

# Considerable delay in diagnosis and acute management of subarachnoid haemorrhage

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## ABSTRACT

**INTRODUCTION:** Rebleeding from subarachnoid haemorrhage (SAH) usually occurs within the first six hours after the initial bleeding. Rebleeding can be prevented effectively with tranexamic acid (TXA). Although a broad consensus has evolved that SAH should be treated as an emergency, it is likely that delays do exist in the diagnosis and treatment of SAH patients. The aim of this study was to prospectively assess the interval between symptom onset, emergency room (ER) admission, initial diagnosis and treatment, and final closure of the aneurysm.

**MATERIAL AND METHODS:** We prospectively studied the time course from the initial bleeding to ER admission, computed tomography (CT), TXA treatment, referral to the neurosurgical department, and to the final closure of the aneurysm.

**RESULTS:** A total of 133 patients with SAH due to ruptured intracranial aneurysms were admitted to two neurosurgical units in Copenhagen, Denmark, during a one-year period. The median time to admission was 60 min. The median delay from admission to CT scan was 55 min. Long pre-hospital delay ( $p = 0.03$ ) and high Glasgow Coma Scale score on arrival ( $p = 0.0006$ ) were associated with a longer time to CT scan. The median time from CT scan to initiation of TXA treatment was 50 min. The median time from initial insult to final closure of the aneurysm was 30 hours.

**CONCLUSIONS:** The present study demonstrates that considerable diagnostic delays exist in connection with CT and TXA treatment after patients' arrival to the ER.

The incidence of subarachnoid haemorrhage (SAH) caused by bleeding from a ruptured aneurysm is approximately 6-7 per 100,000 person-years and mortality reaches 40% including those who never come to medical attention [1, 2].

Rebleeding in the "ultra-early phase" is a major cause of death and disability. Recent reports have shown that the phase most vulnerable to rebleeding is the first six hours after the initial bleeding [3]. During this period the risk of rebleeding is 10-15% [3]. Hillman *et al* managed to reduce the rate of rebleeding from 10.8% to 2.4% by using antifibrinolytic therapy tranexamic acid (TXA) in a prospective, randomized study of 254 treated versus 251 non-treated patients [4]. A re-

cent review has concluded that although additional clinical trials are warranted, it is a reasonable strategy to use early short-term antifibrinolytic therapy to prevent ultra-early rebleeding and thereby possibly improve long-term outcome [5]. According to this evidence, initiation of TXA treatment should be given priority as soon as SAH has been diagnosed. A quantity of 1,000 mg of TXA should be given intravenously without delay and then every six hours until the aneurysm is closed. Treatment should last a maximum of three days after the primary bleeding.

SAH should be treated as an emergency; however, it is likely that clinically significant delays do occur in both the diagnosis and the treatment of SAH patients during the ultra-early phase. Such delays may also comprise TXA therapy.

The aim of this study was to prospectively assess the time profile from onset of symptoms, emergency room (ER) admission, initial computed tomography (CT), initiation of TXA treatment, arrival to neurosurgical unit, first angiographic procedure and to final closure of the aneurysm.

## MATERIAL AND METHODS

The study was performed from 1 August 2007 to 31 July 2008 at the departments of neurosurgery at Glostrup University Hospital and Rigshospitalet, Copenhagen, Denmark. These two clinics manage the neurosurgical service in eastern Denmark, including Copenhagen, with a population of approximately 2.5 million inhabitants. All patients with SAH in this region are referred to one of these two departments except for a few patients who are moribund upon arrival at the primary hospital.

All patients admitted to these two departments with SAH due to a ruptured aneurysm were included. A standardized questionnaire was completed for each patient. Information was gathered by interviewing the patient, the family, and by reviewing the ambulance chart, the ER record and the hospital medical record.

The following events were recorded:

- Symptom onset (indicating time of bleeding)
- Contact to health care system (emergency telephone call, general practitioner, ER)

## ORIGINAL ARTICLE

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 TABLE 1

The delay between events presented as percentiles (cumulative time from bleeding initiation).

