

Review Article

Efficacy of platelet-rich plasma for clinical outcomes after total knee arthroplasty: a systematic review and meta-analysis

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Abstract: *Objective:* The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) and non-RCTs were to evaluate the effect of platelet-rich plasma (PRP) versus placebo on the patients receiving total knee arthroplasty (TKA). *Methods:* In April 2016, a systematic computer-based search was conducted in the Pubmed, ISI Web of Knowledge, Embase, Cochrane Database of Systematic Reviews and Chinese Wanfang database. This systematic review and meta-analysis were performed according to the PRISMA statement criteria. The primary endpoint was the range of motion (ROM), which represents the function after TKA. The Western Ontario Mc-Master Universities Osteoarthritis Index Bellamy (WOMAC), pain at 24 h, 48 h and 7 day and hemoglobin (Hb) at 24 h after TKA were also to assess the effect of PRP on the function and pain after TKA. The complications of infection were also compiled to assess the safety of PRP. After testing for publication bias and heterogeneity across studies, data were aggregated for random-effects modeling when necessary. *Results:* Ten clinical trials with 1001 patients were included in the meta-analysis. The pooled results indicated that administration of PRP significantly increase ROM at third day (mean difference (MD) = 4.05, 95% CI = 1.58-6.52; P = 0.001) and 3 month postoperatively (MD = 3.12, 95% CI = 0.94-5.29; P = 0.005). There is no statistically difference between the two groups in terms of WOMAC questionnaire score at 3 month, pain intensity at 24 h, 48 h and 7 day and Hb at 24 h after TKA. There is no statistically significant difference between the PRP versus placebo in terms of the occurrence of infection (relative risk (RR) = 0.64, 95% CI = 0.19-2.14, P = 0.464). *Conclusion:* Based on the current meta-analysis, PRP can limitedly increase the ROM after TKA in short and long period. What's more, PRP has no effects on the WOMAC score, pain scores and the occurrence of infection. More RCTs and high quality studies are still needed to identify the efficacy and safety of PRP after TKA.

Keywords: Platelet-rich plasma, total knee replacement, meta-analysis

Introduction

Total knee arthroplasty (TKA) is now one of the most well-established orthopedic surgeries that mainly applied to reduce pain, correct deformity and restore the knee function [1]. However, concern remains with regard to blood loss, pain control and achieving good joint functioning [2, 3]. Achieving a satisfactory postoperative knee function largely depend upon adequate primary soft tissue hemostasis [4]. By minimizing the bleeding related complications, the need for transfusion is obligatory. However, blood transfusion has the potential risk of incompatibility reactions, immune disorders and increase the total costs in hospital. Many strategies, such as tourniquet, tranexamic acid

and fibrin sealant have been used to reduce the postoperative blood loss and subsequent homologous blood transfusion [5-8]. All of the above techniques have not reached the satisfactory effects. Recently, platelet-rich plasma (PRP), a so-called buffy coat product prepared from patient's blood, is a mixture substance contains high concentrations of platelet and at least 6 abundant platelet growth factors [9]. The factors such as α -granules can be released from PRP and have been identified to accelerate wound healing after surgery [10]. The advantage of PRP is not only not impart an over immune reaction, but also expected to be effective in hemostasis, pain relief and bone healing.

PRP for clinical outcomes after TKA

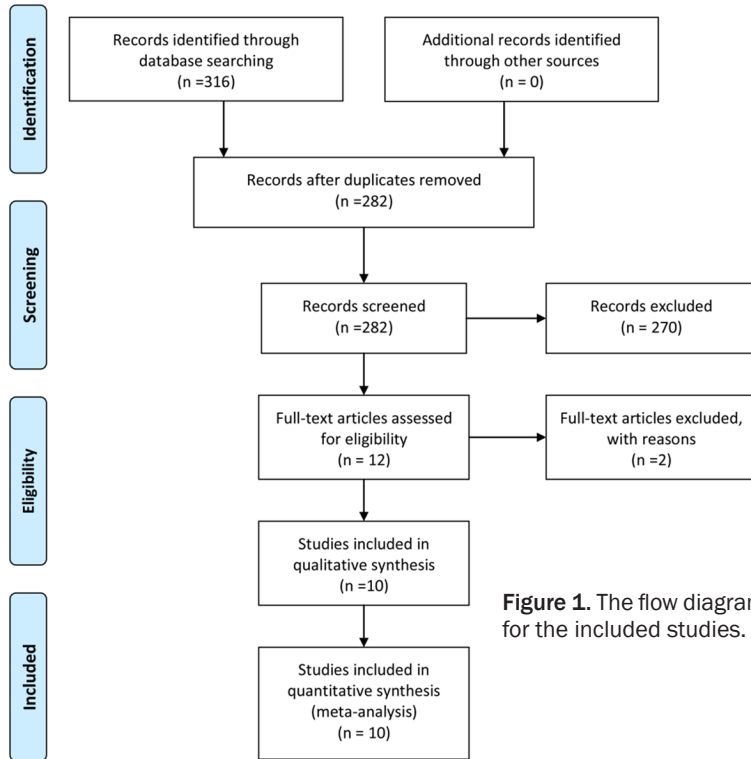


Figure 1. The flow diagram for the included studies.

reviews about platelet-rich plasma after TKA were also cross-checked to identify any initially omitted studies. There is no restriction made on the language and year of the publication.

