Cellular therapy for traumatic brain injury in adults: a meta-analysis of controlled clinical trials

Mujahid Alizada[1,2], Shu Lin[2,3]*, Jinxiang Wu[4], Mirwais Alizada[5], James Reeves Mbori Ngwayi[6], Muhebullah Alizada[7], Hongzhi Gao[1]*

[1]Department of Neurosurgery, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China
[2]Centre of Neurological and Metabolic Research, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China
[3]Diabetes and Metabolism Division, Garvan Institute of Medical Research, Sydney, Australia
[4]Department of Reproductive Medicine, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China
[5]Department of Orthopedics, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China
[6]Department of Orthopedics, Ipswich Hospital, Ipswich IP4 5PD, United Kingdom
[7]Department of Interventional Radiology, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China

***Corresponding authors:**
Prof. Shu Lin
Centre of Neurological and Metabolic Research
The Second Affiliated Hospital of Fujian Medical University
Quanzhou, Fujian Province
E-mail: shulin1956@126.com, shulin1956@126.com

Prof. Hongzhi Gao
Department of Neurosurgery
The Second Affiliated Hospital of Fujian Medical University
Quanzhou, Fujian Province
China
E-mail: gaohongzhi@fjmu.edu.cn

Submitted: 6 July 2024; **Accepted:** 12 October 2024
Online publication: 26 October 2024

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/194535
Copyright © 2024 Termedia & Banach

Abstract

Introduction: Traumatic brain injury (TBI) lacks effective clinical treatment. Cellular therapy, which is the transfer of autologous or allogeneic cells or cellular material into the patient(s) for treatment or prevention of disease, has shown better outcomes in TBI in several clinical and preclinical studies. We performed a meta-analysis to synthesize and evaluate the current evidence on cellular therapy for TBI in adult patients.

Material and methods: We performed a meta-analysis on published articles on the topic of cellular therapy for the treatment of TBI in adult patients. The literature search was conducted via PubMed, China National Knowledge Infrastructure (CNKI), Cochrane Library, Embase, Wan Fang Data and Google Scholar, with no restrictions on publication year. Studies were included based on selection criteria and quality assessment. The following data were extracted from included articles: author names; publication year and place; type of study; number, sex and age of participants; type of cells used; and post-treatment follow-up. The required data related to the Fugl-Meyer Motor Scale (FMMS), the Disability Rating Scale (DRS), and patients' overall improvement were pooled and analyzed using RevMan (Ver. 5.4.1).

Results: Five studies that met the selection criteria and considered as high quality, containing 367 participants, with an average follow-up time of 7.58 ±6.93 months, were included in the meta-analysis. The results showed that cellular therapy significantly improved (OR = 0.26; 95% CI = 0.15 to 0.48; p = 0.0001) the overall performance of the patients. While improvements in the FMMS (MD = 3.79; 95% CI = –2.53 to 10.10; p = 0.24) and DRS (MD = –0.16; 95% CI = –1.51 to 1.19; p = 0.82) were not statistically significant, they may still be clinically significant.

Conclusions: This meta-analysis suggests that cellular therapy improves the clinical condition of TBI patients. Larger, multicenter clinical trials are required to further confirm these findings and clarify the optimal use of stem cells in TBI.

Key words: traumatic brain injury, stem cells, progenitor cells, transplantation, clinical trial.

Creative Commons licenses: This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY -NC -SA 4.0). License (http://creativecommons.org/licenses/by-nc-sa/4.0/).

Introduction

Traumatic brain injury (TBI) is mainly caused by external physical insults to the brain, which may lead to alterations in consciousness, of the mental or physical state of the patient [1]. TBI remains one of the principal causes of deaths and disabilities with almost ten million victims worldwide each year [2, 3]. Nearly 2.5 million Americans suffer from the tragic consequences of TBI. These patients live with impairment in sensory, motor, behavioral, or cognitive functions. The incidence rate for moderate and severe TBI in children has not improved in the last 10 years, with disappointing outcomes for those with severe injures [4–6].

The World Health Organization warns that along with the human loss, TBI is one of the top financial burdens on health-providing platforms [2, 7]. The damage that occurs during the primary impact is referred to as the "primary injury", whereas the damage secondary to the initial insult via cellular, physiological, and biochemical events is referred to as "secondary injury" [8]. Brain edema followed by increased intracranial pressure (ICP) is the characteristic of many neurosurgical diseases. An extreme ICP is believed to be the main cause of death in such patients. The drug of choice to decrease an acute ICP is mannitol or hypertonic saline [9, 10].

The current treatment options for TBI, such as hyperbaric oxygenation, rehabilitation and brain stimulation are only of supportive nature; therefore, it is necessary to seek an absolute therapeutic option [11, 12]. Considering the complex pathomechanism of TBI, a treatment that could maintain or restore the function of injured neurons would be the best approach. Progenitor cells are of great importance in this regard due to their plasticity, migration, and self-renewal capacity [13, 14]. Recently cellular therapy has gained a particular interest in various diseases, such as cerebral palsy, TBI, stroke, spinal cord injury, and autism [15–17].

