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Chloé Alliana

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THESE D'EXERCICE DE MEDECINE

En vue de l'obtention du
Diplôme d'état de docteur en médecine

Présentée par Chloé ALLIANA

**L'ACIDE TRANEXAMIQUE DIMINUE T'IL LE RISQUE DE
TRANSFUSION SANGUINE EN CHIRURGIE PROTHETIQUE DE
HANCHE ET GENOU ? UNE META-ANALYSE**

Soutenue publiquement le 06 juillet 2018 à 19h00
Amphithéâtre 1 René BOURGEON - Faculté de Médecine - Nice

Membres du jury :

Pr Marc RAUCOULES-AIMÉ

Président

Pr Patrick BAQUÉ

Assesseur

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ABREVIATIONS

ASA : Société Américaine d'Anesthésie (ASA)

AVC : Accident Vasculaire Cérébral

CI: Confidence Intervals

Df : Degree of Freedom

ERAS: Enhanced Recovery After Surgery

HAS: Haute Autorité de Santé

MD : Mean Difference

Mls: Milliliters

N/A: data Not Available

NVPO: Nausées Vomissements Post-Opératoires

RBC : Red Blood Cell

RCP: Résumé des Caractéristiques du Produit

RR : Relative Risk

RRR : Relative Risk Reduction

SD: Standard Deviations

SFAR : Société Française d'Anesthésie et de Réanimation

TBL : Total Blood Loss

THA : Total Hip Arthroplasty

TKA : Total Knee Arthroplasty

TXA : Tranexamic Acid

PREMIERE PARTIE : PRE-REQUIS

GENERALITES

L'acide tranexamique est l'antifibrinolytique de référence en raison d'un bon rapport bénéfice/risque et d'une efficacité prouvée dans toutes les indications associées à une activation de la fibrinolyse. Il réduit la mortalité en traumatologie¹, en chirurgie² et réduirait la mortalité par saignement dans l'hémorragie du post-partum^{3,4}.

MODE D'ACTION DE L'ACIDE TRANEXAMIQUE, INTERET EN CHIRURGIE:

Une lésion tissulaire (comme la chirurgie) entraîne, en même temps que le saignement, l'activation du facteur tissulaire contenu dans les cellules endothéliales. L'activation du facteur tissulaire induit le déclenchement de la cascade de la coagulation à l'origine de la formation du caillot sanguin (enchevêtrement de plaquettes et de fibrine) qui permet de combler la brèche vasculaire.

Simultanément, afin de limiter cette réaction de coagulation, toute lésion tissulaire induit l'activation d'un processus de fibrinolyse qui vise à contenir l'extension du thrombus et à le dégrader pour maintenir la perméabilité des vaisseaux sanguins.

Cette réaction de fibrinolyse est déclenchée par la plasmine, enzyme protéolytique, qui va dégrader la trame de fibrine. L'ischémie vasculaire (induite par un garrot ou une plicature des vaisseaux), entraîne elle aussi une activation de la fibrinolyse, plus ou moins importante en fonction de la durée de cette ischémie.

Ceci permet de comprendre l'intérêt de l'acide tranexamique en chirurgie et les variations de son efficacité à réduire non seulement les pertes sanguines mais aussi la transfusion.

L'acide tranexamique est une molécule de synthèse dérivée des analogues de la lysine, il agit en bloquant de manière réversible les récepteurs à la lysine du plasminogène permettant, dans les conditions physiologiques normales, la fixation de ce dernier à la fibrine. (Figure 1) Ainsi il inhibe la formation d'un complexe ternaire plasminogène-fibrine-activateur (t-PA), retarde la fibrinolyse naturelle et donc la dégradation du caillot. Ceci est son principal mode d'action sur la diminution du saignement. Il a été également décrit que l'acide tranexamique pourrait avoir un effet plaquettaire et un effet anti-inflammatoire pouvant participer à la réduction du risque hémorragique.⁵

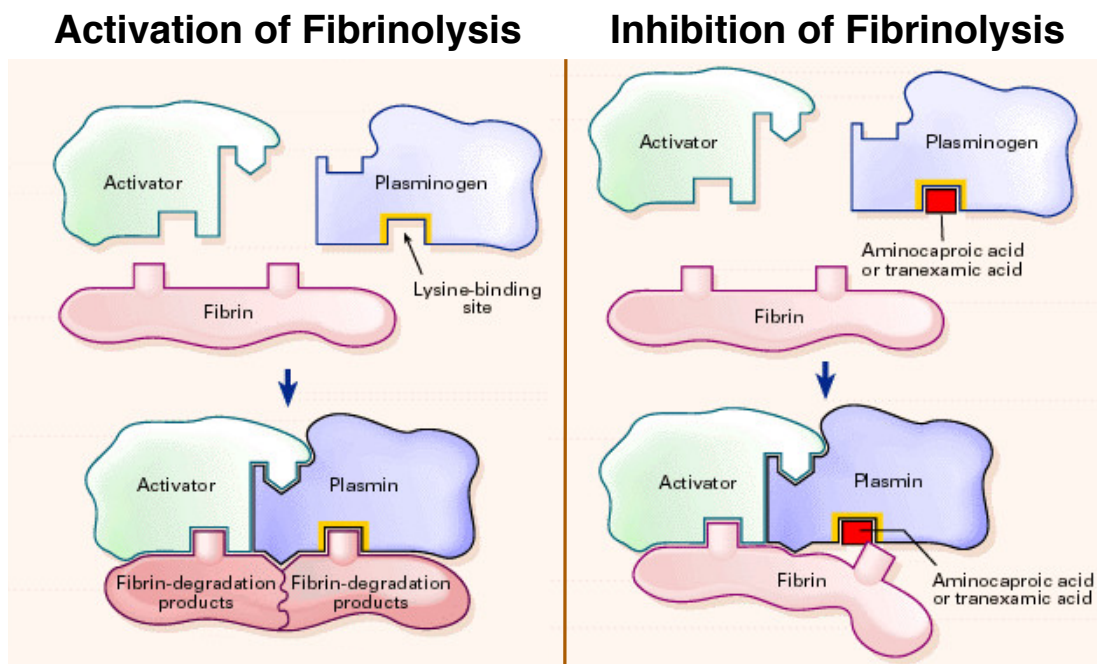


Figure 1 : mécanisme d'action de l'acide tranexamique.⁵

PHARMACOCINETIQUE

L'acide tranexamique possède une demi vie d'élimination courte d'environ 3h. Après administration orale la biodisponibilité est de 30 à 50%. Le volume de distribution plasmatique est de 9 à 12L.

L'acide tranexamique n'est que très légèrement métabolisé par le foie. Il est éliminé à 90% par voie urinaire (excrétion glomérulaire sans réabsorption tubulaire). D'après la RCP, l'acide tranexamique ne doit pas être utilisé en cas d'insuffisance rénale « grave » et la posologie doit être adaptée à la créatininémie chez les patients présentant une insuffisance rénale légère à modérée. Selon le Vidal pour une créatininémie entre 120 et 249 $\mu\text{mol/l}$, la posologie recommandée est de 10 mg/kg deux fois par jour dans l'indication de l'accident hémorragique au lieu de 2 à 4 prises par jour dans les conditions de créatininémie < 120 $\mu\text{mol/l}$; pour des créatininémies entre 250 et 500 $\mu\text{mol/l}$, la posologie recommandée est de 10 mg/kg par jour, enfin au delà de 500 $\mu\text{mol/l}$ la posologie recommandée est de 5 mg/kg par jour.

L'acide tranexamique se présente sous forme de comprimé ou de solution injectable. Il se présente sous différentes appellations dont la plus connue est Exacyl®.

La fenêtre thérapeutique doit probablement être large car il n'existe pas de surdosage décrit en dehors de convulsions à très forte dose justifiant que l'épilepsie soit une contre-indication. Ceci

explique l'absence de consensus sur les doses employées en orthopédie qui varient de 10 à 100 mg/kg selon les études.

SECURITE D'EMPLOI ET POPULATIONS PARTICULIERES

L'effet indésirable le plus fréquent lié à l'acide tranexamique est la survenue de nausées/vomissements lors d'une administration intraveineuse chez un patient éveillé. En obstétrique, l'acide tranexamique donné lors d'une hémorragie du post-partum a augmenté le seuil des NVPO de 2 à 15% et des phosphènes de 2 à 9%.³

Les antifibrinolytiques ont longtemps été contre-indiqués chez des patients aux antécédents thrombotiques artériels ou veineux en raison d'un risque théorique d'aggravation des thromboses dû à l'effet antifibrinolytique. Cependant, dans les études CRASH 2 et WOMAN, incluant respectivement 20211 et 20060 patients, ainsi que dans les 129 essais randomisés en chirurgie incluant un total de 10488 patients, aucune augmentation des infarctus du myocarde, des AVC ou des thromboses veineuses n'a été observée avec l'acide tranexamique.^{1,2,4} D'après le RCP, l'acide tranexamique est contre-indiqué en cas de thrombose veineuse ou artérielle aiguë, il n'est plus contre indiqué en cas d'antécédent de thrombose.

L'aprotinine augmente le risque de dysfonction rénale de 33% par rapport aux patients qui ne reçoivent pas d'antifibrinolytique.⁶ Cet effet n'est pas retrouvé avec l'acide tranexamique dans les études citées précédemment.

