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Short Commentary

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Cervical epidural stem cells in treatment of post-traumatic headaches

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Short commentary

Post-Traumatic Headache (PTHA) is the most common symptom after Traumatic Brain Injury (TBI) and may be debilitating or progress to chronic. PTHA is part of Post-Concussive Syndrome (PCS), a constellation of symptoms including dizziness, fatigue, and disruptions in mood, sleep, and cognition. In 2018, the global incidence of all-cause, all-severity TBI was estimated to be 69 million cases per year, while in 2016, the global prevalence of chronic impairment secondary to TBI was estimated to be 55.5 million cases [1,2]. The prevalence of PTHA in the general population after mild TBI was reported to be between 30% and 90% [3]. Despite its high prevalence, the pathophysiology of PTHA is unknown; etiologies may include impaired descending modulation, neuro-metabolic changes, trigeminal system activation, or irritated nerves in the cervical spine due to trauma sustained during whiplash [4]. Posttraumatic headache does not have a specific phenotype, but may include migraine, tension, cervicogenic (C1-C3), or occipital neuralgia-type. There are no FDA-approved treatments specifically for post-traumatic headaches. Management involves a multifaceted approach tailored to the headache phenotype. This may include medications, musculoskeletal manipulation and treatment, transcranial magnetic stimulation, interventional procedures, or behavioral therapy [3]. Several interventional procedures have been trialed for PTHA, including botox, peripheral nerve blocks, radio-frequency ablation, although these lack controlled trials [5]. Unfortunately, PTHA may be quite resistant to conventional modalities of treatment. A study shows that only 30% of the patients with PTHA reported headache resolution by 24 months after TBI [6]. Another study found that 58% of patients continued to have headaches one year after a traumatic brain injury [7]. Moreover, up to 91% of individuals experienced new or worsened headaches within one year of a Motor Vehicle Accident (MVA) [8]. Stem Cell (SC) based treatment is currently approved by the FDA only as a hematopoietic stem cell transplant for certain types of cancer. Despite this, SC therapy has been used fairly often in the last decade for various conditions of the joints and spine. SC augments the repair of dysfunctional, diseased, or injured tissue. SC therapy is currently being investigated as a potential treatment for chronic headaches [9] and TBI [10]. However, the vast majority of the studies used either IV stem cells infusion or an implant of BM-MSGs and were aimed at safety of the proce-

dure rather than its efficacy [11,12]. SC therapies provide benefit through various mechanisms in the CNS such as replacement of cells, modulating the inflammatory response, and providing neuroprotection [13]. Stem cells, due to their capacity to differentiate into neuronal cells and through releasing neurotrophic factors, may be a valid strategy to use in the treatment of traumatic brain injury [11]. Mesenchymal Stem Cells (MSC) specifically appear capable of regenerating damaged nerve tissue, as demonstrated in several in vivo studies, using animal models of TBI [11]. In our practice we perform a significant number of SC injections for different painful conditions of the spine with very promising results [14,15]. The hUC-MSC (human umbilical cord tissue derived mesenchymal stem cells) used in our clinic are generated from umbilical cord tissue, and are characterized to have standard MSC phenotype according to the International Society for Cellular Therapy criteria. Briefly, the umbilical cord tissue was obtained after full-term deliveries from healthy human donors and were tested negative for infectious agents to meet the eligibility for tissue donation in compliance with Title 21 of the Code of Federal Regulations (21 CFR) part 1271 in the USA. hUC-MSC were isolated and culture expanded from the eligible umbilical cord tissue in a cGMP compliant facility. hUC-MSC suspension was prepared at a concentration of 2 million cells/mL and has been subject to viability, identity, purity and safety testing (sterility, mycoplasma, endotoxin etc.) before release for use in our patients. TBI is a clinical diagnosis based on signs and symptoms. In our practice, neuro-imaging including structural MRI with susceptibility-weighted imaging, volumetric analysis, and diffusion-tensor imaging are performed to further inform the diagnosis and exclude other etiologies. Over the last couple years we observed a significant number of patients diagnosed with mild TBI, who reported significant improvement in PTHA after intralaminar cervical epidural SC injection performed at C6-7 or C7-T1 levels. This procedure was done for herniated disc with or without cervical radiculopathy at the lower levels of the cervical spine (C5-6 or lower). Pathology at these levels should not be the primary cause of the PTHA and TBI. Nevertheless, many of these patients responded to this treatment. As an example of such outcomes, we are presenting a recent case report. 38year old Caucasian male presented to the clinic 11 months after MVA. His previous treatment consisted of medications and PT. The main complaint was daily headaches in the frontal area and bilateral temporal areas. This was accompanied by sleep disturbances, blurred vision, difficulty concentrating and personality changes. The second complain was neck pain at the base of the neck in the midline unrelated to position or activity. After the patient was examined by neurologist and underwent qualitative multiparametric MRI of the brain he was diagnosed with PTHA due to TBI. The MRI of the cervical spine demonstrated C6-7 midline 2.5 mm herniation with indentation of the ventral thecal sac. The patient underwent intralaminar epidural injection at C6-7 with 10 mln hUC-MSC. During his follow up appointment nine weeks later, the patient not only reported 80% improvement in his cervicalgia but also almost complete resolution of his headaches as well as other TBI symptoms. Repeat evaluation in another 6 weeks showed no return of headaches. Based on our observation we believe that cervical epidural injection of SC may potentially be an option in the treatment of PTHA due to TBI. Of course, further prospective studies involving a larger patient cohort and/or randomized controlled trials are needed to confirm this suggestion.

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