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Original Article

Meta-analysis of the effects of knee flexion on blood loss after TKA

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Abstract: Background: it still remained controversial whether postoperative knee flexion was effective in reducing blood loss and promoting range of motion (ROM) in patients after total knee arthroplasty (TKA). Objective: The purpose of this meta-analysis is to evaluate the aforementioned effects. Methods: A comprehensive computerized literature search was conducted in PubMed, EMBASE, SinoMed and Chinese National Knowledge Infrastructure (CNKI) without language restrictions by November 2nd 2015. Prospective randomized controlled trials (RCTs) comparing the outcomes between the postoperative knee flexion and extension with unilateral TKA patients were included. Comparative outcomes of the studies include CBL (calculated total blood loss) and/or HBL (hidden blood loss) and/or DBL (drainage blood loss) and/or ROM. The pooling of data was analyzed by RevMan 5.1. Results: 13 RCTs involving a total of 1238 patients were identified. The results revealed significantly less CBL of flexion group than extension group within subgroups (MD=-194.78; 95% CI -289.48 to -100.08; *P*<0.0001); similar results were detected with respect to HBL (MD=-121.26; 95% CI -176.71 to -65.82; *P*<0.0001) and DBL (MD=-150.47; 95% CI -234.18 to -66.77; *P*=0.0004). Flexion group was more effective in short-term (7 days after operation) postoperative ROM (MD=7.31; 95% CI 5.25 to 9.36; *P*<0.00001), but did not significantly promote long-term (6 weeks after operation) postoperative ROM (MD=1.45; 95% CI -2.57 to 5.48; *P*=0.48). The flexion of knee did not increase the incidence of SI (RR=1.12; 95% CI 0.44 to 2.85; *P*=0.82) and DI (RR=1.32; 95% CI 0.33 to 5.3; *P*=0.69). Conclusion: This meta-analysis suggested that postoperative flexion of knee on patients after TKA could reduce blood loos in terms of CBL, HBL and DBL, and also promote ROM in short-term postoperative period without increased incidence of complications. However, it could not promote ROM in long-term postoperative period.

Keywords: Total knee arthroplasty, blood loss, knee position, range of motion, complication

Introduction

Total knee arthroplasty (TKA) is a well-validated surgery for end-stage osteoarthritis, rheumatoid arthritis and other diseases of knee joint. Although this technique has been widely accepted, continuous improvements are introduced in terms of implant design, articulation bearing surface, surgical technique, perioperative management and so on [1]. Successful perioperative management can alleviate postoperative pain, reduce blood loss, achieve earlier rehabilitation and gain better joint function. Large amount of blood loss induced by TKA is a noteworthy problem, which may lead to more blood transfusions, increased length of hospital stay, swelling of the knee, compromised range of motion (ROM) of knee and delayed rehabilitation of knee function. In addition, more blood transfusion during or post operation face the increased risk of infectious diseases, postoperative infection and immunologic reactions [2]. Several perioperative methods were explored to attenuate the blood loss induced by TKA including preoperative autologous donation [3], deliberate hypotension in surgery [4], administration of erythropoietin [5], topical hemostatic agents and tranexamic acid [6], hemodilution [7], reinfusion systems [8], postoperative flexion of knee [9] and so on.

Accumulating studies have introduced the protocols of the flexion of knee joint after TKA. This independent measure is expected to reduce

postoperative blood loss and promote ROM of knee joint. As a simple intervention which only changes the postoperative position of leg, the knee flexion tends to be acceptable by both surgeons and patients. However, controversy exists among these studies in terms of postoperative blood loss and ROM. The outcomes to evaluate blood loss include the calculated total blood loss (CBL), hidden blood loss (HBL), and postoperative drainage blood loss (DBL). CBL is calculated through the perioperative change of hematocrit and the estimate of total blood volume by the method reported by *Nadler et al* [10] and *Gross et al* [11].

All previous RCTs supported that postoperative flexion of knee could reduce HBL [9, 12-15]; Some studies found that postoperative flexion of knee could reduce CBL [9, 14-16] and DBL [17-20], but others reported contrary results in terms of CBL [12] and DBL [21, 22]. Similarly, increased postoperative ROM was confirmed in some studies [14, 15] but others did not [9, 12, 21]. Controversies concerning blood lost exist among various studies.

Several underlying mechanisms contribute to the effect of knee flexion on reducing postoperative blood loss. Firstly, the flexion of the knee can result in the drainage obstruction, and consequently reduce the DBL [23]; Secondary, the flexion of the knee will lead to relative elevation of the knee joint, which can promote popliteal venous return and then reduce the blood extravasation into the joint space [23]; Thirdly, flexion of the knee can increase the pressure of popliteal soft tissue, which will extrude the blood out from the swelling and traumatic soft tissue to the blood circulation, and thus reduce the HBL.

Herein, this meta-analysis was performed to investigate the effect of postoperative flexion of knee on blood loss and ROM of the patients undergone TKA for the following reasons. Firstly, knee flexion is a simple and economic method to provide potential advantages in term of reducing blood loss and promoting ROM but with controversies; Secondary, to our knowledge, no meta-analysis has been done about this topic before yet; Thirdly, since a previous systematic review published online by Faldiniet. al in October 2013 [24], an exhaustive search was conducted and 9 new RCTs were found for updating this meta-analysis. Five new RCTs [9, 14-16, 20] have been published in English. One RCT [17] published in 2007 have been searched in EMBASE and it had not been included in previous system review [24]. Another three RCTs [13, 18, 19] have been published in Chinese magazines. Fourthly, the previous systematic review [24] did not conduct meta-analysis because only 3 RCTs about knee flexion on postoperative blood loss with complete datum were included. This study consisted of 13 RCTs studies and an integrated meta-analysis was conducted. Divergent result from previous systematic review concerning the effect of knee flexion on long-term ROM was clarified in this meta-analysis. In brief, this meta-analysis may have higher evidence-level than the previous systematic review and would be more interested by potential readers.

