Effect of Tranexamic Acid on Progression of Hematoma in Traumatic Brain Injury: A Randomized Controlled Trial

Rashid MM[1], *Das S[2], Sarker AC[3], Hafiz AM[4], Khan SI[5]

Traumatic brain injury (TBI) is a major cause of morbidity and mortality in Bangladesh and also worldwide. Secondary brain injury from progressive intracerebral hematoma, increasing cerebral edema, raised intracranial pressure and subsequent cerebral ischemia is the main cause for morbidity and mortality following TBI. Secondary brain injury is worsened by post-traumatic coagulopathy, which occurs in brain injured patients and is associated with increase in risk of death and morbidity. The antifibrinolytic agent tranexamic acid (TXA) reduces the hematoma expansion and demonstrated improved clinical outcome also reduced the mortality and morbidity. This was a randomized controlled trial (RCT) done in the Department of Neurosurgery, Dhaka Medical College and Hospital. Included patients were randomized to get either the intravenous tranexamic acid (Group A) or placebo (Group B) treatment based on a computer-generated code list (50 patients in each group) along with usual medical management for traumatic brain injury. The extent of contusion expansion (hematoma plus perihematomal oedema) as the primary outcome at 48 hour after admission and was measured by brain CT scan. The contusion and oedema volume were calculated both the times (on admission and after 48 hours). Glasgow coma scale (GCS) after 48 hours and Glasgow outcome scale (GOS) after 7 days were observed. In this study showed increase in hematoma volume in both groups ($p<0.05$). But the increased hematoma volume in the Group A was significantly less than that in the control group. The mean total hemorrhage expansion was (1.5±1.1) ml and (4.6±1.9) ml in the Group A and Group B, respectively. In Group A- 02(4.0%) patients required operation, whereas in Group B- 11(22.0%) patients required operation. The result was significant ($p=0.023$) between groups. Therefore use of tranexamic acid is associated with lesser hematoma volume progression. Mean GCS (after 48 hours), mean GOS (after 7 days) result were significantly better in Group A ($p<0.001$). This study concluded that tranexamic acid has beneficial effect on the patient with significant traumatic brain injury. Tranexamic acid helps in reduction of intracerebral progression of contusion and improvement of clinical outcomes in patients with TBI.

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Key words: Randomized controlled trial, Traumatic brain injury, Tranexamic acid, Glasgow coma scale, Glasgow outcome scale

Introduction

Traumatic brain injury (TBI) denoted as a non-degenerative, non-congenital wound to the brain happening via an extraneous physical strength which can consequence in that may result in decreased or impaired level of consciousness, causing temporary or permanent disabilities in physical or cognitive functioning. In 2016, globally there were 27.08 million new cases of TBI with age-standardized incidence rates of 369 (331-412) per 100000 population[1]. TBI is a major public health issue worldwide[2]. According to the World Health Organization report, TBI is going to overshadow many other diseases like ischemic heart and cerebrovascular disease, as a major cause of death and disability by 2020 AD[3]. It constitutes the primary reason for mortality and morbidity in persons worldwide below 45 years of age. Primary trauma force results in Primary brain wound that causes cell or tissue damage and distortion instant after injury period.

1. *Dr Md Mamunur Rashid, Assistant Professor, Department of Neurosurgery, Uttara Adhunik Medical College and Hospital, Dhaka, Bangladesh*
2. **Dr Sukriti Das, Professor, Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; E-mail: sukriti66@yahoo.com*
3. *Dr Asit Chandra Sarker, Professor, Department of Neurosurgery, Dhaka Medical College, Dhaka, Bangladesh*
4. *Dr Ahsan Mohammed Hafiz, Associate Professor, Department of Neurosurgery, Uttara Adhunik Medical College and Hospital, Dhaka, Bangladesh*
5. *Dr Shahriar Islam Khan, Assistant Professor , Department of Neurosurgery, Uttara Adhunik Medical College and Hospital, Dhaka, Bangladesh*