Bleeding time = 0 min	Time to ER arrival	Time to CT	Time to TXA	Time to NSU arrival (CT → NSU)	Time to aneurysm closure
50%	+ 60 min.	+ 54 min. (2 hr 35 min.)	+ 53 min. (4 hr)	+ 1 hr 59 min. (5 hr 25 min.)	+ 18 hr 12 min. (31 hr)
75%	+ 2 h. 50 min.	+ 2 hr (6 hr 43 min.)	+ 1 hr 44 min. (12 hr 15 min.)	+ 2 hr 55 min. (12 hr 10 min.)	+ 27 hr 7 min. (2.1 days)
90%	+ 32 h. 9 min.	+ 6 hr 29 min. (41 hr 9 min.)	+ 5 hr 44 min. (30 hr 16 min.)	+ 4 hr 57 min. (2.1 days)	+ 44 hr 48 min. (4.2 days)

ER = emergency room; CT = computed tomography; TXA = tranexamic acid; NSU = neurosurgical unit.

- Presentation to healthcare professionals (paramedic, general practitioner, ER)
- Arrival at the ER
- Time of CT
- Time of initiation of TXA treatment
- Arrival at the neurosurgical unit
- First angiographic procedure
- Closure of the aneurysm
- Rebleeding

The time of bleeding was defined as the time of SAH symptom onset, i.e. sudden headache, nausea, vomiting or altered level of consciousness. If patients were found to be unconscious, the time of the finding was recorded as the time of onset.

The time of contact to the health care system was defined as the time when the patient or family first contacted the general practitioner (GP), used the emergency telephone or presented themselves at the ER.

The time of presentation to healthcare professionals was defined as the time when the patient was first seen by a GP, paramedic or staff at the ER.

The time of admission was defined as the time when the patient presented himself to the ER. The exact time of arrival at the ER is routinely registered on ER records.

For patients who presented themselves directly to the ER, the time of contact, the time of presentation and the admission time coincided.

Rebleeding was recorded as a sudden definitive worsening of the clinical state (e.g. drop in Glasgow Coma Scale (GCS)) of the patient and/or an increased amount of blood on the CT after the SAH diagnosis was established.

## STATISTICS

Statistical analysis was performed using SAS 9.1 for Windows (SAS Institute Inc. Cary, NC, USA). Time data are

presented as median time and range, unless otherwise indicated. Multiple regression analyses were performed to analyse quantitative factors associated with time to CT and time to initiation of TXA treatment. A p-value of < 0.05 was considered statistically significant.

## RESULTS

A total of 133 consecutive patients with a mean age of 56 years (range 18-90 years) were admitted with SAH due to spontaneously ruptured aneurysm. The male/female ratio was 31/69.

The cumulative time from onset of symptoms to final closure of aneurysm is shown in **Table 1**.

**Figure 1** indicates time to first contact to health professionals, presentation to health professionals and to arrival at the ER for the entire patient population.

The median pre-hospital time was 60 min (range 15 minutes to 12 days).

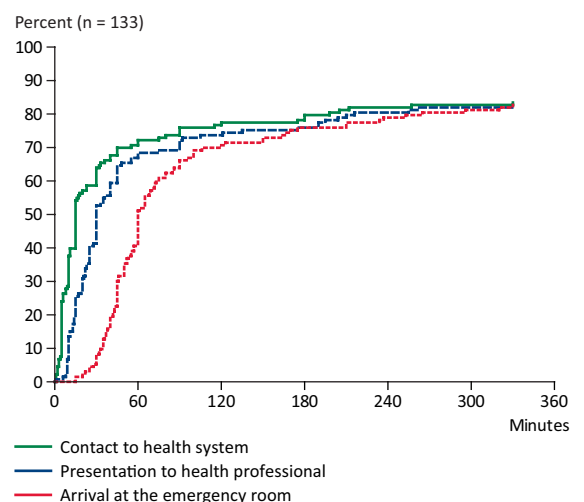
**Figure 2** shows the time course from arrival at the ER to CT, initiation of TXA and arrival at the neurosurgical unit for the entire patient population.

