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PHARMACOKINETICS

Quantitative efficacy of topical administration of tranexamic acid on postoperative bleeding in total knee arthroplasty

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AIMS

Topical tranexamic acid (TXA) is used in patients undergoing total knee arthroplasty to reduce perioperative blood loss. However, the optimal dosing regimen remains undetermined. The aim of the present study was to quantitatively evaluate the effect of topical TXA on the reduction of postoperative drainage, and identify the dosing regimen factors affecting the efficacy of topical TXA.

METHODS

Model-based meta-analysis was used to evaluate the efficacy of topical TXA and the dosing regimen factors influencing clinical efficacy. Data from a systemic literature search was identified and used to build a time-effect model for placebo and TXA in treating perioperative blood loss.

RESULTS

Fourteen studies containing 16 TXA–control groups of drainage volume data were included for MBMA modelling. The model described the postoperative drainage-time profiles adequately. According to the model estimation, TXA can finally reduce the postoperative drainage by about 41.7%, and 10.9 h was needed to reach 50% of the maximal drainage volume. Covariate analysis indicated that both dose and contact time alone did not correlate well with clinical efficacy. However, when considered together, they can dramatically improve fitting of the data. Simulation showed that increasing dose or contact time extensively would produce a plateau-like effect: 2–3 g TXA with contact time of 1–2 h would yield >60% reduction in the drainage volume.

CONCLUSIONS

Dose and contact time together determined the efficacy of TXA. Extensively large dose or long contact time seems unnecessary. These findings may further guide the clinical practice on the topical TXA regimen optimization.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Topical tranexamic acid (TXA) can significantly reduce perioperative blood loss and decrease the need for blood transfusion in patients undergoing total knee arthroplasty.
- There has been debate on the optimal dosing regimen of topical TXA for preventing perioperative blood loss in total knee arthroplasty.

WHAT THIS STUDY ADDS

- Effect of topical TXA on postoperative bleeding was adequately evaluated by a model-based meta-analysis approach.
- The model revealed that both dose and contact time were critical for the efficacy of topical TXA and increasing either of them extensively would produce a plateau-like effect that is far from being desirable.

Introduction

Total knee arthroplasty (TKA) is one of the most effective treatment options for end stage knee disease, which is becoming more and more common with the aging global population. However, this procedure is frequently associated with a very high perioperative blood loss of >1 l, resulting in a prevalent need of blood transfusion, delayed rehabilitation and other serious complications including infections and pulmonary embolism [1].

Tranexamic acid (TXA) is an antifibrinolytic haemostatic that interacts directly with the lysine binding site of plasminogen, preventing the access of plasmin to fibrin, thereby limiting fibrin degradation [2]. Intravenous and intra-articular administration of TXA has been demonstrated as a cost-effective method to reduce total blood loss and transfusion requirements in TKA [3–5]. Although frequently used, intravenous TXA has the potential to increase the risk of thromboembolism, and thus limiting its clinical use [6]. By contrast, topical administration of TXA, remaining predominantly at the bleeding site with little systemic absorption, may be considered to have a better efficacy and safety profile than the intravenously dosed drug.

A variety of dosing regimens have recently been used for topical TXA, but the optimal one has yet to be determined. Although several meta-analyses have been performed on different regimens of topical TXA, suggesting that they are effective on reducing perioperative blood loss and blood transfusions [7, 8], there is still a lack of information as to which regimen is better. There are several limitations to these analyses. First, the efficacy data obtained at different time points were pooled. Second, only a small number (<10) of studies were included. In addition, blood loss reduction after topical TXA dosing usually has a large variability among different trials. The variability induced by different dosing regimens and trials cannot be separated by conventional meta-analysis and thus provides little help in identifying the optimal dosing regimens of topical TXA.

Model-based meta-analysis (MBMA), however, can be used to quantify not only the effects of treatment, but also the influence of different dosing regimens on the clinical responses [9, 10]. By integrating multilevel information of dosing regimens, pharmacokinetic data and efficacy results obtained from different trials, MBMA increases the ability to detect small but clinically significant effects, and thus could effectively evaluate the comparative efficacy of different regimens [11]. To date, no quantitative relationship using summary-level efficacy data across trials has been established between different topical TXA dosing regimens and clinical efficacy end points. Therefore, it is of value to explore this relationship based on literature data regarding TXA topical administration in order to adequately select dosing regimens in clinical practice.

