Case Report

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Central Hyperthermia Treated with Baclofen in a Patient with Epidural Hematoma

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Central hyperthermia is characterized by a rapid-onset elevated temperature, marked temperature fluctuation, and poor response to antipyretics and antibiotics. It is caused by impairment of the central thermoregulatory pathways and is associated with high morbidity and mortality. We report on a case of 31-year-old male who sustained fall injury with massive epidural hematoma and a high-grade fever of 40°C on presentation. Following craniotomy and evacuation of hematoma, antipyretics and antibiotics were used for high-grade fever but were not effective. Baclofen was orally administered which effectively controlled the fever. Here, we also discuss the possible central mechanisms for this effect of baclofen and show that baclofen may be an effective treatment in central hyperthermia.

Key Words: baclofen, brain injury, central hyperthermia, fever

Central hyperthermia, an elevation of body temperature caused due to impairment of thermoregulatory pathways in the brain, responds poorly to antipyretics and antibiotics.[4] It is associated with high morbidity and mortality. Sung CY et al reported that elevated temperature > 39°C and tachycardia > 110 beats/min developed within 24 hours of stroke onset is correlated with high risks of death.[9]

Hyperthermia is detrimental to the already injured brain, and the duration of fever is associated with poor outcome and recovery.[8] High mortality rate of 80% has been described in patients with intracerebral hemorrhage who developed central fever.[1] Mostly fever in stroke is associated with infections. However, fever without documented infection i.e., central fever was determined in 33% of stroke patients in a prospective study.[4] Thus, early identification of central fever is critical as it affects the treatment strategy.

Here we report on a critical patient who had massive epidural hematoma due to fall injury and high-grade fever on presentation. Following craniotomy and evacuation of hematoma, the fever continued despite administration of antipyretics and antibiotics but was successfully treated with baclofen.

Case Report

A 31-year-old man from a remote hilly region was brought to emergency department of Nepalgunj Medical College Teaching Hospital with the history of fall injury one day back. His GCS on presentation was E1V1M3 (5/15). Immediate resuscitation with intubation was done. CT scan revealed massive right-sided epidural hematoma (**Figure 1**). Emergency craniotomy for removal of the hematoma was performed. Intraoperative active bleeding from the superior sagittal sinus tear was encountered

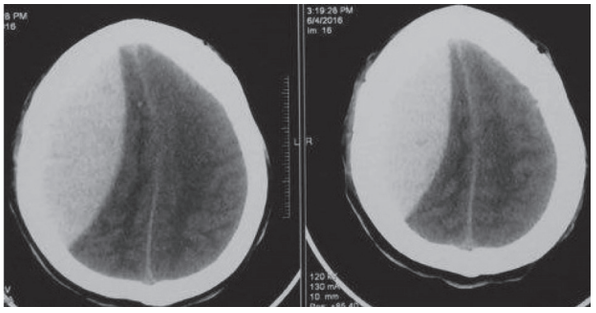

Figure 1: Axial plain CT scan of head showed right-sided epidural hematoma with mass effect.

causing significant decline of BP. Sinorrhaphy was performed to stop the sinus bleeding and the hypovolemic shock was intensively managed.

Postoperatively, the patient was managed in intensive care unit. Antipyretics and broad-spectrum antibiotics were used for high-grade fever (40°C) but were unable to reduce the temperature even after three days. The patient had tachycardia ranging 136-144 beats/min. Laboratory and radiological examinations did not reveal any significant clue for high-grade fever in the patient. Considering the possibility of central hyperthermia, baclofen was administered orally at the dose of 30 mg/day, based on the previous literature reported.[2, 3]

Two days after starting baclofen therapy, the temperature and the pulse rate reduced to 37°C and < 110 beats/min respectively. The temperature ranged from 37°C to 37.6°C for the following week. So, we planned to taper baclofen dosage. However, on tapering the baclofen dose, temperature again elevated to 40°C. Then, the dose was increased to 60 mg/day as per the previous report[6], which normalized the temperature from the next day. A week later, the baclofen dose was reduced to 30 mg/day and then continued. The temperature was stably maintained thereafter (**Figure 2**). He was then discharged to rehabilitation center for intensive physiotherapy for the left sided hemiplegia that ensued from the brain injury.