L'effet indésirable principal est le risque neurologique qui se manifeste principalement par des crises convulsives généralisées. Elles sont essentiellement rapportées en chirurgie cardiaque⁷ et le risque convulsif est proportionnel à la dose d'acide tranexamique utilisée.⁸ Les doses élevées (>2g/prise) doivent être évitées en chirurgie cardiaque ce d'autant qu'elles ne sont pas plus efficaces que des doses inférieures.⁹ En cas de crises convulsives, il convient de prolonger la sédation par du propofol ou d'administrer une benzodiazépine chez un patient ne pouvant être anesthésié. L'augmentation du risque convulsif par l'acide tranexamique chez un patient aux antécédents convulsifs n'est pas connue. Cependant l'acide tranexamique est contre-indiqué chez ces patients dans le résumé des caractéristiques du produit.

Une neurotoxicité a également été décrite chez des patients en insuffisance rénale terminale ayant eu des doses répétées d'acide tranexamique.¹⁰ Comme il s'agit d'un produit à élimination rénale, ces accidents sont probablement en rapport avec une surexposition par accumulation. D'après le

RCP, l'acide tranexamique ne doit pas être utilisé en cas d'insuffisance rénale « grave » (sans précision d'une valeur seuil). Il n'y a pas d'étude pharmacocinétique réalisée avec l'acide tranexamique chez l'insuffisant rénal sévère. Les suggestions qui peuvent être avancées sont d'utiliser pour la première administration la dose minimale efficace, de réinjecter seulement si cela est nécessaire et de réduire la dose des réinjections proportionnellement à la diminution de la filtration glomérulaire.¹¹

ACIDE TRANEXAMIQUE ET CHIRURGIE ORTHOPEDIQUE

Depuis les années 50, de nombreux essais cliniques rapportés dans la littérature et menés sur de petits effectifs de prothèses de hanche ou de genou, ont montré l'efficacité de l'acide tranexamique sur la réduction du risque de transfusion de culot globulaire et sur la réduction des pertes sanguines.

Par la suite, la méta analyse de la Cochrane publiée en 2011 a confirmé l'efficacité des antifibrinolytiques pour la réduction de la transfusion érythrocytaire dans de nombreuses indications chirurgicales (chirurgie orthopédique, cardiaque, hépatique, urologique et vasculaire).⁹

La Société Américaine d'Anesthésie (ASA)¹² ainsi que la Société Française d'Anesthésie et de Réanimation (SFAR)¹³ et la Haute Autorité de Santé (HAS) l'ont intégré dans leurs recommandations de bonne pratique pour les chirurgies à risque hémorragique.¹⁴

A l'heure actuelle il persiste des interrogations quant à la dose et la durée d'administration pour obtenir une efficacité maximale.

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DEUXIEME PARTIE:

BACKGROUND

Perioperative blood management in major orthopedic surgery is relevant in front of higher morbidity and mortality¹ linked to postoperative anemia and allogeneic blood transfusion.^{2,3}

Among interventions developed to reduce allogeneic blood transfusion including preoperative autologous blood donation,⁴ recombinant human erythropoietin protocol,⁵ perioperative cell salvage blood device⁶ and surgical measures with use of tourniquet, electro cautery or drain clamping,⁷ pharmacological agents such as tranexamic acid (TXA) have been investigated to reduce perioperative blood loss⁸. By interfering with fibrinolysis, TXA is a synthetic lysine analogue, blocking the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin and therefore inhibiting fibrinolysis⁸.

Two previous studies^{1,9} analyzed TXA compared to placebo for blood transfusion and blood loss reduction in perioperative time. Although positive results about TXA efficacy, these two studies present an extent of heterogeneity (due to inclusion of all surgeries⁹ or general orthopedic surgery)¹ fail to draw overall conclusions in lower limb arthroplasty.

Moreover, numerous small recent studies evaluate use of TXA in total hip arthroplasty (THA) or total knee arthroplasty (TKA) without determine optimal protocol of TXA administration.

In order to clarify the optimal TXA dosing regimen, we conducted a meta-analysis, including studies from 1950 to 2017, examining efficacy, administration regimen and safety of TXA in patients undergoing total hip and total knee arthroplasty.

MATERIALS ET METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) with a concurrent control group, or randomized head-to-head comparative trials.

Types of participants

The study participants were adults (over 18 years) and undergoing total hip arthroplasty or total knee arthroplasty.

Types of interventions

The intervention considered is the anti-fibrinolytic agent administration, tranexamic acid, in perioperative time.

Types of outcome measures

Primary outcomes

- The proportion of patients who was transfused with allogeneic blood, autologous blood, or with both;

Secondary outcomes

- Peri-operative blood loss
- Post-operative complications (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, any thrombosis, renal failure),

Search methods for identification of studies

Literature Search

An exhaustive literature search computer-assisted in MEDLINE was conducted to identify all randomized studies comparing intravenous tranexamic acid with placebo in total hip arthroplasty and total knee arthroplasty at the end of July 2017. Only key words “*tranexamic acid*”, “*total hip arthroplasty*” and “*total knee arthroplasty*” were used. Only English or French articles were included. All identified articles (from title and abstract) about tranexamic acid in total hip arthroplasty or total knee arthroplasty were analyzed. Furthermore, reference lists in reviews, studies and previous meta-analyses were checked.

Study Selection

Among identified articles about TXA in scheduled surgeries, only controlled studies with a double-blind randomization and a presence of a transfusion protocol were considered. Studies not controlled (no placebo given) and/or unclear randomization or in pediatric patients were excluded. Efficacy and safety of the tranexamic acid needed to be evaluated in screened studies.

For efficacy of TXA, proportion of patients receiving at least one unit of allogeneic/autologous erythrocyte transfusion according to a transfusion protocol, and total volume of blood loss in milliliters (intra-operative and postoperative blood loss) are considered.

To limit evaluation bias on transfusion criteria, screened studies had to have a transfusion protocol including a transfusion threshold of allogeneic/autologous erythrocytes with an adjusted statistical analysis of preoperative hemoglobin between tranexamic acid group and control group. Trials with transfusion protocol missing or not mentioned were excluded. Finally, transfusion protocol could differ between studies.

For safety of TXA, venous thromboembolism event (confirmed by ultrasound or venography for deep venous thrombosis, ventilation-perfusion lung scanning or pulmonary angiography or spiral computed tomography for pulmonary embolism), or arterial thrombosis (myocardial infarction, stroke or limb ischemia) are considered.

Data Extraction

At least two authors (SP, CA) independently extracted study characteristics and outcomes using an article extraction form. The extraction form was used to record information regarding randomization criteria, methodology descriptions, presence of a transfusion protocol, type of surgery involved, treatment outcomes and adverse events.

Data on the following outcomes were recorded on the data extraction form: number of patients receiving any transfusion (allogeneic blood, autologous blood, or both), number of patients experiencing post-operative complications (thrombosis, myocardial infarction, renal failure), and mortality. Data were also recorded on total, intraoperative and postoperative blood loss. Information regarding type of surgery, tranexamic acid dose range, tranexamic acid use protocol, preoperative hemoglobin, transfusion thresholds, preoperative autologous blood donation, cell salvage blood were also recorded.

If more than one group was treated, treatment group with smaller dose of TXA was chosen.

Statistical Analysis

Publication bias was checked using funnel plot technique.

For dichotomous outcomes such as the proportion of patients transfused or having postoperative venous thromboembolism, meta-analyses were performed using a logarithm of relative risk (RR). The RR in intervention group was compared to control group and corresponding 95% confidence intervals (CI) were calculated for each trial using the random effects model. Relative risk reduction (RRR) is calculated from formula "1-RR" and means how much TXA reduces the risk of allogeneic blood transfusion relative to the control group who did not receive TXA. RRR is expressed in percentage. Association and heterogeneity test were performed for each meta-analysis. A value of $p \leq 0.05$ in an association test was considered to be statistically significant proving an effect of tranexamic acid. The presence of heterogeneity of treatment effect was assessed using the Q statistic, which has an approximate chi-square distribution with degrees of freedom equal to the number of studies minus one. A P-value less than or equal to 0.1 was used to define statistically significant heterogeneity. Statistical heterogeneity was also assessed using the I^2 test. The I^2 test describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity. Substantial heterogeneity is considered to exist when $I^2 > 50\%$.

For continuous outcomes such total volume blood loss in milliliters, the meta-analysis was performed using a random-effect model of the standardized mean difference (MD). The mean number of total volume blood loss of each group and the corresponding standard deviations (SD)

were collected for each trial. When confidence intervals were reported rather SD, the CI was transformed to SD using formula:

$$SD = \frac{CI}{Z_{\alpha/2}} \times \sqrt{n}.$$

Like dichotomous outcomes, the standardized MD and the corresponding 95% CI, were calculated for each trial using the random effects model. Association and heterogeneity test were performed for each meta-analysis. A value of $p \leq 0.05$ in an association test were considered to be statistically significant and to occur an effect of tranexamic acid. The presence of heterogeneity of treatment effect was defined using the Q statistic with p-value less than or equal to 0.1 and using the I^2 test with substantial heterogeneity is considered to exist when $I^2 > 50\%$.

Analysis of subgroups was performed to determine whether effect sizes varied according factors, to explain heterogeneity, such as:

- Tranexamic acid dose regimens
- Blood cell salvage use
- Transfusion thresholds
- Preoperative hemoglobin
- The way to measure or estimate the blood loss
- Type of anesthesia.

