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Tranexamic acid in supratentorial brain tumors resection surgery: A study on cerebral oxygenation and metabolism

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Abstract:

Background: Significant blood loss associated with brain tumor resections entails proper hemostasis, and this is essential for adequate cerebral perfusion and metabolism

Objective: to examine the clinical effectiveness of tranexamic acid (TXA) in preserving cerebral blood flow, brain oxygenation and metabolism within the physiologic values with using jugular venous O2 saturation as a primary outcome.

Methods: This study enrolled 50 patients scheduled for supratentorial brain tumors (SBT) resections and divided into two groups; group T (tranexamic acid group) and group C (placebo control group). Group T (n=25): where patients received 1gm bolus dose of TXA over 20 min after anaesthesia induction and before skin incision followed by maintenance of 400 mg/h till end of the surgical technique while group C (n=25): patients received placebo in the form of normal saline infusion of the same volume, rate and time.

Results: Jugular venous oxygen saturation ($SjvO_2$) showed significantly higher values in tranexamic acid group than placebo group at 3h, 4h, 5h intraoperative with p values 0.003,0.02, 0.005 respectively and direct, 2h, 4h, 8h postoperative with p values 0.001,0.04, 0.038, 0.02 respectively.

Conclusion: TXA use in SBT resection surgery demonstrated efficacy in decreasing total blood loss and blood transfusion subsequently improving hemodynamics, cerebral oxygenation and metabolism

Keywords: brain tumor -tranexamic acid- hemostasis- cerebral oxygenation –metabolism.

INTRODUCTION

Significant blood loss is a common complication following resection of supratentorial brain tumors (SBT). And the risky effects of this blood loss operatively result in serious hemodynamic instability that requires transfusion of large amounts of crystalloids, colloids and allogeneic blood. Adding to the above risks, hazards of allogenic blood transfusion as infection transmission, post-operative sepsis and immune modulation**.[1]**

The amount of bleeding is dependent upon size, site, and surgical procedure of tumor resection. The cause of hemorrhage depends on many factors, which include slow oozing from the tumor, rapid loss from vascular structures, bleeding from feeder vessels, release of local tissue activators that activates coagulation cascade and local hyper fibrinolysis. **[2]**

Brain neoplasms release tissue plasminogen activator and tissue factor. This eventually leads to hyperfibrinolysis. Also, the coagulation cascade could be activated by molecules on the tumor surface through non-specific tissue thromboplastin.**[3]**

So, many strategies to minimize blood loss have been evolved. These strategies depend on usage of pre-operative erythropoietin, autologous pre-donation, perioperative blood salvage and usage of drugs including desmopressin, antifibrinolytic, and recombinant Factor VII.**[4]**

Modern blood conversation strategies include the utilization of anti-fibrinolytic agents. TXA is lysine analog acting by competitive inhibition of plasmin and plasminogen to prevent dissolution of clots. **[5]**

The ability of TXA to prevent massive perioperative bleeding is proven in many surgical techniques. But, its use in neurosurgical procedures is limited to spinal and extracranial surgery. **[6]**

Reducing the perioperative blood loss in brain tumor resection surgery has been found to be linked to a greater rate of total tumour resection, improved long-term prognosis and decreased recurrence. **[7]**

The cerebral metabolic rate (CMR) is the rate of utilizing cerebral metabolic substrates [such as oxygen, glucose, or lactate. High cerebral blood flow (CBF) implied for the higher CMR. The brain consumes about 20 percent of basal O_2 consumption (50 ml /minute) at rest and with complete rely on oxygen-dependent glucose metabolism to produce energy. CMRO2 = CBF × (A - V) O_2 content difference. **[8]**

Monitoring of SjvO2 has been proven to be beneficial in caring for comatose patients with head injuries in ICU and in the intraoperative management of neurosurgical patients. **[9]**

Cannulation and sampling of jugular bulb helped a lot in intraoperative monitoring of cerebral hemodynamics that is not an easy task. Measurement of SjvO2 has been utilized evaluate CBF, brain oxygenation and CMR. **[10]**

Hence, we conducted this current randomized double-blinded placebo-controlled trial to examine the effectiveness of TXA in cerebral oxygenation and metabolism through its intraoperative hemostatic effect in subjects undergoing SBT resection surgery.

Hypothesis and Aim of the work

It was hypothesized that tranexamic acid may reduce blood loss during resection of brain tumors. In patients with SBT, perioperative reduction of blood loss was required to preserve cerebral blood volume and flow within the physiologic ranges; an issue that can be achieved using TXA. Our study was aimed at evaluating the clinical effectiveness of tranexamic acid in preserving brain oxygenation and metabolic requirements within the physiologic values.

The primary outcome in our study was SjvO2, which is indicative for brain oxygenation and

CMR, while perioperative evaluation of blood loss, hemodynamics, the need of allogenic blood transfusion, any adverse effects of TXA, and surgical variables (duration of surgery, anesthesia, intensive care unit stay) as secondary outcomes. To our knowledge, there is a little study available in the literature discussing the effectiveness of TXA on cerebral hemodynamics during surgical excision of brain tumors.

