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KNEE ARTHROPLASTY

Hemostatic techniques to reduce blood transfusion after primary TKA: a meta-analysis and systematic review

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Abstract

Purpose To investigate the efficacy of non-tranexamic acid (TXA) on reducing blood loss and requirements of allogeneic blood transfusion (ABT) in total knee arthroplasty (TKA).

Methods The PubMed, EMBASE, and the Cochrane Library databases were researched since incipiency to June 2018. Only randomized controlled trials (RCTs) involved with non-TXA hemostatic techniques in TKA met the inclusion criteria.

Results A total of 36 RCTs, including 1511 patients, were recruited for analysis. The results of subgroup analysis revealed that hemostatic techniques, which could substantially decrease the rate of ABT, were cell salvage with the transfusion trigger of 9 mg/dl, fibrin sealant with a dosage of 10 ml, and postoperative flexion position.

Conclusion The available evidence in this meta-analysis suggests that postoperative flexion position, fibrin sealant, and cell salvage can substantially decrease the rate of ABT in TKA. Further studies, including more hemostatic methods and high-quality research, are expected.

Keywords Total knee arthroplasty · Allogeneic blood transfusion · Meta-analysis

Introduction

Total knee arthroplasty (TKA) is one of the most common elective orthopedic surgeries performed worldwide, and has an increasing prevalence with the aging of population and innovative medical instruments [1]. For patients with end-stage knee osteoarthritis or inflammatory arthritis, TKA is recognized as the highly cost-effective and curative method to relieve pain and improve function when conservative treatment is unsuccessful [2].

TKA is associated with substantial blood loss because of tissues and bony surfaces bleeding. It is reported that patients receiving TKA can cause perioperative blood loss from 0.3 to 1 L, and expanded to 1–2 L when hidden blood loss is included [3, 4]. Historically, to correct acute significant blood loss during or after TKA, allogenic blood transfusion (ABT) is ranked as the standard method to restore normal level of hematocrit and hemoglobin, and is reported to have an occurrence rate of 11–38% [5, 6]. However, the issue about adverse effects of ABT always gives orthopedists a dilemma. The ABT is reported to be associated with blood dissemination diseases and a risk of the surgical site infection after TKA [7–9]. Therefore, it is imperative for surgeons to take measures to reduce or avoid ABT in patients undergoing TKA. The efficacy of tranexamic acid (TXA) in TKA has been intensively researched, and it is well established that TXA is useful to decrease blood loss and the requirements of ABT [10]. However, there are also several drawbacks, like thrombogenesis and restricted dosage in aging patients, of applying TXA in TKA [11]. Hence, many TXA-free strategies, including, platelet-rich plasma (PRP), fibrin sealant, flexion position, tourniquet, and cell

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salvage are developed and applied in TKA to reduce blood loss and the rate of ABT [12–15]. Whereas, whether other strategies for reducing blood loss could actually lower the requirements of ABT still bewilders orthopedists.

The purpose of this meta-analysis is to confirm which non-TXA strategies can decrease the rate of perioperative ABT in patients with TKA. The hypothesis is that tourniquet, cell salvage, and fibrin sealant can make a difference in reducing the requirements of ABT.

Methods

This meta-analysis was designed and conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16].

Research strategy

Two authors independently searched the PubMed, EMBASE, and the Cochrane Library databases for relevant articles published till February 20, 2018. The search algorithm was generated by different combination of keywords: "total knee arthroplasty" or "total knee replacement" or "TKA" or "TKR" AND "allogenic blood transfusion" or "homologous blood transfusion" or "blood transfusion" AND "randomized controlled trial" or "clinical controlled trial" or "randomized". The searches were limited to human subjects and RCTs, and an English language restriction was imposed. In addition, the reference lists of identified articles were checked manually to avoid missing other potentially eligible studies. This process was performed iteratively until no additional articles could be included.

Inclusion and exclusion criteria

The following selection criteria for inclusive articles were applied: (a) published English, full-text, peer-reviewed articles; (b) prospective randomized controlled trails, level 1 or 2; (c) studies were performed to compare homologous or allogenic transfusion rates between experimental and control group in patients with TKA; and (d) studies were eligible for pooling data for meta-analysis. Studies were excluded according to following criteria: (a) cohort studies, retrospective studies, observational studies, case–control studies, case series or reports, or review; (b) animal studies, cadaver studies, or laboratory studies; (c) studies that utilized TXA; and (d) a preoperative HB level < 12 mg/dl. Any disagreements were resolved by discussion with the corresponding author. Where there was disagreement or doubt, the full article was retrieved. The same two authors independently assessed the full study report to see if it met the review inclusion criteria. The corresponding author was consulted in cases of unresolved disagreement.

Data extraction

After all eligible studies were confirmed, two authors (Z.D and J.Q) independently and carefully extracted the following data: the first author, study design, year of publication, country, numbers of cases and controls, transfusion rate, and trigger of blood transfusion. Extracted data were then entered into a standardized Excel (Microsoft Corp) file, and were checked by the corresponding author. Any disagreements were resolved by discussion and consensus.

