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Commentary: Calcitonin Gene Related Peptide and Its Clinical Utility for the Treatment of Traumatic Brain Injury, Subarachnoid Hemorrhage and Associated Migraine

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Commentary

Calcitonin gene related peptide (CGRP) is a potent vasodilator and neurotransmitter that has been extensively studied in the context of migraine pathophysiology. Recently, studies have explored its role in the treatment of traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH). Although a multitude of therapies exist for migraine, there has been little study on the management of migraine following neurologic injury. As the incidence of TBI continues to grow, especially in the United States, it is essential to explore additional therapeutic options such as CGRP inhibition (CGRPi). Given its differential effects in TBI and SAH, an important next step is to see how patients with both TBI and SAH treated with CGRPi respond differently than patients with TBI alone. There is also a need for study in patients with severe TBI who could benefit most from this novel strategy. Calcitonin gene-related peptide (CGRP) is a 37-amino acid neurotransmitter that has been shown to be involved in cranial and facial pathology. Most commonly, CGRP's role as a potent vasodilator [1,2] has been associated with migraine [3]. It's use in the treatment of traumatic brain injury [3-5] and subarachnoid hemorrhage (SAH) [6-9] has recently been explored in the literature. While there have been numerous studies on mice and other animal models describing exogenous CGRP's therapeutic effects, its limited efficacy in humans due to its low half-life [10] has prevented its advancement to human trials.

Migraines are relatively common following TBI, with some studies suggesting the prevalence of migraines to be anywhere from 30-90% [11]. The reported prevalence varies widely for many reasons. Mild TBIs are generally underreported and undertreated, therefore associated migraines are also underreported [12]. This is significant considering migraines appears to be more prevalent in cases of mild TBI compared to more severe TBI [12]. In studies investigating the prevalence of migraines following SAH, results have shown that as many as 41% of patients can develop post-SAH migraines [13]. Furthermore, it has been shown that younger patients with more favorable neurological conditions are more likely to experience migraines than those without [13]. Additionally, they are also less likely to be seen in the emergency room as older adults are four times as likely to seek medical services than younger adults [14]. Taking these findings into account, migraines appear to be a common, underreported, and undertreated symptom following neurologic injury.

Current management of post-traumatic migraine consists of oral medication, musculoskeletal manipulation, interventional procedures, and behavioral therapy [11]. Complicating effective management is that research has shown that the effective treatment modality is dependent on the specific type of post-traumatic migraine [15]. For acute migraines, triptans are an effective treatment, but their use in post-traumatic migraines has not been demonstrated [16,17]. Further studies need to be conducted to not only develop more effective therapies for migraines but also a standard protocol for management of migraines following trauma.

Opioids have received attention as a possible therapeutic for migraines. What researchers found, however, was that the benefits of opioid use for the treatment of migraines do

not exceed the risks [18-20]. Despite the published literature, emergency departments still commonly prescribe opioids for management of acute migraines [21]. For example, the United States Center for Disease Control found that in one fourteen-month period, opioids were ordered for 35.8% of ED visits for acute migraines [22]. However, for patients with TBI and SAH, opioids are not an ideal option for acute migraine management. Quality neurological examinations are vital in both assessing a patient's prognosis and determining the source of the bleed [23]. The use of opioids diminishes the quality of the neurological exam due to sedating effects [24]. The reduced respiratory drive caused by opioids can also lead to hypercapnia which may increase intracranial pressure and exasperate a migraine instead of alleviating it [25]. Opioids are also a leading cause of injury and death in adolescents and young adults in the United States, and there is a high reported opioid prescription misuse [27]. Use and prescription should be reduced and controlled, especially since they are a poor treatment option for migraines. Novel treatments are needed to adequately treat migraine following TBI and SAH.

As highlighted previously, CGRP plays a role in the pathophysiology of migraines and as such may be a potential therapeutic target for migraine management following SAH [3]. Currently, four therapeutic agents modify CGRP activity. Fremanezumab, galcanezumab, and eptinezumab are antibodies against CGRP itself while erenumab is an antibody against the CGRP receptor [27]. Studies have shown that erenumab's mechanism inhibits cAMP signaling at the CGRP receptor, including adrenomedullin and intermedin-induced signaling. Both pathways are present in peripheral tissue and have shown to have vasodilatory effects [28,29]. In contrast, Fremanezumab was shown to inhibit CGRP ligand signaling at the CGRP receptor while allowing adrenomedullin and intermedin signaling to proceed unperturbed [27]. CGRP antagonists represent a new exciting therapeutic agent for patients suffering from migraine.

Finding novel ways to target migraine brought upon by neurologic injury, specifically TBI, is currently at the forefront in the United States. The epidemic of firearm-related violence in the US has caused the incidence of TBI to increase dramatically. From 2019-2020 alone the rate of firearm violence in the US increased from 4.6 to 6.1 per 100,000 persons [30]. Firearm TBIs are also affecting children and younger adults at a rate exceeding older Americans causing an increase in TBI in younger age cohorts [31]. TBI induced by falls has also been increasing in recent years. Studies have shown that the rate of older adults admitted for falls and their complications, including TBI, is increasing. The same study also found that among the adults admitted to the ED for fall-related TBI, 33% of them presented with SAH [32]. In modern-day America, TBI is increasing among all age cohorts. One study looking at the prevalence of traumatic brain injury in the US found that an estimated 1.5 million Americans sustain a TBI each year and that among them, 230,000 are hospitalized and survive, and an estimated 80,000-90,000 people sustain long-term disability [33].

Since migraines are rather common among people who have sustained a TBI [15], it is imperative to find better treatment modalities than what is currently available. As previously stated, CGRP antagonism is a growing area of study that has the potential to provide relief for patients suffering from migraines. Clinical trials have found success in proving the efficacy of CGRP inhibitors in blocking either CGRP or its receptor, increasing tolerability when compared to current migraine therapies, as well as being safer and more effective than other treatments [34,35]. While these trials showed promising results, these studies were limited to short-term clinical trials and the long-term effects of CGRP antagonism are still unknown [36]. Since CGRP has been shown to play a role in healing after brain injury, there use in patients who have suffered a TBI needs further research [3]. Current research is limited but promising. Studies using animal models with mice who have sustained a mild TBI found that early and continuous administration of a CGRP antagonist prevented both acute migraines as well as persistent migraines following TBI [37]. In humans, the use of CGRP antagonists is likewise limited to mild TBI, but their use has provided a safe and effective therapy for the management of migraines following mild TBI [38]. For patients suffering from severe TBI or SAH, the efficacy of CGRP antagonists has not been explored. A randomized trial of patients with TBI and SAH compared to those with TBI but without SAH may provide insight into the use of CGRP antagonism and its differential effects in the context of both TBI and SAH.

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