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Full Length Article

Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis

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ABSTRACT

Background: Antifibrinolytic agents such as tranexamic acid (TXA) are commonly used as adjunctive therapies to prevent and treat excessive bleeding. In non-surgical settings, TXA is known to reduce bleeding related mortality. However, impact of TXA use on thrombosis is uncertain.

Methods: We systematically searched the MEDLINE, EMBASE, and CENTRAL databases from January 1985 to August 2018. Studies with the following characteristics were included: (i) RCT design; (ii) compared systemic (oral or intravenous) TXA for prevention or treatment of bleeding for non-surgical indications and placebo or no TXA, and (iii) reported thrombotic events or mortality. A Mantel-Haenzel, random-effects model was used to calculate risk ratios, and risk of bias was assessed using the Cochrane risk of bias tool.

Results: Our search identified 22 studies representing 49,538 patients. Those receiving TXA had a significantly lower risk of death from any cause (RR = 0.92; 95% CI = 0.87–0.98; I^2 = 0%). There was no significant increase in the risk of stroke (RR = 1.10; 95% CI = 0.68–1.78; I^2 = 31%), myocardial infarction (RR = 0.88; 95% CI = 0.43–1.84; I^2 = 46%), pulmonary embolism (RR = 0.97; 95% CI = 0.75–1.26; I^2 = 0%), or deep vein thrombosis (RR = 0.99; 95% CI = 0.70–1.41; I^2 = 0%) from use of TXA. The results were similar when restricted to studies at low risk of bias.

Conclusions: In our systematic review and meta-analysis, the use of tranexamic acid reduced all-cause mortality without increased risk of venous or arterial thrombotic complications.

1. Background

Tranexamic acid (TXA) is an antifibrinolytic drug used as an adjunctive therapy to prevent and treat excessive bleeding. TXA promotes hemostasis by blocking the binding of plasmin to fibrin, thereby preventing fibrin degradation. Based on its mechanism of action, there are theoretical concerns about prothrombotic potential and increased risk of thromboembolism.

TXA reduces bleeding and improves outcomes in patients undergoing surgical procedures [1]. TXA is also used as an adjunctive hemostatic therapy in patients at high risk of bleeding or those with uncontrolled bleeding. The CRASH-2 trial demonstrated that early administration of TXA reduced bleeding related mortality in trauma patients (4.9% vs. 5.7%; RR = 0.85; 95% CI = 0.76–0.96) compared to later administration or no TXA. However, the impact of TXA use on thrombosis risk is uncertain [1], particularly, in the non-surgical setting. Previous meta-analyses have focused primarily on the effect of TXA on bleeding outcomes in patients undergoing surgery and included studies using non systemic administration of TXA. We therefore undertook the present systematic review to summarize the current evidence regarding the effect of systemic TXA administration on all-cause mortality and thrombotic events for non-surgical indications.

2. Methods

We developed a study protocol before data collection, which was registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017074263. After study selection, we decided to conduct separate meta-analyses evaluating the risk of thrombotic events and mortality with systemic TXA compared to placebo or no treatment (i) as part of a planned surgical protocol and (ii) for a high-risk of bleeding or uncontrolled bleeding (i.e. not part of a planned surgical protocol). The meta-analysis of TXA use in the non-surgical setting is presented here according to PRISMA

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guidelines [2].

2.1. Search strategy and study selection

We systematically searched the MEDLINE, EMBASE, and CENTRAL databases from January 1985 to August 2018 (see Appendix 1 for search strategy). Studies were eligible for inclusion if they were: (i) randomized controlled trials; (ii) included adults with non-surgical indications for TXA (e.g. prevention or treatment of bleeding not part of a planned surgical protocol or as planned medical management), (iii) compared systemic (oral or intravenous [IV]) TXA versus placebo or no TXA (iv) reported thrombotic events (deep vein thrombosis, pulmonary embolism, myocardial infarction, or stroke as defined in individual studies) and/or mortality, and (v) were published in the English language. Two reviewers independently reviewed titles and abstracts followed by full text articles. Conflicts were resolved by discussion.

2.2. Data extraction and quality assessment

Data extraction and risk of bias assessments were conducted independently and in duplicate using a custom data collection form. Disagreements were resolved by consensus. The Cochrane Risk of Bias tool for randomized studies was used to classify the included studies as low, unclear, or high risk of bias [3]. No attempts were made to contact authors for missing data.