Several types of cells, such as bone marrow derived stem cells, neural stem cells (NSCs), embryonic cells, pluripotent cells and umbilical cord blood cells, have improved TBI in different animal models [18–21]. The way transplanted cells help to repair TBI might be via replacing the damaged cells through proliferation and differentiation, or by secreting trophic factors to cause endogenous repair [22]. As cell transplantation for TBI is not only studied in preclinical models, but also tried in various clinical trials, we decided to perform a meta-analysis on the effects of cellular therapy for TBI in adult patients.

Material and methods

This meta-analysis is compliant with PRISMA 2020, and follows a previously described protocol [23].

Search strategy

A systemic search was conducted on PubMed, China National Knowledge Infrastructure (CNKI), Cochrane Library, Embase, Wan Fang Data and Google Scholar using the search terms "traumatic brain injury", "cellular therapy", and "clinical trial" for articles published in English language prior to May 2024. Two researchers independently examined the titles and abstracts of all searched records and excluded those that did not meet eligibility criteria.

Inclusion criteria

The studies were included if they met the following criteria: (1) the main focus of the study was on cellular therapy for TBI; (2) original, controlled clinical trial research article; (3) adult patients aged 18 years or over; (4) full text article available.

Exclusion criteria

The studies were excluded if they met one of the following criteria: (1) patients aged under 18 years; (2) no full text accessible; (3) no control available; (4) case report; (5) letter to editor; (6) preclinical study; (7) review article; (8) study with no quantitative data; (9) meeting abstract; (10) book chapter; (11) low-quality study.

Quality assessment

In order to assess the quality of a study, the Newcastle–Ottawa Scale (NOS) was used. In case-control trials, the NOS covers three areas – selection, exposure, and comparability – while in a cohort study it covers selection, outcome, and comparability [24]. A numbered item in exposure, outcome, or selection categories can be maximally awarded with one star, whereas a maximum of two stars can be given to a numbered item in a comparability category [25]. A study can maximally receive 9 stars, and a study was considered as high quality with 6+ stars, moderate quality with 4–5 stars, and low quality with less than 4 stars [26].

Data extraction

The following data were extracted from all included articles: first authors' names, publication year, country of research, type of study, (number, sex and age) of participants, type of cells used, and post-treatment follow-up. The extracted data were entered into a predesigned data collection sheet, and then tabulated onto a spreadsheet (Table I). Moreover, outcomes such as Fugl-Meyer Motor Scale (FMMS), Disability Rating Scale (DRS), and overall improvement of the patients were extracted and analyzed using RevMan (Ver.5.4.1). FMMS is a broadly accepted scale used in clinical practice to measure motor deficit of the affected limb(s) in

conditions such as stroke or TBI. It has a maximum score of 100, with a score of zero indicating hemiplegia, and 100 representing a normal individual [27, 28]. The DRS measures general functional changes in TBI patients. Its scores range from zero to 29, with zero representing no disability and 29 designating a profound vegetative state [27, 29].

Statistical analysis

The data were analyzed using RevMan (Ver.5.4.1) software. Heterogeneity among the studies was tested, and a p-value < 0.05 or I^2 > 50% was considered to demonstrate significant heterogeneity [10]. Dichotomous data such as in "overall improvement" were expressed as odds ratio (OR) with 95% confidence interval (CI). Continuous data such as in FMMS and DRS were expressed as mean difference (MD) with 95% CI. A p-value less than 0.05 was considered to be statistically significant.

Results

Characteristics and selection of individual studies

Initially, 2553 articles were identified through database searches and reference review. The records were checked for duplicates, and 2432 articles were left after repetitive articles were removed. Screening the titles and abstracts of the remaining articles, 2413 articles were removed, 19 articles were selected to be relevant, and their full texts were accessed. The 19 full text articles were evaluated for eligibility; 6 articles had no control group, the participants of 2 articles were less than 18 years old, 2 articles contained no extractable data, 1 article was a conference abstract, and 3 articles were of low literature quality. After applying the eligibility criteria, 5 controlled clinical trials (Table II) were finally included in the meta-analysis (Figure 1). The included articles contained 367 patients, with a sample size in the range of 24 to 166.

Overall improvement of patients

Two studies [30, 31] provided data on overall improvement of the patients after cellular therapy comparing treatment and control groups. The fixed effect model was chosen based on statistically significant heterogeneity (I^2 = 75%, p = 0.04) among the studies. The pooled mean difference (MD) of overall improvement in treatment groups versus control groups was 0.26 (95% CI: 0.15 to 0.48, p = 0.0001) which indicates that the treatment significantly improves overall condition of the patients (Figure 2 A).

