REVIEW ARTICLE

Tranexamic Acid Prophylaxis in Hip and Knee Joint Replacement

Matthias Goldstein, Carsten Feldmann, Hinnerk Wulf, Thomas Wiesmann

SUMMARY

Background: The antifibrinolytic agent tranexamic acid (TXA) is widely used for the prevention and treatment of hyperfibrinolytic states, such as in severe poly-trauma. It can also be used for the systemic prevention of hemorrhage in elective orthopedic procedures. In this review, we assess the efficacy and risks of the prophylactic administration of tranexamic acid before major endoprosthetic surgery of the hip and knee.

Methods: This review is based on pertinent articles retrieved by a selective literature search in the PubMed and Cochrane Library databases.

Results: Endoprosthetic surgery of the hip and knee is often associated with perioperative blood losses exceeding 500 mL. The prophylactic administration of tranexamic acid immediately before such procedures has been shown in randomized, controlled trials to lessen the quantity of intra- and postoperative bleeding and to reduce the likelihood of blood transfusion (number needed to treat [NNT] 3.7–5.7 for knee replacement and 4.1–8.2 for hip replacement). The rate of thromboembolic events did not differ significantly from the rate in the placebo groups. No reliable data are available on the frequency of epileptic seizures as a complication of TXA use in knee and hip endoprosthetic surgery. On the basis of data from other types of surgery, one may reasonably conclude that the doses of TXA used for knee and hip endoprosthetic procedures are unlikely to cause this problem.

Conclusion: The prophylactic intravenous administration of tranexamic acid lessens the amount of bleeding in endoprosthetic knee and hip procedures and reduces the likelihood of blood transfusion. According to the current state of the evidence, complications are rare. Nonetheless, consideration of the risks and benefits implies that tranexamic acid should not be given for this purpose to patients who have recently had urogenital bleeding, pulmonary embolism, or a myocardial infarction, who have recently undergone percutaneous transluminal coronary angioplasty or stenting, or who are known to have epilepsy.

► Cite this as:

Goldstein M, Feldmann C, Wulf H, Wiesmann T: Tranexamic acid prophylaxis in hip and knee joint replacement. *Dtsch Arztebl Int* 2017; 114: 824–30.
DOI: 10.3238/arztebl.2017.0824

Hip or knee replacement surgery are among the most common procedures in orthopedic and trauma surgery. As the surgical sites are well vascularized, the procedure can lead to substantial blood loss and a high incidence of blood transfusion. Indeed, 42% of patients undergoing total hip replacement, and 34% of patients undergoing total knee replacement, received at least one perioperative blood transfusion (1, 2).

Blood transfusions carry a variety of risks, including transfusion reactions and the transmission of infectious diseases, such as human immunodeficiency virus (HIV), hepatitis B/C, Zika, and potentially as-yet-unknown pathogens. Immune modulation and suppression effects have also been described (3–5).

In addition, retrospective studies have shown that blood transfusions result in longer hospital stay and higher mortality and morbidity (6). Allogeneic blood transfusions are considered to be an independent risk factor for a prosthesis infection (7, 8).

Various strategies are therefore used during clinical routine for patient blood management (9, 10) to reduce intraoperative and postoperative blood loss: improved techniques for surgical hemostasis, minimally invasive surgical procedures, autotransfusion, and heat preservation to optimize coagulation function. The long-used pharmacological therapies for treating apparent coagulation disorders, such as desmopressin for an unwanted drug-induced inhibition of platelet aggregation, or tranexamic acid (TXA) for an identified systemic hyperfibrinolysis, are increasingly being complemented with pharmacological prophylactic strategies.

The purpose of this review is to demonstrate the efficacy of TXA as a prophylactic for hip and knee replacement surgery, to describe the possible risks and complications of this pharmacological strategy, and finally, to highlight some economic aspects. We would like to point out that prophylactic administration of TXA prior to surgical intervention is only a partial aspect of the patient blood management in the perioperative period (9, 10).

Pharmacology

TXA belongs to the group of antifibrinolytics and has been the only substance of this group available in Germany since the suspension of aprotinin (decision of November 2007; Federal Institute for Drugs and Medical Devices [*Bundesinstitut für Arzneimittel und*

FIGURE

Effects of tranexamic acid, modified according to Mannucci (37)

a) Activation of fibrinolysis: tissue-type plasminogen activator (t-PA) and plasminogen bind to fibrin. This catalyzes the conversion of plasminogen into the fibrinolytic plasmin by a factor of 1000.

b) Inhibition of fibrinolysis: TXA inhibits fibrinolysis by blocking the binding site of plasminogen and fibrin.