Risk of bias assessment

Two authors (Y.S and F.W) independently assessed the risk of bias for each identified study. The Cochrane Collaboration's risk of bias tool was applied according to six items as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias [17]. Each outcome of these items was expressed as low, unclear, or high bias. A funnel plot based on each trial's effect size was used to test the possibility of publication bias through visual inspection [18]. Any disagreements were resolved by discussion and consensus.

Statistical analysis

Differences were expressed as risk ratio (RR) or risk difference (RD) with 95% confidence interval (CI) for dichotomous outcomes, and mean differences (WMDs) with 95% CIs for continuous outcomes. Heterogeneity across studies was tested using I^2 statistics and Q test statistics with significance set at $P < 0.10$. Studies with an I^2 statistic of 25–50% were considered as low heterogeneity, those with an I^2 statistic of 50–75% were considered as moderate heterogeneity, and those with an I^2 statistic of > 75% were considered as high heterogeneity [19]. Significant heterogeneity was considered when $I^2 > 50\%$, or $P < 0.1$. A fixed-effects model was used for the outcomes data when there was no statistically significant heterogeneity, otherwise, a random-effects model was used [20]. To explore causes of inconsistency, sensitivity analysis was performed. Additionally, subgroup analyses were performed for pooling data according to different categories, such as trigger of ABT, dosage of fibrin sealant, and time of releasing tourniquet. A P value < 0.05 was judged as statistically significant, except where otherwise specified. All statistical analyses were performed with Review Manager soft-ware (version 5.3; Nordic Cochrane Centre, The Cochrane).

Results

Search results

A total of 1153 studies were identified through the initial database search. After removal of duplicate, 377 records were identified and, 230 records were excluded based on screening the titles and abstracts. The remaining 147 full-text articles were reviewed for more detail evaluation, and 23 full-text articles were excluded due to non-RCTs or insufficient data. Eventually, 36 RCTs that conformed to the inclusion criteria were included in this meta-analysis. The flow diagram of selection process for the meta-analysis is shown in Fig. 1.

Characteristics of included studies

We totally enrolled 1511 TKAs in experimental group and 1304 TKAs in control group, respectively. Five interventions were brought into the meta-analysis for comparing blood transfusion rate between experimental and control group (total transfusion rate, 0.22 vs. 0.34). Most of included RCTs have set a transfusion trigger, such as 8 ml/dl, 9 ml/dl, or clinical symptoms. Other baseline characteristics, like mean age and sex ratio, are listed in Table 1.

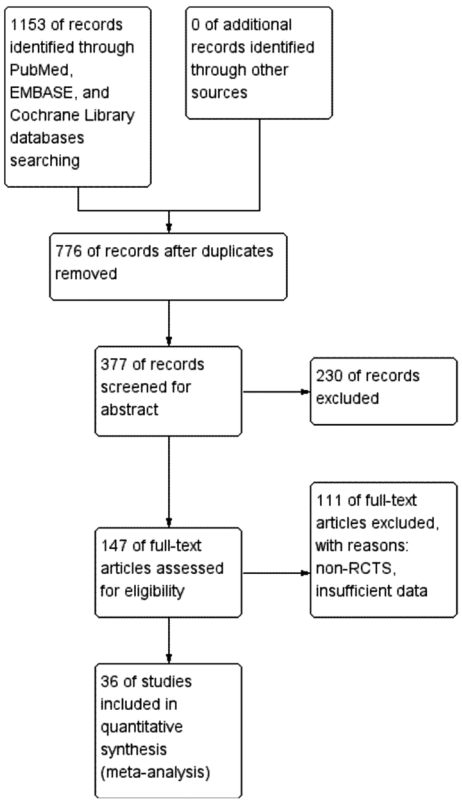

Fig. 1 The flow diagram of the selection process

Risk of bias in included studies

The judgements about each risk of bias item for each included study and about each risk of bias item presented as percentages across all included studies are shown in Fig. 2, respectively. The detection and attrition bias deserved the lowest risk since the transfusion rate was an inpatient assessment. The studies by Blatsoukas et al. and Ozkunt et al. used the order of admission to conduct randomization, and thus they were rated as having a high risk of selection bias [12, 13]. Eight studies did not report the trigger of blood transfusion, which were considered to have a high risk of potential bias [12, 21–27]. None of outcomes have shown a strong evidence of publication bias based on visual inspection of the funnel plots (Fig. 3).

Intervention outcomes

Only three RCTs were included to compare the transfusion rate between PRP group and no PRP group in patients with TKAs [22, 26, 28]. The evidence demonstrated that there were no significance of the transfusion rate between two groups ($P = 1.0$; RD = 0; 95% CI −0.06, 0.06). The results showed low heterogeneity ($P = 1.0$, $I^2 = 0\%$), and no significant heterogeneity was found (Fig. 4).

