

Efficacy and Safety of Tranexamic Acid in Cancer Surgery. An Update of Clinical Findings and Ongoing Research

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Abstract: In cancer patients undergoing surgery, tumor biology and anticancer treatments can increase the risk of perioperative bleeding and blood transfusions. Notably, blood transfusions can be potentially associated with an increased risk of life-threatening immune responses, acute lung injury, postoperative infections, and thromboembolism. Moreover, the link between perioperative transfusion and increased risk of cancer recurrence cannot be excluded. On the other hand, cancer patients have an increased risk of thromboembolism due to cancer itself and antineoplastic systemic treatments including chemotherapy and anti-angiogenic drugs. In this complex scenario, effective and safe strategies aimed at the prevention of blood transfusions are warranted. This narrative review addresses the efficacy, and the safety of the synthetic antifibrinolytic agent tranexamic acid (TXA) when used perioperatively in cancer surgery. Although in not oncologic surgery the use of TXA has been extensively studied, in the setting of cancer patients requiring surgery, the evidence is scarce. An overview of the ongoing clinical research is also provided.

Keywords: tranexamic acid, cancer surgery, oncology, anemia, blood transfusion, anti-fibrinolytic

Introduction

In cancer patients, tumor biology features such as tumor angiogenesis, and local tumor invasion, and anticancer treatments included chemotherapy or radiotherapy can increase the risk of perioperative bleeding. In this population, this risk further increases due to the chronic use of medications such as antiangiogenic agents (eg, bevacizumab), nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulants and antiplatelet drugs.¹ Moreover, during surgery, the extension of the resection area and its vascularization, as well as perioperative conditions such as hemodilution, hypothermia, and metabolic alterations are recognized risk factors for bleeding and coagulopathy.² Remarkably, changes in the fibrinolytic system usually occur.³ For example, pieces of evidence suggested that hyperfibrinolysis can manifest in up to 50% of patients undergoing liver surgery.⁴

Consequently, cancer patients are often treated with transfusion of blood products to treat perioperative blood loss and anemia.³ Nevertheless, transfusion of blood products is not without risk. In fact, it can lead to an increased risk of potentially life-threatening immune responses, acute lung injury, and postoperative infections.⁵ In addition, in these patients, blood transfusions can be strongly associated with the development of new or progressive venous thromboembolism (VTE).^{6,7} Another important issue is the correlation between transfusion and cancer recurrence. Notably, although several studies concluded that perioperative transfusion of red blood cells (RBCs) did not increase the early risk of recurrence after cancer surgery,^{8,9} other data have shown that it was linked with worse cancer prognosis, in different

settings.^{10–12} These potential risks, in addition to the high cost of transfusions, stimulate the use of hemostatic agents to reduce blood loss and the need for transfusions.¹³

On the other hand, as a result of the hypercoagulable state caused by the production of several procoagulant agents, such as tissue factor, fibrinogen, neutrophil extracellular traps, and platelets activation factors, cancer patients have a higher risk of VTE than non-cancer patients.^{14,15} Most solid tumors, in particular those originating from the gastrointestinal tract, cause hypercoagulability of the blood and this phenomenon is due to the production by cancer cells of PCA (cancer procoagulant agent), namely a protease able to activate the coagulation cascade through the direct activation of coagulation factor X. Interestingly, cancer cells can interfere with the fibrinolysis by increasing the fibrinolytic activity through the expression on their cell surface of the tissue plasminogen activator (tPA), and the urokinase-type plasminogen activator (uPA). Nevertheless, they can also induce the production of the inhibitor of plasminogen activator type 1 receptor and –2 (PAI-1 and PAI-2) that limit the lysis of the blood clot.¹⁶

In this complex scenario, effective and safe potential strategies for the prevention of blood transfusions and their complications are needed. These strategies may include numerous pharmacological and operative approaches (eg, minimally invasive surgery, maintenance of normothermia). Tranexamic acid (TXA) is a potential pharmacological opportunity aimed at counteracting alterations in fibrinolysis. It is a low-cost hemostatic agent with a wide range of applications and minimal adverse effects. Synthesized in the second half of the twentieth century, TXA is widely used for its antifibrinolytic properties during abnormal bleeding.¹⁷ A meta-analysis of 129 trials (n=10,488) on its use in surgery concluded that TXA administration reduced the need for a blood transfusion by 38% while the effect on thromboembolic events and mortality was not conclusive.¹⁸