MATERIAL AND METHODS

The current prospective double blinded, randomized, and controlled study was approved by the ethical and scientific committee (IRB) of Mansoura University, with reference number **MD.21.5.476**, and was registered by Pan African Clinical Trials Registry with a registration code **PACTR202204547358213.** Written consents were obtained from consecutive patients undergoing SBT resection surgery at Department of Anesthesia and Surgical Intensive Care, Faculty of Medicine, Mansoura University at a period from September 2022 to September 2023. And was conducted in accordance with the Helsinki Declaration 2013.

A total of 50 patients aged 20-60 years of either sex were enrolled in the study. Patients with American Society of Anesthesiologists physical status (ASA) grades I, II and III patients with Glasgow Coma scale (GCS) > 10 and scheduled for SBT resection surgery were included.

Exclusion criteria:

Exclusion criteria included refusal of participation, infratentorial tumors, allergy to TXA, history of bleeding diathesis, pre-operative thromboembolism or family history of thromboembolic events, administration of drugs that can affect coagulation, epileptic patients, pregnancy, associated sever uncompensated cardiac, renal, hepatic or respiratory diseases.

Randomization

Patients were randomly divided into 2 groups by closed envelops randomization (Figure 1):

-Group T (TXA group): Patients received 1gm bolus dose of TXA over 20 min after induction of anesthesia but before skin incision followed by maintenance of 400 mg/h till end of the operation.

-Group C (placebo control group): Patients received placebo in the form of normal saline of the same volume, rate and time.

Blindness:

Anesthesia physician not involved in patient's management prepared the studied drug. Another anaesthesiologist who was blinded to the allocated group evaluated the drug effect intraoperative and postoperative and collect data.

Anesthetic Management:

The day before the surgery, an informed written consent was signed by each patient. Patients were fasted for 8 hours. And they were subjected to detailed history taking, clinical evaluation including manifestations of increased intra cranial tension, GCS and ECG. Laboratory investigations including; CBC, liver function tests, creatinine level, blood sugar level, prothrombin time and INR.

At the operative day, upon arrival at the preanesthetic room, a 18G intravenous cannula was inserted in a peripheral vein and ringer acetate was infused. The patient was given midazolam 0.03 mg /kg and fentanyl 1 µg/kg as premedication 10 minutes prior to induction. Pre-anesthetic monitoring includes pulse oximetry, ECG, blood pressure measurement (NIBP).

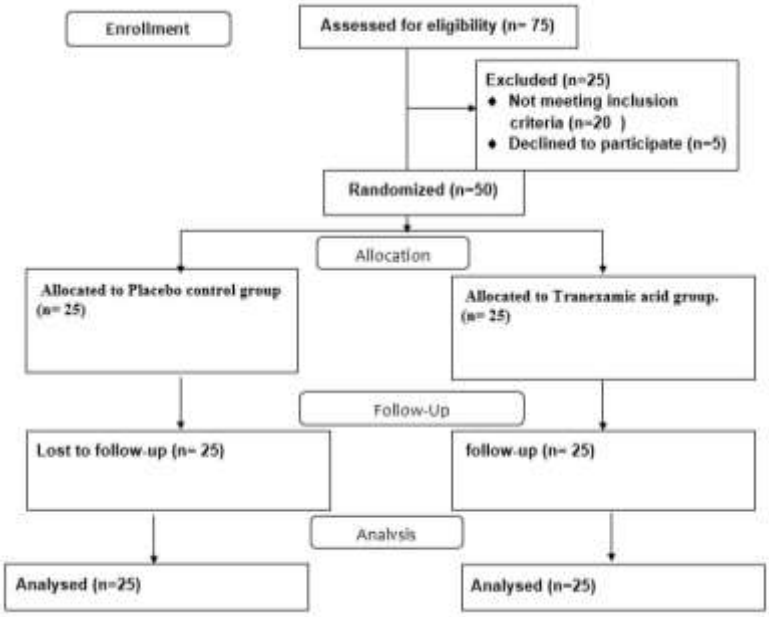

Figure (1): Consort diagram for patient recruitment in the trial

Anesthetic plan:

On the operating theater, the patient was monitored using NIBP measurement, pulse oximetry, ECG, capnography and temperature monitoring probe. Afterwards,100% oxygen was delivered to the patient for 3-5 min. Anesthesia was then induced with propofol (2 mg/kg). Endotracheal intubation was facilitated by atracurium besylate (0.5mg/kg). Dexamethasone 8 mg was given after induction. Maintenance of anesthesia by sevoflurane at a concentration of 2% and incremental doses of 1/5 of the initial atracurium dose every 20 minutes to maintain the muscles relaxed. Fentanyl in repeated doses (20µ) whenever needed (pulse or mean arterial pressure (MAP) are increased > 20% of the basal levels). Normothermia (36ºC) was maintained through adjusting room temperature and infusion of warm fluids. Mechanical ventilation was maintained by Volume controlled mode was attained (TV = 8–10 ml/kg and I/E ratio 1:2 through closed circuit with fresh gas flow about 3 L) with using oxygen 40% in air mixture. Monitoring of end-tidal CO2 was done by using mainstream capnograph. With modifying minute ventilation to maintain EtCO2 about 30 mm Hg.

