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Multidisciplinary Academic Journal Publisher

The role of tranexamic acid in control of traumatic intracranial hemorrhage

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Abstract: Background: Traumatic brain injury (TBI) is a leading cause of death and disability. Intracranial hemorrhage (ICH) secondary to TBI is associated with a high risk of coagulopathy which leads to increasing risk of hemorrhage growth and higher mortality rate. Therefore, antifibrinolytic agents such as tranexamic acid (TA) might reduce traumatic ICH. **Aim of the work:** To assess the effect of TA on intracranial hemorrhage in patients with TBI. **Patients and methods:** This study was conducted on 40 patients with traumatic ICH. Patients were divided into intervention and control groups (20 patients each). All patients received a conservative treatment for ICH, and either intravenous TA or control. The extent of ICH growth as the primary outcome was measured by brain CT scan after 48 h. **Results:** TA administration was likely to be associated with a reduction in hemorrhage growth (difference 0.445 ml and -1.500 in both groups respectively), significant improvement in GCS (difference -0.900 p value 0.007 and 0.350 in both groups respectively) and fewer deaths (5% and 8% in both groups). **Conclusion:** Administration of TA might reduce ICH growth and improve clinical outcomes.
[Radwa Ashraf Mohamed Fathi Fouda, Ashraf Mohamed Faried, MagdyAbd-el Aziz El Mahallawy and Sameh Mohamed Refaat El-Shehdawy. **The role of tranexamic acid in control of traumatic intracranial hemorrhage.** *Nat Sci* 2019;17(12):340-349]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 40. doi:10.7537/marsnsj171219.40.

Keywords: role; tranexamic acid; control; traumatic; intracranial; hemorrhage

1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability. Each year about 1.5 million persons die and more than 10 million persons are hospitalized following TBI worldwide [(1)].

There is no effective therapy for primary brain injury caused by the traumatic insult. Current treatment aimed to reduce the risk factors of secondary brain injury [(2)].

One of the most important and devastating parts of the secondary pathologic cascade that may occur after the initial brain injury is the progression of intracranial hemorrhage (ICH), especially within the first 24 hours. Its frequency varies according to TBI severity [(3)]. In the CRASH-1 (Corticosteroid Randomisation after Significant Head Injury) trial, which included 10,008 patients with mild, moderate and severe TBI, 67% of participants had computerised tomography (CT) scan evidence of ICH [(4)].

In about half of patients with ICH the lesion enlarges after hospital admission [(5,6)]. Narayan et al. [(6)] reported a study in which they included patients with TBI and parenchymal intracranial bleeding confirmed by CT scan of ≥2ml. They repeated the CT scan at 24 and 72 hours and found that in 51% of the included patients the lesions expanded. Patients with large hemorrhages are at substantially greater risk of death than those with small hemorrhages [(7)].

These observations raise the possibility that an intervention administered in the first hours after the injury may prevent the enlargement of intracranial bleeding and therefore might improve patients' outcomes.

About a third of patients with TBI have coagulopathy. Those with coagulopathy have an increased risk of hemorrhage growth and higher mortality [(8)]. Increased fibrinolysis, as indicated by high levels of fibrinogen degradation products, is a common feature of the coagulopathy in TBI, raising the possibility that tranexamic acid (TA) might reduce traumatic ICH [(9)].

The antifibrinolytic TA has been shown to reduce blood loss in surgical patients and the risk of death in patients with traumatic bleeding, with no apparent increase in vascular occlusive events. These findings raise the possibility that it might be effective in other situations in which bleeding can be life threatening or disabling [(10,11)].

In addition to the robust data demonstrating clinical benefit in trauma patients with severe bleeding, TA also has an excellent safety profile [(12)] and has been shown to be cost-effective. Because of the mechanistic potential for TA to decrease secondary

brain injury, it has been considered as a possible therapy to improve clinically important outcomes in patients with TBI [13].