Medizinprodukte, BfArM]) (11). TXA and the chemically related substance ϵ -aminocaproic acid (not available in Germany) belong to the group of ϵ -carboxylic acids. Both substances inhibit the binding of plasminogen to fibrin, thereby also inhibiting formation of an active serine protease plasmin and subsequent fibrinolysis (12). TXA is about a 10-fold stronger inhibitor of fibrinolysis than the related ϵ -aminocaproic acid. The conversion of inactive plasminogen into the fibrinolytically active plasmin by tissue-type plasminogen activator (t-PA) is catalyzed by the binding of t-PA–plasminogen to the lysine residues of fibrin (Figure). As a result, plasmin is formed locally within the blood clot. TXA binds reversibly to the lysine binding sites of plasminogen and thus blocks its conversion to plasmin; as a result, fibrin is not cleaved in the clot (13).

In vivo and *in vitro* experiments have shown that after intravenous bolus administration of TXA (30 mg/kg body weight [BW]), the maximum inhibition of plasmin in blood plasma is reached after about 30 minutes (14).

The substance can be administered enterally (with an oral bioavailability of approximately 33%), parenterally, or topically (14, 15).

Due to its molecular properties, TXA can cross the blood-brain barrier and promote cerebral seizures. It is believed that TXA causes hyperexcitability through an antagonistic action on γ -aminobutyric acid type A (GABA_A) receptors in the brain—the usual level of TXA in the cerebrospinal fluid is approximately one-tenth of its serum concentration (14, 16, 17). Due to the pleiotropic effects of plasmin and its pharmacological inhibition by TXA, further potential indications as well as possible complications could be discovered in the future. For example, TXA can have an anti-inflammatory effect in cardiac surgery (18) but can also worsen the healing of chronic wounds with long-term use (12, 19). TXA is almost not at all metabolized in the body but rather is completely excreted via the kidney. After bolus administration of 10 mg/kg BW, more than 90% of the substance quantity is excreted in the urine within 24 hours. As the elimination half-life of TXA is about 3 hours, accumulation effects are expected only in cases of renal insufficiency but not in those of hepatic insufficiency (13). The dose and dose interval should therefore be adjusted according to the manufacturer's instructions in the case of renal insufficiency (creatinine >1.35 mg/dL) (20) (Table 1).

The systemic antifibrinolytic effect of TXA can be assayed in the laboratory using reduction of D-dimers (fibrin cleavage products) or rotational elastometry (reduction of the clot lysis index) (21, 22).

TXA is approved in Germany for intravenous administration “for the prevention and treatment of bleeding due to local or systemic hyperfibrinolysis in adults and children over the age of 1 year” (20).

Methods

This work is based on a selective literature search from the PubMed database and the Cochrane Library. The keywords “tranexamic acid”, “antifibrinolytic” linked to “endoprosthetic surgery”, “knee arthroplasty”, “hip surgery”, and “hip arthroplasty” were used. From the resulting search hits, works were selected in which the systemic prophylactic use of TXA in endoprosthetics of the knee and the hip was examined in systematic reviews or meta-analyses. Additionally, the keywords

TABLE 1

Manufacturer's recommended dosage (20)

Serum creatinine		Tranexamic acid	
$\mu\text{mol/L}$	mg/dL	dose i.v.	administration
<119	to 1.35	15 mg/kg BW	every 8 hours
<249	to 2.82	10 mg/kg BW	every 12 hours
<499	to 5.65	10 mg/kg BW	every 24 hours
≥ 500	>5.65	5 mg/kg BW	every 24 hours

i.v., intravenous; BW, body weight

TABLE 2

Tranexamic acid in knee arthroplasty—selected meta-analyses

Study	Reduction of total bleeding volume (mL) [95% CI]	Reduction of intraoperative bleeding volume (mL)	Reduction of postoperative bleeding volume (mL) [95% CI]	NNT [95% CI]	Transfusion rate TXA group vs. control group (number of transfusions / total number of patients)	Number of studies for transfusions / patient number	Risk of bias*
Alshryda et al. 2011 (15)	-591 [-536; -647] ($I^2 = 89\%$)	n/a	-245 [-213; -278] ($I^2 = 78\%$)	4.2 [3.3; 5.8] ($I^2 = 75\%$)	23.5% (99/421) vs. 47.1% (190/403)	14/824	moderate
Tan et al. 2013 (38)	-570 [-663; -478] ($I^2 = 77\%$)	n/a	-290 [-385; -196] ($I^2 = 93\%$)	3.9 [3.2; 5.0] ($I^2 = 92\%$)	29.2% (149/511) vs. 55.0% (295/536)	17/1047	moderate to high
Wei & Liu 2015 (28)	-322 [-413; -230] ($I^2 = 95\%$)	n/a	n/a	5.7 [4.6; 7.5] ($I^2 = 69\%$)	14.1% (104/736) vs. 31.7% (212/668)	18/1404	moderate
Wu et al. 2015 (39)	n/a	n/a	n/a	3.7 [3.1; 4.5] ($I^2 = 42.3\%$)	26.5% (201/758) vs. 53.3% (396/743)	23/1501	moderate

