EJCRIM
European Journal
of Case Reports
in Internal Medicine

TRAUMATIC AXONAL INJURY SUCCESSFULLY TREATED WITH SECRETOME FOLLOWED BY MESENCHYMAL STEM CELLS THERAPY

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Received: 24/01/2025
Accepted: 11/02/2025
Published: 10/03/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The patient and/or his family provided informed consent.
Acknowledgements: We would like to thank all team that treated our patient in this report: Dr Deasy Sugesty, MARS (Director of Mayapada Hospital Kuningan) and Dr Irwan Susanto Hermawan, MM (Director of Mayapada Hospital Bandung); Dr Franz Pangalila (Internal Medicine); Dr Inez Widyasari Halim (rehabilitation medic); Dr Jaka Pradipta (pulmonology); Dr Olivia Handayani (cardiology); Dr Armansjah Dara Sjahruddin (dermatovenerology); Terry Renata Lawanto (surgery); Dr Adhi Wicaksono (ophthalmology); Dr Kwan Francesca (nutrition); Dr Herbert Situmorang for data retrieval; Gatot Soebroto Army Hospital, Jakarta, Indonesia, and the Indonesia Stem Cell Committee.

How to cite this article: Faried A, Tatang Y, Wibawa GA, Widowati W, Distya AP. Traumatic axonal injury successfully treated with secretome followed by mesenchymal stem cells therapy. *EJCRIM* 2025;**12**:doi:10.12890/2025_005111

ABSTRACT

Introduction: Traumatic axonal injury (TAI), a head injury condition formerly known as diffuse axonal injury, results from direct mechanical forces causing multiple scattered lesions, either haemorrhagic or non-haemorrhagic, within brain tissue. Despite its clinical significance, no prior research has explored the use of stem cells in a TAI inpatient setting. This case presents the efficacy of stem cell therapy for TAI.

Case description: A 17-year-old boy sustained severe head injuries from repeated blows, resulting in a coma. Initial CT and MRI scans showed cerebral oedema without haemorrhagic lesions. T2-weighted axial FLAIR imaging showed two hyperintensity lesions in the corpus callosum, consistent with diffuse axonal injury grade II. Secretome and umbilical cord mesenchymal stem cell (UCMSC) therapy were administered. The patient showed improvement in motor function and speaking and was discharged without neurological deficits.

Discussion: The pathophysiology of TAI remains unclear because of a lack of unifying theory. It is theorised that not only is direct mechanical injury the cause of primary damage but biochemical changes in neuronal metabolism also play a role as secondary damage. Two main therapeutic options can be recognised. Treatment approaches fall into two categories: secondary axotomy-targeted therapy and promotion of neural regeneration. Multiple treatment options promote both microenvironment correction and neuronal regeneration, including cell and stem cell therapy along with its metabolite.

Conclusion: Stem cell therapy is promising as an alternative treatment modality in a case where there was no other optional therapy for TAI.

KEYWORDS

Diffuse axonal injury, stem cell therapy, umbilical cord mesenchymal stem cells

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- A traumatic axonal head injury (TAI) patient in a coma for one month responded within four days of secretome therapy and further improved and became fully alert four days after mesenchymal stem cell treatment.

INTRODUCTION

Traumatic axonal injury (TAI) is a head injury condition, formerly known as diffuse axonal injury, described as the presence of multiple scattered lesions that may be either haemorrhagic or non-haemorrhagic. These lesions are accompanied by brain swelling and are primarily located in a restricted distribution within the white matter. TAI was initially documented during the mid-twentieth century, characterised by the presence of diffuse microscopic pathological alterations in brain tissue. It was hypothesised that the lesions resulted from the direct effects of mechanical forces on brain tissue following a traumatic event[1].

One of the treatment options is promoting neuronal regeneration using stem cell derived therapy. The beneficial effects of stem cells are conventionally believed to be based on two fundamental principles. Stem cells are being used to repair injured tissues as they migrate to the site of injury, can differentiate into various cell types and secrete other paracrine bioactive factors. However, with stem cell therapy there may be immunological incompatibility, tumorigenicity and transmission of infections. Recent studies suggest that it is the paracrine factors secreted from stem cells that are mainly responsible for their therapeutic effects; these paracrine factors are collectively termed the secretome and can be individually isolated for therapeutic purposes[2]. It is widely believed that stem cells have the capacity for direct cell replacement and secrete neurotrophic substances, thereby boosting the process of neural regeneration[3].