Fluids and Blood transfusion:

In group T: immediately after anesthesia induction and before skin incision 1 gm bolus dose of tranexamic acid (hemoxamine 500mg/5ml, Cid, Egy) was given over 20 minutes followed by continuous infusion of 400 mg/h till end of surgical procedure.

In group C: immediately after the induction and before skin incision placebo (normal saline 0.9%) bolus dose was given over 20 min followed by a maintenance dose infusion in the same volume, rate and time.

Mannitol 20% (1 gm/kg at a rate of 20 mL/minute) was given for diuresis before dura opening in all patients. Fluids in the form of isotonic crystalloids (ringer acetate) and colloids were administered to maintain CVP around 8-10 mmHg. Blood and blood products underwent transfusion to maintain hemoglobin ≥10 gm/ dl and with blood loss (> 20% of total blood volume).

Cannulation:

The Seldinger technique was used to secure the following catheters afterwards induction of

anesthesia

Arterial cannula: First Modified Allen test was done then local infiltration of 0.5 ml lidocaine 2%. The radial artery of patient's non-dominant hand was cannulated with 20 G arterial cannula under complete aseptic technique.

Central venous catheter*:* was secured into right subclavian vein under aseptic conditions guided by ultrasound.

Jugular bulb catheterization technique:

Patients were put in supine position with neutral position of the head. The right internal jugular vein was cannulated in the cephalad direction, at the cricoid cartilage level then catheter was advanced through the introducer into jugular bulb, approximately at mastoid process level **[11].** Once inserted, the catheter was placed as close as possible to jugular bulb's roof to ensure its correct position and to avoid mixing with extra-cerebral blood. The catheter tip's position was confirmed by a lateral or an antero-posterior X-ray of the neck **[12]**. In the lateral view, the tip should be above the disc between C1 and C2 and as close as possible to skull base=. On antero-posterior view, the tip lies above a line connecting the atlanto-occipital joint space to the lower orbital margin. In addition, catheter tip must lie superior to a line that connects the tips of mastoid processes **[12,13].**

Reversal:

After satisfactory reversal of residual neuromuscular block by neostigmine 0.05 mg/kg with atropine 0.02 mg/kg, patient was extubated and transferred to the neuro-surgical ICU.

Postoperative management:

In the neuro-surgical ICU, the patient was monitored for at least 24 hours postoperative.

Perioperative transfusion cut off value: packed RBCs was transferred if Hb concentration <10 g/dl. Fresh frozen plasma was administered if INR > 1.5. Transfusion of platelets was started if platelets <120000.

Grading of patient physical status at hospital discharge by the Extended Glasgow outcome scale (GOSE) ranging from 8 to 1. **[14]**

8(**Good recovery** *Upper):* no existing problems associated with brain injury affecting daily activity, **7** (**Good recovery** *lower***):** minor problems affecting daily activities. **6** (**Moderate disability:** *Upper):* decreased work capability; resuming <50% of preoperative level of social life. **5** (**Moderate disability:** *lower):* cannot work.**4** (**Sever disability:** *Upper):* can be left alone > 8h daily, however cannot travel without help. **3** (**Severe disability** *Lower):* frequently necessitates someone to be around at home for his help mostly all day long. **2** (**Persistent vegetative state):** characterized by unresponsiveness and speechlessness. **1** (patient died)

Monitoring and sampling:

- HR, MAP and SpO2was recorded before induction, after induction then every 1hr up to the end of surgery, also in the ICU direct, 2, 4, 6, 12, 18, 24 hours postoperative.
- ETCO2 was recorded after induction then every 1hr up to the end of surgery while CVP record after cannulation then every 1hr up to the end of surgery, also in the ICU direct, 2, 4, 6, 12, 18, 24 hours postoperative.
- Monitoring of blood loss was done by recording:

a) Total amount of intraoperative and post-operative blood loss for 24 hours.
b) Total number of blood /blood products units that was given.
c) Hb level was recorded basally, direct and 24 h postoperative.

- Monitoring of coagulation profile was carried out by measuring INR, prothrombin time

and bleeding time basally, at the end of the surgery ,6h ,12h,24h postoperative.

- Duration of surgery, urine output, adverse effects of tranexamic acid if present, duration of ICU stay were also recorded
- **Laboratory assessment of blood sampling:**

- **Site**: Simultaneous blood samples obtained from radial artery and jugular bulb. **For** blood gases (arterial and jugular)

- Timing: -Immediately after cannulation, every 1 hour during surgery, at the end of the surgery, 2, 6, 12, 18,24 hours postoperative in ICU

❖ **Calculation of parameters**:

➢ **Estimated cerebral metabolic rate for O2: (eCMRO2): [15]**

CaO2= (SaO2 x Hb x 1.39) + 0.003 x PaO2.

