Original Article

Does tranexamic acid reduce blood loss during head and neck cancer surgery?

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ABSTRACT

Background and Aims: Transfusion of blood and blood products poses several hazards. Antifibrinolytic agents are used to reduce perioperative blood loss. We decided to assess the effect of tranexamic acid (TA) on blood loss and the need for transfusion in head and neck cancer surgery. **Methods:** After Institutional Review Board approval, 240 patients undergoing supramajor head and neck cancer surgeries were prospectively randomised to either TA (10 mg/kg) group or placebo (P) group. After induction, the drug was infused by the anaesthesiologist, who was blinded to allocation, over 20 min. The dose was repeated every 3 h. Perioperative (up to 24 h) blood loss, need for transfusion and fluid therapy was recorded. Thromboelastography (TEG) was performed at fixed intervals in the first 100 patients. Patients were watched for post-operative complications. **Results:** Two hundred and nineteen records were evaluable. We found no difference in intraoperative blood loss (TA - 750 [600–1000] ml vs. *P* - 780 [150–2600] ml, *P* = 0.22). Post-operative blood loss was significantly more in the placebo group at 24 h (P - 200 [120–250] ml vs. TA - 250 [50–1050] ml, *P* = 0.009), but this did not result in higher number of patients needing transfusions (TA - 22/108 and *P* - 27/111 patients, *P* = 0.51). TEG revealed faster clot formation and minimal fibrinolysis. Two patients died of causes unrelated to study drug. Incidence of wound complications and deep venous thrombosis was similar. **Conclusion:** In head and neck cancer surgery, TA did not reduce intraoperative blood loss or need for transfusions. Perioperative TEG variables were similar. This may be attributed to pre-existing hypercoagulable state and minimal fibrinolysis in cancer patients.

Key words: Blood transfusion, cancer surgery, hypercoagulability, tranexamic acid

INTRODUCTION

Administration of blood and blood products carries the risk of post-operative bacterial infection and increased rates of recurrence in various malignancies.[1,2] Lower transfusion trigger, pre-operative autologous blood donation (with or without erythropoietin), intraoperative red blood cell salvage, regional anaesthesia, controlled hypotension and antifibrinolytic agents are all useful means to decrease the need for allogenic transfusions. Tranexamic acid (TA) is a synthetic antifibrinolytic agent that is approximately 7–10 times more potent than aminocaproic acid. It blocks the lysine-binding sites of plasminogen, plasmin and tissue plasminogen activator (tPA), and thus delays fibrinolysis and degradation of blood clot.[3] A recent systematic review of over 10,000 patients undergoing various surgeries suggested that administration of TA reduces the need of receiving transfusion by 38% (relative risk [RR] 0.62, 95% confidence interval [95% CI]: 0.58–0.65; $P < 0.001$).[4] We wanted to find out whether intraoperative administration of TA reduced blood loss in patients undergoing supramajor head and neck cancer surgery.

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Thromboelastography™ (TEG) allows evaluation of kinetics of clot formation and presence and inhibition of fibrinolysis.[5] Hypercoagulability, difficult to detect with routine coagulation tests, can be diagnosed with TEG displaying a short r-time, broad alpha angle and maximum amplitude (MA) >70 mm.

METHODS

This prospective, double-blind, randomised, placebo-controlled trial was conducted after approval from the Institutional Review Board in a Tertiary Referral Cancer Institute in India. We included 240 patients with resectable squamous cell carcinoma of the oral cavity undergoing supramajor surgery viz., composite resection of the mandible along with neck dissection, requiring reconstructive procedures in the form of pedicled flaps. Informed consent was obtained from all patients. Patients with coagulopathy (partial prothrombin time >50 s, or international normalised ratio >1.5, platelets $<50 \times 10^9$/L), or those who had recent history of (<5 days) acetylsalicylic acid ingestion, patients on anticoagulant therapy (heparin received within 4 h or warfarin received 3 days pre-operatively) or those with peripheral vascular disease, pre-existing renal dysfunction (serum creatinine >1.2 mg/dL), liver dysfunction or known allergy to TA were excluded.

The patients were allocated to two groups by random numbers generated using a computer programme, and blocks of 10 were generated. The patient, the anaesthesiologist and the person assessing the blood loss were blinded to the assignment. The study drug, either tranexamic acid (TA) 10 mg/kg in 100 ml of normal saline (TA group) or placebo (100 ml normal saline) was prepared by one investigator as per the randomisation and handed over to the attending anaesthesiologist who was blinded to the group assignment. Patients were stratified *a* priori according to plan of reconstruction (pedicled pectoralis major myocutaneous flap or pectoralis major myocutaneous and deltopectoral flap).