Materials and methods

Search strategy

An exhaustive computerized search of electronic databases was conducted, including PubMed, Cochrane Library, EMBASE, SinoMed, and CNKI (China National Knowledge Infrastructure) up to November the 2nd 2015, the following search terms were used for the database search: total knee arthroplasty, total knee replacement, knee prosthesis, leg position, flexion, extension, splinting, postoperative management, blood loss and ROM. Both English and Chinese published articles were included. The computerized search results were reviewed in terms of the titles and abstracts. Articles searched by the aforementioned keywords were preliminarily included, and then these articles would be further evaluated by the inclusion and exclusion criteria. Additionally, special attention was paid to the references of these articles in case any articles might be omitted.

Inclusion and exclusion criteria

Studies were considered eligible if they met all of the following inclusion criteria: (1) prospective randomized controlled trials (RCTs); (2) studies focusing on the unilateral TKA; (3) studies comparing the postoperative knee flexion group and knee extension group; (4) studies reporting at least include one of CBL, HBL, DBL or ROM.

Studies were excluded if (1) not prospective RCT trials; (2) the outcomes datum not applicable. Full-text articles were read by two reviewers if the studies met the inclusion criteria in

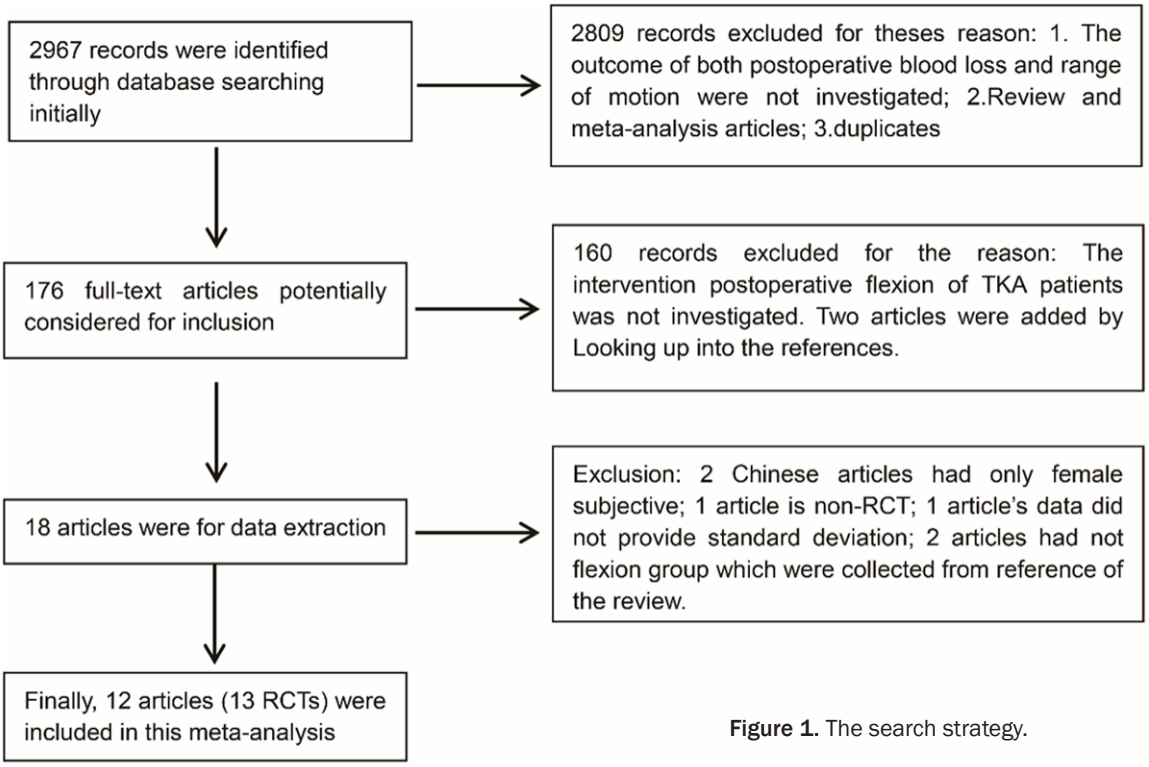

Figure 1. The search strategy.

Table 1. Basic Characteristics of Included Studies

Study	Sample Size		Gender (Female%)		Mean Age (Year)		Published Language	Quality Score	Outcome Relevant
	Flexion Group	Extension Group	Flexion Group	Extension Group	Flexion Group	Extension Group			
liu 2015 [9]	50	50	68	64	73.1±5.1	72.4±4.6	English	9	CBL, HBL, ROM, SI, DI
Yang 2015 [14]	46	46	47.8	43.5	73.6±5.0	72.5±4.7	English	11	CBL, HBL, ROM, SI, DI
Antinolfi 2014 [20]	20	20	65	50	73.0±5.8	70.7±7.3	English	8	DBL
Napier 2014/RCT1 [16]	86	90	74	64	70.4±9.9	71.0±7.6	English	11	DI
Napier 2014/RCT2 [16]	134	140	61.9	72.1	68.9±8.7	70.9±9.0	English	11	CBL, SI, DI
Panni 2014 [15]	50	50	76	80	69±7	69±7	English	8	CBL, HBL, ROM
Li 2012 [12]	55	55	72.7	69.1	71±6	70±8	English	8	CBL, HBL, ROM, SI
Madarevic 2011 [22]	16	47	UC	UC	UC	UC	English	7	DBL
Ma 2008 [21]	49	46	51	47	71.0±9.39	70.6±8.50	English	5	DBL, ROM, SI
Gildone 2007 [17]	24	24	58.3	62.5	73.2	73.2	English	7	DBL
Guo 2013 [13]	30	30	76.7	73.4	72±4.4	71±5.4	Chinese	6	HBL
Hu 2012 [19]	10	10	80	80	74.4±2.44	72.2±3.08	Chinese	8	DBL
Wang 2011 [18]	30	30	83.3	90	69.5±5.4	70.3±5.1	Chinese	7	DBL

Abbreviation: CBL, calculated total blood loss; HBL, Hidden blood loss; DBL, Drainage blood loss; ROM, Range of motion; SI, Superficial infection; DI, Deep infection.

order to determine the final inclusion. Divergents in opinion among the reviewers were solved by discussions and a third reviewer was referred to if necessary.

