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Case study

Effect of tranexamic acid on intraoperative blood loss and transfusion requirements in patients undergoing excision of intracranial meningioma

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ABSTRACT

Surgical excision of meningioma is often complicated by significant blood loss requiring blood transfusion with its attendant risks. Although tranexamic acid is used to reduce perioperative blood loss, its blood conservation effect is uncertain in neurosurgery. Sixty adults undergoing elective craniotomy for meningioma excision were randomized to receive either tranexamic acid or placebo, initiated prior to skin incision. Patients in the tranexamic acid group received intravenous bolus of 20 mg/kg over 20 min followed by an infusion of 1 mg/kg/h till the conclusion of surgery. Intraoperative blood loss, transfusion requirements and estimation of surgical hemostasis using a 5-grade scale were noted. Postoperatively, the extent of tumor excision on CT scan and complications were observed. Demographics, tumor characteristics, amount of fluid infusion, and duration of surgery and anesthesia were comparable between the two groups. The amount of blood loss was significantly less in tranexamic acid group compared to placebo (830 ml vs 1124 ml; $p = 0.03$). The transfusion requirement was less in tranexamic acid group ($p > 0.05$). The patients in tranexamic acid group fared better on a 5-grade surgical hemostasis scale with more patients showing good hemostasis ($p = 0.007$). There were no significant differences between the groups with regards to extent of tumor removal, perioperative complications, hospital stay or neurologic outcome. To conclude, administration of tranexamic acid significantly reduced blood loss in patients undergoing excision of meningioma. Fewer patients in the tranexamic acid group received blood transfusions. Surgical field hemostasis was better achieved in patients who received tranexamic acid.

1. Introduction

Meningiomas account for almost 30% of primary brain tumors. Although, 80–90% of these are benign [1], surgical excision of meningiomas are often complicated by significant blood loss. Major intra-operative blood loss may lead to life-threatening hemodynamic instability requiring massive transfusion of crystalloids, colloids and allogeneic blood. Allogenic blood transfusion has its attendant risks of transmitted infections, post-operative sepsis, immune modulation and an undue wastage of a scarce resource [2,3]. Therefore, there is an increasing focus on strategies to minimize surgical blood loss by employing modalities like preoperative erythropoietin, autologous pre-donation, peri-operative blood salvage and use of pharmacologic agents such as fibrin sealants, antifibrinolytics, desmopressin and recombinant Factor VII [4].

Anti-fibrinolytics are commonly used pharmacological agents in modern blood conservation strategy. Tranexamic acid is a synthetic lysine analog (trans-4-aminomethyl-cyclohexane-1-car boxylic acid) that acts as a competitive inhibitor of plasmin and plasminogen, preventing clot dissolution [5,6]. Its potential to reduce perioperative blood loss has been proven in a variety of surgical procedures [7–12]. However, in the field of neurosurgery, its use is mostly limited to spinal and extracranial surgery [13]. Although tranexamic acid was evaluated way back in the late 1990s for preventing re-bleeding in subarachnoid hemorrhage [14,15], there is a renewed interest now in the same area.

Therefore, this prospective, randomized, double blind, placebo controlled study was conducted to evaluate the effect of tranexamic acid on intra-operative blood loss and transfusion requirements in patients undergoing elective craniotomy for intracranial

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meningiomas. As secondary outcome measures, the effect of tranexamic acid on the quality of surgical hemostasis, perioperative complications, length of hospital stay and neurological outcome were also evaluated.

2. Materials and methods

2.1. Study population

When this project was conceived, literature search did not reveal any study on intraoperative use of tranexamic acid in intracranial procedures. Hence, we extrapolated data from tranexamic acid efficacy in spine surgery [13] and assumed a blood loss reduction of 25% that would entail a sample size of 60 to give the study a power of 80% and alpha error of 0.5.

2.2. Methodology

After obtaining approval from the Institutional Ethics Committee, 60 consecutive American Society of Anesthesiologists (ASA) grade I and II patients, aged between 18 and 60 years, of either sex, scheduled to undergo excision of intracranial meningioma were enrolled in the study, after obtaining a written informed consent. All patients were operated upon by a neurosurgeon with at least 3 years of experience.

Patients who refused to participate in the study or were allergic to tranexamic acid, had a history suggestive of bleeding diathesis, thromboembolic episode prior to surgery or family history of thromboembolism, patients on medication that could interfere with coagulation, epilepsy, plasma creatinine values more than 1.5 mg/dl and pregnant or lactating mothers were excluded from the study. Patients who were planned for preoperative embolization, with tumor size less than 4 cm or operating neurosurgeon's estimate of likely intra-operative blood loss less than 20% of patient's estimated blood volume (EBV) were also not enrolled.