All studies included in the meta-analyses are randomized controlled trials. Bleeding volumes are given (in mL) for comparison between TXA and controls (mean difference, 95% confidence interval).

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; I^2 values, given as an indicator of heterogeneity; n/a, data missing or not calculable; NNT, number needed to treat; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TXA, tranexamic acid

* The authors of this article first determined the bias risk for the individual studies in the meta-analyses using the GRADE system and the PRISMA statements (or the Cochrane risk of bias tool) and then averaged a mean value for every meta-analysis.

“complications“, “thromboembolism“, and “seizure” associated with surgery were searched for, to assess the frequency of typical side effects of TXA.

State of evidence for knee replacements

Knee replacement surgery is currently one of the most commonly performed orthopedic procedures. In 2011, 168 486 knee endoprostheses were implanted in Germany (23).

The average total blood loss (intraoperative and postoperative) in the absence of TXA administration is between 762 and 1789 mL for primary total knee endoprosthesis (TKE) implantation (15). Current data show that transfusion of red blood cell concentrates is necessary for about 25% of patients (with a median of 2.2 units) (24).

Since then, numerous studies have been published in which TXA was administered (mainly as an intravenous bolus shortly before surgery). A meta-analysis by Alshryda et al. analyzed 18 randomized controlled trials (15). They found that overall blood loss was reduced by 591 mL when TXA was administered (95% confidence interval [536; 647]). Further, the rate of intra- and postoperative blood transfusions in the included studies (14 studies, with 824 patients) demonstrated that the relative risk (2.56 [2.1, 3.1]) increased significantly when no TXA was administered. The transfusion rate in the control group was 47.1% (190/403) and in the prophylactic TXA study group, 23.5% (99/421). The absolute risk reduction for a necessary transfusion therapy was thus 23.6%, which corresponds to a number needed to treat (NNT) of 4.2 [3.3; 5.8]. It should be noted, however, that the studies used widely differing transfusion triggers (e.g., hemoglobin levels of 7–10 g/dL). Nevertheless, a reduced likelihood of transfusion was consistently detectable in the included studies.

The articles included in this meta-analysis examined the use of TXA in very different clinical procedures. Some of the studies used thigh tourniquet, while others did not. Likewise, the TXA doses (bolus dose, bolus dose plus continuous dose, multiple bolus dose) were not easily comparable, so that the effect of the drug has still been insufficiently assessed. Studies with and without chemical thrombosis prophylaxis were included. Table 2 shows an overview of selected meta-analyses.

State of evidence for hip replacement

Hip replacement is likewise one of the most common procedures in orthopedic surgery. In 2011, 232 320 hip endoprostheses were implanted in Germany (23).

The total blood loss in hip replacement surgery varies between 1200 and 2100 mL and is approximately 1600 mL on average (depending on the surgical technique) (10, 25). Approximately 30% of patients receive at least one blood unit (with a median of 2.2 units) (24).

In a meta-analysis of randomized controlled trials, Sukeik et al. investigated 11 studies with primary total

hip replacement surgery (26). The total blood loss in the TXA group was reduced by 289 mL [138; 440 mL]. The same effect was observed in the meta-analysis of Farrow and colleagues (27). The rate of intra- and post-operative blood transfusions was significantly lower in the included randomized controlled trials (of seven studies with 750 patients). The relative risk of blood transfusion was 1.9 [1.2; 2.9] for the control group as compared to the TXA group. TXA administration resulted in an absolute risk reduction of the transfusion rate of 12.2% (85/321 in the TXA group compared to 166/429 in the control group). This corresponds to a NNT of 8.2 [5.3; 18.4] (27). It should be noted that Sukeik et al. found a linear relationship between the TXA dose and the postoperative blood loss, but not between the dose and the intraoperative blood loss or the rate of transfusion (26).