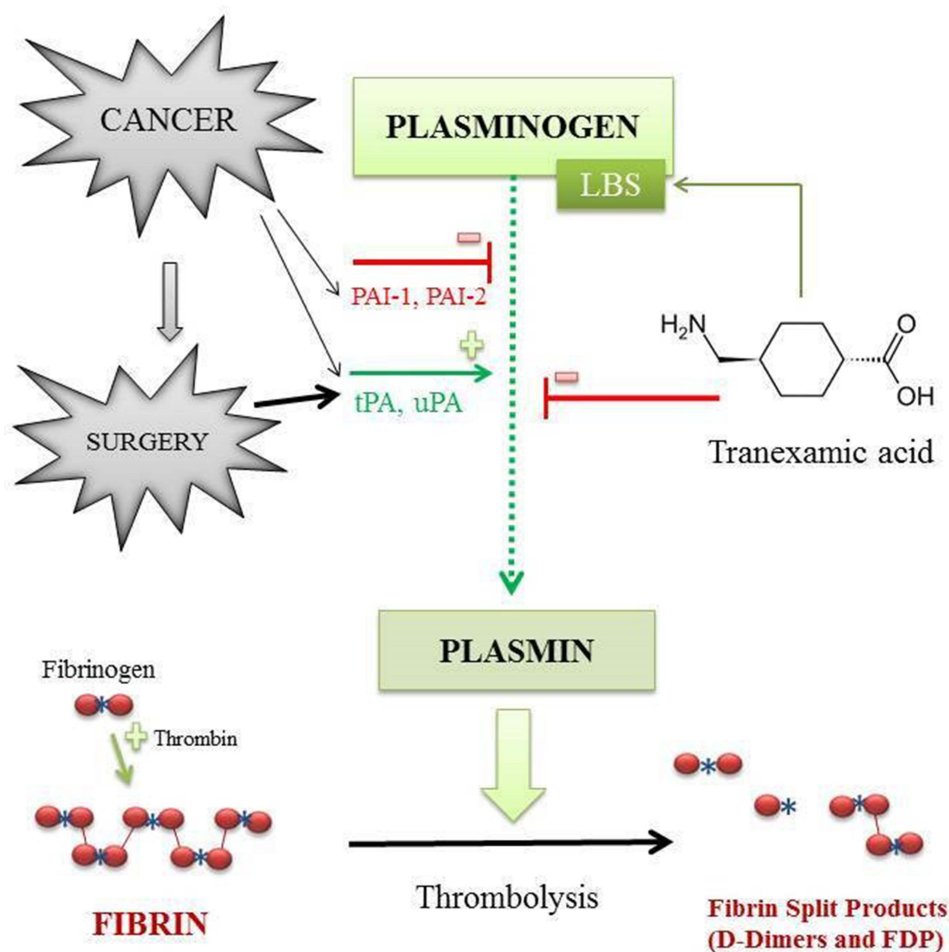
This narrative review is aimed to assess the efficacy and the safety of TXA when used in the context of cancer surgery. The authors also provide an overview of ongoing clinical research.

Mechanism of Action

The physiological coagulation cascade is a very complex process. The starting point is the activation of the tissue factor, contained mainly in the endothelial cells, by a tissue injury like a surgical act. It is a finely regulated process, which involves the sequential activation of coagulation factors. The result is the formation of a blood clot constituted by a tangle of fibrin and platelets that, finally, can fill the vascular damage. There is a feedback control system that prevents excessive clot formation as the fibrinolysis is activated to limit the extension of the clot and to degrade it. In brief, fibrinolysis works through a cellular mechanism involving the action of white blood cells, and a plasma mechanism. The fundamental step of this latter mechanism is the transformation of plasminogen into plasmin. The plasmin, namely the central molecule of fibrinolysis, is a proteolytic enzyme that can disrupt fibrin producing fibrin split products (eg, D-dimers). Regarding fibrinolysis inhibitors, the hemostasis control system provides several mechanisms which, if necessary, shift the balance in favor of coagulation. These mechanisms include inhibitors of the serine proteases tPA (PAI 1,2,3) and uPA, and several antiproteases such as the glycoprotein alpha2-antiplasmin which binds plasmin and is enhanced by calcium ions and coagulation factor XIII, alpha1-antitrypsin, complement C1 esterase inhibitor, and ATIII (antithrombin).

TXA is a synthetic molecule (trans 4 amino methylcyclohexane carboxylic acid) that derives from lysine and produces antifibrinolytic effects by blocking lysine-binding sites on plasminogen. This binding prevents the formation of plasmin which is the activated form of plasminogen and the activation of fibrin. As a result, inhibition of plasminogen activation induces the stabilization of the preformed fibrin structure produced by secondary hemostasis.¹⁹ TXA exerts its main bleeding limiting mechanism by delaying natural fibrinolysis and, therefore, the degradation of the blood clot.

TXA has other interesting effects. By blocking the formation of plasmin, it can reduce the activation of monocytes and neutrophils. This mechanism, in turn, can produce an important anti-inflammatory effect. Furthermore, inhibition of complement activation is also described.²⁰ This process is of paramount importance as an increased complement activation correlates with mortality and organ failure.²¹ Finally, preclinical studies suggested an anticancer effect of TXA²² (Figure 1).



Other effects of tranexamic acid:

- ↓ complement activation
- ↓ flogosis (↓ monocytes and neutrophils activation)
- Anticancer effects ?

Figure 1 The fibrinolytic pathway is altered in cancer surgery. Cancer cells can interfere with the fibrinolysis by increasing the fibrinolytic activity through the expression on their cell surface of different tissue plasminogen activator factors. They can also induce the production of factors that limit the lysis of the blood clot. Hyperfibrinolysis is triggered by surgery. Tranexamic acid (TXA) is a synthetic reversible competitive inhibitor to the lysine receptor found on plasminogen. The binding of this receptor inhibits plasmin activation and delays natural fibrinolysis. TXA can also exert an anti-inflammatory effect by reducing the activation of monocytes and neutrophils; it reduces the complement activation and, probably, could have an anticancer effect.