All analyses were performed using R-project software, package meta/metafor/rmeta.

RESULTS

Description of studies

For THA, the literature search, “tranexamic acid” AND “total hip arthroplasty”, identified 113 studies. Only 17 trials remained potentially relevant after reading through title and abstract. Articles were excluded for several reasons: uncertainly randomization, lack of control group, tranexamic acid not administrated intravenously. Among these 17 trials, 6 studies were withdrawn because trial was not randomized,¹¹ transfusion protocol was not applied,^{12,13,14} hemoglobin preoperative was not analyzed between TXA group and control group,¹⁵ article was not available.¹⁶ For blood loss analysis, 1 study was withdrawn because data were presented as median with lower and upper quartiles.¹⁷

For TKA, the literature search, “tranexamic acid” AND “total knee arthroplasty”, identified 262 studies. Only 23 trials remained potentially relevant after reading through title and abstract. Articles were excluded for several reasons: uncertainly randomization, lack of control group, tranexamic acid not administrated intravenously. Among these 23 trials, 3 studies were withdrawn

because trial was not clearly randomized,¹⁸ hemoglobin preoperative was not analyzed between TXA group and control group,¹⁹ data were not available.²⁰ For blood loss analysis, 5 studies were withdrawn because data were presented as median with lower and upper quartiles,^{21,22,23,24,25} and 1 study was withdrawn because data were not available.²⁶ Figure 1 presents the PRISMA flow chart¹⁰ of our meta-analysis.

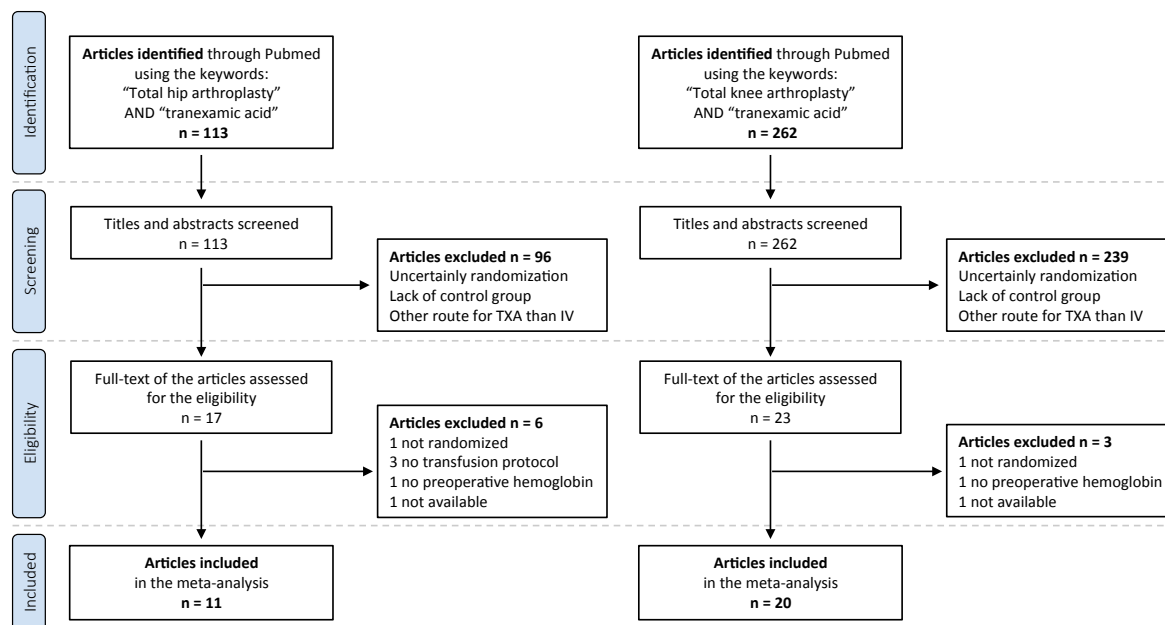


Fig. 1: PRISMA flow chart of meta-analysis

Study design

The tables 1 and 2 show the design of the included studies.

Total Hip Arthroplasty (table 1).

Eleven studies using tranexamic acid in total hip arthroplasty were selected comprising a total of 830 randomized patients.^{17,27,28,29,30,31,32,33,34,35,36} Trials were conducted in many countries including: Sweden (n = 3), Finland (n = 1), Denmark (n = 1), Spain (n = 1), Croatia (n = 1), Iran (n = 1), Canada (n = 1), China (n = 2). Trials were small (38 to 62 patients) and only 4 trials randomized more than 100 patients.^{17,31,35,36} In each study, total dose of tranexamic acid was variable : first TXA dose was ranged from 10 to 15 mg/kg intravenous associated or not with second or third TXA dose three hours after or associated with continuous administration ranged from 1 to 10 mg/kg/h during surgery or for 10 h. In all cases, first TXA dose was delivered just before the surgery beginning (or before skin incision). The transfusion trigger threshold differed between trials. Only 2 studies used partially autologous blood transfusion^{27,29} and only 2 studies used currently a cell salvage blood device.^{27,34} Prophylaxis of deep venous thrombosis used Low Molecular Weight Heparin (LMWH) and venous thrombosis screening was done by ultrasound in 5 studies.^{17,27,29,35,36} Type of anesthesia carried between trials.

Table 1. Characteristics and Outcomes in Selected Studies in Total Hip Arthroplasty

Reference	Year	Patients randomized	Double-blind	Type of Surgery	Type of Anesthesia	Transexamic Acid Regimen	First TXA Administration	Transfusion Protocol of Erythrocyte Units	Preoperative Hemoglobin	Preoperative Hemoglobin Analysis	Autologous Transfusion	Cell Salvage Blood	Method of Blood Loss Measure	DVT Prophylaxis	Screening of DVT
Ekback ²⁷	2000	40	Yes	THA	RA	10 mg/kg + 10 mg/kg 3h after + 1 mg/kg/h for 10h	Before surgery	Ht < 27%	12.5	Yes	Yes	Yes for 2h	Measured (Swabs & Drains)	LMWH for 10 days	Ultrasound
Benoni ²⁸	2001	38	Yes	THA	GA/RA	10 mg/kg	Before surgery	Hb < 8-10 g/dl	13.5	Yes	No	No	Measured (Swabs & Drains)	LMWH for 10 days	Clinical
Husted ³⁰	2003	40	Yes	THA	RA	10 mg/kg + 1 mg/kg/h for 10h	Before surgery	Hb < 10 g/dl	13.5	Yes	No	No	Measured (Swabs & Drains)	LMWH	Clinical
Lemay ²⁹	2004	39	Yes	THA	RA	10 mg/kg + 1 mg/kg/h during surgery	Before surgery	Hb < 7 g/dl	13	Yes	Yes	No	Measured (Swabs & Drains)	LMWH	Ultrasound
Johansson ³¹	2005	100	Yes	THA	RA	15 mg/kg	Before surgery	Hb < 9 g/dl	14	Yes	No	No	Estimated by Nadler	LMWH	Clinical
Niskanen ³²	2005	39	Yes	THA	RA	10 mg/kg + 10 mg/kg 8h after + 10 mg/kg 16h after	Before surgery	Ht < 28-30%	14.4	Yes	No	No	Measured (Swabs & Drains)	LMWH	Clinical
Kazemi ³³	2010	64	Yes	THA	RA	15 mg/kg	Before surgery	Ht < 30%	13.7	Yes	No	No	Measured (Swabs & Drains)	LMWH for 10 days	Clinical
Oremus ³⁴	2014	42	Yes	THA	RA	1,000 mg + 1,000mg 3h after	Before surgery	Hb < 8 g/dl	15.1	Yes	No	Yes for 6h	Measured (Swabs & Drains)	LMWH	Clinical
Wei ³⁵	2014	201	Yes	THA	N/A	3,000 mg	Before surgery	Hb < 9 g/dl	14	Yes	No	No	Estimated by Gross & Nadler	LMWH	Ultrasound
Barrachina ³⁶	2016	108	Yes	THA	RA	15 mg/kg or 10 mg/kg + 10 mg/kg 3h after	Before surgery	Hb < 8.5 g/dl	14.4	Yes	No	No	Estimated by Camarasa	LMWH for 40 days	Ultrasound
Wang ¹⁷	2016	124	Yes	THA	GA/RA	15 mg/kg or 10 mg/kg	Before surgery	Hb < 7 g/dl	13.4	Yes	No	No	Estimated by Gross	LMWH followed Rivaroxaban	Ultrasound

Total Knee Arthroplasty (table 2).