2.3. Statistical analysis

Risk ratios were calculated using the Mantel-Haenzel random-effects method [4]. Results are presented as risk ratio with corresponding 95% confidence interval. Heterogeneity was assessed using the I^2 statistic. Statistical analysis was carried out using RevMan version 5 (The Cochrane Collaboration, Copenhagen, Denmark). We did not attempt to adjust statistically or otherwise account for differences in length of follow-up time.

3. Results

3.1. Study characteristics

We identified 3866 unique references for title and abstract screening after the removal of duplicates. After title and abstract screening, 942 full-text articles were reviewed and 22 studies were included in the final analysis (Fig. 1). Overall, the 22 included studies represented 49,538 patients [5–25]. Characteristics of the included studies are shown in Table 1. The average (mean or median) age ranged from 24 years to 69 years in the TXA group and 25 years to 68 years in the non-TXA group. The route of TXA administration was IV in 12 studies [5,6,8,11,16,18,20–27], oral in 6 studies [9,10,12,14,17,19], and combined oral and IV in 3 studies [7,13,26]. Indications for TXA use were as follows: leukemia-related bleeding (n = 2) [6,18], GI bleeding (n = 3) [12,13,19], heavy menstrual bleeding (n = 2) [9,14], prevention or treatment of post-partum hemorrhage (n = 4) [5,11,15,22], intracranial bleeding or neurologic injury (n = 8) [7,8,20,21,23–26], non-specific traumatic injury (n = 1) [16], hereditary hemorrhagic telangiectasia (n = 1) [10], and melasma (n = 1) [17]. The most common dosage regimen was intravenous administration of 1 g bolus followed by another 1 g over 8 h. IV dosage ranged from 1 g given once to 9 g daily for four weeks. Oral dosage ranged from 0.65 g given three times daily for five days to 1.5 g given twice daily for three months.

3.2. All-cause mortality

One or more deaths occurred in 12 studies [5,7,8,12,13,16,19–21,23–26], while no deaths occurred in in 10 studies. Compared to patients who did not receive TXA, those receiving TXA had a significantly lower risk of death from any cause (RR = 0.92; 95% CI = 0.87–0.98; I^2 = 0%) (Fig. 2). Subgroup analyses by route of administration showed significantly reduced mortality with IV administration (RR = 0.92, 95% CI = 0.87–0.97; I^2 = 0%). Mortality was reduced, but not significantly with oral (RR = 0.98; 95% CI = 0.32–3.02; I^2 = 0%) and combined oral/IV TXA (RR = 0.60; 95% CI = 0.25–1.47; I^2 = 0%).

3.3. Thrombotic events

Reporting of thrombotic complications in individual studies was variable, and event rates were often low or did not occur despite prespecification. With respect to studies where one or more thrombotic event occurred, there was no increase in the risk of stroke (5 studies, RR = 1.10; 95% CI = 0.68–1.78; I^2 = 31%) [5,16,21,23,24], myocardial infarction (3 studies, RR = 0.88; 95% CI = 0.43–1.84; I^2 = 46%) [5,16,21], pulmonary embolism (6 studies, RR = 0.97; 95% CI = 0.75–1.26; I^2 = 0%) [5,7,16,21,23,26] or deep vein thrombosis (8 studies, RR = 0.97; 95% CI = 0.69–1.37; I^2 = 0%) [5,13–16,20,21,23]