Mesenchymal stem cell and secretome have been used in strokes[1,4] and traumatic brain injury[5]. However, no study has been conducted on the use of stem cells in a TAI inpatient setting. This report presents a case that highlights the potential of stem cell therapy for treating TAI.

CASE DESCRIPTION

A 17-year-old boy sustained severe head injuries due to repeated blows to the head. He lost consciousness and was then immediately brought to the emergency department. The Glasgow Coma Score was 3; he was immediately intubated (E1M2V). Neurological examinations showed he was in coma state, with no other neurological deficits; he underwent a head computed tomography (CT) scan without contrast. The CT scan result showed cerebral oedema without haemorrhagic lesion *(Fig. 1)*. He was then admitted to the intensive care unit. The next day, he underwent an MRI scan, and the T2-weighted axial FLAIR showed two hyperintensity lesions at the body of right corpus callosum *(Fig. 2)*. These findings are consisted with the suspected diagnosis of diffuse (traumatic) axonal injury grade II.

After several days with the best medical therapy but no improvement, he underwent a control MRI scan. Diffusion tensor imaging showed no abnormalities; however, T2-weighted sagittal FLAIR showed remain hyperintensity at corpus callosum body *(Fig. 3)*. Subsequently, the family agreed to the administration of secretome at day 30, followed by allogeneic umbilical cord mesenchymal stem cells (UCMSCs) therapy at day 50 of hospitalisation. UCMSCs provided by the manufacturer Regenic Stem Cell are authorised by the Indonesia Food and Drugs Authority (BPOM) for the manufacturing and quality control of cell-based medicinal products for advanced therapies. The secretome was given

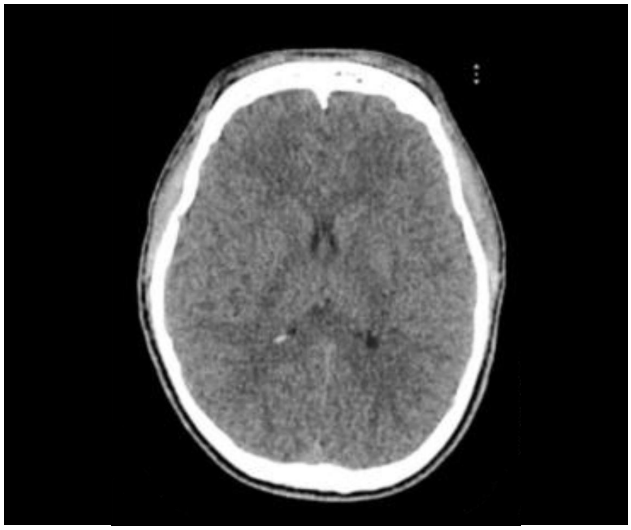

Figure 1. Computed tomography (CT) scan showed cerebral edema without hemorrhagic lesion.

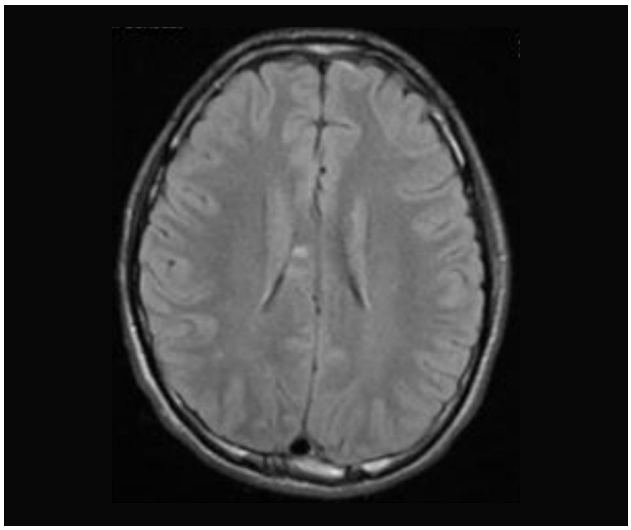

Figure 2. T2-weighted axial FLAIR showed two hyperintensity lesions at the body of right corpus callosum and diagnosed of diffuse (traumatic) axonal injury grade II.

each day intravenously for 14 days. On the fourth day of administration, the patient began to show significant improvement in that he regained consciousness with good eye contact, but dysphagia and dysphonia remained. Four days after stopping secretome administration, he was given UCMSCs intravenously (single dose of 2×10^6 cells per kilogram body weight) and showed more improvement in terms of motor and speaking through a tracheostomy speaking valve. The T2-weighted axial sagittal FLAIR imaging showed no hyperintensity at the body of corpus callosum *(Fig. 4)*. On day 2 after administration of UCMSCs there was adequate contact response and attention, as well as concentration and communications, so we removed the tracheostomy. On day 4 the patient was fully alert and able to communicate and stand without assistance; on day 6 he was able to eat by himself and walk with rollator walker. The next day he was discharged from the hospital without neurological deficits.