In the haemostatic process, coagulation occurs rapidly at the site of a damaged vessel, building a tight net of fibrin, while at the same time the fibrinolytic system removes the fibrin deposits that could cause permanent vascular occlusion once vascular repair has taken place [14]. The coagulation and fibrinolytic system are believed to be in a state of dynamic balance that maintains an intact vascular system.

TA as a potent antifibrinolyticagent reversibly blocks lysine binding sites on plasminogen and plasmin, and acts to prevent proteolytic degradation of fibrin clots formed in the normal physiologic process of hemostasis. Both plasminogen and plasmin are activators of fibrinolysis and active clot-lysing agents. TA thus helps to stabilize fibrin clots, which in turn maintains coagulation and helps to control bleeding [15].

Ethics of the study:

The Research Ethical Committee, Faculty of Medicine, Tanta University approved the design of the study. An informed written consent was taken from close relatives after explanation of benefits and risks.

Privacy of all patient data was granted. There was code number for every patient file that includes all investigations.

2. Patients and Methods

Our study carried out upon forty (40) patients of traumatic brain injury with ICH in Emergency Department, Tanta University Hospital during the period of one year from January 2018 to January 2019. Patients were randomly classified using closed envelops and a computer generated random numbers into two groups each group of twenty (20) patients, group I which received TA and group II which was a control group.

The inclusion criteria were patients with TBI of acute ICH, volume of ICH less than 30 ml based on CT findings and age 18 or more.

The exclusion criteria were GCS total score <8, unknown onset of injury, need for surgery, presence of focal neurologic deficits, cerebral edema with midline shift, use of TA within the previous 14 days, hereditary or acquired hemorrhagic diathesis or coagulation deficiency, creatinine> 20 ml/L, pregnancy, history of current evidence suggestive of venous or arterial thrombotic events, history of hypersensitivity to TA and history of acquired color blindness or visual vascular problems.

All patients were subjected to full history taking either from patient or his relatives or witness andpatient symptoms were also taken if cooperative.

According to ATLS, management consisted of a rapid primary survey, resuscitation of vital functions, a more detailed secondary survey, and, finally, the initiation of definitive care.

Routine laboratory investigations and routine radiological investigations were done.

Initial brain CT scan was done immediately after admission and routine care. The baseline data including demographic data, mechanism of injury, and findings of initial brain CT scan (especially ICH volume) was entered. Then, included patients randomized to get either the intervention or control based on a computer-generated code list (20 patients in each group).

Statistical analysis used:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t- test, Paired t-test, Chi-square by SPSS V20.

1. Mean =

Where = sum & n = number of observations.

2. Standard Deviation (SD):

Student t-test (Unpaired):

Where:

= Mean of the first group.

= Mean of the second group.

SE1 = Standard error of the first group.

SE2 = Standard error of the second group.

Unpaired Student T-test was used to compare between tow groups in quantitative data.

Paired t-test:

Where:

= Mean's difference between pre and post.

SEd = Standard error of the difference between pre and post.

Unpaired Student T-test was used to compare between related sample.

Chi-square the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square.

P-value > 0.05 Non significant.

P-value ≤ 0.05 Significant.

P-value < 0.01 Highly Significant.

3. Results

Our study was done on forty patients, twenty in each group. The results of our study according to gender were the first group included 14 males (70%) and 6 females (30%), while group 2 included 16 males (80%) and 4 females (20%) as males are more exposed to trauma.

The age ranged from 18 to 75 years in the first group, while patients in the second group ranged between 18 and 66 years.

Road traffic accidents were the main cause of trauma and accounted for 60%, the falling of height and direct head trauma each accounted for 20%.

GCS of studied patients in group I ranged from 9-14 at admission, while GCS after 48 hours in same group ranged from 7-15 with significant difference between them.

And GCS of patients in group II ranged from 9-14 at admission, while GCS after 48 hours in the same group ranged from 6-15.

