Systematic Review and Meta-Analysis

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Efficacy of aminocaproic acid in the control of bleeding after total knee and hip arthroplasty

A systematic review and meta-analysis

Yihua Li, MB, Jianwen Wang, MM*

Abstract

Background: To assess the effectiveness and safety of intravenous aminocaproic acid for blood management after total knee and hip arthroplasty.

Methods: Electronic databases: PubMed (1950.1–2018.8), EMBASE (1974.1–2018.8), the Cochrane Central Register of Controlled Trials (CENTRAL, 2017.10), Web of Science (1950.1–2018.8), and CNKI (1980.1–2018.8) were systematically searched for clinical controlled trials comparing intravenous aminocaproic acid and placebo after joint arthroplasties. Heterogeneity was assessed using the chi-square test and I-square statistic. The meta-analysis was performed using STATA 12.0 (College Station, TX).

Results: Six studies with 756 patients were included. Our meta-analysis revealed that there were significant differences between aminocaproic acid and placebo in terms of total blood loss (SMD = −0.673, 95% CI: −0.825 to −0.520, $P < .001$), hemoglobin reduction (SMD = −0.689, 95% CI: −0.961 to −0.418, $P < .001$), drain output (SMD = −2.162, 95% CI: −2.678 to −1.646, $P < .001$) and transfusion rates (RD = −0.210, 95% CI: −0.280 to −0.141, $P < .001$).

Conclusion: Aminocaproic acid results in a significant reduction of total blood loss, postoperative hemoglobin decline and transfusion requirement in patients undergoing arthroplasties. Due to the limited quality of the evidence currently available, the results of our meta-analysis should be treated with caution.

Abbreviations: DVT = deep venous thrombosis, PE = pulmonary embolism, RCT = randomized controlled trials, THA = total hip arthroplasty, TJA = total joint arthroplasty, TKA = total knee arthroplasty.

Keywords: aminocaproic acid, blood loss, meta-analysis, total hip arthroplasty, total knee arthroplasty

1. Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are successful procedures for end-stage osteoarthritis or rheumatoid arthritis.[1] It has been estimated that more than 500,000 total joint arthroplasties are performed annually in China.[2] However, the process is associated with perioperative major blood loss with an average volume of 560 to 1474 ml in TKA[3–5] and 655 to 1520 mL in THA[6–8] which delays rehabilitation, functional recovery, and hospital discharge.

Although numerous strategies have been implemented to minimize the perioperative hemorrhage including electrocautery, application of pharmacologic agents, minimally invasive procedures and autologous donation, anemia is still a frequent occurrence.[9–12] As an antifibrinolytic agent, tranexamic acid (TXA) has been studied in orthopedic surgery and showed improved outcomes in blood management.[13,14] Aminocaproic acid is a derivative and analog of the amino acid lysine, which makes it an effective inhibitor for enzymes that bind particular residue. It has also been extensively and effectively used in cardiac surgery.[15] However, some experts held a cautious attitude. Aminocaproic acid, as an antifibrinolytic agent, may increase the risk of thromboembolic events, especially in orthopedic surgery. Thus, the application of aminocaproic acid has led to further investigation.

Recently, some published studies have compared the efficacy between aminocaproic acid and placebo, and the beneficial effects of such administrations remain controversial. Therefore, we conducted a systematic review and meta-analysis to assess the effectiveness and safety of aminocaproic acid for decreasing perioperative hemorrhage and transfusion rates after total joint arthroplasty (TJA).

2. Methods

This article is reported according to the guideline of PRISMA statement. Ethical approval is not required because it is a meta-analysis of previously published studies.

2.1. Search strategy

Electronic databases: PubMed (1950–2018.5), EMBASE (1974–2018.5), the Cochrane Central Register of Controlled Trials (CENTRAL, 2018.5) and Web of Science (1950–2018.5) were systematically scanned. The title, abstract and mesh search terms included ("total knee arthroplasty") and ("total hip arthro-

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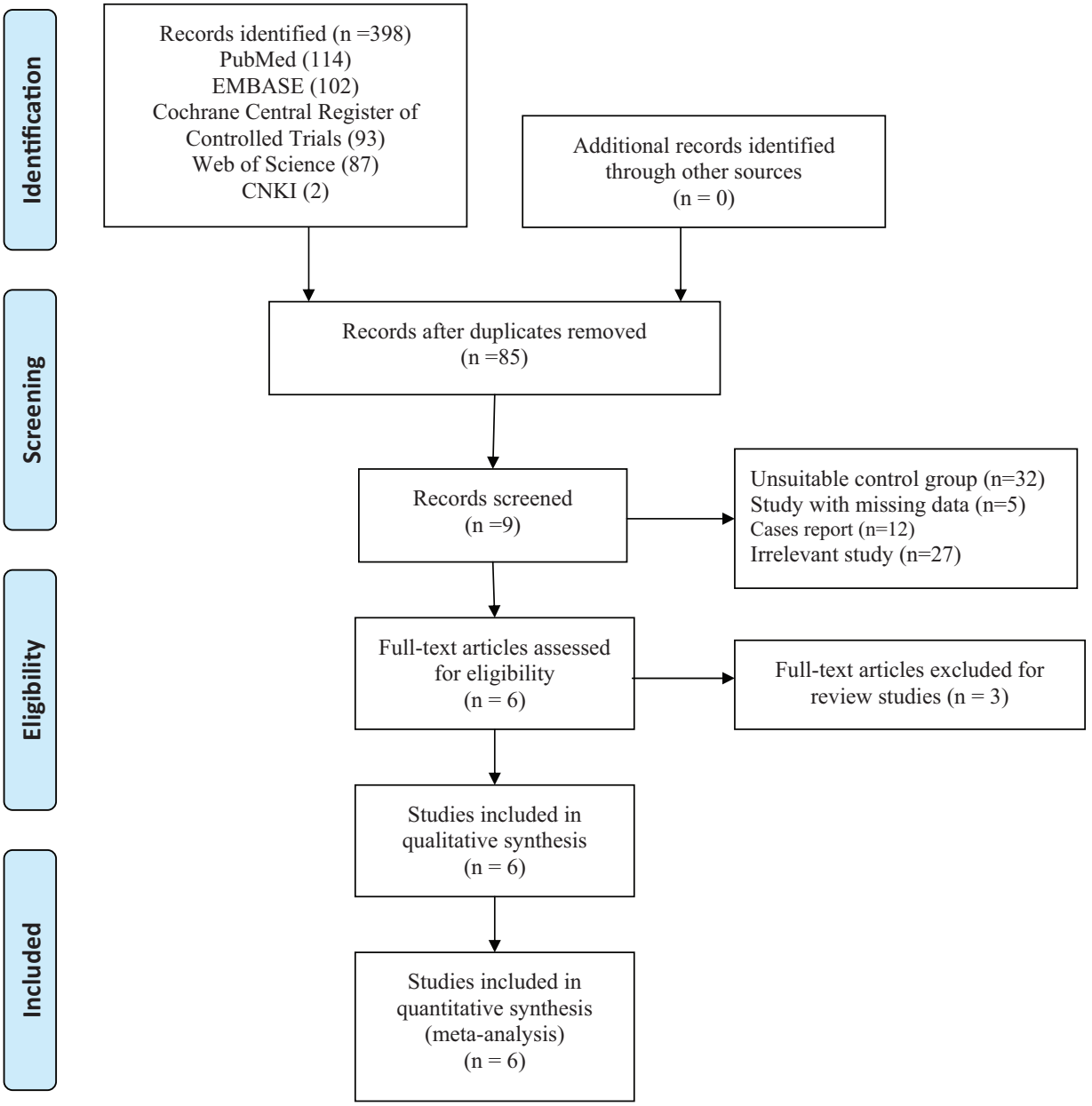