As for knee replacement surgery, the state of evidence for the intravenous application of TXA is very heterogeneous. Very different dosages were used in the published work; for instance, the randomized controlled trial included in the meta-analysis by Farrow et al. investigated doses of 1–4 g/24 hours (27). Studies were included with and without chemical thrombosis prophylaxis. *Table 3* shows an overview of selected meta-analyses.

Complications

Based on its inhibition of fibrinolysis, using TXA is theoretically assumed to active coagulation with an increased tendency for thrombosis.

In the meta-analysis of Alshryda et al. for TXA use in knee arthroplasty, a total of five pulmonary embolisms occurred in 971 patients, with one in the TXA group and four in the control group; this difference was not significant. In the same meta-analysis, no difference was found for the outcome of leg vein thrombosis (15). A recent meta-analysis included 39 randomized controlled trials of TXA in hip and knee replacement procedures (28). In this study, thromboembolic events in the population with perioperative TXA administration also did not increase significantly. The CRASH-2 trial examined TXA administration (with an initial 1 g TXA followed by a continuous dose of 1 g/8 hour) that had been randomized and blinded for over 20 000 patients in severe trauma with hemorrhage in 40 countries, as compared to a placebo group that received no TXA. In addition to the primary endpoints of clinical effectiveness (such as mortality and transfusion rates), the complications were also recorded in detail in this study. The relative risk (RR) values were given as follows:

- Deep vein thrombosis: 0.98 [0.63; 1.51] (41/10 067 for control group, compared to 40/10 060 for TXA group)
- Pulmonary embolism: 1.01 [0.73; 1.41] (71/10 067 for control group, compared to 72/10 060 for TXA group)
- Stroke: 0.86 [0.61; 1.23] (66/10 067 for control group, compared to 57/10 060 for TXA group).

Myocardial infarction was rare in the TXA group, with a relative risk of 0.64 [0.42; 0.97] (55/10 067 for control group, compared to 35/10 060 for TXA group). However, only clear complications were recorded, so that minor thromboembolic events may not have been documented, and a so-called underreporting bias could be present (29).

In a retrospective study of patients with a history of venous thrombosis, Sabbag et al. investigated whether thrombosis occurred with TXA administration. They found no significant differences (RR for TXA: 1.24 [0.51; 3.00]; 2.3% [6/258], compared to RR for placebo: 1.9% [25/1337]) (30).

However, there is still a great need for research on the safe use of TXA in patients with a recent myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), or stent implantation. For these patients, TXA should be given perioperatively for endoprosthetic surgery only after individual risk assessment.

On the other hand, various studies on the use of TXA in coronary artery bypass surgery have shown that thromboembolic complications did not increase. Karski et al. showed no increased incidence of myocardial infarction (RR: 0.75 [0.13; 4.42]; 3/165 in control versus 2/147 in TXA group) (31).

Seizures after TXA administration are additional much-discussed complications. Good studies on seizures are missing for TXA in knee and hip arthroplasty. This important side effect of the drug has been observed especially in high dose applications, for example a bolus of 30 mg/kg BW plus a subsequent continuous dose over several days of 15 mg/hour per kg BW with severely impaired renal function. These high-dose applications are often chosen for procedures using the heart-lung bypass machine to inhibit fibrinolysis. Retrospective analyses from this particular group of patients show that the incidence of postoperative seizures is approximately 2.7% for moderate to high doses of TXA (32, 33). The incidence of seizures in the groups that did not receive antifibrinolytic agents was 0.5%. In a retrospective study published in 2017 by Counture et al., the incidence of seizures was 0.62% (46/7452) for patients who received 1 g TXA bolus intraoperatively and another 400 mg/hour TXA (34).

Nevertheless, it seems plausible that a one-time dose of TXA, as recommended by the manufacturer (*Table 1*), is generally considered to be relatively safe with respect to this complication (14, 16, 32).

In patients with known epilepsy, however, intravenous administration of TXA should be considered with great caution in terms of benefits and risks.

Discussion

The meta-analyses of the use of TXA in total hip and knee replacement have a high degree of heterogeneity in some cases (I^2 values) (*Table 2* and *Table 3*). Further, a publication bias in the meta-analyses cannot be ruled out. The meta-analyses also summarized studies with different dosages and clinical procedures.

