Author's response to reviews

Title: Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial.

Authors:

Surakrant Yutthakasemsunt (surakrant@gmail.com)
Warawut Kittiwatanagul (warawkit@hotmail.com)
Parnumas Piavechvirat (pparsoccer@yahoo.com)
Bandit Thinkhamrop (bandit@kku.ac.th)
Nakornchai Phuenpathom (nakornchai.p@psu.ac.th)
Pisake Lumbiganon (pisake@kku.ac.th)

Version: 2 Date: 23 February 2013

Author's response to reviews: see over
Tranexamic acid for patients with traumatic brain injury
: a randomized, double-blinded, placebo-controlled trial.

Authors

1. Surakrant Yutthakasemsunt, Surgical unit, Khon Kaen Regional Hospital, Srichan Road, Muang District, Khon Kaen, Thailand 40000, Email: surakrant@gmail.com

2. Warawut Kittiwatanagul, Surgical unit, Khon Kaen Regional Hospital, Srichan Road, Muang District, Khon Kaen, Thailand 40000, Email: warawkit@hotmail.com

3. Parnumas Piyavechvirat, Surgical unit, Khon Kaen Regional Hospital, Srichan Road, Muang District, Khon Kaen, Thailand 40000, Email: pparsoccer@yahoo.com

4. Bandit Thinkhamrop, Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Thailand 40002, Email: bandit@kku.ac.th

5. Nakornchai Phuenpathom, Department of Surgery, Faculty of Medicine, Prince of Songkla University, Thailand 90112, Email: nakornchai.p@psu.ac.th

6. Pisake Lumbiganon, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Thailand 40002, Email: pisake@kku.ac.th

Correspondence to: Surakrant Yutthakasemsunt, Khon Kaen Regional Hospital, Srichan Road, Muang District, Khon Kaen, Thailand 40000, Email: surakrant@gmail.com

Word count: 3,005 words (no abstract and references)
Abstract

Background Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding which can worsen after hospital admission. Tranexamic acid (TXA) has been shown to reduce bleeding in elective surgery and there is evidence that short courses of TXA can reduce re-bleeding in spontaneous intracranial haemorrhage. We aimed to determine the effectiveness and safety of TXA in preventing progressive intracranial haemorrhage in TBI.

Methods We enrolled 238 patients older than 16 years with moderate to severe TBI (post-resuscitation Glasgow Coma Scale (GCS) 4 to 12) who had a Computerized Tomography (CT) brain scan within eight hours of injury and in whom there was no immediate indication for surgery. We excluded patients if they had a coagulopathy or a serum creatinine over than 2.0 milligrams%. The treatment was a single dose of 2 grams of TXA in addition to other standard treatments. The primary outcome was progressive intracranial hemorrhage (PIH) which was defined as an intracranial hemorrhage seen on the second CT scan that was not seen on the first CT scan, or an intracranial hemorrhage seen on the first scan that had expanded by 25% or more on any dimension (height, length, or width) on the second scan.

Results Progressive intracranial haemorrhage was present in 21 (18%) of 120 patients allocated to TXA and in 32 (27%) of 118 patients allocated to placebo [RR=0.65 (95%CI 0.40 to 1.05)]. The relative risk of death from all causes in patients allocated to TXA compared with placebo was 0.69 (95% CI 0.35 to 1.39) and the relative risk for unfavourable outcome on the Glasgow Outcome Scale was 0.76 (95% CI 0.46 to 1.27) respectively. There was no evidence of increased risk of thromboembolic events in those allocated to TXA.