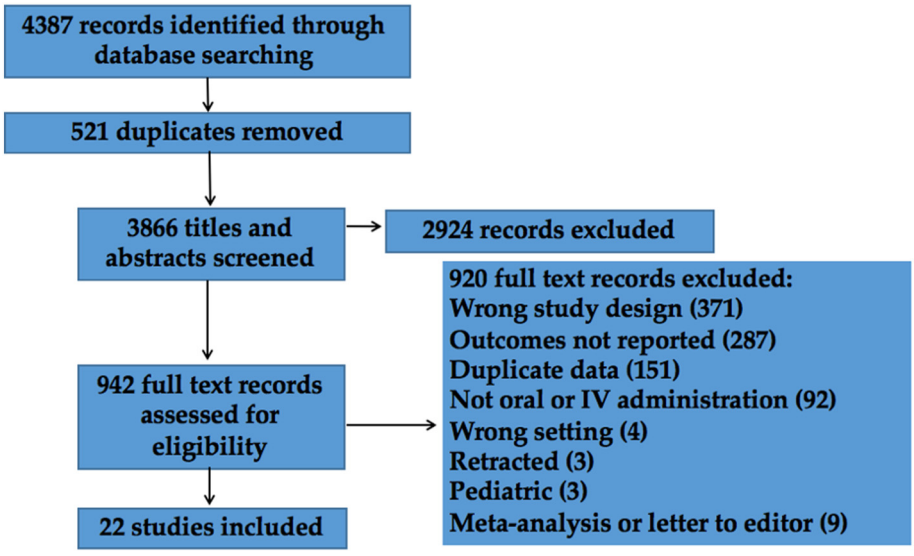

Fig. 1. PRISMA flow diagram of included and excluded studies.

Table 1
Characteristics of Included Studies. Note: AML = acute myeloid leukemia, APL = Acute promyelocytic leukemia, GIB = Gastrointestinal bleed, HHT = hereditary hemorrhagic telangiectasia, HMB = heavy menstrual bleeding, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage TBI = traumatic brain injury, PPH = post-partum hemorrhage.

Study and year	Patients	Route	Dose	Control (n)	TXA patients	Follow-up
Shpilberg 1995	AML	IV	1 g q6h until platelets above $20 \cdot 10^9$/L	Placebo (30)	26	Hospital stay
Avvisati 1989	APL	IV	2 g q8h × 8 days	Placebo (6)	6	14 days
Holstein 1987	GIB	IV, oral	1 g IV q4h × 3 days, then 1.5 g q6h × 3 days	Placebo (82)	72	6 weeks
Hawkey 2001	GIB	Oral	2 g then 1 g QID	Placebo (103)	103	30 days
Smith 2018	GIB	Oral	1 g q6h × 4 days	Placebo (47)	49	28 days
Gaillard 2014	HHT	Oral	1.5 g BID for 3 months	Placebo (61)	57	3 months
Freeman 2011	HMB	Oral	Either 0.65 g or 1.3 g TID × 5 days	Placebo (69)	235	3 menstrual cycles
Lukes 2010	HMB	Oral	1.3 g TID for 5 days per cycle	Placebo (72)	117	6 menstrual cycles
Sprigg 2014	ICH	IV	1 g then 1 g over 8 h	Placebo (8)	16	90 days
Sprigg 2018	ICH	IV	1 g then 1 g over 8 h	Placebo (1164)	1161	90 days
Shin 2013	Melasma	Oral	50 mg per day for 8 weeks	No TXA (21)	23	8 weeks
Chowdhary 1986	SAH	IV, oral	1 g q4h either IV or oral	No TXA (64)	65	Hospital stay
Tsementzis 1990	SAH	IV	9 g a day in six doses for 4 weeks.	Placebo (50)	50	6 months
Roos 2000	SAH	IV, oral	1 g q4h IV for one week, then two weeks 1.5 g q6h PO	Placebo (233)	229	3 months
Hillman 2002	SAH	IV	1 g IV then 1 g IV 2 h later then 1 g IV q6h up to 72 h	No TXA (251)	254	6 months
Fakharian 2018	TBI	IV	1 g then 1 g over 8 h	Placebo (75)	74	3 months
Yutthakasemsunt 2013	TBI	IV	1 g then 1 g over 8 h	Placebo (118)	120	Hospital stay
Shakur 2010	Trauma	IV	1 g then 1 g over 8 h	Placebo (11067)	11,060	Discharge or day 28 if still hospitalized
Arulkumaran 2017	PPH	IV	1 g	Placebo (9985)	10,033	Discharge or day 42 if still hospitalized
Gungorduk 2013	PPH	IV	1 g	Placebo (219)	220	3 weeks
Sentilhes 2018	PPH	IV	1 g	Placebo (1849)	1844	3 months
Sujita 2018	PPH	IV	1 g	Placebo (75)	75	Unclear

in patients receiving systemic TXA compared to placebo/no TXA (Fig. 3). These findings were consistent regardless of route of administration.

3.4. Risk of bias

A risk of bias assessment was conducted using the Cochrane Risk of Bias Tool (Fig. 4). Five studies were judged to be at high risk of bias, 9 studies were judged to be at unclear risk of bias and 7 studies were judged low risk of bias. When the analysis was restricted to studies that were at low risk of bias the significant effect of TXA on all-cause mortality remained (RR = 0.92; 95% CI = 0.87–0.97; I^2 = 0%). Furthermore, there was also no increased risk of myocardial infarction (RR = 0.88; 95% CI = 0.43–1.84; I^2 = 46%), stroke (RR = 0.98; 95% CI = 0.64–1.49; I^2 = 19%), deep vein thrombosis (RR = 1.00; 95% CI = 0.71–1.42; I^2 = 10%), or pulmonary embolism (RR = 0.96; 95% CI = 0.74–1.25; I^2 = 0%) when we only considered studies at low risk of bias.