Inclusion criteria and study selection

RCTs and non-RCTs about comparing PRP with placebo for reducing blood loss and pain intensity after primary unilateral TKA, involving adult human subjects (age >18 years) with no systemic disease, were included in this meta-analysis. Two independent reviewers (B-SQ and C-JH) scanned the title and abstracts of the identified literatures after remove the duplicates of the search results. Any disagreements

about the inclusion and exclusion were solved by the discussion or consult from the expert. Reliability of the studies selection was determined by Cohen kappa test and the set the acceptable threshold value as 0.61 [14, 15].

Data abstraction and quality assessment

A specific extraction for was made to collect the following data from the included trials: patient general characteristic, operative approach, DVT prophylaxis, length of follow up and volume to spray the PRP. Outcomes such as VAS scores, range of motion and complications were abstracted and recorded in a sheet. All the data were extracted by two independent reviewers and disagreement was solved by discussion. The methodological quality of all included RCTs were independently assessed by two reviewers on the basis of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0; (<http://www.cochrane-handbook.org/>). The evaluate content included as follows: (1) randomization generation method; (2) allocation concealment; (3) blinding of participant, personnel and assessor; (4) selective reporting and (5) other bias. The assessment was based on the “low” “unclear” “high” according to the instruction. Non-RCTs were measured by MINORS quality assessment [16].

Many research focused on the effectiveness and safety of PRP in management of TKA, however, the effectiveness and safety of PRP for pain relief and ROM after TKA remain controversial [11-13]. Thus, we conducted a systematic review and meta-analysis to further analyze the effect of PRP on the knee function, pain and the occurrence of infection after TKA.

Material and methods

Search strategies

A literature search of the following databases from the inception to the April, 2016: Pubmed, ISI Web of Knowledge, Embase, Cochrane Database of Systematic Reviews and Chinese Wanfang database. The following search algorithm was used to search the databases, using Boolean operators and the asterisk symbol (*) as truncation (((“Arthroplasty, Replacement, Knee” [Mesh]) OR TKA) OR total knee arthroplasty) OR total knee replacement) OR TKR AND (platelet rich plasma OR platelet gel OR platelet rich-plasma OR “Platelet-Rich Plasma” [MeSH]). The mesh-terms were not used in the Cochrane Central Database of Systematic Reviews, ISI Web of Science and Chinese Wanfang Database. Additionally, the referenes of all selected full-text articles and relevant

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Table 1. The general characteristic of the included studies

Studies	Cases	Mean age	Male patients	Dosage (ml)	Approach	Type of prosthesis	DVT prophylaxia	Length of follow-up (month)	Type of study
Peerbooms 2009	50/52	77/78	13/11	6	Medial parapatellar approach	Cemented	LMWH	3	RCT
Morishita 2014	20/20	72/74.7	2/0	5	Medial parapatellar approach	Cemented	10,000 IU of heparin	1	RCT
Aggarwal 2014	7/14	56.43/53.79	NS	8	Medial parapatellar approach	Cemented	Aspirin 150 mg	6	RCT
Dong 2014	30/30	66.3/65.9	16/17	12	Middle incision of medial patellar approach	Cemented	4100 U LMWH	12	RCT
Horstmann 2011	20/20	67/66	14/13	11	NS	Cemented	0.3 ml LMWH	1.5	RCT
Guerreiro 2015	20/20	66.4/71.6	6/8	10	NS	NS	40 mg of enoxaparin	2	RCT
Diiorio 2012	100/100	67.1/65.4	39/37	6	Medial parapatellar approach	Cemented	NS	6	Co, R
Pace 2013	135/133	67.5/68.7	49/43	5	Subvastus medialis approach	Cemented	Oral warfarin 2 mg	13	Co, R
Tingstad 2015	46/47	64.7/67.1	27/19	6	Medial parapatellar approach	NS	NS	NS	Co, P
Berghoff 2006	71/66	65/68.2	25/12	6	Medial parapatellar approach	Cemented	NS	1.5	Co, R

Co = Cohort study, P = prospective study, R = retrospective study, RCT = randomized control trail, NS = not stated, LMWH = low molecular weight heparin.