Twenty studies using tranexamic acid in total knee arthroplasty were selected comprising a total of 1221 randomized patients.^{21,22,23,24,25,26,34,37,38,39,40,41,42,43,44,45,46,47,48,49} Trials were conducted in many countries including: Sweden (n = 2), Finland (n = 2), Denmark (n = 1), Belgium (n = 1), Germany (n = 1), Spain (n = 3), United Kingdom (n = 1), Croatia (n = 1), Greece (n = 1), Israel (n = 2), Dubai (n = 1), Japan (n = 1), Taiwan (n = 1), Thailand (n = 1), South Korea (n = 1). Trials were small and only 6 trials randomized more than 95 patients.^{45,46,47,48} All studies used pneumatic tourniquet during surgery. In each study, total dose of tranexamic acid was variable: first TXA dose was ranged from 10 to 20 mg/kg intravenous associated with second or third TXA dose three hours after or associated with continuous administration ranged from 1 to 10 mg/kg/h for 6 h or 12 h. Only 2 studies administered tranexamic acid during several days.^{40,46} In all case, first TXA dose was delivered just before the deflation of tourniquet, excluding 2 studies in which tranexamic acid was administered before the surgery.^{34,40} The transfusion trigger threshold differed between trials. Only 2 studies used partially autologous blood transfusion^{42,43} and only 5 studies used currently a blood cell salvage device.^{25,34,42,43,44} Prophylaxis of deep venous thrombosis (when described) used Low Molecular Weight Heparin (LMWH) excluding 2 studies using Warfarin⁴⁴ or Indomethacin⁴⁵. Venous thrombosis screening was done by ultrasound in only 2 studies.^{26,41} Type of anesthesia varied between trials.

Table 2. Characteristics and Outcomes in Selected Studies in Total Knee Arthroplasty

Reference	Year	Patients randomized	Double-blind	Type of Surgery	Type of Anesthesia	Tourniquet Use	Tranexamic Acid Regimen	First TKA Administration	Transfusion Protocol of Erythrocyte Units	Preoperative Hemoglobin	Preoperative Hemoglobin Analysis	Autologous Transfusion	Cell Salvage Blood	Method of Blood Loss Measure	DVT Prophylaxis	Screening of DVT
Hippala ³⁷	1995	28	Yes	TKA	RA	Yes	15 mg/kg	Before deflated tourniquet	Hb < 10 g/dl	13.2	Yes	No	No	Measured (Swabs & Drains)	No	Clinical
Benoni ³⁸	1996	86	Yes	TKA	RA	Yes	10 mg/kg + 10 mg/kg 3h after	Before deflated tourniquet	Hb < 8.5-10 g/dl	13.6	Yes	No	No	Measured (Swabs & Drains)	LMWH for 10 days	Clinical
Hippala ³⁹	1997	77	Yes	TKA	RA	Yes	15 mg/kg + 10 mg/kg 3h after + 10 mg/kg 6h after	Before deflated tourniquet	Hb < 10 g/dl	13.6	Yes	No	No	Measured (Swabs & Drains)	LMWH	Clinical
Jansen ⁴⁰	1999	42	Yes	TKA	GA	Yes	15 mg/kg + 15 mg/kg every 8h for 3 days	Before surgery	PCV < 26%	13.2	Yes	No	No	Measured (Swabs & Drains)	LMWH	Clinical
Ellis ²⁴	2001	20	Yes	TKA	GA	Yes	15 mg/kg + 10 mg/kg/h for 12h	Before deflated tourniquet	Ht < 27%	NA	Yes	No	No	NA	LMWH for 35 days	No
Engel ²²	2001	24	Yes	TKA	RA	Yes	15 mg/kg + 10 mg/kg 3h after	Before deflated tourniquet	Hb < 10 g/dl	NA	Yes	No	No	Measured (Swabs & Drains)	LMWH	Clinical
Tanaka ²³	2001	48	Yes	TKA	N/A	Yes	20 mg/kg	Before deflated tourniquet	Hb < 7 g/dl	11.7	Yes	No	No	Estimated by Gross	NA	Clinical
Veien ²⁵	2002	30	Yes	TKA	RA	Yes	10 mg/kg + 10 mg/kg 3h after	Before deflated tourniquet	Ht < 28%	13.4	Yes	No	Yes	Measured (Swabs & Drains)	LMWH	Clinical
Good ²¹	2003	51	Yes	TKA	RA	Yes	10 mg/kg + 10 mg/kg 3h after	Before deflated tourniquet	Hb < 9 g/dl	13.8	Yes	No	No	Estimated by Nadler	LMWH for 10 days	Clinical
Zohar ²⁶	2004	40	Yes	TKA	GA	Yes	15 mg/kg + 10 mg/kg/h for 12h	Before deflated tourniquet	Ht < 28%	14	Yes	No	No	Measured (Swabs & Drains)	LMWH	Ultrasound
Camarasa ⁴²	2006	95	Yes	TKA	RA	Yes	10 mg/kg + 10 mg/kg 3h after	Before deflated tourniquet	Hb < 8 g/dl	12.6	Yes	Yes	Yes for 5h	Estimated by Camarasa	LMWH for 40 days	Clinical
Orpen ⁴¹	2006	29	Yes	TKA	GA+RA	Yes	15 mg/kg	Before deflated tourniquet	Hb < 9 g/dl	13	Yes	No	No	Measured (Swabs & Drains)	LMWH	Ultrasound
Alvarez ⁴³	2008	95	Yes	TKA	RA	Yes	10 mg/kg + 1 mg/kg/h for 6h	Before deflated tourniquet	Hb < 8 g/dl	13.5	Yes	Yes	Yes for 6h	Estimated by Brecher	LMWH for 30 days	Clinical
Charoencholvanich ⁴⁶	2011	100	Yes	TKA	RA	Yes	10 mg/kg + 10 mg/kg 3h after + 500mg oral three times daily for 5 days	Before deflated tourniquet	Hb < 10 g/dl	12.5	Yes	No	No	Measured (Swabs & Drains)	No	Clinical
Lin ⁴⁵	2011	100	Yes	TKA	GA	Yes	10 mg/kg	Before deflated tourniquet	Hb < 8.5 g/dl	13.3	Yes	No	No	Estimated by Nadler	Indomethacin	Clinical
MacGillivray ⁴⁴	2011	40	Yes	TKA	GA+RA	Yes	10 mg/kg + 10 mg/kg 3h after	Before deflated tourniquet	Hb < 8 g/dl	13	Yes	No	Yes	Measured (Swabs & Drains)	Warfarin	Clinical
Seo ⁴⁷	2013	100	Yes	TKA	N/A	Yes	1,500 mg	Before deflated tourniquet	Hb < 8 g/dl	11.4	Yes	No	No	Measured (Swabs & Drains)	NA	Clinical
Oremus ³⁴	2014	56	Yes	TKA	RA	Yes	1,000 mg + 1,000mg 3h after	Before surgery	Hb < 8 g/dl	15.1	Yes	No	Yes for 6h	Measured (Swabs & Drains)	LMWH	Clinical
Aguilera ⁴⁸	2015	100	Yes	TKA	RA	Yes	1,000 mg + 1,000mg 60-90min after	Before deflated tourniquet	Hb < 8 g/dl	13.5	Yes	No	No	Estimated by Nadler	LMWH	Clinical
Digas ⁴⁹	2015	60	Yes	TKA	RA	Yes	15 mg/kg	Before deflated tourniquet	Hb < 8.5 g/dl	13.2	Yes	No	No	Estimated by Gross & Nadler	LMWH for 30 days	Clinical

Total Hip Arthroplasty (THA)

For exposure to allogeneic/autologous blood transfusion according to a transfusion protocol, 11 trials of TXA versus control involved total hip arthroplasty. These trials included a total of 830 patients, of whom 449 were randomized to TXA, and 381 were randomized to a control group who did not receive TXA. There was a significant 59% relative reduction in the rate of exposure to allogeneic blood transfusion in those patients with TXA (RR 0.41, 95% CI 0.30 to 0.55). Heterogeneity between these trials was not statistically significant ($\text{Chi}^2 = 6.70$, $\text{df} = 10$, $p = 0.7530$; $I^2 = 0\%$). (Figure 2)

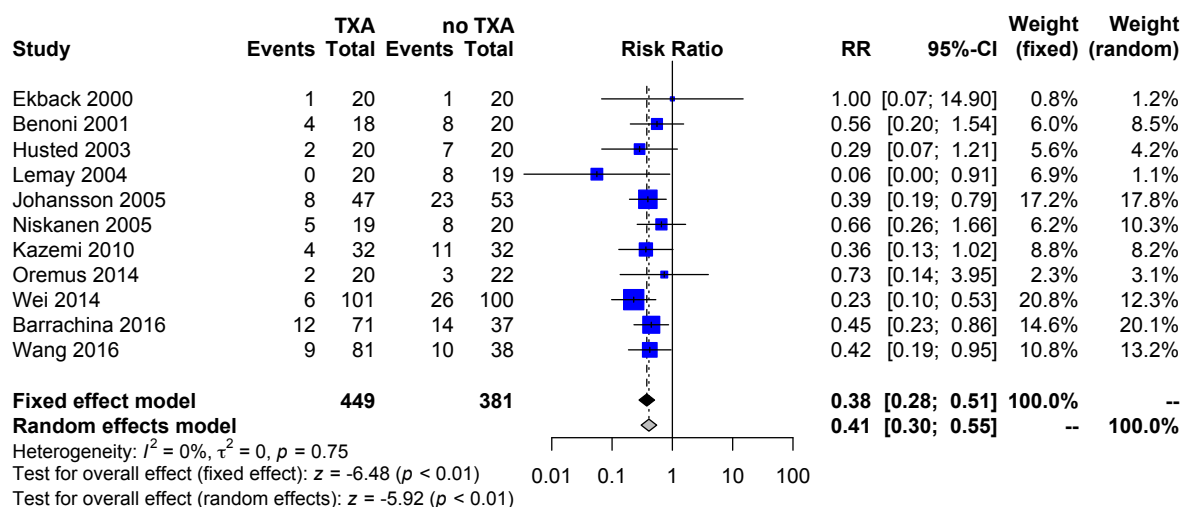


Fig. 2. Meta-analysis of use of tranexamic acid compared with placebo in total hip arthroplasty (THA) on the proportion of patient requiring allogenic/autologous transfusion according to a transfusion protocol. The relative ratio (RR) for individual studies is represented as a square within a bar representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The RR for summaries is represented as a diamond. The length of the diamond corresponds to the 95% CI. An RR < 1 indicated that the tranexamic acid is more effective than placebo. If the value of 1 is included within 95% CI, the result is not significant.