4. Discussion

In this study of almost 50,000 patients we showed that systemic TXA administered for prevention or treatment of bleeding in patients (i.e. not part of a planned surgical protocol) reduced all-cause mortality by 8% without a concomitant increase in the rate of venous or arterial thrombotic events. To our knowledge, this is the largest systematic review and meta-analysis to date of TXA use in patients with non-surgical indications for its use. We included only randomized controlled trials and the risk estimates were associated with a low degree of statistical heterogeneity. The findings were similar when the analysis was restricted to studies judged to be at low risk of bias.

However, the overall confidence in the estimates of effect is limited by heterogeneity between studies such as indication for use, patient population, and dosing strategy. The low rates of thrombotic complications may reflect outcome definitions and methods of ascertainment. Patients with a history of thrombosis or other hemostatic comorbidities were commonly excluded from the studies limiting generalizability [5,16,21,27]. Nevertheless, in observational studies of patients with malignancies who are at increased thrombotic risk, TXA did not increase the risk of thrombosis suggesting this exclusion criteria is not a barrier to generalizability [28,29].

Another limitation of our systematic review is that small numbers of patients or studies for specific indications preclude meaningful subgroup analysis by reason for administration. Additionally, differences in the length of follow up time between studies adds a layer of heterogeneity to our data. Meaningful subgroup analysis may be possible in the future when additional studies are completed. For example, there are multiple ongoing studies of TXA in non-surgical patients; the A-

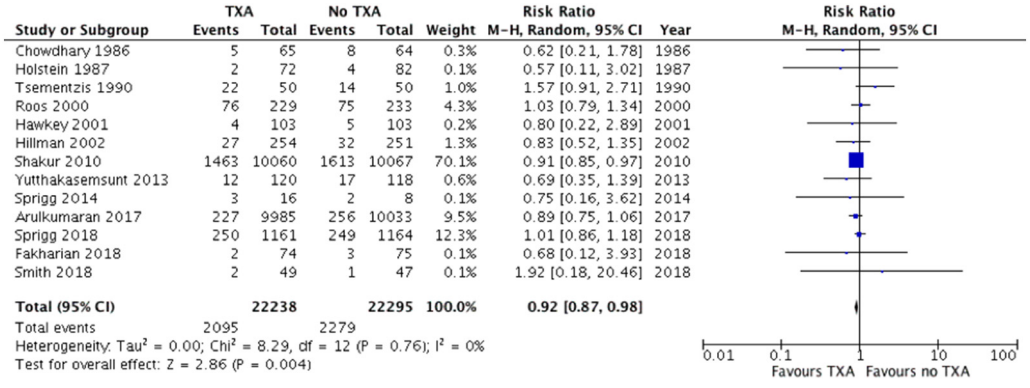

Fig. 2. Forest plot for mortality.

