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The Outcomes of Schwann Cell Therapy on Axonal Regeneration and Remyelination: A Systematic Review and Meta-Analysis Study

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Abstract

Introduction: Cell therapy is considered as one of the most promising therapeutic strategies in treating SCI. This study aimed to evaluate the extent and the effect of Schwann cell therapy on axonal regeneration and remyelination through a systematic and meta-analysis study.

Methods: By a systematic review and meta-analysis, the effect of Schwann cell in axonal regeneration and remyelination was investigated. In this research, all associated papers published from 1950 to the end of 2018 were evaluated through searching in the databanks of PubMed, Google Scholar, Scopus and Web of Science. Searching in the papers was done through the following keywords: Spinal cord injury, Schwann cell, transplantation, axonal regeneration and remyelination.

Results: Transplantation of Schwann cells has been stated as potential treatments for spinal cord injury. In the present study 47 papers were analyzed, out of which 43 were related to animal samples and 4 involved human samples. Totally among the studies on animal samples, 23 articles comprising some complete and incomplete sensory and motor injury as well as contusion and compaction subjects reported a sensory recovery in most cases. Also, all three human articles reported both motor and sensory recovery.

Conclusion: Based on the results extracted from the studies on animal samples, in about 90% of cases applying Schwann cells the outcome of cell therapy was associated with considerable sensory recovery and most of them also reported motor recovery. However, none of the animal researches has been able to guarantee the success of cell therapy in human experiments and beside the cell transplantation the researchers should pay attention to other therapeutic approaches.

Keywords

Schwann cell Therapy; SCI; Axonal Regeneration; Remyelination; Transplantation

Introduction

Spinal Cord Injury (SCI) is a debilitating damage that affects individuals and their families, and incurs heavy psychological, emotional, and financial costs to the involved person, families and society [1]. It has been estimated that 3 million people live with SCI globally, and 180000 patients are added to this group annually [2]. Over 60% of the SCI cases occur in the cervical region, many of which results in complete or severe loss of sensory and motor functions [3].

Over the past two decades, extensive basic and clinical researches have been done on the SCI. Several interconnected processes such as local inflammation, neuronal death, demyelination and disrupted nerve pathways can result to degeneration after spinal cord injury [4]. Clinical treatment for SCI includes injection of Methylprednisolone (MP) in high dose for 48 h after injury. Methylprednisolone (MP) inhibits lipid peroxidation and limits the inflammatory response and preserves the blood-spinal cord barrier, enhancing spinal cord blood flow. However, its use is limited due to several side effects such as increasing risk of urinary tract, respiratory, and wound infections [5]. Cell therapy is one of the most common investigated methods of treating the Spinal Cord Injury (SCI).

Attempts for regenerating nervous tissue in the damaged area regenerating synaptic connections and establishing reconnection between neuronal circuits through transplanting nervous tissues and stem cells have been among the major strategies for repairing the spinal cord [6]. In spite of the advantages of stem cells there are still numerous unknown factors regarding their use in treating SCI. These cells are potentially useful for the involved patients since they are not immunogenic and can be directly harvested. On the other hand transplanting allogenic cells has the risk of rejection thus requiring long-term suppression of the immune system [7]. Spontaneous improvement of SCI is very rare and still no therapeutic method capable of completely repairing SCI has been reported. Various clinical studies have been done in animal phases and more limited studies have also been performed in human phase. The results have indicated that cell transplantation is generally possible but its long-term effectiveness and complications have still remained unknown [8,9].

Schwann cells could support axonal regeneration after injury, and this has suggested their potential application in axonal regeneration and remyelination after spinal cord injury [10]. Schwann cells offer several properties such as the production of a variety of growth factors (including NGF, BDNF, and CNTF), cell adhesion molecules (N-CAM, N-cadherin, and integrins), and extracellular matrix proteins that could enhance recovery after SCI. Acute transplantation of Schwann cells in transected adult rat can promote axonal regeneration and remyelination [11]. Injected Schwann cells in contused adult rat can limit injury-induced tissue loss and promote remyelination, axonal regeneration and improve limb motor function [12].

It is clear that transplantation of Schwann cells into contused spinal cord can result in axonal regeneration and functional recovery similar to the repair models involving a transection of the spinal cord.

Therefore, the present study aimed to investigate the magnitude and the effect of Schwann cell transplantation in axonal regeneration and remyelination through systematic review and meta-analysis.