**for correspondence*

The secondary injuries from TBI cause changes in cellular activity and dissemination of trauma via activities such as free-radical generation, excitotoxicity, calcium homeostasis, depolarization, formation of edema, disruption of blood brain barrier and intracerebral hematoma[4]. The anti-fibrinolytic agent tranexamic acid (TXA) demonstrated improved mortality and morbidity in compared to placebo in severe head trauma patients in the CRASH-2 trial, which enrolled 20,211 patients in 40 countries[5]. In addition to the strong data representative clinical advantage in trauma patients with severe bleeding, TXA also has an excellent safety profile and has been shown to be cost-effective[6,7]. Tranexamic acid reduces bleeding by inhibiting plasmin formation and displaces plasminogen from fibrin by enzymatic breakdown of fibrinogen and fibrin. A regular review of randomized trials of tranexamic acid in surgery showed that tranexamic acid decreases hemorrhage by about one third[8]. Later in 2017, results from an individual patient-level data meta-analysis of randomized trials of tranexamic acid in acute severe hemorrhage showed that although immediate treatment substantially improves survival. But the survival benefit decreases by around 10.0% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit[9]. Early intracerebral hemorrhage is common after TBI and raises the risk of mortality and morbidity[10]. In patients with moderate and severe TBI, intracerebral hemorrhage may continue even subsequent to hospitalization and for several hours after injury. Abnormal coagulation and coagulopathy with increased fibrinolysis may deteriorate intracerebral hemorrhage. Increased levels of fibrin degradation products are frequently found in the first 3 hours[11]. Early use of tranexamic acid in TBI patients might limit intracerebral hemorrhage, sinking morbidity and mortality[12]. Abolfazl Jokar et al. reported that antifibrinolytic agents such as tranexamic acid (TXA) might reduce traumatic ICH. Single-blind randomized controlled trial was conducted on patients with traumatic ICH and divided into intervention and control groups (40 patients each). All patients received a conservative treatment for ICH, as well as either intravenous TXA or placebo. Brain CT scan showed a significant increase in hemorrhage volume in both groups after 48 hours, it was significantly less in the TXA group than in the control group ($p=0.04$)[13]. The CRASH-3 research is an international, randomized, placebo-controlled experiment to quantify the effects of early use of tranexamic acid on mortality and morbidity in patients with TBI. CRASH-3 trial expects tranexamic acid to be more effective than placebo in decreasing mortality and morbidity in patients with TBI[14].

Methods

This study was randomized controlled clinical trial (by computer-generated code list) held in the department of neurosurgery of Dhaka Medical College and Hospital (DMCH), Bangladesh from January 2018 to December 2020. After obtained the Ethical Clearance Certificate from the Ethical Committee of Dhaka Medical College, Bangladesh (Memo No.: MEU-DMC/ECC/2019/ 231 Dated: 04/07/2019) the study was performed. A total of 100 (50×2=100) samples were enrolled subsequently in this study distributed in two groups. The Group A included 50 patients who treated by intravenous tranexamic acid and the Group B include 50 patients, who was treated by intravenous placebo along with usual conservative medical treatments in both groups. The significant traumatic brain injury patients were included. Other inclusion criteria were: age 16 years and more, having GCS 9 or more, within 12 hours of injury onset (time between injury and hospital arrival) and with hemorrhagic contusion based on CT scan findings, were included for the trial. The exclusion criteria were: unknown onset time; significant extradural hematoma, subdural hematoma or intracerebral hematoma, with midline shifting, need for surgery at time of admission, GCS less than 9, use of any antifibrinolytics within 2 weeks, significant extracranial hemorrhage (need for blood transfusion), known kidney disease and pregnancy. Intra-ventricular hemorrhage (IVH) and diffuse axonal injury (DAI) patients were not included. Most severe head injury patient presents with larger hematoma volume or needed immediate surgical intervention. So, these patients were excluded from the study.

Study procedure

Details history was collected from the patient or their family/ attendants. Proper examination of patient was done including general and nervous system examination especially cranial nerves and GCS. Initial CT scan of head and all the relevant

investigations were performed. All patients was given a conservative treatment for traumatic brain injury and cerebral contusions (Prophylactic antibiotics, analgesics, anti-ulcerant, anti-emetic, anti-convulsant, steroid, mannitol etc) and either intravenous TXA (a bolus of 1 gm in 100 ml 0.9% NaCl within 10 minutes followed by a single dose of continuous infusion of 1 gm in 500 ml 0.9% NaCl over 8 hours) or unobvious placebo (same doses of normal saline). The extent of contusion growth as the primary outcome at 48 hours after admission was measured by brain CT scan. The contusion and oedema volume were calculated both the times (on admission and after 48 hours). We subtracted the hematoma volume from that of the absolute oedema (the volume of the hematoma and surrounding oedema) and divided the product by the hematoma volume, to express the perihematoma oedema volume as a ratio of the associated hematoma volume (relative oedema volume) by using the method ABC/2. Glasgow coma scale (GCS) after 48 hours and Glasgow outcome scale (GOS) after 7 days were observed.