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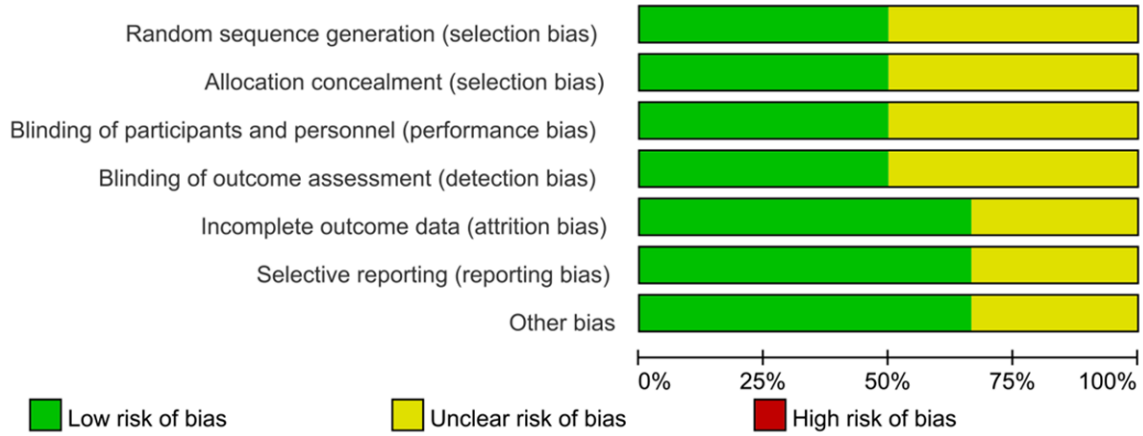


Figure 2. The risk of bias graph for the included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aggarwal 2014	?	+	+	+	+	+	+
Dong 2014	?	?	?	?	?	?	?
Guerreiro 2015	?	?	?	?	?	?	?
Horstmann 2011	+	+	+	+	+	+	+
Morishita 2014	+	?	?	?	+	+	+
Peerbooms 2009	+	+	+	+	+	+	+

Figure 3. The risk of bias summary for the included studies.

Outcome measures and statistical analysis

The main outcome was the ROM at day 3 and 3 month, Western Ontario and McMaster Universities Index (WOMAC) and VAS score after TKA. The occurrence of infection was the second outcome. Continuous outcomes (ROM, WOMAC, pain scores and Hb at 24 h after TKA) were expressed as the mean differences (MD) and respective 95% CIs. Dichotomous outcomes (the occurrence of infection) were expressed as relative risk (RR) with 95% confidence (CIs). Statistical significance was set at $P < 0.05$ to summarize findings across the trials. Risk of bias assessment of each involved article was conducted in light of the Cochrane Handbook for Systematic Reviews of Interventions and the using Software RevMan 5.30 (The Cochrane Collaboration, Oxford, United Kingdom). The meta-analysis was calculated by the software of Stata, version 12.0 (Stata Corp., College Station, TX). Statistical

Table 2. The minors quality score of the non-RCTs

First Author, Year	Minors Scale												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Diiorio 2012	1	1	1	2	2	2	2	0	2	2	2	2	19
Pace 2013	2	2	2	2	2	2	2	2	2	2	2	2	24
Tingstad 2015	2	2	0	2	0	2	2	0	2	1	2	2	17
Berghoff 2006	2	2	1	2	2	2	2	2	2	2	2	2	23

Numbers 1-12 in heading signified: 1, a clearly stated aim; 2, inclusion of consecutive patients; 3, prospective collection of data; 4, endpoints appropriate to the aim of the study; 5, unbiased assessment of the study endpoint; 6 follow-up period appropriate to the aim of the study; 7 loss to follow-up less than 5%; 8 prospective calculation of the study size; 9 an adequate control group; 10 contemporary groups; 11 baseline equivalence of groups; and 12, adequate statistical analyses.

heterogeneity was tested using the chi-squared test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > 0.1$), fixed effects model was adopted; otherwise, a random effect model was chosen. Publication bias was tested using funnel plots and quantitatively assessed by Begg's test. We considered there was no publication bias if the funnel plot was symmetrical and the P value was > 0.05 .

Results

Search results and quality assessment

In the initial search we identified 316 potentially relevant studies. Of these, since two trials shows insufficient data to the inclusion criteria, so these two trials were finally excluded [17, 18]. Finally, we included 10 clinical trials with 1001 patients in the meta-analysis [1, 11-13, 19-23]. The flow diagram can be seen in **Figure 1**. Classification of the remaining studies resulted in a total of six RCTs, four retrospective studies. All the included studies were published between 2006 and 2015, and each of the included studies specified detailed inclusion criteria. The general characteristic of included studies can be seen in **Table 1**. Statistically similar baseline characteristics were obtained between the two groups, the experiment group used platelet-rich plasma, while the control group used saline or nothing. The mean age in PRP group ranged from 56.43 to 77 and control group ranged from 53.79 to 78. The dosage of PRP was from 5 ml to 12 ml. Only two studies did not state the type of prosthesis and the other studies all administration cemented prosthesis.

We used the risk of bias tool implemented in Review Manager 5.30 to evaluate the risk of bias in light of the Cochrane Handbook for Systematic Reviews of Interventions. The detailed information of the risk of bias of the included articles is demonstrated in **Figures 2** and **3**. All of the included articles were described as randomized. However, only three of studies comprehensively described the generation of a randomized sequence, and the remaining studies did not demonstrate the randomization method [12, 21, 24]. Blinding of participants, personnel and outcome assessment were performed in 3 studies [11, 20, 21]. Four of the included articles displayed a low risk of bias for the incomplete outcomes, selective outcome reporting and displayed a low risk of bias for other biases [12, 13, 21, 24]. The quality of non-RCTs was finally shown in **Table 2**.