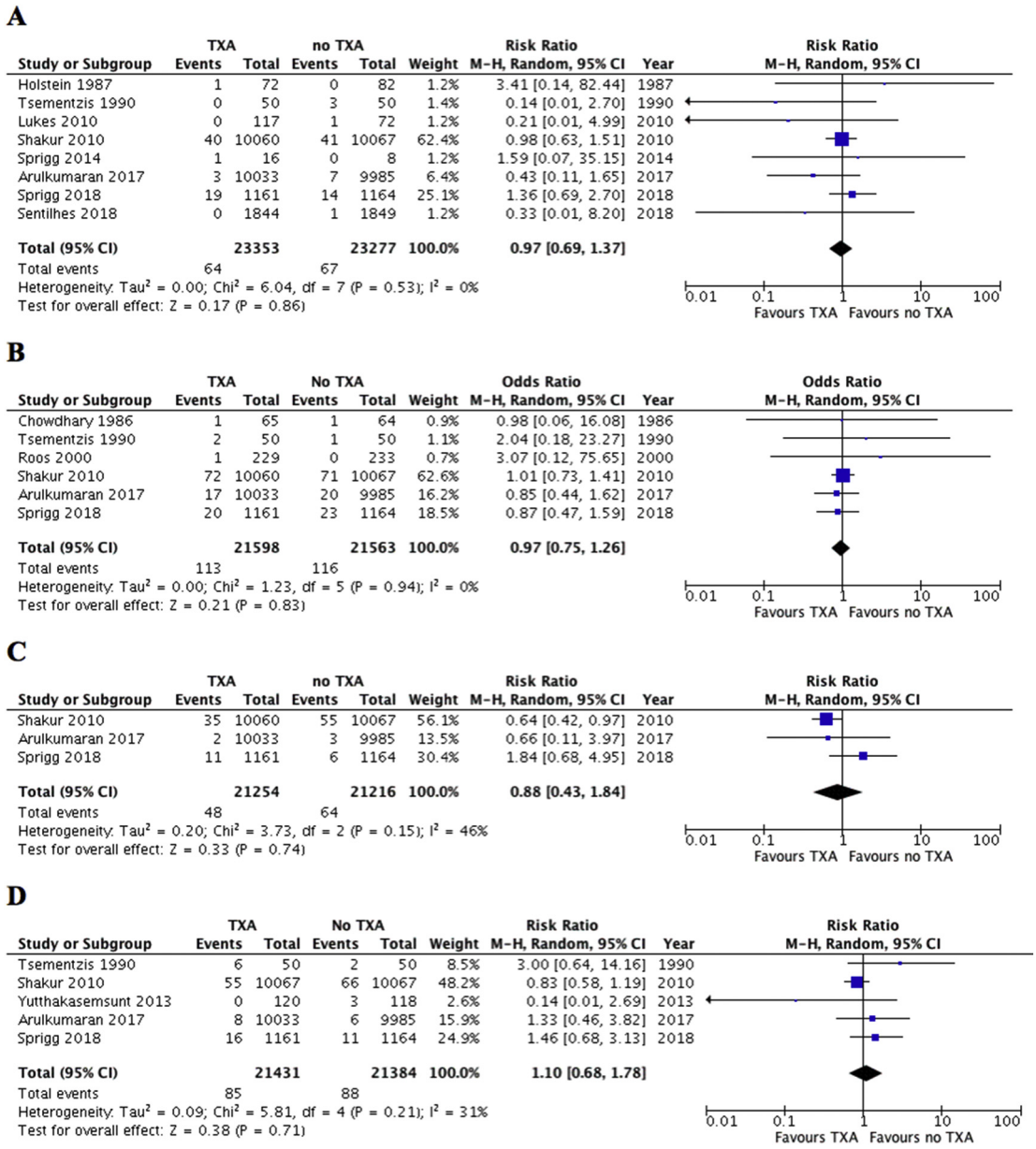

Fig. 3. Forest plots for (A) deep vein thrombosis (B) pulmonary embolism (C) myocardial infarction (D) stroke.

TREAT [30] and TREATT trials [31] are two large RCTs underway comparing TXA to placebo for patients with hematologic malignancies. While beyond the scope of our review, given the shared mechanism of action it is likely that the effect of other antifibrinolytic agents such as aminocaproic acid is similar with respect to thrombotic outcomes.

Despite a large body of evidence supporting its use in patients with disturbances of hemostasis (e.g. cardiac surgery, orthopedic surgery, trauma, post-partum hemorrhage), fear about the risk of thromboembolism with TXA use persists and adherence to recommended TXA administration guidelines [32] appears to be poo [33]. Previous examination of barriers to TXA use suggests that lack of knowledge surrounding evidence for use of TXA contributes to under-utilization, while the degree to which concerns of thrombosis risk affects TXA utilization is less certain [34]. However, these studies are limited in geographical and jurisdictional scope and barriers to use of TXA is a topic that needs further examination.

5. Conclusion

In this systematic review and meta-analysis TXA significantly reduced all-cause mortality (by 8%) without an increased risk of venous or arterial thrombotic complications when given for prevention or treatment of non-surgical bleeding, although the optimal timing and dosing strategy are uncertain. These results should be interpreted with caution for patients with a history of thrombosis as they were excluded from TXA trials. Uncertainty remains regarding the risk of thrombosis in patients receiving systemic TXA prior to planned surgical procedures who were not included in this analysis [1].

Conflict of interest statement

NLJC, KJU, PAM, AS, VS, CCA, and DMS all declare that they have no conflict of interest.