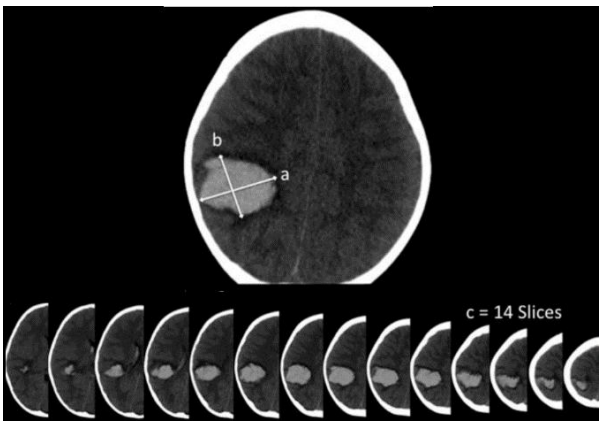

Figure 1: ABC/2 method for estimation of hematoma volume: (a) maximum length, (b) width perpendicular and (c) number of slices

Results

Age and sex distribution of patients were shown in Table I. Study demonstrates that maximum number of patients 53(53.0%) were between 31-45 years' age group. Mean age of the patient was 43.2±8.50 years in Group A and 42.8±8.1 years in Group B. The difference was statistically non-significant. The gender distribution of the patients- Out of 100 cases 67(67.0%) of cases were male and 33(33.0%) were female. Male and female ratio was 1.7:1.

Table I: Distribution of the study subjects according to age and sex (N=100)

	Group A (n=50)	Group B (n=50)	p value
	n (%)	n (%)	
Age (years)			
16-30	06 (12.0)	10 (20.0)	
31-45	28 (56.0)	25 (50.0)	0.761
46-60	16 (32.0)	15 (30.0)	
Mean±SD	43.2±8.5	42.8±8.1	
Gender			
Male	34 (68.0)	33 (66.0)	1.000
Female	16 (32.0)	17 (34.0)	

Table II shows the clinical features of the study subjects according. Common clinical presentations were impaired consciousness, headache and vomiting.

Table II: Clinical features of the study subjects (N=100)

Clinical features	Group A (TXA) (n=50) n (%)	Group B (Placebo) (n=50) n (%)	p value (Chi-square test)
Headache	45 (90.0)	43 (86.0)	0.010
Vomiting	39 (78.0)	42 (84.0)	1.000
Visual disturbance	02 (04.0)	04 (08.0)	1.000
Impaired consciousness	42 (84.0)	44 (88.0)	0.112
Hemiparesis/ hemiplegia	33 (66.0)	28 (56.0)	0.297
Motor aphasia	16 (32.0)	23 (46.0)	0.176
Dysarthria	05 (10.0)	06 (12.0)	0.372

Table III shows the clinical and CT scan findings of TBI patients (on admission). No-significant difference was observed in between groups in respect to Glasgow coma scale (GCS) level, contusion volume and relative perihematomal oedema.

Table III: Distribution of cases according to clinical parameters (on admission) (N=100)

	Group A (TXA) (n=50) Mean±SD	Group B (Placebo) (n=50) Mean±SD	p value (Unpaired 't' test)
Glasgow coma scale (GCS)	10.4±1.2	10.1±1.2	0.267
Contusion volume (ml)	17.1±4.2	16.9±4.7	0.841
Relative perihematomal oedema (ml)	0.12±0.07	0.13±0.07	0.524

Table IV shows the clinical and CT scan findings of TBI patients after 48 hours. Although clinical outcome was better in group A, but difference was statistically not significant ($p \geq 0.05$), mean Glasgow coma scale (GCS) was found 11.4±1.3 vs. 10.9±1.2 in Group A and Group B respectively. But the increased contusion volume in the group A was significantly less than that in the control group ($p=0.012$). Therefore use of tranexamic acid is associated with lesser contusion volume progression.