2.3. Anesthetic technique and intraoperative management

In the operation theatre, after connecting non-invasive monitors, intravenous (IV) access was secured and left radial artery was cannulated following local infiltration of 2% lignocaine. A baseline blood sample was analyzed to rule out any pre-existing coagulopathy or hyperfibrinolysis. Corrective measures was planned if the findings were clinically relevant and confirmed on standard laboratory hemostatic tests [SLTs as Prothombin time (PT), activated partial thromboplastin time (aPTT), International normalized ratio (INR) and Platelet count].

After recording the baseline vital parameters, induction of anesthesia was done with propofol (2 mg/kg) preceded by fentanyl (2 μg/kg). Rocuronium (1 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen mixture, sevoflurane (1–1.5 MAC) and supplemental boluses of rocuronium and fentanyl. Mechanical ventilation was adjusted to maintain an end-tidal carbon-dioxide ($EtCO_2$) of 30–35 mmHg with a fresh gas flow of 2 L/min. Throughout the surgery, HR and MAP were maintained within 20% of the baseline and any deviations managed as per standard practice. Normothermia (36–37 °C) was maintained with the help of convective air warmers and warm IV fluid administration.

2.4. Group allocation

The patients were randomized to receive either tranexamic acid (Group T) or normal saline (Group P, Placebo) based on a computer-generated randomization chart (See Fig. 1).

2.5. Preparation and administration of "test drug" infusion

The study drugs were prepared by an anesthesiologist who was part of the study but not involved in the patient management. For Group T patients, 2000 mg of tranexamic acid was diluted to 50 ml with normal saline (40 mg/ml) in a 50 ml syringe and 50 ml normal saline was taken in same sized syringe for Group P patients. In both the groups, the syringes were labeled as "Test drug" for blinding of the attending anesthesiologists.

The test drug was administered (0.5 ml/kg) over 20 min (tranexamic acid 20 mg/kg) as a loading dose before skin incision followed by a maintenance infusion of 0.025 ml/kg/h (tranexamic acid 1 mg/kg/h) till the completion of skin suture. Infusion of 20% mannitol (1 gm/kg) was completed before dural opening. Hemodynamic variables, $EtCO_2$, oxygen saturation, ST-segment analysis, peak airway pressure, nasopharyngeal temperature and input/ output were continuously monitored. Blood loss estimation in all the cases was done by the principal investigator by subtracting the amount of irrigation fluid from suction aspirate and visual assessment of the soaked sponges, cotton pledgets and area at the operating end. The principle investigator as well as the surgeon were blinded to the test drug. A note of all intra-operative complications was made. Intravenous fluid administration consisted of isotonic crystalloids and colloids (tetrastarch). Transfusion of blood/blood products and intra-operative blood salvage was made at the discretion of the attending anesthesiologist. The hemostatic therapy was guided by ASA task force on blood transfusion. After the maximum possible tumor excision had been achieved, surgeon's estimate of oozing/hemostasis was recorded based on fixed parameters (Appendix I) [18]. At the completion of the skin suture, sevoflurane, nitrous oxide and infusion of the "Test drug" were discontinued. After satisfactory reversal of residual neuromuscular blockade, trachea was extubated. When indicated, elective post-operative ventilation was continued and reasons for ventilation was recorded.

2.6. Postoperative care

All the patients were monitored post-operatively in the neurosurgical ICU. Perioperative, transfusion trigger for packed RBCs was a hemoglobin concentration <8 g/dl. Fresh frozen plasma (FFP) was transfused at INR > 1.5 and for transfusing platelets, a platelet count <100,000/mm^3 was considered as the cut-off value [19]. The amount of transfused packed RBCs, FFP and / or platelets were recorded.

In addition to routine laboratory investigations like hemoglobin concentration, SLT's, blood urea nitrogen, creatinine, electrolytes, chest X-ray and ECG were performed on the first post-operative day. Computed tomography (CT) scan findings for the extent of tumor removal (Simpson's grade) [20] and hematoma formation were recorded. Any complications in the post-operative period were recorded with special emphasis on thrombotic events i.e. stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial ischemia/ infarction, acute renal failure, new onset seizures and visual abnormalities. The diagnosis of myocardial infarction was based on the appearance of significant new ST-segment changes, confirmed by Troponin I test. Ischemic stroke was defined as a focal neurologic deficit lasting more than 24 h, confirmed by a non-contrast CT scan brain and the opinion of attending neurosurgeon. A decrease in urine output below 0.5 ml/kg/h for more than six hours and an increase in post-operative serum creatinine by 1.5-fold was required for the diagnosis of acute renal failure. If DVT/PE was suspected on clinical grounds and laboratory parameters (D-dimer), additional tests like extremity ultrasound, chest X-ray and/or CT scan were performed. The duration of ICU and hospital stay were recorded. Patients' physical status at the time of discharge from the hospital was