DISCUSSION

In the 1980s, Adams introduced the term diffuse axonal injury, defining it as a prolonged loss of consciousness

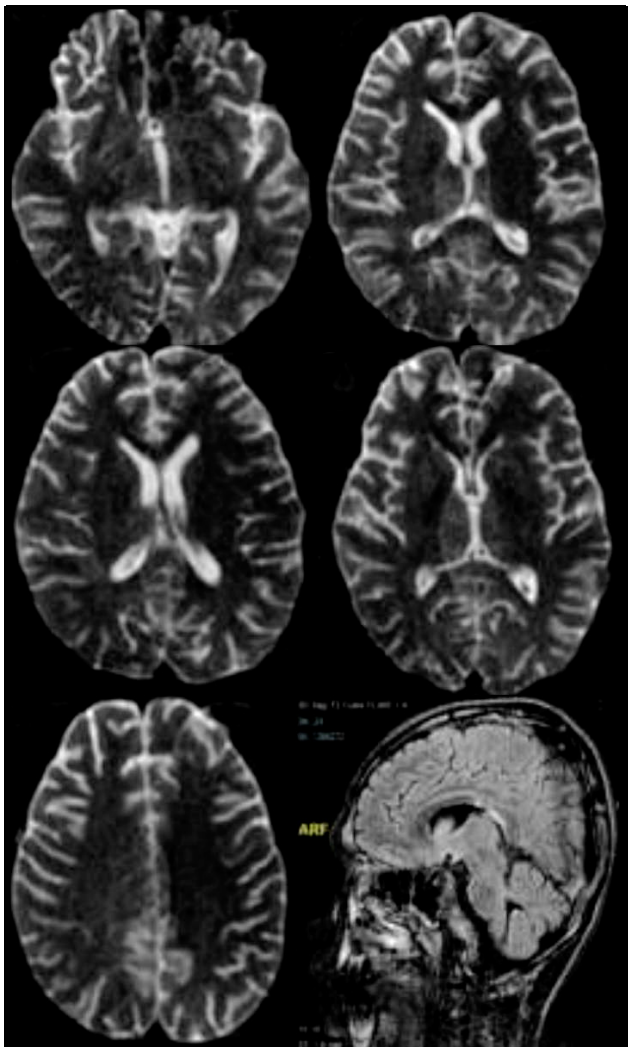

Figure 3. Diffusion tensor imaging (DTI) showed no abnormalities, however, T2-weighted sagittal FLAIR showed similar hyperintensity at body of corpus callosum.

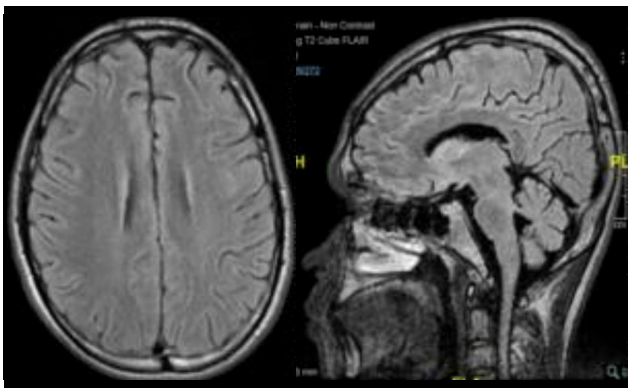

Figure 4. T2-weighted axial dan sagittal FLAIR showed no hyperintensity at the body of corpus callosum after 5 days after administration of UCMSCs.

lasting more than 6 hours, without the presence of a visible mass lesion[6]. Recent studies proposed the term traumatic axonal injury (TAI) to clearly differentiate between diffuse axonal injury caused by trauma and that resulting from non-traumatic factors. TAI is described as the presence of multiple, scattered lesions that may be either haemorrhagic or non-haemorrhagic. These lesions are accompanied by brain swelling and are primarily located in a restricted distribution within the white matter. Furthermore, the condition is linked to impaired axoplasmic transport, axonal swelling and disconnection[1].