Table (1): Age & gender in group I

No. of patient	Group I	
	Age in years	gender
1	54	male
2	27	male
3	48	female
4	55	female
5	18	male
6	29	male
7	41	male
8	33	female
9	19	male
10	22	male
11	56	male
12	75	female
13	47	male
14	19	male
15	18	male
16	20	female
17	58	male
18	24	male
19	54	male
20	19	female
Range	18-75	No. of males: 14 No. of females: 6
Mean ± SD	36.800 ±17.683	Male %: 70 Female %: 30

In group I, the volume of hemorrhage at admission and after 48 hours was decreased by 10.56%. In the group II, the volume of hemorrhage changed at admission and after 48 hours as it increased by 20.67%.

In group I, only 4 patients needed surgical intervention 20%, while 16 patients did not require surgical intervention 80%. In group II, 8 patients required surgical intervention 40%, while 12 patients did not require surgical intervention 60%.

In group I, 3 patients died 15% and 17 patients were alive 85%, while in the second group, 5 patients died 25% and 15 patients were alive 75%.

Table (2): Age & gender in group II

No. of patient	Group II	
	Age in years	gender
1	33	male
2	45	male
3	66	male
4	33	female
5	18	male
6	26	male
7	58	male

No. of patient	Group II	
	Age in years	gender
8	38	male
9	22	female
10	28	male
11	45	female
12	19	male
13	36	male
14	54	male
15	43	male
16	22	male
17	37	female
18	31	male
19	44	male
20	20	male
Range	18-66	No. of males: 16 No. of females: 4
Mean ± SD	35.900± 13.486	Male %: 80 Female %: 20

Table (3): Volume of ICH on admission and after 48 hours

VOLUME of ICH		Groups		T-Test	
		Group I	Group II	t	P-value
On Admission	Range	0.1 - 15	3 - 40	-2.766	0.009*
	Mean ±SD	4.795 ± 4.307	11.170 ± 9.362		
After 48 Hours	Range	0.1 - 15.5	3 - 32	-3.477	0.001*
	Mean ±SD	4.350 ± 4.231	12.670 ± 9.828		
Differences	Mean ±SD	0.445 ± 1.833	-1.500 ± 5.744		
% of Change		10.56	20.67		
Paired Test	P-value	0.291	0.257		

Cases:

Case 1: A 19 yrs old male patient with post traumatic epidural rim and depressed fracture allocated in group I, GCS on admission was 11 and increased to 14 after 48 hours with decease in the ICH volume after 48 hours. Figure (2): CT brain of case 1 at admission.

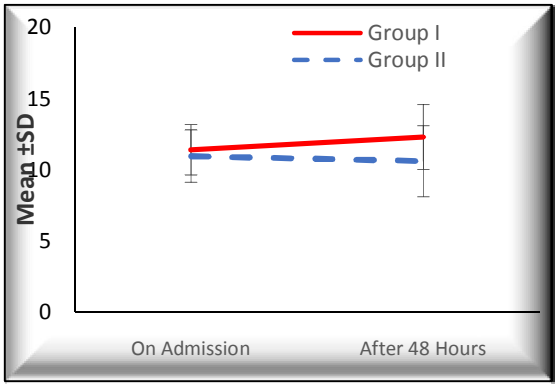

Figure (2): GCS of studied patients on admission and after 48 hours

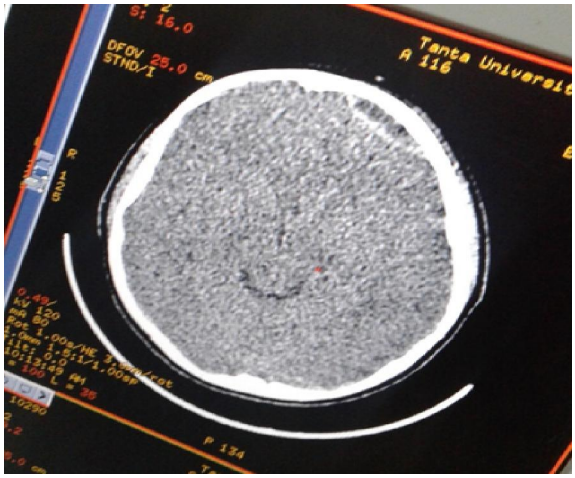

Figure (3): CT brain of case 1 after 48 hrs.

