The efficiency and safety of tranexamic acid for reducing blood loss in open myomectomy
A meta-analysis of randomized controlled trials

Dongdong Wang, MMa, Lixia Wang, MDb, Yifei Wang, MDb, Xinyan Lin, MMb,*

Abstract
Objective: This meta-analysis aimed to perform a meta-analysis including randomized controlled trials (RCTs) to assess the efficiency and safety of tranexamic acid (TXA) for reducing blood loss and transfusion requirements in patients undergoing open myomectomy.

Methods: A systematic search was performed in Medline (1966–2017.03), PubMed (1966–2017.03), Embase (1980–2017.03), ScienceDirect (1985–2017.03), and the Cochrane Library. Study evaluated the efficiency and safety of TXA in myomectomy was selected. Meta-analysis was performed using Stata 11.0 software.

Results: Four RCTs including 328 patients met the inclusion criteria. The present meta-analysis indicated that there were significant differences between groups in terms of total blood loss (standard mean difference [SMD] = −1.512, 95% confidence interval [CI]: −2.746 to −0.278, P = .016), postoperative hemoglobin level (SMD = 0.650, 95% CI: 0.045–1.265, P = .035), transfusion requirements (SMD = −0.102, 95% CI: −0.199 to −0.006, P = .038), and duration of surgery (SMD = −0.514, 95% CI: −0.749 to −0.280, P = .000). In addition, no adverse effect was identified in treatment groups.

Conclusions: Intravenous administration of TXA in open myomectomy was associated with significantly reduced total blood loss, postoperative hemoglobin decline, duration of surgery, and transfusion requirements. Based on the limitations of the current meta-analysis, high-quality RCTs with long-term follow-up are still required.

Abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, PE = deep vein thrombosis, RCT = randomized controlled trials, TXA = tranexamic acid.

Keywords: blood loss, blood transfusion, meta-analysis, open myomectomy, tranexamic acid.

1. Introduction
Uterine fibroids are common benign gynecologic tumors and 25% to 30% of women would be diagnosed at a time during their lives.[1] It could be located at different sites and sometimes implants the uterine cavity. The common symptoms are bellyache, leukorrhagia, menorrhagia, and symptomatic anemia. More importantly, uterine fibroids have a potential impact on fertility. Previous studies have reported that infertility was related to submucosal fibroids[2]; however, it is unclear with regards to the effect of intramural fibroids.

Various methods are available for the treatment of symptomatic myomas including medical and surgical intervention.[3,4] Myomectomy remains the most popular methods for those who have myomas and desire further childbearing. However, substantial perioperative blood loss has been associated with surgical procedure and sometimes hysterectomy has to be performed to control bleeding which results in increased morbidity and mortality. Many strategies have been used to manage blood loss including mechanical tourniquets, administration of hemostatic agents, autologous donation and minimally invasive procedures.[5–7] However, blood transfusions were still required to treat anemia in many cases. Allogenic blood transfusion would increase the risk of adverse events, such as virus infections, immunologically mediated diseases, and cardiovascular dysfunction, resulting in a financial burden and potentially life-threatening effects on patients.[8,9]

Recently, the use of tranexamic acid (TXA) has become popularized in surgical procedure. TXA is a synthetic analog of an amino acid whose biological activity inhibits plasminogen from dissolving clots.[10] In previous studies, the administration of TXA was reported to be associated with reduced perioperative blood loss and transfusion units in cardiac surgery, orthopedic surgery, and organ transplantation.[11–13]

Currently, the application of TXA in myomectomy was seldom reported. Thus, there is a lack of scientific evidence regarding the hemostatic effect of TXA in myomectomy. Therefore, we perform a meta-analysis of randomized controlled trials (RCTs) to assess the efficiency and safety of TXA for reducing blood loss and transfusion requirements in patients undergoing myomectomy.
2. Methods