The present study used the MBMA method to evaluate quantitatively the effect of topical TXA on the reduction of postoperative drainage, and identify the important influencing factors in the topical dosing regimen on the efficacy of TXA, which would provide useful information for further clinical practice on dosing regimen optimization.

Methods

Data extraction

A thorough literature search of published studies on intra-articular administration of TXA for haemostasis after TKA was performed using the online PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/), Cochrane database (http://www.cochranelibrary.com/) and the following keywords: tranexamic acid, intra-articular, topical, total knee arthroplasty and total knee replacement. Inclusion criteria were: (i) randomized, placebo-controlled clinical trial; (ii) dosing consists of a single intra-articular administration of TXA; (iii) drainage volume and recording time points available in tables and/or graphs; (iv) details of TXA dosing regimen and drug contact time provided in the report. Patient treatment information and arithmetic mean of the observed drainage volume were extracted from the published studies qualifying all the inclusion criteria.

Model development

It was hypothesized that bleeding rate after operation would decrease over time in both placebo and TXA group. Therefore, the relationship of drainage volume profiles with time for both treatment groups were described using sigmoid E_{max} models as the basic model described below:

$$Dr_{i,j} = Dr_{placebo,i,j}\text{-}E_{txa,i,j} + \varepsilon_{i,j}/sqrt(N_{i,j}) \quad (1)$$

where

$$Dr_{placebo,i,j} = \frac{(Dr_{max\text{-}placebo} \times e^{\eta_{1,i}}) \times T_j^{\gamma}}{ET_{50\text{-}placebo}^{\gamma} + T_j^{\gamma}} \quad (2)$$

$$E_{txa,i,j} = Dr_{placebo,i,j} \times E\%_{txa,i} \quad (3)$$

$$E\%_{txa,i} = \frac{E\%_{trans} \times e^{\eta_{2,i}}}{E\%_{trans} \times e^{\eta_{2,i}} + 1} \quad (4)$$

In equation (1), $Dr_{i,j}$ is the observed mean volume of the accumulated drainage in the ith TXA-control group at time j, $Dr_{placebo,i,j}$ (also called the fundamental drainage) represents the predicted mean volume of the accumulated drainage when placebo was used in the ith group at time j. $E_{txa,i,j}$ is the predicted mean effect of TXA in the ith group at time j expressed as decreased drainage volume. In the placebo group, $E_{txa,i,j}$ is equal to 0 and consequently $Dr_{i,j}$ is equal to $Dr_{placebo,i,j}$. $N_{i,j}$ is the sample size in the ith group at time j, and $\varepsilon_{i,j}$ is the residual error in the ith group at time j, assumed to be normally distributed with a mean of 0 and variance of $\sigma^2/N_{i,j}$. $\varepsilon_{i,j}$ is weighted by the sample size. In equations (2), (3) and (4), $Dr_{max\text{-}placebo}$ is the maximal volume of the accumulated drainage when placebo is used, $ET_{50\text{-}placebo}$ is the time to achieve 50% of $Dr_{max\text{-}placebo}$, γ is the hill coefficient. $E\%_{txa}$ represents the percentage reduction by TXA in the postoperative drainage compared with $Dr_{placebo,i,j}$, and it also represents the efficacy of TXA when eliminating the effects of other factors on the postoperative drainage in addition to TXA. In this way, the intertrial variability of the drainage volume in the control group was adjusted so the $E\%_{txa}$ value of different dosing regimens in each trial could be directly compared. Since $E\%_{txa}$ can only be between 0 and 1, we developed a transfer equation equation (4) with parameter $E\%_{trans}$ to control the range of $E\%_{txa}$. T_j is the time j, $\eta_{1,i}$ represents the intertrial variability of $Dr_{max\text{-}placebo}$ and $\eta_{2,i}$ is the intertrial variability of $E\%_{trans}$. $\eta_{1,i}$ and $\eta_{2,i}$ are assumed to be independent with each other and normally distributed with a mean of 0 and variance of ω_1^2 and ω_2^2.