Figure 1. Search results and the selection procedure.

plasty") and ("aminocaproic acid"). Further articles that may have been missed in the electronic databases were manually searched from selected studies. No language or date restrictions were applied. Further studies that might have been missed in the electronic databases were manually searched from selected articles. The literature searching process was performed by 2 reviewers (Hua Li and Liqun Bai) independently and any arising differences were settled by discussion with a third party.

2.2. Inclusion and exclusion criteria

(1) Population: adult patients who prepare for TKA or THA;
(2) Interventions: the experimental groups receive intravenous aminocaproic acid;
(3) Comparisons: placebo;
(4) Outcomes: calculated blood loss, perioperative hemoglobin reduction, drain output, transfusion requirement, hospitalization days, and postoperative complications;
(5) Study design: randomized controlled trial (RCT) and non-RCT. Studies excluded from the present meta-analysis were comprised of incomplete data, case reports, conference abstracts, or review articles.

2.3. Date extraction

Literature data are extracted by 2 authors independently. The extracted data included publication date, authors, study design, inclusion, and exclusion criteria, number and demographics of participants, intervention of each group, duration of follow-up, and outcomes. For discrepancies, a third reviewer would be involved.

Table 1

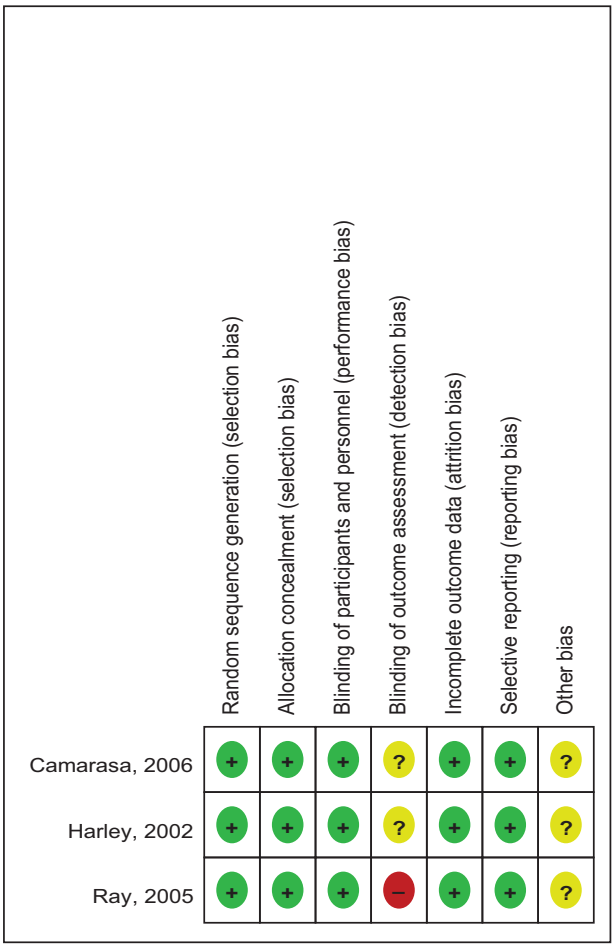
Trials characteristics.