TABLE 3

Tranexamic acid in hip arthroplasty—selected meta-analyses

Study	Reduction of total bleeding volume (mL) [95% CI]	Reduction of intraoperative bleeding volume (mL) [95% CI]	Reduction of postoperative bleeding volume (mL) [95% CI]	NNT [95% CI]	Transfusion rate TXA group vs. control group (number of transfusions/total patient number)	Number of studies for transfusions / patient number	Risk of bias*
Sukeik et al. 2011 (26)	-289 [-440; -138] ($I^2 = 54\%$)	-104 [-44; -164] ($I^2 = 0\%$)	-172 [-263; -81] ($I^2 = 63\%$)	5 [3.4; 9.1] ($I^2 = 15\%$)	n/a	7/346	low
Farrow et al. 2016 (27)	n/a	-190 [-495; -115] ($I^2 = 91\%$)	-341 [-672; -9.87] ($I^2 = 100\%$)	8.2 [5.3; 18.4] ($I^2 = 78\%$)	26.5% (85/321) vs. 38.7% (166/429)	7/750	moderate to high
Zhou et al. 2013 (40)	-305 [-398; -213] ($I^2 = 32\%$)	-86 [-152; -20] ($I^2 = 67\%$)	-177 [-237; -116] ($I^2 = 60\%$)	7.8 [5.8; 12.2] ($I^2 = 11\%$)	10.9% (55/507) vs. 23.6% (128/543)	21/1050	moderate
Huang et al. 2015 (e1)	-369 [-482; -259] ($I^2 = 73\%$)	n/a	n/a	4.1 [3.3; 5.4] ($I^2 = 18\%$)	16% (65/405) vs. 40.6% (167/411)	14/816	moderate
Moskal et al. 2016 (e2)	total bleeding volume: 1089 (± 1251) vs. 1410 (± 111) ($P < 0.001$)	total bleeding volume: 668 (± 1169) vs. 793 (± 1805) ($P = 0.002$)	total bleeding volume: 449 (± 620) vs. 597 (± 1012) ($P = 0.003$)	4.5 [3.5; 6.4]	16.6% (55/332) vs. 38.6% (131/339)	10/671	moderate

All studies included in the meta-analyses are randomized controlled trials. Bleeding volumes are given (in mL) for comparison between TXA and controls (mean difference, 95% confidence interval). CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; I^2 values, given as an indicator of heterogeneity; n/a, data missing or not calculable; NNT, number needed to treat; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation; TXA, tranexamic acid

*The authors of this article first determined the bias risk for the individual studies in the meta-analyses using the GRADE system and the PRISMA statements (or the Cochrane risk of bias tool) and then averaged a mean value for every meta-analysis.

The patient blood management concept was inconsistent in the primary studies. Nevertheless, the blood-sparing effects of TXA are consistently observed in all primary studies.

The meta-analyses from *Table 2* and *Table 3* show similar results, partly due to the use of similar primary studies. *eTable 1* and *eTable 2* provide a detailed overview of the overlaps of the individual meta-analysis.

Using TXA as prophylaxis for bleeding in large joint arthroplasty (hip, knee) seems to be effective. Pre-operative TXA administration reduces intra- and post-operative bleeding as well as the amount of transfusions necessary. The current state of knowledge suggests that the thromboembolic risk does not increase with low-dose, short-term administration for these indications within normal clinical use of postoperative prophylaxis for drug thrombosis. The risk of seizures does not seem to increase significantly, although there is still insufficient data for this.

Topical application of TXA results in lower plasma levels and therefore may have a reduced risk of complications, according to theoretical considerations.

Alshryda et al. recently published a meta-analysis on topical application of TXA in total hip and knee replacement (35). They observed a marked reduction in both blood loss during knee replacement surgery and the need for transfusions (RR: 4.5 [3.0; 6.7]) as compared to placebo. Overall, only a few studies involving the systemic administration of TXA as a further comparison group could be evaluated, which have revealed no relevant differences in the transfusion rate between the two forms of application.

Economic aspects of the prophylactic administration of TXA

Blood is a scarce, valuable resource in medicine. In Germany, about 4 million units of blood per year are transfused. In addition to the risks already described, transfusion of red blood cells is also a relevant cost factor. The direct production costs of packed red blood cells are approximately 140 to 230 Euro per concentrate (10, 36). Comparing this with the cost of two applications of 1 g TXA (5 euros for 500 mg—about 20 euros for 2 g) for a 70 kg patient with normal kidney function, and using a NNT of 3.7–8.2, to avoid a necessary transfusion reveals a possible savings potential. The above-mentioned complications and risks of blood transfusions, and especially that of postoperative prosthetic joint infection, can lead to significantly prolonged hospital stays and considerable costs (6–8).