Conclusion Finally TXA may reduce PIH in patients with TBI. Large clinical trials are needed to confirm and to assess the effect of TXA on death or disability after TBI.
Keywords: Traumatic brain injury, Adults, Moderately severe TBI, Intracranial haemorrhage, Progressive haemorrhage, Delayed haemorrhage, Expanding haemorrhage, Antifibrinolytic agent, Tranexamic acid, Randomized controlled trial

Word count: 315 words (without keywords)
Background

Each year, world-wide more than 1.5 million people die and about 10 million people are hospitalized following traumatic brain injury (TBI).\textsuperscript{[1]} Many survivors experienced long term disability.\textsuperscript{[2]} In Thailand, each year around 8,000 people died following acute TBI and tens of thousands were hospitalized. A follow up study of 418 patients who were admitted to Khon Kaen regional hospital following TBI found that 29% of patients were either dead or severely disabled six months following the injury.\textsuperscript{[3]}

TBI is commonly accompanied by intracranial bleeding which occurs in 25% to 45%, 3% to 12% and 0.2% of severe, moderate and mild TBI cases respectively.\textsuperscript{[4]} There were evidences indicating that this bleeding can develop or continue after hospital admission and that larger bleeds have a worse prognosis. \textsuperscript{[5-12]} Delayed enlargement of traumatic intraparenchymal contusions and hematomas is the most common cause of clinical deterioration and death in patients who had a lucid interval after TBI.\textsuperscript{[8, 13]}

A systematic review of randomized controlled trials (RCT) shows that antifibrinolytic agents are effective in reducing bleeding in elective surgery. The review summarized data from 211 RCTs involving 20,781 participants showed that both aprotinin and tranexamic acid (TXA) reduced the need for blood transfusion in elective surgery by about one third (Relative risk = 0.61 [95% CI 0.54 to 0.69]), with no evidences of increased adverse effects.\textsuperscript{[14]} If antifibrinolytics reduced intracranial bleeding in patients with TBI this would have important clinical implications. However, a systematic review of haemostatic drugs in patients with TBI found no RCTs.\textsuperscript{[15]}

There were some evidences on the use of TXA in patients with spontaneous (aneurysmal) intracranial bleeding. A systematic review of RCTs of TXA in aneurysmal hemorrhage found that although re-bleeding was reduced by 45% (odds ratio = 0.55[95% CI 0.42 to 0.71]), this benefit was offset by cerebral ischaemia such that there was no overall
However, these trials used high doses TXA for about six weeks, and it has been suggested that a shorter and lower dose might prevent re-bleeding whilst avoiding the risk of ischaemia. Indeed, since the review was published a trial of early short course (3 days) TXA showed that it reduced re-bleeding from 10.8% to 2.4% without ischaemic adverse effects.\textsuperscript{17}

We conducted a double blind randomized controlled trials to evaluate the effect of early short course TXA on the occurrence of progressive intracranial hemorrhage (PIH) in patients with TBI treated at a large regional trauma centre in rural Thailand.

**Methods**

A randomized, double-blind, placebo-controlled, parallel group trial was conducted. The trial protocol was approved by the Khon Kaen Hospital Ethics Committee and the Khon Kaen University Ethics Committee. The trial protocol was registered with www.clinicaltrials.gov with the trial identifier NCT00755209. All informed consents were signed by legally acceptable representative because eligible subjects were comatose patients during entry time.

**Participants**

All patients, older than 16 years, with moderate to severe TBI (post-resuscitation Glasgow Coma Scale (GCS) 4 to 12) who had a Computerized Tomography (CT) brain scan performed within eight hours of injury, and whom there was no immediate indication for surgery, were eligible for inclusion. Patients were excluded if they were pregnant, had evidences of coagulopathy, known to be receiving a medication which affects haemostasis, or had a serum creatinine over than 2mg/decilitre. Coagulopathy was considered present if any of the following hematological parameters were observed: (1) platelet count less than 100,000 cells/mm3; (2) Prothrombin Time (PT) or International Normalized Ratio (INR) prolonged
more than 1.5 times normal value; (3) activated Partial Thromboplastin Time (aPTT) more
than 10 seconds greater than normal value.

**Intervention**

Patients were randomly allocated to receive TXA (loading dose of 1.0 gram over 30
minutes followed by a maintenance dose of 1.0 gram infused over eight hours) or matching
placebo. The placebo was sterile water and was purchased on the open market in Thailand.

