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RANDOMIZED CONTROL TRIAL STUDY OF ROLE OF TRANEXAMIC ACID IN PREVENTION OF RE- BLEEDING IN RUPTURE ANEURYSMAL PATIENT BEFORE ANEURYSMAL SURGICAL TREATMENT.

Neurosurgery

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ABSTRACT

One of the major causes of mortality and morbidity in aSAH patients is recurrent bleeding. The highest risk of rebleeding occurs within the first 3 days. It usually occurs within 24 hours. Early studies suggested iv TXA in aSAH patients reduced the incidence of recurrent bleeding as well as probably functional outcome, but increased complications such as delayed cerebral ischemia and thromboembolic events.Patients with aSAH were randomly divided into two groups; the control group and patients receiving standard treatment with the addition of receiving TXA. TXA was given 1 gm bonus IV, followed by 1 gm IV every 8 hours for the next 72 hours. The outcome was measured in terms of bleeding, side effects, and functional outcome.A total of 149 cases of SAH were enrolled in the study. Of those, 38.9% received TXA and the rest (61.1%) received standard treatment. In the TXA group re-bleeding was seen in 5.2% of cases, delayed cerebral ischemia was seen in 17.2% of cases, and hospital mortality in 3.4% of cases, significantly lower as compared to the non-TXA group, and favourable outcome (3 months) MRS in 74.1% of cases showed significant improvement in the TXA group.The study suggested short-term use (72 hours) of Iv TXA significantly decreased re-bleeding in aSAH patients. there was also a reduction in hospital mortality and improved functional outcome without increased complications like delayed cerebral ischemia, thromboembolic events, or hydrocephalus.

KEYWORDS

Aneurysmal subarachnoid haemorrhage (a SAH), Tranexamic acid (TXA), Rebleeding

INTRODUCTION:

In India, the incidence of subarachnoid haemorrhage caused by a ruptured aneurysm is 6-16/100,000 people. ([1] The most common complication is re-bleeding, which carries significant mortality and morbidity. [2, 3, 4] The incidence of re-bleeding is highest in the first week after initial hemorrhage, in which most of the re-bleeding occurs within the first 24 hours. [5,6,7,8,9,10,11,12,13] The case fatality rate after re-bleeding is approximately 30%. [14,15,16]

The primary aims of treatment of ruptured aneurysms are to prevent re-bleeding and cerebral vasospasm. [4,17] Re-bleeding can be prevented by aneurysmal occlusion treatment by either coiling or clipping [18,19], but in developing countries like India, in daily clinical practice, surgical treatment is often delayed by delay in diagnosis or transfer to a tertiary centre. [20]

Anti-fibrinolytic agents like Tranexamic acid can use for alternative treatment to reduce risk of re-bleeding before aneurysmal occlusion surgery. [21,22,23]

Tranexamic acid is a synthetic derivative of amino acid lysine, which binds 5 lysine binding sites on plasminogen. This inhibits plasminogen formation and displaces plasminogen from the fibrin surface. Tranexamic acid prolongs the duration of the formed clot within and about the wall of the aneurysm and thus prepares the way for mechanical repair of rupture. [24,25,26,27]

Prolonged use of tranexamic acid increases the risk of delayed cerebral ischemia and thromboembolic events, so short-term treatment with tranexamic acid (for 72 hours) may protect the re-bleeding without an associated increased risk of cerebral ischemia and thromboembolic events. [28,29,30,31,32,33,34]

The aim of this study is to describe the role of tranexamic acid in the prevention of re-bleeding in ruptured aneurysmal patients before aneurysmal surgical treatment and to evaluate delayed cerebral ischemia and thromboembolic events.

MATERIAL AND METHODS:

This study was single centre, randomized control trial, prospective study. This study was conducted at the tertiary centre for two years from Dec 2019- Dec 2021, after taking permission from the ethics committee of the institution and written informed consent from patients or their close relatives.

Patient Selection:

Patients older than eighteen years of age with severe headache and SAH, which were proven by CT scan brain included in the study. Patient who had peri mesencephalic bleeding, history of trauma, patient taking treatment for DVT, history of hypercoagulability disorder, pregnancy, and patient having severe renal (s. Creatinine > 150 mmol/l) or hepatic failure (AST > 150 U/L or gamma GT > 150 U/L) were excluded from the study.

The patients were receiving TXA, with normal angiography excluded from the study.

