Use of Baclofen and Propranolol for treatment of neurogenic fever in a patient with Pontine Hemorrhage; A Case Report.

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TITLE:

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KEY CLINICAL MESSAGE

Neurogenic fever (NF) is a potentially life-threatening complication commonly seen in patients with pontine hemorrhage. This case report highlights the successful use of oral Baclofen and Propranolol as an effective treatment strategy to manage NF.

ABSTRACT

Neurogenic fever (NF) is a common complication following pontine hemorrhage and poses significant challenges for clinicians in terms of diagnosis, management, and patient outcomes. This study delves into the efficacy of treatment methods involving baclofen and propranolol for neurogenic fever in patients with pontine hemorrhage. The results demonstrated a significant reduction in the duration and intensity of fever. Moreover, the treatment modality was well-tolerated and devoid of any adverse effects. These findings suggest that the use of oral baclofen and propranolol may be a promising therapeutic option for managing neurogenic fever in patients with pontine hemorrhage.

KEYWORDS

Neurogenic fever, Pontine hemorrhage, Baclofen, Propranolol, Central hyperpyrexia

INTRODUCTION

Hyperthermia is a prevalent occurrence, affecting nearly 70% of neuro-critically ill patients who are admitted with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH). Among these cases, half are attributed to noninfectious causes but are frequently misdiagnosed and managed as infectious fever, leading to unwarranted use of antibiotics, antimicrobial resistance, adverse drug reactions, increased treatment costs, and extended hospital stays.[1, 2]

The temperature elevation associated with neurogenic fever is notably high and often resistant to antipyretic medications, necessitating prompt and aggressive treatment to prevent secondary brain injury.[3] In addition to external cooling methods, appropriate drug therapy is crucial. However, the lack of clinical practice guidelines for treating central hyperpyrexia leaves a knowledge gap. A multi-modal approach involving propranolol, baclofen, amantadine, bromocriptine, and intravascular cooling has been recommended. This case report describes a successful treatment of severe traumatic brain injury with neurogenic fever using a combination of baclofen and propranolol.

CASE PRESENTATION

A 27-year-old male arrived at the emergency department following a road traffic accident involving a collision with a four-wheeler while riding a bike. Initial medical attention was provided at a local hospital, where endotracheal intubation was performed due to a low Glasgow Coma Scale (GCS). Subsequently, he was referred to our center for advanced care.

Upon presentation, his vital signs were as follows: blood pressure 130/80mmHg, heart rate 116 beats/min, temperature 38°C, and respiratory rate 24 breaths/min under controlled mechanical ventilation. His Spo2 was 97% on fio2 of 90%. The GCS score was 5/15.

A magnetic resonance imaging (MRI) scan revealed diffuse axonal injury with pontine hemorrhage and subdural hematoma (figure 1). He received conservative management to control intracranial pressure, prophylactic antibiotics, antiepileptic medication (Levetiracetam), and other supportive treatments. Mean arterial pressure (MAP) was targeted to maintain cerebral perfusion pressure above 60 mmHg.

Laboratory results indicate leukocytosis with a total white cell count of 20,300 Cells/Cumm.

On the third day of ICU admission, the patient developed a continuous fever. Initial culture reports and a new set of laboratory tests (CBC, ESR, CRP, and Procalcitonin) all returned negative for infections. A chest x-ray was performed to rule out ventilator-associated pneumonia, but no definitive cause for the fever could be identified.

Antipyretics and surface cooling measures were initiated, and empiric antibiotic therapy was upgraded to intravenous meropenem and polymyxin-B. Despite these efforts, the patient remained hyperpyretic (figure 2).

On the seventh day of ICU admission, repeat cultures were taken, and procalcitonin levels remained low, yet the patient's clinical condition did not improve. Antimicrobials were further upgraded to intravenous tigecycline, and antifungal medication (caspofungin) was added. Echocardiography ruled out infective endocarditis, and a review of medications found no evidence of drug fever.

By the fourteenth day of ICU admission, with all infectious causes excluded, a diagnosis of central hyperpyrexia was established. Neuroleptic malignant syndrome too was excluded as other clinical features suggestive of the same were absent.

Following a thorough literature review, oral baclofen (10 mg Q8H) and propranolol (20 mg Q12H) were introduced. After 48 hours, the patient's temperature decreased to 38°C, occasionally spiking to 38.5 - 39°C. The doses of both medications were increased to; Baclofen 20 mg Q8H and Propranolol 20 mg Q8H.

After 10 days of treatment with Baclofen and Propranolol, the patient's temperature and heart rate returned to normal (figure 3). Both medications were continued for an additional 4 days and then stopped, as the

temperature and heart rate remained stable with no recurrence of fever. The patient was subsequently transferred to the ward.

DISCUSSION

Neurogenic fever is a diagnosis of exclusion and remains a challenging condition to manage effectively. The traditional approach of supportive care and antipyretic medications often proves inadequate in controlling the underlying dysregulation of the autonomic nervous system. In this case report, we highlight the successful management of neurogenic fever using a combination of baclofen and propranolol.

