European Journal of Trauma and Emergency Surgery (2019) 45:719–726
https://doi.org/10.1007/s00068-018-0974-z

ORIGINAL PAPER

Benefits of the tranexamic acid in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients

Olfa Chakroun-Walha[1] · Amal Samet[1] · Mouna Jerbi[1] · Abdennour Nasri[1] · Aziza Talbi[1] · Hassen Kanoun[1] · Basma Souissi[2] · Kamilia Chtara[3] · Mounir Bouaziz[3] · Hichem Ksibi[1] · Noureddine Rekik[1]

Received: 15 March 2018 / Accepted: 12 June 2018 / Published online: 19 June 2018

Abstract

Introduction Tranexamic acid (TXA) is one of the debated therapies in the management of traumatic brain injury (TBI). We conducted this study to evaluate the benefits of TXA in TBI on the mortality and its safety in these patients.

Methods This was a prospective randomized open-label trial including all patients, aged at 18 years or older, hospitalized in the emergency room during a 13-month period, for TBI. After the realization of the body CT scan, the patients were included if they had intracranial bleeding, and were then randomized according to their medical file number to receive or not the TXA. The eligibility criteria were based on the uncertainty principle, patients with significant extracranial bleeding were excluded since there was evidence that TXA improve their outcome.

Results We enrolled 180 patients aged at 42 ± 20 years, with an 88% men-proportion. Subarachnoid haemorrhage was the most frequent lesion in the brain CT-scan (67.5%). After randomization, 96 patients were in the TXA group (53%). Demographic data, clinical, biological and radiological features were statistically comparable in the two groups of patients ('TXA' and 'noTXA'). The needs of transfusion or neurosurgery, the mortality rate, the in-hospital length of stay and the dependency at 28-post-traumatic day were similar in the two groups of patients. However, pulmonary embolism was statistically more frequent in 'TXA' group (11.5 versus 2.4%, $p = 0.02$).

Conclusion TXA is an interesting treatment in haemorrhagic shock. Its efficiency in head trauma is still debated and controversial. Its impact on the mortality and the needs of transfusion or surgery were not demonstrated in this study. Nevertheless, its safety worth to be studied in larger samples as we found a higher rate of pulmonary embolism in the treated group.

Keywords Tranexamic acid · Traumatic brain injury · Management · Prognosis · Emergency department · Pulmonary embolism

Introduction

Traumatic brain injuries (TBI) are a public health problem around the world [1–5]. They are a major cause of mortality, disability and huge costs to the society. The target of their acute management is to prevent or to reverse the primary and the secondary injuries. One of the challenges in their management is the early control of the hypercoagulability and the excessive hyperfibrinolysis. The effectiveness of tranexamic acid (TXA) in severely injured patients with bleeding was demonstrated in several studies [6–8]. However, its benefits in TBI without extracranial haemorrhage are still debated in recent studies [5, 9–19].

The aims of the present study were to compare the 28th-day mortality and blood transfusion and neurosurgery needed among TBI patients without extracranial bleeding who did or did not receive TXA. We also aimed to compare thromboembolic complications in the two groups of patients.

✉ Olfa Chakroun-Walha
chakroun_olfa@medecinesfax.org

[1] Emergency Department, University Hospital Habib Bourguiba, Service des urgences et SAMU04 SFAX, Route EL Aïn Km 0,5, 3029 Sfax, Tunisia

[2] Radiology Department, University Hospital Habib Bourguiba, Sfax, Tunisia

[3] Intensive Care Unit, University Hospital Habib Bourguiba, Sfax, Tunisia

Methods

Clinical setting

This is a prospective study conducted over a period of 13 months (from 1st August 2016 to 30th September 2017). The study population consisted of consecutive patients admitted in the emergency room (ER) of the emergency department of Habib Bourguiba University Hospital, in Sfax, for TBI. This hospital is the unique academic trauma centre in the south of Tunisia. Patients with life-threatening pathologies or requiring continuous monitoring are admitted in the ER, a 10-bed unit where monitors and invasive therapies (mechanical ventilation, vasoactive therapies) are available. Patients with no disturbance in vital signs are managed in the non-vital area of the emergency department.