The pathophysiology of TAI remains unclear because of lack of unifying theory. It is theorised that not only is direct mechanical injury the cause of primary damage but biochemical changes in neuronal metabolism also play a role as secondary damage. Regarding mechanical injury, two primary mechanisms have been identified: direct impact and acceleration-deceleration. The latter mechanism causes shearing and tearing of axonal fibres, leading to TAI. The direct injury is also called primary axotomy. However, in cases when the inertial forces show low amplitude and fail to cause complete primary axotomy, they may yet possess sufficient strength to cause partial axonal injury. This, in turn, might initiate a molecular cascade leading to what is currently referred to as secondary axotomy[7]. Therefore, primary axotomy refers to a mechanical injury caused by shearing forces. In contrast, secondary axotomy is an apoptotic or neurodegenerative process that results in the subsequent loss of axons following a traumatic incident.

The key factor contributing to secondary axotomy is the presence of axonal microtubules, which serve as pathways for intracellular transport and facilitate energy-dependent, directional movement within the cell. Additionally, there is an increased level of intracellular calcium ions, which can be attributed to various mechanisms such as the activation of calcium ATPase, the release of calcium stored within the axon, and the mechanical dysfunction of voltage-gated sodium channels. Increased levels of intracellular calcium have been observed to induce several intracellular mechanisms that ultimately result in cellular death[8]. Clinically, the hallmark of TAI is prolonged loss of consciousness in the absence of a

visible mass lesion. This may be caused by minor rotational forces exerting a transverse effect on the brainstem. Biomechanically, the relationship between the plane of the brainstem and the rotating force may influence both the incidence and duration of loss of consciousness[9].

MRI is the imaging method most often used for diagnosing TAI, as TAI lesions may be easily missed with conventional CT scans. Additionally, MRI exhibits greater sensitivity in detecting lesions in the brainstem and deep white matter, hence enhancing its capacity to diagnose axonal injury in comparison to CT[10]. The MRI sequence considered the gold standard in diagnosing TAI is susceptibility weighted imaging, due to its higher sensitivity compared to the gradient echo sequence, making it more effective for early detection of TAI. Hyperintensities on T2-weighted FLAIR images are also useful for diagnosing TAI. In this study, imaging findings revealed hyperintensities at the body of the corpus callosum on T2-weighted FLAIR sequences, consistent with a diagnosis of diffuse (traumatic) axonal injury grade II. Histopathologically, traditional findings in TAI include large axonal dilations due to complete axotomy, known as retraction bulbs. Recent studies have shown that beta-amyloid precursor protein accumulation is a highly sensitive marker for detecting TAI, becoming detectable within 2 hours post-trauma. Therefore, this is considered the gold standard for the pathological diagnosis of TAI[11].

The primary approach to managing TAI primarily involves addressing the fundamental issues associated with both focal and systemic injuries. Currently, there are no therapeutic options specifically designed for TAI. The administration of treatment follows the Guidelines for the Management of Severe Traumatic Brain Injury[11]. Recent studies show potential therapeutic options based on the molecular theory mentioned above; two main therapeutic options can be identified. There are two distinct types of therapeutic approaches: secondary axotomy-targeted therapy, and promotion of neural regeneration. The therapeutic approach of secondary axotomy-targeted therapy is centred on its underlying pathophysiology. As a result several treatments, such as nimodipine as a calcium channel blocker and paclitaxel as a microtubule stabilising agent, have been extensively investigated in various studies[12].

Multiple treatment options that promote neuronal regeneration, including stem cell therapy, have been reported. The beneficial effects of stem cells are generally postulated to be centred on two fundamental principles. It is widely believed that stem cells have the ability for direct cell replacement and secrete neurotrophic substances, thereby facilitating the process of neural regeneration. In the context of therapeutic angiogenesis, stem cells proposed as potentially beneficial for treatment include embryonic stem cells, neural stem cells and bone marrow-derived stem cells. The use of neural stem cells has been linked to improved motor recovery and cognitive function, as demonstrated by previous studies. The use of bone marrow-derived stem cells resulted in a notable improvement in functional outcomes[13].

We gave the patient both secretome and stem cell therapy, because of its maintenance effect; since secretome has a short half-life in the body, continuing with the living cells can exert the therapeutic effects for a longer period[5].

CONCLUSION

This study demonstrated that the administration of secretome and UCMSCs is believed to have the ability for release of paracrine factors, modulating microglia (inflammation) activation, thereby augmenting the brain repair; this resulted in notable improvements in motor and functional outcomes. Consequently, we conclude that this therapy is efficacious for cases of TAI.

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