CjO2 = (SJVO2 x Hb x 1.39) + 0.003 x PJVO2.

Ca-jO2= CaO2– CjO2.

$$e\mathrm{CMRO2} = \mathrm{Ca-jO2} \times \frac{\mathrm{PaCO2}}{100}$$

Where Ca-jO2 is arterio-jugular O2 content difference.

PaCO2 is arterial partial pressure of CO2

➢ **Cerebral Extraction Ratio of O2 (CEO2): [16]**

Difference between arterial O2 saturation and jugular bulb oxygen saturation,

CEO2 = SaO2 – SJO2

➢ **Cerebral Blood Flow equivalent (CBFe):[17]**

Calculated as a reciprocal of arterio-jugular O2 content difference (Ca-jO2) and this is indicator for relating flow and metabolism

$$\boldsymbol{CBFe = \frac{1}{Ca-JO_2}}$$

Sample size

A pilot study was carried out on ten patients per group. G. Power program (3.1.9.7.). was applied for calculation of this study power. A priory analysis using two-tailed t test for difference among 2 independent means as a statistical test with the difference between the SjvO2 as the primary outcome. With calculation of the effect size as 1.07, α error was 0.05 and power (1-ß error) of 0.95 resulted in a sample size of 48 subjects. 50 patients were enrolled to compensate for any dropout or deviation from normality, and so each group included 25 patients.

Statistical analysis

The SPSS program V 22 was used for the statistical analysis of data. The normality of data distribution was tested with Shapiro-Wilk test only if significant data revealed to be non-parametric. Unpaired student-t test was utilized to compare numerical variables among groups, otherwise for non-parametric; the Mann–Whitney test was applied. Data described as means (±SDs) for quantitative data or as numbers and percents for qualitative data. Chi-square test was utilized for qualitative data. The result with probability (P) < 0.05 was considered statistically significant.

Results

Demographics including age, sex, body mass index, ASA status, pre-operative GCS, pathological features of the tumor and surgery duration were presented without significant difference between both groups **(Table 1).**

A non-significant difference existed among the two groups regarding urinary output, duration of ICU stay and GOSE score. Hb level showed higher values in Group T versus group C

postoperative immediately and 24 h postoperative. Both Total intraoperative and postoperative blood loss showed significantly lower values in group T than in group C with p values (0.04& 0.01) respectively, also intra-operative and post-operative blood transfusion rates were significantly lower in group T versus group C with p values <0.001 **(Table 2).**

Heart rate showed significantly lower values in tranexamic acid group than placebo group at 2h, 3h, 4h, 5h intraoperative and direct, 2h, 4h postoperative readings **(Table 3).**

MAP showed significantly higher values in tranexamic acid group than placebo group at 2h, 3h, 4h, 5h intraoperative readings **(Table 4).**

End tidal carbon dioxide (ETCO2) showed significantly higher values in tranexamic acid group at 2h, 3h, 4h intraoperative readings **(Table 5).**

Central venous pressure (CVP), INR, prothrombin time (PT), bleeding time (BT) showed no significant difference between the two studied group **(Table 6& 7).**

Jugular venous oxygen saturation (SJVO2) showed significantly higher values in tranexamic acid group than placebo group at 3h, 4h, 5h intraoperative and direct, 2h, 4h, 8h Post operative **(Table 8).**

Estimated cerebral metabolic rate for O2 (eCMRO) showed significantly lower values in tranexamic acid group than placebo group at 1h, 2h,3h, 4h, 5h intraoperative and direct, 2h, 4h Post operative **(Table 9).**

Cerebral extraction ratio of O2(CEO2) showed significantly lower values in tranexamic acid group than placebo group at 3h, 4h intra operative and direct, 2h, 4h, 8h Post operative **(Table 10).**

Arterio-Jugular oxygen content difference (CaO2-jO2) showed significantly lower values in tranexamic acid group than placebo group at 1h, 2h, 3h, 4h, 5h intraoperative and direct, 2h, 4h, 8h postoperative **(Table 11).**

Cerebral blood flow equivalent (CBFe) showed significantly higher values in tranexamic acid group than placebo group at 1h, 2h, 3h, 4h, 5h intraoperative and direct, 2h, 4h, 8h postoperative **(Table 12).**

Table (1): Demographic data of the studied groups (Age, Sex, BMI) , ASA status, preoperative GCS, Pathology of the lesion and duration of surgery. Data are expressed in mean ± (SD) or number and %.