Fugl-Meyer Motor Scale

FMMS related information was obtained from two studies [27, 32], comparing treatment and

Table I. Summarized characteristics of studies included in meta-analysis

Study	Country	Type of study	Treatment (*n*)	Control (*n*)	Sex (M/F)	Age [years]	Type of cells used	Follow-up
Masahito Kawabori 2021	Japan	Double-blind, randomized, controlled, phase 2 clinical trial	46	15	43/18	34.4 ±11.8	Allogeneic modified bone marrow-derived MSCs (SB623 cells)	6 m
Charles S Cox Jr 2017	USA	Open label, non-randomized, controlled, phase I/IIa clinical trial	15	9	18/6	32 ±3	Autologous bone marrow mononuclear cells (BMMNCs)	6 m
Sen Wang 2013	China	Randomized, single-blind, controlled clinical trial	20	20	32/8	28.07 ±9.78	Umbilical cord mesenchymal stem cells (UCMSCs)	6 m
Chunlei Tian 2013	China	Nonrandom, open-labeled, controlled clinical trial	97	69	NA	29.5 ±7.91	Autologous bone marrow mesenchymal stem cells (BMMSCs)	14 d
Victor I. Seledtsov 2005	Russia	Randomized, controlled, clinical trial	38	38	56/20	37.70 ±11.51	Fetal brain neural & hematopoietic liver cells	(18–24) m
Total			216	151				

NA – not available, y – year, m – month, d – day, M – male, F – female.

Table II. Quality assessment of trials included in meta-analysis using Newcastle–Ottawa Scale

Study	Selection	Comparability	Outcome	Total score
Masahito Kawabori 2021	****	**	***	9/9
Charles S Cox Jr 2017	***	**	***	8/9
Sen Wang 2013	***	**	**	7/9
Chunlei Tian 2013	***	**	***	8/9
Victor I. Seledtsov 2005	***	**	**	7/9

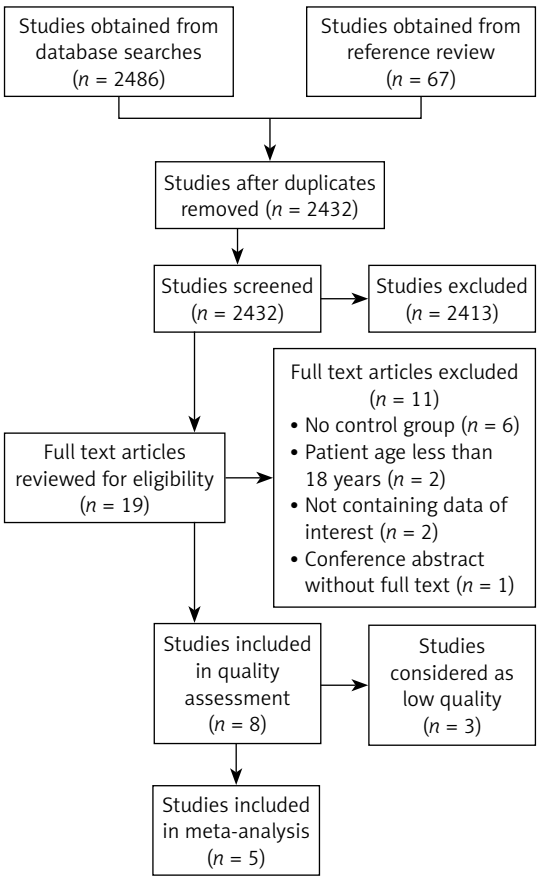


Figure 1. Flow chart showing study identification and selection strategy

control groups. Heterogeneity (I^2 = 0%, p = 0.55) across the studies was not significant based on the fixed effect model. The pooled MD of FMMS in the two groups was 3.79 (95% CI: –2.53 to 10.10, p = 0.24). Although the data show that the treatment's effect on improving motor activity is not statistically significant, it may still have clinical significance (Figure 2 B).

Disability Rating Scale

DRS was reported by two studies [27, 33], comparing treatment and control groups. There was no heterogeneity among the studies (I^2 = 0%, p = 0.90) with the fixed effect model. The pooled MD was –0.16 (95% CI: –1.51 to 1.19, p = 0.82) showing that cellular therapy does not significantly improve disability in TBI patients (Figure 2 C).

Risk of bias

To estimate the risk of publication bias, funnel plots were obtained and visually assessed for all studies included in the meta-analysis. Based on the symmetric distribution of the studies' effect sizes in the funnel plots, it was concluded that no publication bias was present (Figures 2 D–F).

Discussion

Our meta-analysis included five clinical trials covering overall outcome, motor activity and disability improvement of adult TBI patients after cell therapy. Pathophysiological events during TBI fall into two categories: primary and secondary. The biomechanical or physical insults that lead to the immediate events are followed by a flow of events such as, production of free radicals, excitotoxicity, hypoperfusion, ischemia, disturbance to cerebrovascular autoregulation, intracranial hypertension and metabolic dysfunction [34]. The flow of events that release various biological factors causes cellular death, which results in local or global cerebral atrophy [35]. Thyroid cancer stem cells (TCSCs) are interesting biomarkers and possible targets for clinical intervention since they are essential to the pathophysiology, metastasis, and therapeutic response of thyroid cancer. Numerous studies conducted in the last few years have shown a strong correlation between cancer stem cells (CSCs) and the development and progression of tumors [36]. Research findings suggest that global injury occurs more commonly, which is mainly evidenced in the frontal lobe, hypothalamus, temporal lobe, basal ganglia, corpus callosum, fornices, hippocampus, and superior cerebral peduncles [37, 38]. Salidroside can reduce both the neurological impairment score and the infarct volume of the rat brain in the focal cerebral ischemia/reperfusion injury model in rats [39]. Injury to these structures initially causes mood disorders, psychiatric deficits, depression, and neurobehavioral alterations [40].