Covariate selection

Effect of dose and contact time on $E\%_{txa}$ was firstly tested separately, considering that the aim of the current investigation is to look into the influence of both factors on clinical efficacy of TXA. Additionally, it might also be the case that for TXA to exert its pharmacological effect, a certain amount of drug needs to be applied for a long enough period of time, and therefore the effect of dose and contact time on $E\%_{txa}$ were tested as a combinational covariate as shown in equation (5).

$$E\%_{txa} = k \times \frac{Dose}{D_{50} + Dose} \times \frac{Con.T}{T_{50} + Con.T} \quad (5)$$

The parameters in equation (5) are as follows: $E\%_{txa}$ represents the efficacy of TXA in the form of percentage reduction; Dose represents the dose of TXA; Con.T represents the topical contact time with the drug. Under the cases where TXA was injected via the drainage tube, which was subsequently clamped, contact time equals clamping time. k represents the maximal effect coefficient of the $E\%_{txa}$ and was set to be 1; D_{50} and T_{50} are the dose and the contact time required to achieve 50% of the maximal dose-dependent and contact time-dependent effect, respectively. A difference in objective function value (OFV) of 6.63 (χ^2, α = 0.01, d.f. = 1) was considered statistically significant in the covariate model building process.

Model validation

The accuracy of the model fit was evaluated by graphic assessment. Monte Carlo simulations were performed 1000 times to predict 90% confidence intervals of the postoperative drainage in control and TXA group. Simulation-estimation exercise was conducted 100 times to validate the robustness of the present model.

Software

The model estimation and simulation were performed using NONMEM 7 (Level 3.0, ICON Development Solutions, USA). Diagnostic graphs and visual predictive check were performed using the R software (version 3.0.1, The R Foundation of Statistical Computing).

Results

Characteristics of the selected studies

Literature search identified 49 studies for consideration of inclusion in the analysis, and 35 were excluded based on our inclusion criteria. From the 14 studies included in the analysis, there were in total 63 mean drainage volume data from TXA group and 50 from placebo group. A total of 16 TXA-control groups were included for model building (Figure 1, Table 1).

The included studies all passed the Joanna Briggs critical appraisal checklist for observational studies and were published between 2011 and 2015 in some professional journals, such as *The Journal of Arthroplasty* and *Journal of Bone and Joint Surgery*. Taken together, the studies included in the analysis comprised a population of 1326 patients, with individual patient population of each study ranging from 40 to 157 (median: 86). Study duration ranged between 20 h and 48 h, with a median of 48 h. Details of the including studies are shown in Table 1.

Model building and validation

The OFV values of the three models tested are listed in Table 2. Based on these values and goodness-of-fit plots, the nonlinear mixed effects E_{max} model was selected as the basic model to go forward for covariate analysis.

Typical value of $E\%_{txa}$ estimated in the basic model was 41.7%. However, there was a lack of statistically significant correlation between the estimated $E\%_{txa}$ value and the dose of TXA or the contact time (Figure 2C). To explore whether pharmacological effect of TXA is dependent on a combination of both drug amount and application time, dose and contact time were introduced into the model simultaneously for covariate search. As shown in Table 2, the OFV value was