Conclusion

From our point of view, the prophylactic use of systemic TXA for knee and hip arthroplasty can be used as an effective and relatively safe concept in practice. Contraindications and risks, embedded in a more extensive patient blood management concept, must be considered. This could result in significant reductions of intra- and postoperative blood loss as well as consecutive allogenic blood transfusions. However,

whether a prophylactic strategy should be applied to all patients who undergo elective large joint arthroplasty, or whether stratified concepts should be favored in the future that consider underlying disease, baseline hemoglobin values, and local transfusion probabilities, needs to be clarified in further studies. Initial results from a retrospective study suggest that TXA administration may not be an absolute contraindication in patients with leg vein thrombosis. None-the-less, the prophylactic use of TXA for patients with knee and hip arthroplasty and urogenital bleeding, pulmonary embolism, recent heart attack, PTCA, or stent implantation, as well as known epilepsy, should be avoided according to the risk-benefit assessment.

Conflict of interest statement

PD Dr. Wiesmann has received consultant honoraria from B. Braun Melsungen (Germany).

Prof. Wulf has received consultant honoraria from B. Braun and Sintetica, speaking honoraria from MSD, Grünenthal, and Edwards, and study support (third-party funds) von Teleflex.

The remaining authors declare that no conflict of interest exists.

Manuscript received on 22 February 2017, revised version accepted on 13 September 2017.

Translated from the original German by Veronica A. Raker, PhD.

REFERENCES

- Mohib Y, Rashid RH, Ali M, Zubairi AJ, Umer M: Does tranexamic acid reduce blood transfusion following surgery for intertrochanteric fracture? A randomized control trial. *J Pak Med Assoc* 2015; 65: 17–20.
- Camarasa MA, Ollé G, Serra-Prat M, et al.: Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. *Br J Anaesth* 2006; 96: 576–82.
- Triulzi DJ, Vanek K, Ryan DH, et al.: A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion* 1992; 32: 517–24.
- Lannan KL, Sahler J, Spinelli SL, et al.: Transfusion immunomodulation: the case for leukoreduced and (perhaps) washed transfusions. *Blood Cells Mol Dis* 2013; 50: 61–8.
- Blumberg N, Heal JM: Immunomodulation by blood transfusion: an evolving scientific and clinical challenge. *Am J Med* 1996; 101: 299–308.
- Elsamadicy AA, Adogwa O, Vuong VD, et al.: Association of intraoperative blood transfusions on postoperative complications, 30-day readmission rates, and 1-year patient-reported outcomes. *Spine* 2017; 42: 610–15.
- Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J: Periprosthetic joint infection: the incidence, timing, and predisposing factors. *Clin Orthop Relat Res* 2008; 466: 1710–15.
- Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W: Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. *Transfusion* 2005; 45: 103–10.
- Meybohm P, Fischer D, Schnitzbauer A, et al.: Patient blood management. *Chirurg* 2015; 87: 40–6.
- Shander A, van Aken H, Colomina MJ, et al.: Patient blood management in Europe. *Br J Anaesth* 2012; 109: 55–68.
- Bundesinstitut für Arzneimittel und Medizinprodukte: Trasylol® (Aprotinin): Umsetzung der Kommissionsentscheidung zum Ruhen der Zulassung. www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RI/2008/RI-aprotinin.html (last accessed on 22 June 2017).

KEY MESSAGES

- Endoprosthetic surgery of the knee and hip cause relevant bleeding and often require transfusions, which can lead to further complications (including transmission of infections, increased prosthetic infections, and higher mortality and morbidity).
- The prophylactic administration of tranexamic acid is a useful part of the blood-saving perioperative patient blood management concept in the field of elective hip and knee arthroplasty.
- Whether it is safe to use tranexamic acid after myocardial infarction, percutaneous transluminal coronary angioplasty, or stent implantation still needs considerable research. In these cases, therefore, the risks and benefits must be weighed individually.
- The rate of thromboembolic complications is not higher as compared to control groups in randomized controlled trials.