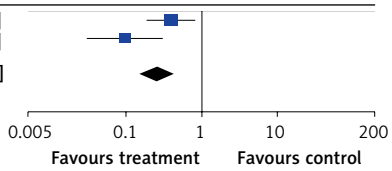
Various preclinical studies have shown the regenerative ability of stem cells in animal TBI models [41–45]. Several preclinical TBI models have

A Overall improvement

Study or subgroup	Treatment Total	Treatment Events	Control Total	Control Events	Weight (%)	Odds ratio M-H, fixed, 95% CI
Chunlei Tian 2013	59	97	55	69	55.8	0.40 [0.19, 0.81]
Victor I. Seledtsov 2005	5	38	23	38	44.2	0.10 [0.03, 0.31]
Total (95% CI)		**135**		**107**	**100.0**	**0.26 [0.15, 0.48]**
Total events	64		78			

Heterogeneity: $\chi^2 = 4.06$, $df = 1$ ($p = 0.04$); $I^2 = 75$

Test for overall effect: $Z = 4.39$ ($p < 0.0001$)

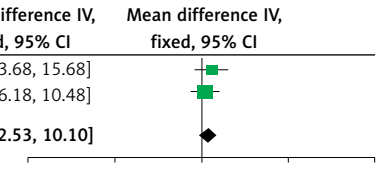


B Fugl-Meyer Motor Scale (FMMS)

Study or subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, fixed, 95% CI
Masahito Kawabori 2021	60.6	20.8	46	54.6	15	15	42.5	6.00 [–3.68, 15.68]
Sen Wang 2013	33.05	14.03	20	30.9	12.81	20	57.5	2.15 [–6.18, 10.48]
Total (95% CI)			**66**			**35**	**100.0**	**3.79 [–2.53, 10.10]**

Heterogeneity: $\chi^2 = 0.35$, $df = 1$ ($p = 0.55$); $I^2 = 0\%$

Test for overall effect: $Z = 1.18$ ($p = 0.24$)

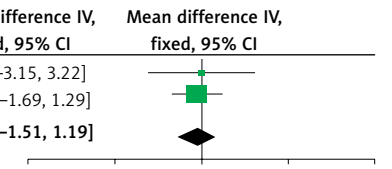


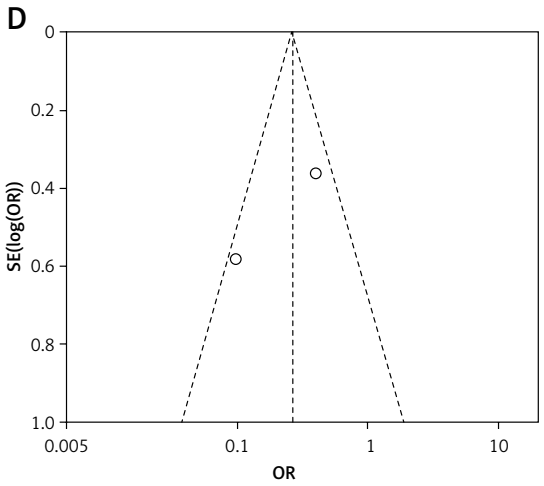
C Disability Rating Scale (DRS)

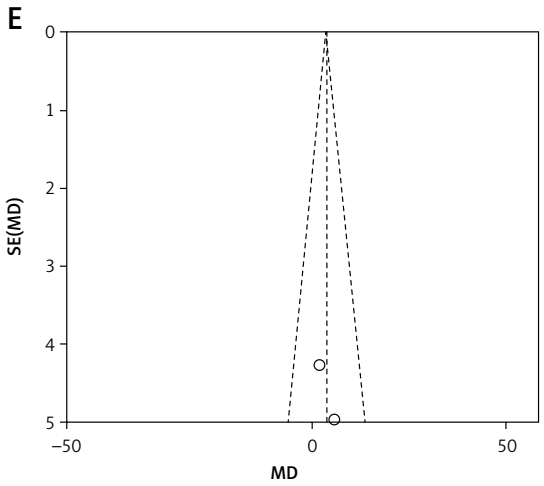
Study or subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, fixed, 95% CI
Charles S. Cox Jr 2017	4.923	2.783	13	4.889	4.285	9	17.9	0.03 [–3.15, 3.22]
Masahito Kawabori 2021	4.1	2.4	46	4.3	2.6	15	82.1	–0.20 [–1.69, 1.29]
Total (95% CI)			**59**			**24**	**100.0**	**–0.16 (–1.51, 1.19]**

Heterogeneity: $\chi^2 = 0.02$, $df = 1$ ($p = 0.90$); $I^2 = 0\%$

Test for overall effect: $Z = 0.23$ ($p = 0.82$)