Nine trials of TXA versus control involving total hip arthroplasty reported data on the total volume of blood loss. These trials included a total of 669 patients, of whom 348 were randomized to TXA, and 321 were randomized to a control group who did not receive TXA. The use of TXA in THA reduced total volume of blood loss by around 390 mls per patient (MD -389.66 mls, 95% CI -499.18 to -280.14 mls). Heterogeneity between these trials was statistically significant ($\text{Chi}^2 = 14.05$, $\text{df} = 8$, $p = 0.0805$; $I^2 = 43\%$). (Figure 3)

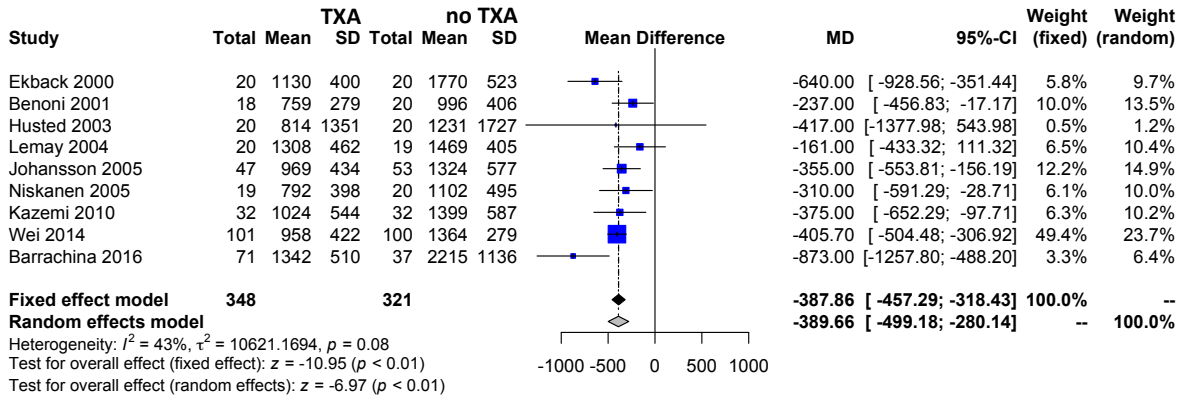


Fig. 3. Meta-analysis of use of tranexamic acid compared with placebo in total hip arthroplasty (THA) on the total volume of blood loss in milliliters of patient. The standardized mean difference (MD) for individual studies is represented as a square within a bar representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The MD for summaries is represented as a diamond. The length of the diamond corresponds to the 95% CI. An MD < 0 indicated that the tranexamic acid is more effective than placebo. If the value of 0 is included within 95% CI, the result is not significant.

Funnel plots did not suggest that low-quality studies and/or publication bias (absence of studies showing no significant beneficial effect) exaggerated the magnitude of estimated treatment effect, confirmed by trim and fill method (no added studies). (Figure 4)

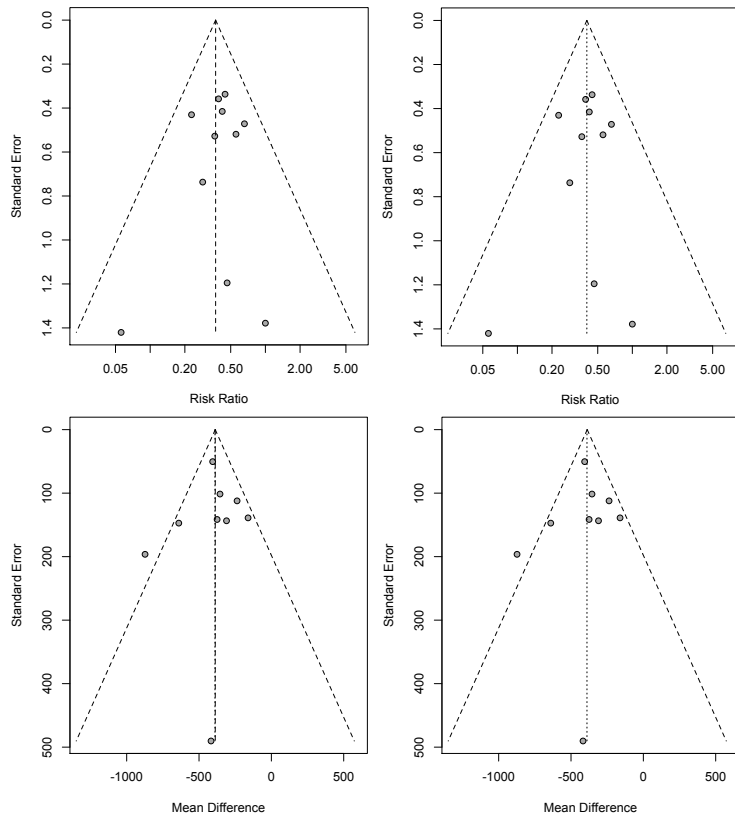


Fig. 4. Funnel plot of use of tranexamic acid compared with placebo in THA, upper on the proportion of patient requiring allogenic/autologous transfusion according to a transfusion protocol, and bottom on the total volume of blood loss in milliliters of patient. The left funnel plots are a scatter plot of the treatment effect estimated from individual studies (logarithm of RR or MD, horizontal axis) against a measure of study size (SE of logarithm of RR or MD, vertical axis). Dashed line is pooled RR or MD. In the absence of publication bias, studies are symmetrically distributed around the pooled RR or MD, and the plot resembles a symmetric inverted funnel. Asymmetric funnel plots may indicate publication bias or be due to exaggeration of treatment effects in small studies of low quality. The right funnel plots represented funnel plot by the trim and fill method. This method estimate the number of studies missing from a meta-analysis due to the suppression of the most extreme results on one side of the funnel plot. The method then augments the observed data so that the funnel plot is more symmetric.

Total Knee Arthroplasty (TKA)

For exposure to allogeneic/autologous blood transfusion according to a transfusion protocol, twenty trials of TXA versus control involved total knee arthroplasty. These trials included a total of 1221 patients, of whom 599 were randomized to TXA, and 622 were randomized to a control group who did not receive TXA. There was a significant 63% relative reduction in the rate of exposure to allogeneic blood transfusion in those patients with TXA (RR 0.37, 95% CI 0.27 to 0.52). Heterogeneity between these trials was statistically significant ($\text{Chi}^2 = 72.08$, $\text{df} = 19$, $p < 0.0001$; $I^2 = 74\%$). (Figure 5)

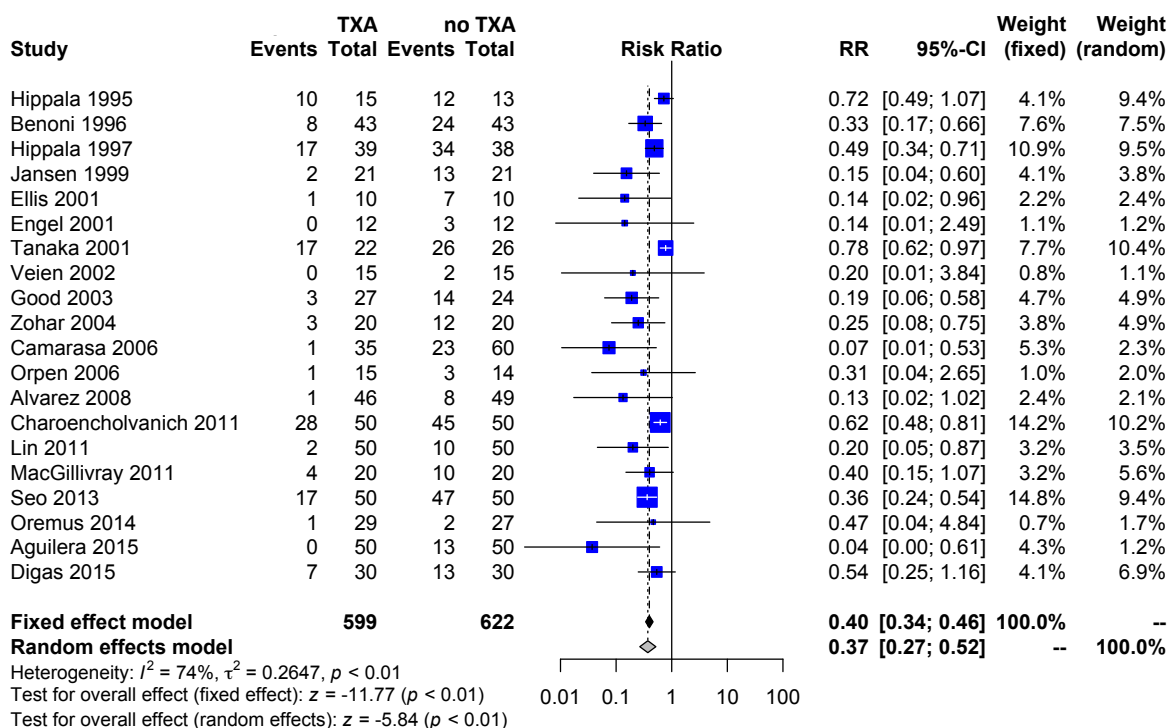


Fig. 5. Meta-analysis of use of tranexamic acid compared with placebo in total knee arthroplasty (TKA) on the proportion of patient requiring allogeneic/autologous transfusion according to a transfusion protocol. The relative ratio (RR) for individual studies is represented as a square within a bar representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The RR for summaries is represented as a diamond. The length of the diamond corresponds to the 95% CI. An RR < 1 indicated that the tranexamic acid is more effective than placebo. If the value of 1 is included within 95% CI, the result is not significant.

