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Outcome of Stem Cell Transplantation in Patient with Spinal Cord Injury: A Systematic Review

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ABSTRACT

Spinal cord injury (SCI) is well known as a severely disabling injury that can result in long term neurological impairment and a great impact on social and economic aspects of the patients. To investigate the controversy regarding Stem Cell Transplantation as a treatment modality to alleviate the devastating effect of Spinal Cord Injury, we performed literature research according to PRISMA guidelines through Pubmed, Cochrane, and EMBASE Library to find studies about SCI and its stem cell management up to October 20th, 2020 with the keywords "stem cell transplantation" OR "spinal mesenchymal stem cell" OR "treatment" AND "spinal cord injury" OR "traumatic spinal cord injury") OR "outcome". The search was filtered to include clinical human studies in last 5 years publication period and written in English only. A total of 15 non-duplicate citations were found. 14 articles remained after a title and abstract screening. Ten studies are excluded from this study because they do not contain any outcomes of interest. Four articles are selected for this systematic review. A total of 72 patients were included in this review from 4 prospective cohort studies. Most studies classified their neurological status based on ASIA (American Spinal Injury Association) classification for quantifying the SCI severity. In conclusion, Stem Cell transplantation yielded satisfactory results in comparison to conventional management of SCI patients. Future studies with longer terms should be performed to cement the validity of this finding.

Keywords: Spinal cord injury, Stem cell, Transplantation, Systematic review, and ASIA score.

INTRODUCTION:

Spinal cord injury (SCI) is well known as severely disabling injury that can result in long term neurological impairment and great impact in social and economic aspect of the patients. Patients are usually rendered paraplegic or tetraplegic related to the sensory and motoric deficits. The most lethal complication of SCI is impairment of bladder function, cardiovascular problems, and intestinal flora disturbances so the advanced therapeutic approach and strategies is very important to overcome these issues (Kader *et al.,* 2018). Direct mechanical damages and secondary injuries are the underlying mechanisms of SCI. Vertebral fracture and dislocation is the main cause of direct mechanical damages leading to SCI. Dislocated discs or bone fragments can cause compression and contusion of the spinal cord. Secondary injuries leading to SCI can be related to inflammation, swelling, and

neural apoptosis of the spinal cord (Kakulas *et al.,* 2015). Besides that, another condition such as oxidative stress and disturbance of electrolyte also can lead to SCI. Some other condition can cause both primary, and also secondary SCI such as demyelination, severe tissue destruction, Wallerian degeneration, axonotmesis, syringomyelia, and formation of glial scar. There were some approach and strategies that have been developed and proposed to this condition, including surgery techniques, medications, and rehabilitation. But, there were still questions regarding the efficacy of the treatment options (Xu *et al.,* 2019).

Recently, the standard of care for acute SCI is surgical treatments which mainly aim to spinal cord decompression and rehabilitation (Sunshine *et al.,* 2017). However, there is still no neuroprotective and regenerative modalities that is effective and useful. High-dose methylprednisolone has been proposed to have beneficial effects in patients with SCI, but the consensus on the efficacy of this approach is still unclear (Qin *et al.,* 2018). The clinical use of stem cell transplantation has become new trend in these decade and some studies reported its effectiveness in treating SCI in animal models. Some variety of stem cells which consist of neural stem cells, mesenchymal stem cells (MSCs), Schwann cells, embryonic stem cells, and induced pluripotent stem cells have been used and developed for transplantation. Among these stem cell variety, MSCs have been known for its importance in repairing the damaged spinal cord (Muheremu *et al.,* 2016). Beside their superiority in differentiation and replacement for the damaged cells, MSCs also secrete many neuroprotective factors and cytokines, including brain-derived neurotrophic factor (BDNF), glial-cell-line-derived neurotrophic factor (GDNF) and vascular endothelial growth factor (VEGF). The fore mentioned factors had important roles in improving regeneration of neural tissues, promoting axon growth, and repairing damaged neurons. Currently, the outcome of MSCs transplantation to treat SCI in animal models have been verified (Abbasi *et al.,* 2021; Cho *et al.,* 2009) .

Despite of its effect on animal models, the outcome of MSCs in treating SCI in humans is still questionable. No review study has extensively evaluated the outcome of MSCs for SCI treatment. These studies will discuss previous studies investigating the outcome of stem cell transplantation usage in treating patient with SCI.