A total of 417 TKAs included in 7 studies were recruited to compare the transfusion rate between fibrin sealant group and placebo group [4, 27, 29–33]. The results suggested the superiority of fibrin sealant group compared with placebo group ($P < 0.01$; RR = 0.54; 95% CI 0.41, 0.72), and no significant heterogeneity was found ($P = 0.50$, $I^2 = 0\%$). The subgroup analysis was performed according to different dosages of fibrin sealant, and the evidence revealed there was no significant difference between two groups when the dosages of fibrin sealant were less than 10 ml ($P = 0.06$; RR = 0.66; 95% CI 0.42, 1.02) (Fig. 5).

Five RCTs were enrolled to determine whether post-operative positions could have an effect on decreasing the transfusion rate of patients with TKA [24, 34–37]. The results indicated that flexion position had a better performance in decreasing the transfusion rate than extension position ($P < 0.01$; RR = 0.51; 95% CI 0.32, 0.82). There was low heterogeneity ($P = 0.47$, $I^2 = 0\%$), and no significant heterogeneity was found (Fig. 6).

Seven studies were available to pool data for determining whether the usage of tourniquet could influence the transfusion rate of patients with TKA [12, 21, 23, 25, 38–40]. The pooled data demonstrated that there was no significant difference of the transfusion rate between tourniquet group and no tourniquet group ($P = 0.12$; RR = 0.84;

Table 1 Baseline data of included studies

Study	Year	Country	LOE	Number		Male/Female	
				Exp	Con	Exp	Con
Horstmann	2011	Netherlands	1	20	20	14/6	13/7
Morishita	2014	Japan	1	20	20	18/2	20/0
Guerreiro	2015	Brazil	1	20	20	6//14	8/12
Levy	1999	Israel	1	29	29	6/23	6/23
Wang	2001	America	1	25	28	N.A	N.A
Mollory	2007	Ireland	1	50	50	N.A	N.A
Notarnicola	2012	Italy	1	60	30	40/20	20/10
Kluba	2012	Germany	1	12	12	6/6	4/8
Auguilera	2013	Spain	1	42	42	6/36	6/36
Randelli	2014	Italy	1	31	31	5/26	9/22
Ong	2002	England	1	20	20	8 /12	7/13
Ma	2008	Australia	1	49	46	24/25	24/22
Panni	2014	Italy	1	50	50	12/38	10/40
Liu	2015	china	1	50	50	16/34	18/32
Yang	2015	China	1	46	46	24/22	26/20
Harvey	1997	Canada	1	52	27	N.A	N.A
Clarke	2001	England	1	20	10	N.A	N.A
Tetro	2001	Canada	1	33	30	15/18	11/19
Matziolis	2005	Germany	1	10	10	2/8	3/7
Tai	2012	China	2	36	36	9/27	8/28
Ledin	2012	Sweden	1	25	23	10/15	9/14
Ozkunt	2017	Turkey	2	44	25	NA	N.A
Majkowski	1991	England	2	20	20	6/14	6/14
Newman	1997	England	1	35	35	N.A	N.A
Shenolikar	1997	England	1	50	50	21/29	24/26
Adalberth	1998	Sweden	1	24	24	4/20	8/16
Thomas	2001	England	1	115	116	44/71	55/61
Cheng	2005	Hong Kong	1	26	34	6/20	12/22
Dramis	2006	England	1	32	17	11/21	4/13
Abuzakuk	2007	England	1	52	52	43/61	
Moonen	2007	Netherlands	1	45	32	N.A	N.A
Amin	2008	England	1	92	68	43/49	39/27
Atay	2010	Istanbul	1	20	21	2/18	7/14
Blatsoukas	2010	Greece	2	163	85	31/132	12/73
Dutton	2012	England	1	23	25	10/13	10/15
Cip	2013	Austria	2	70	70	N.A	N.A

Study	Age		Trigger	Intervention
	Exp	Con		
Horstmann	67 (57–81)	66 (51–78)	N.A	PRP
Morishita	72 ± 4.1	74.7 ± 5.7	N.A	PRP
Guerreiro	66.4 (50–86)	71 (55–81)	7 mg/dL	PRP
Levy	68.9 ± 6.3	70.2 ± 8.2	Non-restriction	Fibrin sealant
Wang	N.A	N.A	N.A	Fibrin sealant
Mollory	N.A	N.A	Hematocrit< 0.25	Fibrin sealant
Notarnicola	69.2 ± 8.2		8 mg/dl	Fibrin sealant
Kluba	70.8	71	Non-restriction	Fibrin sealant
Auguilera	72.6 ± 11.0	74.9 ± 7.0	8 mg/dL	Fibrin sealant

Table 1 (continued)