Outcome for meta-analysis

ROM at day 3 and 3 month postoperatively

The data of ROM at day 3 and 3 month postoperatively were reported in five studies. The pooled results indicated that the administration of PRP significantly increase ROM at day 3 (MD = 4.05, 95% CI = 1.58-6.52; $P = 0.001$, **Figure 4**) and 3 month postoperatively (MD = 3.12, 95% CI = 0.94, -5.29; $P = 0.005$, **Figure 4**) with no heterogeneity ($I^2 = 0.0\%$, $P = 0.815$). Funnel plot indicated that there is no publication bias among the included studies (**Figure 5**) and P value calculated by Begg's test is 0.721 (**Figure 6**).

WOMAC at 3 month

Three trials reported the results of WOMAC questionnaire score at 3 month after TKA. The pooled results indicated that there is no statistically difference between the two groups in terms of WOMAC questionnaire score at 3 month (MD = -4.88, 95% CI = -12.12-2.41; $P = 0.190$, **Figure 7**) with no heterogeneity ($I^2 = 0.0\%$, $P = 0.440$).

Pain in 24 h, 48 h and 7 day

Three studies (217 patients) reported the pain intensity at 24 h and meta-analysis indicated that there is no statistically significance

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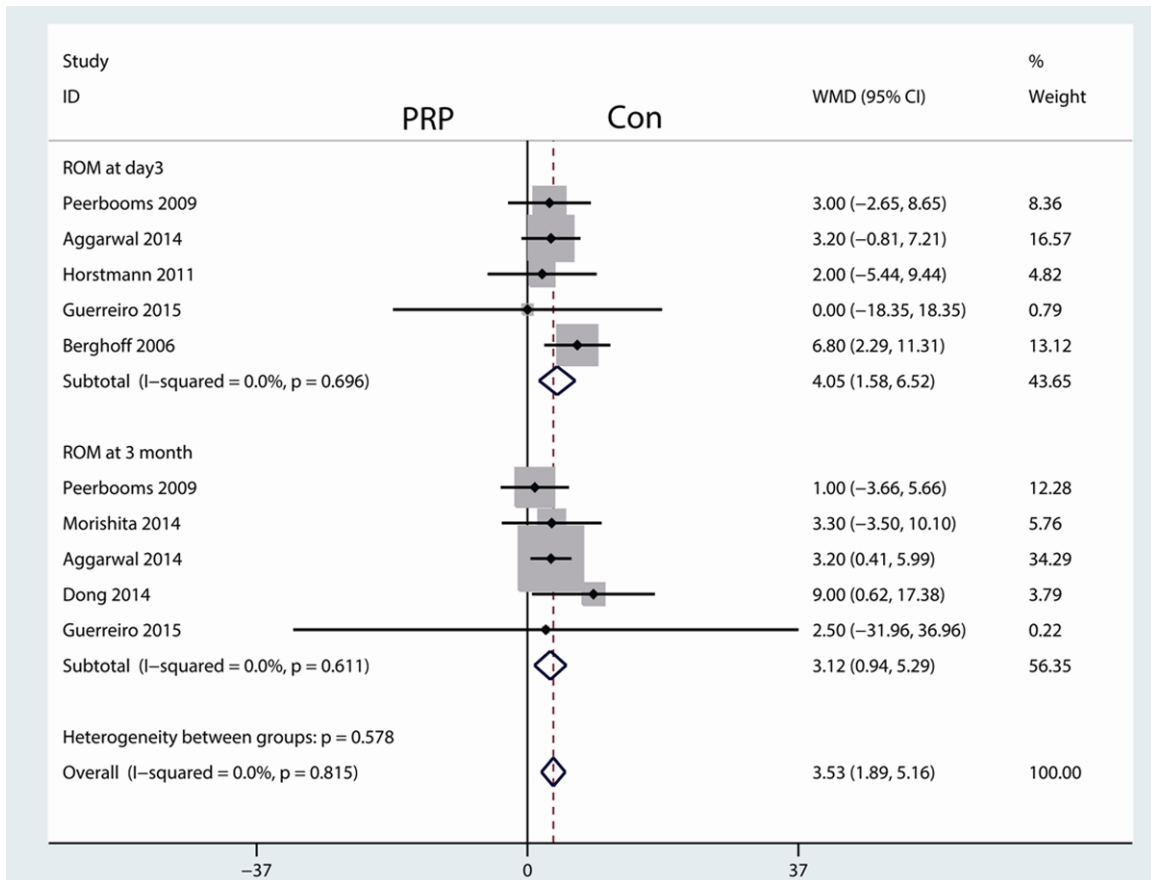


Figure 4. The forest plot comparing PRP versus placebo for ROM at 3 day and 3 month after TKA, an Inverse-Variance Fixed-effects model was used. Mean difference with 95 percent Cis.

between the two groups in pain intensity at 24 h (MD = -0.54, 95% CI = -1.14-0.06; P = 0.077, **Figure 8**), 48 h (MD = -0.78, 95% CI = -2.64-1.08; P = 0.760, **Figure 8**) and day 7 (MD = 0.01, 95% CI = -1.11-1.12; P = 0.988, **Figure 8**) postoperatively.