Abbreviations: LBS, lysine-binding sites; tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator; PAI-1 and PAI-2, inhibitor of plasminogen activator type 1 receptor and -2.

Pharmacological Properties

TXA is available as intravenous and oral formulations. The recommended posology varies greatly between studies, ranging from 10 mg/kg to 100 mg/kg.¹⁶ It is poorly metabolized by the liver and is mainly excreted by the kidney as renal clearance is the primary mechanism of excretion.¹⁶ This correlates to an increased incidence of complications in the case of renal dysfunction.^{23,24} Thus, a dose reduction in both oral and intravenous formulations should be considered depending on serum creatinine values.¹⁶ Indeed, for a serum creatinine between 120 and 150 µg/L, the recommended

dose is 10 mg/kg twice a day instead of 2 to 4 gr per day,¹⁶ for a serum creatinine between 250 and 500 µg/L, the recommended posology is 10 mg/kg/24h, and 10 mg/kg/48h when the serum creatinine is greater than 500 µg/L.¹⁶

The therapeutic plasma concentration of TXA varies from 5 mg/kg to 10 mg/kg.²⁵ Plasma concentration after an intravenous dose of 10 mg/kg is maintained for up to 3 hours, but it appears that this dosage is insufficient in some types of surgery such as urologic^{25,26} and orthopedics surgery.²⁷ A dose of 10 mg/kg can maintain a therapeutic level for 8 hours but appears to increase the risk of thromboembolic events.^{25,27}

After oral administration, TXA bioavailability is 30 to 50%. The volume of distribution is 9 to 12 liters and the half-time is of 2 hours.¹⁶ When studied in healthy volunteers, intravenous TXA has a half-life of 2 hours.¹⁸ Finally, food intake does not affect time to maximum concentration, as detected by the area under the receiver operating characteristic curve (ROC AUC).^{16–18,28}

Compared to the other lysine analog epsilon-aminocaproic acid, TXA is up to ten times more potent in binding affinity to plasminogen. Moreover, TXA provokes inhibition of fibrinolysis, which manifests as reductions in serum D-dimer levels without affecting the results of serum markers of coagulopathy.¹⁶ Furthermore, since concomitant heparin use does not influence the activity of TXA, it can be safely administered in heparinized patients.¹⁸

The main contraindications of TXA are arterial or venous thromboembolism diseases, and convulsions.¹⁶ Furthermore, precautions should be taken in case of renal dysfunction and/or hematuria (eg, due to potential obstructive urinary complications). The side effects of TXA are rare and they are mainly nausea, vomiting, and diarrhea, as well as visual or ocular adverse effects, dizziness, hypotension, and seizures (particularly during cardiovascular surgery).¹⁶ It only exceptionally can cause dangerous allergic reactions. Remarkably, in old studies, due to its inhibitory role on complement, it has even been used to treat anaphylactic shock.²⁹ About drug interactions, concomitant use of chlorpromazine may result in an increased risk of bleeding.¹⁷ The drug is contraindicated in patients with subarachnoid hemorrhage, in those with active intravascular clotting, and in the case of a previous severe hypersensitivity reaction after TXA administration. The Food and Drug Administration (FDA) approved TXA in individuals with hemophilia for short-term use (2–8 days) to reduce or prevent hemorrhage especially in the case of tooth extraction, and for heavy menstrual bleeding. Nevertheless, several off-label uses of oral, topical, and intravenous TXA are described in the literature, mostly in surgical settings and in trauma to reduce blood loss.^{17–24}

Clinical Usage and Efficacy of Tranexamic Acid in Oncologic Surgery

The efficacy and safety of TXA in oncological surgery has been investigated in several clinical settings. The main results are summarized according to the surgical context.

Head and Neck Surgery

In patients with head/neck cancer, the use of TXA is poorly investigated (Table 1). In 2016, Kulkarni et al¹⁶ published a double-blind, placebo-controlled study, whose data showed that preoperative intravenous TXA, given at the dosage of 10 mg/kg (after induction and repeated every 3 hours), did not reduce blood loss and the need for blood transfusions in patients undergoing major surgery for oral cancers, with or without reconstruction. Moreover, the TXA administration was safe and the incidence of deep venous thrombosis (DVT) did not increase. In another randomized, controlled trial, Chen et al³⁰ demonstrated that, compared to placebo, TXA did not significantly reduce drainage time.

Urological Surgery

To date, there is only a randomized controlled trial evaluating the TXA during cystectomy for bladder cancer (10 mg/kg intravenously before incision, followed by a 5 mg/kg/h maintenance infusion).²⁶ The study is still ongoing (clinicaltrials.gov identifier: NCT01869413). Results are pending and they will soon be published.