Inclusions and exclusions

Patients were eligible for the study when aged 18 years or over, admitted in the ER for TBI, and who satisfied all of the following criteria: intracranial bleeding in the first or the second brain CT-scan, and with a delay of management in the study centre under 24 h after trauma. Patients with significant extra cranial bleeding (that is, not in need of immediate blood transfusion) or with evidence that TXA improve outcome, were excluded. In our institution, each time the GCS on admission is under 13 or if there is any neurological deterioration with a normal imaging on admission, a second brain CT-scan is performed after 6 h.

Patients were not included with known renal failure, a history or current evidence suggestive of venous or arterial thrombosis (including deep vein thrombosis, pulmonary emboli, cerebral vein thrombosis, cerebrovascular accident), or a congenital or acquired coagulopathy. Pregnant women were also not eligible for the study.

Patients' enrolment and follow-up

This was a prospective randomized open-label trial. The eligibility criteria were based on the uncertainty principle. When the body computerized tomography scan (CT-scan) was performed, the eligibility of the patient for the study was verified by the responsible clinician. Adults with traumatic brain injury, who were within 24 h of injury and had any intracranial bleeding on CT-scan were eligible if the responsible doctor was substantially uncertain as to whether or not to use TXA. Included subjects were randomized according to their medical file number to receive or not the TXA: patients in 'TXA' group were those having an even medical file number during the first 6 months and those having an odd medical file number during the last 6 months of the study.

In the intervention group, intravenous TXA was administered as soon as possible after randomisation, with a first dose of 1 g in 100 mL of normal saline in 10 min and then with a maintenance dose of 1 g per 500 mL of normal saline for 8 h [13].

No other changes in the management were indicated. No extra tests were required for the trial. All of the clinical, radiological and biological data were recorded. During the first 24 h of admission, we assessed the severity of the patients using the Injury Severity Score (ISS) and the simplified acute physiologic score (SAPS II). The sequential organ failure assessment score (SOFA score) was calculated at day-1, day-3 and day-7 of hospitalization.

The primary study endpoints were the benefits of TXA in reducing the needing of surgery or transfusion and the mortality rate up to 28 days after trauma. The secondary endpoints of this study included the safety of TXA in TBI—including pulmonary embolism or deep vein thrombosis—and disability assessed by one investigator using the Glasgow Outcome Scale (GOS) at day-28 post trauma. The GOS score varied from 1 to 5 points on the basis of the patient's functional status. A higher score indicates better recovery [20].

The diagnosis of pulmonary embolism (PE) is usually suspected in patients with unexplained hypoxemia and/or shock and arterial hypotension. In our institution, a daily assessment of hospitalized patients is performed by expert staff in the ER and in the intensive care unit. The diagnosis of PE was suspected in the presence of clinical or biological disorders (unexplained hypoxemia and/or shock and arterial hypotension). PE was then confirmed by a spiral computed tomography (CT) scan showing one or more filling defects or obstructions in the pulmonary artery or its branches. In all cases, the CT-scan classification was performed by experienced university radiologists. The local institutional ethics committee approval was obtained.

Statistical analysis

Normal distribution of the data was verified. Data reported in the text and tables indicate the mean ± standard deviation for numeric variables and percentages or ranges for dichotomous variables. To compare qualitative variables, we used the Pearson's Chi-square test and the Fisher's exact test. To compare quantitative variables, we used the student's *t* test. Receiver-operating characteristic (ROC) curve was used to analyse the correlation between the delay of TXA administration and the risk of pulmonary embolism. The area under the ROC curve was estimated by the method of Hanley and

McNeill [21]. In addition, Kaplan–Meier survival curve (log-rank method) was used for survival analysis. The significance level was a two-sided $p < 0.05$.

Results

We enrolled 180 among 475 cases of severe trauma hospitalized in the ER for severe trauma (Fig. 1). There were 77 patients aged over 60 years (42.8%), the mean age was 41 ± 19 years (extremes: 18 and 87 years). Most patients were men (163 men and 17 women). In 71.1% of cases, the patients had no medical history. In the other cases, diabetes and hypertension were the most common chronic pathologies (10.0 and 5.6%, respectively). The leading mechanism of trauma was road traffic accident ($n = 160$; 88.9%) (Table 1).