Hb at 24 h after TKA

Two studies reported the Hb at 24 h after TKA and pooled results indicated that there is no significant difference between the PRP group versus placebo group in terms of Hb at 24 h after TKA (MD = -0.18, 95% CI -0.79, 0.43; P = 0.561, **Figure 9**).

The occurrence of infection

Six literatures reported the occurrence of infection, the result of meta-analysis indicated that there is no statistically significant difference between the PRP versus placebo in terms of the occurrence of infection (RR=0.64, 95% CI = 0.19 = 2.14, P = 0.464, **Figure 10**).

Discussion

To our knowledge, this is the first systematic review and meta-analysis of RCTs and non-RCTs comparing the efficacy and safety of PRP versus placebo in the management of function, pain and the occurrence of infection after TKA. The present meta-analysis was conducted on the basis of 6 RCTs and 4 non-RCTs, and revealed that better ROM in PRP group when compared to controls. However, there is no significant difference between the WOMAC, pain intensity and the occurrence of infection.

A successful outcome in TKA requires adequate intraoperative and postoperative hemostasis in order to avoid hematoma and decrease the need for transfusion. Achieving a satisfactory ROM not only depends on the exercise, but also depends on adequate primary soft tissue hemostasis. As far as we know, efficient blood loss control and fast recovery from TKA can increase the patients satisfaction and decrease

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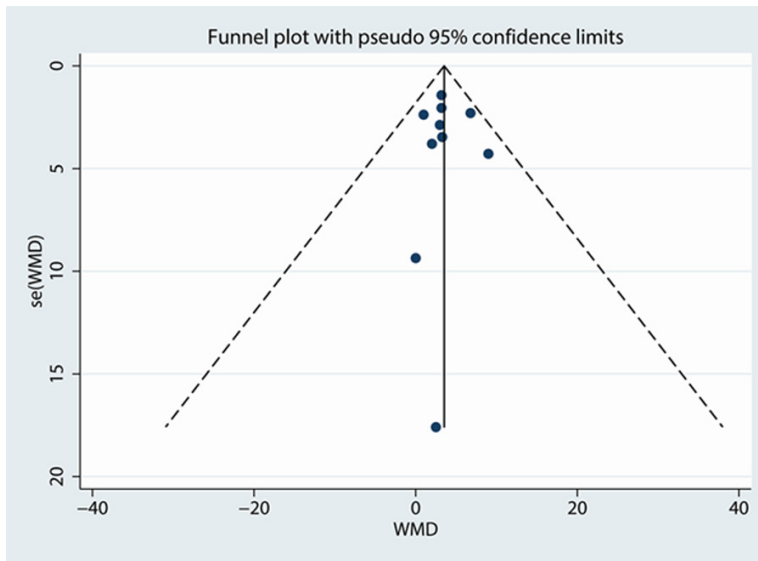


Figure 5. The publication bias between the studies indicated by the funnel plot.

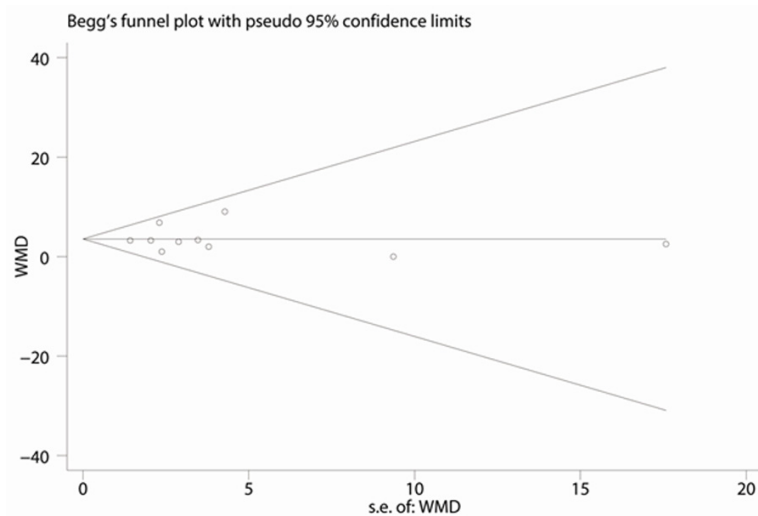


Figure 6. The result of Begg's test for the postoperative range of motion.