The technique of induction, maintenance and reversal of anaesthesia was left to the discretion of the attending anaesthesiologist. The study drug, prepared in the calculated dose, or placebo was infused over 20 min after induction of anaesthesia before the surgical incision was taken. In the event of prolonged surgeries, the infusion was repeated every 3 h.

Intraoperative blood loss was calculated by gravimetry, the blood collected in the suction bottle and visual assessment of blood loss in the surgical field. Maximum allowable blood loss (MABL) was calculated with a transfusion trigger of 8 g% haemoglobin (Hb) using the formula: MABL = ([Hb − minimum Hb]/Hb) × (weight in kg) × (ml of blood per kg body weight). The blood loss was replaced with Ringer's lactate or a colloid until it exceeded the calculated MABL. Then, it was replaced with either whole blood or packed red cells. The anaesthesiologist could override the trigger if the patient developed haemodynamic instability (heart rate >120 beats/min, or a systolic blood pressure decrease by >20% of pre-operative value) despite adequate volume replacement. Assessment of volume status and the amount of fluid to be infused was left to the judgement of the attending anaesthesiologist.

The primary endpoint was reduction in blood loss, while the secondary endpoint was the number of patients needing transfusion. We noted demographics, comorbidities, pre-operative and post-operative Hb concentration on day 1 and platelet count. We performed TEG in the first 50 patients in each group at five intervals: Pre-operatively, 1 h after the first dose, 1 h after the second dose, immediately post-operatively on transfer to recovery room and on the morning of the first post-operative day. Post-operative blood loss was assessed from the blood collected in the suction drain bottles over the first 24 h. The type and duration of surgery, experience of the surgeon and mean arterial blood pressure during surgery were also recorded. We also noted the urine output in the first 24 h and serum creatinine on post-operative day 1 and 3. The patients were monitored for development of skin flap and reconstruction flap necrosis (both graded as edge necrosis, flap loss either more or <50%), oro-cutaneous fistulas, symptomatic deep vein thrombosis, need for surgical re-exploration and other incidental complications until discharge from the hospital.

From our previous data, the mean blood loss in patients undergoing composite resections and reconstruction was 750 ml (standard deviation [SD] 100). For the trial to have 80% power to detect a reduction of 40% in the average blood loss, at $\alpha = 0.05$, (PS programme, Copyright© 1997, Vanderbilt University Medical Center - http://www.mc.vanderbilt.edu/prevmed/ps/) we calculated that 100 patients in each group were needed. To compensate for protocol violation such as failure to administer drug, change of surgical plan and non-availability of case record forms, we enrolled 240 patients.

Statistical analysis was performed on intention to treat basis using Student's *t*-test and Chi-square test. Serial measurements were analysed by paired *t*-test (for two observations) and by repeated measures ANOVA (for more than two observations) and a $P < 0.05$ was considered statistically significant.

RESULTS

Two hundred and nineteen of 240 records were evaluable. Patients in the TA and control groups were similar in sex, age, weight, comorbidities and baseline investigations including the coagulation parameters obtained with TEG. The type of reconstructive surgery and duration of surgery was also similar [Table 1]. Anaesthetic technique including the use of narcotic analgesics and haemodynamic parameters revealed no differences in two groups. The intraoperative blood loss and total blood loss (a total of intraoperative blood loss and post-operative blood loss) in the first 24 h in perioperative period was similar in both groups (750 ml in TA vs. 780 ml in control group, $P = 0.22$, 1000 ml in TA group and 1100 ml placebo group, respectively). The difference in post-operative blood loss reached statistical significance (TA 250 ml vs. 320 ml in the control group, $P = 0.009$), but did not seem to be clinically significant and did not result in an increase in need for blood transfusion. Of 108 patients, 22 needed blood transfusion in TA group while in the placebo group, 27 of 111 needed transfusion ($P = 0.51$). No patients were transfused in the post-operative period. Intraoperative fluid replacement, crystalloids and colloids were similar in both groups [Table 2]. The TEG showed hypercoagulable profile at baseline, i.e., shorter than normal r-time, k-time and wide α angle indicating faster acceleration (kinetics) of fibrin build up and cross-linking in both groups. At all points when TEG was performed the MA was higher than the normal range, and there was absence of significant fibrinolysis in both groups indicated by high clot lysis index at 60 min [Table 3].