Concerning prostate cancers, Crescenti et al³¹ demonstrated that, compared to placebo, the intraoperative use of TXA (500 mg 20 minutes before the surgery, then 250 mg/h until skin suture) was able to reduce the transfusion rate. Similar results were also obtained by Pourfakhr et al.³² Several investigations have been conducted on transurethral resection of the prostate (TURP), but the results seem to be inconclusive.^{33–36} In a systematic review and meta-analyses, Longo et al³⁷ demonstrated that, in patients who undergo prostatectomy and TURP, TXA was able to reduce both intraoperative blood loss and the need for

Table I Summary of Tranexamic Acid in Head and Neck Surgery

Author (Year)	Country	Surgery/ Disease	Sample Size [Total n _ (n TXA/ nPlacebo)]	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Statistics
Kulkarni AP (2016) ¹⁶	India	Head and neck	219 (108/111)	10 mg/kg	TXA 750 (600–1000)	PLACEBO 780 (150–2600)	TXA 1000 (735–1250)	PLACEBO 1110 (850–1467)	TXA 22 (20%)	PLACEBO 27 (24.3%)	TXA 0	PLACEBO 0	NS for blood losses and blood transfusions
Chen CC (2008) ³⁰	Taiwan	Head and neck	55 (26/29)	20 mg/kg	–	–	–	–	–	–	N/E		NS in the coagulation profiles and drainage amount.

Abbreviations: TXA, tranexamic acid; N/E, not evaluated; NS, not significant; S, significant.

blood transfusion, without increasing in complications, such as DVT and pulmonary embolism. However, presently, there are few and very heterogeneous (both in the dosage and method of administration of TXA) high-quality studies. Therefore, more clinical trials with a large number of patients and with a robust methodology are necessary to confirm these findings (Table 2).

The advantages of TXA on postoperative outcomes can also be evaluated indirectly. For example, TXA seems to decrease surgical time during TURP.^{38,39} This advantage is desirable to decrease the potential complications, like thromboembolism events, blood loss, and effects due to irrigating fluid absorption, especially in oncological patients.

Neurosurgery

Patients undergoing craniotomy for tumor excision are at high risk for major bleeding. They usually require allogeneic red blood cells (RBC) transfusions which can increase the risk for infectious disease transmission, transfusion reaction, and immunosuppression. Previous studies have suggested that the leptomeninges are rich in tPA.⁴⁰ Therefore, it can be supposed that blood loss in intracranial meningiomas might be made worse by local tPA induced by hyperfibrinolysis. So, prolonged intracranial surgery and the following surgical stress may be complicated by a consumption-induced coagulopathy.⁴¹

To the best of our knowledge, there are currently two studies evaluating the TXA effectiveness in patients undergoing craniotomy for tumoral excision. Indeed, Vel et al⁴² and Hooda et al⁴³ showed that TXA at 10 mg/kg and 20 mg/kg, respectively, with a maintenance dose of 1 mg/kg/h until the end of the surgery, can reduce the blood loss but not the need for blood transfusions. Moreover, the duration of surgery was not affected by TXA use.

Other investigations have been conducted in oncological surgery of the spine. Bednar et al⁴⁴ performed a pilot study including a small number of patients with spinal metastases who required surgery for spinal stabilization. They showed that intravenous TXA did not significantly reduce blood loss and the need for blood transfusion. Damade et al⁴⁵ in a similar trial, did not show a significant decrease in intraoperative and postoperative blood loss in patients receiving TXA for spinal tumor surgery. However, they demonstrated that blood transfusions are statistically less frequent in the group that received TXA. More recently, in a retrospective analysis, Zhang et al⁴⁶ proved that, about surgery for spinal tumors, TXA can significantly reduce ($p<0.05$) the amount of intraoperative blood loss and postoperative drainage without increasing the risk of DVT. The duration of the surgical intervention was not significantly reduced by the administration of the TXA^{41,42} (Table 3).

Despite limitations, further data can be obtained from studies conducted on non-cancer patients. In a large study enrolling patients treated with spinal reconstructive surgery, Wong et al⁴⁷ demonstrated that the administration of TXA significantly reduced the perioperative blood loss by up to 30%, if compared with those not receiving TXA. However, the amount of perioperative blood products transfusions was not different among groups.

Visceral Surgery

Several studies have been conducted to evaluate the efficacy of TXA in visceral surgery (Table 4).

In 2006, Wu and al⁴⁸ published a prospective randomized study evaluating the rate of blood transfusion in patients who received TXA before hepatectomy for primary or secondary malignancies. They concluded that a perioperative intravenous low dose administration of TXA (500 mg intravenously administered before surgery followed by 250 mg, every 6 hours, for 3 days) was associated with a significantly lower amount of blood loss ($p=0.0001$) and blood transfusions ($p<0.0001$). The duration of surgical intervention was significantly lower in the group receiving TXA ($p=0.003$). In addition, even if the length of hospitalization was similar, the global hospital cost was significantly lower in the experimental group receiving TXA ($p=0.036$).

More recently, Grass et al⁴⁹ carried out a retrospective study in patients ($n=213$) who underwent elective colorectal surgery for cancer and received 1 g of TXA intravenously as induction therapy and before anesthesia emergence. Despite their study failed to prove a significant reduction of post-operative transfusions rate, the authors provided insight into the potential benefits of perioperative TXA administration in this surgical setting. Regarding major oncologic surgery (eg, cytoreductive surgery with heated intraperitoneal chemotherapy, esophagectomy, and pancreatectomy), Wright et al⁵⁰ conducted a double-blind, placebo-controlled randomized testing the effects of a single dose (1 g) of TXA before surgery