	Group C (n=25)	**Group T (n=25)**	**p**
Age (years)	44.72±11.25	48.12±12.48	0.317
Sex n (%) • **Male** • **Female**	 14 (56%) 11 (44%)	 17 (68%) 8 (32%)	0.382
BMI (kg/m^2)	33.60±1.53	33.96±1.95	0.471
ASA status • **I** • **II**	 13(52%) 12(48%)	 12(48%) 13(52%)	0.777
Preoperative GCS	14.8 ± 0.33	14.8 ±0.37	0.69
Pathology • **Meningioma** • **Glioma**	 9 (36%) 16 (64%)	 8 (32%) 17 (68%)	0.765
Duration of surgery (hr)	4.30±0.5	4.96±0.14	0.278

Group C; placebo control group, Group T; tranexamic acid group.
BMI: Body Mass Index, ASA: American Society of Anaesthesiologists status, GSC: Glasgow coma scale

Table (2): Intraoperative and postoperative data of the studied groups: urinary output, blood loss, blood transfusion intraoperative and postoperative, ICU stay postoperative and GOSE score. Data expressed in mean± SD or number and %.

	Group C n=25	**Group T n=25**	**P value**
UOP (ml)	1096±213	1168±137	0.162
Hb (g/dl)			
Preoperative	11.8±0.59	11.7±0.65	0.48
Immediate postoperative	10.6±0.4	10.8±0.4	0.03*
24 h postoperative	10.5±0.3	10.8±0.3	0.04*
Total intraoperative blood loss (ml)	678±260	532±114	0.04*
Total postoperative blood loss (ml)	554±165	474 ±155	0.01*
Intraoperative Blood transfusion (unit)			
0	3 (12 %)	16 (64.0 %)	<0.001*
1	7 (28 %)	9 (36.0 %)	
2	15 (60%)	0	
Postoperative blood transfusion (unit)			
0	4 (16 %)	20 (80 %)	<0.001*
1	19 (76 %)	5 (20 %)	
2	2 (8 %)	0	
GOSE score	8.28±1.4	8.0±0.0	0.322

Group C; placebo control group, Group T; tranexamic acid group.
UOP: Urine output. Hb: Hemoglobin, GOSE score; Extended Glasgow outcome score.
Statistically significant p < 0.05, when compared with the other group.

Table (3): Heart rate changes (beat/minute) in the studied groups:

	HR (beat/min)		
	Group C n=25	**Group T n=25**	**P**
Basal IO	79.64±8.67	80.56±8.84	0.712
P I	83.60±8.41	86.36±8.95	0.267
1 h IO	85.24±7.11	84.36±8.82	0.699
2h IO	93.80±8.86	79.76±8.29	0.001*
3h IO	96.92±9.47	79.64±8.08	0.001*
4h IO	99.25±9.09	84.5±8.45	0.001*
5h IO	103.87±7.25	91.38±6.44	0.001*
Direct PO	100.64±10.8	88.76±7.76	0.001*
2h PO	98.08±11.47	85.28±7.76	0.001*

4h PO	96.16±11.37	85.12±7.87	0.001*
6h PO	88.08±10.03	83.60±8.28	0.09
12h PO	84.24±9.79	81.72±9.16	0.352
18h PO	81.72±9.15	79.96±7.88	0.511
24h PO	80.84±9.22	79.20±7.82	0.501
Data are expressed in mean ± SD. **Group C; placebo control group, Group T; tranexamic acid group.** Statistically significant $p < 0.05$, when compared with the other group.			

Table (4): Mean arterial blood pressure (MAP)(mmHg) in the studied groups;

	MAP (mmHg)		
	Group C n=25	**Group T n=25**	**P**
Basal IO	87.6±10.04	81.60±11.10	0.051
P I	83.04±9.46	78.68±8.41	0.092
1 h IO	82.56±9.49	81.92±11.01	0.827
2h IO	73.40±7.34	80.28±9.58	0.006*
3h IO	72.24±7.28	80.44±9.94	0.002*
4h IO	73.76±7.46	81.16±9.17	0.003*
5h IO	73.76±7.46	81.16±9.17	0.003*
Direct PO	84.44±12.67	85.92±9.89	0.647
2h PO	82.08±11.72	85.92±9.89	0.367
4h PO	77.93±9.52	80.56±8.19	0.593
6h PO	86.88±12.41	82.88±11.51	0.243
12h PO	86.6±10.88	82.0±10.75	0.139
18h PO	86.16±11.05	81.88±11.06	0.177
24h PO	86.8±10.86	81.32±11.15	0.085
Data expressed as Mean ±SD. **Group C; placebo control group, Group T; tranexamic acid group.** MAP; mean arterial blood pressure . Statistically significant $p < 0.05$, when compared with the other groups.			

Table (5): End tidal carbon dioxide (ETCO2) (mmHg) in the studied groups. Data expressed as Mean ±SD.

	ETCO2(mmHg)		
	Group C n=25	**Group T n=25**	**P**
Basal IO			
P I	36.72±1.31	36.28±1.40	0.256
1 h IO	32.96±1.51	33.56±1.87	0.219
2h IO	32.24±1.83	33.40±1.71	0.025*
3h IO	32.40±1.55	33.76±1.64	0.004*
4h IO	33.04±1.55	34.92±2.39	0.002*
5h IO	34.87±1.96	36.0±1.85	0.193

Group C; placebo control group, Group T; tranexamic acid group.
ETCO2; End tidal carbon dioxide.
Statistically significant $p < 0.05$, when compared with the other groups.