Fifteen patients did not receive TXA. Among these, six patients were moribund at admission, four patients had their insult more than three days prior to admission, one patient was suspected of coagulopathy, and one was misdiagnosed as having an intracerebral haemorrhage. Three patients did not receive TXA for unknown reasons.

The time to CT was evaluated in relation to age, sex, GCS on arrival and pre-hospital delay. Significant associations were found for pre-hospital delay ( $p = 0.03$ ) and for GCS ( $p = 0.0006$ ).

 FIGURE 1

The cumulative percentage of patients as a function of time from symptom onset to arrival at the emergency room.



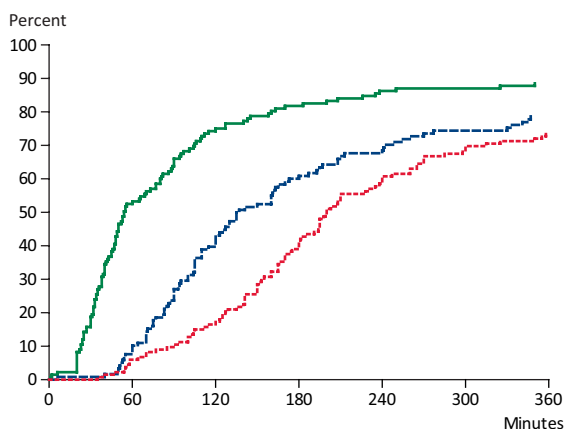
There was no association between TXA treatment and age, sex, GCS on arrival and time to CT.

**Figure 3** illustrates the time course from arrival at the neurosurgical unit to first angiographic procedure and closure of the aneurysm by either clips or coils for the entire patient population.



**FIGURE 2**

The cumulative percentage of patients as a function of time from arrival at the emergency room to a CT was performed, and until tranexamic acid was received and arrived at the neurosurgical unit.



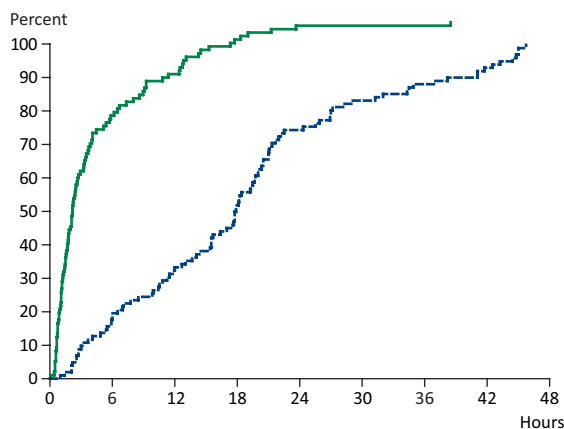
— CT (n = 133)  
— Tranexamic acid (n = 118)  
— Arrival at neurosurgery unit (n = 133)

Time = 0 represents emergency room admission.  
CT = computed tomography.



**FIGURE 3**

The cumulative percentage of patients as a function of time from arrival at the neurosurgical unit until an angiographic procedure was performed and the aneurysm was closed.



— Angiographic procedure (n = 116)<sup>a</sup>  
— Aneurysm closure (n = 110)

Time = 0 represents arrival at a neurosurgical unit.  
a) = Eight patients had a CT-angiography performed prior to arrival at the neurosurgical unit.  
CT = computed tomography.

Seventeen patients did not have an angiographic procedure performed; in 14 patients the primary bleeding was so severe that further investigation was without therapeutic consequence, and three patients proceeded directly to surgery with removal of the haematoma and aneurysm clipping without a preceding angiography.

The median time from arrival at the neurosurgical unit to closure of the aneurysm was 18 hours and 12 minutes (range 60 minutes to 17 days).