Studies	Study design	Country	Sample size (A/C)	Mean age (A/C)	Female patient (A/C)	Surgical type	Anesthesia type	Aminocaproic acid group	Control group	Follow up
Harley, 2002 [18]	RCT	Canada	26/29	69/69	16/18	THA	General anesthesia	An hourly aminocaproic acid infusion of 12.5 mg/kg for 5 hours	Equivalent dose of placebo	median 6 weeks (2 to 12 weeks)
Ray, 2005 [19]	RCT	Australia	15/15	72/69	9/10	THA	General anesthesia	10 g of aminocaproic acid in 250 mL of intravenous saline	Equivalent dose saline	median 6 weeks (4 to 10 weeks)
Camarasa, 2006 [20]	RCT	Spain	32/60	73/72	28/48	TKA	NS	Aminocaproic acid 100 mg kg^{-1} before tourniquet deflation followed by continuous perfusion (1 g h^{-1}) during 3 h	Normal saline	median 3 months (0.5 to 6 months)
Jessica, 2016 [21]	Non-RCT	USA	25/25	65/67	21/15	TKA	General anesthesia	Either 5 g (for patients weighing 50 kg or less) or 10 g (for patientsweighing more than 50 kg) infusion	Equivalent dose saline	median 1 month (0.5 to 3 months)
Sucher, 2016 [22]	Non-RCT	USA	80/80	60/59	43/53	THA	NS	5 g aminocaproic acid diluted in 100 ml normal saline was applied intra-operatively	Normal saline	median 6 weeks (1 to 20 weeks)
Hobbs, 2017 [23]	Non-RCT	USA	184/185	62/63	14/14	TKA and THA	General anesthesia	5 g intravenous over 20 minutes just before incision, and the same dose again during closure	Equivalent dose of placebo	median 1 month (0.5 to 2 months)

A = aminocaproic acid; C = control; IV = intravenous; NS = not stated.

Table 2

Methodological quality of the randomized controlled trials.



2.4. Assessment of risk of bias

The Cochrane Handbook for systematic review of interventions was used to evaluate the bias risk for RCTs.[16] The domains evaluated were selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessments), attrition bias (incomplete outcome data), reporting

Table 3

Methodological quality of the included non-RCTs.

Quality assessment for non-randomized trials	Jessica 2016 [21]	Sucher 2016 [22]	Hobbs 2017 [23]
A clearly stated aim	2	2	2
Inclusion of consecutive patients	2	2	2
Prospective data collection	2	2	2
Endpoints appropriate to the aim of the study	2	2	2
Unbiased assessment of the study endpoint	0	0	0
A follow-up period appropriate to the aims of study	2	2	2
Less than 5% loss to follow-up	2	2	2
Prospective calculation of the sample size	0	1	2
An adequate control group	2	2	2
Contemporary groups	1	0	1
Baseline equivalence of groups	2	2	1
Adequate statistical analyses	2	2	2
Total score	19	19	20

RCT = randomized controlled trial.

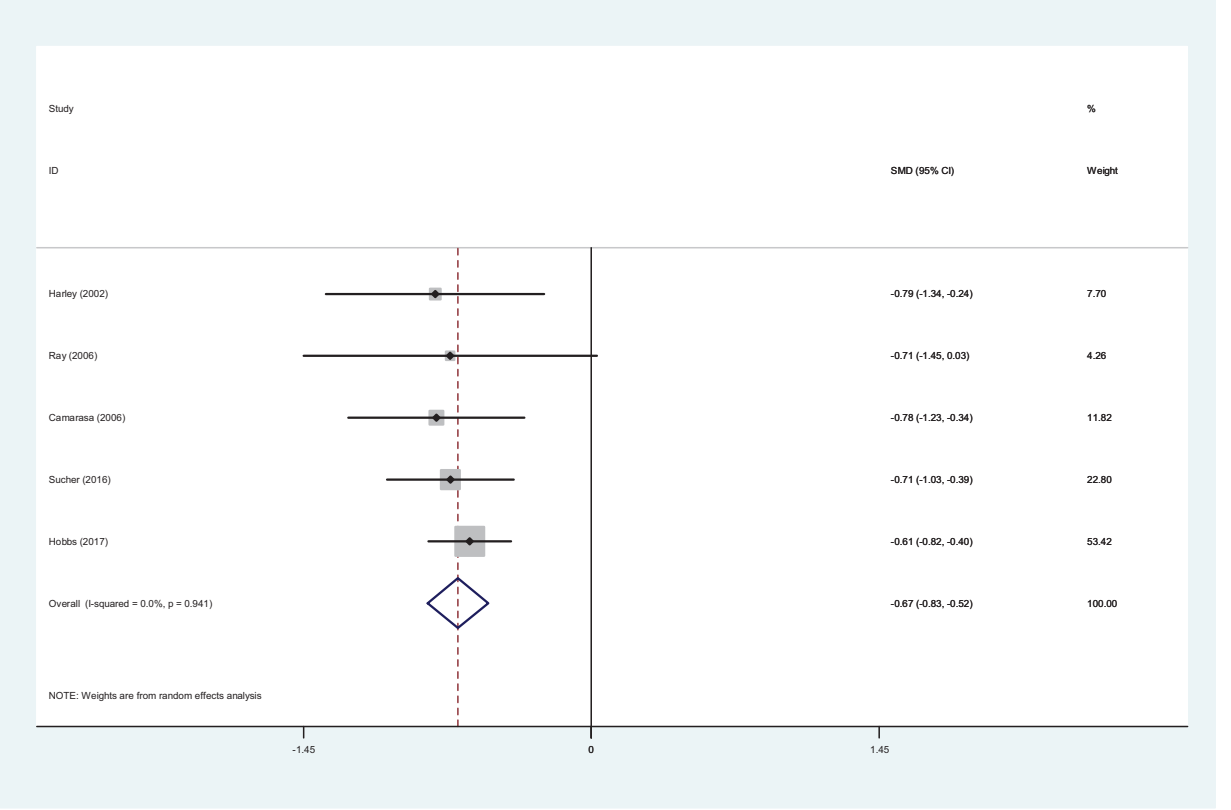


Figure 2. Forest plot diagram showing effect of aminocaproic acid on total blood loss.