Fourteen trials of TXA versus control involving total knee arthroplasty reported data on the total volume of blood loss. These trials included a total of 1022 patients, of whom 499 were randomized to TXA, and 523 were randomized to a control group who did not receive TXA. The use of TXA in TKA reduced total volume of blood loss by around 513 mls per patient (MD -513.49 mls, 95% CI -609.25 to -417.73 mls). Heterogeneity between these trials was statistically significant ($\text{Chi}^2 = 65.35$, $\text{df} = 13$, $p < 0.0001$; $I^2 = 80\%$). (Figure 6)

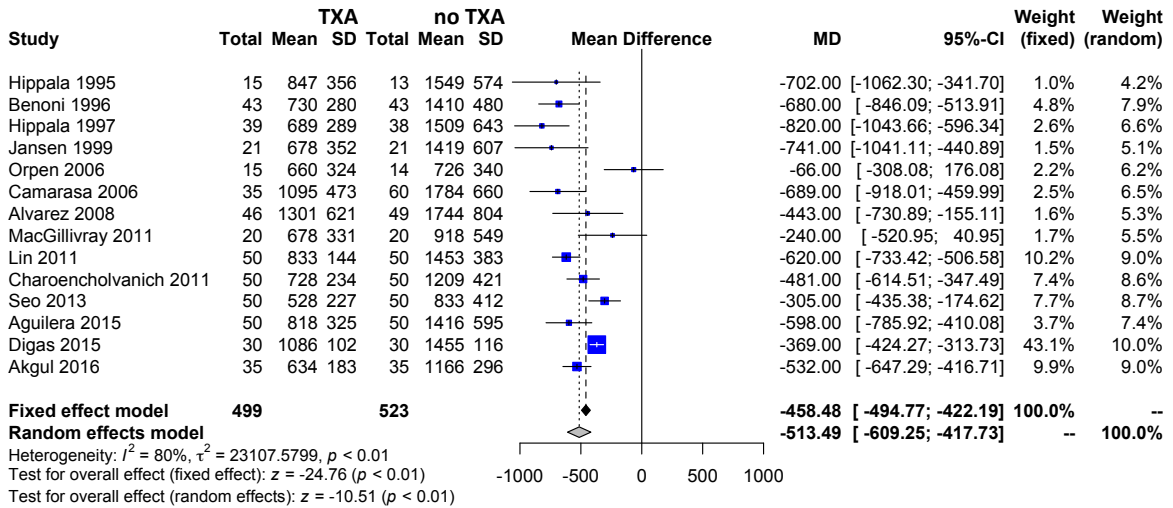


Fig. 6. Meta-analysis of use of tranexamic acid compared with placebo in total knee arthroplasty (TKA) on the total volume of blood loss in milliliters of patient. The standardized mean difference (MD) for individual studies is represented as a square within a bar representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The MD for summaries is represented as a diamond. The length of the diamond corresponds to the 95% CI. An MD < 0 indicated that the tranexamic acid is more effective than placebo. If the value of 0 is included within 95% CI, the result is not significant.

Funnel plots did suggest that low-quality studies and/or publication bias (absence of studies showing no significant beneficial effect) exaggerated the magnitude of estimated treatment effect, confirmed by trim and fill method (10 added studies for exposure to allogeneic/autologous blood transfusion, and 3 added studies for total blood loss). (Figure 7)

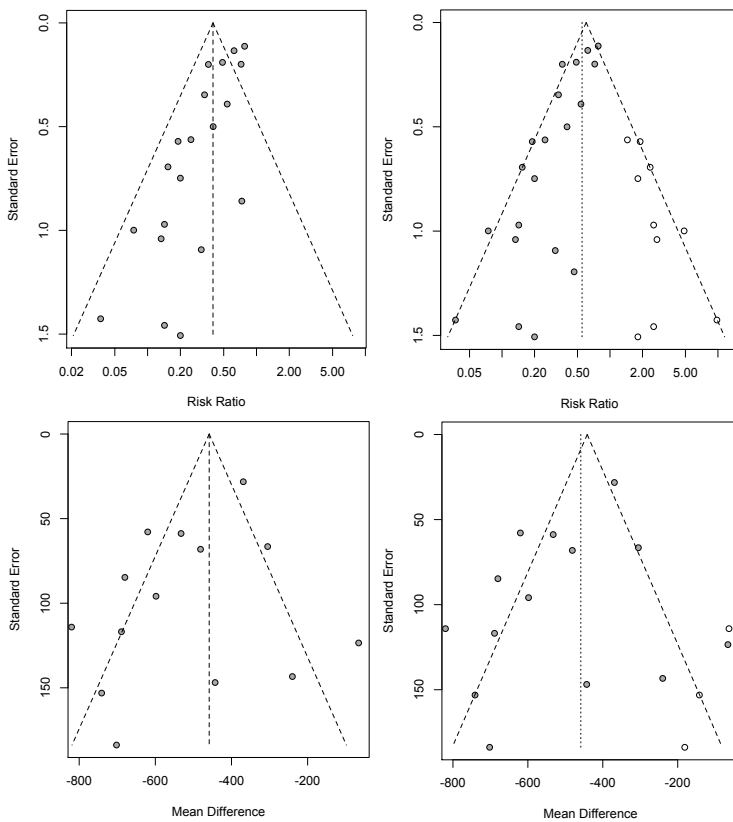


Fig. 7. Funnel plot of use of tranexamic acid compared with placebo in TKA, upper on the proportion of patient requiring allogeneic/autologous transfusion according to a transfusion protocol, and bottom on the total volume of blood loss in milliliters of patient. The left funnel plots are a scatter plot of the treatment effect estimated from individual studies (logarithm of RR or MD, horizontal axis) against a measure of study size (SE of logarithm of RR or MD, vertical axis). Dashed line is pooled RR or MD. In the absence of publication bias, studies are symmetrically distributed around the pooled RR or MD, and the plot resembles a symmetric inverted funnel. Asymmetric funnel plots may indicate publication bias or be due to exaggeration of treatment effects in small studies of low quality. The right funnel plots represented funnel plot by the trim and fill method. This method estimate the number of studies missing from a meta-analysis due to the suppression of the most extreme results on one side of the funnel plot. The method then augments the observed data so that the funnel plot is more symmetric.

For exposure to allogeneic/autologous blood transfusion, subgroup analysis did not find any influence of the transfusion threshold with RR for TXA compared with control was 0.42 [0.34; 0.52] in threshold between 8.5 to 10g/dl and 0.36 [0.27; 0.48] in threshold between 7 to 8.5g/dl (heterogeneity test between subgroups was not statistically significant; $p = 0.37$; $I^2 = 0\%$). The efficacy of TXA seemed to be modified by the used TXA regimen, the blood cell salvage use, the preoperative hemoglobin level and the type of anesthesia. First, the efficacy of TXA versus placebo was greater with a continuous dose regimen (RR 0.19 [0.08; 0.47]) than one or more single dose regimen (RR 0.49 [0.38; 0.63] and RR 0.37 [0.29; 0.47] respectively). The heterogeneity test between these dose regimens was statistically significant ($p = 0.07$; $I^2 = 63\%$). In regarding only single and more single TXA dose, the heterogeneity was not clear ($p = 0.11$, $I^2 = 60\%$). Second, the efficacy of TXA versus placebo was greater with blood cell salvage use (RR 0.18 [0.09; 0.39]) than without (RR 0.42 [0.35; 0.50]). The heterogeneity test between these dose regimens was statistically significant ($p = 0.04$; $I^2 = 77\%$). Third, the efficacy of TXA versus placebo was greater with preoperative hemoglobin superior to 13 g/dl (RR 0.34 [0.26; 0.45]) than preoperative hemoglobin inferior to 13 g/dl (RR 0.53 [0.43; 0.65]). The heterogeneity test between these dose regimens was statistically significant ($p < 0.01$; $I^2 = 86\%$). Fourth, the efficacy of TXA versus placebo was greater with general anesthesia (RR 0.23 [0.13; 0.41]) than regional anesthesia (RR 0.41 [0.33; 0.52]). The heterogeneity test between these dose regimens was statistically significant ($p = 0.06$; $I^2 = 71\%$). (Figure 8)