A total of 110 (83%) patients had their aneurysm closed. Thus, in 23 patients (17%), the aneurysm was not treated. In 20 patients, aneurysm closure was not possible due to the severity of the patients' initial clinical condition. In two patients it was not technically possible to close the aneurysm, and one patient (aged 87) declined treatment. The median time from primary bleeding until closure of the aneurysm was 31 hours (range 2 hours 30 min-3 weeks). Among the patients who had their aneurysm closed, 60 patients (55%) were treated endovascularly by coils and 50 (45%) patients were treated surgically by clipping the aneurysm.

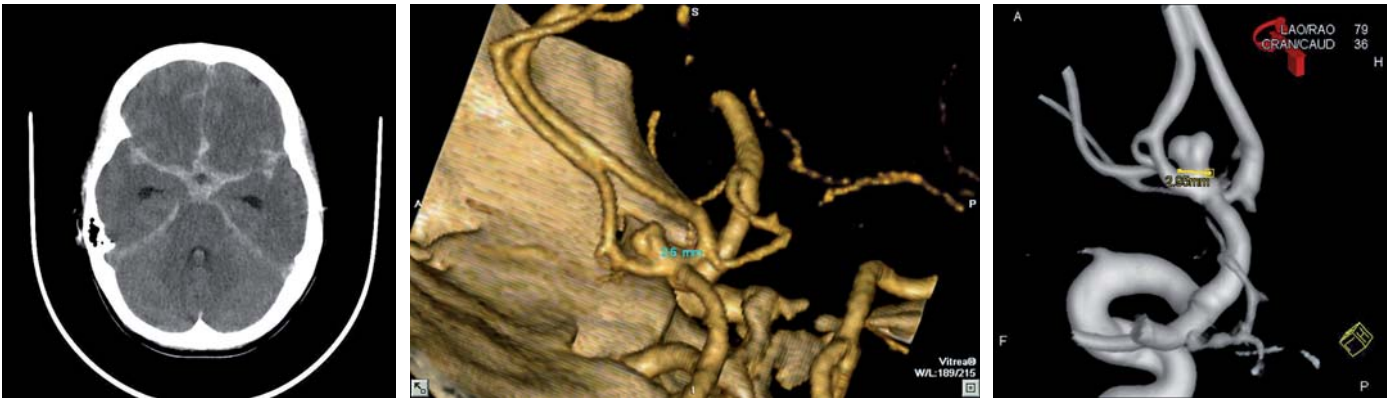
Rebleeding was recorded in 11 patients (8%). Among these, five (4%) had rebleeding after initiation of TXA. Twenty-eight patients (21%) died during their stay at the neurosurgical unit.

## DISCUSSION

Early delays are of particular interest in early prevention of rebleeding from an intracranial sacculate aneurysm as the risk is particularly high during the first six hours [3]. This is analogous to other acute conditions, e.g. ischaemic stroke or acute coronary syndrome (ACS) for which effective early treatments are available. Early delays are the result of a number of different circumstances and they are often rooted in tradition, attitudes and the organisation of the healthcare system.

### Pre-hospital delays

We found a median time from symptom onset to arrival at the ER of 60 min. The delay in the arrival of SAH patients to the ER has not previously been studied in detail. However, numerous studies have investigated the factors delaying the treatment and diagnosis of ischaemic stroke and ACS. *Evenson et al* [6] evaluated 48 studies on delay and treatment of ischaemic stroke and concluded that the median delay from symptom onset to arrival at the ER was 3-6 hours. A Danish study by *Jørgensen et al* [7] showed that 35% of the patients with ischaemic stroke were referred to a stroke unit within six hours. They also found that the severity rather than the type of stroke is related to a shorter time to admission. The onset of SAH is usually dramatic with sudden headache, unlike ischaemic stroke where symptom onset is usually painless and therefore less



A 39-year-old woman with subarachnoid haemorrhage from an anterior communicating artery aneurysm. Shown, from left to right, with computed tomography (CT), CT-angiography, and digital subtraction angiography.

dramatic. In ACS the main symptom, as in SAH, is pain. In a Danish ACS study from 1998, the median pre-hospital delay was 3.9 hours [8]. The shorter delay for SAH patients probably reflects the severity of SAH symptoms compared with ACS symptoms. A public stroke awareness program could probably reduce the pre-hospital delay, but a carefully performed cost-benefit analysis should be made in order to avoid public anxiety and a subsequent increase in the number of unnecessary CT scans performed.

