Improvement After Celecoxib Treatment in Patients with Thalamic Hemorrhage – A Case Report

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Abstract

Purpose: Perihematomal edema of intracerebral hemorrhage (ICH) is caused by a hematoma-induced inflammatory reaction, which usually contributes to delayed deterioration of neurological function and poor outcomes. Celecoxib is a commonly used nonsteroidal anti-inflammatory drug that selectively inhibits cyclooxygenase-2. High-dose celecoxib (400 mg twice daily) for 14 days has been shown to reduce perihematomal edema and hematoma enlargement in patients with ICH, but without improvement in long-term functional outcome, which may be confounded by the heterogeneity of hematoma location. Low-dose celecoxib may be an effective management for symptoms caused by perihematomal edema in patients with ICH, particularly those involving the thalamus.

Case report: We reported two patients with acute thalamic ICH; a common symptom between the two was delayed onset of drowsiness caused by perihematomal edema involving the thalamus. Their consciousness improved after low-dose celecoxib (200 mg once daily) administration for 3 and 2 days in case A and B, respectively. Furthermore, other symptoms that concomitantly improved included poor appetite caused by perihematomal edema involving the left hypothalamus in case A, and limb weakness caused by perihematomal edema of the internal capsule in case B.

Conclusion: These cases revealed that low-dose celecoxib may be an effective management for symptoms caused by perihematomal edema in patients with ICH, particularly those involving the thalamus.

Keywords: Brain edema; Celecoxib; Intracerebral hemorrhage.

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INTRODUCTION

Intracerebral hemorrhage (ICH) accounts for 10%–15% of all strokes and is associated with high morbidity and mortality rates[(1)]. The pathophysiological mechanisms of ICH include primary injuries due to the compression effect of hematoma, and secondary injuries, such as perihematomal edema, induced by toxic blood degradation products and inflammation[(1)]. Moreover, secondary injuries may cause severe neurological deficits and even death[(2)]. Current ICH treatment guidelines target only at primary injuries by preventing re-bleeding via controlling blood pressure, and correcting coagulopathy for anticoagulant-related ICH[(3)]. However, effective treatment strategies for

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secondary injuries are still lacking.

Cyclooxygenases (COXs) play an important role in inflammation. COX-2, a subtype of COX, is constitutively expressed in the brain and upregulated locally after ICH, thereby mediating various inflammatory reactions[4,5]. Celecoxib, a commonly used COX-2 inhibitor, has been shown to have anti-inflammatory and neuroprotective effects in the acute stage of a rat ICH model[6]. High-dose celecoxib treatment (400 mg twice daily) administered for 14 days in acute ICH patients reduced perihematomal edema and hematoma growth in a randomized control trial[7]; however, celecoxib had no significant effect on the 90-day functional outcome, which may be confounded with the heterogeneity of hematoma locations. Thalamus is a common location for ICH, in which drowsiness or hemibody numbness are usually present[8]. Adjacent structures of thalamus, such as hypothalamus or internal capsule, may also be involved in these patients. Focusing the hematoma location on thalamus might minimize clinical heterogeneity and facilitate the observation of the clinical benefit of celecoxib. Herein, we present two cases of thalamic ICH whose consciousness and other neurological deficits related to perihematomal edema rapidly improved after using low-dose celecoxib over a short period.

CASE REPORT

Case A

A 71-year-old man had hypertension, chronic kidney disease stage III, asthma, and gouty arthritis. He presented to the emergency department 1 h after the onset of right limb weakness and stuttering. His initial blood pressure was 179/127 mmHg, Glasgow coma scale (GCS) score was E4VaM6, and the National Institute of Health Stroke Scale (NIHSS) score was 13. Neurological examinations revealed transcortical motor aphasia, right hemiparesis, and right body hypesthesia. Non-contrast computed tomography (CT) of the brain showed a 7 mL left thalamic hematoma with intraventricular hemorrhage (Fig. 1A).