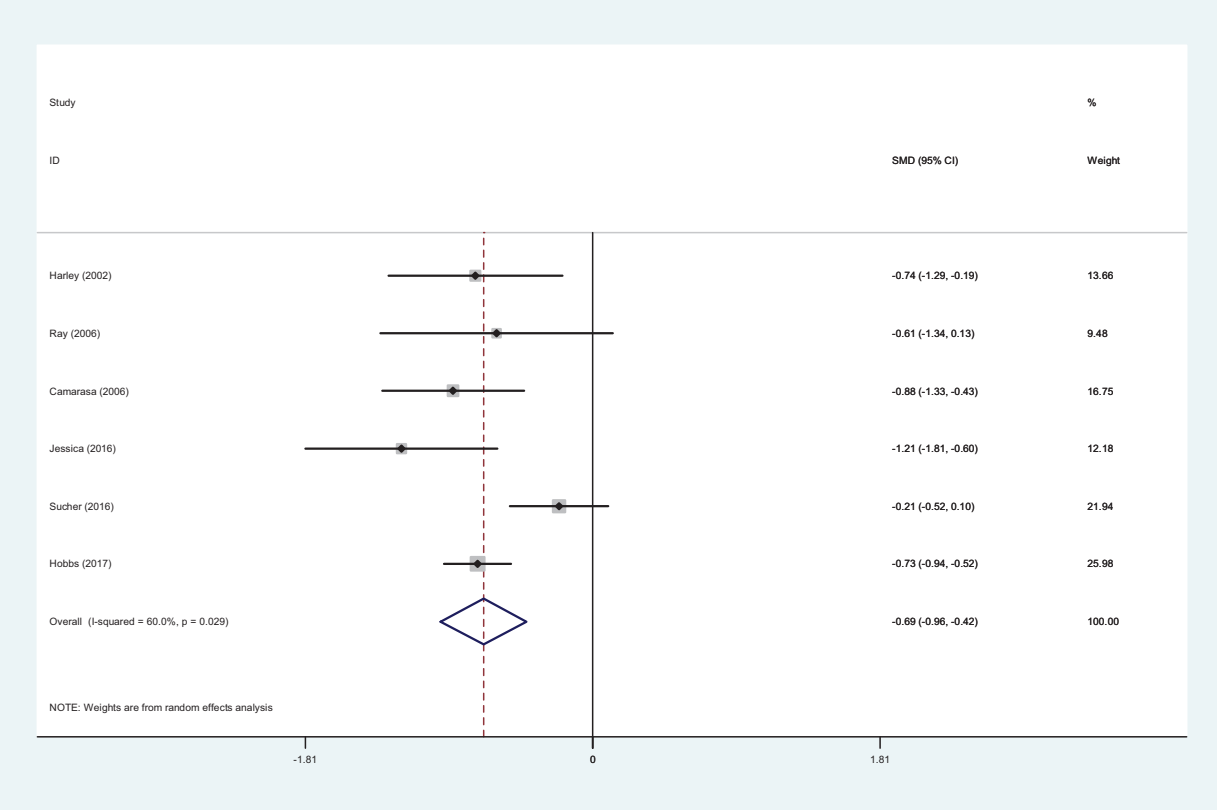


Figure 3. Forest plot diagram showing effect of aminocaproic acid on hemoglobin decline.

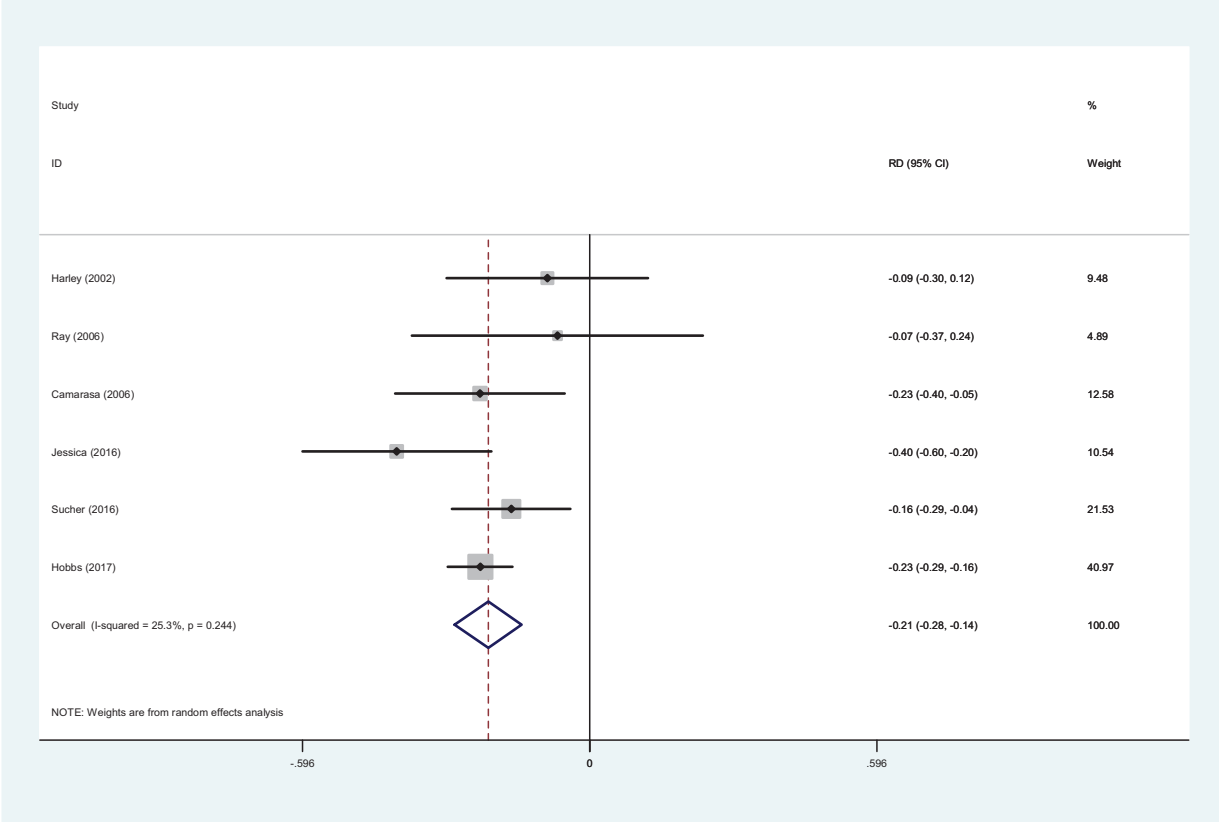


Figure 4. Forest plot diagram showing effect of aminocaproic acid on transfusion requirement.

bias (selective reporting), and other bias (other sources of bias). For non-RCTs, the risk of bias was evaluated by the Methodological Index for Non-Randomized Studies (MINORS) scale[17] with scores ranging 0 to 24.