Assessment of methodological quality and risk of bias

The included studies were assessed independently by two reviewers in terms of study design, baseline characteristics, surgical intervention and postoperative management. The risk of bias was evaluated by using the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [25] including the following evaluation terms: 1. random sequence generation; 2. allocation sequence concealment; 3. blinding of participants; 4. blinding of personnel; 5. blinding of outcome assessors; 6. incomplete outcome data; 7. selective

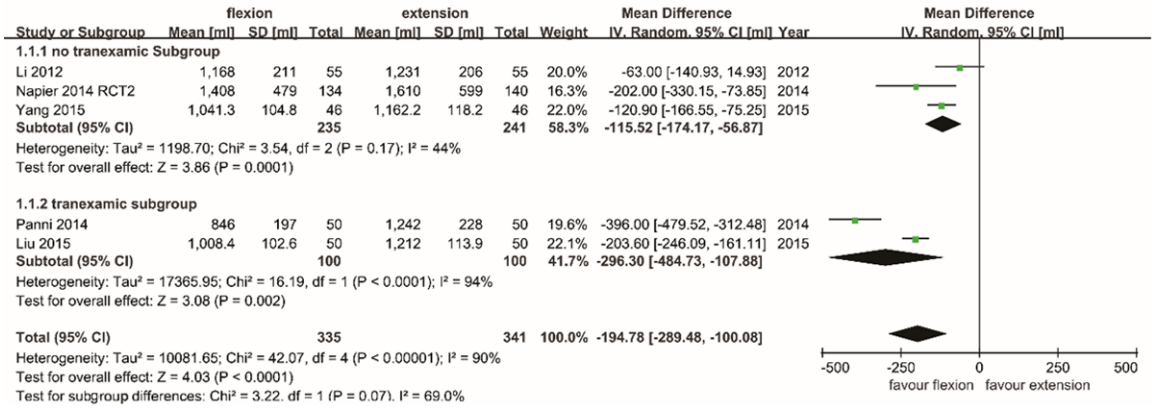

Figure 2. Forest plot of effect of knee flexion and extension on calculated total blood loss in postoperative TKA patients.

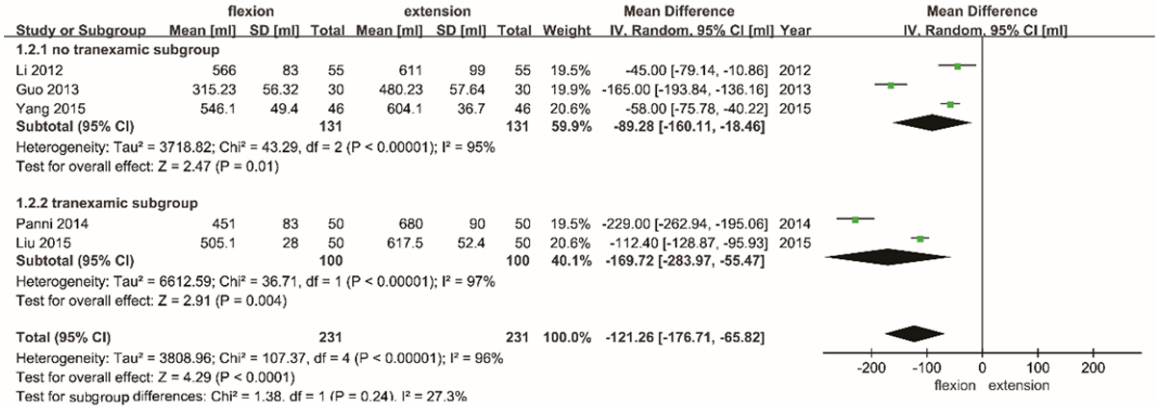

Figure 3. Forest plot of effect of knee flexion and extension on hidden blood loss in postoperative TKA patients.

outcome reporting; and 8. other potential sources of bias. Assessment results for every study included "high risk", "low risk", and "unclear risk". Disagreement was resolved by discussion among the authors.

Data extraction

Two reviewers extracted relevant data from each included study independently and recorded them on multiple worksheets. The following data were extracted: first name of authors, published year, sample size, age, gender and available outcomes. The primary outcomes included CBL and ROM; The secondary outcomes included HBL, DBL, and postoperative complication including SI and DI.

Statistical methods and strategies

The pooling of data was analyzed by Revman 5.3. The Chi-Square tests and I-square test were primarily used to evaluate the heterogeneity among the outcome datum. A fixed-effects model was used if the I-square value was less than 50%, or $P>0.1$. Random effects model was used if the I-square value was 50% or more, or if the p value was 0.1 or less. Funnel plot was performed by RevMan 5.3 to investigate the potential publication bias. For continuous variables, such as CBL, HBL, DBL and ROM, inverse variance of statistical method were used and the mean difference (MD) and 95% confidence interval (95% CI) were calculated. For dichotomous variables such as the incidence of SI and DI, the relative risk (RR) and 95% CI were calculated. $P<0.05$ was considered statistically significant.

