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Systematic Review

Stem Cell Therapy in Treatment of Traumatic Brain Injury: A Systematic Review

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Abstract

Introduction: Cell therapy is broadly applied to the cure of the majority of diseases, particularly Traumatic Brain Injury) TBI). The study aimed to review stem cell therapy in the treatment of TBI.

Method: Online databases such as Scopus, ISI Web of Knowledge, and PubMed were searched. Keywords used were traumatic brain injury, cell therapy, and human neural stem cells. Two reviewer authors individually searched and assessed the abstracts and titles; a third reviewer resolved disagreements. Data documented cited study location, type of complications, various traumatic brain injuries and type of neural stem cell, and cell transplantation.

Results: Seven studies, including two studies regarding stem cell therapy after chronic TBI, one study about the Treatment of Severe Adult Traumatic Brain Injury using Bone Marrow Mononuclear Cells, and four records about Transplantation and Migrate Stem Cells were included. Treating severe adult traumatic brain injury using an intravenously delivered autologous bone marrow mononuclear cell infusion proved safe and logistically feasible. Inflammatory biomarkers are downregulated after cell infusion. Data indicated that Stem Cells migrate to sites of TBI damage and that their presence correlates with cognitive improvement. The results validated the potential of Cryobanked Human Neural Stem Cells to improve function after TBI and demonstrate long-term bio-banking effects.

Conclusion: Mature stem cells have demonstrated prospective novel situations for TBI Cell therapy. Novel approaches could use biological matrices that allow cell survival and separation of grafted stem cells in excellent ratios compared to standard treatment.

Keywords: Traumatic Brain Injury; Cell Therapy; Stem Cell Therapy.

Introduction

A prominent cause of mortality and inability is Traumatic brain injury (TBI). The evaluated world occurrence of sharp TBI in 2016 was 27 million cases, and The World Health Organization (WHO) assesses about 69 million (95% CI 64–74 million) [1]. The primary causes of TBI are war, assaults, car accidents, violence, falls, sports-related injuries, and transportation-related [2,3,4]. The TBI has two phases: first and second phase. The first phase is pertained to the imposed injury at the time of damage and is considered in many cases. However, the first injury is followed by many times of second damage that severity of the primary insult, creating the central part of weave death. Secondary injury, the target of most therapy strategies, is caused by many factors. These factors include oxidative stress, apoptosis, axonal degeneration, excitotoxicity, mitochondrial dysfunction, and neuroinflammation. Whereas the systems of the second injury usually harm the damaged environment, a document is for activating some central nervous system ancestor tanks with potential remaking capabilities [2,3,4]. The secondary damage contains a mixed cascade of cellular and molecular statuses, comprising oxidative stress, toxicity, mitochondria abnormality in function, swelling, and blood-brain dam infraction responsible for futurity fatality/necrosis of brain weave [5, 6].

TBI notably wrecks victims' self-care and is the main load on the healthcare systems world. TBI is a significant outcome of sports trauma and army-related trauma and men who never seek services healthcare [7]. Treatment TBI focuses on patient recording promptly after trauma and long-dated curative attention. Many medicines for intermediate TBI are passive in clinical examinations [8-10].

Stem cell implantation improves practical outcomes following Central Nervous System (CNS) damage [11-13]. In TBI, the grafted bone-marrow obtained mesenchymal/stromal cells have been broadly surveyed [14,15], and many clinical trials using manufactured mesenchymal stem cells have been accepted (NCT02525432, NCT02416492), in progress (NCT02028104, NCT01851083) or have been perfected (NCT00254722, NCT01575470) [16,17-21]. Although, human-grafted mesenchymal/stromal cells usually do not survive long-time in TBI gnawing mammal kinds [22-25]. The act's supposed mechanism(s) are brief-cell survival and a declining response. Cell shift and/or safe modulation or long-time graft-mediated trophic support shortage to less cell survival can obstruct the ability to assess long-time cellular stock to make proper.

Cell therapy, a new approach to treating diseases with a high load on the healthcare systems, is progressing rapidly [26]. Several studies demonstrated various aspects of this method in treating traumatic patients, especially TBI. Therefore, we aimed to review multiple aspects of stem cell therapy in treating TBI.