2.5. Data analysis

All meta-analyses were performed by using STATA 12.0 (College Station, TX). The standard mean difference (SMD) is recommended to assess continuous variable outcomes with a 95% confidence interval [CI]. For continuous data, standard mean differences (SMD) with 95% confidence intervals (CIs) were applied to weigh the effect interval.

$$\mathrm{SMD} = \frac{\text{new treatment improvement} - \text{comparator (placebo) improvement}}{\text{pooled standard deviation}}$$

As for dichotomous data, risk difference (RD) with 95% CIs was used to figure the effect interval.

$$RD = \frac{\text{experimental events}}{\text{experimental events} + \text{experimental non} - \text{events}} - \frac{\text{control events}}{\text{control events} + \text{control non} - \text{events}}$$

The random effect models were used in all the meta-analysis for more conservative results regardless of the heterogeneities between studies. Subgroup analysis was performed based on the surgical type (TKA or THA).

3. Results

3.1. Search result

In the primary search, a total of 398 studies (PubMed: 114, EMBASE: 102, the Cochrane Central Register of Controlled Trials: 93, Web of Science: 87, CNKI: 2) are searched and 311 duplicate kinds of literature are excluded. Then, 76 irrelevant records and 3 review articles are removed by reading the full paper. The reference lists of all the 85 articles were reviewed. Finally, 3 RCTs[18–20] and 3 non-RCTs[21–23] with 756 patients are included in this meta-analysis. The flow path of how to search, exclude, and include papers in this meta-analysis were displayed in Figure 1.

3.2. Study characteristics

The included articles are published from 2002 to 2017. The sample size, gender ratio, average age were also noted. Experiential groups receive intravenous aminocaproic acid for perioperative blood management and control groups receive placebo. The detailed baseline characteristics of the included studies were presented in Table 1.

3.3. Risk of bias

Cochrane Collaboration's tool was adopted to assess the risk of bias. As shown in Table 2, all RCTs reported that participants were randomized with a computerized random number generator. Three RCTs[18–20] showed that opaque, sealed envelope was used to make sure allocate concealment. All studies performed double blinding. However, no paper confirmed the blinding of

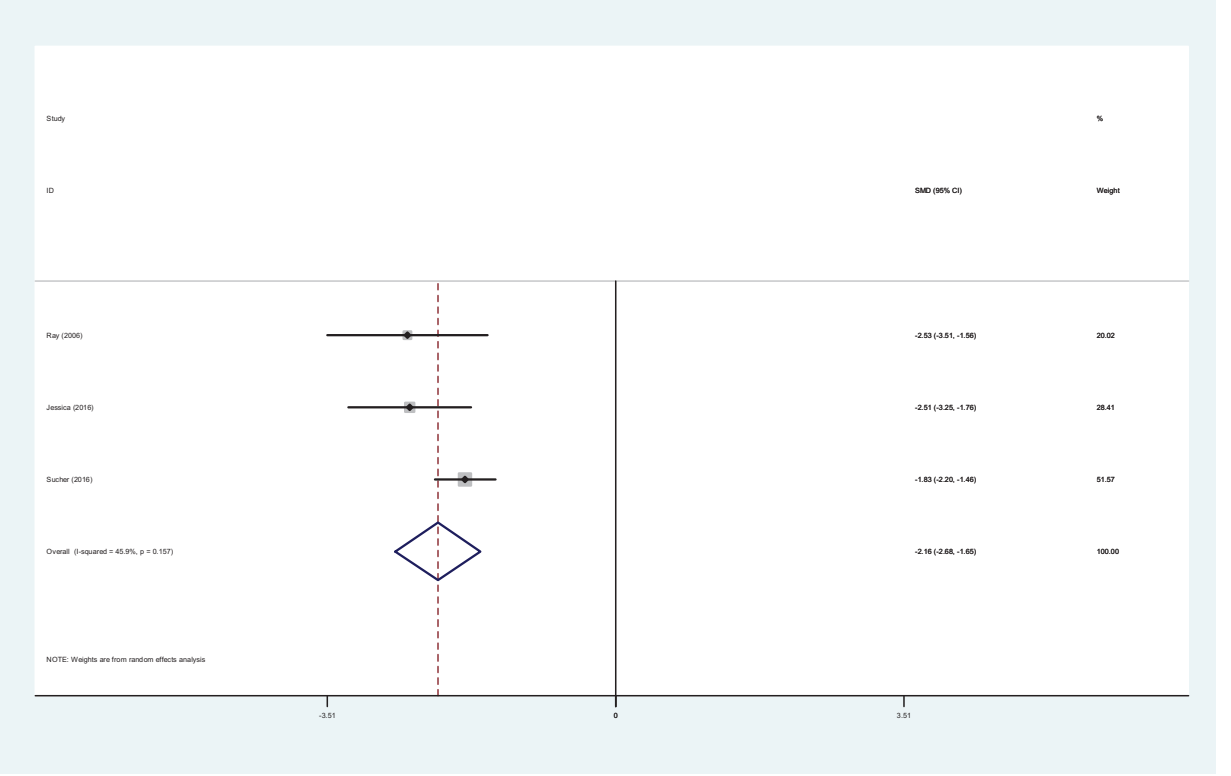


Figure 5. Forest plot diagram showing effect of aminocaproic acid on postoperative drain output.