Results

Study characteristics

Totally 2967 articles were found through the primary search. According to the (2) (3) and (4) inclusion criteria, 18 articles were primarily pre-

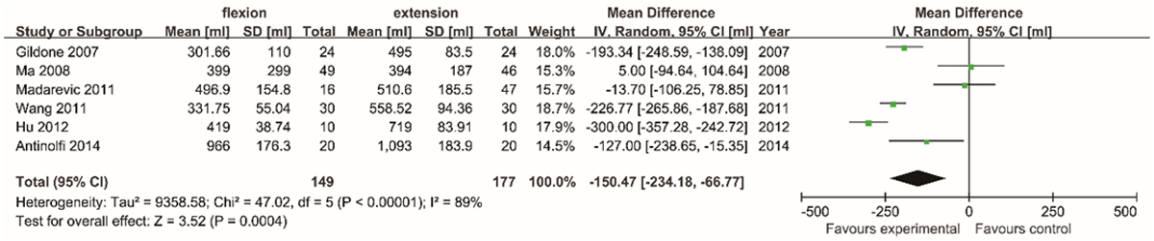

Figure 4. Forest plot of effect of knee flexion and extension on drainage blood loss in postoperative TKA patients.

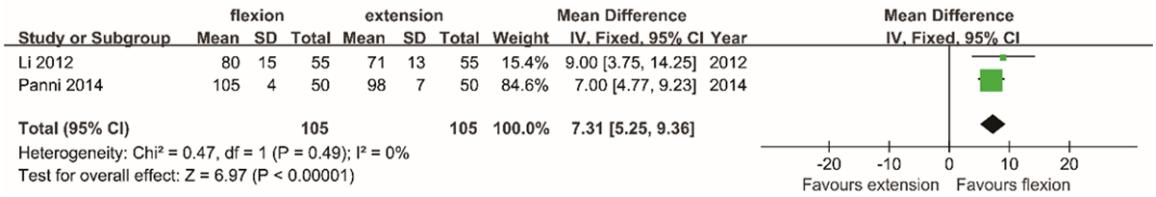

Figure 5. Forest plot of effect of knee flexion and extension on short-term ROM in postoperative TKA patients.

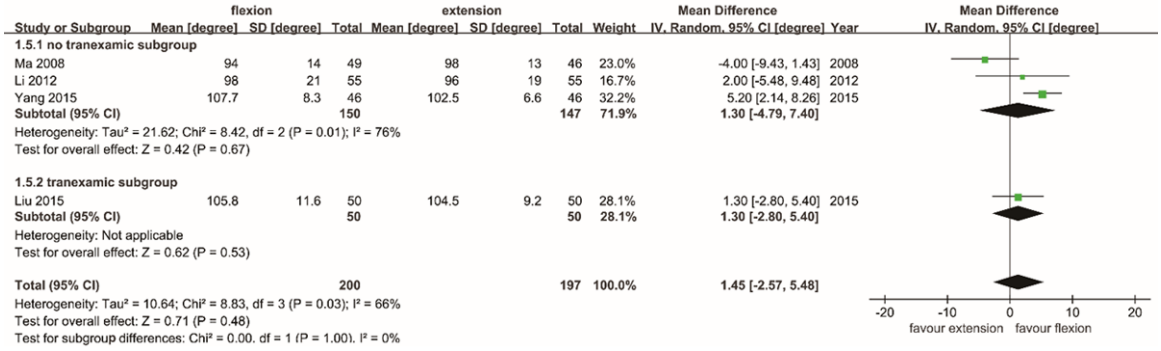

Figure 6. Forest plot of effect of knee flexion and extension on long-term ROM in postoperative TKA patients.

pared for data extraction. After reading the whole articles, 6 studies were excluded for 2 Chinese studies only having female subjects, 1 study not RCT [26], 1 study's data not providing the standard deviation value [23] and 2 articles lacking flexion group [27, 28]. Finally, 12 studies (13 RCTs) including 1238 cases (600 patients were included in the postoperative flexion group and 638 patients were included in the extension group) were included in the final analysis (the search strategy were shown in **Figure 1** and the basic characteristics of these included studies were shown in **Table 1**).

Assessment of methodological quality and risk of bias

The assessments of methodological quality and risk of bias were shown in every forest plot and gathered in **Figures 10** and **11**. The baseline among the studies included gender and age as showed in **Table 1**. Among the 13 RCTs, 4 RCTs didn't provide detailed information about the randomized method, although they claimed performance of randomization. One in the 13 RCTs had high risk method of randomization. Only 2 RCTs both conducted by *Napieret.al* [16] provided allocation concealment details; 4 RCTs from 3 articles [9, 14, 16] provided the method of participant blinding, 3 RCTs from 2 articles [14, 16] provided personnel blinding details and 3 RCTs [9, 14, 15] mentioned the blinding method of assessment. The majority of these studies had complete outcome data and most of them did not have selective reporting issues. The study conducted by *Ma et al* [21] had 49 patients in experimental group and 46 patients in control group. The inequality of patients between the two

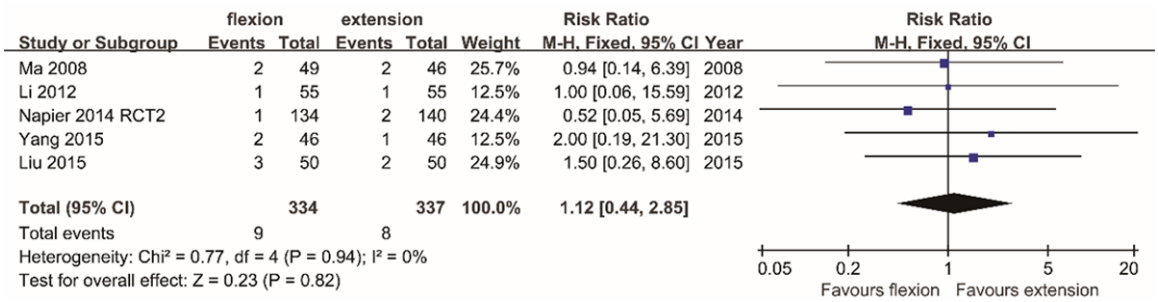

Figure 7. Forest plot of effect of knee flexion and extension on superficial infection in postoperative TKA patients.