In 21.7% of cases ($n = 39$), patients were referred from other hospitals in the southern regions of Tunisia after stabilisation of their vital signs. After CT-scan and randomisation, 96 patients were enrolled in 'TXA group' and 84 patients were in 'noTXA' group (Fig. 1). The median delay of TXA administration was 8 h after trauma (1–20 h). TXA was administered during the first 3 h of trauma in 10% of cases. Two patients were included in the TXA group after the second brain CT-scan, the delay of TXA infusion was at 10 and 12 h after trauma.

The two groups of patients had comparable demographic and clinical features (Table 1). The rate of prothrombin on admission was statistically more frequently lower than 60% in the 'noTXA' group ($p < 0.001$). There were no further statistical differences in the laboratory or the CT-scan findings in the two groups of patients (Table 2).

The needing of transfusion was comparable in the two groups during the first 7 days of hospitalization (Table 3). There was no evidence of any decreased needing of surgery (Table 3). We found no decrease in the mortality rate and the disability assessed by the GOS at the 28th post-traumatic day (Fig. 2; Table 4). Oppositely, thromboembolic events were approximately five times more frequent in the TXA group. This event was not correlated to the delay of administration of TXA (Fig. 3).

Discussion

This study showed no significant improvement of clinical outcome in TBI treated by TXA. After TBI, there is a massive release of thromboplastin followed by the activation of the coagulation and fibrinolytic pathways [22, 23]. Increased fibrinolysis, is the main cause of coagulopathy in TBI even with no extra cranial bleeding. Many studies reported the efficacy of TXA in the safe reduction of haemorrhagic intracranial lesions [24, 25]. However, several others studies showed that TXA did not reduce significantly the growth of haemorrhagic lesions [15, 16, 26, 27]. The differences in timing of CT scanning, difference in measurement of the volume and other diagnostic criteria can explain these

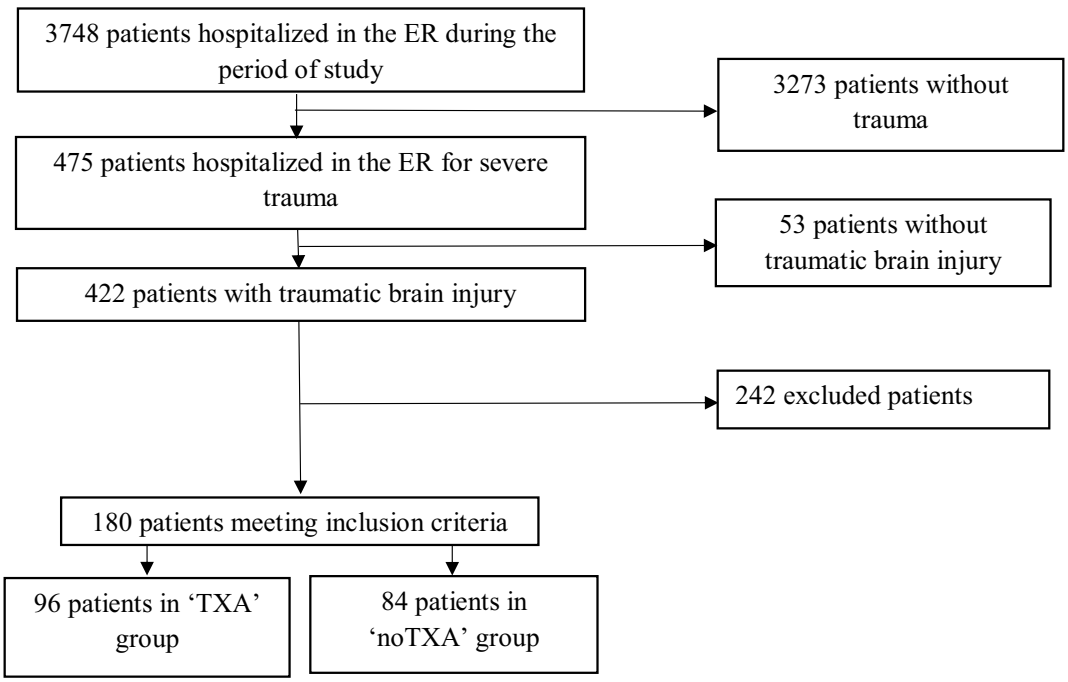

Fig. 1 Flow-chart explaining the sample of the study

Table 1 Comparison of demographic and clinical data in 'TXA' and 'noTXA' groups of patients