Study	Age		Trigger	Intervention
	Exp	Con		
Randelli	69 ± 8	71 ± 8.5	9 mg/dl	Fibrin sealant
Ong	71	74	8 mg/dL	Postoperative position
Ma	71 ± 9.39	70.6 ± 8.5	N.A	Postoperative position
Panni	69 ± 7	62 ± 6	8 mg/dL	Postoperative position
Liu	73.1 ± 5.1	72.4 ± 4.6	8 mg/dL	Postoperative position
Yang	73.6 ± 5.0	72.5 ± 4.7	9 mg/dL	Postoperative position
Harvey	72.4 ± 68.3	73.4	8 mg/dL	Tourniquet
Clarke	N.A	N.A	N.A	Tourniquet
Tetro	69.8 ± 6.7	69.8 ± 9	Non-restriction	Tourniquet
Matziolis	72.4	76.6	N.A	Tourniquet
Tai	72.1 ± 6.9	71.5 ± 6.8	Non-restriction	Tourniquet
Ledin	70 ± 8	71 ± 6	N.A	Tourniquet
Ozkunt	69.05		N.A	Tourniquet
Majkowski	71.3	70.3	9 mg/dL	Cell salvage
Newman	N.A	N.A	Clinical signs	Cell salvage
Shenolikar	70.4	64.9	9 mg/dL	Cell salvage
Adalberth	71 (69–74)	72 (69–75)	9 mg/dL	Cell salvage
Thomas	70.5 (32–95)	67.4 (38–85)	9 mg/dL	Cell salvage
Cheng	72 (57–84)	69 (55–78)	9 mg/dL	Cell salvage
Dramis	69 (49-83)	72 (62–91)	9 mg/dL	Cell salvage
Abuzakuk	68.5		9 mg/dL	Cell salvage
Moonen	69 ± 9.5	69.5 ± 7.3	Clinical signs	Cell salvage
Amin	70.3	70.4	8 mg/dL	Cell salvage
Atay	65.25 ± 12.57	68.19 ± 6.62	8 mg/dL	Cell salvage
Blatsoukas	69 ± 7	68.5 ± 7	9 mg/dL	Cell salvage
Dutton	68.7	70.5	Clinical signs	Cell salvage
Cip	70	69	8 mg/dL	Cell salvage

PRP platelet rich plasma, *LOE* level of evidence, *Exp* experimental, *Con* control, *N.A* not applicable

95% CI 0.67, 1.05), and no significant heterogeneity was detected ($P = 0.46$, $I^2 = 0\%$). We further conduct the subgroup analysis according to tourniquet release before or after wound closure, however, the subgroup analysis revealed no difference with overall effect (Fig. 7).

A total of 14 RCTs were included to prove whether cell salvage contributed to reducing the allogeneic blood transfusion rate of patients with TKA [13, 41–53]. The evidence revealed that cell salvage could significantly decrease the allogeneic blood transfusion rate compared with no cell salvage ($P < 0.01$; RR = 0.5(2)8; 95% CI 0.50, 0.67), and a high heterogeneity was detected across these studies ($P < 0.01$, $I^2 = 71\%$). Sensitivity analysis was conducted and showed the exclusion of studies did not change the statistical results. However, a detailed subgroup analysis was performed according to different triggers of blood transfusion, and the results indicated that there was no significant difference between two groups across the studies which set 8 mg/dl as the trigger of blood transfusion ($P = 0.14$; RR = 0.75; 95% CI 0.51, 1.10) (Fig. 8).

Discussion

There are several interesting findings in our meta-analysis. Cell salvage, flexion position, and fibrin sealant are determinate non-TXA strategies which have positive effects on reducing the rate of ABT in patients undergoing TKA. Noteworthily, according to the subgroup analysis, fibrin sealant group is not superior to control group when the volume is less than 10 ml; cell salvage group has a better performance than control group only in the case that the transfusion trigger is set as 9 mg/dl of hemoglobin. Surprisingly, using a tourniquet during TKA do not actually decrease the rate of ABT, neither do PRP.