2.1. Search strategy

Electronic databases were systemically searched including Embase (1980–2017.03), Medline (1966–2017.03), PubMed (1966–2017.03), ScienceDirect (1985–2017.03), web of science (1950–2017.03), and Cochrane Library for potential relevant studies. Reference lists of all the potential included studies and relevant reviews were hand-searched for any additional trials. No restrictions were imposed on language. The search terms “Tranexamic acid”, “myomectomy”, and “blood loss” were used in combination with Boolean operators AND or OR. The retrieval process is presented in Figure 1. The study was approved by the ethics committee of the Second Hospital of Dalian Medical University.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: published clinical RCTs; patients undergoing open myomectomy experiment group received intravenous TXA for blood management and control group received placebo or nothing; the primary outcomes included total blood loss, postoperative hemoglobin level, transfusion rate, and drainage volume. Secondary outcomes included duration of surgery and postoperative adverse effects such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Studies would be excluded from current meta-analysis for incomplete data, case reports, conference abstract, or review articles.

2.3. Selection criteria

Two authors independently reviewed all the abstracts of the potential studies identified by the above searches. After an initial decision, full text of the studies that potentially met the inclusion criteria was reviewed and final decision was made. A senior reviewer is consulted in case of disagreement regarding which studies to include.

Figure 1. Search results and the selection procedure.
2.4. Date extraction

A standard form for date extraction is printed for date extraction. Two authors independently extracted the relevant data from the included articles. Details of incomplete data of included studies are obtained by consulting the corresponding author. Following data were extracted: first author names, published year, sample size, study design, comparable baseline, dosage of TXA, and duration of follow-up. Other relevant data were also extracted from individual studies.

2.5. Quality assessment

Quality assessment of the included studies was assessed by 2 authors independently. Modified Jadad score (7-point scale), which was based on Cochrane Handbook for Systematic Reviews of Interventions, is used for assessment of RCTs. Studies which score >4 points were considered high-quality. We conducted “risk of bias” table including the following key points: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting, and other bias; each item was recorded by “Yes,” “No,” or “Unclear.”

The qualities of evidence of main outcomes in present meta-analysis were evaluated using the Recommendations Assessment, Development, and Evaluation (GRADE) system including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence is classified into the following categories: high, which means that further research is unlikely to change confidence in the effect estimate; moderate, which means that further research is likely to significantly change confidence in the effect estimate and may change the estimate; low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; very low, which means that any effect estimate is uncertain.

2.6. Data analysis and statistical methods

All calculations were performed using Stata 11.0 software (The Cochrane Collaboration, Oxford, United Kingdom). Statistical heterogeneity was assessed based on the value of \( I^2 \) test. When \( I^2 > 50\% \), and \( P < .1 \) was considered to be of significant heterogeneity, random-effect model was performed for meta-analysis. Otherwise, fixed-effect model was used. If possible, sensibility analysis is conducted to explore the origins of heterogeneity. The results of dichotomous outcomes were expressed as risk difference (RD) with 95% confidence intervals (CIs). For continuous various outcomes, mean difference and standard mean difference (SMD) with a 95% CI was applied for assessment. Sensitivity analysis was conducted for the main results according to the dosage of TXA.

3. Results

3.1. Search result

A total of 458 studies were preliminarily reviewed. By screening the titles and reading the abstracts and entire contents, 454 reports were excluded from present meta-analysis following inclusion criteria. No gray reference was included. Finally, 4 RCTs \[14–17\] which had been published between 2008 and 2016, were enrolled in the present meta-analysis and include 164 patients in the TXA groups and 164 patients in the control groups.

3.2. Study characteristics

Demographic characteristics, the details about the included studies are summarized in Table 1. The sample size of the included studies ranged from 34 to 132. All of them evaluated the efficiency and safety of TXA for reducing blood loss in open myomectomy. Experimental groups received intravenous TXA, whereas control groups received placebo or none. There is a variation in dosage of TXA in experimental groups. Three studies \[14,16,17\] performed general anesthesia and 1 \[15\] did not give a detailed description. All \[14–17\] studies reported that open myomectomy was performed by same team. The indication of blood transfusion was based on postoperative hemoglobin level. None of the included studies performed a sample size calculation. All of them suggest the outcomes for at least 95% of the patients. The follow-up period ranged from 1 to 2 months.