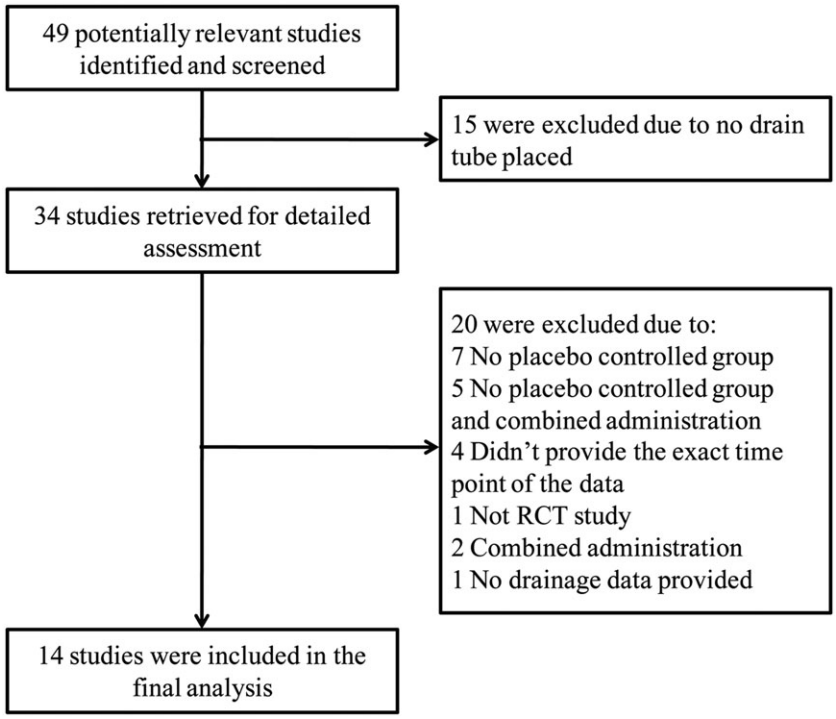

Figure 1

Flowchart for screening relevant articles

Table 1

Summary of included placebo-controlled trials of topical tranexamic acid (TXA)

Source	Number of subjects (TXA/control)	Dosing regimen [dose (g), contact time (h)]	Time points (h)	TXA-control group number
K. Ishida *et al.* [17]	50/50	2, 0.5	1,3,6,12,24,48	1
P. Sangasoongsong *et al.* [18]	45/45	0.5, 2	1,2,4,6,8,10,12,16,20,24,36,48	2
P. Sangasoongsong *et al.* [19]	24/24	0.25, 2	1,2,4,6,8,10,12,16,20,24,36,48	3
S. Roy *et al.* [20]	25/25	0.5, 1	2,4,6,48	4
P. Sangasoongsong *et al.* [18]	45/45	0.25, 2	1,2,4,6,8,10,12,16,20,24,36,48	5
R. Maniar *et al.* [13]	40/40	3, 0.083	24,48	6
G. Digas *et al.* [21]	30/30	2, 3	24	7
S. Alshryda *et al.* [22]	79/78	1, 0.5	48	8
H. Mutsuzaki *et al.* [23]	70/70	1, 1	48	9
X. Aguilera *et al.* [24]	50/50	1, 1	24	10
L. Zhaohui *et al.* [25]	43/47	0.75, 4	2,8,20	11
P. Antinolfi *et al.* [26]	20/20	0.5, 0.667	12,24,36,48	12
M. Sarzaeem *et al.* [14]	50/50	1.5, 1	48	13
M. Sarzaeem *et al.* [14]	50/50	3, 0.083	48	14
S. Lin *et al.* [27]	40/40	1, 1	24	15
W. Guowei *et al.* [28]	50/50	1,4	48	16

Table 2

Models evaluated and their objective function values. The final model is indicated by a bold italic font

Model	Attributes	OFV
E_{max} + linear mixed effects (lme) model	Interstudy/interarm variance + Additive error	1223.387
E_{max} + nonlinear mixed effects (nlme) model	Interstudy variance + Additive error	1113.138
E_{max} + nlme model (BASE MODEL)	Additive error	1114.638
Exponential + nlme model	Additive error	1167.391
Covariate model	*BASE MODEL + Dose + Contact time*	*1103.740*

