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SOCIETY FOR NEUROSCIENCE
IN ANESTHESIOLOGY AND CRITICAL CARE

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Tranexamic acid in neurosurgery

Neuroanesthesia Quiz # 83

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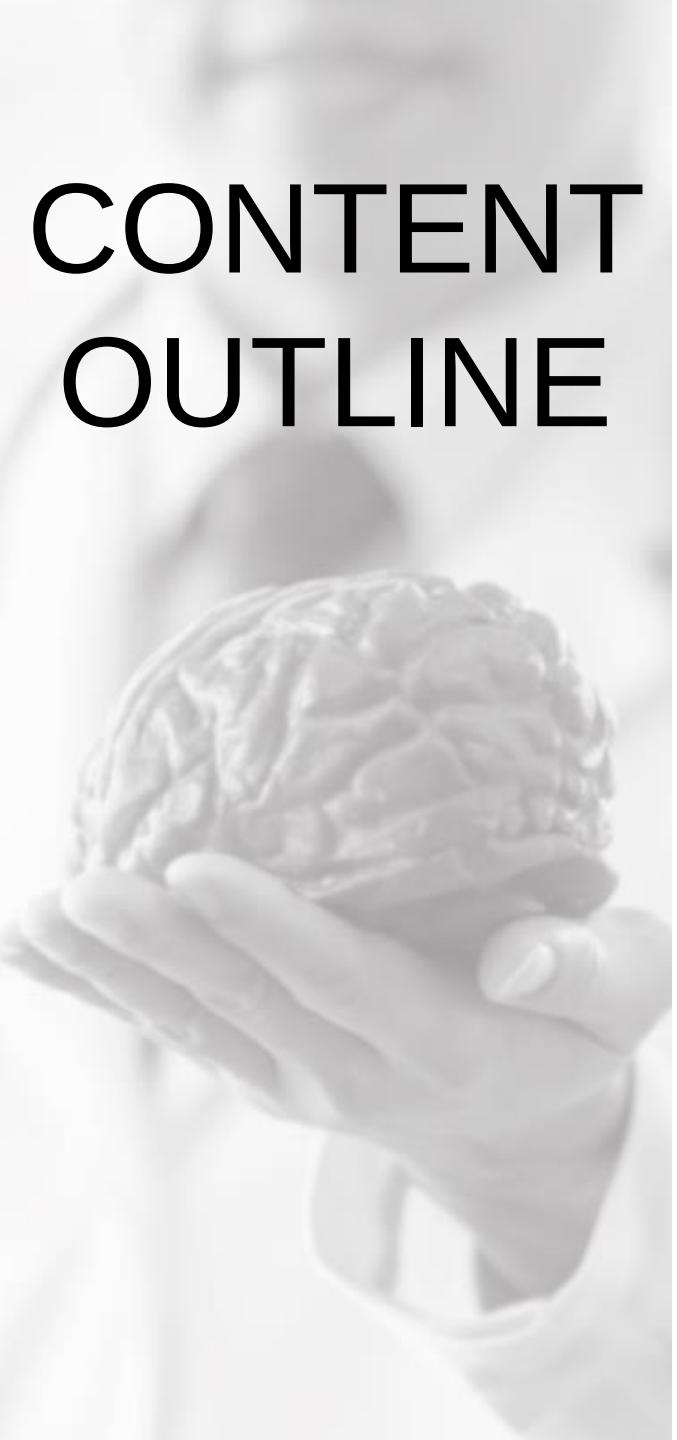
CONTENT OUTLINE



Title Slide

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QUESTION 1

All of the following statements about tranexamic acid (TXA)are true EXCEPT:

Please click on any of the following links to proceed to that question/topic.

A: TXA is a synthetic analogue of lysine that inhibits the activation of plasminogen into plasmin

B: TXA is excreted unchanged in the urine and excretion decreases with increasing creatinine

C: TXA crosses the blood brain barrier and enters the eye

D: TXA is structurally similar to glycine and activates the glycine and GABA receptors

Content Outline

Q2, Q3, Q4, Q5

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Sorry! Incorrect.

EXPLANATION

A. TXA is a synthetic analogue of lysine that inhibits the activation of plasminogen into plasmin

This statement is correct.