3.3. Risk of bias assessment

Modified Jadad score, which was based on Cochrane Handbook for Systematic Reviews of Interventions, is used for assessment of RCTs (Table 2). All of the RCTs reported a clear inclusion and exclusion criteria and suggest a methodology of randomization; all of them demonstrated that randomization sequence was generated by computer. Three of them \[14–16\] reported allocate concealment was achieved by sealed envelopes. Double blinding was provided in 3 RCTs \[15–17\]. Only one \[15\] of them had attempted to blind assessors. Each risk of bias item is presented as the percentage across all included studies, which indicates the proportion of different levels of risk of bias for each item (Table 3). All RCTs provided complete outcome data. None of them performed intent-to-treatment analysis; thus, a potential risk for type II statistical error would exist.

Table 1

| Cohort characteristics. | Studies | Cases (T/C) | Mean age (T/C) | Surgical methods | Number of myomas (T/C) | TXA intervention | Basal Hb (T/C) | Transfusion trigger | Follow-up |
|-------------------------|---------|------------|----------------|------------------|-----------------------|------------------|---------------|---------------------|-----------|
| Caglar et al, 2008[16]  | 50/50   | 34.2/36.5  | Open myomectomy | 2.0/3.3          | E: intravenous 10 mL/kg of TXA C: none | 11.4/11.2 | HB < 7 g/dL | NS                  |           |
| Shaaban, 2016[14]       | 66/66   | 35.0/34.6  | Open myomectomy | 4.87/5.11        | E: intravenous 10 mg/kg of TXA C: none | 10.77/10.73 | HB < 7 g/dL | 1 Mo                 |           |
| Ngichabe, 2015[15]      | 17/17   | 36.0/35.0  | Open myomectomy | NS               | E: intravenous 1 g of TXA C: none | 12.6/12.8 | HB < 8 g/dL | 2 Mo                 |           |
| Opoku-Anane, 2015[17]   | 30/30   | 35.5/34.7  | Open myomectomy | 3.8/4.3          | E: intravenous 15 mg/kg of TXA C: equivalent volume of saline | 11.37/11.81 | HB < 7 g/dL | 2 Mo                 |           |

C = control group, E = experimental group, Hb = hemoglobin, NS = not stated, T = TXA group, TXA = tranexamic acid.
3.4. Outcomes for meta-analysis

3.4.1. Total blood loss. Four studies\(^{[14–17]}\) reported total blood loss following open myomectomy. Statistical heterogeneity was observed in present meta-analysis (\(\chi^2 = 65.74, \text{df} = 3, I^2 = 95.4\%\), \(P = .000\)); therefore, a random-effects model was applied. We found that there was significant difference between the TXA groups and control groups regarding the total blood loss (SMD = −1.512, 95% CI: −2.746 to −0.278, \(P = .016\); Fig. 2).

3.4.2. Postoperative hemoglobin level. Four studies\(^{[14–17]}\) reported postoperative hemoglobin level following open myomectomy. There was significant heterogeneity (\(\chi^2 = 19.45, \text{df} = 3, I^2 = 84.6\%\), \(P = .000\)); therefore, a random-effects model was used. The result of meta-analysis showed that there was significant difference between the TXA groups and control groups regarding the postoperative hemoglobin level (SMD = 0.650, 95% CI: 0.045 to 1.255, \(P = .035\); Fig. 3).

3.4.3. Transfusion requirements. Transfusion requirements following open myomectomy were presented in 4 studies.\(^{[14–17]}\) There was no significant heterogeneity (\(\chi^2 = 4.93, \text{df} = 3, I^2 = 39.2\%\), \(P = .177\)) and a fixed-effects model was used. The present meta-analysis showed that there was significant difference between the TXA and control groups in terms of transfusion requirement (SMD = −0.102, 95% CI: −0.199 to 0.006, \(P = .038\); Fig. 4).