Table 2 Summary of Tranexamic Acid in Urological Surgery

Author (Year)	Country	Surgery	Sample [Total n – (n TXA/ nPlacebo)]	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Statistics
Breau RH (2018) ²⁶	Canada	Radical Cystectomy	–	10 mg/kg loading dose intravenously, followed by a 5 mg/kg/h infusion	–		–		–		–		Study in progress
Crescenti A (2011) ³¹	Italy	Radical Prostatectomy	200 (100/100)	500 mg 20 minutes before surgery, then 250 mg/h until skin suture	TXA 1103 ± 500.8	PLACEBO 1335 ± 686.5	TXA N/E	PLACEBO N/E	TXA 34%	PLACEBO 55%	TXA 0	PLACEBO 2	S for intraoperative blood loss and blood transfusions
Pourfakhr P (2016) ³²	Iran	Prostatectomy	80 (40/40)	After prostate removal, TXA 500 mg (5 mL total volume) was locally sprayed	N/E	N/E	340 ± 152.1	515 ± 233	0%	5.4%	0	0	S for intraoperative blood loss and blood transfusions
Balik R (2020) ²⁵	Czech Republic	RARP	100 (50/50)	1.5 g TXA at the induction	337.5	386	50	80	N/E	N/E	0	1	NS for perioperative blood loss S for 24h blood loss
Jendoubi A (2017) ³³	Tunis	TURP/TURV	60 (30/30)	10 mg/kg TXA 30 minutes before surgery follow by 1 mg/kg/h during 24h	N/E	N/E	N/E	N/E	13.3%	13.3%	0	0	NS for the need of blood transfusions
Meng QQ (2019) ³⁴	China	TURP	60 (30/30)	1 gr TXA after the induction of anesthesia	102.0 ± 11.4	303.6 ± 24.8	63.9 ± 5.2	77.4 ± 5.0	N/E	N/E	0	0	S for intraoperative blood loss but NS for 24h postoperative blood loss

(Continued)

Table 2 (Continued).

Author (Year)	Country	Surgery	Sample [Total n _ (n TXA/ nPlacebo)]	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Statistics
Miller RA (1980) ³⁶	UK	TURP/TURBT	100 (52/48)	1 gr TXA 3 times daily for 3 weeks from the first postoperative day	N/E	N/E	N/E	N/E	N/E	N/E	N/E	N/E	TXA reduced the incidence of secondary haemorrhage without increased thromboembolic events
Mirmansouri (2016) ³⁵	Iran	TURP	80 (40/40)	15 mg TXA 15 min before surgery follow by 1mg/kg/h infusion for 5h	N/E	N/E	N/E	N/E	TXA 10%	PLACEBO 30%	N/E	N/E	S for blood transfusion
Rannikko A (2004) ³⁸	Finland	TURP	136 (70/66)	TXA 2g orally 3 times per day on the operative and first postoperative day	TXA 128	PLACEBO 250	N/E	N/E	6 (8.6%)	5 (7.6%)	0	0	S for perioperative blood loss NS for the need to blood transfusions
Samir R (2021) ³⁹	Egypt	TURP	186 (95/91)	50 mg/kg TXA before induction and 5 mg/kg/h infusion until the end of the TURP	N/E	N/E	N/E	N/E	4 (4.2%)	5 (5.5%)	0	0	NS for the need for blood transfusions

Abbreviations: TXA, tranexamic acid; TURP, transurethral resection of the prostate; TURBP, transurethral resection for bladder tumour; RARP, robot-assisted radical prostatectomy; N/E, not evaluated; NS, not significant; S, significant.

Table 3 Summary of Tranexamic Acid in Neurosurgical Surgery

Author (Year)	Country	Surgery	Sample Size (n)	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Satistics
Vel R (2015) ⁴²	India	Cerebral tumor	100 (50/50)	10 mg/kg for 10 minutes, then 1mg/kg/h intra-op.	TXA 817 ± 42 3.3	PLACEBO 1084 ± 604.8	TXA N/E	PLACEBO N/E	TXA 21 (42%)	PLACEBO 30 (60%)	TXA 0	PLACEBO 0	S for perioperative blood loss but not for blood transfusion
Hooda B (2017) ⁴³	India	Intracranial meningioma	60 (30/30)	20 mg/kg for 20 minutes, then 1 mg/kg/h intra-op.	TXA 830	PLACEBO 1124	TXA NA	PLACEBO NA	TXA 13 (43.3%)	PLACEBO 17 (56.7%)	TXA N/E	PLACEBO N/E	S for blood loss but not for blood transfusion
Damade C (2019) ⁴⁵	France	Spinal tumor	83 (36/47)	15 mg/kg at the time of induction then the same dose continuously over 8h.	TXA 444 ± 356	PLAECBO 370 ± 419	TXA 568 ± 250 but not specified the moment	PLACEBO 631 ± 299 but the time is not specified	TXA Rate N/E 348 mL (1.2 ± 1.4 units)	PLAECBO Rate N/E 528 mL (1.8 ± 2.3)	TXA N/E	PLACEBO N/E	NS for blood loss but S for blood transfusion
Zhang HZ (2020) ⁴⁶	China	Spinal canal tumors	60 (30/30)	10 mg/kg 30 min before the operation, followed by a maintenance dose of 1 mg/kg per h.	TXA 253.32 ± 54.04	PLACEBO 362.57 ± 62.31	TXA 84.34 ± 30.74	PLACEBO 140.65 ± 34.35	TXA N/E	PLACEBO N/E	TXA N/E	PLACEBO N/E	S for blood loss
Bednar DA (2006) ⁴⁴		Metastatic tumors of the Spine	28 (14/14)	Loading dose of 1000 mg and maintained with infusion of 1 mg/kg/hour during their operations.	TXA 1385 (trace to 4000)	PLACEBO 1815 (400–5000)	N/E	N/E	14 (100%)	14 (100%)	TXA 0	PLACEBO 0	NS for blood loss intraoperative and for the need to blood transfusions

Abbreviations: TXA, tranexamic acid; N/E, not evaluated; NS, not significant; S, significant.