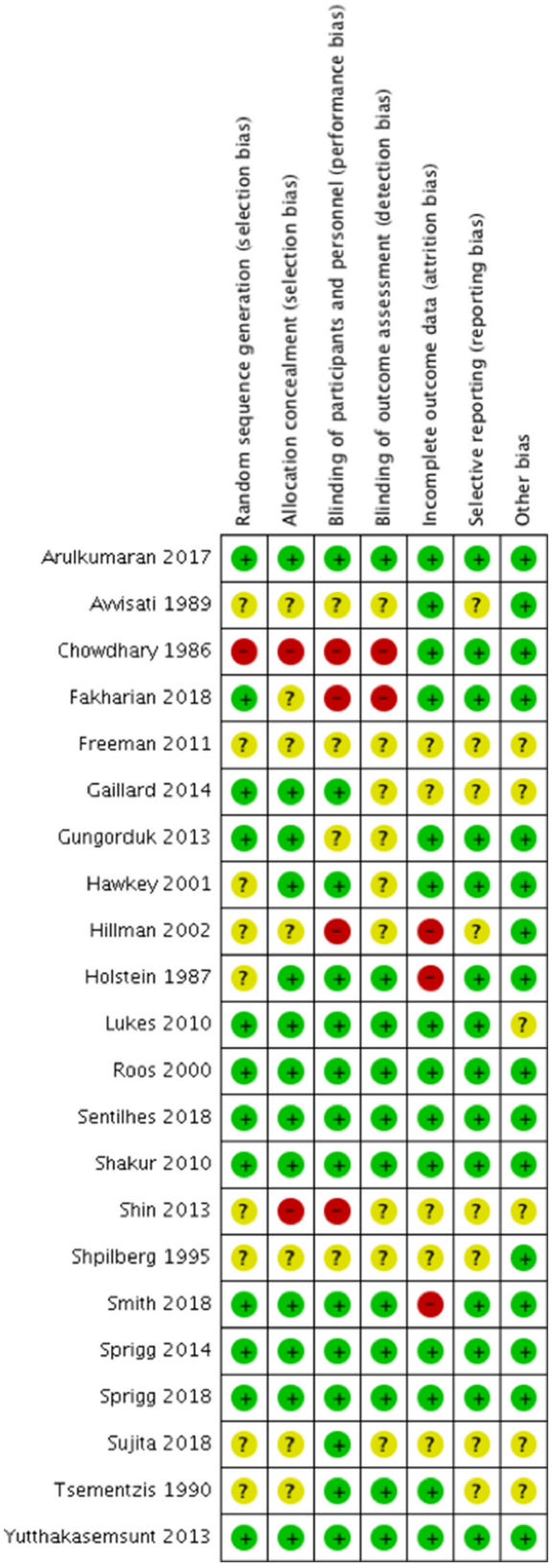

Fig. 4. Risk of bias of included studies.

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Appendix 1

Search strategy for EMBASE

1. exp TRANEXAMIC ACID/ or TRANEXAMIC ACID.mp.
2. Antifibrynolytic agents/
3. (tranexamic adj3 acid$).ti,ab.
4. Antifibrinolytic.mb
5. or/1-4
6. randomized controlled trial/
7. controlled clinical trial/
8. randomi$.ti,ab
9. placebo.ti,ab.
10. trial.ti,ab.
11. Or/6-10
12. 5 and 11

The search syntax or MEDLINE was the same (via OVID)
Search Strategy for CENTRAL

1. MeSH Descriptor: [Tranexamic Acid] explode all trees
2. MeSH Descriptor: [Antifibrinolytic Agents] explode all trees
3. (tranexamic near acid$):ti,kw,ab
4. #1 or #2 or #3
5. MeSH Descriptor: [Randomized Controlled trials as Topic] explode all trees
6. MeSH Descriptor [Randomized Controlled Trial] explode all trees
7. MeSH Descriptor [Controlled Clinical Trial] explode all trees
8. MeSH Descriptor [Clinical Trials as Topic] explode all trees
9. MeSH Descriptor [Clinical Trials, Phase III as Topic] explode all trees

10 MeSH Descriptor [Pragmatic Clinical Trials as Topic] explode all trees
11 MeSH Descriptor [Pragmatic Clinical Trial] explode all trees