Methods

Online databases such as Scopus, ISI Web of Knowledge, Medline, PubMed, Wiley, Embase, International Clinical Trials Registry Platform and Clinical Trials, Cochrane Library, and Google Scholar were searched. Keywords used were traumatic brain injury, cell therapy, stem cell therapy, mesenchymal stem cells, neurogenesis, spatial learning and memory, adult neurogenesis, neural stem cells, chronic traumatic brain injury, and human neural stem cells. Elimination indicators were the existence of kind of major neurologic illness, other neurologic, neuromuscular, or orthopedic ill that restricted physical function, clinically significant results on MRI of the brain that did not belong to TBI, and confirmative results on tests for hidden malignancy unless a nonmalignant cause. Differences variations of the search words were used to reach the most amount of literature (Figure1).

Data searches were done by two authors independently. Then, the same two authors independently reviewed the full-text studies, and the list of papers was completed without disagreement. The final documents selected were then cross-verified by the 3rd reviewer. The authors' agreement reached 90%. Data were documented regarding study location, study design, type of complications, number of patients, various types of traumatic brain injury and type of neural stem cell, and cell transplantation (Table1).

Results

Of 256 enrolled patients, three died during the first post-operation period, one due to Ischemic Heart Disease (IHD), one due to pulmonary emboli, and one because of CMV infection. Patients' demographics and health factors are illustrated in Table 1 Records identified through database searching in this review was 15000. Then Records, after duplicates were removed and screened to be included in quantitative synthesis, were seven studies. Seven studies include two investigations about stem cells therapy and cell remedy past old Traumatic Brain Injury, one study about the Treatment of Severe Adult Traumatic Brain Injury using Bone Marrow Mononuclear Cells, and four records about Transplantation and Migrate Stem Cells were included in the study. The main stem cell treatment and cell remedy in traumatic brain injury were to improve function after TBI and demonstrate that long-term bio-banking of cells and thawing aliquots before use may be suitable for clinical deployment. One of the significant results was no dose-restricting toxicities or mortalities, and 100% of patients experienced therapy-urgent harmful incidents versus 93.3% of the control group. In the laboratory, cells of the circumventricular organs construct glial markers, neurospheres, and present neural [27,28]. Specifically, CVOs [28], along the meninges and the third and fourth ventricles [18], have been defined as novel stem cell centers in the adult brain.