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Materials and Methods

The present study was a systematic review and meta-analysis about the importance and the effect of Schwann cell transplantation in axonal regeneration and remyelination. In this research, all papers published from 1950 to 2018 were evaluated through searching in PubMed, Google Scholar, Scopus, and Web of Science. Searching the papers was done as advanced search using the following keywords: Transplantation, Treatment, spinal cord injuries, axonal regeneration, remyelination, Schwann cell. Search was limited to English and Persian languages, animal and human samples. The abstract of selected papers were assessed by two independent reviewers for relevancy and in case of any controversial subject the final decision was made by a third reviewer. The searching strategy and included or excluded papers are shown in Figure 1.

Results

Totally 163 associated papers were investigated within the years 1950-2018. In the screening stage, 24 papers were removed. In addition, 92 papers were excluded because of their irrelevant title and abstract. Eventually, 47 papers were identified. Out of them, 43 papers included animal samples and 4 papers involved human samples. Eventually, 47 papers were investigated. The total number of analyzed papers in animal cases is presented in Table 1 in terms of Schwann cells used in spinal transplant, the experimental species, gender, origin of extracting transplant cells, mechanism of action, and the indices evaluated for anatomical or functional improvement, the name of main authors and the year of publication. The primary trauma incurred to the spinal cord can result in a developing set of complex complications and secondary damages (Table 1).

Overall, with the studies that their summaries are provided in Table 2 out of the animal samples, 13 articles comprising some complete and incomplete sensory and motor injury as well as contusion and compaction subjects reported a sensory recovery for the majority of cases (Table 2).

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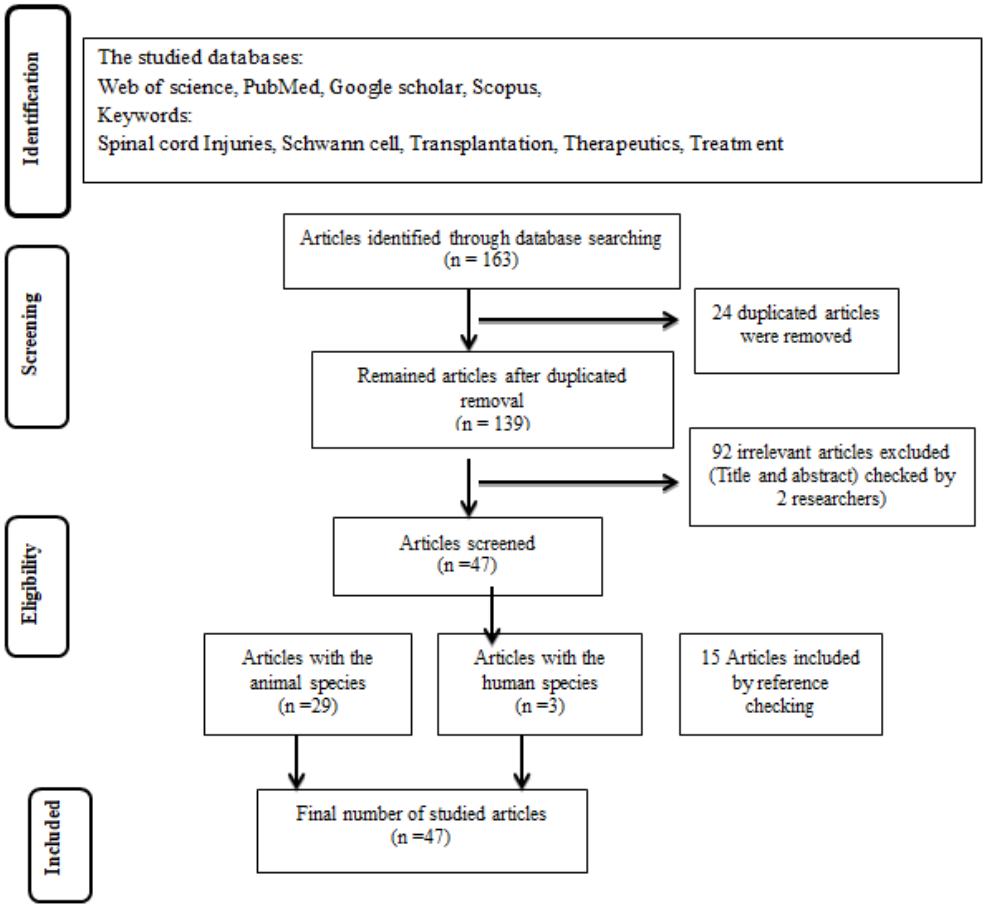

Figure 1: The strategy for searching the papers.