Review of Literature

Search strategy

This systematic review was arranged based on the PRISMA guideline (**Fig. 1**).

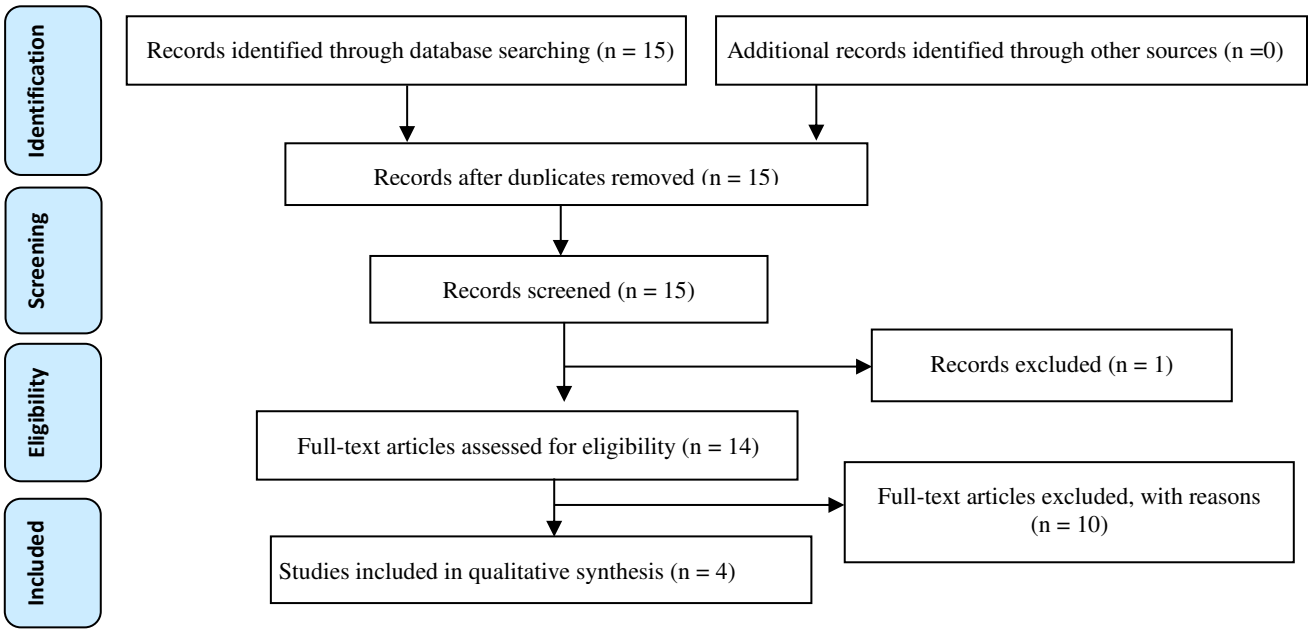

Fig. 1: Flow diagram describing the strategy for conducting this study based on PRISMA guideline.

Inclusion criteria

The inclusion criteria were outcome of stem cell transplantation for the management of SCI. Case series and case reports were also included in this review. Due to the limited number of studies, we did not establish restriction for demographics of the patients, though some reports and literatures not in English were excluded. Study that focus in rat study of stem cell transplantation and systemic review study are excluded from this review (**Table 1**).

Table 1: The criteria of inclusion & exclusion according to population, intervention, comparison & outcome.

Characteristic	Inclusion	Exclusion
Population	Patients with SCI	Rats with SCI (animal studies)
Intervention	Stem-cell transplantation in human	Stem-cell transplantation in animal
Comparison	Management of SCI without stem cell transplantation	Management of SCI without stem cell transplantation in animal study
Outcome	Neurological outcome and complication	-

Quality evaluation

After the search was performed, all authors screened to find studies which eligible. The all authors read the titles and abstracts and choose the article according to the inclusion criteria. Then, all authors continued to screen the full version of articles collected. The authors then gathered together and discussed about highly relevant studies that would be included in this review. Appraisal of study quality was performed by each authors independently and discussion was held if there was any disagreement about the selection and appraisal of the studies. The inherent aspects of the studies that consist of quality of the study, variables of relevant data, and also bias risk assessment were independently appraised by all authors by using forms filled by themselves. The first author then collected the forms and the contents of the form were evaluated to find any possible disagreements. The authors then had a meeting again to talk about any contradictions found and to find the decision according the appraisal of the studies.