**Study outcomes**

The primary outcome was progressive intracranial hemorrhage. PIH was defined as an
intracranial hemorrhage seen on the second CT scan that was not seen on the first CT scan, or
an intracranial hemorrhage seen on the first scan that had expanded by 25% or more on any
dimension (height, length, or width) on the second scan. Progressive pressure effect was
defined as either an increase in midline shift of greater than 1 mm or an increase in basal
cistern between the first and second CT scan. The second CT scan was to be taken 24 hours ±
8 hours after the first CT scan. Improved Glasgow Coma Scale (GCS) motor score was also
recorded to see if there is compatible change between clinical and radiological progression at
24 hours.

The presence or absence of PIH was assessed by two independent readers. Both were
neurosurgeons at KKH with experiences in reading posttraumatic CT scans. When there was
disagreement about the presence or absence of PIH this was resolved by a third neurosurgeon
reader. Inter-rater reliability was assessed by kappa statistic.

Secondary outcomes were: death, functional status assessed using the Glasgow
Outcome Scale (GOS) at hospital discharge, blood transfusion, neurosurgical operation and
any in-hospital thromboembolic events (myocardial infarction, pulmonary embolism, deep
vein thrombosis, and stroke).
Sample size

We planned to randomize approximately 240 patients, 120 to each group. We estimated that the proportion of patients with PIH would be 30% in the placebo group and that TXA would reduce to be 15%. A trial with 240 patients would have about 80% power at the 0.05 level of significance (two-sided test) to detect a treatment effect of this magnitude.

Randomisation and blinding

The randomisation sequence (with a randomly varied block size) was generated by computer by a person who was not involved with the trial and this sequence was used to prepare the sequentially numbered treatment packs. Whenever an eligible patient was recruited, the recruiting clinician asked that the next sequentially numbered sealed opaque treatment pack be opened and that the trial loading dose and maintenance infusion be prepared and sent to the relevant ward. This preparation was done out of sight of the recruiting clinician and research participants by nurses who were not involved in the trial. Each treatment pack contained unlabelled vials of either drug or placebo. Although drug and placebo vials contained an identical amount of colorless solution, there was a small size discrepancy between the drug and placebo vials. It was for this reason that the vials were enclosed within sequentially numbered sealed opaque envelopes that were opened by nurses who were not involved in the trial. This approach ensured good allocation concealment and also ensured that those caring for the patient and those conducting the trial did not know the assigned treatment. The allocation scheme was kept confidential from all research participants until the end of the study.

Statistical methods

The primary analysis was on an intention-to-treat (ITT) basis with complete case analysis for other outcomes and was done using STATA software (version 10.0; STATA, College Station, Texas, USA). The presence or absence of PIH was analyzed as a dichotomous
variable. The Glasgow Outcome Scale was also dichotomized such that death, persistent vegetative state, and severe disability constituted an unfavorable outcome while favorable outcome included moderate disability and good recovery. We calculated relative risks, risk difference with their 95% confidence intervals and hypothesis testing between the two treatment groups.

Results

Patient recruitment

Figure 1 shows the participant flow into the trial. The first patient was recruited on the 23rd October 2008 and the last patient on 14th August 2009 by which time a total of 238 patients had been included in the trial. All patients received the allocated trial treatments (TXA or placebo) and there were no protocol violations. There were nine patients for whom a second CT scan could not be obtained: seven patients died before the second CT scan, one patient could not be scanned because of agitation, and one patient refused the second scan. There were two consents withdrawal in the placebo group after randomization because they were signed by the unauthorized relatives. The related ethic committees were informed with an agreement for this exclusion. The inter-rater reliability of the assessment of the presence or absence of PIH was high with a kappa statistic of 0.95. The patients were enrolled with comparable profile including about mean age (40 years), male gender (80%), injury onset (within 7 hours) and initial haematocrit level (38 volumes %) with moderately severe GCS severity. There were similar pressures effects finding of the first CT scan in both groups. Treatment and control groups were approximately balanced with respect to baseline characteristics (Table 1).