- Draxler DF, Medcalf RL: The fibrinolytic system—more than fibrinolysis? *Transfus Med Rev* 2015; 29: 102–9.
- Müller-Berghaus G, Pötsch B: *Hämostaseologie*. Berlin, Heidelberg: Springer-Verlag 2013; 1.
- McCormack PL: Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs* 2012; 72: 585–617.
- Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM: Tranexamic acid in total knee replacement: a systematic review and meta-analysis. *J Bone Joint Surg Br* 2011; 93: 1577–85.
- Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA: Tranexamic acid-associated seizures: causes and treatment. *Ann Neurol* 2016; 79: 18–26.
- Koscielny J, Jambor C: Perioperativer Einsatz von Antifibrinolytika. *Vascular Care* 2008; 15: 32–51.
- Later AFL, Sitniakowsky LS, van Hilten JA, et al.: Antifibrinolytics attenuate inflammatory gene expression after cardiac surgery. *J Thorac Cardiovasc Surg* 2013; 145: 1611–6.
- Shen Y, Guo Y, Mikus P, et al.: Plasminogen is a key proinflammatory regulator that accelerates the healing of acute and diabetic wounds. *Blood* 2012; 119: 5879–87.
- PFIZER PHARMA PFE GmbH: Fachinformation „Cyclocapron®“. Fa. Pfizer. www.pfizermed.de/fileadmin/produkt Datenbank/pdf/008797_freigabe.pdf (last accessed on 21 February 2016).
- Levrat A, Gros A, Rugeri L, et al.: Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth* 2008; 100: 792–7.
- Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE: Tranexamic acid in trauma: how should we use it? *Trauma Acute Care Surg* 2013; 74: 1575–87.
- Wengler A, Nimptsch U, Mansky T: Hip and knee replacement in Germany and the USA—analysis of individual inpatient data from German and US hospitals for the years 2005 to 2011. *Dtsch Arztebl Int* 2014; 111: 407–16.
- Gombotz H, Rehak PH, Shander A, Hofmann A: The second Austrian benchmark study for blood use in elective surgery: results and practice change. *Transfusion* 2014; 54: 2646–57.
- Yamasaki S, Masuhara K, Fuji T: Tranexamic acid reduces postoperative blood loss in cementless total hip arthroplasty. *J Bone Joint Surg Am* 2005; 87: 766–70.

26. Sukeik M, Alshryda S, Haddad FS, Mason JM: Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg Br* 2011; 93: 39–46.
27. Farrow LS, Smith TO, Ashcroft GP, Myint PK: A systematic review of tranexamic acid in hip fracture surgery. *Br J Clin Pharmacol* 2016; 82: 1458–70.
28. Wei Z, Liu M: The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. *Transfus Med* 2015; 25: 151–62.
29. CRASH-2 trial collaborators, Shakur H, Roberts I, et al.: 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* 2010; 376: 23–32.
30. Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW: Tranexamic acid was safe in arthroplasty patients with a history of venous thromboembolism: a matched outcome study. *J Arthroplasty* 2017; 32: 246–250.
31. Karski J, Djaiani G, Carroll J, et al.: Tranexamic acid and early saphenous vein graft patency in conventional coronary artery bypass graft surgery: a prospective randomized controlled clinical trial. *J Thorac Cardiovasc Surg* 2005; 130: 309–14.
32. Lin Z, Xiaoyi Z: Tranexamic acid-associated seizures: A meta-analysis. *Seizure* 2016; 36: 70–3.
33. Keyl C, Uhl R, Beyersdorf F, et al.: High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement. *Eur J Cardiothorac Surg* 2011; 39: e114–21.
34. Counture P, Lebon JS, Laliberté É, et al.: Low dose versus high dose tranexamic acid reduces the risk of non-ischemic seizures after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2017; in press.
35. Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM: A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. *Bone Joint J* 2014; 96-B: 1005–15.
36. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR: Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010; 50: 753–65.
37. Mannucci PM: Hemostatic drugs. *N Engl J Med* 1998; 339: 245–53.
38. Tan J, Chen H, Liu Q, Chen C, Huang W: A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. *J Surg Res* 2013; 184: 880–87.
39. Wu Q, Zhang H, Liu S, Meng T, Zhou X, Wang P: Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol* 2015; 25: 525–41.
40. Zhou X, Tao L, Li J, Wu L: Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch Orthop Trauma Surg* 2013; 133: 1017–27.

Corresponding author

Matthias Goldstein
Klinik f. Anästhesie und Intensivtherapie
Universitätsklinikum Gießen und Marburg (UKGM)
Campus Marburg
Baldingerstr.,
35033 Marburg, Germany
matthias.goldstein@staff.uni-marburg.de

Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref4817

eTables:

www.aerzteblatt-international.de/17m0824

Supplementary material to:

Tranexamic Acid Prophylaxis in Hip and Knee Joint Replacement

by Matthias Goldstein, Carsten Feldmann, Hinnerk Wulf, and Thomas Wiesmann

Dtsch Arztebl Int 2017; 114: 824–30. DOI: 10.3238/arztebl.2017.0824

eREFERENCES

- e1. Huang F, Wu Y, Yin Z, Ma G, Chang J: A systematic review and meta-analysis of the use of antifibrinolytic agents in total hip arthroplasty. Hip Int 2015; 25: 502–9.
- e2. Moskal JT, Capps SG: Meta-analysis of intravenous tranexamic acid in primary total hip arthroplasty. Orthopedics 2016; 39: 883–92.