Fig. 2 Risk of bias graph

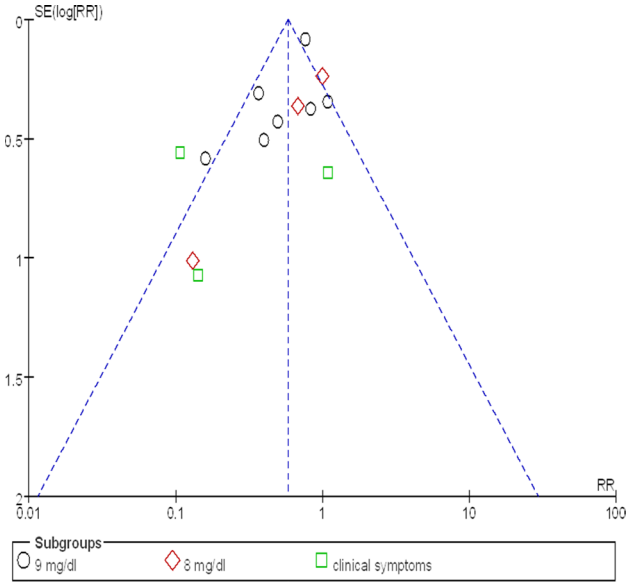

Fig. 3 Funnel plots

Postoperative flexion in TKA has been considered to be a contributing factor for reducing postoperative blood loss and improving range of motion [24, 34, 35]. Whereas, inconsistency exists regard with the effects of the knee flexion position on decreasing the requirements of ABT associated with TKA. The results of this study demonstrated that the flexion position was preferable to lower the rate of perioperative ABT compared with the extension position. The findings were somewhat matched with a previous meta-analysis which reported that the high-flexion position could significantly reduce the requirements of ABT and improve postoperative range of motion [54]. The hidden blood loss, the blood extravasating into the articular cavity and soft tissues, can approximately account for half of total blood loss and can lead to different extent of knee swelling following TKA [3]. Knee swelling could increase the tension of soft tissues around the knee, reducing knee flexion motion and even hindering wound healing due to decreased oxygen tension at the skin edges [36, 55]. In theory, the extension position could increase the tension of lower limb venous, blocking venous return and increasing venous pressure, resulting in more blood loss. Moreover, the hidden blood loss could aggravate the weight of the affected lower limb, demanding more muscle force for straight-leg raising exercises [36, 37]. The flexion position is hypothesized to reduce blood loss by bending popliteal vein and increasing local tension [34]. Since no local or general complications were documented, the flexion position following TKA may be a safe and cost-effective method to reduce the ABT requirements.

Cell salvage, alternatively known as 'autotransfusion', is a terminology which consists of diverse methods that filter blood from operative fields or wound sites, and re-transfuse

Fig. 4 Pooled results of PRP

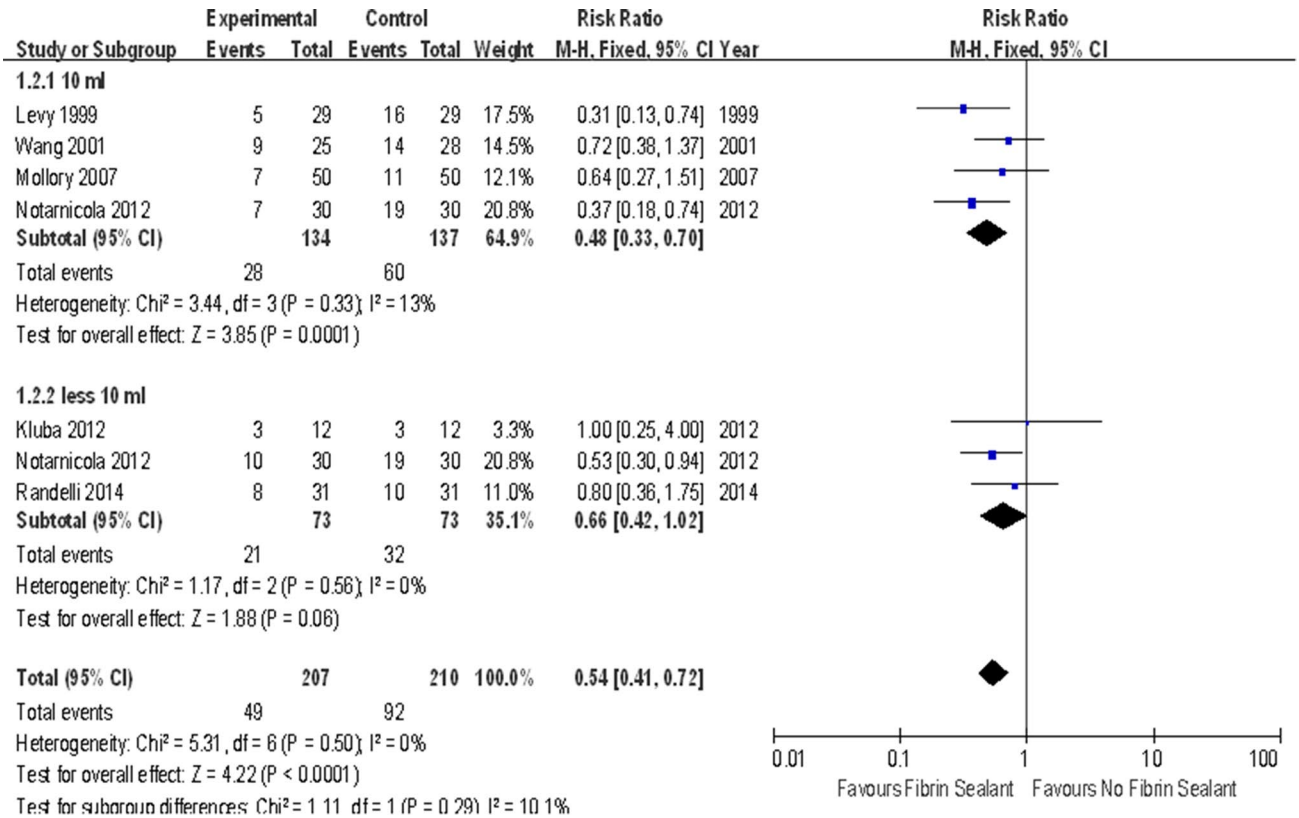

Fig. 5 Pooled results of fibrin sealant

the treated blood into the circulatory system [56]. Since the end of 1970s, cell salvage, as a means of preventing potential risks of ABT, has been frequently used in the setting of orthopedic surgery, and can be performed in both the intra- and postoperative periods. There is still no consensus with respect to whether cell salvage is able to reduce the requirements of ABT in patients undergoing TKA [44–46, 51]. The pooled results indicated that the rate of ABT in the cell salvage group was significantly lower than the control group. In the subgroup with a more restrictive transfusion trigger of 8 mg/dl, the rate of ABT was not significantly different between the two groups. Carless et al. conducted a meta-analysis and concluded that the application of cell salvage in surgery was effective to lower the rate of ABT by a relative 38%, and even more when applied in the elective cardiac and orthopedic surgery [57]. In another recent meta-analysis, the authors found that the positive impact of cell salvage faded when associated a more restrictive trigger of 8 mg/dl for ABT; the authors also found a time period effect with studies published since 2010 presenting no significant