3.4.4. During of surgery. Three studies\(^{[14,16,17]}\) provided the operation time among studies. No significant heterogeneity was found (\(\chi^2 = 4.73, \text{df} = 2, I^2 = 57.8\%\), \(P = .094\)); therefore, a fixed-effects model was used. Meta-analysis revealed that there was significant difference between the TXA and control groups in terms of duration of surgery (SMD = −0.514, 95% CI: −0.749 to 0.280, \(P = .000\); Fig. 5).

3.4.5. DVT. Four articles\(^{[14–17]}\) reported the incidence of DVT following open myomectomy. A fixed-effects model was used because of the low significant heterogeneity among these studies (\(\chi^2 = 0.50, \text{df} = 3, I^2 = 0\%\), \(P = .919\)). No significant difference was found between the groups (RD = 0.000, 95% CI: −0.036 to 0.036, \(P = .999\); Fig. 6).

3.4.6. PE. PE was reported in 4 studies.\(^{[14–17]}\) A fixed-effects model was used because no significant heterogeneity was found among the studies (\(\chi^2 = 0.66, \text{df} = 2, I^2 = 0\%\), \(P = .717\)). No significant difference was found in the PE incidence between the 2 groups (RD = 0.007, 95% CI: −0.020 to 0.033, \(P = .617\); Fig. 7).
3.4.7. Sensitivity analysis. Sensitivity analysis was conducted for the main results according to the dosage of TXA, which is presented in Table 4.

4. Discussion

To the best of our knowledge, this study is the first meta-analysis from RCTs to assess the efficiency and safety of TXA for reducing blood loss and transfusion requirements in patients undergoing myomectomy. The most important finding of the present meta-analysis was that the intravenous application of TXA could significantly reduce the total blood loss, hemoglobin decline, and transfusion requirements after open myomectomy. Moreover, no increased risk of the incidence of DVT and or PE was identified. All outcomes in this meta-analysis were evaluated using the GRADE system. The evidence quality for each outcome was high to moderate (Table 5), which means that further research is likely to significantly change confidence in the effect estimate and may change the estimate.

TXA, which acts as antifibrinolytic agent, is famous for proven success in reducing peri- and postoperative blood loss and widely used in surgical procedure. Konig et al[18] reported that topical application of TXA for patients undergoing primary total hip arthroplasty is effective and safe. Fu et al[19] conducted a meta-analysis from 22 RCTs and showed that TXA is beneficial for patients undergoing total knee arthroplasty, which can significantly reduce total blood loss. Recently, TXA has been studied in gynecology and obstetrics field. Previous articles have reported that TXA acts as a nonhormonal treatment for excessive hemorrhage during the menstrual period.[20]

Uterine fibroid represents a major health issue with an estimated 234 million women affected all over the world.
Symptomatic fibroid that required intervention accounts for about 25% of all cases. Myomectomy is one of the most common surgical procedures for treatment of the uterine fibroid, which may be associated with massive perioperative blood loss. With the advanced of surgical techniques, there was a significantly reduced hemorrhage during operation. Laparoscopic myomectomy is an alternative to the abdominal approach with fewer complications and shortened hospital stay. Although it has been proved to be beneficial on blood management, the surgical indication depends on the size, number, and location of the myoma, which limited the clinical application. Therefore, open myomectomy is widely performed; however, it was associated with more hemorrhage from tissue and vessels dissection that might necessitate hysterectomy resulting in increased morbidity and mortality.

TXA can be applied by various routes including intravenous, oral, and intramuscular. The optimal routes of TXA have been more studied in orthopedic and cardiac surgery. All included patients received intravenous TXA and the dose of TXA differed between trials. TXA can inhibit the activation of plasminogen by plasminogen activator and blocks the lysine-binding sites of plasminogen to fibrin. Previous fundamental research has reported that the levels of plasminogen activators increased 30 minutes after the initiation of surgery. Thus, the theoretical basis could explain a potential efficiency for reducing blood loss for surgical procedures. The present meta-analysis indicated that intravenous TXA could significantly decrease total blood loss and hemoglobin decline following open myomectomy. Significant heterogeneity was identified regarding the target parameters and it would be influenced by several factors such as anesthesia.
Figure 6. Forest plot diagram showing effect of intravenous tranexamic acid on risk of deep vein thrombosis.