Patented by S. Okamoto in 1957 TXA (trans-4- aminomethyl-cyclohexane-1-carboxylic acid) is a synthetic analog of lysine, which, by competition, inhibits the activation of plasminogen into plasmin. At high concentrations, TXA blocks non-competitive plasmin, inhibiting the dissolution and degradation of fibrin clots. The binding of TXA to plasminogen is 6 to 10 times more potent that of epsilon-aminocaproic acid (e-ACA).

Ng WCK, Jerath A, Wasowicz M (2015) Tranexamic acid: a clinical review. Anestezjol Intens Ter 47:339–350.

Pfizer Canada Inc. Cyklokapron® — Product monograph [Internet]. Kirkland: Pfizer Canada Inc; 2013 p. 1–22.

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Sorry! Incorrect.

EXPLANATION

B. TXA is excreted unchanged in urine and excretion decreases with increasing creatinine

This statement is correct

Approximately 95% of TXA is excreted unchanged in the urine, and excretion decreases with increasing plasma creatinine levels. However dose-adjustment in patients with renal impairment remains an unknown factor.

Ng WCK, Jerath A, Wasowicz M (2015) Tranexamic acid: a clinical review. Anestezjol Intens Ter 47:339–350.

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Sorry! Incorrect.

EXPLANATION

C. TXA crosses the blood brain barrier and enters the eye

This statement is correct

TXA crosses the blood-brain barrier and enters the eye, reaching around 10% of the plasma concentration in the CSF. This, in turn, can lead to changes in color vision, especially in patients who use the drug chronically.

Ng WCK, Jerath A, Wasowicz M (2015) Tranexamic acid: a clinical review. Anestezjol Intens Ter 47:339–350.

McCormack PL: Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs 2012; 72: 585–617.

Return to Question

Great Job!! Correct.

EXPLANATION

Next Question

D. TXA is structurally similar to glycine and activates the glycine and GABA receptors

This statement is incorrect

TXA is structurally similar to glycine, and competitively inhibits glycine receptors in the cortical and spinal cord neurons in rats; TXA also inhibits the GABA-A receptors in cortical and spinal cord neurons. Both inhibitory pathways of TXA cause an increased excitatory synaptic stimulus, as evidenced by convulsion-like events induced at TXA concentrations of 31 µg/mL. These events are similar to those measured in the cerebrospinal fluid (CSF) of patients undergoing extracorporeal circulation. Peak CSF TXA concentrations occur when the infusions are stopped after CPB, later than peak serum levels. When taken together, this explains the late-onset of unexpected seizures in patients emerging from anesthesia after CPB.

Lecker I, Orser B a, Mazer CD: "Seizing" the opportunity to understand antifibrinolytic drugs. Can J Anaesth 2012; 59: 1–5.

Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M: High- -dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 2010; 110: 350–353.

Sharma V, Katznelson R, Jerath A et al.: The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. Anaesthesia 2014; 69: 124–130.

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QUESTION 2

A 44 year old is scheduled for a multilevel spine fusion surgery. All statements regarding the use of TXA in patients undergoing spine surgery are true EXCEPT:

Please click on any of the following links to proceed to that question/topic.

A: TXA reduces blood loss

B: TXA administration shortens hospital stay

C: TXA increases the risk of DVT and PE at the doses routinely administered

D: There is no widely accepted guideline for the dosage of TXA in spine surgery

Content Outline

Q1, Q3, Q4, Q5

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Sorry! Incorrect.

EXPLANATION

A. TXA reduces blood loss

This statement is correct.

Most studies on use of TXA in spine surgery have pointed out the potential of TXA in reduction in bleeding in the intraoperative and postoperative periods. TXA can reduce intraoperative bleeding in spinal column surgery by up to 49%.

Cheriyan T, Maier SP 2nd, Bianco K et al (2015) Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. Spine J 15:752–761.

Winter SF, Santaguida C, Wong J, Fehlings MG. Systemic and topical use of tranexamic acid in spinal surgery: a systematic review. Global Spine J. 2016;6(3):284–295.

Yerneni K, Burke JF, Tuchman A, et al. Topical tranexamic acid in spinal surgery: a systematic review and meta-analysis. J Clin Neurosci. 2019;61:114–119.

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Sorry! Incorrect.

EXPLANATION

B. TXA administration shortens hospital stay

This statement is correct.

TXA administration significantly shortens hospital stay in open spine surgery. However, this is only reported by studies using topical TXA. Further studies using both IV TXA and topical TXA are required to assess this outcome.