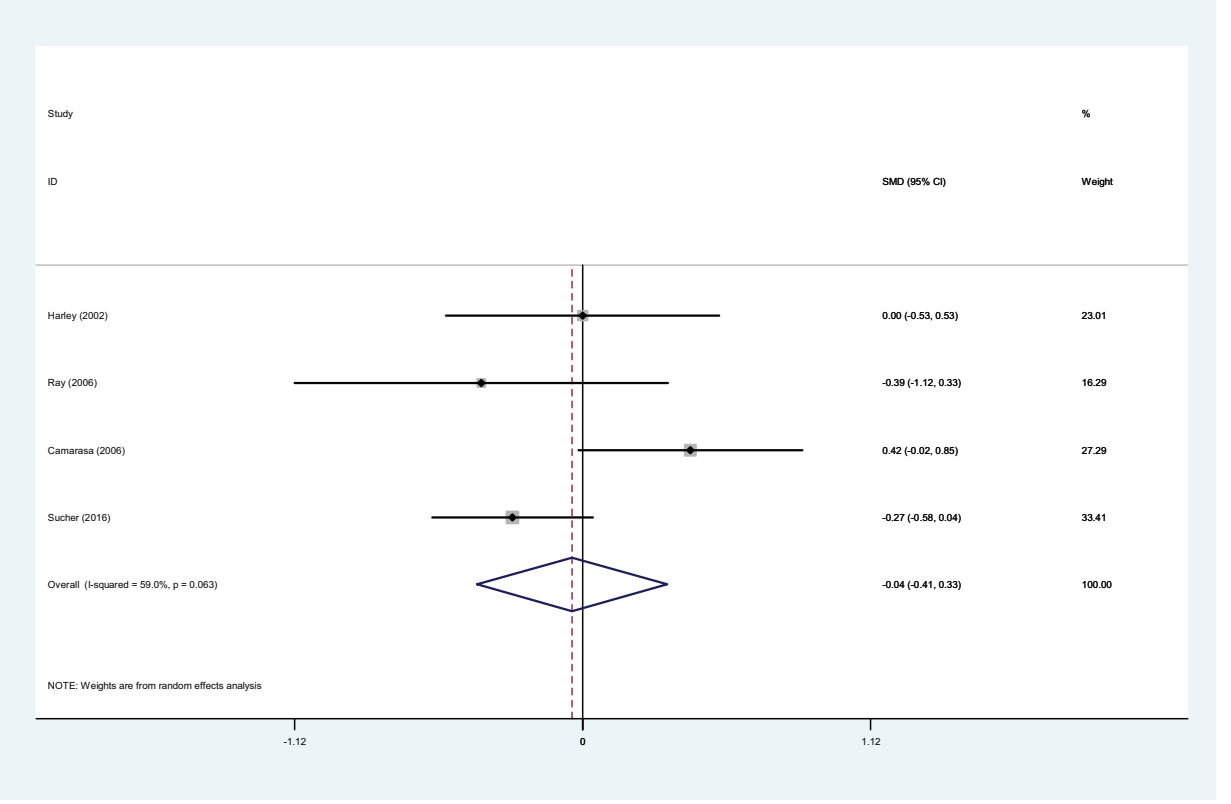


Figure 6. Forest plot diagram showing effect of aminocaproic acid on length of hospital stay.