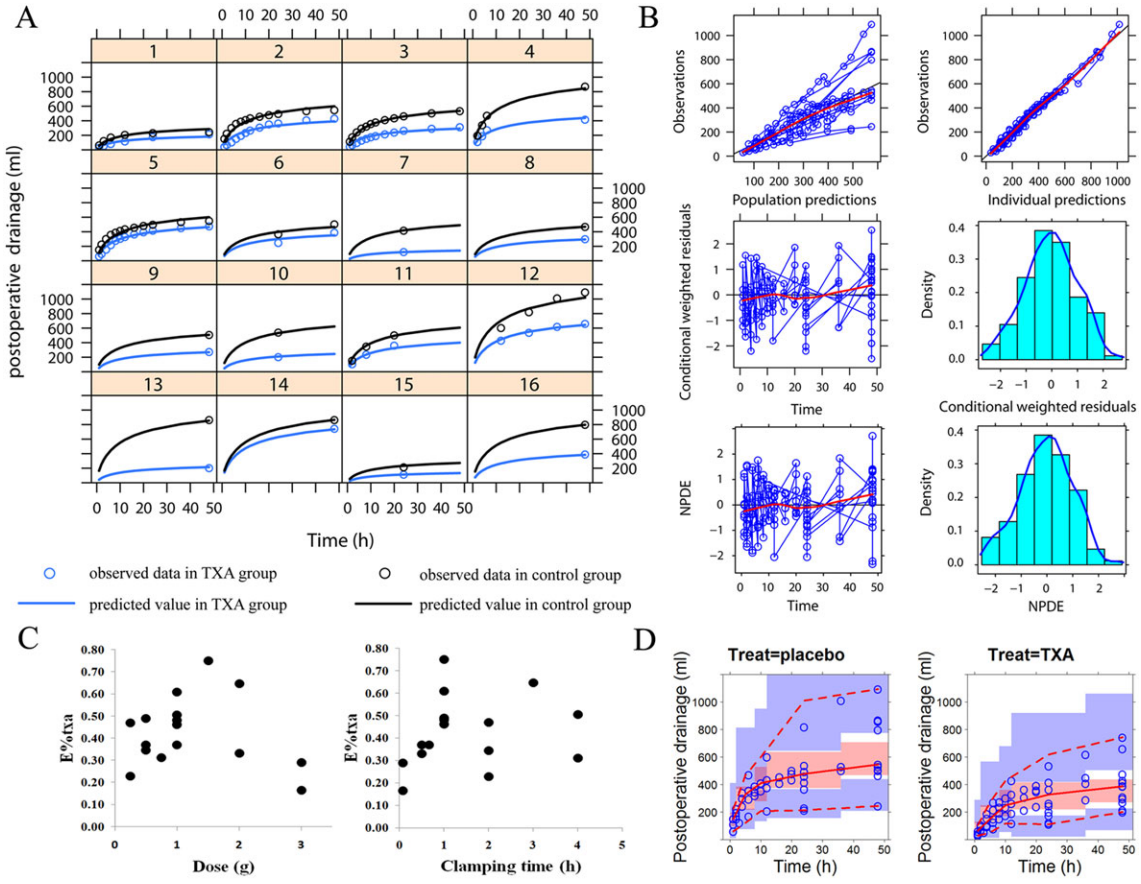

Figure 2

Model evaluation. (A) Time course of the postoperative drainage volume. The line represents the predicted value and the circle represents the observed value. The black represents the control group and the blue represents the tranexamic acid (TXA) group. (B) The goodness-of-fit plot. The upper left is the plot of population study prediction (PRED) *vs.* mean observation (DV). The upper right is the plot of individual study prediction (IPRED) *vs.* mean observation (DV). The middle left is the plot of conditional weighted residuals (CWRES) *vs.* time. The middle right is the plot of Density *vs.* CWRES. The lower left is the plot of normalized prediction distribution errors (NPDE) *vs.* time. The lower right is the plot of density *vs.* NPDE. (C) The correlation between the estimated $E\%_{txa}$ and dose of TXA (left) and the correlation between the estimated $E\%_{txa}$ and contact time (right). (D) Visual predictive check (VPC) of the model. The left is the VPC plot for control group and the right is the VPC plot for TXA group

significantly decreased after introducing this combinational covariate.

The parameters estimated in the final model are shown in Table 3. The typical value obtained for $Dr_{max\text{-}placebo}$ was 767 ml and 10.9 h were needed to reach 50% of $Dr_{max\text{-}placebo}$. Meanwhile, the typical value of D_{50} and T_{50} were 0.554 and 0.279 respectively. After the model establishment, we simulated the profiles of $E\%_{txa}$ changing with TXA dose and contact time, and compared with the estimated $E\%_{txa,i}$ value in the basic model (Figure 4A).