	noTXA $n=84$	TXA $n=96$	p
Demographic data			
Age, years (mean ± DS)	39 ± 18	44 ± 20	0.1
M/F sex-ratio	8.3	11	0.6
Living in Sfax city, *n* (%)	42 (50.0)	52 (54.2)	0.7
Medical history, *n* (%)			
Hypertension	5 (5.9)	5 (5.2)	0.8
Diabetes	6 (7.1)	12 (12.5)	0.2
COPD	2 (2.4)	6 (6.2)	0.2
Mechanism of trauma, *n* (%)			
Road traffic accident	74 (88.1)	89 (95.8)	0.08
Assault	2 (2.4)	2 (2.1)	1
Domestic accidents	8 (9.5)	2 (2.1)	0.05
Injuries associated to head trauma at clinical examination, *n* (%)			
Isolated traumatic brain injury	38 (45.2)	39 (40.6)	0.5
Chest trauma	36 (42.9)	32 (33.3)	0.2
Abdominal trauma	5 (6.0)	25 (26.0)	$<10^{-3}$
Pelvic trauma	1 (1.2)	5 (5.2)	0.2
Limb trauma	16 (19.0)	20 (20.8)	0.8
Vital signs and clinical disorders			
Mean blood pressure, mmHg (mean ± DS)	88.8 ± 16.8	87.1 ± 16.5	0.5
Heart rate, bpm (mean ± DS)	86 ± 19	87 ± 16	0.7
Signs of shock, *n* (%)	5 (6.0)	5(5.2)	0.8
Respiratory rate, cpm (mean ± DS)	18 ± 6	19 ± 6	0.7
Tracheal intubation, *n* (%)	58 (69.0)	64 (66.7)	0.7
Glasgow Coma scale score, points (mean ± DS)	10 ± 5	9 ± 5	0.5
Seizures, *n* (%)	1 (1.2)	4 (4.2)	0.4
Severity scores, (mean ± DS)			
ISS	23.5 ± 25.6	21.8 ± 23.2	0.6
SAPS II	19.3 ± 15.4	24.2 ± 17.7	0.05
SOFA at day 1	3.5 ± 2.7	3.8 ± 2.9	0.5
SOFA at day 3	5.7 ± 3.3	5.7 ± 3.2	0.9
SOFA at day 7	5.2 ± 3.1	5.8 ± 2.7	0.4

differences. For this reason, we decided to study the impact of TXA use on the mortality rate, the transfusion and/or surgery needs and the posttraumatic disability level at the 28th day of follow-up. Our results revealed that TXA did not improve the outcome for patients after 28 days as there was no significant difference in the number of patients who had subsequently died or had neurosurgery between the 'TXA' and 'noTXA' groups. Persistent vegetative state (GOS 2) at the 28th day of follow-up was more reported in TXA group (13.5 vs 4.8%; $p=0.04$) and this was the unique significant finding. All other outcome measures were comparable in the two groups of patients. These results concur with other studies [15, 16, 26, 27]. Oppositely, Valle et al. [28] reported that TXA increased mortality in high injury acuity patients and this finding was explained by the rapid availability of fluids and emergency operative interventions at the trauma centers.

In this study, the use of TXA was not as safe as reported in literature [15, 26, 27, 29, 30]. The used doses of TXA were as described in previous studies (a bolus and a continuous infusion) [10, 29] and the eligibility criteria methods of this study were similar to those of the CRASH-3 trial [10, 13]. We see our work as presenting a rather different view of the safety of TXA in TBI. Indeed, we found a higher incidence of pulmonary embolism in TXA group (11.5 vs 2.4%). This finding can be attributed to the open-label randomisation, the assessment of this complication was probably influenced by the TXA use. Nowadays, the safety of TXA in TBI is still widely debated. Some authors demonstrated the correlation between the late administration of TXA and the risk of thromboembolic complications; and its administration during the first 3 h after trauma are thought to be the safest [31, 32]. These