Table 2 shows the effect of TXA on the study outcomes by the intention to treat analysis with assuming poor outcome which is used to represent the effectiveness of treatment effect. Progressive intracranial haemorrhage was present in 21 (18%) of patients allocated to
TXA and in 32 (27%) of patients allocated to placebo [RR=0·65 (95%CI 0·40 to 1·05)]. The relative risk of death from all causes in patients allocated to TXA compared with placebo was 0·69 (95%CI 0·35 to 1·39) and the relative risk for unfavourable outcome on the Glasgow Outcome Scale was 0·76 (95%CI 0·46 to 1·27). The relative risk of blood transfusion need in patients allocated to TXA compared with placebo was 0·92 (95%CI 0·61 to 1·40). Although we had informed the clinical condition and proposed for emergency neurosurgical operation in all patients with PIH to their relatives. The neurosurgical interventions were not done in placebo group because the patients’ relatives did not allow us to perform the operation hence the relative risk for neurosurgical interventions could not be calculated. There were very few adverse effects in both groups. There was no patient in TXA group who developed vascular occlusion event in this study.

Table 3 shows the effect of various methods of handling missing response in the primary outcome. The different analyses have different assumptions on existing PIH. A complete case analysis may be undertaken for primary outcome to avoid the assumption about PIH without imputation for the unavailable outcome. However different analyses give similar trend of potential benefit for treatment with tranexamic acid.

**Discussion**

**Principal findings**

We found a substantial reduction in the risk of PIH in patients allocated to TXA with no evidence of any increased risk of adverse events. The risks of death and of unfavorable outcome on the Glasgow Outcome Score were lower for patients allocated to TXA. The safety of early short course treatment of TXA in our TBI patients was compatible to no increasing risk of non-fatal vascular occlusive events with early short course treatment of TXA in traumatic bleeding patients in CRASH2 trial.\[^{18}\]

**Strengths and weaknesses**
This is the leading randomized trial to examine the effectiveness of the early administration of a short course of TXA in patients with acute TBI. We are aware of a recent study publication of CRASH2 trial and we anticipate that the results of all relevant trials will ultimately be combined in the Cochrane systematic review of haemostatic drugs for TBI.  

Our trial was properly randomized with good allocation concealment. The timing of the second CT scan was pre-specified in the protocol and all outcome measurements were made without knowledge of treatment allocation. The main weakness of our study is the low power to estimate the effect of TXA on clinical outcomes. In particular, although our study has shown that TXA can reduce PIH, because of the low power to examine the effect of TXA on death and on disability, the clinical implications of our findings are still limited.

**PIH in TBI**

Various terms have been used to describe the development or enlargement of intracranial bleeding after TBI. Terms include delayed traumatic intracranial haemorrhage (DTICH) [7], expanding hematoma [19] and progressive hemorrhagic injury. [10] In this paper we combined these concepts such that we included both new haemorrhage and expanding haemorrhage (progressive intracranial hemorrhage). Our rationale was that both lesions may exacerbate intracranial hypertension and the occurrence of both may be affected by the administration of TXA.

Although patients were excluded if they had evidence of coagulopathy at baseline the proportion of patients with PIH among the patients was surprisingly high. Had we not excluded coagulopathic patients it is likely that the proportion of patients with PIH would have been even higher. Previous estimates of the occurrence of PIH vary widely from 7% to 60%. [20] These differences are likely to reflect difference in timing of the CT scan, clinical setting and diagnostic criteria. Nevertheless, given the relatively high prevalence of PIH in patients with TBI observed in this study the potential for TXA to improve clinical outcomes could be high.
Methods of handling missing response in trial

We summarize the result of handling missing outcome for the primary outcome in Table 3.