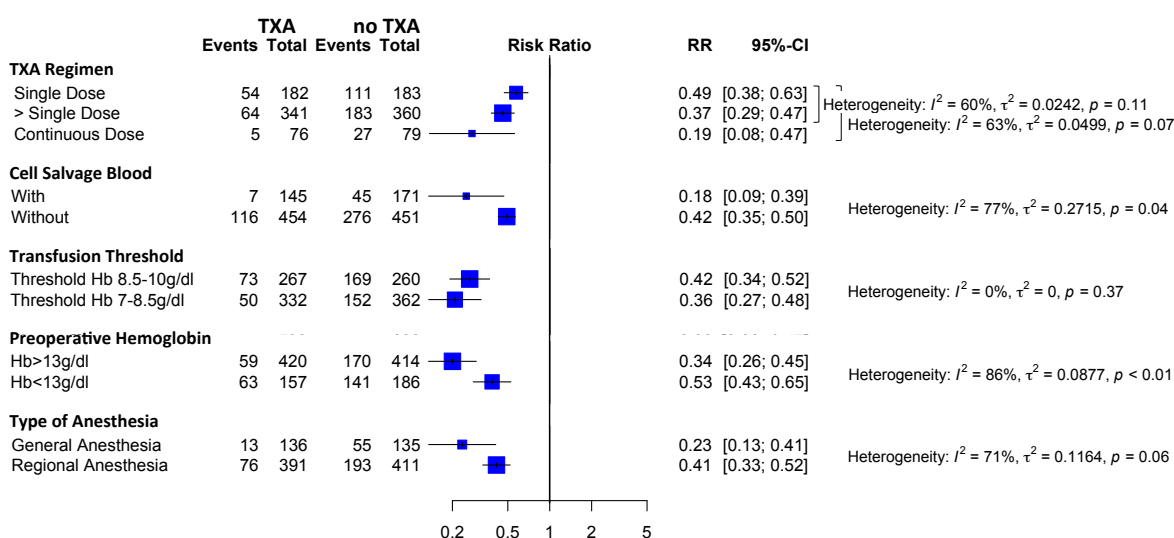


Fig. 8. Subgroup analysis of TXA use compared with placebo in TKA on the proportion of patient requiring allogenic/autologous transfusion according to a transfusion protocol. A significant heterogeneity test ($p < 0.1$ or $I^2 > 50\%$) indicated that factor influenced directly or not directly the TXA benefic effect.

For total blood loss, analysis of subgroup did not find any influence of cell salvage blood use, method of blood loss measure and type of anesthesia. First, the efficacy of TXA versus placebo was similar with cell salvage blood use (MD -528 mls [-701; -355]) than without (MD -548 mls [-607; -489]) (heterogeneity test between subgroups was not statistically significant; $p = 0.83$; $I^2 = 0\%$). Second, the efficacy of TXA versus placebo was similar with measured method (MD -523 mls [-594; -451]) than estimated method (MD -577 mls [-675; -480]) (heterogeneity test between subgroups was not statistically significant; $p = 0.37$; $I^2 = 0\%$). Third, the efficacy of TXA versus placebo was similar with general anesthesia (MD -499 mls [-616; -382]) than regional anesthesia (MD -607 mls [-683; -530]) (heterogeneity test between subgroups was not statistically significant; $p = 0.13$; $I^2 = 56\%$). In regarding TXA regimen, the efficacy of TXA versus placebo was similar with single dose (MD -490 mls [-560; -419]), more than a single dose (MD -608 mls [-705; -511]) and continuous administration (MD -443 mls [-731; -155]). Heterogeneity test between these dose regimens was not statistically significant ($p = 0.13$; $I^2 = 51\%$). But in regarding only single and more than single TXA dose, the efficacy of TXA versus placebo seemed greater with multiple doses (MD -608 mls [-705; -511]) than single dose (MD -490 mls [-560; -419]) with a heterogeneity test between these dose regimens clearly statistically significant ($p = 0.05$; $I^2 = 73\%$). (Figure 9)

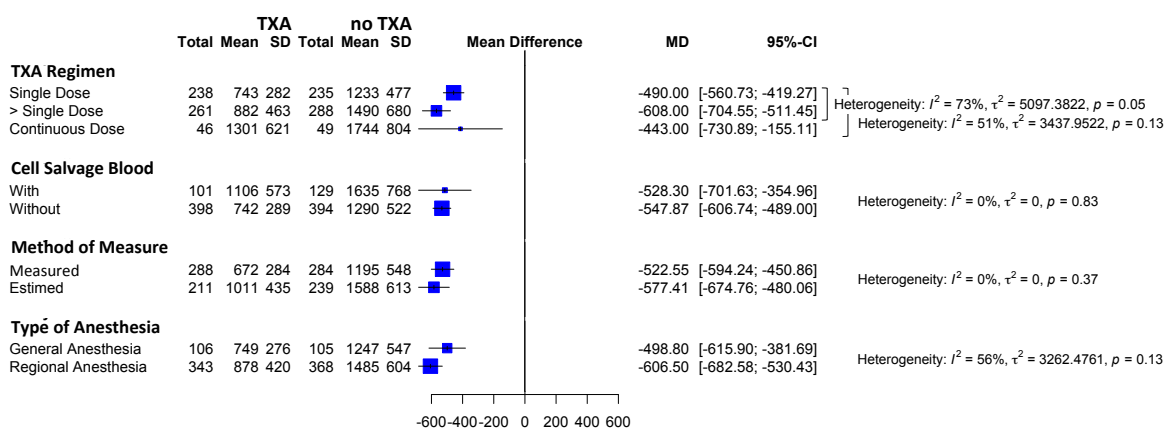


Fig. 9. Subgroup analysis of TXA use compared with placebo in TKA on the total volume of blood loss in milliliters of patient. A significant heterogeneity test ($p < 0.1$ or $I^2 > 50\%$) indicated that factor influenced directly or not directly the TXA benefic effect.

Adverse events

In all studies, no myocardial ischemia, no limb ischemia, no stroke, no acute kidney failure and no death were described. For venous thromboembolism events, this meta-analysis did not show a statistically significant increased risk of venous thromboembolism events for tranexamic acid (RR 1.00, 95% CI 0.54 to 1.85). Heterogeneity between these trials was not statistically significant ($\text{Chi}^2 = 7.80$, $\text{df} = 12$, $p = 0.85$; $I^2 = 0\%$). (Figure 10)

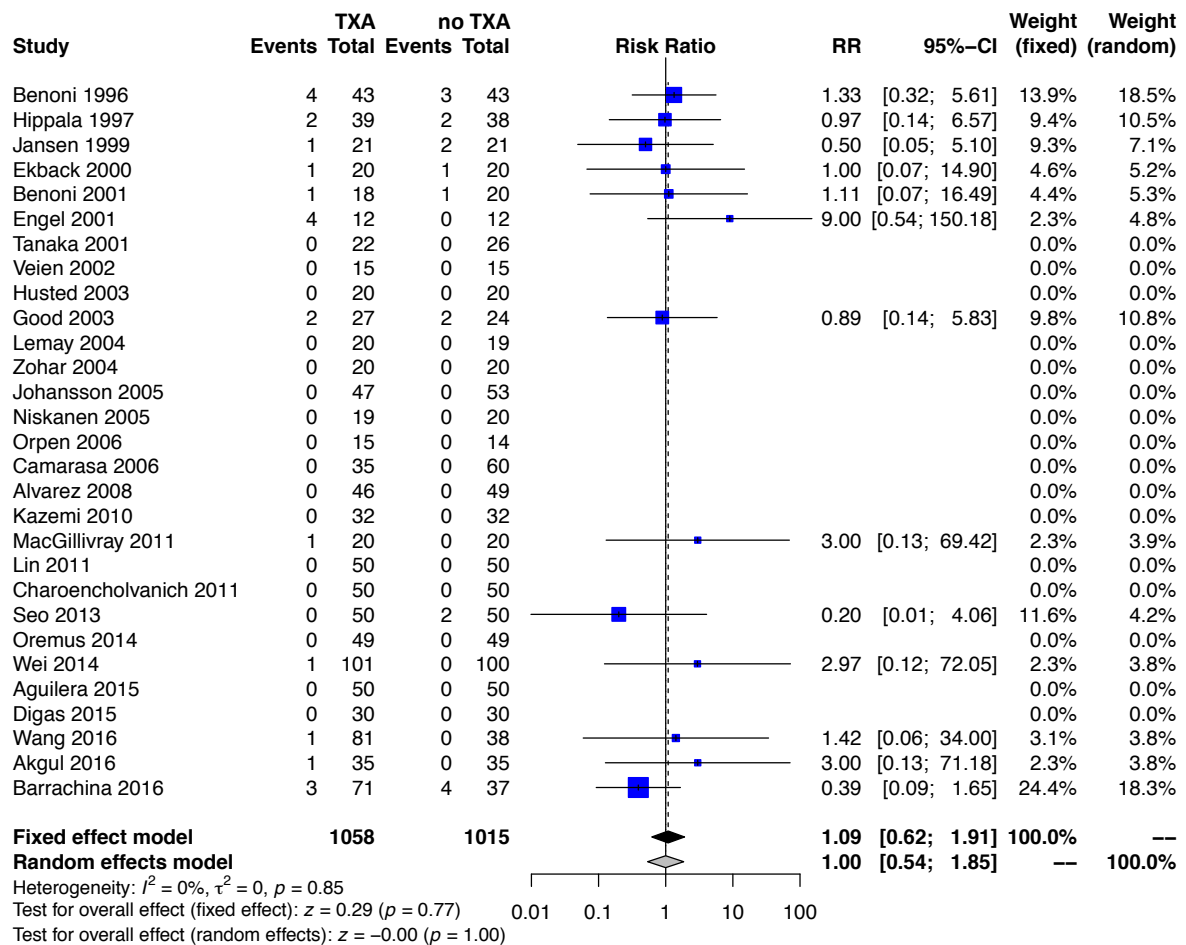


Fig. 10. Meta-analysis of use of tranexamic acid compared with placebo in THA and TKA on the proportion of patient with venous thromboembolism events. The relative ratio (RR) for individual studies is represented as a square within a bar representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The RR for summaries is represented as a diamond. The length of the diamond corresponds to the 95% CI. An RR > 1 indicated that the tranexamic acid is at risk compared with placebo. If the value of 1 is included within 95% CI, the result is not significant.