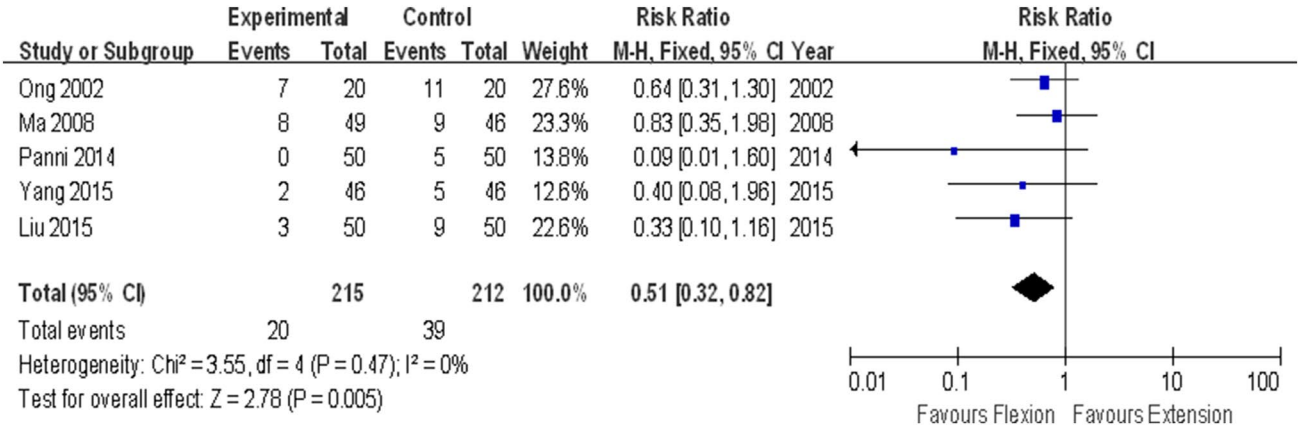

Fig. 6 Pooled results of postoperative position

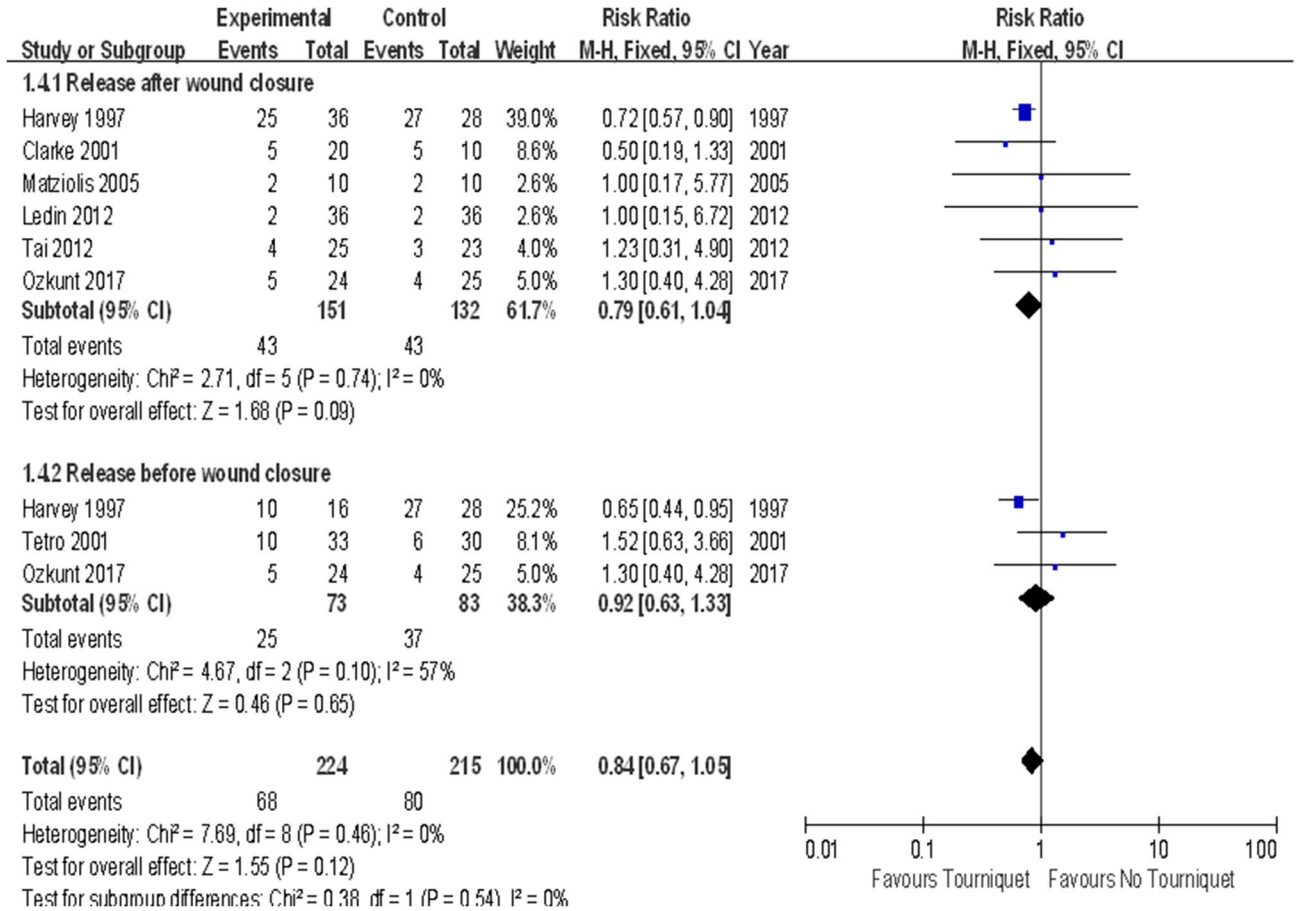

Fig. 7 Pooled results of tourniquet

decrease in rate of ABT for the technique of cell salvage [58]. However, one study included in their review recruited patients undergoing both primary and revision TKA and reported a higher rate of ABT in the cell salvage group compared to the control, [59] hence was considered to have a substantial heterogeneity among the studies. There indeed exist documented adverse effects following the procedure of cell salvage, such as bacterial contamination, air embolism, coagulation disorders, and nephrotoxicity [60, 61]. Whereas the benefit of preventing the risks of transfusion-transmitted