Table (6): Central venous pressure (CVP) (mmHg) in the two studied groups; Data expressed as Mean ± SD.

	CVP (mmHg)		
	Group C n=25	**Group T n=25**	**P**
PC	9.04± 1.33	9.2 ± 0.86	0.556
1 h IO	9.16 ± 2.19	8.8 ± 0.76	0.445
2h IO	8.7 ±1.39	8.6 ±1.15	0..398
3h IO	8.88 ± 1.1	8.36 ± 0.9	0.159
4h IO	8.6 ± 1.1	8.3 ± 0.85	0.231
5h IO	9.1 ± 0.99	8.7 ± 0.8	0.209
Direct PO	8.5 ± 1.3	8.6 ± 1	0.976
2h PO	8.9 ± 1.2	8.8 ± 1	0.944
4h PO	8.7 ± 1	8.8 ± 0.7	0.878
6h PO	8.5 ± 1	9.04 ± 0.8	0.069
12h PO	9.2 ± 1	9.3 ± 0.6	0.992
18h PO	9.16 ± 2.2	9.16 ± 2.2	0.445
24h PO	8.7 ± 0.81	9.1 ± 1	0.21

Group C; placebo control group, Group T; tranexamic acid group.
CVP ;central venous pressure.
Statistically significant $p < 0.05$, when compared with the other groups.

Table (7): International normalised ratio (INR), bleeding time (minutes) and prothrombin time (seconds) in the studied groups. Data are expressed in mean ±SD.

	Group C n=25	**Group T n=25**	**P**
INR basal	1.10±0.1	1.09±0.10	0.774
At the end of the surgery	1.21±0.14	1.16±0.13	0.181
6 h postoperative	1.22±0.13	1.18±0.14	0.290

12 h postoperative	1.19±0.14	1.16±0.12	0.385
24 h postoperative	1.16±0.11	1.15±0.12	0.715
Bleeding time			
basal	3.88±0.83	4.0±0.82	0.609
At the end of the surgery	3.96±0.84	4.0±0.82	0.865
6 h postoperative	3.96±0.84	4.0±0.82	0.865
12 h postoperative	3.96±0.84	3.96±0.82	0.865
24 h postoperative	3.50±1.24	3.54±1.74	0.865
prothrombin time			
basal	13.50±1.24	13.54±1.74	0.926
At the end of the surgery	15.72±2.49	15.52±1.50	0.733
6 h postoperative	16.60±4.04	16.0±2.14	0.515
12 h postoperative	16.48±3.48	16.12±2.52	0.677
24 h postoperative	16.40±3.16	15.96±2.78	0.604

Group C; placebo control group, Group T; tranexamic acid group.
INR: International normalised ratio.
Statistically significant $p < 0.05$, when compared with the other groups.

Table (8): Jugular venous oxygen saturation (SjvO2) (%) in the studied groups. Data are expressed in mean ±SD.

	SjvO2 (%)		
	Group C n=25	**Group T n=25**	**P**
PC	71.68±3.80	71.36±2.69	0.733
1 h IO	70.08±3.30	71.16±2.32	0.187
2h IO	66.04±3.47	67.48±3.18	0.132
3h IO	63.64±4.48	67.20±3.58	0.003*
4h IO	62.70±5.87	66.20±4.06	0.02*
5h IO	60.73±5.48	67.39±2.92	0.005*
Direct PO	64.44±4.98	68.28±2.32	0.001*
2h PO	62.88±5.78	66.88±3.11	0.004*
4h PO	64.0±6.84	67.16±2.88	0.038*
6h PO	64.24±6.85	66.32±2.88	0.168
12h PO	67±6.76	66.84±3.13	0.915
18h PO	66.08±7.47	67.84±3.30	0.286
24h PO	66.80±7.91	68.16±3.24	0.458

Group C; placebo control group, Group T; tranexamic acid group.
SJVO2; jugular Oxygen saturation(%).
Statistically significant $p < 0.05$, when compared with the other groups.

Table (9): Estimated cerebral metabolic rate for O_2 (eCMRO2) (ml/100 g/min) in the studied groups. Data are expressed in mean ±SD.

eCMRO2(ml/100gm/min)			
Time	**Group C n=25**	**Group T n=25**	***P***
PC	1.87±0.24	1.98±0.2	0.133
1 h IO	2.1±0.14	1.98±0.22	0.03*

2h IO	2.28±0.25	2.13±0.17	0.016*
3h IO	2.27±0.25	2.10±0.22	0.01*
4h IO	2.33±0.37	2.14±0.25	0.048*
5h IO	2.47±0.94	2.01±0.15	0.006*
Direct PO	2.22±0.32	1.95±0.18	0.001*
2h PO	2.44±0.39	2.18±0.25	0.01*
4h PO	2.38±0.59	2.12±0.2	0.05*
6h PO	2.45±0.55	2.28±0.22	0.183
12h PO	2.19±0.5	2.22±0.19	0.806
18h PO	2.33±0.53	2.24±0.37	0.513
24h PO	2.13±0.56	2.06±0.35	0.618

Group C; placebo control group, Group T; tranexamic acid group.
e CMR : estimated cerebral metabolic rate for O2.
Statistically significant p < 0.05, when compared with the other groups.