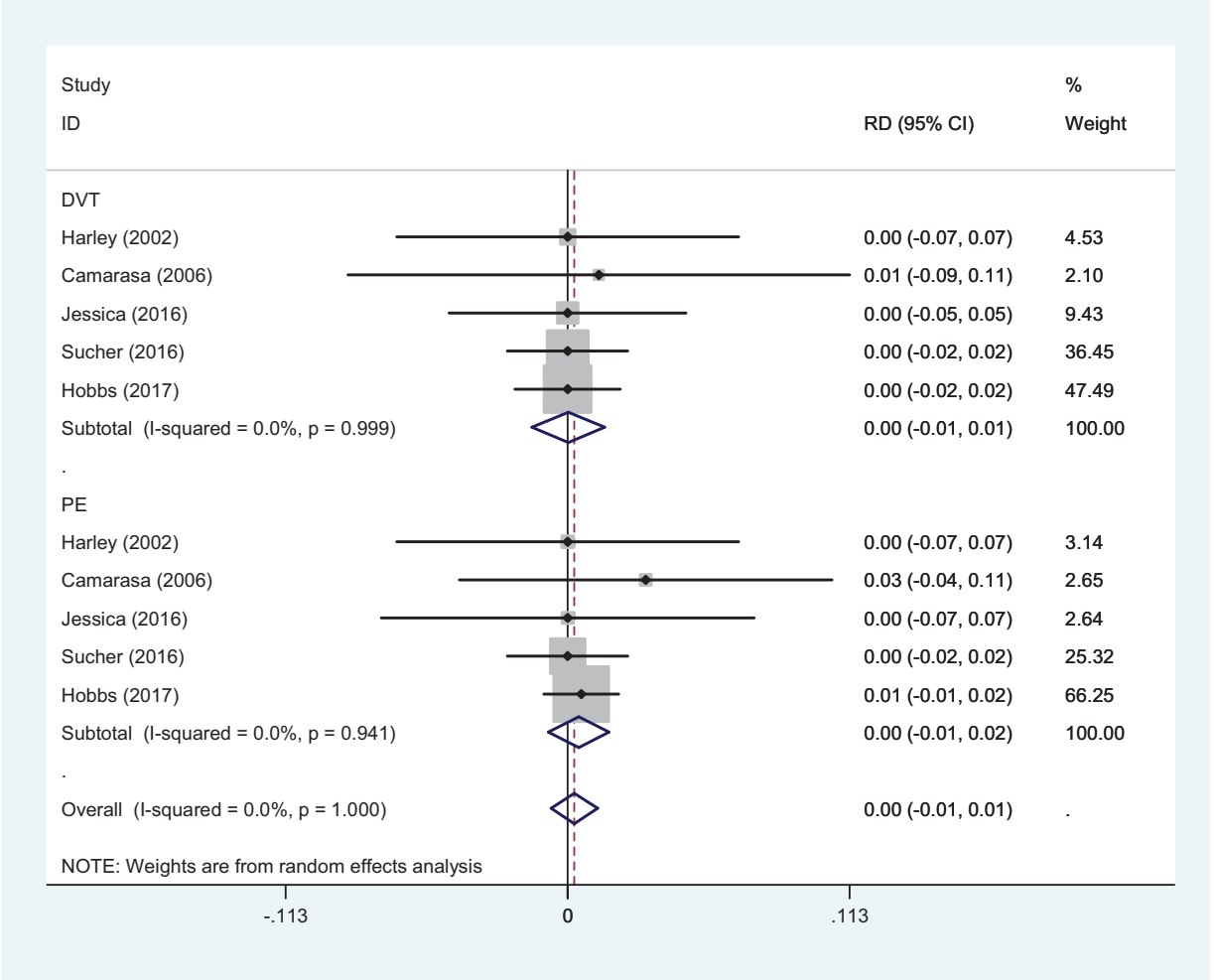


Figure 7. Forest plot diagram showing effect of aminocaproic acid on the incidence of venous thromboembolism.

outcome assessor. Other assessment of bias was nuclear. Quality assessment for non-RCTs was shown in Table 3.

4. Meta-analysis results

4.1. Total blood loss

Five articles[18–22] showed the total blood loss after TJA. A random-effect model was adopted ($\chi^2=0.78$, df=4, $I^2=0\%$, $P=.941$). The present meta-analysis revealed that there was significant difference between 2 groups regarding the total blood loss (SMD=−0.673, 95% CI: −0.825 to −0.520, $P<.001$; Fig. 2).

4.2. Hemoglobin decline

Six studies[18–23] reported postoperative hemoglobin decline following TJA. A random-effect model was used ($\chi^2=12.49$, df=5, $I^2=60\%$, $P=.029$). There was significant difference in postoperative hemoglobin decline between groups (SMD=−0.689, 95% CI: −0.961 to −0.418, $P<.001$; Fig. 3).

4.3. Transfusion requirement

Six studies[18–23] showed transfusion requirement after TJA. A random-effect model was used ($\chi^2=6.69$, df=5, $I^2=25.3\%$, $P=.244$). *The pooled results revealed that there was significant difference in transfusion requirement between groups (RD=−0.210, 95% CI: −0.280 to −0.141,* P<.001*; Fig. 4).*

4.4. Postoperative drain output

Three articles[19,21,22] reported postoperative drain output. There was significant difference in terms of postoperative drain output between groups (SMD=−2.162, 95% CI: −2.678 to −1.646, $P<.001$; Fig. 5).

4.5. Duration of hospitalization

Four articles[18–20,22] showed duration of hospitalization after TJA. A random-effect model was applied ($\chi^2=7.31$, df=3, $I^2=59\%$, $P=.063$). There was no significant difference in duration of hospitalization stay between groups (SMD=−0.041, 95% CI: −0.409 to 0.327, $P=.829$; Fig. 6).

4.6. Incidence of venous thromboembolism

Five studies[19–23] provided the postoperative complications including deep venous thrombosis (DVT) and pulmonary embolism (PE). A random-effect model was adopted ($\chi^2=0.97$, df=9, $I^2=0.0\%$, $P=1.000$). There was no significant