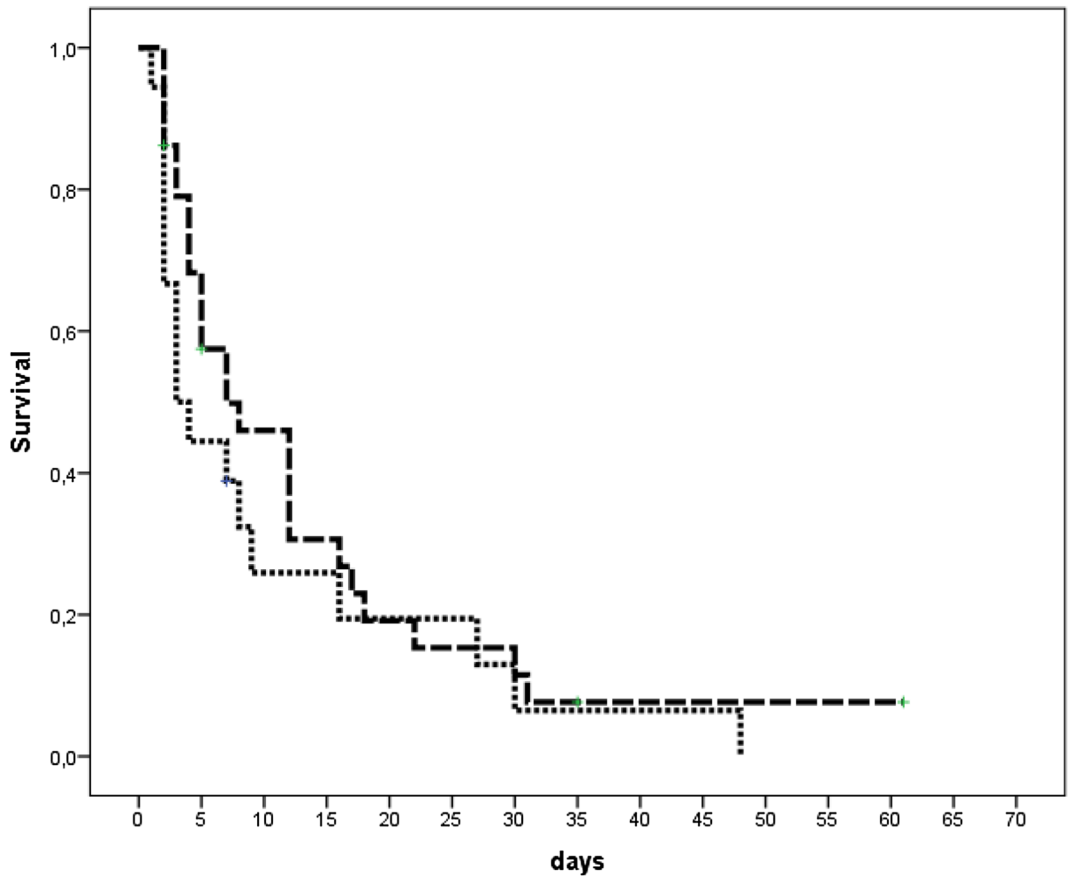

Fig. 2 Survival analysis of 'TXA' (dashed line) and 'noTXA' (dotted line) groups of patients using the Kaplan–Meier survival curve

Table 2 Comparison of laboratory and the CT-scan findings in 'TXA' and 'noTXA' groups of patients

	noTXA $n=84$	TXA $n=96$	p
Laboratory findings on admission			
Haemoglobin < 10 g per dl; *n* (%)	12 (14.3)	15 (15.6)	0.8
Platelets rate < 100,000 per mm^3; *n* (%)	2 (2.4)	4 (4.2)	0.7
Prothrombin rate < 60%; *n* (%)	4 (4.8)	21 (21.9)	$<10^{-3}$
Glucose (mmol/l); mean ± SD	7.5 ± 2.9	8.4 ± 3.3	0.09
Urea (mmol/l); mean ± SD	4.8 ± 2.6	5.1 ± 2.6	0.5
Creatinine (µmol/l); mean ± SD	72.2 ± 95.5	65.9 ± 40.2	0.9
Bilirubin (UI/L); mean ± SD	11.7 ± 12.4	11.5 ± 10.0	0.9
Head CT scan findings			
Subarachnoid haemorrhage; *n* (%)	51 (60.7)	67 (69.8)	0.2
Extradural hematoma; *n* (%)	24 (58.6)	23 (24.0)	0.4
Subdural hematoma; *n* (%)	30 (35.7)	43 (44.8)	0.2
Intracerebral haemorrhage; *n* (%)	41 (48.8)	55 (57.3)	0.3
Petechial haemorrhage; *n* (%)	14 (16.7)	20 (20.8)	0.5
Diffuse axonal injury; *n* (%)	5 (5.9)	8 (8.3)	0.5
Brain herniation; *n* (%)	12 (14.3)	10 (10.6)	0.4
Cerebral oedema; *n* (%)	14 (16.7)	13 (13.8)	0.6
The sum of cerebral lesions; mean ± SD	2.3 ± 1.3	2.5 ± 1.3	0.3