Table 4 Summary of Tranexamic Acid in Visceral Surgery

Author (Year)	Country	Surgery	Sample Size (n)	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Statistics
Wu C-C (2006) ⁴⁸	Taiwan	Liver tumor resection	214 (108/106)	500 mg preop, then 250 mg every 6h for 3 days	TXA 190 (20–1910)	PLACEBO 450 (30–2590)	TXA 300 (30–2100)	PLACEBO 600 (40–3410)	TXA 0	PLACEBO 17 (16%)	TXA N/E	PLACEBO N/E	S for blood losses and blood transfusions
Grass F (2019) ⁴⁹	United States	Colorectal	213 (81/132)	1 g of TXA intravenously at induction and at closure	Higher proportion of patients with less than 250 mL blood loss	Higher proportion of patients with less than 250 mL blood loss	TXA N/E	PLACEBO N/E	TXA 3 (3.7%)	PLACEBO 11 (8.33%)	TXA 1	PLACEBO 1	NS for blood loss and blood transfusion
Wright GP (2020) ⁵⁰	United States	Major oncologic surgery	76 (39/37)	1 g of TXA pre-incision	N/E	N/E	TXA 365 (150–850)	PLACEBO 450 (250–750)	TXA 8 (20.5%)	PLACEBO 5 (13.5%)	TXA 1	PLACEBO 1	NS for blood loss and blood transfusion

Abbreviations: TXA, tranexamic acid; N/E, not evaluated; NS, not significant; S, significant.

on perioperative transfusion rate. They did not find lower perioperative allogeneic blood transfusion rates, but TXA did not increase the incidence of postoperative adverse effects.

Currently, the TAC-DP (Tranexamic Acid during Pancreatic Duodenectomy) study is ongoing.⁵¹ It is a multicentre randomised, double-blind, placebo-controlled trial whose objectives are to investigate the effect of TXA on the incidence of perioperative blood transfusions, operation time, anesthesia time, postoperative laboratory elements, and complications. The study also investigates the safety of TXA, especially in terms of incidence of thromboembolic events within 28 days of surgery or requiring readmission. Results are pending.

Gynecological Surgery

Myomectomy can be associated with a high rate of perioperative blood loss. In a randomized controlled trial, Abdul et al⁵² combined TXA (10 mg/kg before incision) with the use of the tourniquet. This strategy significantly reduced intraoperative blood loss per 100 g of fibroid removed, when compared to tourniquet alone. In a retrospective study including women with uterine cancer who underwent surgery, Celebi et al⁵³ divided the sample size (n=105) into 4 groups: group I received crystalloid solutions, group II colloid agent, group III received TXA (10 mg/kg), and group IV received (100 mg/kg) epsilon-aminocaproic acid. They found an important decrease (up to 30%) in perioperative blood loss in those who received TXA compared to the crystalloid group ($p<0.05$). They also proved that, compared to the epsilon-aminocaproic group, women who received TXA had approximately 24% of reduced occurrence of perioperative blood loss ($p<0.05$). Another placebo-controlled study (n=100) demonstrated that a single dose of TXA (15 mg/kg just before surgery) significantly reduced blood loss and transfusion rates ($p=0.03$) in patients with advanced ovarian cancer treated with surgery.⁵⁴ Given these results, it seems that TXA could be recommended as a standard prophylactic strategy in advanced ovarian cancer surgery and other types of gynecological surgery for cancer (Table 5). Nevertheless, to determine if TXA can be used as a standard of care, it is necessary to conduct good quality, randomized and controlled trials to provide solid evidence on the efficacy, and safety profile of the drug. In this regard, a Cochrane analysis concluded that the evidence is not sufficient to recommend the routine use of TXA for reducing blood loss during cytoreductive surgery for advanced ovarian cancer.⁵⁵

Breast Surgery

In a retrospective monocentric trial (n=868), intravenous TXA (1 g intravenously before incision and 1 g at the end of the surgery) was administrated in women who received implant-based breast reconstruction.⁵⁶ The authors highlighted a clinical benefit of TXA in plastic reconstruction surgery, with a statistical decrease in postoperative hematoma. Moreover, adverse effects such as DVT and other thromboembolic issues were not observed.

A Norwegian two-center, double-blind randomized trial investigated the effects of wound « moistening » through TXA (25 mg/mL) before closure.⁵⁷ The authors observed a reduction of postoperative bleeding within 24h in patients undergoing mastectomy⁵⁷ (Table 6).