Table 3

Estimated parameters in the final model

Parameters	Value	RSE (%)	95% CI
$Dr_{max\text{-}placebo}$ (ml)	767	15.5	534, 1000
$ET_{50\text{-}placebo}$ (h)	10.9	35.2	3.37, 18.4
D_{50} (g)	0.554	24.9	0.284, 0.824
T_{50} (h)	0.279	33.8	0.094, 0.464
γ	0.742	10.4	0.591, 0.893
η_1	0.136	36.0	0.040, 0.232
η_2	0.250	35.0	0.078, 0.422
$\varepsilon \times 10^4$ (ml)	3.79	27.4	1.75, 5.83

CI, confidence interval; RSE, relative standard error

Model evaluation

As shown in Figure 2A, good agreement existed between predicted value of the final model and observed data from each individual trial. The large intertrial variability might have reflected the difference in operation procedures and operators. The goodness-of-fit plots shown in Figure 2B demonstrated that the data were fitted well by the final model. Specifically, there was good accordance between observed and population model-predicted effects, and between observed and individual model-predicted effects. The conditional weighted residuals and the normalized prediction distribution errors magnitude were small and randomly distributed around a straight line through 0, and located within ±3 from the centre.

Monte Carlo simulations (1000 times) showed that the 90% confidence interval of the 5%, median and 95% predicted percentiles covered the corresponding observed data, which indicated that the model had an adequate prediction capability (Figure 2D). The parameter estimations in simulation-estimation exercise for 100 times were all successfully convergent and the estimated parameter values were randomly distributed around the typical value in the final model with the ratio located within 0.5–2 as shown in Figure 3.

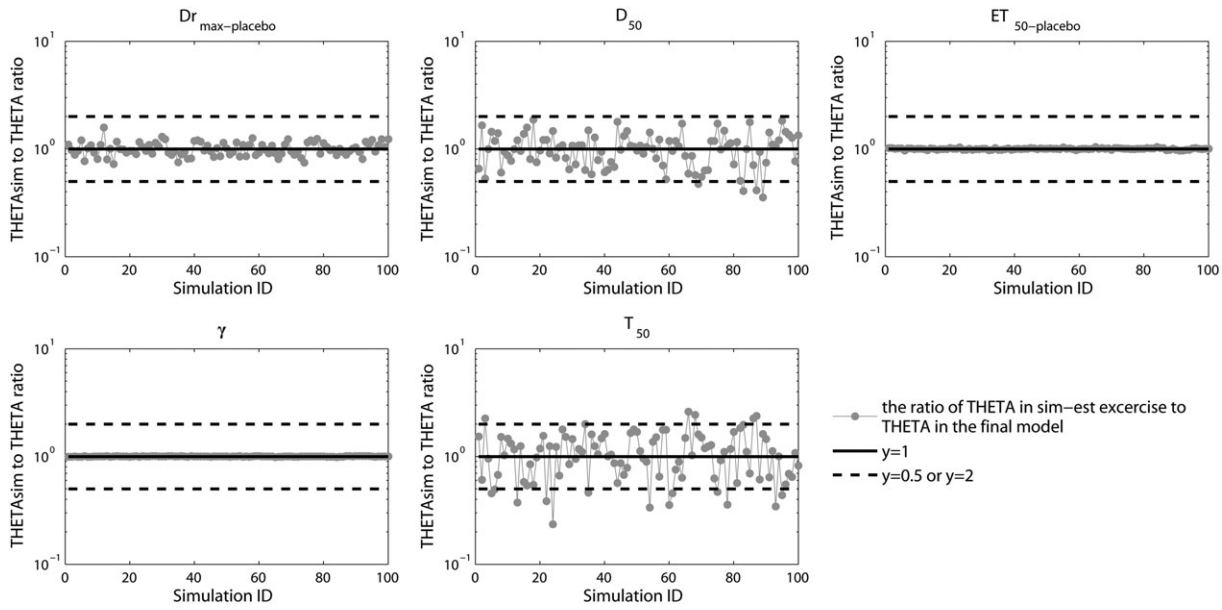

Figure 3

Ratio of the estimated parameter values in the simulation-estimation exercise to the typical parameter values in the final model. The simulation-estimation exercise was executed for 100 times. The control lines in the figure from top to bottom are for ratios of 2, 1 and 0.5 respectively