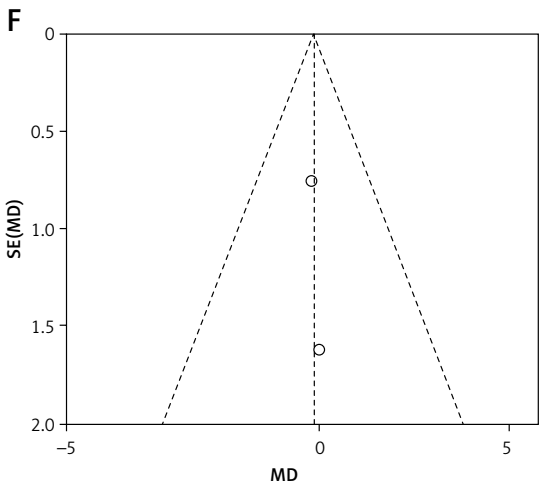


Figure 2. Forest and funnel plots of all studies included in meta-analysis. Forest plots of overall improvement (**A**), Fugl-Meyer Motor Scale (**B**), and Disability Rating Scale (**C**) comparing treatment versus control groups. Funnel plots for observing any possible publication bias in overall improvement (**D**), Fugl-Meyer Motor Scale (**E**), and Disability Rating Scale (**F**)

demonstrated improvement in motor, behavioral and cognitive functions after neural, mesenchymal, or progenitor stem cell therapy. These effects are most likely caused by production of neurotrophic factors, improvement of angiogenesis and downregulation of astrogliosis [18, 46, 47]. Treating unilateral limbal stem cell deficits has shown promise with autologous limbal epithelium transplantation [48]. When existing treatment options and accepted medical standards are inadequate, transplantology is a branch of medicine that saves lives [49]. Ma *et al.* indicated that transplanted cells significantly decrease at the early stage of transplantation. The possible reason could be the post-traumatic inflammatory cascade in the recipient brain that affects the survival of the cells [50, 51]. Zhang *et al.* applied bone marrow derived autologous mesenchymal stem cells in seven TBI patients via intracranial and intravenous route. They found that it was safe and the patients showed significant improvement in neurological functions [52]. Moreover, Cox *et al.* and Liao *et al.* also transplanted bone marrow mononuclear cells to severe TBI patients through the intravenous route, and they too reported the treatment to be safe and clinically significant [53, 54]. Histopathological damage and the CNS inflammatory response progressively resolve and return. Consequently, microglia may be one of the key targets of thermal stimulation-mediated central nervous system injury, and controlling their polarization by restricting M1 or encouraging M2 activation may develop into a viable therapeutic approach for disorders that produce heat-induced brain damage [55]. The administration of autologous bone marrow mononuclear cells to chronic TBI patients by Sharma *et al.* also improved the condition of the patients without any major side effect [1].

Studies have shown that NSC therapy improved the neurological functions in preclinical models of TBI [56–58]. Several potential mechanisms have been proposed for obtaining these effects, such as immunomodulation and restoring neuronal circuits [59], production of neurotrophic factors [60], secretion of specific neurotransmitters [61], and neuronal cell replacement [62]. Research on spinal cord injury (SCI) in animals has demonstrated that SCI causes two types of damage: mechanical damage; and secondary injury caused by neuronal apoptosis in the central nervous system (CNS), which causes the damage to spread. According to our research, the rs531564 polymorphism may cause down-regulation of miR-124, which in turn may enhance the production of BIM. This could lead to death in cells and prolong the time required for patients to recover following SCI [63]. Together, necrosis and apoptosis result in death of neurons and glia during TBI. Some preclinical studies show that NSC transplantation reduces apoptosis around the ischemic spots, resulting in functional improvement [64]. Osteoblast progenitors found in bone marrow stem cells (MSCs) in blood clots can result in the production of bone on scaffolds in the presence of growth stimuli [65].

It is also possible that these transplanted cells enhance endogenous repair responses such as improving synaptogenesis, neurogenesis, and angiogenesis [66–69]. Some researchers also propose that the secretion of specific trophic factors such as BDNF, NGF, GDNF, and VEGF by transplanted cells could be a possible mechanism for neuronal regeneration and repair [70, 71]. As the capacity of the brain is very limited to regenerate neurons, it is challenging to repair a damaged structure in the brain. At present, no treatment exists to treat diffuse axonal injury and to divert the cascade of pathological events that leads to cellular death [1]. Even in preclinical TBI models, transplantation of NSCs leaves several questions unanswered, such as the ideal time of therapy, effective route of administration, and optimal dose for the cells [72]. Cellular therapy demonstrated potential to repair cerebral damage via neuroprotective and neurorestorative mechanisms. It is believed that stem cells use their neurogenic ability to repair injured brain [41]. After all, stem cell therapy remains the only hope for the future of TBI patients.

In conclusion, this meta-analysis suggests that cellular therapy significantly improves (p = 0.0001) the overall condition of adult TBI patients. Moreover, the pooled data for the Fugl-Meyer Motor Scale (p = 0.24) and Disability Rating Scale (p = 0.82) show a non-statistically significant improvement, which is still of great clinical importance.