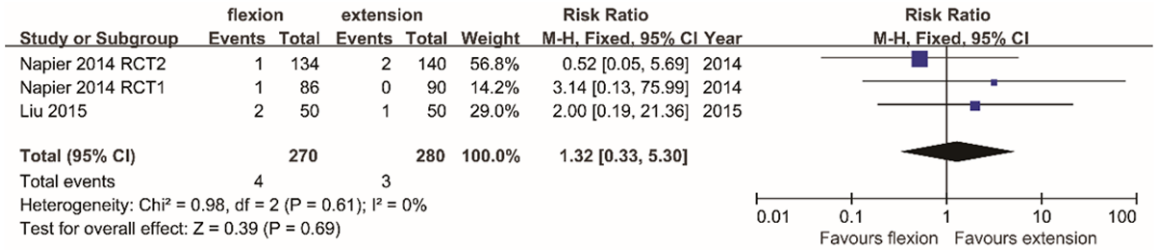

Figure 8. Forest plot of effect of knee flexion and extension on deep infection in postoperative TKA patients.

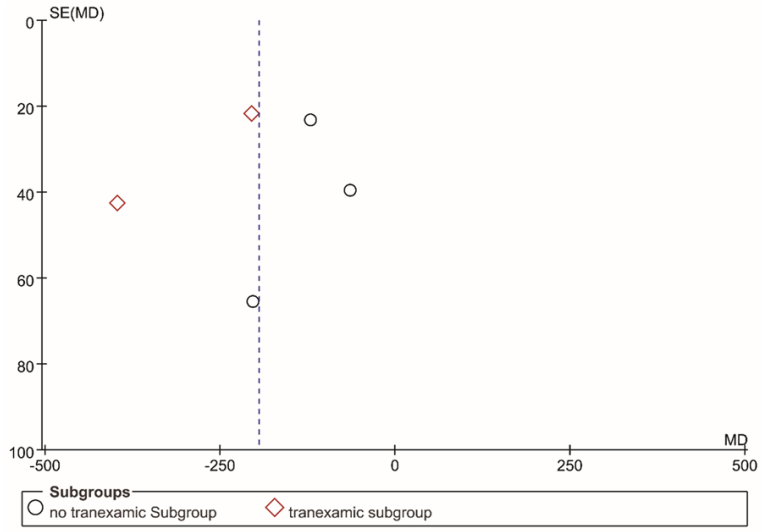

Figure 9. Funnel plot for evaluation of the publication bias.

groups was not explained in that study, thus the risk of attrition bias caused by incomplete outcome data was unclear. No publication bias is detected demonstrated by funnel plot. There was no disagreement between the two independent reviewers.

Synthesis of results

The evaluation of CBL: CBL was calculated in the formula that perioperative change of haematocrit multiplies the whole volume of blood [(preoperative haematocrit-postoperative haematocrit) × the whole volume of blood/preoperative haematocrit] reported by *Nadler et al* [10] and *Gross et al* [11]. Five eligible studies all covered the CBL [9, 12, 14-16]. Tranexamic is reported to significantly reduce postoperative blood loss in two studies [29]. Therefore, 5 studies were finally divided into two subgroups according to patients whether treated with tranexamic or not. The non-tranexamic subgroup had low heterogeneity with I^2=44%, but the tranexamic subgroup and the total group showed high heterogeneity with I^2=94% and 90%, respectively. Then the random effect model was used and the results revealed significant difference in CBL between flexion and extension intervention, within the no tranexamic subgroup (MD=-115.52; 95% CI -174.17 to -56.87; *et P*=0.0001), the tranexamic subgroup (MD=-296.3; 95% CI -484.73 to -107.88; *P*=0.002)and all the studies (MD=-194.78; 95% CI -289.48 to -100.08; *P*<0.0001), respectively (**Figure 2**). The results indicated

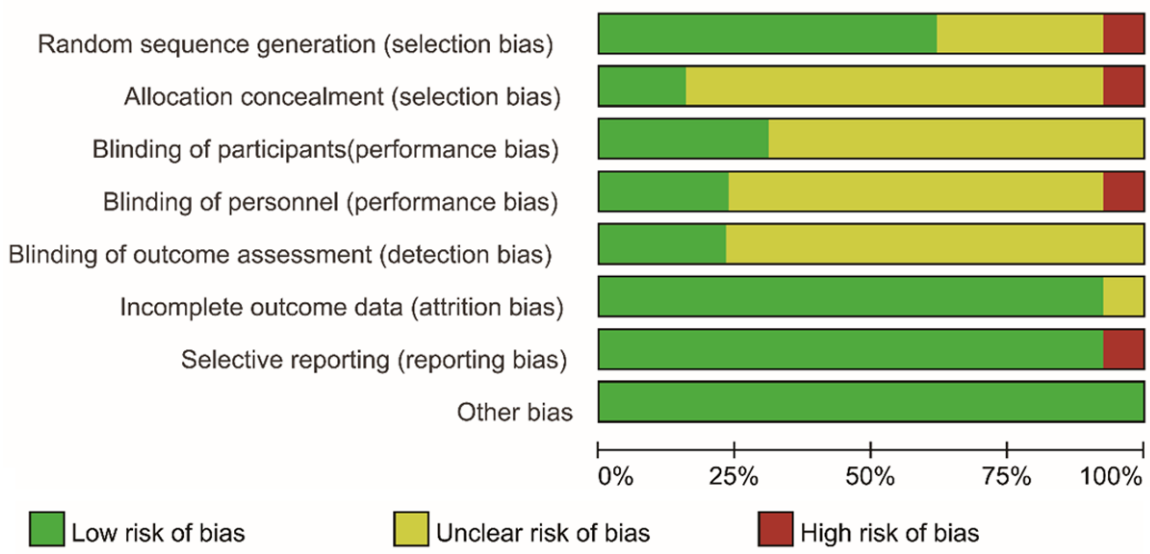

Figure 10. Risk of bias graph of the included RCTs.

that these patients with postoperative flexion of the knee had less CBL. No publication bias was found according to the funnel plot of CBL (**Figure 9**).