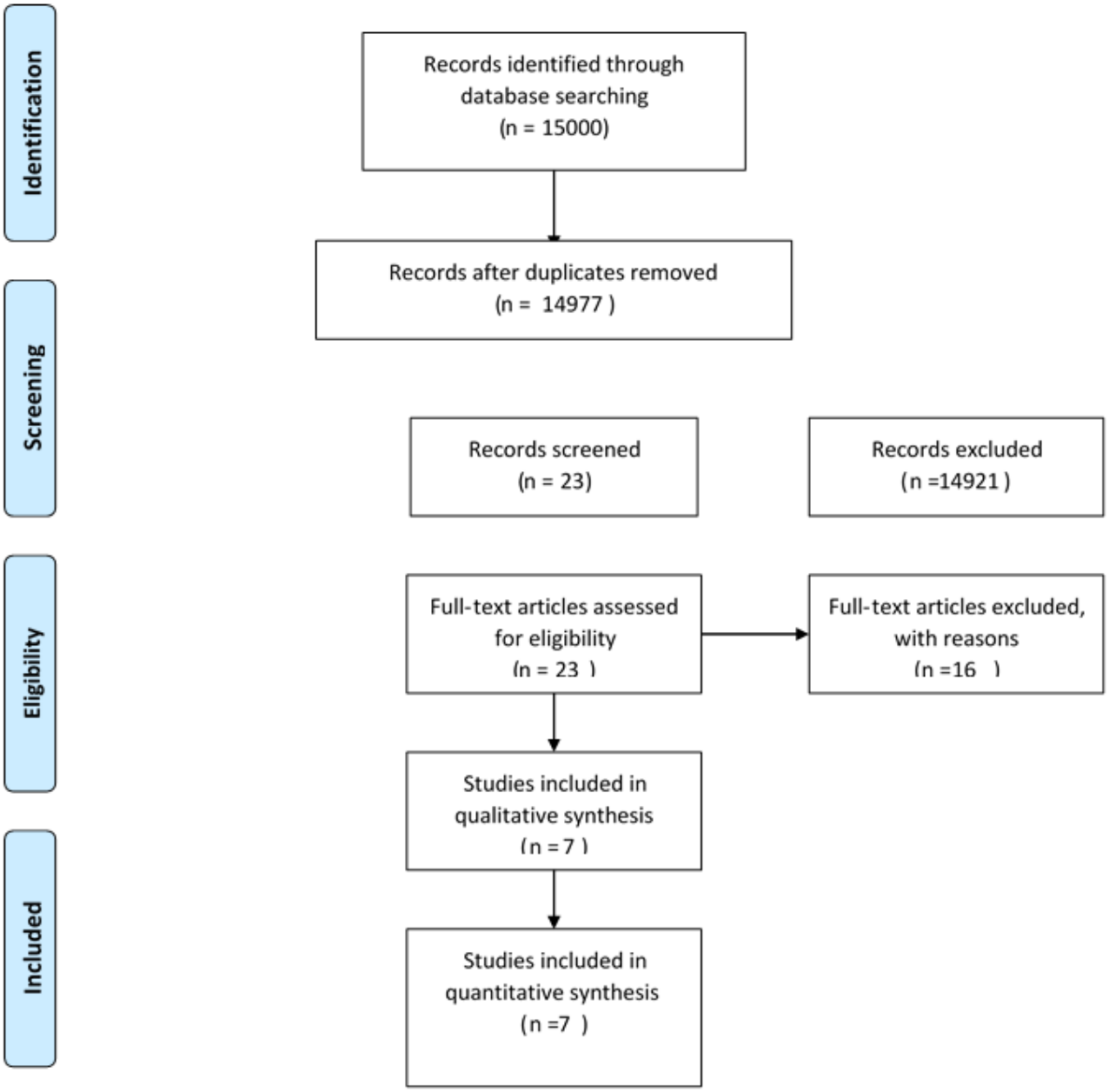

Figure 1: PRISMA flow chart of the study

Table 1: The reviewed studies in this study.