Table IV: Distribution of cases according to clinical parameters (after 48 hour) (N=100)

Distribution	Group A (TXA) (n=50) Mean±SD	Group B (Placebo) (n=50) Mean±SD	p value (Unpaired 't' test)
Glasgow coma scale (GCS)	11.4±1.3	10.9±1.2	0.078
Contusion volume (ml)	17.8±4.7	20.6±5.1	0.012
Relative perihematomal oedema (ml)	0.08±0.05	0.07±0.04	0.326

Table V shows the relationship of Glasgow coma scale (GCS) on admission and after 48 hours with contusion expansion after 48 hours. Result was significant in between groups.

Table V: Differences of Glasgow coma scale (GCS) (on admission and after 48 hours) with contusion expansion between groups (N=100)

Differences	Group A (TXA) (n=50)	Group B (Placebo) (n=50)	p value (Chi-square test)
	Mean±SD	Mean±SD	
GCS on admission	10.4±1.2	10.1±1.2	<0.001
GCS after 48 hrs	11.4 ± 1.3	10.9 ± 1.2	
Contusion expansion (ml)	1.5 ±1.1	4.6± 1.9	

Table VI shows the relationship of mean contusion volume (ml) and mean relative perihematomal oedema (ml) between groups. In Group A mean Contusion volume not significantly expanded after 48 hours, but in Group B difference was significant. Mean Relative perihematomal oedema was significant in both groups after48 hours, means treatment with TXA have no remarkable impact on perihematomal oedema reduction.

Table VI: Differences of mean contusion volume (ml) and mean Relative perihematomal oedema (ml) (N=100)

Differences	Group A (TXA) (n=50)	Group B (Placebo) (n=50)	p value (Unpaired t test)
	Mean±SD	Mean±SD	
Mean Contusion volume (ml)			
On admission	17.1±4.2	16.9±4.7	0.841
After 48 hours	17.8±4.7	20.6±5.1	0.012
Mean Relative perihematomal oedema (ml)			
On admission	0.12±0.07	0.13±0.07	0.524
After 48 hours	0.08±0.05	0.07±0.04	0.326

Table VII shows the comparison of operated patients between groups. In Group A- 2(4.0%) patients required operation, whereas in Group B- 9(22.0%) patients required operation. The result was significant (p=0.023) between groups. So, tranexamic acid has impact on requirement of operation or neurosurgical intervention.

Table VII: Comparison of surgical intervention between groups (N=100)

Comparison	Group A (TXA) (n=50)	Group B (Placebo) (n=50)	p value (Unpaired t-test)
	n (%)	n (%)	
Requiring surgery	02 (04.0)	11 (22.0)	0.023

Table VIII shows the relationship among mean Glasgow coma scale (GCS) (after 48 hours), mean contusion volume (ml) and mean Glasgow outcome scale (GOS) (after 7 days). The difference between groups was statistically significant.

Table VIII: Differences among mean Glasgow coma scale (GCS) (after 48 hour), mean contusion volume (ml) (after 48 hour) and mean Glasgow outcome scale (GOS) (after 7 days) (N=100)

Differences	Group A (TXA) (n=50)	Group B (Placebo) (n=50)	p value (Unpaired 't' test)
	Mean±SD	Mean±SD	
Mean GCS	11.4±1.3	10.9±1.2	
Mean contusion volume (ml)	17.8±5.2	20.6±6.9	<0.001
Mean GOS	4.82±0.81	4.32±0.89	

Figure 2 in the parentheses indicate estimated contusional hematoma Volume (ml). The mean total hemorrhage expansion was (1.5±1.1) ml and (4.6±1.9) ml in the Group A and Group B, respectively (p<0.001).