Table 3 Comparison of the need of transfusion or surgery in 'TXA' and 'noTXA' groups of patients

	noTXA $n=84$	TXA $n=96$	p
Packed red cells transfused at day 1 (units/day); mean ± SD	0.2 ± 0.6	0.5 ± 1.2	0.05
Packed red cells transfused at day 3 (units/day); mean ± SD	0.3 ± 0.6	0.4 ± 1.0	0.6
Packed red cells transfused at day 7 (units/day); mean ± SD	0.1 ± 0.4	0.1 ± 0.5	0.8
Fresh frozen plasma transfused at day 1 (units/day); mean ± SD	0.3 ± 1.6	0.8 ± 1.9	0.05
Fresh frozen plasma transfused at day 3 (units/day); mean ± SD	0.5 ± 1.8	0.4 ± 1.2	0.6
Platelets transfused at day 1 (units/day); mean ± SD	0.0 ± 0.0	0.3 ± 1.4	0.05
Platelets transfused at day 3 (units/day); mean ± SD	0.5 ± 2.0	0.6 ± 2.2	0.8
Platelets transfused at day 7 (units/day); mean ± SD	0.0 ± 0.0	0.2 ± 1.4	0.4
Length of mechanical ventilation (days); mean ± SD	6.7 ± 9.4	8.2 ± 10.7	0.3
Neurosurgery; *n* (%)	16 (19.0)	23 (24.0)	0.4
Extra cranial surgery; *n* (%)	3 (3.6)	6 (6.3)	0.5
Delay of surgery (h); mean ± SD	12.7 ± 58.0	16.4 ± 83.3	0.7

Table 4 Comparison of the outcome of 'TXA' and 'noTXA' groups of patients

	noTXA $n=84$	TXA $n=96$	p
SOFA score at the 3rd day post-trauma; mean ± SD	5.7 ± 3.3	5.7 ± 3.2	0.9
SOFA score at the 7th day post-trauma; mean ± SD	5.2 ± 3.1	5.8 ± 2.7	0.4
Hypoxia at the 7th day post-trauma; *n* (%)	1 (1.2)	1 (1.0)	1.0
Shock at day the 3rd day post-trauma; *n* (%)	0 (0.0)	6 (6.2)	0.03
Shock at the 7th day post-trauma; *n* (%)	1 (1.2)	0 (0.0)	0.6
Pulmonary embolism; *n* (%)	2 (2.4)	11 (11.5)	0.02
Deep venous thrombosis; *n* (%)	3 (3.6)	3 (3.1)	1.0
Length of ICU stay (days); mean ± SD	12.5 ± 13.8	16.9 ± 16.8	0.1
Length of in-hospital stay (days); mean ± SD	14.4 ± 16.3	15.0 ± 15.5	0.8
Mortality rate at the 28th day post trauma; *n* (%)	19 (22.6)	27 (28.1)	0.4
Persistent vegetative state (GOS 2) at the 28th day post trauma; *n* (%)	4 (4.8)	13 (13.5)	0.04
Severe disability (GOS 3) at the 28th day post trauma; *n* (%)	7 (8.3)	10 (10.4)	0.5
Moderate or good recovery (GOS 4 and 5) at the 28th day post trauma; *n* (%)	54 (64.3)	50 (52.1)	0.09

practises are approved in patients with polytrauma or with shock and are still controversial in intracranial bleeding. In the study of Fakharian et al. [27], patients with TBI were included up to 8 h after trauma and TXA was not associated with an increased risk of thromboembolic events. Long-term administration of TXA in patients with post-traumatic chronic subdural hematoma was also studied; it was safe and was associated to the decrease of the bleeding [33]. In our study, almost half of our patients were administered TXA during the first 8 h. Nevertheless, there was no association between the timing of the administration of TXA and the risk of pulmonary embolism as shown in Fig. 3.