Orthopedic Surgery

In non-cancer orthopedic surgery, TXA has been extensively studied. Recently, the American Association of Hip and Knee Surgeons, the American Society of Regional Anesthesia and Pain Medicine, and the American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society published their combined clinical-practice guidelines regarding the use of TXA in total joint arthroplasty.⁵⁸ According to them, TXA is profoundly changing the perioperative management of arthroplasty patients. The aforementioned guidelines recommend that in patients without a known history (strong evidence) and in those with a history of a VTE, or myocardial infarction (moderate evidence) TXA does not increase the risk of thromboembolism phenomena.

Nevertheless, there is a lack of evidence about the safety of TXA in cancer patients undergoing orthopedic surgery. Varady et al⁵⁹ evaluated the safety of TXA in patients with current or former cancer undergoing hip and knee arthroplasty. They found that TXA was not associated with an increased risk of VTE. The same results were found in other studies.^{60,61} For example, Atalay et al⁶⁰ demonstrated that preoperative TXA (15 mg/kg as a bolus) significantly reduced postoperative bleeding amount and transfusion needs in wide-margin tumor resection and prosthesis surgery for

Table 5 Summary of Tranexamic Acid in Gynecological Surgery

Author (Year)	Country	Surgery	Sample Size (n)	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Statistics
Abdul IF (2019) ⁵²	Nigeria	Myomectomy (tourniquet)	80 (40/40)	10 mg/kg TXA before incision	TXA 907.25 ± 529.85 104.09 ± 1.97 / 100 gr from fibroid	PLACEBO 998.72 ± 607.21 139.80 ± 2.28 /100 gr from fibroid	TXA N/E	PLACEBO N/E	TXA 30%	PLACEBO 45%	TXA 0	PLACEBO 0	NS for blood loss and blood transfusion but S for blood loss/100 gr fibroid
Kietpeerakool C (2016) ⁵⁵	Thailand	Cytoreductive surgery for advanced ovarian cancer (laparotomy)	100 (50/50)	15 mg/kg immediately before the start of surgery	TXA N/E	PLACEBO N/E	TXA 520	PLACEBO 730	TXA 30%	PLACEBO 44%	TXA 0	PLACEBO 0	S for blood transfusion S for 24h blood loss
Celebi (2006) ⁵³	Turkey	Hysterectomy	105	10 mg/kg before surgery	TXA N/E	PLACEBO N/E	TXA 270	PLACEBO 390	TXA N/E	PLACEBO N/E	TXA 0	PLACEBO 0	S

Abbreviations: TXA, tranexamic acid; N/E, not evaluated; NS, not significant; S, significant.

Table 6 Summary of Tranexamic Acid in Breast Surgery

Author (Year)	Country	Surgery	Sample Size (n)	TXA Dose	Early Hematoma (%)		Arterial or venous thromboembolism		Statistics
Weissler JM (2020) ⁵⁶	United Kingdom	Breast reconstruction following mastectomy	868 (217/651)	1000 mg of intravenous tranexamic acid before mastectomy incision and 1000 mg at the conclusion of the procedure	TXA 0.46%	PLACEBO 2.9%	TXA 0	PLACEBO 0	S
Ausen K (2019) ⁵⁷	Finland	Mastectomy	208	Topical moistening of 20 mL TXA 25 mg/mL	TXA 1%	PLACEBO 6.93%	TXA 0	PLACEBO 0	S

Abbreviations: TXA, tranexamic acid; S, significant.

cancer lesions of the proximal femur. Other studies investigated different modalities of TXA use. Haase et al⁶¹ for example, found that topical TXA can reduce perioperative blood loss, transfusion rates, hospitalization, and VTE occurrence.

Differently, Owen et al⁶² did not show a reduction in blood loss and in blood transfusions when intravenous TXA was administrated before bipolar hemiarthroplasty for metastatic disease and at the time of closure. However, this study was conducted on a small and heterogeneous cohort of patients. Therefore, further investigations via multicenter RCTs are needed (Table 7).

Ongoing Research

Several clinical investigations addressing multiple important issues are still ongoing (Table 8). Some of them, for example, is establishing the effective and safe dose of TXA to be used.

In the NCT04360629 trial, patients with advanced ovarian cancer are randomized to receive three different TXA doses. Group I, receive a low dose of TXA (10 mg/kg bolus followed by an infusion of 1 mg/kg/h); Group II, a high dose of TXA (20 mg/kg bolus followed by an infusion of 5 mg/kg/h); Group III, placebo.

Another hot issue to be elucidated is the occurrence of late-onset postoperative complications. In a randomized controlled trial, researchers are collecting the postoperative thrombotic complications including myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction, 1 month after surgery for colorectal cancer. Patients receive TXA (intravenous bolus of 10 mg/kg) or placebo (NCT03606785). In the NCT03128866 trial on patients undergoing hemipelvectomy, the effect of TXA on postoperative complications, length of intensive care unit (ICU), and hospital stays are under investigation.

Notably, there is also a study in patients with skin cancer (NCT04630886). The hypothesis is that a subcutaneous infiltration of TXA (2% lidocaine with 1:100,000 epinephrine mixed 50/50 with 50 mg/mL TXA) can reduce perioperative complications including bleeding, infections, as well as flap and graft loss. About the topic use of TXA, a study was designed to evaluate the use of topical application of the drug (3 g diluted in 10 mL of normal saline) to the surgical wound to decrease hematoma formation in patients undergoing bilateral breast reduction (NCT04918576).