the economic costs [17]. The pooled results indicated that administration PRP significantly increase ROM at day 3 and 3 month postoperatively. The PRP can increase the ROM for 4.05 degree and 3.12 degree at 3 month. PRP have been tried to administrate in TKA for the first time with good results in 2000 during the congress of the American Academy of Orthopaedics. PRP was promoted as an ideal biological blood-derived product that can be administrated to various tissues to enhance wound healing. It contains a high concentration of platelet, cytokines and fibrin products. Platelets provide a

concentrated and directed supply of growth factors that stimulate the migration and maturation of mesenchymal cells to the exposed tissues, synovium, and the lining of the wound at closure [25]. Platelet-derived growth factor (PDGF) and transforming growth factor- β (TGF- β), which have been associated with many beneficial haemostatic and wound-healing effects, also have an important role in regarding to cell proliferation, chemotaxis, cell differentiation and angiogenesis. In addition to the above cytokines presented in PRP, there are also other proteins including thromboxane A₂, thrombin and adenosine diphosphate. These proteins potentiate the activity of the originally applied platelets in forming a platelet plug, and thus allowing for earlier hemostasis and repair [26, 27]. These outcomes are correlated to the better pain control of PRP after TKA. PRP has a proven anti-inflammatory effect and has been administrated to this function in relation to knee osteoarthritis [28].

The pain and function questionnaire (WOMAC) results indicated that PRP can improve the postoperative knee function and reduce the pain intensity after TKA. However,

there is no statistically significance and clinical importance between the two groups. The platelet concentration and type of PRP were different from each other. The type of PRP can be differentiated according to the concentration of leukocytes and their form of activation [29]. Recently, hospital are becoming more cost conscious and are requesting clearly defined patient benefits from using additional surgical adjuncts that may offer claims to justify their added costs. It is reported that the per-patient hospital cost of PRP was 582\$ and 444\$ for fibrin sealant [30].

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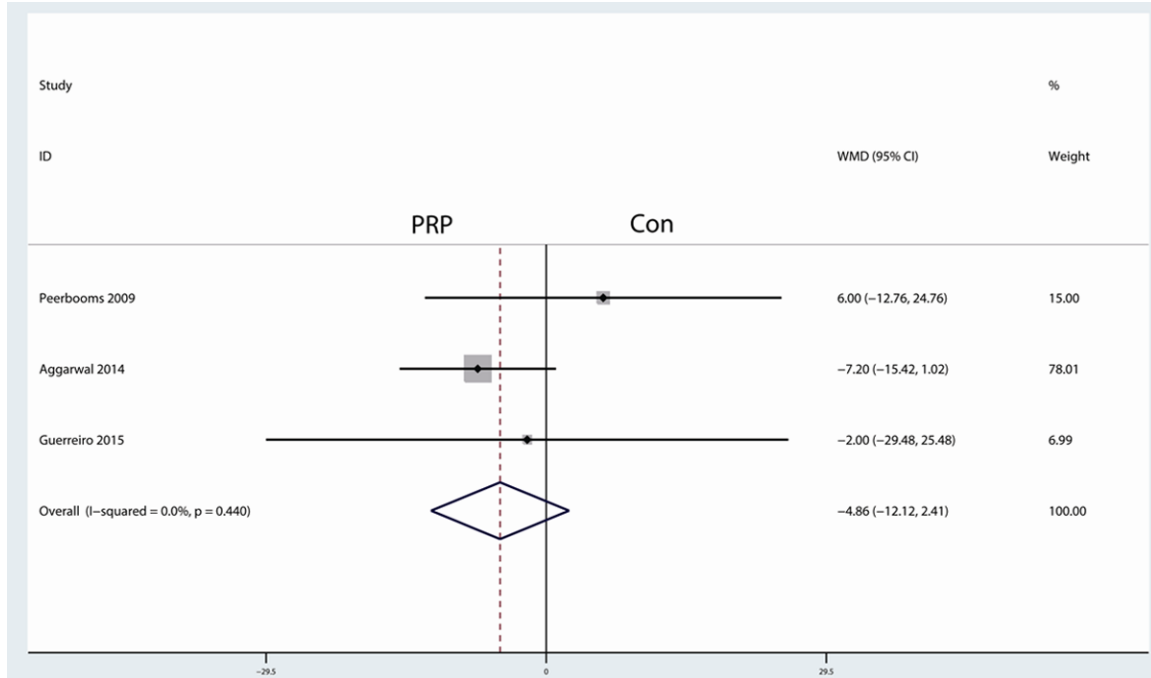
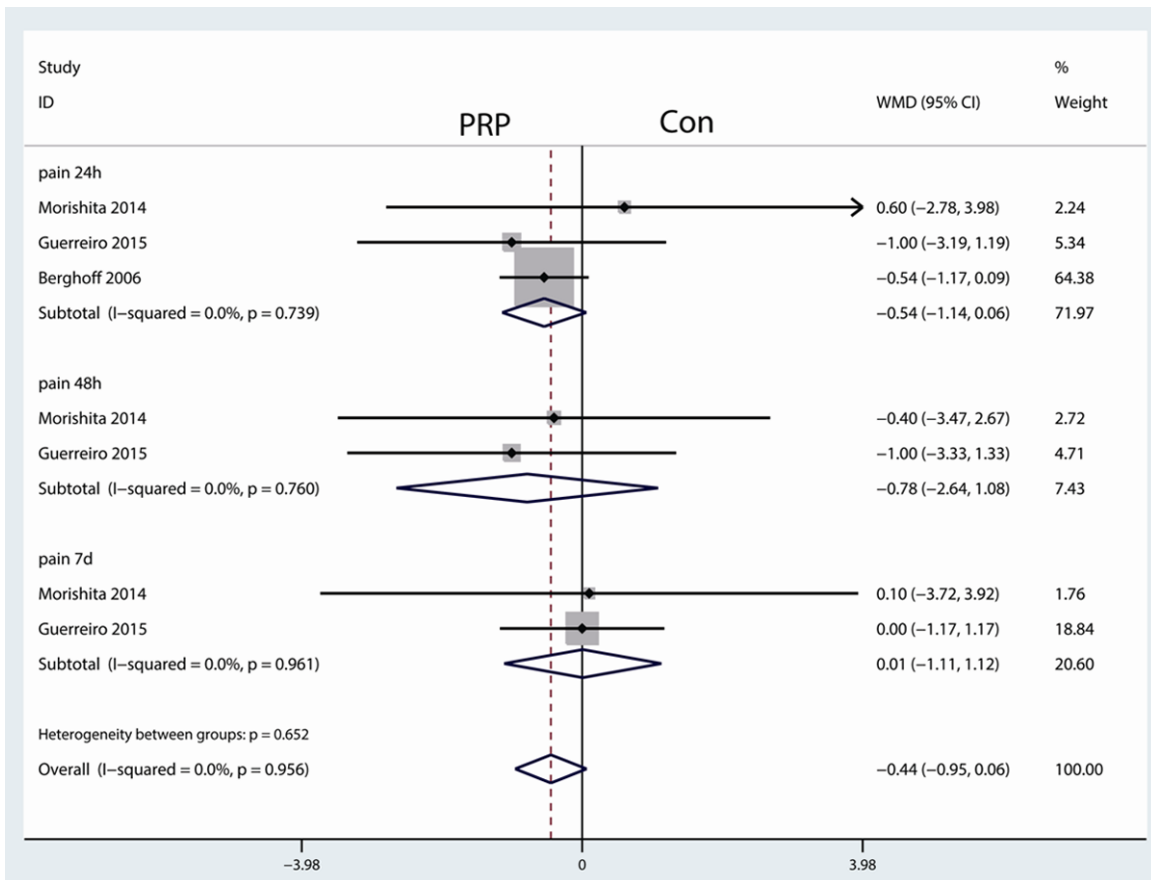