Randomization:

In this randomization done by using permuted blocks and with stratification, to equalization of patient in both study groups.

Treatment Protocol:

All SAH patients were treated according to the standard treatment protocol at the study centre. The treatment group who were randomly assigned to a study group also received additional administration of tranexamic acid.

Tranexamic acid was given as soon as possible by 1 gm bonus intravenously followed by 1 gm every 8 hourly for next 72 hours. If aneurysm surgery (coiling or clipping) was performed before 72 hours, tranexamic acid was discontinued before the procedure. Tranexamic acid treatment may also be discontinued if CT angiography or DSA suggests no aneurysm. Patients included in the control group did not receive Tranexamic acid treatment.

Data Collection:

Baseline characteristics data such as age, sex, medical history, WFNS grade, Modified Fisher grade, Hunt and Hess score at time of admission, location of aneurysm, treatment (coiling or clipping) and time interval from the onset of SAH to treatment were collected.

The favourable functional outcome was assessed at 3 months after the SAH by a validated telephone interview. The MRS score was dichotomized into favourable (MRS 0-3) and poor (MRS 4-6) outcomes.

Secondary outcomes such as case fatality rate, rebleeding rate, per procedural complication (delayed cerebral ischemia, thromboembolic event, hydrocephalus) are also measured.

Data was entered into an excel sheet. Continuous data was summarised in the form of a mean and standard deviation. The difference in mean was analysed using the student 't' test for subgroup analysis. Discrete data was expressed in the form of proportions and the difference in proportion was analysed using a chi-square test. The level of significance was kept at 95% for all statistical analysis. For analysis,

SPSS 25.0 for statistics was used.

RESULT:
Total 149 cases of aSAH were enrolled in our study from Dec 2019 to Dec 2021. Out of them 58(38.9%) received TXA and rest 91(61.1%) received standard treatment.

Table 1:
Mean age of cases of TXA group was 52. 4±9.3 years and of Non TXA group were 54. 6±10.7years. Among cases who received TXA, most 35 (60.3%) cases were female similar sex presentation was seen among cases who received standard therapy. In TXA group majority 46 (79.3%) cases had I-III WFNS grade, similarly in Non TXA group 63 (69.2%) had I-III WFNS grade. Similarly, most of cases had 0-3 Fisher grade among both subgroups.

Among both subgroups most common aneurysm location was anterior circulation. Around one third 17 (29.3%) cases in TXA group were smoked and in Non TXA group 25 (27.5%) were smoked. Around half of the cases were hypertensive in TXA group (53.4%) and Non TXA group (50.5%). Time of a SAH of admission, a SAH to treatment, Admission to treatment, aSAH to start TXA with TXA group was 2. 1±1.0, 8.1±1.5, 6±1.3 and 2. 1±1.0 days respectively, while in Non TXA group it was 2. 1±0.9, 8.0±1.5 and 5. 9±1.1 days respectively, and the difference in time in cases of both study groups was statistically insignificant. Difference in age, sex, WFNS grade, Fisher grade, aneurysm location, aneurysm treatment and Co-morbidities was statistically insignificant (p value>0.05).

Table 2:
In TXA group re-bleeding was seen in 3(5.2%) cases which were significantly lower in Non TXA group 17(18.7%) cases (p value <0.05)

In TXA group, delayed cerebral ischemia was seen in 10 (17.2%) cases, Treatment ischemia in 1 (1.7%) case, Hydrocephalus in 8 (13.8%) cases, in hospital mortality in 2 (3.4%) cases and favourable outcome (3 months) MRS in 43 (74.1%) cases while in Non TXA group delayed cerebral ischemia was seen in 27 (29.7%) cases, Treatment ischemia in 9 (9.9%) cases, Hydrocephalus in 17 (18.7%) cases, In hospital mortality in 16 (17.6%) cases and favourable outcome (3 months) MRS in 59(64.8%) cases.

The difference in the proportion of cases who had hospital mortality among both subgroups was found to be statistically significant (p value < 0.05), while the difference in other hospital outcomes among both groups was statistically insignificant (p value>0.05).

DISCUSSION:
In the RCT study, we focused on assessing the role of tranexamic acid in aneurysmal SAH patients in the prevention of re-bleeding before occlusion surgery.

Re-bleeding was thought to be a major cause of morbidity and mortality in aneurysmal SAH patients. Early intervention has resulted in a significant decrease in poor outcome due to re-bleeding.