Case 2: A 55 yrs old male allocated to group II presented with post traumatic parenchymal contusions and SAH, GCS at admission was 14 and decreased to 12.

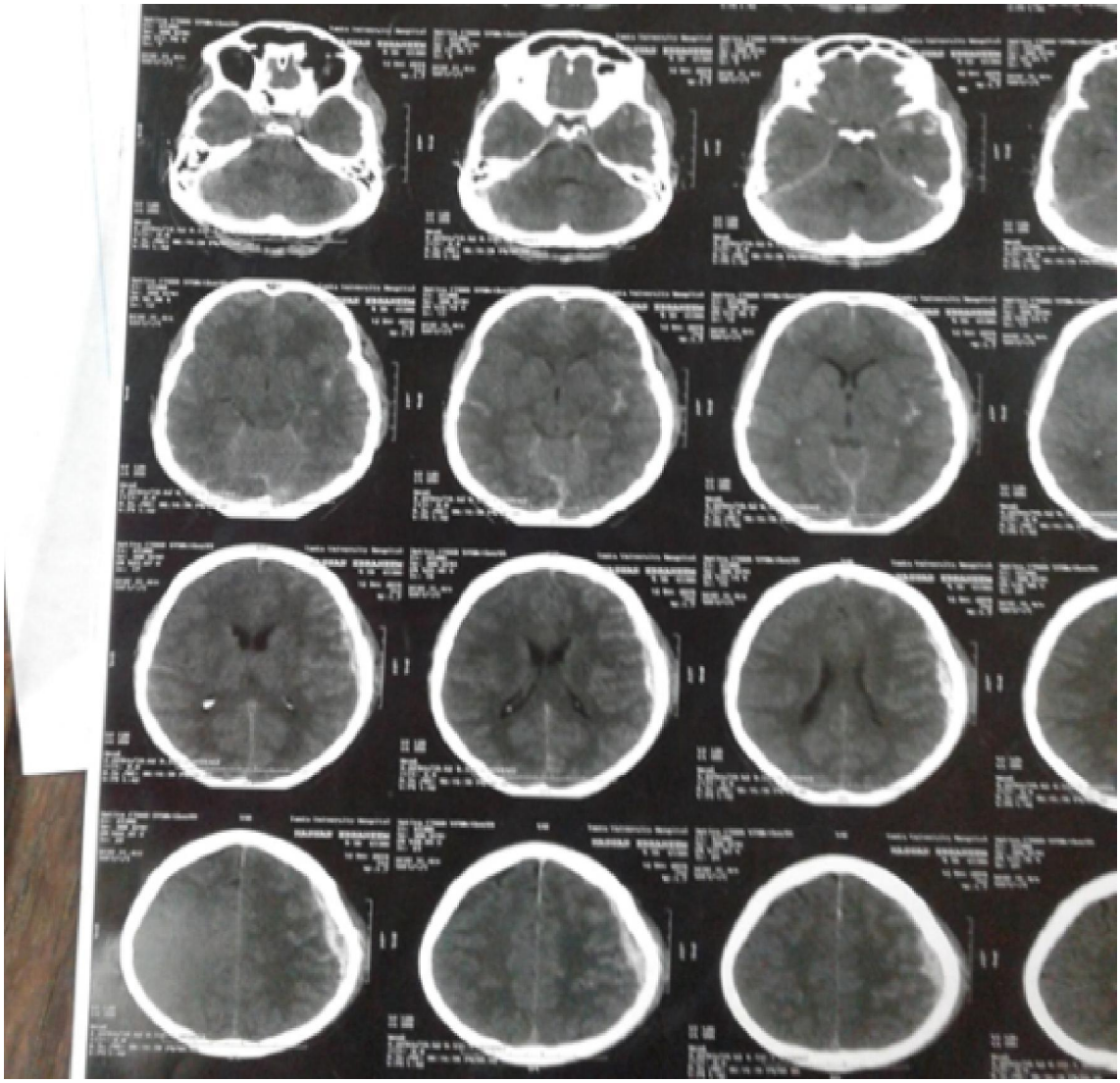

Figure (4): CT brain of case 2 at admission.