13. #5 or #6 or #7 or #8 or #9 or #10 or #11
14. #4 and #12

References

[1] K. Ker, P. Edwards, P. Perel, H. Shakur, I. Roberts, Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis, BMJ 344 (2012) e3054.
[2] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (7) (2009) e1000100.
[3] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, G. Cochrane Bias Methods, G. Cochrane Statistical Methods, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[4] D.R.a.L. N, Meta-analysis in clinica trials, Control. Clin. Trials 7 (1986) 177–188.
[5] W.T. Collaborators, Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial, Lancet 389 (2017) 2105–2116.
[6] G. Avvisati, J.W. Ten Cate, H.R. Buller, F. Mandelli, Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia, The Lancet July(2) (1989) 122–124.
[7] S.K., U.M. Chowdhary, Prevention of early recurrence of aneurysmal subarachnoid haemorrhage by tranexamic acid: a controlled clinical trial, Vasc. Endovasc. Surg. (January/February) (1986) 9–13.
[8] E. Fakharian, M. Abedzadeh-Kalahroudi, F. Atoof, Effect of tranexamic acid on prevention of hemorrhagic mass growth in patients with traumatic brain injury, World Neurosurg. 109 (2018) e748–e753.
[9] E.W. Freeman, A. Lukes, D. VanDrie, R.G. Mabey, J. Gersten, T.L. Adomako, A dose-response study of a novel, oral tranexamic formulation for heavy menstrual bleeding, Am. J. Obstet. Gynecol. 205 (4) (2011) e1–e7 319.