#### Primary hospital delays

Headache is estimated to account for 2.2% of all ER visits and intracranial bleeding as the reason for headache accounts for 0.6% [9]. Thus SAH is a relatively rare condition at the ER. It is a clinical challenge to distinguish the small number of SAH patients from the far larger group with benign causes such as migraine or tension-type headache. We found the median time from arrival at the ER to CT to be 54 minutes. Long pre-hospital delay and high GCS on arrival were associated with longer delay to CT. This emphasizes the importance of recognising sudden headache as a sign of SAH rather than focusing on the level of consciousness during the initial evaluation of ER patients [10].

Once the SAH diagnosis is confirmed, TXA treatment should be initiated promptly. We found a median time of 53 minutes from CT scan to initiation of TXA treatment.

No association between age, sex, GCS on arrival, CT delay and delay to initiation of TXA was found. This suggests that the delay in TXA treatment is independent of the patient's condition.

TXA is a relatively new treatment for SAH patients and therefore generally unknown by the medical staff at general hospitals. The diagnosis of SAH by CT should lead to an awareness of an emergency situation in which there is a high risk of rebleeding. A better coordination

between the departments involved in the acute management of SAH patients, education of the health professionals involved in the handling of SAH patient and implementation of national treatment guidelines would most certainly reduce the time delay to administration of TXA.

#### Neurosurgical delays

Only few studies have investigated the delays in the diagnosis and treatment of SAH in the pre-neurosurgical phase [11-15]. These studies have investigated the time from symptom onset to arrival at the neurosurgical unit, and found a median pre-neurosurgical delay of 6 hours to 3 days. The differences between the studies with regard to the number of included patients, inclusion and exclusion criteria, differences in health services organisation, demography and cultural differences between countries make comparison difficult. We found a median pre-neurosurgical delay from primary bleeding to arrival at the neurosurgical unit of approximately 5 hours and 30 minutes.

In our study we found that 50% of the patients had their aneurysm closed within 24 hours after arrival at the primary hospital. *Hillman* found that approximately 67% of the patients had their aneurysm closed within 24 hours [4]. This difference probably reflects that emergency aneurysm surgery is not routinely performed in Denmark. We found that 50% of the patients had their aneurysm closed within 18 hours after arrival to the neurosurgical unit and 75% after 27 hours. This delay is clearly too long and needs to be addressed. The optimal time for aneurysm closure still remains to be established and further studies are needed to determine if emergency aneurysm surgery will improve outcome [16].

#### Rebleeding

In this study 11 patients suffered rebleeding. Six patients experienced rebleeding prior to TXA treatment and five

patients had rebleeding after initiation of TXA. Two rebleedings occurred after the patients arrived at the neurosurgical unit and therefore could have been avoided if emergency aneurysm surgery had been performed. The overall mortality rate in the rebleeding group was 45%. Two patients experienced rebleeding within 30 min. after treatment start. As TXA is given intravenously, the effect on the systemic haemostasis is presumed to be instant. This may indicate that the mechanisms causing rebleeding are associated with the immediate area surrounding the aneurysm rather than a systemic hyperfibrinolytic state of the blood.

### CONCLUSION

In the present study we have presented the time profile for the diagnosis and treatment of SAH patients. We have presented the time intervals from arrival at the ER to CT (median 54 min.) and from CT to administration of TXA (median 53 min.). These time profiles reflect various local conditions in the acute management of SAH. In order to reduce these time intervals, greater awareness of the life-threatening situation and the treatment modalities that exist for SAH patients is necessary.

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**CONFLICTS OF INTEREST:** None

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