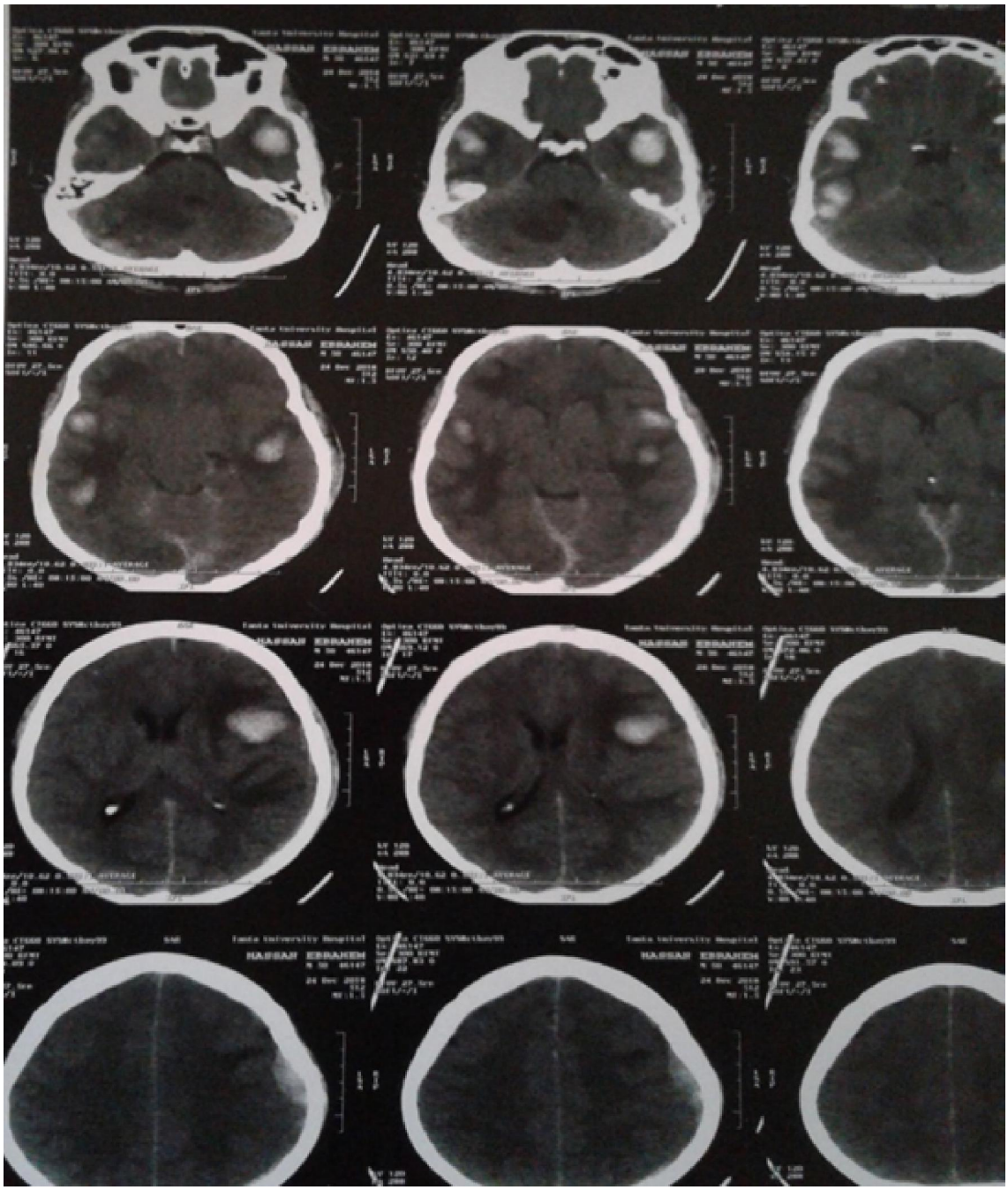

Figure (5): CT brain of case 2 after 48 hrs.