Zhen-Gang Liu, Fan Yang, Yu-Hang Zhu, et al. Is tranexamic acid beneficial in open spine surgery? And its effects vary by dosage, age, sites and locations: A meta-analysis of randomized controlled trials. World Neurosurg 2022; 14: S1878-8750(22)00992-5.

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Great Job!! Correct.

EXPLANATION

Next Question

C. TXA increases the risk of DVT and PE at the doses routinely administered

This statement is incorrect

Multiple studies have demonstrated absence of increased incidence of thrombotic events such as deep vein thrombosis (DVT) and pulmonary embolism (PE) with the use of TXA in spine surgery. TXA can reduce blood loss without elevating the incidence of postoperative thrombotic complications.

Li G, Sun TW, Luo G, Zhang C. Efficacy of antifibrinolytic agents on surgical bleeding and transfusion requirements in spine surgery: a meta-analysis. Eur Spine J. 2017;26(1):140–154.

Ko BS, Cho KJ, Kim YT, Park JW, Kim NC. Does tranexamic acid increase the incidence of thromboembolism after spinal fusion surgery? Clin Spine Surg. 2020;33(2):E71–E75

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Sorry! Incorrect.

EXPLANATION

D. There is no widely accepted guideline for the dosage of TXA in spine surgery

This statement is correct.

There has been no widely accepted guideline for the dosage of TXA in open spine surgery. TXA has a favorable safety profile and reliable hemostatic effects regardless of the dose. IV TXA in spine surgery is typically provided as a bolus with a dose range of 10 to 20 mg/kg preoperatively and with a maintenance infusion of 1 to 10 mg/kg per hour of surgical duration.

Yang B, Li H, Wang D, et al. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. PLoS One 2013;8:e55436.

McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs 2012;72:585-617.

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QUESTION 3

A 17 year old presents with ruptured intracranial aneurysm. All of the following statements regarding use of TXA in this patient are true EXCEPT:

Please click on any of the following links to proceed to that question/topic.

A: Use of TXA can considerably reduce the risk of rebleed

B: TXA treatment has no significant effect on all cause mortality

C: TXA does not increase the incidence of delayed cerebral ischemia

D: TXA reduces the incidence of hydrocephalus

Content Outline

Q1, Q2, Q4, Q5

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Sorry! Incorrect.

EXPLANATION

A. Use of TXA can considerably reduce the risk of rebleed

This statement is correct

Risk of rebleeding is a major complication in rupture of intracranial aneurysms occurring in 10 to 22% of affected patients. Its highest incidence occurs in the first 24 h, peaking in the first 6 h after the event. The prognosis in such patients is quite poor (60% mortality rate). The use of TXA can considerably reduce the risk of rebleeding rate.

Baharoglu MI, Germans MR, Rinkel GJE, Algra A, Vermeulen M, van Gijn J, Roos YBWEM (2013) Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev 2013.

Gaberel T, Magheru C, Emery E, Derlon JM (2012) Antifibrinolytic therapy in the management of aneurismal subarachnoid hemorrhage revisited. A meta-analysis. Acta Neurochir (Wien) 154:1–9.

Roos YBWE, Beenen LFM, Groen RJM, Albrecht KW, Vermeulen M (1997) Timing of surgery in patients with aneurysmal subarachnoid haemorrhage: Rebleeding is still the major cause of poor outcome in neurosurgical units that aim at early surgery. J Neurol Neurosurg Psychiatry 63:490–49 3.

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Sorry! Incorrect.

EXPLANATION

B. TXA treatment has no significant effect on all cause mortality

This statement is correct

TXA treatment whether given short term (≤ 3 days) or long term (> 3 days) has no significant effect on either short term mortality (≤ 90 days) or long term (> 90 days mortality) compared with control treatment.

Min Shi, Chao Yang, Zu-han Chen, et al. Efficacy and Safety of Tranexamic Acid in Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Surg 2021; 8: 790149.

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Sorry! Incorrect.

EXPLANATION

C. TXA does not increase the incidence of delayed cerebral ischemia.

This statement is correct

Previous trials investigating the long term administration of antifibrinolytic treatment with TXA (administered throughout hospital admission) in patients with subarachnoid hemorrhage showed a reduction in rebleeding, but the positive effect of TXA was negated by a concomitant rise in delayed cerebral ischemia. Shortening the duration of tranexamic acid treatment to a maximum of 72 h has shown a reduction in the risk of rebleeding, without an increase in delayed cerebral ischemia.