Conclusions

We have not shown that TXA improves clinical outcomes and this information would be required in order to make any recommendation about the use of TXA in clinical practice. Our results have important implications for research. If an early short course of TXA could be demonstrated to improve clinical outcomes after TBI without any important adverse effects, then this treatment, because it is cheap and widely practicable, could contribute importantly to reducing mortality and disability after TBI.
Figure 1: Participant flow diagram

Assessed for eligibility (n = 2,922)

Excluded patients 2,682
Mild TBI 1,240
No relative for consent 728
Age <16 year 313
No TBI 170
Need OR in 8 hour 95
Onset > 8 hour 91
Unstable 42
Penetrating TBI 4
Coagulopathy 1

Allocated to TXA (n = 120)
Allocated to placebo (n = 120)

Received TXA (n = 120)
Received placebo (n = 120)

Second CT scan obtained (n = 115)
Second scan not obtained (n = 5)
(dead 3, agitation 1, refused 1)
Second CT scan obtained (n = 116)
Second scan not obtained (n = 4)
(dead 4)

2 consents withdrawn (unauthorized relatives)

PIH analysis (n = 115)
Secondary outcomes (n = 120)
PIH analysis (n = 114)
Secondary outcomes (n = 118)
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TXA  (n=120)</th>
<th>Placebo  (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization (years)</td>
<td>34.8 (16.0)</td>
<td>34.1 (15.3)</td>
</tr>
<tr>
<td>Male</td>
<td>103 (86%)</td>
<td>107 (91%)</td>
</tr>
<tr>
<td>Glasgow Coma Scale (GCS) severity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (9 – 12)</td>
<td>52 (53%)</td>
<td>47 (47%)</td>
</tr>
<tr>
<td>Severe (4 – 8)</td>
<td>68 (49%)</td>
<td>71 (51%)</td>
</tr>
<tr>
<td>Baseline haematocrit (volume%)</td>
<td>38 (7.4)</td>
<td>38 (6.7)</td>
</tr>
<tr>
<td>Time since injury (hours)</td>
<td>6.6 (1.69)</td>
<td>7.1 (1.29)</td>
</tr>
<tr>
<td>Midline shift (&gt;3mm) on first CT (mm)</td>
<td>2 (0.02%)</td>
<td>3 (0.03%)</td>
</tr>
<tr>
<td>Basal cistern compression on first CT</td>
<td>54 (45%)</td>
<td>53 (45%)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>TXA (n =120)</td>
<td>Placebo (n = 118)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Progressive intracranial haemorrhage (PIH)</td>
<td>21 (18%)</td>
<td>32 (27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate TBI (n =24)</td>
<td>7 (6%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Severe TBI (n =20)</td>
<td>9 (8%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Indicated neurosurgery</td>
<td>6 (5%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Increase in pressure effect*</td>
<td>* 11 (10%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved GCS motor score at 24 hours</td>
<td>37 (31%)</td>
<td>37 (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosurgical intervention</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood products transfusion</td>
<td>31 (26%)</td>
<td>33 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>12 (10%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable (GOS) outcome</td>
<td>21 (18%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adverse events**

- Myocardial infarction: 0 in TXA, 3 in Placebo
- Stroke: 0 in TXA, 0 in Placebo
- Pulmonary embolus: 0 in TXA, 0 in Placebo
- Deep vein thrombosis: 0 in TXA, 1 in Placebo
- Gastro-intestinal bleeding: 0 in TXA, 7 in Placebo