Table (10): Cerebral extraction ratio of O_2(CEO_2)(%) in the studied groups. Data are expressed in mean ±SD.

CER%			
Time	**Group C n=25**	**Group T n=25**	***P***
PC	27.76±4.44	28.64±2.69	0.401
1 h IO	29.80±3.42	28.84±2.32	0.252
2h IO	33.96±3.47	32.52±3.18	0.132
3h IO	36.36±4.48	32.80±3.58	0.003*
4h IO	37.29±5.87	33.79±4.06	0.02*
5h IO	36.07±31.13	32.63 ±2.92	0.761
Direct PO	35.56±4.98	31.72±2.32	0.001*
2h PO	37.12±5.78	33.12±3.11	0.004*
4h PO	36±6.84	32.84±2.88	0.038*
6h PO	35.76±6.85	33.68±2.88	0.168
12h PO	33±6.76	33.16±3.13	0.915
18h PO	33.92±7.47	32.16±3.30	0.286
24h PO	33.12±7.91	31.84±3.24	0.258

Group C; placebo control group, Group T; tranexamic acid group.
CEO2: Cerebral Extraction Ratio of O2 .
Statistically significant p < 0.05, when compared with the other groups.

Table (11): Arterio-Jugular oxygen content difference (CaO_2-jO_2)(ml O2/100ml blood) in the studied groups.Data are expressed in mean ±SD.

CaO2-jO2(ml O2/100ml blood)			
Time	**Group C n=25**	**Group T n=25**	**P**

PC	5.65 ± 0.57	5.41 ± 0. 52	0.14
1 h IO	4.77 ±0.56	5.17 ±0.38	0.019 *
2h IO	4.51± 0.61	5.61 ±0. 45	0.001*
3h IO	6.45 ± 0.74	5.46 ± 0.59	0.003*
4h IO	6.12 ± 0.98	5.62 ±0. 67	0.021*
5h IO	6.53 ± 0.91	5.43 ± 0.48	0.005*
Direct PO	5.91 ± 0.82	5.28±0. 38	0.001*
2h PO	6.17 ± 0.96	5.51 ± 0.51	0.004*
4h PO	5.99 ± 0.11	5.46±0. 47	0.039*
6h PO	5.95 ± 0.11	5.6 ± 0.47	0.168
12h PO	5.49 ± 0.11	5.52 ±0. 52	0.915
18h PO	5.97 ± 0.12	5.69 ± 0.53	0.286
24h PO	5.51 ± 0.13	5.29 ± 0.53	0.46

Group C; placebo control group, Group T; tranexamic acid group.
CaO2-jO2: Arterio-Jugular oxygen content difference.
Statistically significant p < 0.05, when compared with the other groups.

Table (12): Arterio-Jugular oxygen content difference (CaO_2-jO_2)

	CBF e (ml blood/ml O2)		
	Group C n=25	**Group T n=25**	**P**
PC	0.17±0.03	0.18±0.01	0.128
1 h IO	0.2±0.02	0.19±0.02	0.017*
2h IO	0.22±0.03	0.2±0.01	0.001*
3h IO	0.17±0.02	0.18±0.01	0.004*
4h IO	0.17±0.03	0.18±0.02	0.04*
5h IO	0.16±0.02	0.18±0.01	0.01*
Direct PO	0.17±0.02	0.19±0.01	0.005*
2h PO	0.16±0.02	0.18±0.01	0.005*
4h PO	0.22±0.03	0.2±0.01	<0.001*
6h PO	0.17±0.03	0.18±0.01	0.515
12h PO	0.18±0.03	0.19±0.01	0.475
18h PO	0.17±0.03	0.18±0.01	0.446
24h PO	0.18±0.03	0.19±0.01	0.822

Group C; placebo control group, Group T; tranexamic acid group.
CBFe : Cerebral blood flow equivalent.
Statistically significant p < 0.05, when compared with the other groups.