Funding

This research received financial support from the Science and Technology Bureau of Quanzhou (grant number 2020CT003).

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Sharma A, Sane H, Kulkarni P, Yadav J, Gokulchandran N, Biju H. Cell therapy attempted as a novel approach for chronic traumatic brain injury – a pilot study. SpringerPlus 2015; 4: 26.
2. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation 2007; 22: 341-53.

3. Ruff RL, Riechers RG. Effective treatment of traumatic brain injury: learning from experience. JAMA 2012; 308: 2032-3.
4. Bowman SM, Bird TM, Aitken ME, Tilford JM. Trends in hospitalizations associated with pediatric traumatic brain injuries. Pediatrics 2008; 122: 988-93.
5. Hutchison JS, Ward RE, Lacroix J, Hébert PC, Barnes MA, Bohn DJ. Hypothermia therapy after traumatic brain injury in children. N Engl J Med 2008; 358: 2447-56.
6. Adelson PD, Ragheb J, Kanev P, Brockmeyer D, Beers SR, Brown SD. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. Neurosurgery 2005; 56: 740-54.
7. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017; 16: 987-1048.
8. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. Dis Models Mech 2013; 6: 1307-15.
9. Diringer MN. The evolution of the clinical use of osmotic therapy in the treatment of cerebral edema. Acta Neurochirur Suppl 2016; 121: 3-6.
10. Shi J, Tan L, Ye J, Hu L. Hypertonic saline and mannitol in patients with traumatic brain injury: a systematic and meta-analysis. Medicine 2020; 99: e21655.
11. Coronado VG, McGuire LC, Sarmiento K, Bell J, Lionbarger MR, Jones CD. Trends in traumatic brain injury in the U.S. and the public health response: 1995-2009. J Saf Res 2012; 43: 299-307.
12. Wang Z, Luo Y, Chen L, Liang W. Safety of neural stem cell transplantation in patients with severe traumatic brain injury. Exp Ther Med 2017; 13: 3613-8.
13. Aertker BM, Bedi S, Cox CS Jr. Strategies for CNS repair following TBI. Exp Neurol 2016; 275: 411-26.
14. Walker PA, Shah SK, Harting MT, Cox CS Jr. Progenitor cell therapies for traumatic brain injury: barriers and opportunities in translation. Dis Models Mech 2009; 2: 23-38.
15. Sharma A, Gokulchandran N, Chopra G, Kulkarni P, Lohia M, Badhe P. Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life. Cell Transpl 2012; 21 Suppl 1: S79-90.
16. Sharma A, Sane H, Paranjape A, Gokulchandran N, Kulkarni P, Nagrajan A. Positron emission tomography-computer tomography scan used as a monitoring tool following cellular therapy in cerebral palsy and mental retardation-a case report. Case Rep Neurol Med 2013; 2013: 141983.
17. Sharma A, Gokulchandran N, Sane H, Nagrajan A, Paranjape A, Kulkarni P. Autologous bone marrow mononuclear cell therapy for autism: an open label proof of concept study. Stem Cells Int 2013; 2013: 623875.
18. Kim HJ, Lee JH, Kim SH. Therapeutic effects of human mesenchymal stem cells on traumatic brain injury in rats: secretion of neurotrophic factors and inhibition of apoptosis. J Neurotrauma 2010; 27: 131-8.
19. Ul Hassan A, Hassan G, Rasool Z. Role of stem cells in treatment of neurological disorder. Int J Health Sci 2009; 3: 227-33.
20. Liu S, Qu Y, Stewart TJ, Howard MJ, Chakrabortty S, Holekamp TF. Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. Proc Natl Acad Sci USA 2000; 97: 6126-31.
21. Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol 2002; 174: 11-20.
22. Hsu YC, Chen SL, Wang DY, Chiu IM. Stem cell-based therapy in neural repair. Biomed J 2013; 36: 98-105.
23. Zhang J, Zhang Y, Zou J, Cao F. A meta-analysis of cohort studies: traumatic brain injury and risk of Alzheimer's disease. PLoS One 2021; 16: e0253206.
24. Goebell PJ, Kamat AM, Sylvester RJ, Black P, Droller M, Godoy G. Assessing the quality of studies on the diagnostic accuracy of tumor markers. Urol Oncol 2014; 32: 1051-60.
25. Oremus M, Oremus C, Hall GB, McKinnon MC. Inter-rater and test-retest reliability of quality assessments by novice student raters using the Jadad and Newcastle-Ottawa Scales. BMJ Open 2012; 2: e001368.
26. Zheng F, Dong Y, Xia P, Mpotsaris A, Stavrinou P, Brinker G. Is clipping better than coiling in the treatment of patients with oculomotor nerve palsies induced by posterior communicating artery aneurysms? A systematic review and meta-analysis. Clin Neurol Neurosurg 2017; 153: 20-6.
27. Kawabori M, Weintraub AH, Imai H, Zinkevych I, McAllister P, Steinberg GK. Cell therapy for chronic TBI: interim analysis of the randomized controlled STEMTRA trial. Neurology 2021; 96: e1202-14.
28. Wiesner K, Schwarz A, Meya L, Kaufmann JE, Traenka C, Luft AR. Interrater reliability of the Fugl-Meyer Motor assessment in stroke patients: a quality management project within the ESTREL study. Front Neurol 2024; 15: 1335375.
29. Nichol AD, Higgins AM, Gabbe BJ, Murray LJ, Cooper DJ, Cameron PA. Measuring functional and quality of life outcomes following major head injury: common scales and checklists. Injury 2011; 42: 281-7.
30. Tian C, Wang X, Wang X, Wang L, Wang X, Wu S. Autologous bone marrow mesenchymal stem cell therapy in the subacute stage of traumatic brain injury by lumbar puncture. Exp Clin Transplant 2013; 11: 176-81.
31. Seledtsov VI, Rabinovich SS, Parlyuk OV, Kafanova MY, Astrakov SV, Seledtsova GV. Cell transplantation therapy in re-animating severely head-injured patients. Biomed Pharmacother 2005; 59: 415-20.
32. Wang S, Cheng H, Dai G, Wang X, Hua R, Liu X. Umbilical cord mesenchymal stem cell transplantation significantly improves neurological function in patients with sequelae of traumatic brain injury. Brain Res 2013; 1532: 76-84.
33. Cox CS Jr, Hetz RA, Liao GP, Aertker BM, Ewing-Cobbs L, Juranek J. Treatment of severe adult traumatic brain injury using bone marrow mononuclear cells. Stem Cells 2017; 35: 1065-79.
34. Smith DH, Chen XH, Pierce JE, Wolf JA, Trojanowski JQ, Graham DI. Progressive atrophy and neuron death for one year following brain trauma in the rat. J Neurotrauma 1997; 14: 715-27.
35. Bramlett HM, Dietrich WD. Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. Progress Brain Res 2007; 161: 125-41.
36. Peng X, Zhu P, Zhang Q, Li J. The prognostic value of cancer stem cell markers in thyroid cancer: a systematic review. Arch Med Sci 2024; 20: 686-90.
37. Jorge RE, Starkstein SE. Pathophysiologic aspects of major depression following traumatic brain injury. J Head Trauma Rehabil 2005; 20: 475-87.