Figure 7. Forest plot diagram showing effect of intravenous tranexamic acid on risk of pulmonary embolism.

Table 4
The outcome of sensitivity analysis for main results.

| Variables                      | Studies (n) | Patients (n) | P     | SMD or RD (95% CI)       | Heterogeneity, P (I²) | Model     |
|--------------------------------|-------------|--------------|-------|--------------------------|------------------------|-----------|
| Total blood loss               |             |              |       |                          |                        |           |
| Dosage of TXA 10 mL/kg         | 2           | 232          | .000  | −1.422 (−1.731 to −1.112) | .000 (98.3%)           | Random-effects |
| Dosage of TXA >10 mL/kg        | 2           | 94           | .000  | −1.133 (−1.576 to −0.690) | .034 (77.8%)           | Random-effects |
| Postoperative hemoglobin level |             |              |       |                          |                        |           |
| Dosage of TXA 10 mL/kg         | 2           | 232          | .000  | 0.639 (0.372 to 0.906)   | .001 (91.2%)           | Random-effects |
| Dosage of TXA >10 mL/kg        | 2           | 94           | .000  | 0.785 (0.356 to 1.215)   | .005 (87.1%)           | Random-effects |
| Transfusion requirements       |             |              |       |                          |                        |           |
| Dosage of TXA 10 mL/kg         | 2           | 232          | .007  | 0.800 (0.521 to 1.227)   | .076 (68.3%)           | Fixed-effects |
| Dosage of TXA >10 mL/kg        | 2           | 94           | .056  | 0.625 (0.386 to 1.012)   | .912 (0.0%)            | Fixed-effects |

CI = confidence interval, RD = risk difference, SMD = standard mean difference, TXA = tranexamic acid.
### Table 5

| Effect | No. of patients/Quality assessment group | TXA | Control | Relative | Limitations | Inconsistency | Indirectness | Imprecision | Quality | Importance |
|--------|----------------------------------------|-----|---------|----------|-------------|---------------|---------------|-------------|---------|------------|
| Total blood loss (follow-up 1–4 mo) | 164/164 | Yes | No serious | No serious | No serious | No serious | No serious | None | High | Critical |
| Postoperative hemoglobin level (follow-up 1–2 mo) | 164/164 | Yes | No serious | No serious | No serious | No serious | No serious | None | High | Critical |
| Transfusion requirement (follow-up 1–2 mo) | 37/164, 58/164 (22.6%, 35.4%) | Yes | No serious | No serious | No serious | No serious | No serious | None | Moderate | Critical |

| Analysis |
|----------|
| DVT or PE. Although the methods of thromboprophylaxis differ among included studies, no significant heterogeneity was shown in pooled results. However, owing to the limitation of the included studies, larger sample size with longer follow-up is required to confirm whether the intravenous TXA is safe without increasing thrombotic events. Several potential limitations of this study should be noted. First, only 4 RCTs were included, and the sample size was relatively small. Second, some important outcome parameters such as drainage volume and range of motion were not fully described and could not be included in the meta-analysis. Third, because of the limited number of included studies, subgroup analyses were not performed for total blood loss and postoperative hemoglobin level; therefore, we could not determine the sources of heterogeneity. Fourth, short-term follow-up may lead to the underestimation of complications. Lastly, publication bias is an inherent weakness that exists in all meta-analyses. Despite the aforementioned limitations, this study is the first meta-analysis to pool the results from randomized controlled trials to evaluate the efficiency and safety of TXA for reducing blood loss in patients undergoing open myomectomy. High-quality RCTs with long-term follow-up are needed to explore optimal dose, appropriate application methods, and adverse effects in future studies.**

### 5. Conclusions

Intravenous administration of TXA in open myomectomy was associated with significantly reduced total blood loss, postopera-
tive hemoglobin decline, duration of surgery, and transfusion requirements. Based on the limitations of the current meta-analysis, high-quality RCTs with long-term follow-up are still required.