There are some limitations that must be considered. This study was an open-label trial as abovementioned, whereas a double or triple-blinded trial would be more accurate to assess the safety of TXA. Moreover, we did not perform a power evaluation and the small sample size is due to the monocentric type of this study. Further, markers of coagulopathy were not measured to compare the two groups of patients. Despite these limitations, we think that our work will be interesting to medical practitioners, and to colleagues who are focusing on TXA in TBI.

Conclusion

In summary, this study shows that the benefits of TXA in TBI without significant extracranial bleeding are to be considered. The timing and the indications of its use are still not defined and the assessment of the outcome and the adverse effects are still controversial.

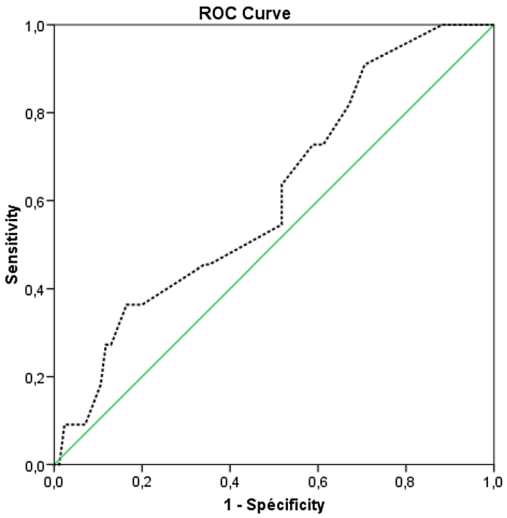

Fig. 3 Receiver-operating characteristic curve (ROC curve) for the correlation between the delay of administration of TXA and the risk of pulmonary embolism. The area under the curve was 0.5 indicating a poor correlation ($p = 0.2$)

Author contributions Study concept and design (OCW, KCH); acquisition of the data (AS, AT, JM, AN, HK, BS); analysis of the data (OCW); drafting of the manuscript (OCW, AS, AN); critical revision of the manuscript (OCW, MB, NR); approval of final manuscript (OCW, NR).

Funding None.

Compliance with ethical standards

Conflict of interest Olfa Chakroun-Walha, Amal Samet, Mouna Jerbi, Abdennour Nasri, Aziza Talbi, Hassen Kanoun, Basma Souissi, Kamilia Chtara, Mounir Bouaziz, Hichem Ksibi and Noureddine Rekik declare that they have no competing interest.

References

1. Chelly H, Bahloul M, Ammar R, et al. Clinical characteristics and prognosis of traumatic head injury following road traffic accidents admitted in ICU "analysis of 694 cases". Eur J Trauma Emerg Surg. 2017. https://doi.org/10.1007/s00068-017-0885-4 **(Epub ahead of print)**.
2. Bahloul M, Chelly H, Ben Hmida M, et al. Prognosis of traumatic head injury in South Tunisia: a multivariate analysis of 437 cases. J Trauma. 2004;57:255–61.
3. Jackisch J, Sethi D, Mitis F, et al. European facts and the Global status report on road safety. 2015; (WHO 2015). http://www.euro.who.int/__data/assets/pdf_file/0006/293082/European-facts-Global-Status-Report-road-safety-en.pdf. Accessed 15 June 2018.
4. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien). 2015;157:1683–96. https://doi.org/10.1007/s00701-015-2512-7.
5. Boudreau R, Johnson M, Veile R, et al. Impact of tranexamic acid on coagulation and inflammation in murine models of traumatic brain injury and hemorrhage. J Surg Res. 2017;215:47–54. https://doi.org/10.1016/j.jss.2017.03.031.
6. CRASH-2 trial collaborators, 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. https://doi.org/10.1016/S0140-6736(10)60835-5.
7. Roberts I. Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013;17(10):1–79. https://doi.org/10.3310/hta17100.
8. CRASH-2 trial collaborators, Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011;377(9771):1096–101. https://doi.org/10.1016/S0140-6736(11)60278-X **(1101 e1091-2)**
9. Majima N, Nishihara I, Yamaguchi K, et al. Usefulness of tranexamic acid in patients with severe head injury. Masui. 2013;62:410–5 **(PMID: 23697191)**.
10. Mahmood A, Roberts I, Shakur H. A nested mechanistic sub-study into the effect of tranexamic acid versus placebo on intracranial haemorrhage and cerebral ischaemia in isolated traumatic brain injury: study protocol for a randomised controlled trial (CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study [CRASH-3 IBMS]). Trials. 2017;18:330. https://doi.org/10.1186/s13063-017-2073-6.
11. Mahmood A, Roberts I, Shakur H. Does tranexamic acid improve outcomes in traumatic brain injury? BMJ. 2016;354:i4814. https://doi.org/10.1136/bmj.i4814.
12. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg. 2012;147:113–9. https://doi.org/10.1001/archsurg.2011.287.
13. Dewan Y, Komolafe EO, Mejia-Mantilla JH, et al. CRASH-3-tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. Trials. 2012;13:87. https://doi.org/10.1186/1745-6215-13-87.
14. Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma. J Trauma Acute Care Surg. 2013;74:1575–86. https://doi.org/10.1097/TA.0b013e318292cc54.
15. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, et al. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. BMC Emerg Med. 2013;13:20. https://doi.org/10.1186/1471-227X-13-20.
16. Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, et al. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury a nested randomised, placebo-controlled trial. Health Technol Assess. 2012;16(13):iii–xii. https://doi.org/10.3310/hta16130 **(1–54)**.
17. Gayet-Ageron A, Prieto-Merino D, Ker K,et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40138 bleeding patients. Lancet. 2018;391(10116):125–32. https://doi.org/10.1016/S0140-6736(17)32455-8.
18. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury (Review). Cochrane Database Syst Rev. 2015;9:CD004896. https://doi.org/10.1002/14651858.CD004896.pub4.