No	Athours	Title	Year	Result
1	Anna Badner et, al.	Freshly Thawed Cryobanked Human Neural Stem Cells Engraft within Endogenous Neurogenic Niches and Restore Cognitive Function after Chronic Traumatic Brain Injury	2021	NSCs have been previously reported to home to the neurovascular niche in a stromalderived factor 1alpha (SDF1alpha) and CXCR4 dependent manner. Consistent with this pathway, Shef-6.0 hNSCs were found to express CXCR4 and exhibited a significant chemotactic response to SDF1alpha at 100–200 ng in vitro. The findings validate the potential of hNSCs to improve function after TBI and demonstrate that long-term biobanking of cells and thawing aliquots before use may be suitable for clinical deployment.
2	Masahito Kawabori et al.	Cell Therapy for Chronic TBI	2021	The primary efficacy endpoint of significant improvement from baseline of Fugl-Meyer Motor Scale score at 6 months for SB623-treated patients was achieved. SB623-treated patients improved by (least square [LS] mean) 8.3 (standard error 1.4) vs 2.3 (standard error 2.5) for control at 6months, the LSmean difference was 6.0 (95% confidence interval 0.3–11.8, p = 0.040). Secondary efficacy endpoints improved from baseline but were not statistically significant vs control at 6 months. There were no dose-limiting toxicities or deaths, and 100% of SB623-treated patients experienced treatment-emergent adverse events vs 93.3% of control patients (p = 0.25).
3	Margarita Gutova et al.	Intranasally Administered L-Myc-Immortalized Human Neural Stem Cells Migrate to Primary and Distal Sites of Damage after Cortical Impact and Enhance Spatial Learning	2021	The data indicate that IN-administered LM-NSC008 cells migrate to sites of TBI damage and that their presence correlates with cognitive improvement.
4	Rami Ahmad Shahror et, al.	Transplantation of Mesenchymal Stem Cells Overexpressing Fibroblast Growth Factor 21 Facilitates Cognitive Recovery and Enhances Neurogenesis in a Mouse Model of Traumatic Brain Injury	2020	MSC-FGF21 treatment significantly improved TBI-induced spatial memory deficits, impaired hippocampal neurogenesis, and abnormal dendritic morphology.
5	Aditi Falnikar et al.	Differential Response in Novel Stem Cell Niches of the Brain after Cervical Spinal Cord Injury and Traumatic Brain Injury	2018	The CCI induced a pronounced increase in Sox2- and doublecortin-labeled cells in the AP and Iba1-labeled microglia in the SFO. Lastly, plasma derived from CCI animals significantly increased NSC expansion in an in vitro neurosphere assay, whereas plasma from SCI animals did not exert such an effect, suggesting that signaling factors present in blood may be relevant to stimulating CVO niches after CNS injury and may explain the differential in vivo effects of SCI and TBI on the novel stem cell niches.
6	Stefania Beretta et, al.	Effects of Human ES-Derived Neural Stem Cell Transplantation and Kindling in a Rat Model of Traumatic Brain Injury	2017	Shef6-derived hNSCs may be beneficial as a therapy for TBI, but not in animals or patients with posttraumatic hyperexcitability.
7	Charles s cox Jr et, al.	Treatment of Severe Adult Traumatic Brain Injury Using Bone Marrow Mononuclear Cells	2016	Despite the treatment group having greater injury severity, there was structural preservation of critical regions of interest that correlated with functional outcomes. Key inflammatory cytokines were downregulated. Treatment of severe, adult traumatic brain injury using an intravenously delivered autologous bone marrow mononuclear cell infusion is safe and logistically feasible. There appears to be a treatment signal as evidenced by central nervous system structural preservation, consistent with previous pediatric trial data. Inflammatory biomarkers are downregulated after cell infusion.

This CVO-achieved Sox2+ proliferated progenitors, mainly in the situation after trauma, showed doublecortin explanation four daytimes following trauma, showing neuronal potential. At the same time, their effects on cognitive development stay to be evaluated. The CVOs showed increased proliferative response to TBI (including the median eminence, position posttraumatic, and subfornical organ) [29]. Also,

meningeal forefathers have been evaluated in reply to ischemia [30], spinal cord trauma [21], and increased ataxia [31]. The datum determines that meningeal makers can make neurons. Recent acts have displayed Graft of exogenous human neurotic stem cells with the meninges following TBI, highpoint a possible interplay among endo and exogenous forefathers in this place [32]. Mesenchymal stem/stromal cells (MSCs) are trilineage forefathers, identified by their capability to stick to plastic and transform into chondroblasts, osteoblasts, also adipocytes [33]. It has been determined to have potent ant-inflammatory actions, usually by trophic assistance. Mesenchymal stem/stromal cells have been role in leading endogenous the growth and development of nervous tissue [34].

Anna Badner et al. (2021) reported that newly de-freeze cryobank human nervous stem cells graft in innate Neurogenic places restitute Cognitive performance after Chronic Brain Injury.

The findings accredit the possibility of hNSCs to better action after TBI and show long-term biobanking of cells and thawing aliquots before applying them to clinical deployment [32].

Masahito Kawabori et al. (2021) demonstrated cell Therapy for Chronic TBI. The early efficacy endstage of considerable recovery from foundation line Fugl-Meyer Motor Scale privilege at six months for SB623 - heald patients was achieved. There were no dose-limiting poisonousness or mortalities. All patients cured with SB623 experienced more adverse events than 93.3% of control patients. Patients cured with SB623 recovered with (least square [LS] mean) 8.3 (standard deviation 1.4) than 2.3 (standard deviation 2.5) to rein in six months. Sec efficacy endstages recovered from baseline but were not using statistics more meaningful than control at six months [35]. Margarita Gutova et al. (2021) evaluated intranasally Administered L-Myc-Immortalized Human Neural Stem Cells Migrate to early and Distal areas of trauma after Cortical strike and Raise Spatial Learning. The data show that IN-administered LM-NSC008 cells migrate to sites of TBI injury and that their presence correlates with cognitive recovery [36].