References

[1] Buttram VCJr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril 1981;36:433–45.
[2] Schwartz SM, Marshall LM, Baird DD. Epidemiologic contributions to understanding the etiology of uterine leiomyomata. Environ Health Perspect 2000;108(suppl 5):821–7.
[3] Thompson MJ, Carr BR. Intramural myomas: to treat or not to treat. Int J Womens Health 2016;8:145–9.
[4] Mimura T, Hasegawa J, Ishikawa T, et al. Laparoscopic ultrasound procedure can reduce residual myomas in laparoscopic myomectomy for multiple myomas. J Med Ultrason (2001) 2016;43:407–12.
[5] Saha MM, Khushboo, Biswas SC, et al. Assessment of blood loss in abdominal myomectomy by intramyometrial vasopressin administration versus conventional tourniquet application. J Clin Diagn Res 2016;10:QC10–3.
[6] Lee B, Kim K, Cho HY, et al. Effect of intravenous ascorbic acid infusion on blood loss during laparoscopic myomectomy: a randomized, double-blind, placebo-controlled trial. Eur J Obstet Gynecol Reprod Biol 2016;199:187–91.
[7] Kalogianidis I, Xiromeritis P, Prapas N, et al. Intravaginal misoprostol reduces intraoperative blood loss in minimally invasive myomectomy: a randomized clinical trial. Clin Exp Obstet Gynecol 2011;38:46–9.
[8] Varney SJ, Guest JF. The annual cost of blood transfusions in the UK. Transfus Med 2003;13:203–18.
[9] Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood 2000;106:2617–26.
[10] Goobie SM. Tranexamic acid: still far to go. Br J Anaesth 2017;118:293–5.
[11] Wang C, Xu GJ, Han Z, et al. Topical application of tranexamic acid in primary total hip arthroplasty: a systemic review and meta-analysis. Int J Surg 2015;15:134–9.
[12] Takagi H, Ando T, Umemoto T, et al. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies. J Cardiovasc Surg (Torino) 2017;Mar 6. doi: 10.23736/S0021-9509.17.09877-9. [Epub ahead of print].
[13] Massicotte L, Denault AY, Beaulieu D, et al. Aprotinin versus tranexamic acid during liver transplantation: impact on blood product requirements and survival. Transplantation 2011;91:1273–8.
[14] Shaaban MM, Ahmed MR, Farhan RE, et al. Efficacy of tranexamic acid on myomectomy-associated blood loss in patients with multiple myomas: a randomized controlled clinical trial. Reprod Sci 2016;23:908–12.
[15] Ngichabe S, Obura T, Stones W. Intravenous tranexamic acid as an adjunct haemostat to oxapressin during open myomectomy. A randomized double blind placebo controlled trial. Ann Surg Innov Res 2015;9:10.
[16] Caglar GS, Tasci Y, Kayikcioglu F, et al. Intravenous tranexamic acid use in myomectomy: a prospective randomized double-blind placebo controlled study. Eur J Obstet Gynecol Reprod Biol 2008;137:227–31.
[17] Opoku-Anane J, Vargas MV, Moawad G, et al. Use of intravenous tranexamic acid during myomectomy: a randomized double-blind placebo controlled trial. J Minim Invasive Gynecol 2015;22:S197.
[18] Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. J Arthroplasty 2013;28:1473–6.
[19] Fu DJ, Chen C, Guo L, et al. Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. Chin J Traumatol 2013;16:67–76.
[20] Eder S, Baker J, Gersten J, et al. Efficacy and safety of oral tranexamic acid in women with heavy menstrual bleeding and fibroids. Womens Health (Lond) 2013;9:397–403.
[21] Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol 2004;104:393–406.
[22] Ajayi A, Ajayi V, Biobaku O, et al. Laparoscopic myomectomy: a 6-year experience at Nordica Fertility Center, Lagos. Nigeria J Minim Invasive Gynecol 2015;22:S235.
[23] Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol) 1980;14:41–7.
[24] Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57:1005–32.
[25] Singh VA, Yong LM, Vijayananthan A. Is DVT prophylaxis necessary after oncology lower limb surgery? A pilot study. Springer Plus 2016;5:943.