Finally, other studies are evaluating the use of TXA in different settings of major oncological surgery. Among the various studies the NCT01980355 from the United States (TXA 1 g prior to surgery), the multi-centre Phase IV TRACTION Trial (NCT04803747) from Canada and investigations in pediatric oncological surgery (NCT05024253, NCT04410042) will surely provide interesting data.

Conclusions

Despite the harmful effects of blood transfusions, administration of TXA is not standard clinical practice for patients undergoing cancer surgery. Based on the results of current studies, the use of TXA could be associated with an important reduction in blood loss and transfusions need, and importantly, it seems to positively impact the incidence of some feared side effects, such as thromboembolic phenomena. Nevertheless, most of the published studies on the subject are small

Table 7 Summary of Tranexamic Acid in Orthopedic Surgery

Author (Year)	Country	Surgery	Sample Size (n)	TXA Dose	Intraoperative Blood Loss (mL)		24h Blood Loss (mL)		Red Blood Cell Transfusion		Arterial or Venous Thromboembolism		Statistics
Owen A (2021) ⁶²	United States	Orthopedic surgery	66	1 g of TXA at the time of incision and 1g at the of closure.	TXA N/E	PLACEBO N/E	TXA 980 ± 560 mL	PLACEBO 1010 ± 560 mL	TXA 9 (41%)	PLACEBO 18 (41%)	TXA 3 (14%)	PLACEBO 5 (11%)	NS for 24h blood loss NS for blood transfusions NS for DVT
Haase DR (2020) ⁶¹	United States	Orthopedic surgery	90	1 g of topical TXA administered into the wound bed before closure.	TXA N/E	PLACEBO N/E	TXA 981 ± 290 mL	PLACEBO 1542 ± 746 mL	TXA 8 (23.5%)	PLACEBO 25 (44.6%)	TXA 1 (2.9%)	PLACEBO 2 (3.6%)	S for 24h blood loss and blood transfusion NS for VTE
Varady NH (2021) ⁵⁹	United States	Hip/knee arthroplasty	282	1 g intravenous TXA preoperatively and 1 g intravenous TXA during wound closure.	TXA N/E	PLACEBO N/E	TXA N/E	PLACEBO N/E	TXA N/E	PLACEBO N/E	TXA 3 (4.1%)	PLACEBO 20 (9.6%)	NS for VTE
Atalay IB (2020) ⁶⁰	Turkey	Tumor resection and reconstruction	46	Preoperative bolus 15 mg/kg TXA.	TXA 1026.7 ± 727.9	PLACEBO 1290.3 ± 490.1	TXA 433.3 ± 327.1	PLACEBO 517.7 ± 201.1	TXA 7 (46.7%)	PLACEBO 29 (93.5%)	TXA 0	PLACEBO 0	S for 24h blood loss and blood transfusion NS for perioperative blood loss

Abbreviations: TXA, tranexamic acid; NS, not significant; S, significant; DVT, deep venous thrombosis; VTE, venous thromboembolism.

Table 8 Summary of Ongoing Clinical Research on Tranexamic Acid in Oncological Surgery

Country	Study Design	Setting/Surgery	Intervention	Trial ID	Estimated Completion Date
United States	RCT	Major oncological surgery	TXA 1 g prior to surgery (IV)	NCT01980355	Completed
Canada	RCT (phase IV)	Major oncological surgery	TXA 2 grams (IV)	NCT04803747	November 2021
United States	RCT	Skin cancer	TXA 50 mg/mL (subcutaneous)	NCT04630886	June 2022
Egypt	RCT	Colorectal cancer	TXA 10 mg/kg (IV)	NCT03606785	Completed
United States	RCT	Hemipelvectomy	TXA prior to surgery and continuously during the procedure (IV)	NCT03128866	Completed
China	RCT	Ovarian cancer	TXA 10 mg/kg bolus followed by infusion of 1mg/kg/h; TXA 20 mg/kg bolus followed by infusion of 5mg/kg/h (IV)	NCT04360629	Completed
United States	RCT	Limb salvage procedure of malignant bone tumor (children)	TXA 10 mg/kg (max 1 g). Repeated after 6 hours (IV)	NCT04410042	March 2025
Egypt	RCT	Bone tumor surgery (children)	TXA 10 mg/kg (IV)	NCT05024253	December 2024
United States	RCT	Sarcoma (bone and soft tissue)	TXA 1g prior to incision and at the closure (IV)	NCT04347122	December 2024
United States	RCT	Endoscopic pituitary surgery	TXA 1 g prior to surgery (IV)	NCT04863339	

Abbreviations: TXA, tranexamic acid; IV, intravenous; RCT, randomized clinical trial.

and often questionable in terms of statistical power. Consequently, further randomized clinical trials are warranted to corroborate the abovementioned findings, and more importantly, randomized investigations are needed to determine efficacy, safety, adequate therapeutic doses, and the appropriate treatment regimen of TXA. Finally, it is necessary to verify in which surgical areas the use of TXA is most appropriate. For example, pelvic surgery for cancer is associated with an increased risk of VTE and, in this setting, extended prophylaxis is recommended with low-molecular-weight heparin or, more recently, direct oral anticoagulants. The potential interaction of these strategies with TXA requires proper investigation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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