DISCUSSION

An hyperfibrinolytic phase leading to increase bleeding is observed during and immediately after major orthopedic surgery²³: we understand global interest for antifibrinolytic agents like acid tranexamic in limiting blood loss and transfusion in perioperative protocols.

There is no consensus for TXA doses to administer to surgical patients. Usely, dosing is based on patient' s weight (loading doses range from 2.5 to 100 mg/kg, maintenance doses range from 0.25 to 4 mg/kg/h⁹) as well as the type of surgery. Indeed in cardiac surgery, a loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/h produces plasma concentrations sufficient to inhibit fibrinolysis whereas larger dose does not provide any additional hemostatic benefit^{50,51}. In contrast, in CRASH-2 trial⁵², led in trauma patients, authors conclude to a loading dose of 1g over 10 min

then infusion of 1 g over 8 hours inhibiting fibrinolysis and so providing hemostatic benefit for larger patients (>100 kg) but also safe in smaller patients (<50 kg).

Our meta-analysis for total hip arthroplasty, including 830 randomized patients, highlight that patients receiving TXA have a significant 59% relative reduction in the rate of exposure to allogeneic blood transfusion and a significant 390 mls reduction in the total blood loss. These results are statistically homogeneous regardless year of publication, country, TXA regimen (loading doses range and maintenance doses range, single or multiple boluses or continuous infusion), preoperative hemoglobin, transfusion threshold and blood cell salvage device use. In contrast, our results for TKA remain heterogenic despite of significant 63% relative reduction rate of exposure to allogeneic blood transfusion and a significant 513 ml reduction in the total blood loss.

Some factors might explain variation in effect size of TXA treatment. On the one hand, higher variability of TXA administration regimen is found among included studies for TKA: TXA continuous administration seems more effective than single or multiple boluses but these results should be nuanced due to small patient number. On the other hand, postoperative fibrinolysis may vary in duration and intensity depending on type of surgery and if a tourniquet is applied. In TKA, Katsumata & Al⁵³ showed a rate of fibrinolysis factors significantly higher confirmed by other studies.^{54,55,56}

So, to explain the variation in the effect size of the treatment between THA and TKA in our study, we hypothesize that the tourniquet could participate (all TKA was performed using a tourniquet in studies included in meta analyses).

Regarding the safety, our review did not demonstrate a statistically significant increased risk of thromboembolic events with the use of TXA. Nevertheless, some precautions should be taken with these results: trials selected in our analysis were designed to assess efficacy and not to detect adverse events. Moreover, because of the relative scarcity of those events, large sample trials would be required to assess the safety.

In this worldwide era of enhanced recovery after surgery (ERAS), use of TXA takes part in perioperative blood management in patients undergoing total joint arthroplasty with an important clinical and economic impact⁵⁷. ERAS protocols are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining pre-operative organ function and reducing stress response following surgery. ERAS protocols are a melting pot of both surgical and anesthetic interventions. Key elements include preoperative counseling, optimization of nutrition, standardized analgesic/anesthetic regimens and early mobilization. ERAS leads to

superior outcomes, improved patient satisfaction, reduced length of hospital stay, and cost benefits, without affecting rates of readmission after surgery.^{58,59} Most surgeons generally focus on surgical techniques and disregard the perioperative management of patients while other items should be taken into account: optimized application of tourniquet,^{60,61,62} early removal of drain clamping⁶³ even more giving up using them.^{64,65}

There are several limitations in our study. First of all, about potential sources of bias in this review, most of the studies included in our review were small trials raising concerns about publication bias: funnel plot of TKA trials reveals possible evidence of a “missing” population with small negative trials. Secondly, about the literature search, we only screened MEDLINE database. Finally, evaluation of surgical time and impact on blood coagulation pathway is missing.

AUTHOR'S CONCLUSION

In conclusion, this analysis suggests that the use of TXA in total hip or knee arthroplasty significantly reduces the risk of allogeneic erythrocyte transfusion. Based on the results of randomized trials, its efficacy does not appear to be offset by serious events. In total hip arthroplasty, TXA reduces homogeneously RBC transfusion and total blood loss regardless of dose regimen. In total knee arthroplasty, TXA reduces significantly RBC transfusion and total blood loss with substantial heterogeneity. Thus, TXA clearly appears as an effective treatment, easily to implement and low-cost drug, able to reduce the transfusion rate and its complications. Larger prospective trials are now required to define the optimal regimen in total knee arthroplasty.

Implication for the practice

Tranexamic acid is effective for reducing perioperative blood loss and allogeneic transfusion rate in patients undergoing THA after one dose of 10 mg/kg administered before surgery.

Implication for the research

To understand changes in blood coagulation fibrinolysis due to pneumatic tourniquet during TKA, randomized clinical trial is needed to assess efficacy of TXA in reducing allogeneic transfusion in patients undergoing total knee arthroplasty with tourniquet versus patients undergoing total knee arthroplasty without tourniquet: results might be equivalent to hip arthroplasty in TKA without tourniquet. Furthermore, we find a trend for a better efficacy of TXA administrated continuously and larger randomized controlled trials have to confirm those results.

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SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

ABSTRACT**Does tranexamic acid reduce allogeneic blood transfusion rate in total hip or knee arthroplasty? a meta-analysis.****BACKGROUND:**

Perioperative blood management in major orthopedic surgery is relevant in front of higher morbidity and mortality linked to postoperative anemia and allogeneic blood transfusion. Whereas tranexamic acid (TXA) has been evaluated in several previous studies with positive results about efficacy, results present a real degree of heterogeneity reducing their clinical scope. Moreover, optimal protocol of administration remains unknown.

OBJECTIVES:

Assess efficacy, administration regimen and safety of TXA in patients undergoing total hip or knee arthroplasty.

SEARCH STRATEGY:

Electronic database PubMed (1950-July 2017) was systematically searched comparing intravenous tranexamic acid with placebo in THA and TKA.

SELECTION CRITERIA:

Only studies with a double-blind randomization, a control group and a presence of a transfusion protocol, were included.

DATA COLLECTION AND ANALYSIS:

Two authors independently assessed trial quality and extracted data. The primary outcome is the use of red blood cell (RBC) transfusion in perioperative time. The secondary outcomes are perioperative total blood loss evaluation and the incidence of deep venous thrombosis. Discontinuous and continuous outcomes are compiled as relative risk (RR) and weighted mean difference (MD) with 95% confidence intervals (CI), respectively. Statistical heterogeneity among trials is evaluated with Q-statistic (chi-square) and I-square tests.

RESULTS:

A total of 11 randomized controlled trials (RCTs) are included in THA meta-analysis and a total of 20 RCTs are included in TKA meta-analysis. In THA, comprising a total of 830 randomized patients, the meta-analysis demonstrates that TXA reduced significantly RBC transfusion [(RR 0.41, 95% CI 0.30 to 0.55), $\text{Chi}^2 = 6.70$, $\text{df} = 10$, $p = 0.7530$; $I^2 = 0\%$] and total blood loss [(MD -389.66 mls, 95% CI -499.18 to -280.14 mls), $\text{Chi}^2 = 14.05$, $\text{df} = 8$, $p = 0.0805$; $I^2 = 43\%$] regardless of TXA dose regimen, blood cell salvage use and preoperative hemoglobin. In TKA, comprising a total of 1221 randomized patients, the meta-analysis demonstrates that TXA significantly reduced RBC transfusion (RR 0.37, 95% CI 0.27 to 0.52) and total blood loss (MD -513.49 mls, 95% CI -609.25 to -417.73 mls) with a strong heterogeneity ($\text{Chi}^2 = 72.08$, $\text{df} = 19$, $p < 0.0001$; $I^2 = 74\%$ AND $\text{Chi}^2 = 65.35$, $\text{df} = 13$, $p < 0.0001$; $I^2 = 80\%$ respectively). This heterogeneity may be explained by the variability of TXA dose regimen, blood cell salvage use, preoperative hemoglobin and tourniquet use. TXA doesn't homogeneously and significantly increase venous thromboembolism events [(RR 1.00, 95% CI 0.54 to 1.85), $\text{Chi}^2 = 7.80$, $\text{df} = 12$, $p = 0.85$; $I^2 = 0\%$].

AUTHOR'S CONCLUSIONS:

In THA, tranexamic acid significantly reduces and homogeneously RBC transfusion and total blood loss regardless of TXA dose regimen. In TKA, tranexamic acid significantly reduces RBC transfusion and total blood loss with substantial heterogeneity probably explained by the variability of TXA dose regimen and most probably by specific fibrinolysis due to tourniquet use.