Author	Type of cell used for transplantation	Cell source	The factor accompanying transplantation	Species	Age	Objective
Oscar de la Garza-Castro [14]	Schwann cells	Sciatic nerve	17-β stradiol (E2) [43]			axon regeneration and sprouting [16,22, 31,32, 34-36,43]
Toshihiro Takami [15]			GFP-Schwann cell [44]			Myelination [16,22, 34,35,36,41,42,43]
Susana R. Cerqueira [16]			bisperoxovanadium administration [45]			Functional recovery [37,40]
Dinh, PT [17]					young	Cyst volume size reduction [44,45]
Er-zhu YANG [18]				Rat		
Lei Yang [19]						
Namjoo Z [20]						
Yee-Shuan Lee [21]						
Chandler L. Walker [22]						

Table 1: Schwann cells transplantation, the studied species, and the expected objectives.

Type of injury	Author	Type of cell	Co-transplant agent	Result of recovery		
				Motor	Sensory	Autonomic
Complete lesion	Fouad K [23]	Schwann cells	Matrigel and OEC [22]	Yes	Yes	No
		Olfactory ensheathing cells				
	Xu X.M [24]	Schwann cells and adult Pluripotent progenitor cells	-	Yes	No	No
	Oscar de la Garza-Castro [14]	Schwann cell	-	Yes	Yes	No
	Er-zhu YANG [18]	Schwann cell	Multichannel polymer scaffold [41]	Yes	Yes	-
	Lei Yang [19]	Schwann cell	Dominant-active β-cantenin-GFP of lentiviral vector [42]	Yes	Yes	No
Incomplete lesion	Dinh PT [17]	Schwann cell	-	Yes	Yes	No
	Chandler L. Walker [22]	Schwann cell	Bisperoxovanadium administration [45]	Yes	yes	No
Contusion	Takami T [25]	Schwann cells	cAMP [16]	Yes	No	No
		Olfactory ensheathing cells				
	Toshihiro Takami [15]	Schwann cells	-	Yes	Yes	No
		Olfactory ensheathing cells				
	Pearse D.D [26]	Schwann cells	cAMP [36]	Yes	Yes	No
	Susana R. Cerqueira [16]	SC transplantation in iPN or Matrigel [39]	Matrigel [39]	Yes	Yes	No
	Namjoo Z [20]	Schwann cells	17-β stradiol (E2) [43]	Yes	Yes	No
	Yee-Shuan Lee [21]	Schwann cells	GFP-Schwann cell [44]	Yes	Yes	No

Table 2: The outcomes of using Schwann cell therapy based on the type of lesion on laboratory animals.

Level and severity of injury	Author	Type of cell	Number of patient	Result (recovery)		
			Yes	Motor	Sensory	Autonomic
Thoracic level ASIA: A-C	Saberi H, et al. [27]	Schwann cell derived from sural nerve	4	Yes (only in 1 patient)	Yes (only in one patient)	-
Thoracic (n=24) and cervical (n=9) ASIA: A, B	Saberi H, et al. [9]	Schwann cell derived from sural nerve	33	Yes Improved light touch sensory scores (5.5 score) minimal improvement in pin-prick sensation (9 piont)	Yes motor scores improved (0.7 point) in some items, there were mild improvements, such as bathing, dressing upper body, toileting, toilet transfer, bed and wheelchair transfer, and walking	Yes uninary sensation improved from 37.5% to 50% of patients, and the urinary control rate improved from 25% to 62.5% of patients. Fecal sensation was initially present in 25% of patients and improved to 37.5% postoperatively.
Cervical and Thoracic ASIA: A-C	Zhou, et al. [28]	Schwann cell derived from sural nerve	6	Yes (in all patient)	Yes (in all patient)	Yes (in all patient) skin nutrition improvement, reduced spasticity, increased bladder volume, decreased residual urine volume, smooth intestinal defecation

Table 3: The outcomes of using Schwann cell therapy according to the type of lesion in studies on human.