eTABLE 1

Overlap of primary studies in meta-analyses on the use of tranexamic acid in knee arthroplasty

Alshryda et al. 2011 (15)	Tan et al. 2013 (38)	Wei & Liu 2015 (28)	Wu et al. 2015 (39)
Primary studies that were used in 4 meta-analyses:			
Good 2003	Good 2003	Good 2003	Good 2003
Ellis 2001	Ellis 2001	Ellis 2001	Ellis 2001
Camarasa 2006	Camarasa 2006	Camarasa 2006	Camarasa 2006
Alvarez 2008	Alvarez 2008	Alvarez 2008	Alvarez 2008
Tanaka 2001	Tanaka 2001	Tanaka 2001	Tanaka 2001
Kakar 2009	Kakar 2009	Kakar 2009	Kakar 2009
Orpen 2005	Orpen 2005	Orpen 2005	Orpen 2005
Veien 2002	Veien 2002	Veien 2002	Veien 2002
Zohar 2004	Zohar 2004	Zohar 2004	Zohar 2004
Primary studies that were used in 3 meta-analyses:			
Benoni 1996	Benoni 1996		Benoni 1996
Jansen 1999	Jansen 1999		Jansen 1999
Hiippala 1995	Hiippala 1995		Hiippala 1995
Hiippala 1997	Hiippala 1997		Hiippala 1997
Ido 2000	Ido 2000	Ido 2000	
Engel 2001	Engel 2001		Engel 2001
Zhang 2007	Zhang 2007		Zhang 2007
Molloy 2007		Molloy 2007	Molloy 2007
	Cchareancholvanich 2011	Cchareancholvanich 2011	Cchareancholvanich 2011
Primary studies in which 2 meta-analyses were used:			
Wong 2010		Wong 2010	
		Martin 2014	Martin 2014
	Maniar 2012		Maniar 2012
		Georgiadis 2013	Georgiadis 2013
		McConnell 2012	McConnell 2012
		Ishida 2011	Ishida 2011
		Roy 2012	Roy 2012
Primary studies that were used in 1 meta-analyses:			
Zohar 1999	Lin 2011	Oremus 2014	Pachauri 2013
		Gautam 2013	Aguilera 2013
		Raviraj 2012	Seo 2013
		Yamasak 2005	Lee 2013
		MacGillivray 2011	Alshryda 2013
		Konig 2013	Kim 2014
		Dahuja 2013	Onodera 2012
		Alipour 2013	Gautam 2011
			Wong 2010
			Abrishami 2010

eTABLE 2

Overlap of primary studies in meta-analyses on the use of tranexamic acid in hip arthroplasty

Sukeik et al. 2011 (26)	Farrow et al. 2016 (27)	Zhou et al. 2013 (40)	Huang et al. 2015 (e1)	Moskal et al. 2016(e2)
Primary studies that were used in 4 meta-analyses:				
Johansson 2005		Johansson 2005	Johansson 2005	Johansson 2005
Benoni 2001		Benoni 2001	Benoni 2001	Benoni 2001
Ekbäck 2000		Ekbäck 2000	Ekbäck 2000	Ekbäck 2000
Garneti 2004		Garneti 2004	Garneti 2004	Garneti 2004
Niskanen 2005		Niskanen 2005	Niskanen 2005	Niskanen 2005
Claeys 2007		Claeys 2007	Claeys 2007	Claeys 2007
Benoni 2000		Benoni 2000	Benoni 2000	Benoni 2000
Primary studies that were used in 3 meta-analyses:				
Yamasaki 2004			Yamasaki 2004	Yamasaki 2004
Husted 2003		Husted 2003		Husted 2003
Lemay 2004		Lemay 2004		Lemay 2004
		Kazemi 2010	Kazemi 2010	Kazemi 2010
Primary studies that were used in 2 meta-analyses:				
		Rajesparan 2009	Rajesparan 2009	
		Yamasaki 2004		Yamasaki 2004
		Malhotra 2011	Malhotra 2011	
Ido 2000		Ido 2000		
			McConnell 2011	McConnell 2011
Primary studies that were used in 1 meta-analysis:				
	Lee 2015	Singh 2010	Yue 2014	Hsu 2015
	Sadeghi 2007	Jamie 2011	Oremus 2014	Wei 2014
	Zuffery 2010	Norio 2012		Imai 2012
	Emara 2014	Clave 2012		
	Mohib 2015	Fu 2012		
	Vijay 2013			
	Tengberg 2016			