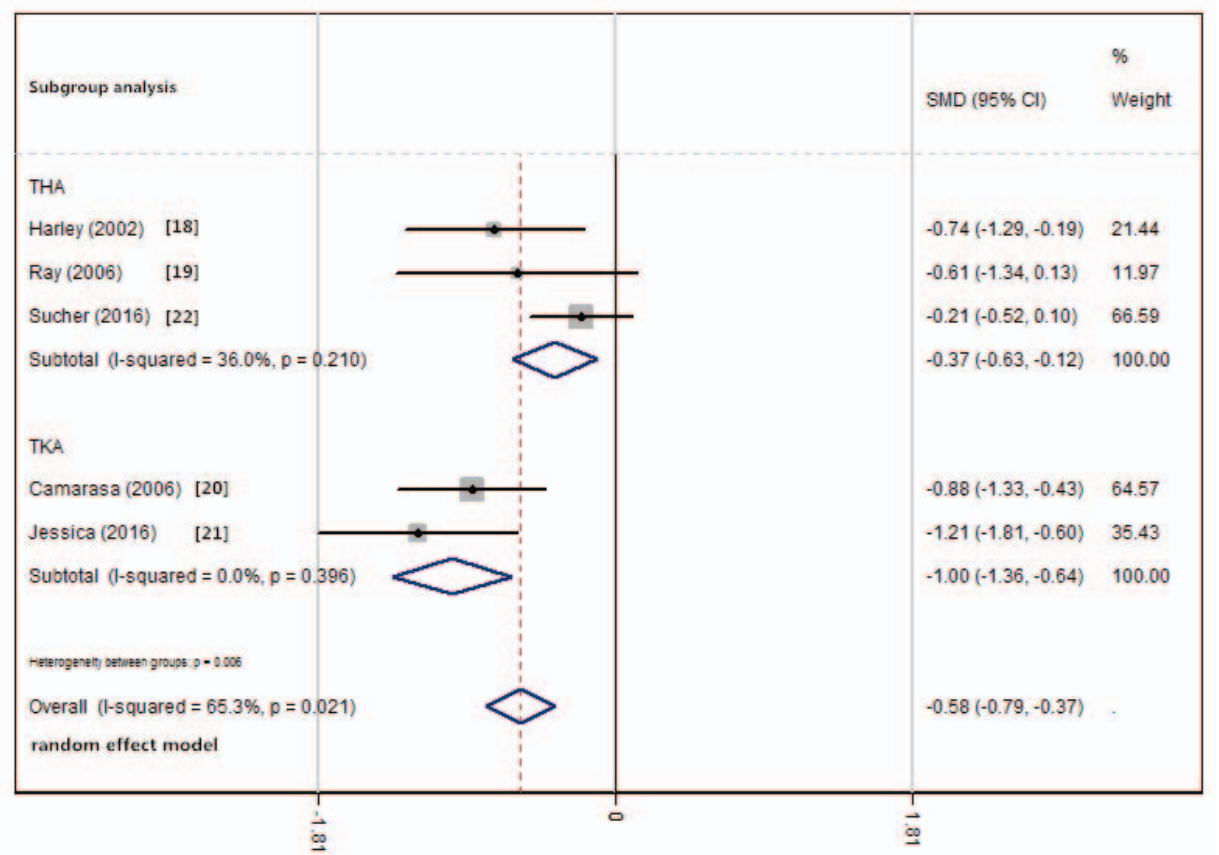


Figure 8. Subgroup analysis of postoperative hemoglobin decline.

difference between groups regarding the incidence of venous thromboembolism (RD = 0.003, 95% CI: −0.007 to 0.012, $P = .566$; Fig. 7).

4.7. Subgroup analysis

Subgroup analysis was conducted for the outcome of postoperative hemoglobin decline, which showed that the existence of heterogeneity was due to the different surgical type (Fig. 8).

5. Discussion

Up to now, the systematic review and meta-analysis of comparative studies about aminocaproic acid in patients with joint arthroplasties have not yet been performed. Thus, we performed this meta-analysis from recently published studies and found that intravenous aminocaproic acid is associated with a significant reduction of total blood loss, hemoglobin decline, drain output, and transfusion requirement after TJA. The overall evidence level is low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate. Although previous meta-analysis has been published, our meta-analysis performed a more detailed search strategy including Chinese database and all outcomes were expressed by standard mean difference. It was more reasonable than weighted mean difference which was used by Dong et al.[24] Another strength was that subgroup analysis and evidence level were completely shown in our paper, which was more convincing.

Blood management after total joint replacement is an extremely important issue. The most dramatic single change came with the application of antifibrinolytic agents for THA and TKA. Antifibrinolytic agents, such as tranexamic acid are widely used and show improved outcome for decreasing blood loss and transfusion rates through oral and intravenous administration in general surgery, cardiac surgery, obstetrics, orthopedics, and trauma.[25–28] Aminocaproic acid is also in the lysine analog class of antifibrinolytics and therefore acts by preventing the premature dissolution of the normal fibrin clot. Aminocaproic acid was first used for the prevention of blood loss in 1960.[29] Since then, aminocaproic acid was well established in the field of cardiothoracic surgery with evidence that it was associated with fewer seizures.[29] Lower medical cost made it more popular for patients. Recently, several studies have emphasized the clinical application of aminocaproic acid in joint surgery: especially TKA and THA. However, evidence for aminocaproic acid is still limited due to the small sample sizes of previous studies. Thus, we performed the meta-analysis to indicate that intravenous aminocaproic acid was associated with a significant reduction of blood loss and hemoglobin decline.

Osteoarthritis is the most common form of arthritis. It is a slowly progressive, which may cause pain, stiffness and disability, decreasing quality of life.[30] With the aging population, the incidence of OA has increased year by year. TJA is a successful surgical procedure for the treatment of end-stage osteoarthritis. However, it may be associated with a huge amount of blood loss, thus allogenic blood transfusion becomes necessary to relieve anemia. However, potential adverse effects may occur, for

instance, infection, allergic reactions, and nonhemolytic febrific reaction.[31,32] Although some articles confirmed that antifibrinolytics could minimize the blood loss, no reliable evidence has been proposed to decrease transfusion rate. Ray et al[19] showed similar outcomes between aminocaproic acid and placebo regarding the transfusion requirement. Similarly, Hobbs et al[23] reported that blood transfusion was significantly lower in the aminocaproic acid group compared to the control group. Based on the current controversy, meta-analysis is performed as major statistical method in the present study. All included articles of the 756 patients showed the outcomes of transfusion rates. The present meta-analysis showed that the requirement for allogeneic blood transfusion was significantly reduced in patients receiving aminocaproic acid.

Hemostatic efficacy is not the only concern when assessing the effectiveness of aminocaproic acid in surgeries. DVT has been considered a common postoperative complication that may develop to PE following major orthopedic surgery. Aminocaproic acid is an antifibrinolytic agent; theoretically, it can increase the risk of venous thromboembolism. The overall incidence of DVT is 4/362 in the intervention groups compared with 5/394 in the control groups. No significant differences in terms of the risk of venous thromboembolism were observed. More high-quality RCTs with long term follow-ups are still required to assess the safety of aminocaproic acid.

The present study has several limitations.

(1) The sample size of the included articles are relatively small, which may affect the results of the meta-analysis;
(2) Three non-RCTs are included in our study, to some extent, decreases the evidence grade;
(3) Other important outcome such as functional outcome is not available and cannot be analyzed;
(4) Combining clinical outcomes from different follow-up time points will introduce heterogeneities and potential biases;
(5) Although there was no obvious publication bias among studies, it was still unavoidable;
(6) The duration of follow up was short, which underestimated the complications.

6. Conclusion

Aminocaproic acid results in a significant reduction of total blood loss, postoperative hemoglobin decline and transfusion requirement in patients undergoing arthroplasties. Due to the limited quality of the evidence currently available, the results of our meta-analysis should be treated with caution.

Author contributions

WJW signs the study. LYH collects the data and writes the manuscript. All authors read and approved the final manuscript.
Conceptualization: Jianwen Wang.
Data curation: Jianwen Wang.
Writing – original draft: Yihua Li.

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