Discussion

Sung CY et al. suggested the following criteria to diagnose central hyperthermia: 1) no preceding infections or fever at least 1 week prior to stroke onset, 2) high fever (>39°C) developing within 24 hours after onset of stroke, and 3) negative work-ups for fever of infectious origin.[9] Thus, central hyperthermia remains a diagnosis of exclusion.

The exact pathophysiological mechanism underlying central fever remains unknown. Hypothalamus coordinates several physiological mechanisms involved in thermoregulation. Baclofen, a gamma-aminobutyric

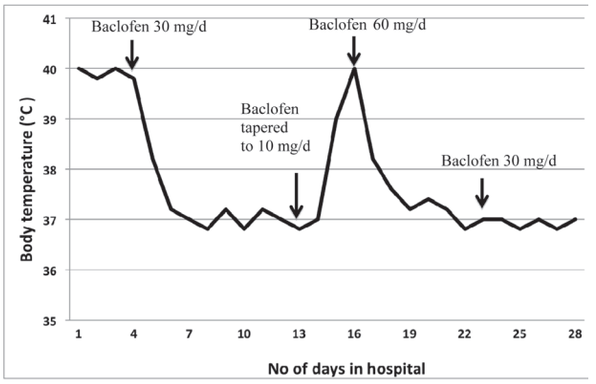

Figure 2: Clinical course of change in body temperature during the hospital stay showed effective response to baclofen administration.

acid (GABA) agonist, has been hypothesized to reduce central hyperthermia. In-vivo experiments using mice have shown that GABA receptor activation by baclofen injection largely reduced the body temperature.[5] There have been two case reports so far on pubmed search showing that baclofen abolished central fever in patients with brain injury.[2,3]

Huang YS hypothesized that baclofen functioned as inhibitory signals directly acting on the raphe nuclei to suppress brown adipose tissue (BAT) activation, which in turn suppresses the body temperature.[2] BAT is an important effector organ for non-shivering thermogenesis. The efferent signals from the preoptic chiasma/anterior hypothalamic nuclei are the inhibitors of GABA to reach ventromedial hypothalamic nucleus. The signals from the ventromedial hypothalamic nucleus reach the raphe nuclei through the lower midbrain. The thermoregulatory signal is connected to the sympathetic chain. The sympathetic chain controls the BAT for non-shivering thermogenesis. The detailed mechanism about the effects of baclofen on BAT in thermoregulation is not yet clarified. In animal models of cerebral ischemia, decreased GABA receptor density has been demonstrated in *in-vivo* and *in-vitro* studies.[7] Thus, we hypothesize that in our patient who had suffered secondary ischemic injury due to massive epidural hematoma, replacement of GABA by baclofen administration might have been beneficial in the overall improvement of the patient.

Reports have also shown that bromocriptine, a dopamine agonist, acting at the level of hypothalamus and corpus striatum, effectively managed central hyperthermia in brain injury.[6, 10] Hypothalamic dysfunction can lead to wide fluctuations in the core body temperature. Therefore, bromocriptine may also be used to control central hyperthermia. It may be helpful in the cases with major side effects of baclofen such as drowsiness and generalized weakness.

Early detection of central fever and its differentiation from infectious fever is very important as the treatment strategies completely vary. Although central hyperthermia in brain injury holds poor prognosis with high morbidity and mortality, early identification and intervention with centrally acting drugs might be effective in managing this condition and preventing the grave outcomes associated with it.

Conclusions

Here we presented a patient with severe brain injury who developed central hyperthermia. Use of baclofen successfully abolished the fever. However, the mechanisms by which baclofen acts on the central thermoregulatory pathways are not clearly understood. This case report advocates that central hyperthermia should be considered as a possible diagnosis in a brain-injured patient with fever and baclofen may also be an effective treatment for such condition.

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