Case 3: A 33 yearrs old male presented with post traumatic parenchymal contusion allocated to group I, there is no significant change in ICH in both CT scans but GCS of patient improved from 12 to 15.

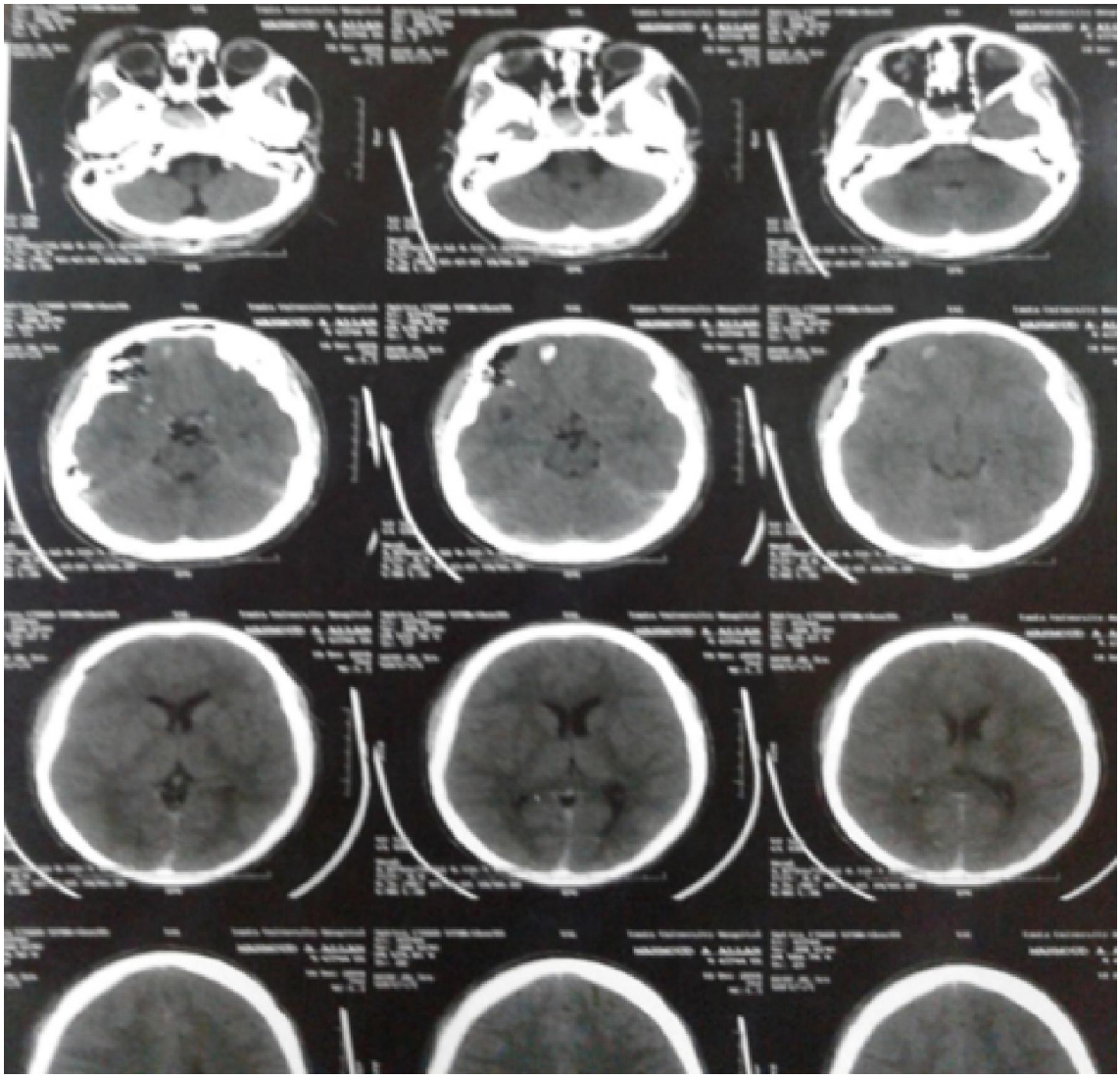

Figure (6): CT brain of case 3 at admission.