Rami Ahmad Shahror et al. (2020) reported transplantation of Mesenchymal Stem Cells overexpressing Fibroblast Increase Factor 21 Facilitates Cognitive improvement and raises Neurogenesis in a Mouse Model of Traumatic Brain Injury. MSC-FGF21 remedies significantly better TBI-induced spatial memory deficiencies, abnormal dendritic morphology, and impaired hippocampal neurogenesis [37].

Aditi Falnikar et al. (2018) introduced Differential Response in Novel Stem Cell Niches of the Brain after Cervical Spinal Cord Injury and Traumatic Brain Injury. The CCI caused a pronounced growth in Sox2- and doublecortin-labeled cells in the AP and Iba1-labeled microglia in the SFO. Finally, plasma from CCI animals considerably grew NSC development in an in vitro neurosphere assay. While plasma gained from SCI animals did not put on such an outcome. It indicates that signaling agents stocked in the blood may be related to stimulating CVO niches post-CNS trauma and may illustrate SCI and TBI's disparate in vivo outcomes on the new stem cell niches [38].

Stefania Beretta et al. (2017) reported Results of Human ES-gained nervous Stem Cell grafting and sorting at a Rat pattern in Traumatic Brain Injury. Shef6-gained hNSCs may be a proper treatment for TBI but not in animals or patients with after-injury hyperexcitability [39].

Charles s cox Jr et al. (2016) explained the therapy of Severe Adult TBI by applying Bone Marrow Mononuclear Cells. Contrary to the therapy group having greater trauma severity, there was the structural keeping of critical areas of significance related to functional results. The primary inflammatory cytokines were decreased. Treating severe adult TBI applies cell injection is secure and logistically possible. There becomes visible to be a therapy signal as documented by central nervous system structural maintenance, constant with past pediatric trial data. Inflammatory biomarkers are decreased by one-time cell injection [40].

Discussion

Cell treatment, including mature SCs, in connection with novel meanings about the facility of the wake of the mature, neurotic structure, has put on prospective novel situations for the therapy of traumas [41-42]. Trauma Brain Injury is identified to factor inabilities in cognitive processes, memory, emotion, sensation, and movement in rats and humans [43] with a high occurrence in the population. Although these results show promise, later research is required. The rate of the brain ulcers and their mutability is ascertained by the requirements to

detect intermittent to raise cell survivorship and segregation of the implanted SCs. TBIs account for 20% of indicative epilepsy in the general civilian population, and 10% of the people with severe TBI exhibit PTE [44]. Many studies have reported acute seizures and hippocampal hyperexcitability to stimulation or pro-convulsant drug exposure in TBI models. But a few previous studies have survived an animal model of spontaneous chronic seizures post-experimental head trauma [45].

TBI studies in bestial patterns to today have centralized on short-time (hours to days) histologic and demeanor results [46]. Whereas such research is possibly instructive to evaluate the hot answer to different forms of intermediation, the study must thoroughly survey prolonged treatment effectiveness and certify that every demeanor achievement is caused by therapy and not automatic improvement [22]. Stem Cells transplantation in Innard neurogenesis places and reinstate Cognitive Performance Post- Chronic TBI had been done by Shi et al. in which a multitude of methods was used to optimize the migration, delivery, and differentiation of human umbilical cord mesenchymal stem cells (hUCMSCs) in a rat pattern of scalpel cavitation pattern of TBI [25,26,37,39,47]. CXCR4, a gene corresponding to stem cell migration, was shifted to these cells to ensure suitable migration of hUCMSCs, as shown by Son et al. [48]. The cells were maintained along with operated astrocytes to trigger the proliferation of hUCMSCsCXCR4 [49].