The evaluation of HBL: HBL was estimated by subtracting the intraoperative blood loss and postoperative DBL from the CBL at 48 h postoperatively. 5 included studies reported the HBL [9, 12-15]. Due to the tranexamic intervention existed in two studies, 5 studies were divided into tranexamic subgroup and no tranexamic subgroup. The random effect model was employed because the two subgroups and the total group showed high heterogeneity with I^2=95%, 97% and 96%, respectively. So, the results showed significant less HBL in flexion group than extension group, within the no tranexamic subgroup (MD=-89.28; 95% CI -160.11 to -18.46; *P*=0.01), the tranexamic subgroup (MD=-169.72; 95% CI-283.97 to -55.47; *P*=0.004) and all the studies (MD=-121.26; 95% CI -176.71 to -65.82; *P*<0.0001), respectively (**Figure 3**).

The evaluation of DBL: 6 studies were included into the DBL meta-analysis [17-22]. No subgroup analysis was employed due to there is no tranexamic group in these studies. Random effect model was used for the high heterogeneity with I^2=89% among these 6 studies. The results revealed postoperative flexion significantly decreased DBL than the postoperative extension among these studies (MD=-150.47; 95% CI -234.18 to -66.77; *P*=0.0004) (**Figure 4**).

The evaluation of short-term and long-term postoperative ROM: The short-term postoperative ROM was measured at 7 days after operation. 2 studies were included for this meta-analysis [12, 15]. The fixed effect model was used for no heterogeneity existing with I^2=0%. The result showed apparently better ROM in flexion group than extension group in the 2 studies (MD=7.31; 95% CI 5.25 to 9.36; *P*<0.00001) (**Figure 5**). The long-term postoperative ROM was measured 6 weeks after operation. The meta-analysis consisted of 4 studies [9, 12, 14, 21]. These 4 studies were divided into the tranexamic subgroup and the no tranexamic subgroup for the high heterogeneity with I^2=66%. However, high heterogeneity still existed in both no tranexamic subgroup and total group, with I^2=76% and I^2=66%, respectively. So random effects model were used. No obvious difference were observed in ROM between flexion and extension intervention among the 4 studies (MD=1.45; 95% CI -2.57 to 5.48; *P*=0.48) (**Figure 6**).

Complications: The SI meta-analysis consist of 5 studies [9, 12, 14, 16, 21]. The outcome of the SI incidence of these 5 studies showed low heterogeneity with I^2=0%, so fixed effect model was used. The result did not yield any significant difference in the incidence of SI between

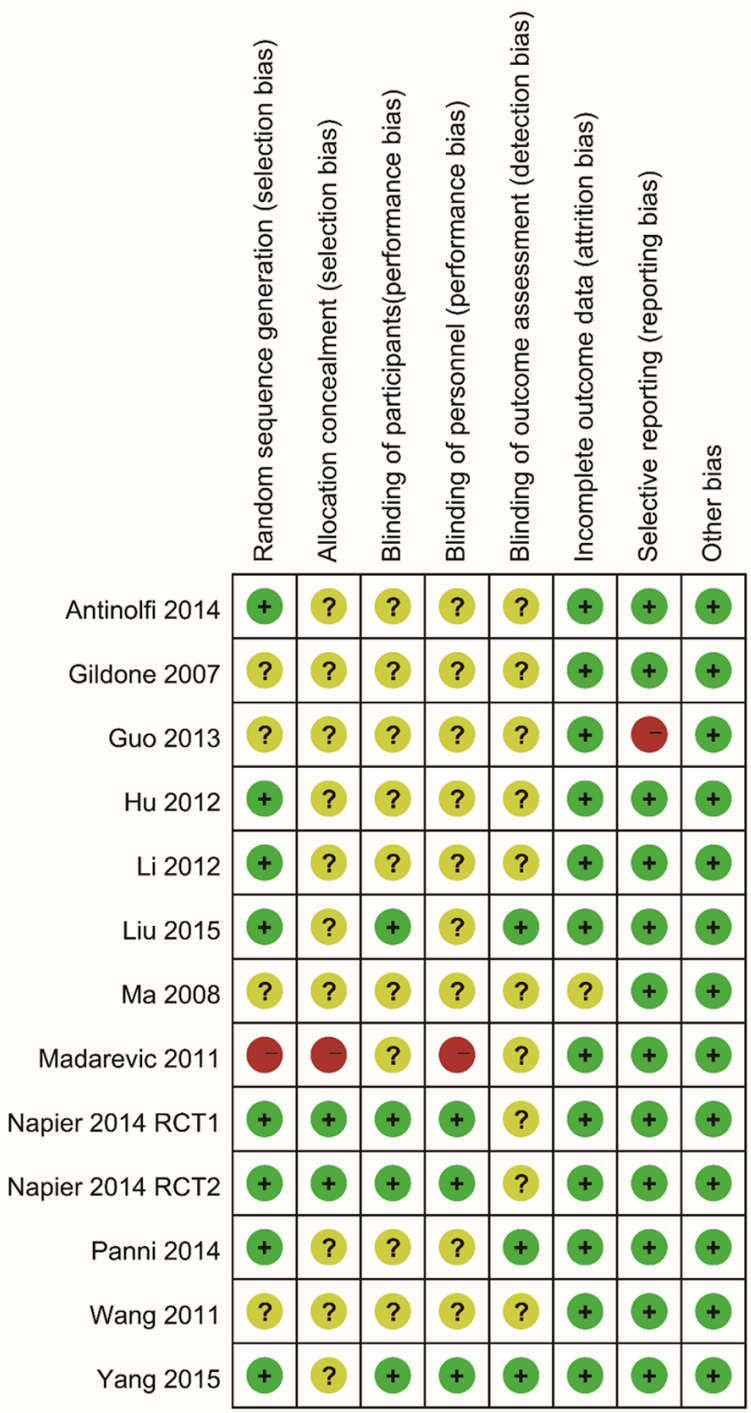

Figure 11. Risk of bias summary of the included RCTs.

flexion and extension group (RR=1.12; 95% CI 0.44 to 2.85; *P*=0.82) (**Figure 7**). The DI meta-analysis consisted of 3 studies [9, 16]. The fixed effect model was used for the low heterogeneity with I^2=0%. No significant difference was observed in the incidence of DI between flexion and extension intervention among the 4 studies (RR=1.32; 95% CI 0.33 to 5.3; *P*=0.69) (**Figure 8**). Transient lower limb sensory nerve palsy occurred in 2 patients of the flexion group in the study of *Napier 2014* RCT2 [16] and no DVT or skin necrosis occurred.