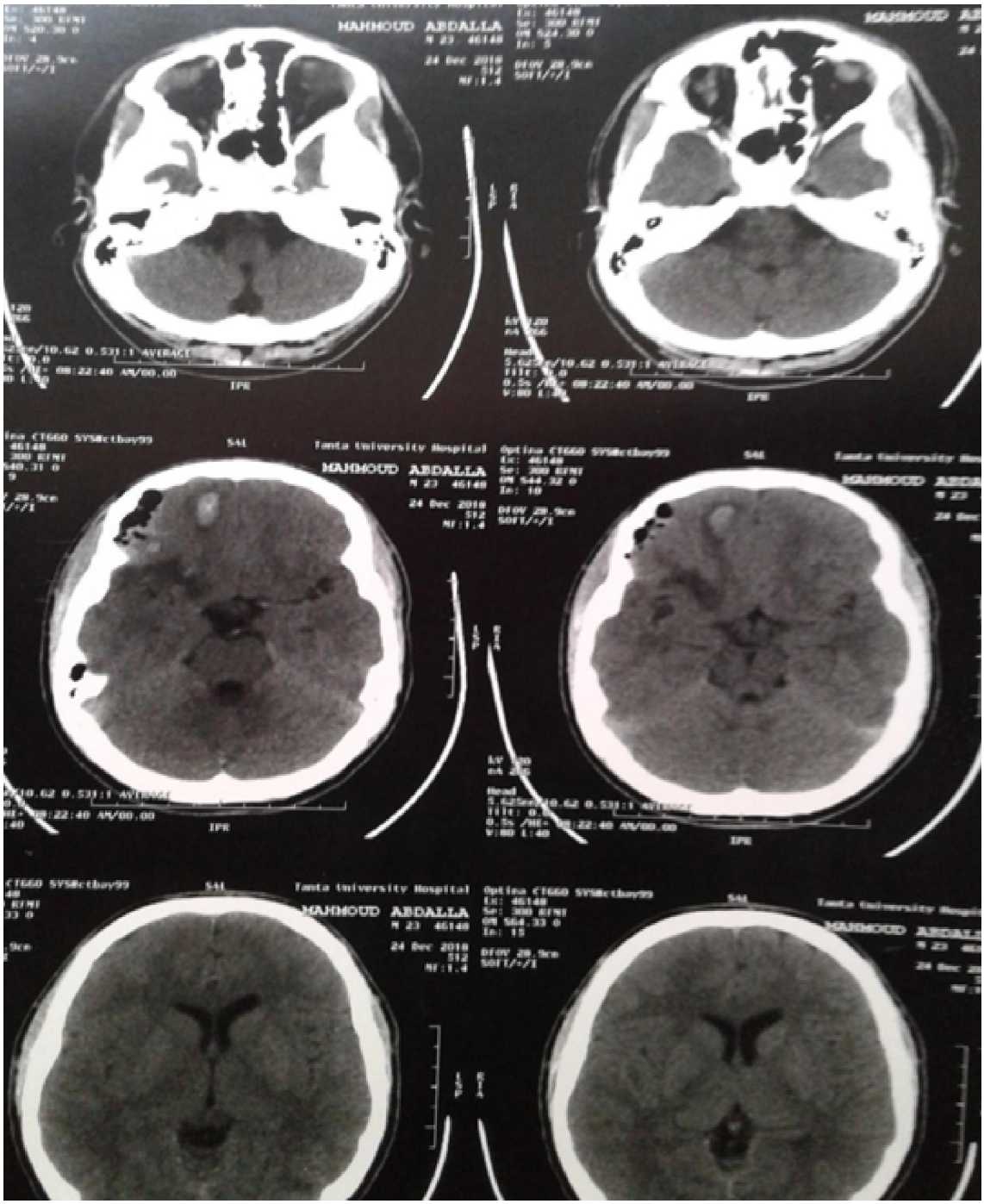

Figure (7): CT brain of case 3 after 48 hours.

