness, physical function, and adverse event	0.5, 1, 3, and 6
Zhang, 2018 [13]	China	30	65.5 ± 5.8	53	LR	Double	NR	30	66.2 ± 4.9	60	HA	VAS and Lysholm	1 and 3

HA = hyaluronic acid; LP = leucocyte-poor; LR = leucocyte-rich; PRP = platelet-rich plasma; VAS = Visual Analogue Scale; WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index; IKDC = the International Knee Documentation Committee Subjective Knee Form; KOOS = the Knee Injury and Osteoarthritis Outcome Score; EQ-VAS = EuroQol Visual Analogue Scale; HHS = Household Hunger Scale; MMO = maximum mouth opening; NR = Not report; TENS = transcutaneous electrical nerve stimulation; Lysholm = the Lysholm score; NRS = numeric rating scale.

PRP treatment for both time periods. The overall SMD between the groups at short term was −0.74 (95% CI: −1.11 to 0.36, $P = 0.0001$) (Figure 3A), at medium term −0.50 (95% CI: −0.75 to −0.25, $P = 0.0006$) (Figure 3B), and at long term −0.68 (95% CI: −0.1.09 to −0.27, $P = 0.001$) (Figure 3C); the results of both were heterogeneous ($I^2 =$ 88%, 81%, and 84%, respectively).

Subgroup analysis

The meta-analysis revealed no significant effect for all follow-up periods regarding pain relief or joint function improvement (Figure 4) in the case when data were pooled with a proportion of women of less than 50%. While subgroup analyses showed that PRP treatments have consistently a supportive effect, no conclusion can be drawn about the treatment effects of different PRP protocols (category, spinning approach, and activator). Both, leucocyte-poor and Leucocyte-rich PRP preparations were shown to both have a significant effect on pain relief in all follow-up periods. In addition, a positive effect on pain relief and function improvement at short term and medium term but not in the long term was observed with $CaCl_2$ as an activator.

Discussion

The meta-analysis of the entire dataset of all randomised control PRP treatments fulfilling the selection criteria for this study demonstrated that the injection of PRP has only a supportive effect on pain relief and function improvement in patients with OA. A superior effect of PRP treatments was not observed in the subgroup of large trials, as no significant effect on pain relief or joint function improvement was observed at short-, medium-, and long-term follow-up time points. The same result was seen when data were analysed in which the proportion of female patients was less than 50%.

Several systematic reviews or meta-analysis investigating the effectiveness of PRP for OA have been published [5–8,44–56], but pooled RCTs and clinical controlled trials would increase the risk of selection bias [6,45,48–50,55]. A meta-analysis was performed to compare outcomes between PRP injections versus HA or placebo for knee OA where PRP injections were shown to be more effective in reducing pain and improving functions, as measured by the scale stratified analysis. Another meta-analysis revealed that at 12-month post-injection, PRP was associated with superior pain relief and function improvement [47]. Similarly, a meta-analysis including ten RCTs also showed significantly higher outcome scores with PRP injections when compared with HA [7]. These results were similar to our overall meta-analysis. Interestingly, we observed that larger trials showed no statistical difference when comparing PRP treatments with controls, and our meta-analysis also indicates that gender composition of the patient group has a major impact. The data of treatment effects were drastically different in subgroups with less than 50% women, for which we observed no significant benefit of PRP treatments, suggesting that PRP may not be effective in male patients. One possible explanation is that the existence of different OA phenotypes, PRP may only be effective for a certain phenotype, so when the sample size is expanded, the direction would be changed. Similar conclusions were found as CR4056 is effective for metabolic OA phenotype and males but not for all population [57]. This conclusion requires further validation, possibly by conducting a study or studies focussing specifically on gender or specific phenotype. In addition, from the data of this meta-analysis, we could not draw conclusion of which PRP preparation method is the best one.