Study Selection

A total of 15 non-duplicate citations were found. 14 articles remained after a title and abstract screen. Full texts were screened using the pre-determined exclusion and inclusion criteria. Ten studies has to be excluded from the review because they do not have any outcomes of interest. Four articles were selected for this systematic review.

Study Characteristics

There were 72 patients in total were included in this review. 62 patients underwent operative management while 10 patients had non-operative management. There were a total of 4 cohort prospective studies. Most studies classified their preoperative neurological status based on American Spinal Injury Association (ASIA) assessment protocol. The ASIA assessment protocol consists of a motor examination, two sensory examinations, and a framework of classification or impairment scale to quantify the severity of SCI. 26 from total patients have ASIA A preoperative neurological status. Most SCI occurred on Thoracolumbal region as much as 62 patients. Operative management included stem cells administration that sourced from iliac crest, umbilical cord tissue, and mesenchymal stromal cells. All of the stem cells injected at spinal cord lesion included intratechal and subarachnoid administration. All the patients have improvement after stem cells administration based on ASIA (American Spinal Injury Association) assessment. There is adverse event reactions from the stem cells administration such as mentioned on Vaquero *et al.* (2017) (84.21%) were considered mild headache, 3 (15.79%) moderate headache.

Table 2: Study Characteristic.

No	Reference	Journal	Study Design	Level of Evidence
1	Mendonça, 2014	Stem cell research & therapy	cohort prospective study	level III
2	Cheng, 2014	Journal of Translational Medicine	cohort prospective study	Level III
3	Hur, 2015	the journal of spinal cord medicine	cohort prospective study	level III
4	Vaquero, 2016	International Society for Cellular Therapy	cohort prospective study	level III

But from Mendonça, *et al* study, none of the subjects had fever, infection or meningitis after intervention. Follow up period varies from 3 months to 12 months.

DISCUSSION:

This systematic review included 4 studies which evaluated the outcome of stem cell transplantations comprehensively for management of SCI patients. Although the effectiveness of stem cell transplantation for the management of SCI patients remains debatable and unclear, this study found that stem cell transplantation significantly improved the neurological functions and outcomes (reflected by the ASIA and VAS) if compared to rehabilitation therapy. This systematic review only found cohort prospective study. There was no RCT study regarding the outcome of SC transplantation for SCI patients. This finding might be happen because this treatment of SC transplantation is relatively new treatment for SCI patients (Muheremu *et al.,* 2016).

Table 3: Summary of total sample, demographic data, spinal level and preoperative spinal status.

No	Reference	Total Sample Size	Group		Age	Gender		Spinal Level	Preoperative Neurological Status
			Control	Intervention		Male	Female		
1	Mendonça, 2014	14	0	14	23 - 61 (mean 35.7)	10 (71, 42%)	4 (28, 58%)	thoracic & lumbal	ASIA A
2	Cheng *et al.* (2014)	34	10	24	35.25 ± 8.96 years	N/A		CV Th10-CV L1	ASIA Score, manual muscle strength, muscle tension scale, the Barthel Index
3	Hur (2015)	14	N/A	14	range 19-69	12 (85.7%)	2 (14.3%)	7 cervical region 6 thoracal 1 lumbal region	1 patient: ASIA D 1 patient: ASIA B 12 patients: ASIA A
4	Vaquero, 2016	10	N/A	10	42.20 years (SD: 9.30 years)	8 (80%)	2 (20%)	5 cervical region 2 thoracal region 3 lumbal region	1 patient : ASIA D 5 patient : ASIA C 4 patients : ASIA B

Most studies classified their preoperative neurological status based on ASIA assessment protocol including two sensory examinations, a motor examination and a classification framework or impairment scale. There were 26 from total 72 patients had ASIA A preoperative neurological status. All the patients had improvement after stem cells administration based on ASIA assessment. Most spinal cord injury occurred on thoracolumbal region as much as 62 patients. This might occur because of thoracolumbar region is the most frequent site of SCI patients (Cho *et al.,* 2009). Although there were some adverse effects according to the results of this study.

Table 4: Stem cell transplantation surgery technique.

