Massive pontine hemorrhagic transformation associated with an anticoagulant for basilar artery occlusion

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Symptomatic hemorrhagic transformation is common in supratentorial and cerebellar infarction, but is rare in brainstem infarction. It is seldom reported in basilar artery occlusion. Although early arterial recanalization by thrombolytic agent has become the new trend of treatment, for some neurologists anticoagulant is still a conventional alternative treatment of basilar artery occlusion, especially in longer-existing ischemic deficits. We report a case of massive pontine hemorrhage associated with enoxaparin (low-molecular-weight heparin) treatment for basilar artery occlusion. On the basis of the clinical information and neuroimaging, an embolism was the most likely cause of stroke. The case presented herein adds massive pontine hemorrhagic transformation to the list of possible complications of anticoagulants for basilar artery occlusion. Apart from no evidence-based benefit in treatment of basilar artery occlusion, anticoagulant may contribute to devastating hemorrhagic transformation.

Key words: Anticoagulants, basilar artery occlusion, enoxaparin, hemorrhagic transformation

Introduction

Hemorrhagic transformation is common in patients with supratentorial and cerebellar embolic stroke. Emboli migration with a subsequent reestablishment of the blood flow into the infarcted tissue (migratory embolism) probably accounts for most hemorrhagic transformations. Pathological examinations of pontine infarction often show petechial hemorrhages, but massive hemorrhagic infarction is relatively uncommon. Kimura et al reported a massive pontine hemorrhagic infarction associated with embolic basilar artery occlusion (BAO). To our knowledge, the present case is the first reported case of massive pontine hemorrhagic infarction secondary to enoxaparin (low-molecular-weight heparin).

Case Report

A 66-year-old right-handed man with borderline hypertension experienced unsteadiness on walking an hour after waking up in the morning. He rapidly became unresponsive, with right facial droop and generalized weakness several minutes later. A brain noncontrast computed tomography (CT) scan on admission to the emergency department of an outlying local hospital showed a hyperdense basilar artery without evidence of intracranial hemorrhage [Figure 1]. He was transferred to our hospital for evaluation. At the time of admission (12 hours after onset), his blood pressure was 148/89 mmHg and serum glucose was 12.5 mmol/L (normal < 7.8 mmol/L). Results of a physical examination revealed normal heart sounds. The carotid pulses were equal and there were no bruits. The patient was deep comatose with Glasgow Coma scale of E1V1M1. The pupils were 2 mm in diameter, round and with a sluggish reaction to light. Eye movements were marked limited in all directions with oculocephalic maneuvers. Corneal reflexes were suppressed bilaterally.

Figure 1: Initial brain CT showed no evidence of brain stem hemorrhage or infarction. However, hyperdense basilar artery was noted

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Bilateral motor function was graded at 0, throughout, with slightly increased tone. The deep-tendon reflexes were normal, but plantar responses were extensor. An electrocardiogram (ECG) showed a normal rhythm at a rate of 110 beats per minute. The patient was intubated due to respiratory distress. The clinical diagnosis was BAO. Due to severe neurological condition and longer-existing ischemic deficit, enoxaparin 60mg subcutaneously twice daily was administered instead of thrombolytic agent. Antiplatelet was discontinued. His systolic blood pressure had been controlled below 180 mmHg with oral labetalol.

On the morning of the second hospital day, the pupils became anisocoric (3 mm/4 mm in diameter) and not reactive to light. Intermittent vomiting was also noted. A repeat CT scan showed infarction in the brainstem, bilateral cerebellum, bilateral occipital lobes and bilateral thalami. Massive pontine hemorrhagic transformation with obstruction hydrocephalus was noted [Figures 2 and 3]. CT angiography (CTA) showed patent basilar and vertebral arteries without marked atheromatous stenosis [Figure 4]. Enoxaparin was then discontinued. The patient’s condition deteriorated progressively and he expired on the fourth hospital day. On applying Naranjo’s algorithm, a probability score of 4 is obtained, hence this can be regarded as a possible adverse effect of enoxaparin. [4]

**Discussion**

Occlusion of basilar artery has been considered to convey a grave prognosis with a very high mortality if not reanized. [5] In a recent large prospective study, Voetsch et al showed that the prognosis of BAO is not as grave as previously thought. [6] A decreased level of consciousness was the most powerful clinical predictor of a poor outcome. [6] In our reported case, the presence of a consciousness deficit pointed to a poor outcome. The patent basilar artery on CTA excluded severe vascular atherosclerosis, aneurysm or dissection. However, the initial hyperdense basilar artery was an early sign of thrombosis. [7] On the basis of the clinical data and neuroimaging, embolism was the most likely cause of stroke. Due to the rapid deterioration of the clinical status and a normal physical examination with only mild sinus tachycardia on ECG, no further cardiac survey was done.

Hemorrhagic transformation is common in patients with supratentorial and cerebellar embolic infarction. [3] Embolus migration with a subsequent reestablishment of the blood flow into the infarcted tissue (migratory embolism), a well-known theory proposed by Fisher et al, probably accounts for most hemorrhagic transformation. [2] The other factor associated with hemorrhagic transformation is the size of the infarction. [8] The predilection of large infarcts to undergo hemorrhagic transformation may be explained by the frequent association with extensive edema that can compress small vessels, causing endothelial damage. After edema subsides, reperfusion of those vessels with altered endothelia permits the diapedesis of the blood. [2,8] The incidence of embolism-induced basilar artery occlusion was around 14% in one report, [6] but there are no records
of massive pontine hemorrhagic infarction. The possible explanation is that pontine infarction, even in basilar artery occlusion, is restricted to a relatively small territory that is not usually affected by a similar mechanism.

For many years, the usefulness of emergent anticoagulants for BAO has been a subject of debate. In a recent study of basilar artery occlusion or stenosis, anticoagulants were found to be statistically nonsignificant in terms of outcome when compared with antiplatelet agents. Furthermore, on the basis of the results of several trials, Adams concluded that the emergency administration of anticoagulants is associated with increased risk of symptomatic hemorrhagic transformation of ischemic strokes, especially among patients with severe strokes. The data do not imply that low molecular weight heparin is either more dangerous or safer than heparin.

The current first choice of acute ischemic stroke is thrombolytic agent and intravenous administration of rtPA within three hours of onset is the only FDA-approved therapy. Some observational studies have suggested that recanalization therapies for BAO can potentially benefit patients up to 24 to 36h after the onset of symptoms. Lindsberg et al indicate that some of their patients with BAO had improvement when intravenous rtPA was given more than 12h after symptom onset. They postulated that symptomatic hemorrhages occurred only to patients without recanalization. Reperfusion injury and brain edema seem to be less frequent as compared with large anterior circulation strokes. In our case, the initial deep comatose condition suggested that the occluded area of basilar artery was large and the hemorrhagic transformation after enoxaparin was likely caused by recanalization with reperfusion injury. While the risk of hemorrhage associated with administration of thrombolytic agents appears to be more than that with anticoagulants, the problem arises whether the thrombolysis for BAO in deep coma patients with longer duration of symptom onset is really indicated or not. The present case may further suggest a contraindication of thrombolysis in such patients.

In conclusion, this case adds massive pontine hemorrhagic transformation to the list of possible complications of low-molecular-weight heparin for treatment of BAO. In patients with a severe neurological condition and longer-existing ischemic deficit, we should be more cautious and conservative because the emergency use of low-molecular-weight heparin and even thrombolysis for BAO might lead to a more devastating outcome.

References


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