Influence of dose and contact time on the efficacy of TXA

As shown in Figure 2C, neither the dose nor the contact time alone significantly correlate with the efficacy of TXA ($E\%_{txa}$). However, the influence on the drug efficacy was prominent when both of contact time and dose are considered together. Influence of the dose and the contact time on $E\%_{txa}$ could be described by the simulated curved surface in Figure 4A. Increasing of dose or contact time could both increase the drug effect. However, the increase induced by each single variable is moderate, as drug effect plateaued rapidly with the increasing of a single variable. For example, a very short contact time such as 5 min can only yield an efficacy <20%, even though the TXA dose is as high as 3 g (Figure 4B). A combination of both dose and contact time, by contrast, could exert the maximum pharmacological effect. As shown in Figure 4B, 2–3 g TXA with 1–2 h contact time would lead to >60% reduction in the postoperative drainage volume compared to the placebo group. Further increasing the dose or extending the contact time seems unnecessary.

Discussion

For TKA patients, TXA could significantly reduce perioperative blood loss, therefore decreasing the need for blood transfusion, accelerate postoperative recovery, and reduce the average duration of hospital stay. Topical use of TXA was considered superior to intravenous administration because of the maximization of drug effect at the site of action and the minimization of systemic drug exposure-induced side effect. Recent meta-analyses have shown that various topical dosing regimens were effective. They reported a wide range of 0.25–3 g in a single dose and of 5 min to 12 h for the drug contact time [12–14]. However, the optimal regimen