Figure 7. The forest plot comparing PRP versus placebo for WOMAC at 3 month after TKA, An Inverse-Variance Fixed-effects model was used. Mean difference with 95 percent Cis.



PRP for clinical outcomes after TKA

Figure 8. The forest plot comparing PRP versus placebo for pain control at 24 h, 48 h and 7 day after TKA, An Inverse-Variance Fixed-effects model was used. Mean difference with 95 percent Cis.

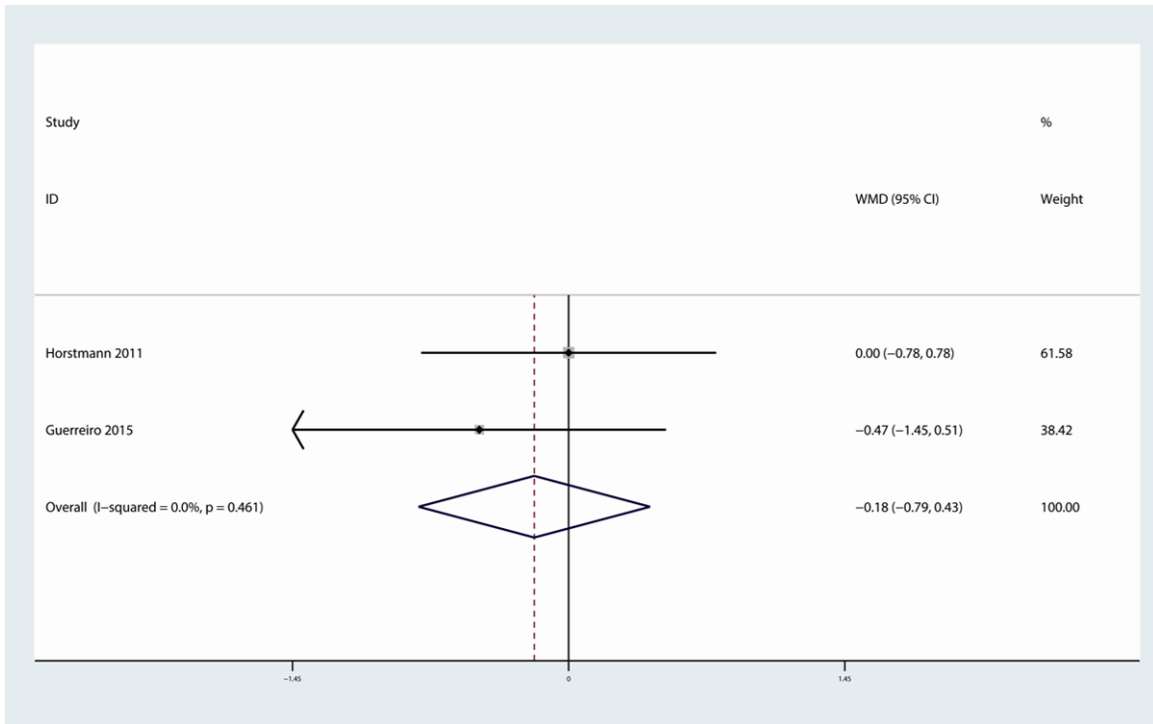


Figure 9. Forest plot comparing the Hb at 24 h after TKA between the PRP group versus control group.

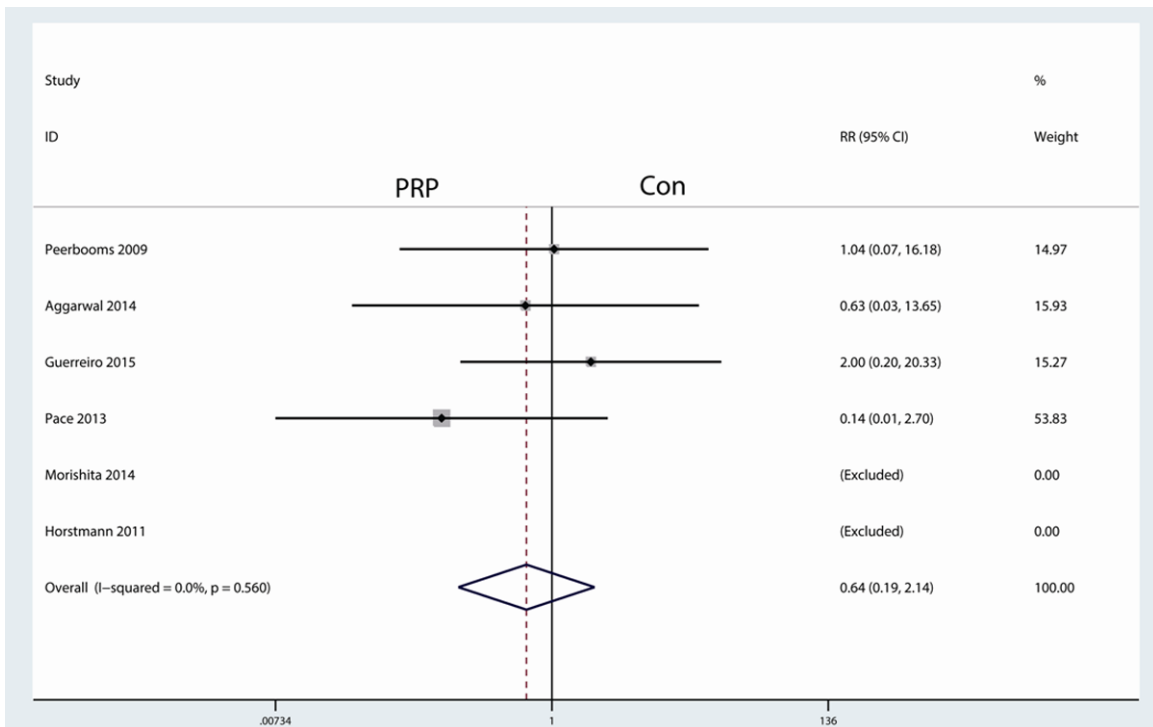


Figure 10. Forest plot comparing the occurrence of infection between the PRP group versus control group.

As for infection, the result of meta-analysis postulated there is no significant difference between the two groups. In addition, PRP has antimicrobial properties that preventing infections. When platelets become activated, growth factors are released and participated into the process of wound healing. The reason may the PRP is prepared directly from patients' auto blood, so the risk of infection is essentially non-existent. Furthermore, it can be suggested that PRP can reduce infection incidence after TKA since the numerous types of growth factors released from platelet. And, the buffy coat, which is sequestered in the process, also contains concentrated leucocytes, may add an anti-bacterial component to the PRP [26]. However, more RCTs are still needed to further identified.

There were several limitations in this meta-analysis: (1) only 6 RCTs and 4 non-RCTs were included, and the sample sizes in each trial were not large enough, which would affect the final results; (2) the duration of follow-up in some studies was unclear, and long-term follow-up was needed for this analysis; (3) the publication bias that existed in the meta-analysis also influenced the results; and (4) variations in the ways of obtaining, preparing and applying PRP currently constitute a limitation on any comparison between studies.

In conclusion, the administration of PRP can increase the ROMs at 3 day and 3 month after TKA. However, the effect of pain control, WOMAC and the occurrence of infection still need for studies to further identified. So, high-quality RCTs and well-designed trials are still required to identify the effect and safety of PRP in TKA and the optimal dose of PRP to administrate.

Disclosure of conflict of interest

None.

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