Post-operative investigations revealed no differences in two groups and no renal or hepatic dysfunction in the TA group [Table 4]. Two patients died in the post-operative period, one had a hypoxic cardiac arrest on the second post-operative day in the ward due to a blocked tracheostomy tube (TA group), while the other patient had an unexplained asystolic cardiac arrest (placebo group). Other post-operative complications were similar in both groups viz., two patients in each group had skin flap necrosis while three each had >50% necrosis of reconstruction flap (P = NS). One patient (placebo group) needed

Table 1: Baseline characteristics, type of reconstruction and duration of surgery

Demographics	TA group (108 patients)	Placebo group (111 patients)	*P*
Age (years)	51.26 (11.30)	50.67 (11.68)	
Male:female ratio	79:27	87:23	-
Weight (kg)	55.73 (13.74)	53.21 (10.81)	
Comorbidities (number of patients)			
HT	15	7	0.068
DM	13	7	0.15
IHD	0	1	1.0
Others	4	6	0.751
Pre-operative investigations			
Haemoglobin (g/dl)	12.24 (1.79)	12.15 (1.73)	0.706
Platelets (×1000/mm^3)	2.17 (0.78)	3.98 (1.17)	0.202
Urea (mg%)	23.34 (8.89)	22.51 (7.8)	0.489
Creatinine (mg%)	0.98 (0.19)	1.03 (0.89)	0.693
Bilirubin (mg%)	0.67 (0.31)	0.61 (0.4)	0.349
Reconstruction			
Single flap (number of patients)	63	66	0.673
Double flap (number of patients)	45	45	0.67
Duration of surgery (h)	5.45 (1.55)	5.51 (1.57)	0.95

IHD – ischaemic heart disease; DM – Diabetes mellitus; HT – Hypertension; TA – Tranexamic acid

Table 2: Blood loss, fluids and blood replacement

Blood loss, fluids, blood replacement	Median (IQR)		*P*
	TA group (108)	Placebo group (111)	
Intraoperative blood loss (ml)	750 (600-1000)	780 (150-2600)	0.22
Transfusion (number of patients)	22	27	0.51
Post-operative blood loss (ml) 24 h	200 (120-250)	250 (50-1050)	0.009
Blood loss 24 h (total, in ml)	1000 (735-1250)	1110 (850-1467)	0.133
Intraoperative crystalloids (ml)	3000 (1000-6000)	3000 (1000-7000)	0.66
Intraoperative colloids (ml)	500 (0-3000)	500 (0-1500)	0.673

IQR – Interquartile range; TA – Tranexamic acid

Table 3: Baseline TEG parameters

TEG parameter	Median (IQR)		*P*
	TA group (*n*=52)	Placebo group (*n*=49)	
r (10-14 s)	4.6 (3.33-5.78)	4.3 (3.05-5.75)	0.882
k (3-6 s)	1.3 (1.02-1.60)	1.3 (1.0-1.7)	0.349
α (54-67 s)	72.8 (68.6-76.3)	71.9 (66.6-75.65)	0.406
MA (59-68 mm)	71.75 (67.5-75.2)	72 (65.75-77.20)	0.305
A60 (mm)	68.25 (58.3-72.5)	67 (59.4-73.45)	0.685
CLI	93.29 (85.04-99.65)	94.66 (89.24-100.28)	0.59

IQR – Interquartile range; TEG – Thromboelastography; TA – Tranexamic acid; MA – Maximum amplitude; CLI – Clot lysis index

Table 4: Post-operative (day 1) investigations

Investigation	Mean (SD)		*P*
	TA group	Placebo group	
Haemoglobin (g/dl)	11.5 (2.6)	10.68 (1.98)	0.87
Platelets (1000/mm^3)	267.88 (104.2)	245.01 (83.3)	0.282
Urea (mg%)	22.95 (10.76)	21.96 (8.96)	0.606
Creatinine (mg%)	0.941 (0.21)	1.08 (1.59)	0.728
Bilirubin (mg%)	0.836 (0.69)	0.87 (0.66)	0.249

SD – Standard deviation; TA – Tranexamic acid

re-exploration of the wound for bleeding on the day of surgery. The incidence of oro-cutaneous fistula was also similar seen in two patients in TA group and three patients in placebo group. There were no thromboembolic complications in either group.