* Denominator for outcomes is 114 for TXA group and 115 for placebo group. This is an analysis based on complete case analysis that is not assumed the missing outcome.
<table>
<thead>
<tr>
<th>Methods of analysis</th>
<th>PIH in TXA and placebo group</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>n/N</td>
<td>Rate (person)</td>
<td>Rate (%)</td>
<td>RD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[95% CI]</td>
</tr>
<tr>
<td>1. Complete case analysis</td>
<td>TXA</td>
<td>16/115</td>
<td>14%</td>
<td>-0.11</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28/114</td>
<td>25%</td>
<td>[(-0.21)-(-0.01)]</td>
<td>[0.32-0.99]</td>
</tr>
<tr>
<td>2. Assuming poor outcome</td>
<td>TXA</td>
<td>21/120</td>
<td>18%</td>
<td>-0.10</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>32/118</td>
<td>27%</td>
<td>[(-0.20)-(-0.01)]</td>
<td>[0.40-1.05]</td>
</tr>
<tr>
<td>3. Assuming good outcome</td>
<td>TXA</td>
<td>16/120</td>
<td>13%</td>
<td>-0.10</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28/118</td>
<td>24%</td>
<td>[(-0.20)-(-0.01)]</td>
<td>[0.32-0.98]</td>
</tr>
<tr>
<td>4. Extreme case favoring placebo</td>
<td>TXA</td>
<td>21/120</td>
<td>18%</td>
<td>-0.06</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28/118</td>
<td>24%</td>
<td>[(-0.16)-(-0.04)]</td>
<td>[0.44-1.22]</td>
</tr>
<tr>
<td>5. Extreme case favoring TXA</td>
<td>TXA</td>
<td>16/120</td>
<td>13%</td>
<td>-0.14</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>32/118</td>
<td>27%</td>
<td>[(-0.24)-(-0.04)]</td>
<td>[0.29-0.85]</td>
</tr>
</tbody>
</table>
List of abbreviations

aPTT       activated Partial Thromboplastin Time
CI         Confidence Interval
CRASH2     Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage
CT         Computerized Tomography
DTICH      Delayed Traumatic Intracerebral Haematoma
GCS        Glasgow Coma Scale
GOS        Glasgow Outcome Scale
INR        International Normalised Ratio
ITT        Intention-To-Treat
KKH        Khon Kaen Hospital
KKU        Khon Kaen University
LSHTM      London School of Hygiene & Tropical Medicine
mg         milligram
mm         millimeters
mm$^3$     cubic millimeters
OR         Operative Room treatment
PIH        Progressive Intracranial Hemorrhage
PT         Prothrombin Time
RCT        Randomized Controlled trial
RD         Risk Difference
RR         Relative Risk
TBI        Traumatic Brain Injury
TXA        Tranexamic Acid
USA        United States of America
Competing interests

The authors declare that they have no financial competing interests. However this manuscript is a result of study which Surakrant Yutthakasemsunt uses as a thesis proposal submitted in partial fulfillment of the requirements for his degree of Doctor of Philosophy in Clinical Science, Graduate School, Khon Kaen University in 2012. A thesis proposal is entitled “Tranexamic acid for preventing progressive intracranial haemorrhage in adults with traumatic brain injury; a randomised, double-blinded, placebo-controlled trial.” The thesis advisors are Professor Dr. Pisake Lumbiganon, Professor Dr. Nakornchai Phuenpathom. Also Professor Dr. Ian Grey Roberts has supported in writing manuscript with associate professor Bandit Thinkhamrop has contribution as a statistical consultant. Therefore this thesis is an approval and copyright of Khon Kaen University with academic competing interests by relevant authors.

Authors' contributions

Surakrant Yutthakasemsunt, Nakornchai Phuenpathom, Bandit Thinkhamrop and Pisake Lumbiganon contributed in literature search, figures, study design, data collection, data analysis, data interpretation and writing. Warawut Kittiwatanagul and Parnumas Piyavechvirat contributed in study design, data collection, data interpretation and writing.

Authors' information

Surakrant Yutthakasemsunt, Warawut Kittiwatanagul and Parnumas Piyavechvirat are attending neurosurgeon in Khon Kaen hospital (KKH) over than ten years. KKH is a tertiary care hospital with a service as trauma center level I. TBI is a major health burden in KKH about three thousand TBI patients a year. Surakrant Yutthakasemsunt has been studying in research based program in Khon Kaen University since 2007 and working for KKH. This study has been conducted as his thesis proposal in order to improve TBI patients care with kindly support from the thesis advisors and consultants.
Acknowledgment

We thank Khon Kaen Hospital (KKH), the Thailand Research Fund, the Faculty of Medicine, Khon Kaen University (KKU), Thailand. We thank Ian Roberts from London School of Hygiene & Tropical Medicine (LSHTM) for advice on the protocol and the manuscript. We also thank the patients and relatives involved in the trial and the staffs who cared for them.
References