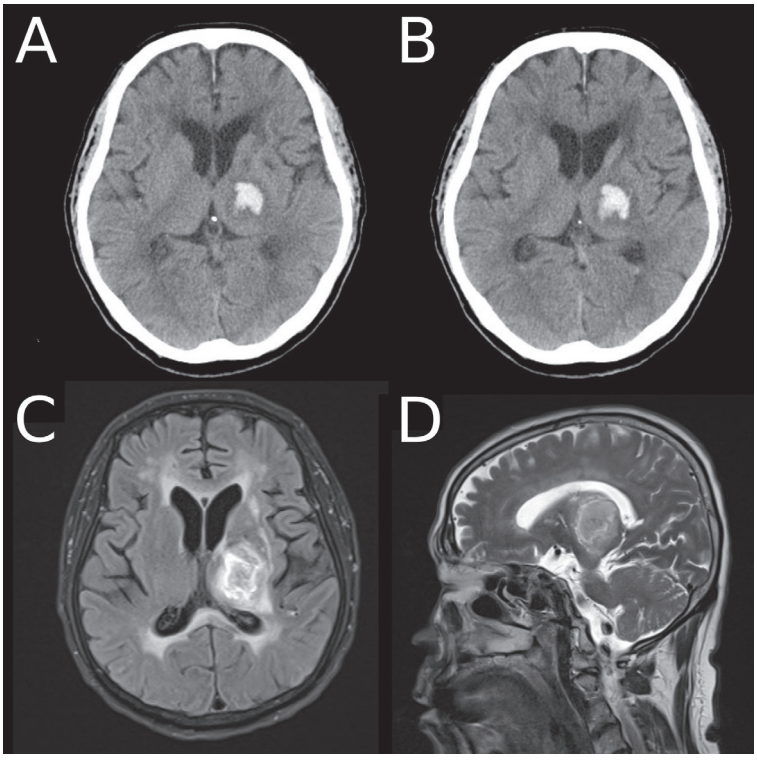

Figure 1. Brain imaging findings of case A

(A), (B): Non-contrast brain CT on day 1 (A) shows a left thalamic hematoma, while that taken on day 2 (B) shows an unchanged hematoma size with mild perihematomal edema. (C), (D): MRI FLAIR findings on day 9 reveal prominent perihematomal edema involving the left thalamus and hypothalamus.

Systolic blood pressure was controlled below 160 mmHg to prevent hematoma enlargement.

He became drowsy (GCS score E3V5M6) at 9 h after the onset of symptoms and the NIHSS score deteriorated to 15. The follow-up brain CT showed a stationary hematoma with mild perihematomal edema (Fig. 1B). Pneumonia developed on day 3, as fever and cough with increased lung infiltration on a chest radiograph. After appropriate antibiotics treatment, his white count improved to 5.8 k/μL with low procalcitonin level (0.186 ng/mL) and reduced lung infiltration on chest radiograph since day 8. However, his drowsiness persisted even after the infection was controlled. Additionally, poor appetite concomitantly arose on day 2, with an oral intake amount of 120-200 g of food per day. He had normal bowel sounds and abdominal radiography findings, and no abdominal discomfort, nausea, or headache. His appetite did not improve with prokinetics.

Brain magnetic resonance imaging (MRI) on day 9 revealed left thalamic subacute hematoma with perihematomal edema and multiple microbleeds (Fig. 1C and D). The perihematomal edema involved the intralaminar nucleus of the left thalamus and the left hypothalamus. Gouty arthritis occurred on his left ankle on the same day; thus, celecoxib (200 mg once daily) was administered for 7 days. After celecoxib treatment for 3 days, his consciousness improved from drowsy (E3V4M6) to alert (E4V4M6), and his appetite improved to an oral intake amount of 590 g per day. His NIHSS score improved to 12. He received intensive rehabilitation and was discharged on day 17. Fig. 2A is a timeline graph showing the temporal relationship among pneumonia, course of antibiotics and celecoxib, and clinical improvement.

Case B

A 77-year-old man had hypertension, chronic hepatitis B, and hepatocellular carcinoma. He had been taking lenvatinib as anti-cancer therapy for 13 months before his stroke, which is a risk factor for worsened hypertension. He presented at the emergency department with acute-onset slurred speech that began 30 minutes