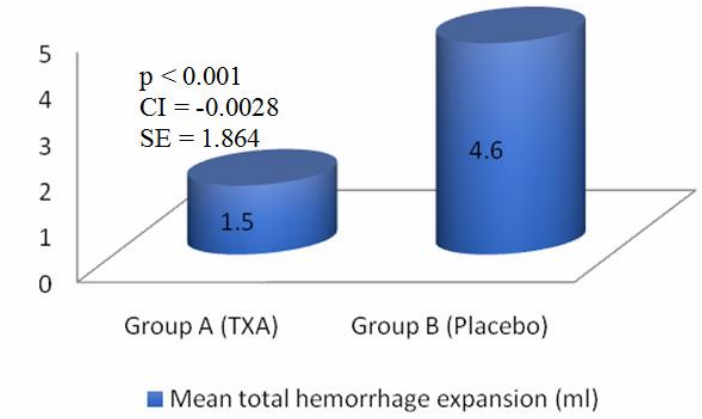

Figure 2: Imaging findings of mean total hemorrhage expansion (n=100). Unpaired t test was done to measure the level of significance.

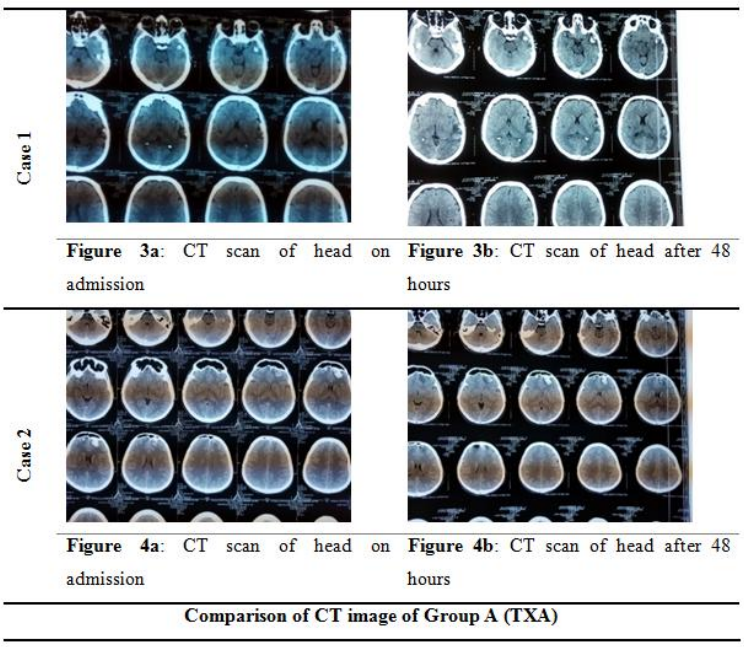

Figure 3a: CT scan of head on admission

Figure 3b: CT scan of head after 48 hours

Figure 4a: CT scan of head on admission

Figure 4b: CT scan of head after 48 hours

Comparison of CT image of Group A (TXA)

Case 3

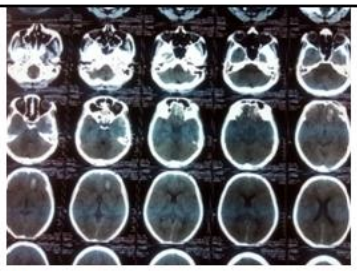

Figure 5a: CT scan of head on admission

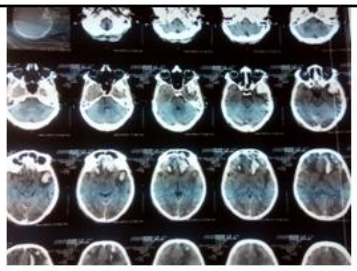

Figure 5b: CT scan of head after 48 hours

Case 4

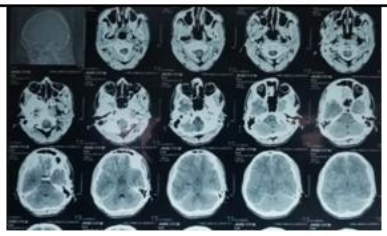

Figure 6a: CT scan of head on admission

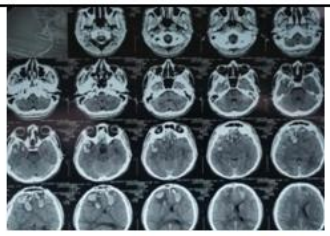

Figure 6b: CT scan of head after 48 hours

Comparison of CT image of Group B (Placebo)