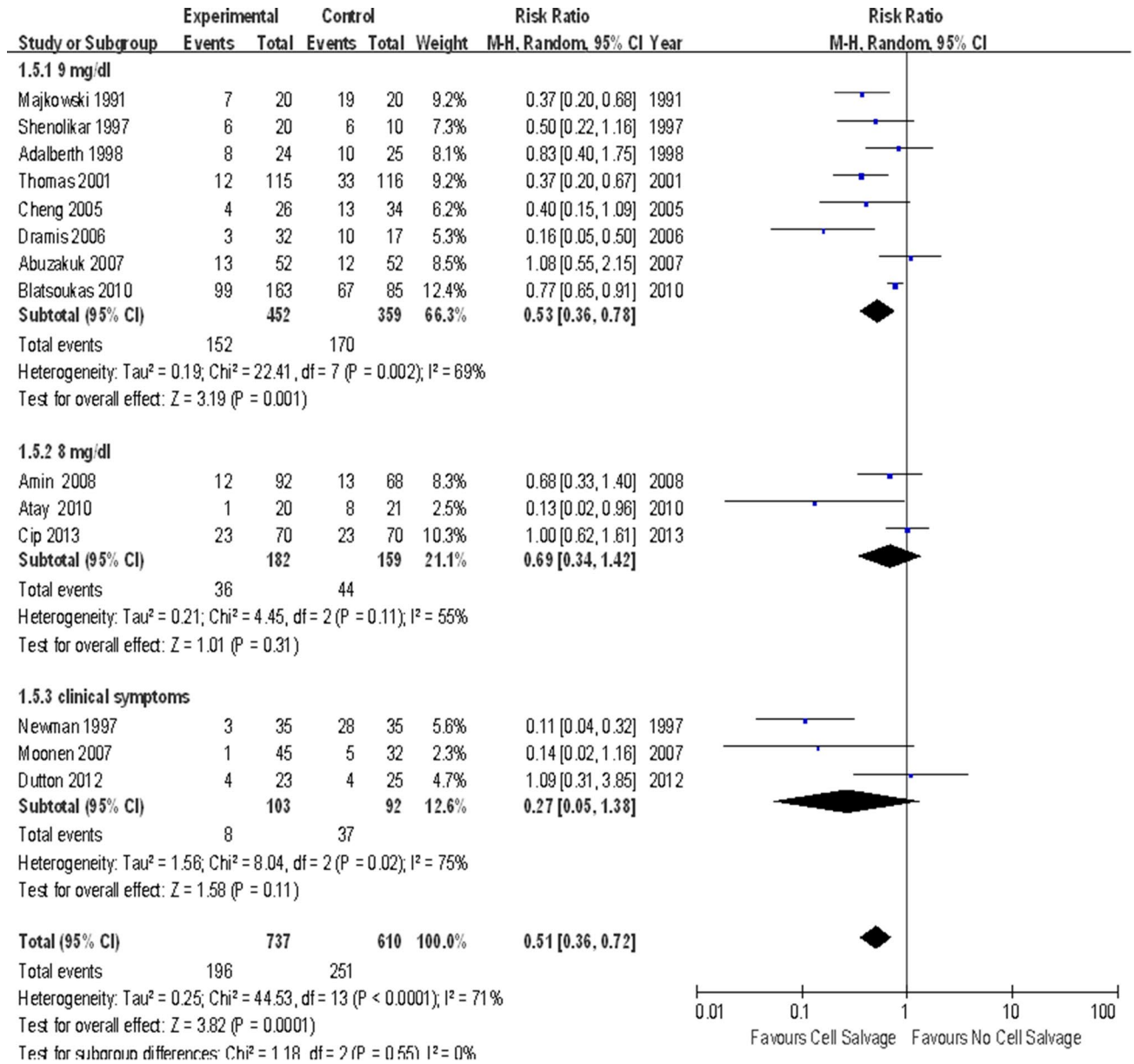

Fig. 8 Pooled results of cell salvage

disease is more attractive if the cell salvage can avoid ABT thoroughly. Febrile reactions are fairly commonplace following the application of cell salvage. The most possible explanation is either a reaction to the debris of damaged cells or the effect of several exogenous pyrogens [62]. Using corticosteroids is reported to effectively weaken the febrile reactions after major orthopedic surgery [62]. Dramis A et al. showed that cell salvage was cost-effective to allogeneic blood requirements in primary TKA [47].

Fibrin sealant, mainly consisting of fibrinogen and thrombin, has been developed into a versatile tool for hemostasis, sealing, and gluing in a variety of surgical procedures, including, recently TKA [31, 63, 64]. In the study, there was a lower rate of ABT in the fibrin group compared to the control group. Furthermore, a dosage effect was detected by the subgroup analysis which demonstrated that there was no significant difference for the rate of ABT between the two groups when the volume of fibrin sealant was less than 10 ml. The procedures of TKA include opening the soft tissue and cutting the bone, as well as the preventive application of anticoagulants to avoid deep venous thrombosis and possible pulmonary embolism. The functions of cell salvage involve sealing and plugging the bone-marrow sinusoids to reduce blood oozing, and suppressing the enhanced fibrinolytic status to prevent extravasation from the incision edges of

tissues [31]. Fibrin sealant is theoretically associated with a risk of thrombosis, whereas this has not yet been documented. There is a learning curve for surgeons to master the knowledge and technique of applying fibrin sealant [65]. According to the results of subgroup analysis, it is should be kept in mind that the dosage of fibrin sealant should be adequate.

The application of tourniquet in surgical settings can date back over a century. Pneumatic tourniquet is commonly used during TKA to reduce intraoperative blood loss, create a bloodless operative view, and facilitate the cement–bone interdigitation [66]. The results of this study showed that tourniquet application did not help to decrease the requirements of ABT in TKA, neither did the subgroup analysis. The hazards caused by the application of tourniquet are well documented: thigh pain, nerve palsy, vascular injury, quadriceps weakness, and postoperative swelling [21]. A tourniquet is