Re-bleeding occurs in the first 7 days after the initial rupture of the aneurysm; in most cases, re-bleeding occurs within 24 hours. For prevention of re-bleeding before the intervention, early administration of TXA was associated with a reduced risk. Although there is an increased risk of delayed cerebral ischemia and thromboembolic events in most of other studies.

Our study results suggest that Tranexamic acid may reduce rebleeding risk in aSAH. There are drug-related adverse events like cerebral ischemia or thromboembolic events that were not increased in our study as compare to other studies.

Baharoglue studied the effects of two antifibrinolytic drugs, Tranexamic acid and EACA, in aSAH patients. The study concluded that antifibrinolytics reduced the risk of bleeding, but they found an increased risk of cerebral ischemia.

According to Hilman et al, study, short-term use of anti-fibrinolytics not only reduces the incidence of recurrent bleeding but also improves outcomes.

In our study, we compared treatment with short-term use of TXA in aneurysmal SAH before definitive aneurysmal occlusion surgery in our institute. The study suggested short-term use (72 hours) of intravenous TXA signification decreases re-bleeding in aneurysmal SAH patients. There was also a reduction in hospital mortality in patients who received additional Tranexamic acid treatment. The study suggested that hospital mortality was higher in patients who suffered from recurrent bleeding. As compared to the Tranexamic acid treatment group, non-Tranexamic acid group patients have a poor favourable outcome in 3 month follow-up (MRS).

In our study, Complications like delayed cerebral ischemia, thromboembolic events, and hydrocephalus were found to be less as compared to the non-TXA group, but it's not significant.

The study has several limitations. For starters, most of the patients who arrived at the hospital 2 to 3 days after ictus already had vasospasm or hemiparesis. As a result, patients with low WFNS grades had poor long-term outcomes. For second aneurysmal occlusion surgery, also not done very early, there was a median time interval between a SAH and the surgery of 8 days. Third, 3-month MRS score based on a telephonic interview with relatives and dichotomizing into good (MRS 0-3) and poor (MRS 4-6). There is a possibility of interpretation bias.

CONCLUSION:
The definitive way to prevent re-bleeding in aneurysmal SAH is early intervention surgery by coiling or clipping. In developing countries like India, there is a lack of health facilities and trained doctors in remote areas, making it very challenging to perform early occlusion surgery. So, prevention of re-bleeding can be done by using intravenous Tranexamic acid. We found that short-term use of tranexamic acid decreases re-bleeding, hospital mortality and shows favourable outcome after 3 months without an increase in thromboembolic complications. However, a randomised control trial study over a large population is needed to determine the safety and efficacy of short-term tranexamic acid in patients.

Table 1 Baseline Characteristics Of 149 Patients With Aneurysmal Subarachnoid Hemorrhage.

	TXA (n=58)	Non TXA (n=91)	P value
Female	35(60.3)	55(60.4)	0.873
Age (years)	52.4±9.3	54.6±10.7	0.2
WFNS grade			
I-III	46(79.3)	63(69.2)	0.244
IV-V	12(20.7)	28(30.8)	
Fisher Grade			
0-3	44(75.9)	62(68.1)	0.407
4	14(24.1)	29(31.9)	
Causative aneurysm location			
Anterior circulation	49(84.5)	79(86.8)	0.875
Posterior circulation	9(15.5)	12(13.2)	
Aneurysm treatment			
None	3(5.2)	6(6.6)	0.869
Coiling	43(74.1)	64(70.3)	
Clipping	12(20.7)	21(23.1)	
Co-morbidities			
Smoking	17(29.3)	25(27.5)	0.955
Hypertension	31(53.4)	46(50.5)	859
Time (days)			
aSAH to admission	2.1±1.0	2.1±0.9	1
aSAH to treatment	8.1±1.5	8.0±1.5	0.692
Admission to treatment	6±1.3	5.9±1.1	0.615
aSAH to start TXA	2.1±1.0		

Table 2: Complication And Outcome Per TXA Group And Non-TXA Group

	TXA (n=58)	Non TXA (n=91)	P value
Rebleeding	3(5.2)	17(18.7)	0.035
Delayed cerebral ischemia	10(17.2)	27(29.7)	0.129
Treatment ischemia	1(1.7)	9(9.9)	0.108
Hydrocephalus	8(13.8)	17(18.7)	0.58
In hospital mortality	2(3.4)	16(17.6)	0.02
Favorable outcome (3 months) MRS	43(74.1)	59(64.8)	0.312

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