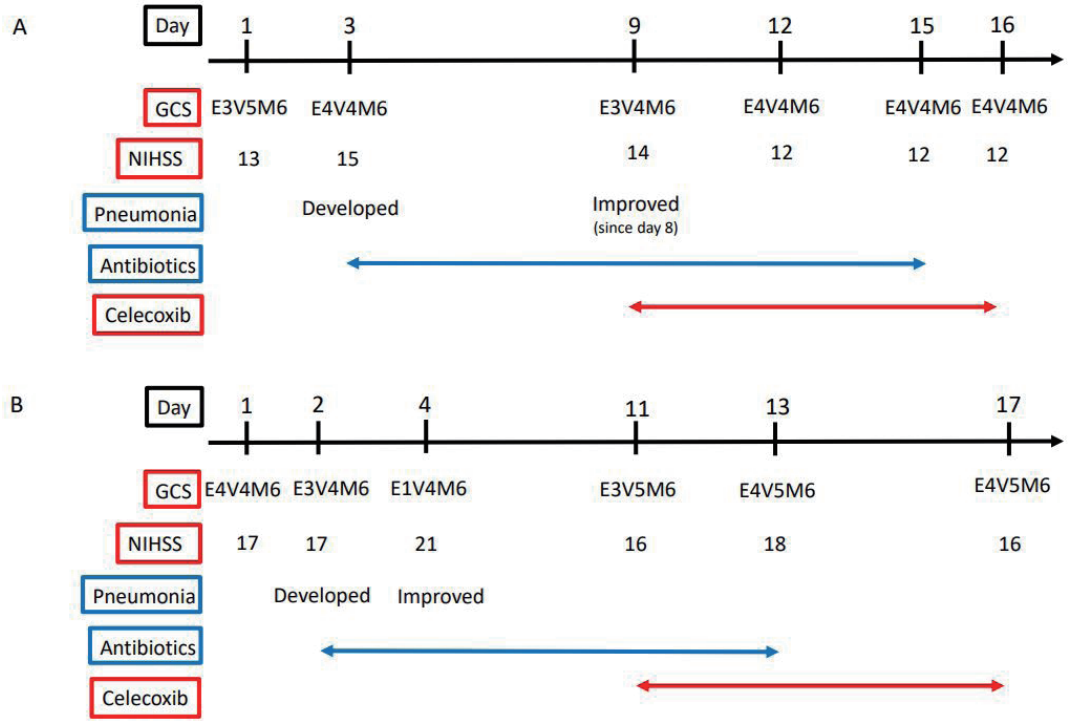

Figure 2. Time-line graph of case A and B

(A), (B): showing the temporal relationship among pneumonia, course of antibiotics and celecoxib, and clinical improvement of case A and B, respectively.

prior, accompanied by weakness and numbness of the left upper limb. His initial blood pressure was 205/99 mmHg. Neurological examination revealed alert consciousness with confusion (GCS score E4V4M6), impaired repetition, left hemineglect, left homonymous hemianopia, left central type facial palsy, dysarthria, left hemiplegia, and left hemibody numbness. The initial NIHSS score was 17. Non-contrast brain CT revealed a hematoma on the right putamen to the thalamus (37 mL) with intraventricular hemorrhage, minimal midline shift, and a subarachnoid hemorrhage (Fig. 3A). His systolic blood pressure was maintained below 160 mmHg, and lenvatinib was discontinued.

He had persistent drowsiness since 13 h after onset. Follow-up brain CT showed a stationary hematoma with some perihematomal edema (Fig. 3B). Pneumonia that occurred on day 2 was presented with fever and increased lung infiltration on a chest radiograph. After antibiotics treatment, his white count was normalized to 8.68 k/μL with low C-reactive protein and procalcitonin levels on day 4. Fever or leukocytosis did not develop since that day. However, his consciousness remained too drowsy to maintain alertness for longer than one minute after waking up. Celecoxib (200 mg once daily) was administered between days 11 and 21 to manage the headache and perihematomal edema. His consciousness improved from drowsy (E3V5M6) to clear (E4V5M6) with better attention after receiving two doses of celecoxib. In addition, his muscle strength also improved from grade 2 to 3 of manual muscle testing in his left limbs; moreover, he was able to participate in intensive rehabilitation under alert consciousness. Brain MRI performed on day 16 revealed an unchanged hematoma size, obvious perifocal edema, and several microbleeds (Fig. 3C and D). He was discharged on day 17. The timelines of pneumonia, antibiotics course, celecoxib use, and clinical improvement were shown in Fig. 2B.