Discussion

Anesthetic goals during brain tumor surgeries include maintenance of adequate cerebral perfusion pressure (CPP) to avoid cerebral ischaemia, adequate brain metabolism, brain oxygenation and CBF, preserving hemodynamic stability; with decreasing intracranial pressure for optimum surgical settings known surgically slack brain **[18].**

In this study, group T showed lower blood loss and lower blood transfusion rate due to its anti-fibrinolytic effect through its competitive inhibition of the activation of plasminogen and also non-competitive inhibition of plasmin. In accordance with our result, **Hooda et al**, at 2017 and **Vel et al**, at 2015 have been demonstrated the impact of TXA on blood loss post-craniotomy for excision of brain tumors and showed significant decrease in blood loss with no increase in adverse events **[1,19].**

Prasad et al, 2018 compared single IV bolus vs. peri-operative continuous infusion of TXA in abdominal tumor resection, and reported a significant decrease in hemoglobin at 6, 24h. Also, total blood transfusion units were higher in control group, than single intravenous and continuous infusion of tranexamic acid groups and this concurrent with this study **[20].**

During neuro-anesthesia, changes in position, drugs pharmacokinetics, surgical stimulation, temperature variations and blood volume changes, all can affect autonomic function with subsequent changes in systemic haemodynamics **[21].** In the current trial, MAP was significantly higher while HR was significantly lower in T group than C group. To clarify such a finding, TXA could significantly decrease blood loss and hence maintained better hemodynamics.

Similar to our results, in another study, the mean HR in patients received TXA was significantly lower than controls ($P < 0.001$). Also, the MAP remained higher in TXA group than controls ($P < 0.05$) in neurosurgical patients **[19]**.

In previous study, coauthors proved that the HR, blood pressure, and MAP showed no difference in tranexamic acid and control group **[22]**.

The SjvO2 is a simple, reliable and reasonable method to indicate an adequate CBF. It reflects total perfusion and the balance between oxygen supply and demands. Jugular desaturation (SjvO2 <50 %) indicates inadequacy of CBF for cerebral metabolism **[9].**

SjvO2 was significantly higher in group T compared to group C (both within the physiological values). This can be because of the concomitant increase in CBF and decrease in eCMRO2 that occurred in TXA patients when compared to controls. Based on the Fick principle, the eCMRO2 and CBF are important parameters that determine the SjvO2. Changes in CBF could have resulted in our results.

The decreased SjVO2 in control group represents an increased CEO2 that was observed in this group. This might be resulted from low CBF in this group secondary to low blood pressure or high intracranial tension with increased

crystalloid transfusion with a subsequent reduction in CPP. Another study has been proved that jugular venous bulb oxygen saturation is directly dependent upon MAP **[23]**.

cerebral metabolism changes are linked in parallel with CBF changes (Flow-Metabolism coupling). Coupling explains the cerebral autoregulation that maintains a constant CBF over a wide range of CPP. Under normal conditions, coupling does exist between CBF and CMRO2. Also, in some altered physiologic conditions such fever and seizure, coupling still to exist. However, in pharmacologic and pathologic conditions e.g. brain tumours, it is disturbed **[24,25].**

In this study CBF e is higher in group T than group C even though both within the normal physiological values. CBF depends directly upon CPP and radius of cerebral blood vessels. CPP represents the difference between MAP and mean cerebral venous pressure. MAP was lower in placebo group so they had lower CPP that could explain this significant difference between both groups.

Changes that observed in CMRO2 (i.e. higher $eCMRO_2$ in group C than group T) could be because of the more significant decrease in MAP in group C than group T affecting the cerebral perfusion and consequently increasing CMRO2.

The Ca-jO2 is inversely correlated with CBF and is directly related to CMR in absence of ischaemia, when ischaemia exists, this relationship becomes erratic. When CBF is decreased, the Ca-jO2 is increased. However, when cerebral oxygen extraction reaches maximal level, more reduction in CBF will cause cerebral oxygen uptake to become supply-dependent and then relationship of Ca-jO2 with CBF cannot be predicted **[26]**. So, the decrease of $Ca\text{-}jO_2$ in TXA group can be because of increased CBF.

In our study, CEO2 is lower in group T than group C. As SjvO2 is higher in tranexamic acid group this mean they have less extraction secondary to preserved CBF. This reflects more adequacy of CBF to accomplish the metabolic needs of brain in TXA group.

In our trial, no significant difference existed between both groups as regards in INR, PT, BT. This is parallel with **Hooda et al., 2017;** who proved that administration of TXA in cases having craniotomy for resection of intracranial meningioma had no significant difference in INR. Also, **Goobie et al, 2017** studied effectiveness of TXA in pediatric craniosynostosis surgery showed no changes in INR and PT **[1,22].**

In this study GOSE score, ICU stay time demonstrated insignificant difference among both groups. This agrees with **Hooda et al., 2017** study that proved that administration of TXA in cases having craniotomy for resection of intracranial meningioma had no significant difference in terms of length of hospital stay and neurologic outcome **[1].**

In conclusion, TXA use in supratentorial brain tumor resection surgery demonstrated efficacy in decreasing total blood loss and transfusion subsequently improving hemodynamics and cerebral oxygenation and metabolism.
Limitations of the study, different surgeons as the operator were not the same in all operations, that may affect surgical bleeding and consequences. Also, inability to measure the intracranial pressure, as its values might assess the effect of the drug on cerebral hemodynamics. Multiple doses of TXA in comparative large sized study are recommended to establish actual potential in decreasing blood loss during brain tumour surgeries.

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