DISCUSSION

In this randomised, double-blind, placebo-controlled study, intravenous administration of TA did not reduce blood loss in patients undergoing supramajor surgery for oral cancers. The need for blood transfusions was also not reduced. Post-operative blood loss was lower in the patients receiving TA but this difference was neither clinically significant and nor did it cause increased requirement for transfusion in the placebo group. TA administration was safe as there was no surgical complication, organ dysfunction or thromboembolic episode.

Coagulation and fibrinolysis are both activated by surgical trauma.[6] Inhibiting fibrinolysis reduces blood loss by increasing clot strength. During major surgery, exposure of tissues to injury causes release of enzymes, mainly tPA, thereby activating the fibrinolytic system.[7] The fibrinolytic response is most pronounced in the intraoperative and early post-operative period. Ekbäck *et al*. found increased levels of tPA, plasmin-antiplasmin complex and thrombin-antithrombin complex, indicating activation of coagulation. Hyperfibrinolytic phase, indicated by increased levels of D-dimers was seen in the placebo group from 4 h onwards intraoperatively.[8] The D-dimers levels returned to baseline on the first post-operative day. In contrast, the D-dimers levels were much lower throughout in patients given TA indicating inhibition of fibrinolysis. Benoni *et al*. measured levels of thrombin fragments (1 + 2), D-dimers plasminogen, α2 antiplasmin, tPA and plasminogen activator inhibitor (PAI-1) in blood from wound as well as peripheral venous blood.[9] They found significant activation of coagulation and fibrinolysis in both samples, much more in the blood than the wound. D-dimer levels were lower in TA group indicating inhibition of fibrinolysis. In both these studies, blood loss was lower in patients receiving TA. In patients undergoing an orthotopic liver transplant, there was significant fibrinolytic activity, i.e., high levels of D-dimer and fibrin degradation products, in the normal saline group in contrast to patients receiving TA. Inhibition of fibrinolysis by TA was evident from higher clot lysis index than patients given placebo.[10] However, the need for transfusion was similar in both groups.

TA has been shown to reduce blood loss in a variety of surgical procedures such as coronary revascularisation, orthotopic liver transplantation, scoliosis correction surgery, other orthopaedic procedures and caesarean sections.[8,11-16] A recent meta-analysis of over 1100 patients also demonstrated the efficacy of antifibrinolytic agents in reducing blood loss in patients undergoing hip athroplasty and total knee replacement.[17] The likelihood of patients needing transfusion was reduced by 52%. TA was the most efficacious (RR 0.47 [95% CI: 0.40–0.55]). The incidence of venous thromboembolism with antifibrinolytic agents was similar to placebo. In trauma patients, TA reduced all-cause mortality as well as the risk of mortality due to bleeding.[18] It has been suggested that TA should be added for routine use in treatment of trauma patients.[19]

Reducing the need for transfusion in cancer patients may be particularly important as the literature suggests increased recurrence rates in head and neck, colorectal, oesophageal and hepatocellular malignancies after blood transfusion.[20-24] Blood transfusion was associated with earlier recurrence in patients with advanced ovarian cancer undergoing cytoreductive surgery.[25] The literature on the use of TA in cancer patients to reduce blood loss is scarce, with varied results. In 200 patients undergoing retropubic radical prostatectomy, TA led to a 21% absolute reduction (95% CI: 7–34%) in transfusion rate.[26] The median no of units transfused was also reduced (0 [interquartile range (IQR): 0–1] vs. 1 [IQR: 0–1.5]; $P = 0.004$) in patients who received TA. The blood loss was higher in placebo group (1103 ml [SD 500.8] vs. 1335 ml [SD 686.5], [95% CI: 29.7–370.7; $P = 0.02$]). In a small case series with historical controls, Bednar *et al*. found that mean estimated blood loss was not reduced by TA in patients undergoing surgical treatment for metastatic tumours of the spine.[27] In patients undergoing

various procedures for head and neck cancers, TA administration did not reduce the drainage duration.[28] In patients undergoing hepatectomy for hepatic tumours, perioperative administration of TA was shown to reduce blood loss (300 ml [30–2100] vs. 600 ml [40–3410]).[29]