No	Reference	Source of Stem Cell	Transplantation Technique
1	Mendonça, 2014	iliac crest	Confluent autologous MSCs at passages 3 to 5 were resuspended in saline solution containing 20% human serum albumin (CSL Behring, King of Prussia, PA, USA). MSC suspensions (1 × 107 cells/ml) were transferred into 1 ml syringes for local injection in subjects.
2	Cheng *et al.* (2014)	umbilical cord tissue	25 µl of cell suspension was injected into two sites of the spinal cord at each site
3	Hur, (2015)	lipoaspirates of subcutaneous fat tissue	three 1-mL DMEM aliquots containing 3 × 107 autologous cells/each were prepared and in total 9 × 107 autologous ADMSCs per patient were administered on day 1, at 1 month, and at 2 months respectively into the intrathecal space over 5 minutes through lumbar spinal tapping.
4	Vaquero, 2016	autologous bone marrow MSC (mesenchymal stromal cells)	subarachnoid administrations 30 × 106 autologous bone marrow MSCs, supported in autologous plasma, at months 1, 4, 7 and 10

The all of them were only mild and temporary side effects, including fever, headache, urinary tract infections, nausea, numbness, backache, and abdominal distension, which mainly due to spinal puncture. There were no puncture wound infection, intracranial infection, leakage of cerebrospinal fluid from the incision, or any other severe or long term adverse effects observed in the subjects, indicating that stem cell transplantation is a considerably safe modality.

Table 5: Outcome of stem cell transplantation.

No	Reference	Functional		Follow up period	Adverse event
		Neurological	VAS		
1	Mendonça, 2014	A to B = 6 Samples, A to C = 1 sample, still A = 5 (2 excluded from the study)	after 6 months follow up (3 to 0 =1), (4 to 0 =1), (5 to 6=1), (6 to 3 =1), (1 to 0 =1), (7 to 7=1), (10 to 8=1), (5 to 7=1), (8 to 0=1), (6.5 to 3 =1), (6 to 8.5 = 1), (10 to7 =1)	3 months and 6 months	All of the subjects were discharged within 48 hours after surgery, None of the subjects had fever, infection or meningitis
2	Cheng *et al.*(2014)	improvement in sensation	N/A	before treatment and 6 months after treatment	N/A
3	Hur (2015)	ASIA motor score : 5 patients ASIA sensory score : 10 patients Voluntary Anal Contraction : 1 patient (partial improvement) MRI & Electrophysiological changes (no improvement)	N/A	8 months	UTI Headache Nausea Vomiting
4	Vaquero, 2016	progressive improvement was observed in both sensitivity and motor scores, reaching, at month 12, an improvement in the ASIA total score that ranged between 13 and 85 points from the baseline score, with a mean of 47.30 ± 28.81 points, and with a P value of 0.005	N/A	12 months	17 (84.21%) were considered mild Headache , 3 (15.79%) moderate headache

There were some limitations exist in this study. First, this review only included 4 studies due to the limitation of literatures, so there were some important subgroup analyses that was not be able to be performed such as the disease's different courses and number of cells transplanted to the subjects. The second limitation is that only papers published in English were included in this systematic review, so there may be another eligible studies in language other than English that relevant and can be included in this review. Review which included multi-centric randomized control trials with large size of randomizes subjects, reasonable generation of random sequence, adequate allocation concealment, and low risk of reporting bias will be needed to find evidence base with higher quality.

CONCLUSION:

Stem cells transplantation yielded satisfactory result in comparison to conventional management of SCI patients, in which all the patients was found to have improvement after stem cells administration based on ASIA assessment. Many neuroprotective factors and cytokines, including BDNF, GDNF, and VEGF that were secreted by MSCs thought to be the reason in its superiority in differentiation and replacement for the damaged cells. Some adverse effects were observed, including fever, headache, urinary tract infections, nausea, numbness, backache, and abdominal distension, which mainly due to spinal puncture, and were found to be only mild and temporary. There was no puncture wound infection, leakage of cerebrospinal fluid from the incision, intracranial infection, or any other severe or long term adverse effects observed in the subjects, indicating that stem cell transplantation is a considerably safe modality. Future prospective studies with longer observation periods should be performed to cement the validity of this finding.

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CONFLICTS OF INTEREST:

All authors declare that they have no competing interests. No funding was received for this study

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