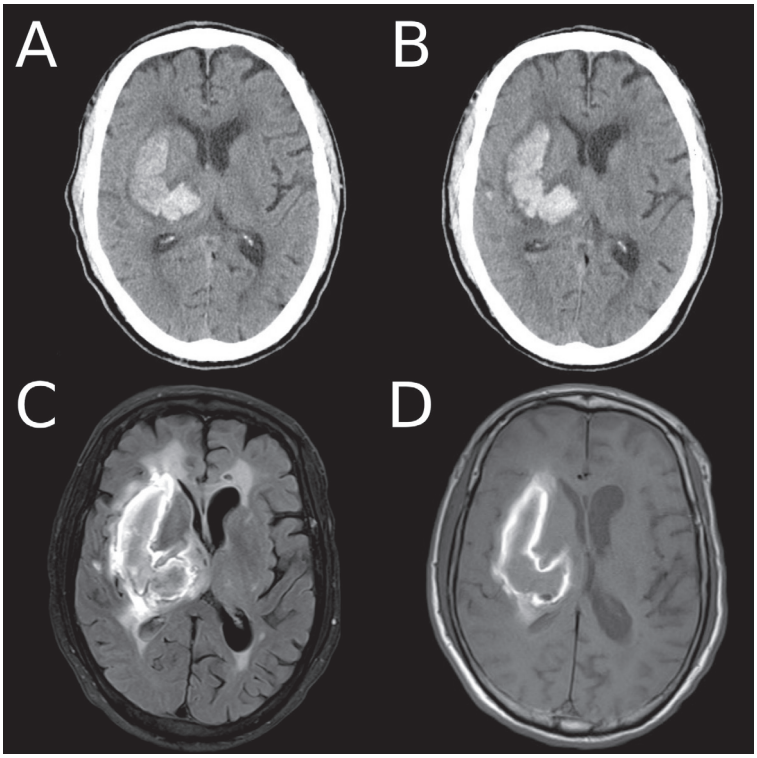

Figure 3. Brain imaging findings of case B

(A), (B): Non-contrast brain CT taken on day 1 (A) shows hemorrhage at the right putamen and thalamus, while that on day 2 (B) shows stationary hematoma size and some perihematomal edema. (C): Axial MRI FLAIR taken on day 16 reveals obvious perihematomal edema affecting the right thalamus and internal capsule. (D): Axial T1-weighted MRI taken on day 16 shows that the right internal capsule is unaffected by the hematoma.

DISCUSSION

These two cases of acute thalamic ICH were characterized by a delayed onset of drowsiness due to perihematomal edema involving the thalamus, with good response to short-term low-dose celecoxib. This affected region in the thalamus included intralaminar nucleus, which helps maintain alertness[9]. Furthermore, the radiological findings of the brain excluded the possibility of hematoma enlargement. Other structures adjacent to the thalamus were also affected by perihematomal edema, such as the hypothalamus in case A, and the internal capsule in case B, whose symptoms had a parallel improvement with consciousness after celecoxib administration. These two cases demonstrate that low-dose celecoxib may alleviate symptoms caused by perihematomal edema in patients with ICH.

Celecoxib has been proven to reduce perihematomal edema in patients with ICH and animals[6,7]. The association of perihematomal edema with functional outcomes was determined by hematoma location and volume[2]. In these two cases of thalamic ICH, continuous improvement with celecoxib treatment occurred, allowing intensive rehabilitation and prevention of further complications. In a previous clinical trial[7], celecoxib reduced perihematomal edema but did not lead to better functional outcomes, which may be confounded with the heterogeneity of hematoma locations and volumes. The outcomes of patients with very mild or very severe ICH might not be affected by anti-inflammatory effect of celecoxib. In contrast, celecoxib could induce significant and persistent functional recovery in a mouse ICH model, wherein the hematoma was consistently located in the striatum[6]. The similar thalamic hematoma location of our cases reduced the clinical variability; moreover, the adjacent structures affected by the hematoma had neurological symptoms, allowing the observation of the effects of celecoxib.

In our cases, the improved consciousness and other neurological functions occurred rapidly after using celecoxib for 3 and 2 days from day 9 and 11, respectively, indicating the potentially reversible nature of perihematomal edemas. Although both cases developed pneumonia on day 3 and day 2, respectively, the serial laboratory data and chest radiograph findings showed that their infection had been resolved before adding celecoxib. Thus, the clinical improvement after using celecoxib was more likely to be the effect of celecoxib on the perihematomal edema instead of the resolution of infection.

Perihematomal edema typically peaks between 2 and 3 weeks[10]. Therefore, the improvement presented in our cases may not be attributed to the natural resolution of perihematomal edema. The pathophysiology of perihematomal edema at this stage involves mixed vasogenic edema induced by lysed erythrocytes, and cytotoxic edema provoked by intraparenchymal hemoglobin[11]. The rapid reversibility of the symptoms related to perihematomal edema in response to celecoxib in these two cases suggested predominantly vasogenic edema. Since we did not perform brain MRI immediately before adding celecoxib, we could not tell whether there was any change of the size of perihematomal edema after using celecoxib. It was possible that some improvement of perihematomal edema and local brain inflammation might not be shown on the brain images, while the functional improvement could be observed in clinical presentations. Further clinical trial will be warranted to prove the effect of celecoxib on the perihematomal edema and neurological functions.

In conclusion, perihematomal edema in patients with thalamic ICH treated with low-dose celecoxib effectively targeted the symptoms caused by perihematomal edema, including consciousness, appetite, and muscle strength. Further studies are warranted to investigate the effectiveness of low-dose celecoxib treatment in patients with ICH in specific locations, particularly at the thalamus.

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