NF is likely a result of direct pontine destruction or indirect compression. It is characterized by an unchanged setting of the thermoregulatory center so antipyretics have no effects on central hyperthermia.[4, 5] The combination of negative cultures; absence of infiltrate on chest radiographs; diagnosis of SAH, intraventricular hemorrhage, or tumor; and onset of fever within 72 hours of admission, predict NF with a probability of 0.90.[6]

Post-traumatic brain injury-related hyperthermia, also known as neurogenic fever is characterized by the development of hyperthermia, tachycardia, hyperhidrosis, hypertension, and sometimes seizures.[7]

Traumatic brain injury mechanisms include growth factor deficiency, which reduces sweating capacity and increases the risk of developing hyperthermia; direct injury to the hypothalamic-pituitary area and inflammatory changes within the hypothalamus; and diffuse white matter damage, which causes brain edema, hyperglycemia, leukocytosis, hypotension, and seizure. All of these mechanisms result from autonomic dysfunction. This condition is also known as dysautonomia, paroxysmal sympathetic hyperactivity (PSH), or diencephalic syndrome.[8]

We hypothesized that baclofen would be effective in this case as it had an effect on central hyperthermia for patients with pontine hemorrhages. Baclofen, a GABA agonist, functions as an inhibitory signal directly acting on the raphe nuclei to suppress BAT activation, which in turn suppresses the body temperatures. Thus, baclofen may control central hyperthermia by replacing neurotransmitters (GABA, glutamate) that were blocked due to the location of hemorrhage.[9]

We used baclofen at a dosage of 30 mg/day and titrated up to 60 mg/day, resulting in a complete resolution of fever. A study by Lee HC et al. also reports the efficacy of baclofen at a similar dosage to achieve normothermia in patients with central hyperthermia secondary to pontine hemorrhage. They started at a dose of 30 mg/day to a maximum of 60 mg/day with the reduction of fever from >39 to 37.5.[10]

Another study done by Huang YS et al successfully treated neurogenic fever with 30 mg/day of baclofen.[8]

Propranolol, a sympathetic blocking agent that can pass the blood-brain barrier can blunt the sympathetic storming phenomenon resulting in successful control of paroxysmal hyperthermia.[11] We expected that combining propranolol with baclofen would have a two-fold effect of lowering his temperature as well as his heart rate in our patient, who also had sinus tachycardia with a heart rate ranging from 120-150.

Meythaler et al. published one of the earliest case reports of three cases of NF in severe TBI patients treated with propranolol.[12] Garg M et.al. Stated that propranolol 10 mg thrice daily was effective in alleviating fever and tachycardia for severe traumatic brain injury.[13]

The Dosages mentioned in both studies were lower than the propranolol dose used in our study. In our patient, 60 mg/day of propranolol combined with 60 mg/day of baclofen provided adequate temperature and heart rate regulation. This dose of nonselective beta blocker has no negative effects.

CONCLUSION

Our understanding of thermoregulatory failure in patients with brainstem hemorrhage has been enhanced by the current case. We should take prolonged central hyperthermia into account as a potential source of fever in cases of pontine strokes and take baclofen and propranolol into account as treatment options.

ACKNOWLEDGMENTS

We sincerely thank the patient and the members of our critical care department for their efforts.

ETHICAL CONSIDERATIONS

This case report did not require the approval of any Ethical Committee. Written informed consent was obtained from the patient.

FUNDING

None

CONFLICT OF INTEREST

None

REFERENCES: Dimopoulos G, Falagas ME. Approach to the febrile patient in the ICU. Infect Dis Clin North Am 2009;

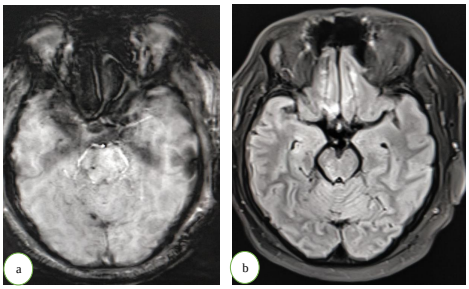

Fig. 1. (a and b) Plain MRI of the brain shows diffuse axonal injury with pontine hemorrhage

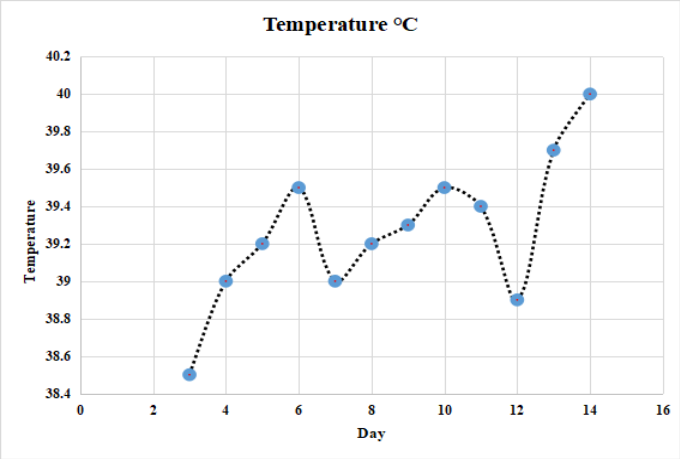

Fig. 2. Daily body temperature of the patient before initiation of baclofen and propranolol.

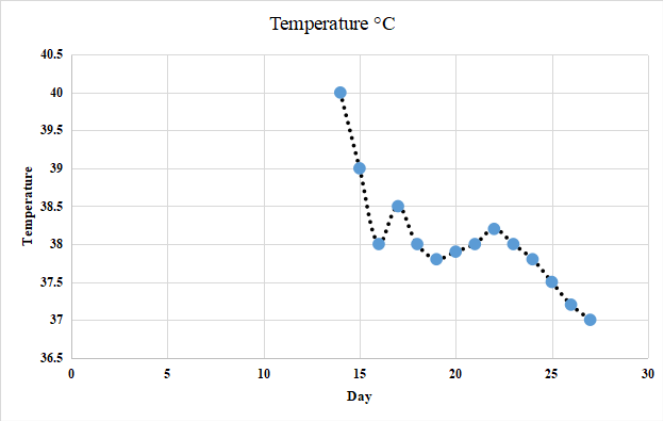

Fig. 3. Daily body temperatures of the patient after initiation of baclofen and propranolol.