Cancer patients are hypercoagulable due to the production of various procoagulant activities, such as tissue factor and cancer procoagulant.[30] Cancer cells also increase fibrinolytic activity as tPA and urokinase-type plasminogen activator and PAI-1 are expressed on their surface. We wanted to document effective inhibition of fibrinolysis with TA, and, therefore, we performed TEG in first 100 patients. Modrau *et al*. found a distinct difference in coagulation profile when comparing patients with benign and malignant colorectal lesions.[31] Patients with malignant lesions were hypercoagulable and also showed fibrinolysis inhibition. Our patients were hypercoagulable to start with (shortened r and k-time and wide α angle), and there was also decreased fibrinolytic activity in both groups (high MA and >80% clot lysis index at 60 min). This explains why TA administration did not lead to a reduction in blood loss. It is unlikely that the dose of TA used by us was inadequate to achieve inhibition of fibrinolysis as it was similar to doses used in other studies that demonstrated reduced blood loss.[32-34] An even smaller dose of TA (2 mg/kg/h infusion) reduced fibrinolysis in patients undergoing orthotopic liver transplantation.[17] In a dose response study, the D-dimer concentration was reduced with the smallest dose (2.5 mg/kg) of TA as compared to placebo but the reduction of blood loss became significant from the doses upwards of 10 mg/kg.[35]

Our patients did not experience any episodes of symptomatic venous thromboembolism. This may be because the fibrinolytic activity is more pronounced in the wound than in the peripheral blood in patients undergoing surgery.[9] The site of action of TA is, therefore, more likely to be limited to the surgical field than being generalised. Therefore, TA may be safely used in these patients.

CONCLUSIONS

TA (10 mg/kg) did not reduce blood loss and need for transfusion of red cells in patients undergoing head and neck cancer surgeries under general anaesthesia.

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Conflicts of interest

There are no conflicts of interest.

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Announcement

Conference Calender - 2016

Name of the conference: 64th Annual National Conference of the Indian Society of Anaesthesiologists, ISACON 2016
Date: 25th to 29th November 2016
Venue: Punjab Agricultural University, Ludhiana
Organising Secretary: Dr. Sunil Katyal
Contact: +91 98140 30552
E-mail: katyalsunilmd@gmail.com
Website: www.isacon2016.com

Name of the conference: ISACON TELANGANA - 2016
2nd Annual State Conference of ISA Telangana State Chapter
Date: 27th to 31st July 2016
Venue: Govt. Medical College & Teaching Hospital, Nizamabad
Organising Secretary: Dr. Chintala Kishan
Contact: +91 98480 71377 & 99490 46637
E-mail: isacontelangana2016@gmail.com, chintala_kishan@yahoo.in
Website: www.isatelangana.org

Name of the conference: ISACON SOUTH - 2016
22nd Annual South Zone Conference of ISA
Date: 19th to 21th August 2016
Venue: KLE Centenary Convention Center, J N Medical College Campus, Nehru Nagar, Belagavi, Karnataka
Organising Secretary: Dr. Manjunath C. Patil
Contact: +91 97431 10637
E-mail: isaconsouth2016@gmail.com
Website: www.isaconsz2016.in

Name of the conference: ISACON KERALA – 2016
40th Annual State Conference of ISA Kerala State Chapter
Date: 7th to 9th October 2016
Venue: MAC FAST Auditorium, Tiruvalla
Organising Secretary: Dr. Koshy Thomas
Contact: +91 94473 98170
E-mail: thomaskoshy59@gmail.comin

Name of the conference: 17th Annual Conference of Indian Society of Neuroanaesthesiology and Critical Care (ISNACC)
Date: 5th to 7th February 2016
Venue: NIMHANS Convention Centre, Bengaluru
Organising Chairperson: Dr. Badarinarayan V
Organising Secretary: Dr. H K Venkatesh
Contact: +91 97399 73940
E-mail: venkatneuro@gmail.com
Website: www.isnacc2016.org

CMEs Calender

Name of the CME: ISAMIDKON 2016
PG Quest & Midterm CME of ISA Kerala State Chapter
Date: 12th to 13th March 2016
Venue: MOSC Medical College, Kolenchery, Ernakulam
Organising Secretary: Dr. Sam Philip
Contact: +91 94472 09010
E-mail: isamidkon2016@gmail.com
Website: www.isamidkon2016.com

Name of the CME: PG Excel - 2016
Annual CME of ISA Karnataka State Chapter
Date: 13th to 14th February 2016
Venue: Mysore Medical College & Research Institute, Mysuru
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