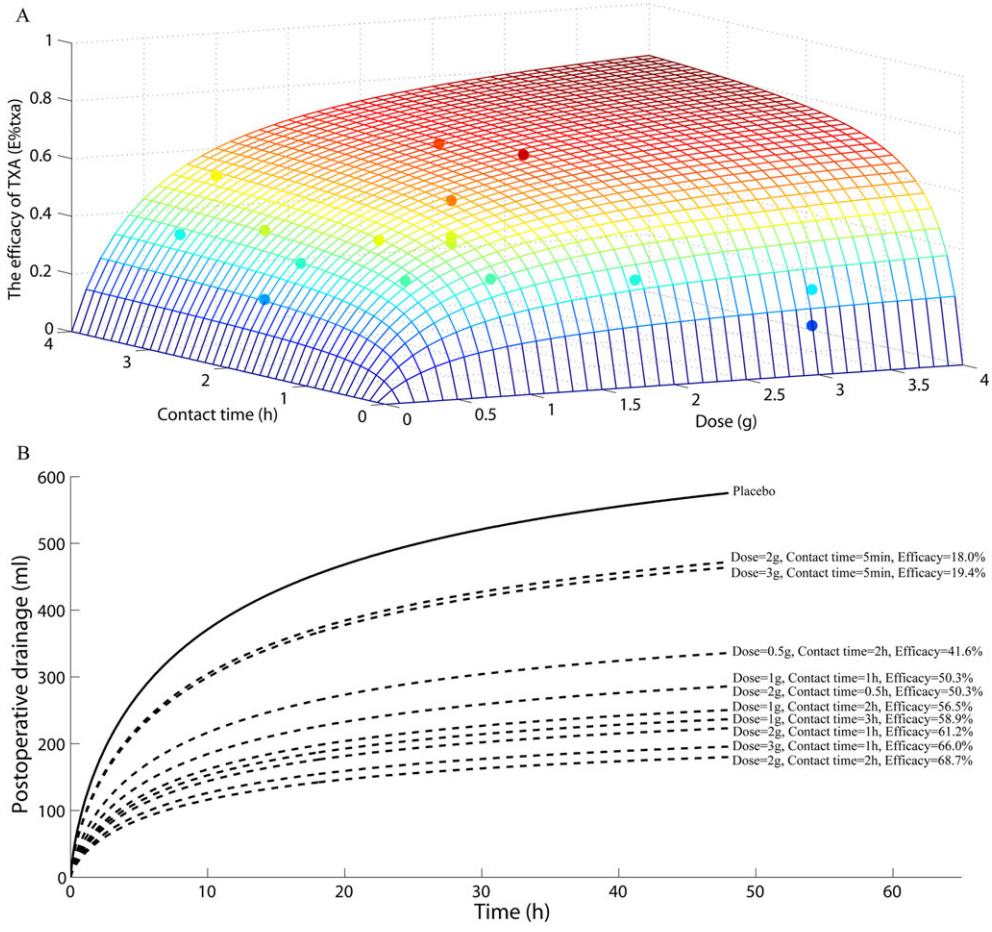

Figure 4

Influence of the dose and the contact time on the efficacy of tranexamic acid (TXA). (A) Simulation for the TXA efficacy profile changing with TXA dose and contact time. The simulation is according to the equation (5) in the final model and is shown as a wireframe surface with different colours. The surface was further compared with the estimated $E\%_{txa,i}$ value in the basic model which were shown as the points with different colours. The colour is determined by the value of *z* axis (i.e. the efficacy of TXA) and is proportional to it. The surface overlaps the point if there is a coincidence between point and surface with similar colour. (B) Simulation for the postoperative drainage-time profiles under a series of dosing regimens using the typical parameter value in the final model. The black line is for the placebo group and the black dotted line is for the TXA group. Different dosing regimens and the corresponding efficacy value were marked on the left

remains undetermined. The direction of the dosing regimen optimization is especially confusing.

The conventional meta-analysis is limited by pooling of data at different time points and large intertrial variability (shown in Figure 2A) in the drainage volume of the placebo group across studies. Thus, although helpful in establishing clinical efficacy of this treatment, it cannot quantitatively identify a better dosing regimen. MBMA, using a mathematical model to describe the details of the efficacy data, could overcome the above disadvantages of meta-analysis. In the present study using MBMA method, we successfully estimated the efficacy of TXA (i.e. $E\%_{txa}$), which could be directly compared between different trials with different dosing regimens, consequently, the better dosing regimen could be evaluated.

Both the dose and the contact time, when considered alone, did not correlate well with the efficacy of TXA. However, model fitting was significantly improved when dose and contact time are considered together as evidenced by a statistically significant drop in OFV. This implies that for TXA to exert its pharmacological effect, the drug need to be applied in enough quantity for a certain period of time. The extreme cases where high doses combined with short application time or low doses applied for extended period of time might be less optimal.

The influence of the dose and the contact time on the efficacy of TXA as simulated in Figure 4A showed a saturated effect. According to parameters estimated in the final model shown in Table 3, T_{50} is less than D_{50}, which means extending the contact time is more likely to induce the plateau effect than increasing the dose. Previous studies [15, 16] reported that a longer clamping time would cause intra-articular haematomas and increase the risk of postoperative infection. Considering the present results, a shorter contact time and a larger dose of TXA are recommended as the reasonable dosing regimen. According to the simulation results, we can predict that dosing 2–3 g TXA with 1–2 h contact time would yield >60% reduction in the drainage volume and further increasing the dose or contact time would increase the risk of adverse effect, which is far from being desirable.

Although a large intertrial variability was observed in the dataset included for analysis, the interstudy variance was not added into the final model because data fitting was not further improved by adding interstudy variance. This might have been due to the fact that the intertrial variability of the postoperative drainage volume (i.e. Dr) was already explained by the interstudy variance of parameter $Dr_{placebo}$ (i.e. η_1), which accounts for a large proportion of the total variability of Dr. The fundamental drainage (i.e. $Dr_{placebo}$) in each trial is determined by a combination of factors including different doctors/nurses, medical equipment and operation procedures. Since the focus of the model was the drainage reduction percentage as the efficacy of TXA, it is not only difficult but also unnecessary to characterize the variability of $Dr_{placebo}$ further using more covariate parameters.

In addition to the postoperative drainage, postoperative haemoglobin (Hb) level is also an important end point of the TXA effect. However, until now, only a few papers have provided the complete time cause of Hb level after the operation. Further clinical study is needed to investigate the effect of TXA on the Hb level. Further clinical studies could also add additional merit to the optimized dosing regimen provided in the present study, which is based on modelling and simulation methods.

The present study uses the MBMA method to quantify the effect of topical TXA on the postoperative drainage and to analyse the important dosing regimen factors that significantly influence the efficacy of TXA. These findings would further guide the clinical practice on the topical TXA regimen optimization.

Competing Interests

There are no competing interests to declare.

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