Vermeulen M, Lindsay KW, Murray GD, et al. Antifibrinolytic treatment in subarachnoid hemorrhage. N Engl J Med. 1984; 311: 432-437.

Baharoglu MI, Germans MR, Rinkel GJ et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2013; 8CD001245.

Return to Question

Great Job!! Correct.

EXPLANATION

Next Question

D. TXA reduces the incidence of hydrocephalus

This statement is incorrect

As a common complication of aneurysmal subarachnoid hemorrhage (aSAH), hydrocephalus is usually caused by the accumulation of blood in the ventricle, affecting the reflux of cerebrospinal fluid. TXA reduces plasminogen activity in cerebrospinal fluid, leading to poor absorption of intraventricular hemorrhage, which is more likely to cause hydrocephalus. Thus, TXA significantly increases hydrocephalus in aSAH patients.

Vermeij FH, Hasan D, Vermeulen M, Tanghe HL, van Gijn J. Predictive factors for deterioration from hydrocephalus after subarachnoid hemorrhage. Neurology. (1994) 44:1851–5

Junwei Ren, Dongxi Qian, Jiaming Wu, et al. Safety and effeicacy of tranexamic acid in aneurysmal subarchnoid hemorrhage: A meta-analysis of randomized controlled trials. Front Neurol 2022; 12: 710495.

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QUESTION 4

All of the following statements are true regarding TXA associated seizures EXCEPT:

Please click on any of the following links to proceed to that question/topic.

A: TXA causes seizures by crossing the BBB and antagonizing GABA-A and glycine receptors

B: TXA increases the risk of seizures when administered at low dose (2 g/day or less)

C: TXA increases the risk of seizures when administered at high dose (> 4g/day)

D: Anesthetics may reverse TXA induced seizures

Content Outline

Q1, Q2, Q3, Q5

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Sorry! Incorrect.

EXPLANATION

A. TXA causes seizures by crossing the BBB and antagonizing GABA-A and glycine receptors

This statement is correct.

TXA is a competitive antagonist of $GABA_A$ and glycine in brain. In in vitro and animal experiments, it has been shown that higher TXA level in the cerebral spinal fluid, correlates with higher serum concentration, and is associated with the increased incidence of seizures.

*Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. Ann Neurol. 2016;**79**(1):18–26.*

*Schlag MG, Hopf R, Zifko U, et al. Epileptic seizures following cortical application of fibrin sealants containing tranexamic acid in rats. Acta Neurochir (Wien) 2002;**144**:63–69.*

Return to Question

Great Job!! Correct.

EXPLANATION

Next Question

B. TXA increases the risk of seizures when administered at low dose (2g/day or less)

This statement is incorrect.

In in vitro and animal experiments, it has been shown that higher TXA level in the cerebral spinal fluid, correlates with higher serum concentration, and is associated with the increased incidence of seizures. Administration of high dose TXA has been shown to be associated with increased risk of seizures in cardiac surgery.

*Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. Ann Neurol. 2016;**79**(1):18–26.*

*Schlag MG, Hopf R, Zifko U, et al. Epileptic seizures following cortical application of fibrin sealants containing tranexamic acid in rats. Acta Neurochir (Wien) 2002;**144**:63–69.*

*Kalavrouziotis D, Voisine P, Mohammadi S, et al. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg. 2012;**93**(1):148–154.*

*Murkin JM, Falter F, Granton J, et al. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2010;**110**(2):350–353.*

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Sorry! Incorrect.

EXPLANATION

C. TXA increases the risk of seizures when administered at high dose (> 4g/day)

This statement is correct.

In in vitro and animal experiments, it has been shown that higher TXA level in the cerebral spinal fluid, correlates with higher serum concentration, and is associated with the increased incidence of seizures. Administration of high dose TXA has been shown to be associated with increased risk of seizures in cardiac surgery.

*Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. Ann Neurol. 2016;**79**(1):18–26.*

*Schlag MG, Hopf R, Zifko U, et al. Epileptic seizures following cortical application of fibrin sealants containing tranexamic acid in rats. Acta Neurochir (Wien) 2002;**144**:63–69.*

*Kalavrouziotis D, Voisine P, Mohammadi S, et al. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg. 2012;**93**(1):148–154.*

*Murkin JM, Falter F, Granton J, et al. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2010;**110**(2):350–353.*

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Sorry! Incorrect.