Discussion

This meta-analysis verified that postoperative flexion of knee could reduce blood loos in terms of CBL, HBL and DBL in patients after TKA. Meanwhile, postoperative flexion of knee could promote ROM in earlier postoperative period. However, ROM 6 weeks postoperative was not promoted by postoperative flexion of knee. On the other hand, the incidence of SI or DI was not increased in the postoperative flexion group. Transient lower limb sensory nerve palsy, DVT and skin necrosis were rarely seen in the group of knee flexion in previous studies. Most results of this meta-analysis were consistent with the previous studies, although a few studies were controversial in terms of CBL, DBL and ROM. The details and possible reason of the disagreement between previous studies and this meta-analysis in terms of blood loss, ROM and complication were analyzed as the following.

Firstly, in aspect of blood loss, most previous RCT studies were consistent with this meta-analysis and few ones had inconsistent results. The general outcomes to evaluate blood loss are CBL, HBL and DBL. Most articles [9, 14-16] claimed that flexion of knee could reduce CBL after TKA, however, one study conducted by *Li et al* in 2012 [12] did not yield the difference of CBL. To date, all related studies [9, 12-15] suggested that postoperative flexion of knee could reduce the HBL in patients after

TKA. With respect of DBL 4 studies [17-20] supported the decreasing effect of knee flexion on DBL and 2 studies conducted by Ma and Madarevic [21, 22] did not yield any significant difference. The reasons why the aforementioned studies did not yield any significant difference were as follows. Firstly, blood loss could be affected by many factors such as different surgical duration, different baseline of patients and other factors of bias; Secondly, the sensitivity for detecting the difference of postoperative blood loss was limited for the small sample amount of the patients. Additionally, the decreasing effect of postoperative knee flexion on blood loss might be decreased for the method to collect data, e.g. the data was questioned in the study conducted by *Ong et al* in 2008 [23]. In Ong's study, the elevation of leg was demonstrated to reduce the blood loss effectively. Therefore, the relative elevated leg might be attributed to the effect of reducing blood loss when knee flexion. This speculation was dubious because at least a horizontal flexion group should be set as the control group to verify whether knee flexion could reduce blood loss or not.

Secondly, previous investigations of the knee flexion evaluated effects on ROM usually included both the short-term and long-term indicators, respectively at 7 days and 6 weeks postoperative. With respect to short-term ROM, two studies [12, 15] showed better outcome in flexion group than in extension group. However, with respect to long-term ROM, three RCTs [9, 12, 21] showed there was no significant difference between flexion group and extension group. Only one RCT [14] demonstrated the flexion group had better outcome of long-term ROM than extension group. As far as we know, our meta-analysis firstly demonstrated that the knee flexion could induce beneficial effects on the ROM in short-term postoperative period, but made no sense in long-term postoperative period. Several researchers speculated that if the knee was laid flexion after operation, hidden blood loss reduced and the knee swelling eased, resulting in the decrease of the knee circumference, and ultimately increased ROM. However, in the long-term period, the condition of soft tissue swell around knee was similarly recovered in the patients of both groups. Therefore, no significant difference was observed in the term of ROM.

Thirdly, a previous study reporting knee flexion after TKA might lower oxygen tension, thereby increase the wound complication [30]. However, no single RCT demonstrated significant difference between flexion and extension group in terms of the wound complication, especial SI and DI. SI and DI results in this meta-analysis were consistent with that in each single RCT. Transient lower limb sensory nerve palsy occurred in only two patients [16] among these included 13 RCTs of this meta-analysis.

Additionally, this meta-analysis was in accord with the system review article reported by *Faldini et al* [24] in the aspect of postoperative blood loss. In this article, the short-term ROM and long-term ROM were further divided to analyze respectively which previous system review had not done. Therefore, the results of that review were in consistent with ours.

Special attention should be paid to the clinical applicability of this meta-analysis. The results of this meta-analysis could only be applied for these patients with primary TKA, not for arthroplasty revision patients because no revision arthroplasty participants were involved in the present study. In arthroplasty revision patients, many clinical factors should be taken into account, such as the stability of the joint and the soft tissue quality. The exact flexion degree of the knee should be decided by clinical practice, because there were short of specific RCTs investigating on this topic. As for the effect of different duration of knee flexion on blood loss, the study conducted by Napier's investigation in 2014 reported blood loss was decreased in 6-hours flexion group than in 3-hours flexion group. Therefore, longer duration of postoperative knee flexion seemed to be expected to reduce more blood loss. More investigation on degree and duration of knee flexion were needed to be conducted to draw a definite conclusion.

Nonetheless, our meta-analysis is not without limitations. Firstly, some included studies lack sufficient data. Thirteen RCTs were included in this meta-analysis, but several RCTs among them did not provide complete aimed outco mes. Secondary, high heterogeneity was existed in terms of CBL, HBL and DBL. It might be on account of several factors such as different knee flexion degree, different knee flexion durations and different surgical duration, applica-

tion of medicine for anticoagulation and application of tourniquet. These variable factors can be controlled by dividing the patients into subgroups, to some extent. However, further investigation is impeded for the lack of enough studies. Although the heterogeneities were high, the differences were still significant when evaluating the effects on blood loss on the premise of using random effect model between the postoperative flexion group and postoperative extension group.