Both cell types were cultured in a new biomaterial engraft system, R-B-SPH (RADA16- BDNF self-assembling peptide hydrogel scaffold). This mix of astrocytes and hUCMSCs displayed higher levels of growth survival, differentiation of neurons, and the shape of synapses. These data confirmed Anna Badner et al. (2021) report about NSCs have been previously reported to be home to the neurovascular niche in a stromal-derived agent 1alpha (SDF1alpha) and CXCR4-dependent way.

The studies showed the potential of hNSCs to increase function post-TBI and exhibit that long-term biobanking of cells and thawing aliquots before application may be proper for clinical deployment. Masahito Kawabori et al. (2021) [35], Gutova M et al. (2021) [36], and Charles et al. (2016) explained using SB623 cells in therapy for severe adult TBI. MSC-FGF21 treatment significantly improved TBI-induced spatial memory deficits, impaired hippocampal neurogenesis, and abnormal dendritic morphology [37]. The CCI induced a pronounced increase in Sox2- and doublecortin-labeled cells in the AP and Iba1-labeled microglia in the SFO. Lastly, plasma-derived from CCI animals significantly increased NSC expansion in an in vitro neurosphere assay.

In contrast, plasma from SCI animals did not exert such an effect, suggesting that signaling factors present in the blood may be relevant to stimulating CVO niches after CNS injury and may explain the differential in vivo impact of SCI and TBI on the novel stem cell niches [38]. Shef6-derived hNSCs may be beneficial as a therapy for TBI, but not in animals or patients with posttraumatic hyperexcitability [39]. Despite the treatment group having greater injury severity, structural preservation of critical regions of interest correlated with functional outcomes. Vital inflammatory cytokines were downregulated. Treatment of severe adult traumatic brain injury using an intravenously delivered autologous bone marrow mononuclear cell infusion is safe and logistically feasible. There appears to be a treatment signal consistent with previous pediatric trial data, as evidenced by central nervous system structural preservation. Inflammatory biomarkers are downregulated after cell infusion [40].

The SB623 cells are mature bone marrow cells infected with transitory passway with a plasmid construct encoding the intracellular domain of human Notch-1. The first outcome was assessing the motor functions by applying the Fugl–Meyer Motor Scale (FMMS) from base to six months in SB623 patients contrasted to the control group. Clinical trials in the chronic impact that utilized forced apply, limitation-induced, and cultured stem cell therapies used an MCID for the total FMMS of ≥10 points. Although, this was not regulated for base FMMS and did not mirror the relative degree of recovery. The result reflects the transition from partial to complete volitional move and reaction activity, illustrating a meaningful recovery in upper and lower physical function in a patient with a base FMMS score of 52 [50-52].

Schepici G et al. (2020) evaluated using stem cell-based therapy in TBI. They assessed the safety and efficacy of stem cells in this disease through a review study. They reported that the results known so far are rare; thus, forthcoming studies are required to evaluate stem cell transplantation's safety and efficacy in TBI [53].

Conclusion

Trauma Brain Injury is a very rolled disease. No well-known effective therapies are capable decrease the results of brain trauma. Cell treatments have been shown as valuable equipment that could reduce acts of TBI. That treatments lead to security and have appeared the potency to better neurologic and physical performances in TBI. Cell treatment, including mature SCs, in connection with novel meanings about the facility of the wake of the mature, neurotic structure, has put on prospective novel situations for the therapy of TBI. Any growth in this context, as in several other fields of study of the nervous system, will need cooperation among baseline and clinical scholars and clinic scholars. Scientific and tentative research are required to turn on the procedures by which stem cell treatments advance improvement sequent TBI to assess the convincingness of treatments. Future results and later studies will be needed to accomplish the application of cell implantation for TBI administration. Therefore, brain injury extent and variation are determinatives in cell treatment action. Novel viable ways could be the application of biological activity matrices. This permits cell survivorship and segregation of inserted stem cells in larger ratios toward the usual treatment.

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Conflict of Interest Disclosures

Authors have not any conflict of interest.

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Authors' Contributions

All authors contributed equally to accomplishing this study.

Ethical Statement

Department of Neurosurgery, Baqiyatallah University of Medical Sciences Confirmed protocol of this study.

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