[10] S. Gaillard, S. Dupuis-Girod, F. Boutitie, S. Riviere, S. Moriniere, P.Y. Hatron, G. Manfredi, P. Kaminsky, A.L. Capitaine, P. Roy, F. Gueyffier, H. Plauchu, A.S. Group, Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease, J. Thromb. Haemost. 12 (9) (2014) 1494–1502.
[11] K. Gungorduk, O. Asicioglu, G. Yildirim, C. Ark, A.I. Tekirdag, B. Besimoglu, Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? A randomized controlled study, Am. J. Perinatol. 30 (5) (2013) 407–413.
[12] C.A., G.M. Hawkey, A.S. McIentyre, R.G. Long, C.J. Hawkey, Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points, Gut 2001 (49) (2001) 372–379.
[13] E.S. Von Holstein CS, R. Kallen, Tranexamic acid as an aid to reducing blood transfusion requirements in gastric and duodenal bleeding, BMJ 294 (1987) 7–10.
[14] M.K., A.S. Lukes, K.N. Muse, J.K. Gersten, B.R. Hecht, M. Edlund, H.E. Richter, S.E. Eder, G.R. Attia, D.L. Patrick, R. Arkady, G.A. Shangold, Tranexamic acid treatment for heavy menstrual bleeding, Obstet. Gynecol. 116 (4) (2010) 865–875.
[15] W.N., L. Sentilhes, E. Azria, M.-V. Senat, C. Le Ray, D. Vardon, F. Perrotin, R. Desbriere, F. Fuchs, G. Kayem, G. DUcarme, M. Doret-Dion, C. Huissous, C. Bohec, P. Deruelle, A. Darsonval, J.-M. Chretien, A. Seco, V. Daniel, C. Deneux-Taraux, Tranexamic acid for the prevention of blood loss after vaginal delivery, N. Engl. J. Med. 379 (2018) 731–742.
[16] C.-t. collaborators, Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial, Lancet 376 (2010) 23–32.
[17] P.J., J.U. Shin, S.H. Oh, J.H. Lee, Oral tranexamic acid enhances the efficacy of low-fluence 1064-nm quality-switched neodymium-doped yttrium aluminum garnet laser treatment for melasma in Koreans: a randomized, prospective trial, Dermatological Surgery 39 (2013) 435–442.
[18] O. Shpilberg, R. Blumenthal, O. Sofer, Y. Katz, A. Chetrit, B. Ramot, A. Eldor, I. Ben-Bassat, A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukemia, Leuk. Lymphoma 19 (1–2) (1995) 141–144.
[19] M.D., S.R. Smith, P.G. Pockney, C. Bendinelli, B.D. Draganic, R. Carrol, Tranexamic acid for lower GI hemorrhage: a randomized placebo-controlled clinical trial, Dis. Colon Rectum 61 (1) (2018) 99–106.
[20] N. Sprigg, C.J. Renton, R.A. Dineen, Y. Kwong, P.M. Bath, Tranexamic acid for spontaneous intracerebral hemorrhage: a randomized controlled pilot trial (ISRCTN50867461), J. Stroke Cerebrovasc. Dis. 23 (6) (2014) 1312–1318.
[21] N. Sprigg, K. Flaherty, J.P. Appleton, R.A.-S. Salman, D. Bereczki, M. Beridze, H. Christensen, A. Ciccone, R. Collins, A. Czlonkowska, R.A. Dineen, L. Duley, J.J. Egea-Guerrero, T.J. England, K. Krishnan, A.C. Laska, Z.K. Law, S. Ozturk, S.J. Pocock, I. Roberts, T.G. Robinson, C. Roffe, D. Seiffge, P. Scutt, J. Thanabalan, D. Werring, D. Whynes, P.M. Bath, Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial, Lancet 391 (10135) (2018) 2107–2115.
[22] A. Sujita, S. Songthamwat, M. Songthamwat, Effectiveness of tranexamic acid for reducing postpartum blood loss in the first two hours after vaginal delivery: a randomised controlled trial, J. Clin. Diagn. Res. 12 (3) (2018) QC01–QC04.
[23] H.E., S.A. Tsementzis, C.H.A. Meyer, Benefits and risks of antifibrinolytic therapy in the management of ruptured intracranial aneurysms, Acta Neurochir. 102 (1990) 1–10.
[24] K.W., S. Yutthakasemsunt, P. Piyavechvirat, B. Thinkamrop, N. Phuenpathom, Lumbiganon, Tranexamic acid for patients with traumatic braininjury: a randomized, double-blinded, placebo-controlled trial, BMC Emerg. Med. 13 (20) (2013).
[25] F.S. Hillman, O. Nilsson, Zengquan Yu, H. Saveland, K.E. Hakobsson, Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study, J. Neurosurg. 97 (2002) 771–778.
[26] R.Y., Antifibrinolytic treatment insubarachnoid hemorrhage: a randomized placebo-controlled trial, Neurology 54 (2000) 77–82.
[27] L. Sentilhes, N. Winer, E. Azria, M.V. Senat, C. Le Ray, D. Vardon, F. Perrotin, R. Desbriere, F. Fuchs, G. Kayem, G. Ducarme, M. Doret-Dion, C. Huissoud, C. Bohec, P. Deruelle, A. Darsonval, J.M. Chretien, A. Seco, V. Daniel, C. Deneux-Tharaux, G. Groupe de Recherche en Obstetrique et, Tranexamic acid for the prevention of blood loss after vaginal delivery, N. Engl. J. Med. 379 (8) (2018) 731–742.
[28] I. Appelmann, S. Kreher, S. Parmentier, H.H. Wolf, G. Bisping, M. Kirschner, F. Bergmann, K. Schilling, T.H. Brummendorf, P.E. Petrides, A. Tiede, A. Matzdorff, M. Griesshammer, H. Riess, S. Koschmieder, Diagnosis, prevention, and management of bleeding episodes in Philadelphia-negative myeloproliferative neoplasms: recommendations by the Hemostasis Working Party of the German Society of Hematology and Medical Oncology (DGHO) and the Society of Thrombosis and Hemostasis Research (GTH), Ann. Hematol. 95 (5) (2016) 707–718.
[29] E.A., F.U. Eleje, G.O. Igberase, A.O. Igwebe, L.I. Eleje, Palliative interventions for controlling vaginal bleeding in advanced cervical cancer, Cochrane Database Syst. Rev. 3 (2019 Mar 19) CD011000.
[30] American Trial Using Tranexamic Acid in Thrombocytopenia (A-TREAT), ClinicalTrials.gov (Identifier: NCT02578901).
[31] TRial to EvaluAte Tranexamic Acid Therapy in Thrombocytopenia (TREATT), ClinicalTrials.gov (Identifier: NCT03136445).
[32] T. Nishida, T. Kinoshita, K. Yamakawa, Tranexamic acid and trauma-induced coagulopathy, J. Intensive Care 5 (2017) 5.
[33] J.G.G. Wiese, D.J. van Hoving, L. Hunter, S.A. Lahri, S.R. Bruijns, Poor adherence to Tranexamic acid guidelines for adult, injured patients presenting to a district, public, South African hospital, African Journal of Emergency Medicine 7 (2) (2017) 63–67.
[34] A. Alburaih, Tranexamic acid (TXA) in trauma patients: barriers to use among trauma surgeons and emergency physicians, Emerg. Med. Int. 2017 (2017) 4235785.