19. Roberts I. Tranexamic acid in trauma: how should we use it? J Thromb Haemost. 2015;13(Suppl 1):S195–9. https://doi.org/10.1111/jth.12878.
20. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1(7905):480–4.
21. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29–36.
22. Nakae R, Takayama Y, Kuwamoto K, et al. Time course of coagulation and fibrinolytic parameters in patients with traumatic brain injury. J Neurotrauma. 2016;33(7):688–95. https://doi.org/10.1089/neu.2015.4039.
23. Harhangi BS, Kompanje EJO, Leebeek FWG, et al. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien). 2008;150:165–75. https://doi.org/10.1007/s00701-007-1475-8.
24. CRASH-2 Collaborators. Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ. 2011;343:d3795. https://doi.org/10.1136/bmj.d3795.
25. French KF, White J, Hoesch RE. Treatment of intracerebral hemorrhage with tranexamic acid after thrombolysis with tissue plasminogen activator. Neurocrit Care. 2012;17(1):107–11. https://doi.org/10.1007/s12028-012-9681-5.
26. Zehtabchi S, Abdel Baki SG, Falzon L, et al. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. Am J Emerg Med. 2014;32:1503–9. https://doi.org/10.1016/j.ajem.2014.09.023.
27. Fakharian E, Abedzadeh-kalahroudi M, Atoof F. Effect of tranexamic acid on prevention of hemorrhagic mass growth in patients with traumatic brain injury. World Neurosurg. 2018;109:e748–53. https://doi.org/10.1016/j.wneu.2017.10.075.
28. Valle EJ, Allen CJ, Van Haren RM, et al. Do all trauma patients benefit from tranexamic acid? J Trauma Acute Care Surg. 2014;76:1373–8. https://doi.org/10.1097/TA.0000000000000242.
29. Jokar A, Ahmadi K, Salehi T, et al. The effect of tranexamic acid in traumatic brain injury: a randomized controlled trial. Chin J Traumatol. 2017;20(1):49–51. https://doi.org/10.1016/j.cjtee.2016.02.005.
30. Roberts I, Edwards P, Joshi M, et al. Tranexamic acid in bleeding trauma patients: an exploration of benefits and harms. Trials. 2017;18:48. https://doi.org/10.1186/s13063-016-1750-1.
31. Ker K, Roberts I, Shakur H, et al. Antifibrinolytic drugs for acute traumatic injury (Review). Cochrane Database Syst Rev. 2015;9:CD004896. https://doi.org/10.1002/14651858.CD004896.pub4.
32. Schöchl H, Schlimp CJ, Maegele M. Tranexamic acid, fibrinogen concentrate, and prothrombin complex concentrate: data to support prehospital use? Shock. 2014;41(Suppl 1):44–6. https://doi.org/10.1097/SHK.0000000000000093.
33. Kageyama H, Toyooka T, Tsuzuki N, Oka K. Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. J Neurosurg. 2013;119(2):332–7. https://doi.org/10.3171/2013.3.JNS122162.