Discussion

This randomized controlled trial was carried out to assess the clinical outcome of using tranexamic acid in traumatic brain injury. Study demonstrates that maximum number of patients 53(53.0%) were between 31-45 years' age group. Mean age of the patient was 43.2±8.50 years in Group A and 42.8±8.1 years in Group B. Out of 100 cases 67(67.0%) of cases were male and 33(33.0%) were female. Male and female ratio was 1.7:1. The variation was not significant statistically. Result consistent with other studies. Jokar et al. reported mean age of the patient was 36.2±14.9 years in their study. Globally, over ten million people died or hospitalized each year due to traumatic brain injury[15]. Road traffic accident is the leading cause of severe TBI. Bangladesh and South Asia have particularly high TBI rates, due to overcrowding, rapid urbanization and high rate of traffic crashes.

In this study brain CT scan taken at 48 hours after TBI showed a significant increase in hemorrhage volume in both groups ($p<0.05$). But the enlarged hematoma volume in the Group A was significantly a lesser amount of than that in the control group ($p=0.044$). The mean total hemorrhage expansion was (1.5±1.1) ml and (4.6±1.9) ml in the Group A and Group B, respectively ($p<0.001$). Similar study by Jokar et al.[13] showed that TXA could reduce contusional hematoma growth after TBI. Other studies established decline in ICH succession, too[16,17,18]. The release of thromboplastin after TBI is followed by the commencement of the free-radicles, coagulation factors and fibrinolysis pathways. Excessive fibrinolysis, high levels of fibrinogen degradation factors is a main cause of coagulopathy in TBI, raising the probability that TXA can decrease traumatic contusion. Therefore, the earlier TXA is directed, the more likely it will stop entire activation of fibrinolysis[19]. On the other hand, other studies demonstrated no improvement of clinical outcomes in TBI patients with TXA[17,18]. CRASH-2 collaborators although reported that TXA significantly reduced all-cause mortality, in a subgroup analysis of traumatic contusion patients, TXA showed non-significant trend to reduce mortality or dependency[16]. They originated that neither moderate benefits nor moderate harmful effects of TXA can be barred after TBI. Also, showed that there was no evidence of TXA benefit in TBI patients. Other study reported that TXA increased mortality in high injury acuity patients which can probably be attributed to the rapid availability of fluids and emergency operative interventions at the trauma centers[20,21]. It was evident from this study that

overall clinical outcome was almost similar in both group. Although GCS status mildly better in Group A, but difference was statistically non-significant ($p \geq 0.05$), mean GCS was found 11.4±1.3 vs. 10.0±1.2 in Group A and Group B respectively. Therefore use of tranexamic acid has no impact on overall clinical outcome. A systematic review demonstrated statistically significant reduction in contusion progression with tranexamic acid and a non-statistically significant improvement of clinical outcomes in TBI patients[18]. The results of a trial suggesting a trend towards decreased intracranial contusion progression with early administration of TXA should be viewed with caution. Contusion expansion has been associated with poor outcome in patients with TBI[22]. Although this consequence likely deceit on the causal pathway to clinical outcomes such as functional status and mortality, surrogate outcomes do not always translate into actual clinical outcomes[23]. For example, while an initial phase II clinical trial demonstrated reduction in the hematoma growth and mortality after administration of activated factor VII to patients with non-traumatic intracranial hemorrhage, subsequent phase III trial confirmed the reduction in hematoma growth but failed to show improved survival or functional outcomes[18]. In 2017, published meta-analysis of randomized trials of tranexamic acid in acute severe bleeding showed that instantaneous treatment improved survival by more than 70.0% (OR 1.72, 95% CI 1.042 - 2.10; $p<0.0001$) but thereafter, the survival benefit decreased by about 10.0% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit[9]. It was evident from this study that Glasgow outcome score (GOS) was better in Group A than Group B significantly but similar data was not available from previous any studies.

Conclusion

Traumatic brain injury (TBI) is the major causes of morbidity and mortality following RTA in Bangladesh and south Asian countries. Lot of patients of TBI got admitted regularly and managed in Dhaka Medical College Hospital (DMCH) every day. Some of them are managed conservatively, although surgical intervention is required in many patients. Use of tranexamic acid reduces the progression of hematoma. Thereby reduces the need for surgical interventions, surgery related cost, morbidities and mortalities.

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