In different studies, various cells have been investigated in treating SCI. Extensively, the cells used in SCI transplantation include Schwann cells [29-34]. Transplanting Schwann cells under the acute conditions or under thoracic acute SCI in rodents has been resulted in increased number of peripheral axons and myelin, as well as relative improvement in coordination of the front and hind movement limbs. Some studies emphasized the importance of cell-derived factors in neuronal protection. For example, when secretion of Brain-Derived Neurotrophic Factor (BDNF) was impaired, the neuronal protection effects of Bone Marrow Mesenchymal Stem Cells (BMSCs) following the SCI were decreased. However, whether loss or reduction of BDNF secretion will directly or indirectly result in diminished BMSC survival is still unknown [35-37].

The results obtained from Schwann cell transplantation are different, based on the species, age and source of applied cells, as well as culture conditions, and the use of complementary and combination therapy as Table 1.

Furthermore, the passed time after damage and the site of cell transplantation can affect the outcome of cell transplantation [38]. In most studies, after cell transplantation, improved post-treatment functioning has been evaluated through mechanisms such as neuronal protection, immune modulation, axon sprouting/axon regeneration, and myelin regeneration [39].

Discussion

The present study investigated the importance and effect of Schwann cell transplantation on axonal regeneration and remyelination through a systematic review and meta-analysis. Based on the results extracted from the studies on animal samples, in about 90% of cases applying Schwann cells the outcome of cell therapy was associated with considerable sensory recovery [40]. These results were revealed among cases with complete sensory and motor lesions, incomplete lesions, contusion lesions [41-43].

Schwann cells are among the best myelin-generating cells of glia for the peripheral nervous system, which will conduct axon regeneration in peripheral nerve damages. NSCPs are pluripotent progenitor cells, which typically can be differentiated as neuro spheres into neurons, astrocytes and oligodendrocyte progenitor cells under the experimental conditions [44]. OECs are glia cells that support growth of olfactory axon in the olfactory bulb. Mesenchymal stem cells are pluripotent progenitor cells, which are found in many tissues including the bone marrow. Immature cells or stem cells are potentially able to proliferate into different types of cells.

Researchers studying on SCI, usually use the term of improved functioning as a term to mention a statistically significant improvement in the functioning of cases in the treatment group against the control group, though the real improvement has rarely been observed. Accordingly, it is suggested to avoid the use of this term, and a special improvement in the intervention group should be investigated.

The important point is that since no effective treatment has been found for SCI so far, it is not known what degree of functional improvement in animal models has been significant clinically.

The capacity of transplant cells for myelination is only based on several human experiments. However, the important point is that the endogenous capacity of OPCs and Schwann cells for effective myelination in bare axons during SCIs or demyelinated axons after the lesions may remain for a long time.

Investigation of 45 related papers in human and animal models suggested that in many cases (about 17 papers) of animal models of SCI, there has been a significant spontaneous improvement, particularly sensory improvement. For example, during the moderate contusion of thoracic spine, initially a flaccid paralysis is observed in hind limbs. However, during several weeks, in comparison with the control groups, the animals gain the ability of bearing the bodyweight in ascending steps. Nevertheless, improvement to normal state comparable to a healthy animal is not observed.

In the animal models, it has been reported that myelinated axons have remained for several months after the lesion. Persistence survival of demyelinated axon following SCI, in human samples, without treatment has been investigated by only a few numbers of studies, in which they have mentioned the survival of some demyelinated axons in general [48].

Although increased growth of axon is considered as one of the main strategies and goals of cell transplantation in SCI, there are challenges in data interpretation. Some believe that axon regeneration occurs, to some extent following SCI, even without treatment.

Conclusion

The results extracted from the studies on animal samples showed that in about 90% of cases applying Schwann cells, the outcome of cell therapy was associated with considerable sensory recovery and most of them also reported motor recovery. However, none of the animal researches has been able to guarantee the success of cell therapy in human experiments, and beside the cell transplantation the researchers should pay attention to other therapeutic approaches.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Ilam University of Medical Sciences and is in accordance with national declaration of ethics in researches.

Consent for publication. Not applicable.

Availability of Data and Materials

The dataset supporting the conclusions of this article is available upon request.

Competing Interests

There is no conflict of interest for this study.

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Authors' Contributions

AM, SH and JT participated in the conception and design of the study and acquisition of data as well as first draft preparation. AK analyzed and interpreted the data, and critically reviewed the article for intellectual content. All authors read and approved the final version of the paper before the submission.

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