EXPLANATION

D. Anesthetics may reverse TXA induced seizures

This statement is correct.

Because the tonic current generated by glycine receptors is highly sensitive to TXA inhibition, drugs that reverse this inhibitory effect may mitigate TXA-associated hyperexcitability. Isoflurane and propofol, as well as other anesthetics that increase glycine receptor function, might be effective either for treating or for preventing TXA-associated seizures. Consistent with this notion that anesthetics protect against TXA-induced seizures, many patients first develop seizures during emergence from propofol sedation. Also, case reports indicate that propofol is effective for treating seizures in patients who inadvertently received an intrathecal injection of TXA. Benzodiazepines, which do not modify glycine receptors but rather upregulate $GABA_A$ receptor function, have been used to treat seizures following inadvertent intrathecal injection of TXA after cardiac surgery.

Downie DL, Hall AC, Lieb WR, et al. Effects of inhalational general anaesthetics on native glycine receptors in rat medullary neurones and recombinant glycine receptors in Xenopus oocytes. Br J Pharmacol 1996;118:493–502.

Hales TG, Lambert JJ. The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones. Br J Pharmacol 1991;104:619–628.

Lecker I, Wang DS, Romaschin AD, et al. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest 2012;122:4654–4666

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QUESTION 5

A 70 year old suffers from a traumatic brain injury (TBI) from a motor vehicle accident and presents for evacuation of an acute subdural hematoma. All of the following statements are true regarding use of TXA in this patient EXCEPT:

Please click on any of the following links to proceed to that question/topic.

A: TXA reduces the risk of death in mild to moderate TBI patients

B: TXA is more effective when treatment is given after 3 hours of injury

C: TXA does not reduce death in severe TBI patients who have extensive intracranial hemorrhage

D: The most commonly administered dose of TXA is a loading dose of 1 gm, followed by infusion of 1g for 8 h

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Sorry! Incorrect.

EXPLANATION

A: TXA reduces the risk of death in mild to moderate TBI patients

This statement is correct.

The CRASH-3 trial, which remains the largest clinical trial in the setting of TBI and carries the greatest weight showed that treatment with TXA in mild-to-moderate head injuries leads to a substantial reduction in mortality due to bleeding in patients with TBI regardless of the cause. The 2016 European guidelines, on the management of major bleeding and coagulopathy following trauma strongly recommends (grade 1A) the use of TXA in trauma patients who are bleeding or at risk of significant bleeding.

CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019 Nov 9;394(10210):1713-1723.

Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma. Crit Care. 2019;23(1):98

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Great Job!! Correct.

EXPLANATION

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B. TXA is more effective when treatment is given after 3 hours of injury

This statement is incorrect.

Tranexamic acid reduces the risk of death in mild to moderate TBI patients when treatment is given within 3 h, according to a recent CRASH-3 trial. These data suggest a fundamental truth regarding the pathophysiology of life-threatening hemorrhage—namely, that early activation of the fibrinolytic protease cascade is intimately linked to poor outcomes in patients with bleeding, perhaps because of various mechanisms, including worsened bleeding due to clot breakdown, activation of inflammatory pathways, and increased endothelial permeability leading to tissue, especially brain edema. Tranexamic acid offers a means to mitigate this maladaptive response to injury.

CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019 Nov 9;394(10210):1713-1723.

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Sorry! Incorrect.

EXPLANATION

C: TXA does not reduce death in severe TBI patients who have extensive intracranial hemorrhage

This statement is correct.

Based on the results of the CRASH-3 trial there is a significant reduction in risk of head injury-related mortality when tranexamic acid is administered within 3 h of injury to patients with mild-to-moderate TBI, but not in patients with severe head injury.

CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019 Nov 9;394(10210):1713-1723.

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Sorry! Incorrect.

EXPLANATION

D: The most commonly administered dose of TXA is a loading dose of 1 gm, followed by an infusion of 1g for 8 h

This statement is correct.

The dose of TXA that has been most commonly studied in patients with TBI is 1 g intravenous bolus followed by an infusion of 1 g given over 8 hours. This dose is thought to maximize efficacy and safety in both larger (>100 kg) and smaller (<50 kg) patients.

Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23-32.

CRASH-3 trial collaborators . Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394(10210):1713-1723.

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