Our findings have important implications for clinical practice and further research. It becomes obvious that it is essential to find novel, highly efficient therapeutic strategies for OA treatment. Our meta-analysis demonstrated that PRP has a minor beneficial effect on pain relief and function improvement when the entire dataset was analysed. In contrast to this, no significant effects were observed in large trials. In addition, if the patient cohort was composed of a majority of male patients, no efficacy of the treatment could be shown. Both sample size and gender effects suggest

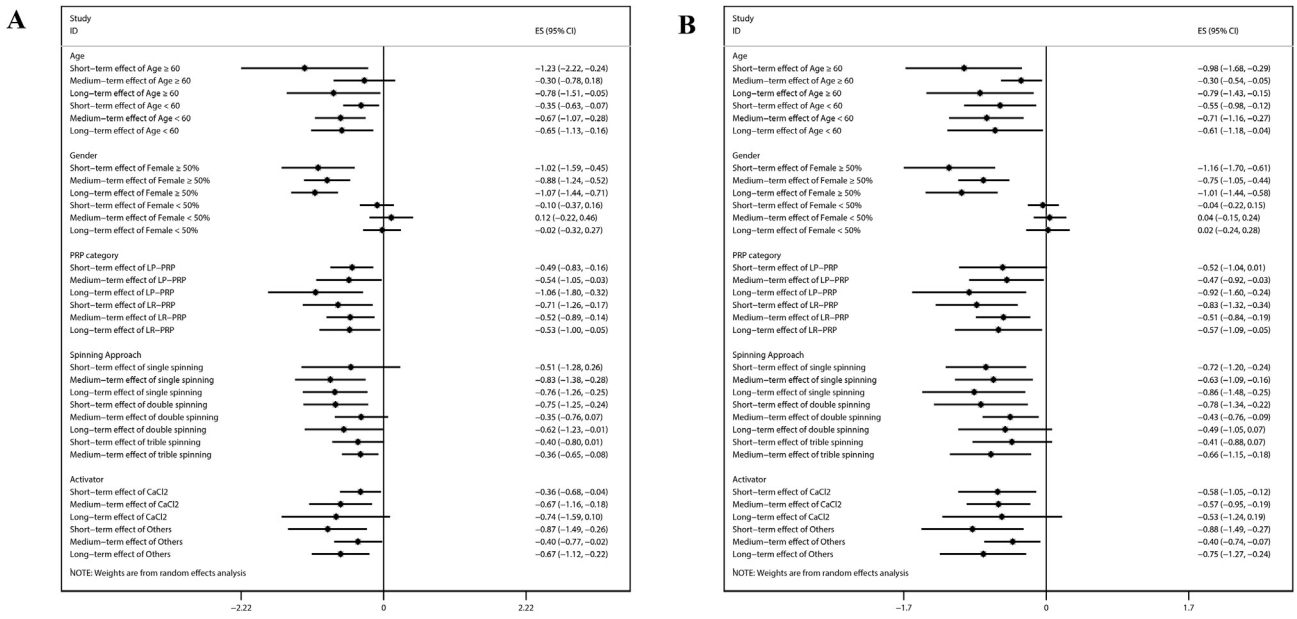

Figure 4. Subgroup analysis of meta-analysis. (A) Pain relief result; (B) function improvement result.

that, it is essential to develop disease-modifying drugs in future research and to pay special attention to gender to validate our conclusion of this meta-study on the efficacy of PRP.

To the best of our knowledge, this meta-analysis is a comprehensive update that systematically and quantitatively evaluates the effectiveness of PRP for OA by including RCTs for a more accurate analysis. Our meta-analysis provided another perspective to analyse the treatment effect of PRP for OA by trial size. In addition, we used different time points for our analysis instead of an end time point, which also highlights the temporal effect of PRP efficacy.

Some limitations include the significant heterogeneity in each calculation and the variation of nonstandardised evaluation tools used across different studies. Besides, the OA grade also is an important factor that influences the efficacy of PRP and satisfaction of patients. However, owing to the limitations of the original research, we cannot obtain the efficacy data of different OA grades, which limits the guiding significance of our research for clinical treatment.

Conclusions

According to the currently available evidence, PRP injections are beneficial for pain relief and function improvement in OA. However, this meta-analysis demonstrated that the efficacy of PRP is related to sample size and gender composition. To fully evaluate the benefits of this treatment, it is obvious that more high-quality randomised controlled trials with larger patient numbers need to be conducted and the phenotypes subpopulation and gender difference should be considered. To advance the treatment or improve its efficacy, it is also necessary to understand the underlying cellular and molecular mechanisms occurring after PRP injections. This would ideally lead to the optimisation and standardisation of the PRP preparation method in the future.

Conflict of interest

The authors have no conflicts of interest to disclose in relation to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2019.10.002.

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