Conclusion

This meta-analysis suggested that postoperative flexion of knee on patients after TKA could reduce blood loos in terms of CBL, HBL and DBL, and could also promote ROM in short-term postoperative period without any detrimental effects on the incidence of complication. However, it could not promote ROM in long-term postoperative period.

Disclosure of conflict of interest

None.

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References

[1] Mulcahy H, Chew FS. Current concepts in knee replacement: complications. Am J Roentgenol 2014; 202: W76-86.

[2] Levine BR, Haughom B, Strong B, Hellman M, Frank RM. Blood management strategies for total knee arthroplasty. J Am Acad Orthop Surg 2014; 22: 361-71.

[3] Bou Monsef J, Figgie MP, Mayman D, Boettner F. Targeted pre-operative autologous blood donation: a prospective study of two thousand and three hundred and fifty total hip arthroplasties. Int Orthop 2014; 38: 1591-1595.

[4] Paul JE, Ling E, Lalonde C, Thabane L. Deliberate hypotension in orthopedic surgery reduces blood loss and transfusion requirements: a meta-analysis of randomized controlled trials. Can J Anaesth 2007; 54: 799-810.

[5] Bedair H, Yang J, Dwyer MK, McCarthy JC. Preoperative erythropoietin alpha reduces postoperative transfusions in THA and TKA but may not be cost-effective. Clin Orthop Relat Res 2015; 473: 590-6.

[6] Kim C, Park SS, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. J Blood Med 2015; 6: 239-44.

[7] Olsfanger D, Fredman B, Goldstein B, Shapiro A, Jedeikin R. Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement. Br J Anaesth 1997; 79: 317-21.

[8] Moonen AF, Knoors NT, van Os JJ, Verburg AD, Pilot P. Retransfusion of filtered shed blood in primary total hip and knee arthroplasty: a prospective randomized clinical trial. Transfusion 2007; 47: 379-84.

[9] Liu J, Li Y, Cao JG, Wang L. Effects of knee position on blood loss following total knee arthroplasty: a randomized, controlled study. J Orthop Surg Res 2015; 10: 69.

[10] Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962; 51: 224-32.

[11] Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology 1983; 58: 277-80.

[12] Li B, Wen Y, Liu D, Tian L. The effect of knee position on blood loss and range of motion following total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2012; 20: 594-9.

[13] Guo B, Chen X, Wei G. (The effect of position on postoperative hidden blood loss after primary TKA). Orthop J China 2013; 21: 305-306.

[14] Yang Y, Yong-Ming L, Pei-Jian D, Jia L, Ying-ze Z. Leg position influences early blood loss and functional recovery following total knee arthroplasty: A randomized study. Int J Surg 2015; 23: 82-86.

[15] Panni AS, Cerciello S, Vasso M, Del Regno C. Knee flexion after total knee arthroplasty reduces blood loss. Knee Surg Sports Traumatol Arthrosc 2014; 22: 1859-64.

[16] Napier RJ, Bennett D, McConway J, Wilson R, Sykes AM, Doran E, O'Brien S, Beverland DE. The influence of immediate knee flexion on blood loss and other parameters following total knee replacement. Bone Joint J 2014; 96-B: 201-9.

[17] Gildone A, Punginelli B, Manfredini M, et al. A comparison of two rehabilitation protocols after total knee arthroplasty: does flexion affect mobility and blood loss? J Orthop Traumatol 2007; 8: 6-10.

[18] Wang SQ, Huang G, Xia J, et al. The efficacy of postoperative knee position in reducing blood loss after total knee arthroplasty. Chinese J Jt Surg 2011; 5: 106-164.

[19] Hu HY, Wang LH, Lu FJ. comparision on blood loss between different position and drainage method after total knee arthroplasty. J Nurs Rehabil 2012; 11: 910-912.

[20] Antinolfi P, Innocenti B, Caraffa A, Peretti G, Cerulli G. Post-operative blood loss in total knee arthroplasty: knee flexion versus pharmacological techniques. Knee Surg Sports Traumatol Arthrosc 2014; 22: 2756-62.
[21] Ma T, Khan RJ, Carey Smith R, Nivbrant B, Wood DJ. Effect of flexion/extension splintage post total knee arthroplasty on blood loss and range of motion–a randomised controlled trial. Knee 2008; 15: 15-9.
[22] Madarevic T, Tudor A, Sestan B, Santic V, Gulan G, Prpic T, Ruzic L. Postoperative blood loss management in total knee arthroplasty: a comparison of four different methods. Knee Surg Sports Traumatol Arthrosc 2011; 19: 955-9.
[23] Ong SM, Taylor GJ. Can knee position save blood following total knee replacement? Knee 2003; 10: 81-5.
[24] Faldini C, Traina F, De Fine M, Pedrini M, Sambri A. Post-operative limb position can influence blood loss and range of motion after total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc 2015; 23: 852-9.
[25] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; CochraneStatistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
[26] Hewitt B, Shakespeare D. Flexion vs. extension: a comparison of post-operative total knee arthroplasty mobilisation regimes. Knee 2011; 8: 305-9.
[27] Zenios M, Wykes P, Johnson DS, Clayson AD, Kay P. The use of knee splints after total knee replacements. Knee 2002; 9: 225-8.
[28] Horton TC, Jackson R, Mohan N, Hambidge JE. Is routine splintage following primary total knee replacement necessary? A prospective randomised trial. Knee 2002; 9: 229-31.
[29] Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. Transfus Med 2015; 25: 151-62.
[30] Johnson DP. Infection after knee arthroplasty. Clinical studies of skin hypoxia and wound healing. Acta Orthop Scand Suppl 1993; 252: 1-48.