38. Schwarzbold M, Diaz A, Martins ET, Rufino A, Amante LN, Thais ME. Psychiatric disorders and traumatic brain injury. Neuropsych Dis Treat 2008; 4: 797-816.
39. Yin L, Ouyang D, Lin L, Xin X, Ji Y. Salidroside regulates imbalance of Th17/Treg and promotes ischemic tolerance by targeting STAT-3 in cerebral ischemia-reperfusion injury. Arch Med Sci 2021; 17: 523-34.
40. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 2007; 130: 2508-19.
41. Tajiri N, Duncan K, Antoine A, Pabon M, Acosta SA, de la Pena I. Stem cell-paved biobridge facilitates neural repair in traumatic brain injury. Front Systems Neurosci 2014; 8: 116.
42. Lee JA, Kim BI, Jo CH, Choi CW, Kim EK, Kim HS. Mesenchymal stem-cell transplantation for hypoxic-ischemic brain injury in neonatal rat model. Pediatr Res 2010; 67: 42-6.
43. Guo S, Zhen Y, Wang A. Transplantation of bone mesenchymal stem cells promotes angiogenesis and improves neurological function after traumatic brain injury in mouse. Neuropsychiatr Dis Treat 2017; 13: 2757-65.
44. Anbari F, Khalili MA, Bahrami AR, Khoradmehr A, Sadeghian F, Fesahat F. Intravenous transplantation of bone marrow mesenchymal stem cells promotes neural regeneration after traumatic brain injury. Neural Regen Res 2014; 9: 919-23.
45. Acosta SA, Tajiri N, Hoover J, Kaneko Y, Borlongan CV. Intravenous bone marrow stem cell grafts preferentially migrate to spleen and abrogate chronic inflammation in stroke. Stroke 2015; 46: 2616-27.
46. Wennersten A, Meier X, Holmin S, Wahlberg L, Mathiesen T. Proliferation, migration, and differentiation of human neural stem/progenitor cells after transplantation into a rat model of traumatic brain injury. J Neurosurg 2004; 100: 88-96.
47. Yan ZJ, Zhang P, Hu YQ, Zhang HT, Hong SQ, Zhou HL. Neural stem-like cells derived from human amnion tissue are effective in treating traumatic brain injury in rat. Neurochem Res 2013; 38: 1022-33.
48. Gao M, Chen Y, Zhai F, Liu Z, Liu Q, Wang Z. The effect of cultured autologous oral mucosal epithelial cells on ocular surface reconstruction. Arch Med Sci 2024; 20: 813-21.
49. Sawicka OP, Kocięba-Łaciak AH, Gałuszka D, Ślusarczyk K, Kasperowicz J. Parents' attitudes towards children's transplantology. Arch Med Sci 2024; 20: 326-31.
50. Lenzlinger PM, Morganti-Kossmann MC, Laurer HL, McIntosh TK. The duality of the inflammatory response to traumatic brain injury. Mol Neurobiol 2001; 24: 169-81.
51. Modo M, Stroemer RP, Tang E, Patel S, Hodges H. Effects of implantation site of stem cell grafts on behavioral recovery from stroke damage. Stroke 2002; 33: 2270-8.
52. Zhang ZX, Guan LX, Zhang K, Zhang Q, Dai LJ. A combined procedure to deliver autologous mesenchymal stromal cells to patients with traumatic brain injury. Cytotherapy 2008; 10: 134-9.
53. Cox CS Jr, Baumgartner JE, Harting MT, Worth LL, Walker PA, Shah SK. Autologous bone marrow mononuclear cell therapy for severe traumatic brain injury in children. Neurosurgery 2011; 68: 588-600.
54. Liao GP, Harting MT, Hetz RA, Walker PA, Shah SK, Corkins CJ. Autologous bone marrow mononuclear cells reduce therapeutic intensity for severe traumatic brain injury in children. Pediatr Crit Care Med 2015; 16: 245-55.
55. Wang L, Zhao J, Zhu B, Shen J, Ye Z, Peng Q. Microglia polarization in heat-induced early neural injury. Arch Med Sci 2024; 20: 1307-13.