considered to be associated with a higher risk of postoperative deep venous thrombosis and possible pulmonary embolism [25, 39, 67]. This may be explained by venous stasis and endothelial injury with platelet adhesion secondary to distal limb ischemia. In addition, using a tourniquet is found to hamper wound healing and increase the occurrence of wound infection [21]. Ledin et al. reported that tourniquet could not improve fixation [23]. PRP, a compound of platelet- and leukocyte-rich plasma derived from freshly drawn autologous blood, is expected to promote wound healing and reduce blood loss in a variety of surgical fields [26, 68]. The local application of PRP at wound gained attention recently to decrease postoperative bleeding in TKA [69]. However, the results of this study did not support that PRP is beneficial for decreasing requirements of ABT.

The preoperative Hb level is thought to be the primary risk factor for exposing to ABT. Hence, this meta-analysis selected only RCTs without patients who had a preoperative Hb level less than 12 mg/dl. These methods, available in lowering the rate of ABT, can be combined with others for optimum usage. For example, fibrin sealant can be used combined with TXA as a kind of "cocktail" applied at incision. Surgeons should make an individual design of blood-saving methods, and take account of all risk factors, such as preoperative Hb level, difficulty and duration of the operation, estimated blood loss, and related primary comorbidities. There were several limitations in the current meta-analysis: (1) only 36 RCTs were included for 5 hemostatic methods, and the PRP only had 3 RCTs; (2) there was not a consistent trigger for ABT, and the subgroup analysis indicated that the transfusion triggers could affect the results; (3) the volume of ABT was not assessed in this literature due to insufficient data; (4) other hemostatic methods were not involved in this study (5) publication bias was unavoidable, which could also have an effect on the results.

Conclusion

The available evidence in this meta-analysis suggests that postoperative flexion position, fibrin sealant, and cell salvage can substantially decrease the rate of ABT in TKA. However, there are no contributions for ABT saving with the application of PRP and tourniquet. Further studies, including more hemostatic methods and high-quality research, are expected.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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