4. Discussion

Traumatic brain injury is a leading cause of death and disability. An effective, widely practicable and affordable treatment for TBI could save many thousands of lives and substantially reduce the burden of disability [(16)].

In our study we found 30 males (75%) and 10 females (25%). This can be explained by the fact that males in our community are more active and accordingly more exposed to trauma.

In agreement with our study, **AbolfazlJokar, et al. (2017);** [(17)] this study was conducted on 80 patients, 60 males and 20 females. The males were more than females with percent 75%.

Another study agreed with our study, **David Yuen Chung Chan, et al. (2019);** [(18)] this study conducted on 651 patients, males percent was 62.9%

(410) and females percent was 37.1% (241). Which proved also that males are more exposed to traumatic brain injury.

And also, **OlfaChakroun Walha, et al. (2018);** [19] this study was conducted on 180 patients, most patients were males (163 males and 17 females).

The mean of age in group I was 36.8 and in group II was 35.9 which revealed that middle age group are more subjected to traumatic brain injury.

In a study reported by, **AbolfazlJokar, et al. (2017);** [17] which recruited 80 patients (40 allocated to TA and 40 allocated to placebo) in 2014 aged from 15 and more, the mean age of patients in group allocated to TA was 35.4 and the mean of age in patients group allocated to placebo was 36.2 which is also middle age as our study revealed.

And also in, **OlfaChakroun Walha, et al. (2018);** [19] among 180 patients there were 77 patients aged over 60 years (42.8%), the mean age was 41 ± 19 years (extremes: 18 and 87 years).

Volume of ICH in group I on admission ranged from 0.1-15 with mean±SD 4.79±4.30, while after 48 hrs ranged from 0.1-15.5 with mean±SD 4.35±4.23 and difference between them mean±SD 0.445±1.833.

And volume of ICH in group II on admission ranged from 3-40 with mean±SD 11.170±9.36, while after 48 hrs ranged from 3-32 with mean±SD 12.67±9.82 and difference between them mean±SD -1.500±5.744.

The mean total hemorrhage expansion was 0.445±1.833 and 1.500±5.744 in group I and II respectively, which is not significant.

In agreement with our study, **AbolfazlJokar, et al. (2017);** [17] the initial ICH in TA group mean±SD 21.6 ± 5.37, while after 48 hrs mean±SD 23.3 ± 6.4 the mean total hemorrhage expantion was 1.7 ± 9.7 and the initial ICH in placebo group mean±SD 22.2 ± 4.9, while after 48 hrs mean±SD 26.5 ± 6.4 the mean total hemorrhage expantion 4.3 ± 12.9 which is not significant.

In agreement with our study, **EsmaeilFakharian, et al (2017);** [20] The mean and standard deviation of the volume of hemorrhagic lesion in the TA group was 9.4 ± 15.3 and in the placebo group 10.2 ± 10.1. This difference was not significant (p = 0.27).

In **Surakrant Yutthakasemsunt, et al (2013);** [21] this study done on 120 patients received TA and 118 patients were placebo. Progressive intracranial hemorrhage was present in 21 (18%) of patients allocated to TA and in 32 (27%) of patients allocated to placebo. The difference was not statistically significant.

And in, **P Perel, et al (2012);** [22] This study done on 270 patients, 133 allocated to TA and 137 allocated to placebo, The mean total haemorrhage growth was 5.9 ml (standard deviation (SD) 26.8 ml) and 8.1 ml (SD 29.2 ml) in the TA and placebo group respectively. The adjusted analysis showed a greater reduction in total haemorrhage growth in the TA group than in the placebo group. And that was in disagreement with our study.

Conclusions

In summary, our study shows that the benefits of tranexamic acid in traumatic intracranial hemorrhage are to be considered. Although tranexamic acid prevented hemorrhagic mass growth, however the difference was not statistically significant. Clinical outcome is improved in tranexamic acid group, as shown in the results there was significant improvement in GCS and fewer deaths.

As tranexamic acid is cheap and widely practicable, it should be contributed importantly to reduce mortality and disability after traumatic brain injury.

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12/11/2019