56. Riess P, Zhang C, Saatman KE, Laurer HL, Longhi LG, Raghupathi R. Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury. Neurosurgery 2002; 51: 1043-52.
57. Shear DA, Tate MC, Archer DR, Hoffman SW, Hulce VD, Laplaca MC. Neural progenitor cell transplants promote long-term functional recovery after traumatic brain injury. Brain Res 2004; 1026: 11-22.
58. Skardelly M, Gaber K, Burdack S, Scheidt F, Hilbig H, Boltze J. Long-term benefit of human fetal neuronal progenitor cell transplantation in a clinically adapted model after traumatic brain injury. J Neurotrauma 2011; 28: 401-14.
59. Fujiwara Y, Tanaka N, Ishida O, Fujimoto Y, Murakami T, Kajihara H. Intravenously injected neural progenitor cells of transgenic rats can migrate to the injured spinal cord and differentiate into neurons, astrocytes and oligodendrocytes. Neurosci Letters 2004; 366: 287-91.
60. Harting MT, Sloan LE, Jimenez F, Baumgartner J, Cox CS Jr. Subacute neural stem cell therapy for traumatic brain injury. J Surg Res 2009; 153: 188-94.
61. Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Morshead CM, Fehlings MG. Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. J Neurosci 2006; 26: 3377-89.
62. Chu K, Kim M, Park KI, Jeong SW, Park HK, Jung KH. Human neural stem cells improve sensorimotor deficits in the adult rat brain with experimental focal ischemia. Brain Res 2004; 1016: 145-53.
63. Zhang Z, Sui R, Xia D. A variant in microRNA-124 is involved in the control of neural cell apoptosis and associated with recovery after spinal cord injury (SCI). Arch Med Sci 2022; 18: 1399-403.
64. Lladó J, Haenggeli C, Maragakis NJ, Snyder EY, Rothstein JD. Neural stem cells protect against glutamate-induced excitotoxicity and promote survival of injured motor neurons through the secretion of neurotrophic factors. Mol Cell Neurosci 2004; 27: 322-31.
65. Chen J, Lu Y, Xu J, Hua Z. Clinical evaluation of maxillary sinus floor elevation with or without bone grafts: a systematic review and meta-analysis of randomised controlled trials with trial sequential analysis. Arch Med Sci 2024; 20: 384-401.
66. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J Cell Physiol 2007; 213: 341-7.
67. Harting MT, Baumgartner JE, Worth LL, Ewing-Cobbs L, Gee AP, Day MC. Cell therapies for traumatic brain injury. Neurosurg Focus 2008; 24: E18.
68. Maegele M, Schaefer U. Stem cell-based cellular replacement strategies following traumatic brain injury (TBI). Minim Invasive Ther Allied Technol 2008; 17: 119-31.
69. Schouten JW, Fulp CT, Royo NC, Saatman KE, Watson DJ, Snyder EY. A review and rationale for the use of cellular transplantation as a therapeutic strategy for traumatic brain injury. J Neurotrauma 2004; 21: 1501-38.
70. Gao J, Prough DS, McAdoo DJ, Grady JJ, Parsley MO, Ma L. Transplantation of primed human fetal neural stem cells improves cognitive function in rats after traumatic brain injury. Exp Neurol 2006; 201: 281-92.
71. Lu P, Jones LL, Snyder EY, Tuszynski MH. Neural stem cells constitutively secrete neurotrophic factors and

promote extensive host axonal growth after spinal cord injury. Exp Neurol 2003; 181: 115-29.
72. Ma H, Yu B, Kong L, Zhang Y, Shi Y. Transplantation of neural stem cells enhances expression of synaptic protein and promotes functional recovery in a rat model of traumatic brain injury. Mol Med Rep 2011; 4: 849-56.