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REVIEW ARTICLE

Comparison of intramedullary transplantation of olfactory ensheathing cell for patients with chronic complete spinal cord injury worldwide

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ABSTRACT

Objectives: Traumatic spinal cord injury (tSCI) remains a major clinical challenge. Cell transplantation brings a glimmer of light, among them olfactory ensheathing cells (OECs) have shown some neurorestorative effect. Due to the results of each group lack basic consistency, many technical details are believed to affect the overall outcome. We compare the clinical outcome of intramedullary transplant of olfactory ensheathing cells for patients with spinal cord injury at multi-centers worldwide, and to explore the potential standardized transplantation that suits for the clinical requirements.

Methods: Here, we used the Pubmed and CNKI databases to search online the literatures published in the last 20 years for the clinical studies/trials of OECs for chronic spinal cord injury in the representative clinical center. The results of these representative clinical treatment centers were searched and analyzed. The parameters which may affect the effect including the concentration of cells, the total number of cells, the choice of incision, the site of transplantation, the number of transplantation sites, the advantages and disadvantages of transplantation equipment, and postoperative management, were compared carefully to clarify its impact on the clinical results.

Results: In these literatures, 2 Chinese centers, 1 Australian center and 1 European center were selected for intraspinal transplantation. The reason of different results may be due to the excessive injection times and/or the excessive total injection volume.

Conclusions: Cell implant to the spinal cord parenchyma is effective for restoring neurological functions, but improper procedures may lead to ineffective results. Concise surgery appears to be more suitable for clinical application than ostensibly precise and complex injection procedures. Sufficient rehabilitation training is surely necessary for the integration of motor recovery after cell transplantation.

1 Introduction

Traumatic spinal cord injury (tSCI), especially chronic complete spinal cord injury can cause enormous economic burden and suffering for families and society. Currently, the neurorestoratologic strategies have developed new therapies for patients with tSCI from the laboratory to the clinic. Significant progress

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has been made in the field of clinical cell therapy application for SCI, which includes neural stem cells, oligodendrocytes, Schwann cells (SCs), olfactory ensheathing cells (OECs), various mesenchymal stromal cells, etc. [1, 2]. Many reports have been published from different clinical centers worldwide in his regard. OECs are a special type of glial cells with multiple functional properties such as astrocytes, oligodendrocytes, and SCs. The neurorestorative potency of the OEC has been better than other now known types of glial cells; it can induce and guide axonal growth, help regenerate olfactory nerve fibers across glial scars and the barrier between peripheral and central axons, promote the damaged nerve restoration including axonal regeneration, myelination repair, and restore other structural and functional impairments [3, 4]. Thus, it is generally believed that these cells have greater application prospects [5–7]. Currently intramedullary transplantation is one of the delivery routes for OEC therapy in SCI cases [8–16]. However, the results of clinical studies have been reported to be inconsistent. Because procedures for cell injection into the spinal cord parenchyma are different, they may result in inconsistent clinical outcomes. In this review, a comparison is made to better promote the standardization of cell transplantation for SCI.

2 Methods

We used the Pubmed and CNKI databases to search online for a clinical studies and trials of olfactory ensheathing cells (OECs) for chronic spinal cord injury in a representative clinical center published in the recent two decades. The language is limited to Chinese and English (Table 1). In the end, we selected two Chinese centers, one Australian center, and one European center, which used intraspinal parenchymal cell transplantation to treat chronic complete SCI. The detailed clinical process parameters, including the size of the spinal incision, the concentration of transplanted cells, the total amount of transplanted cells, the site of implantation, the total number of transplant sites, the design and selection of transplantation devices, and postoperative clinical management were carefully analyzed to compare their clinical outcomes.

3 Results

The comparison between the parameters, complications, and clinical efficacy of intra-spinal transplantation of olfactory ensheathing cells (OECs) in the eligible studies have been shown in Table 2. The overall results

Table 1 List of selected clinical studies on olfactory ensheathing cell transplantation for treatment of chronic complete spinal cord injury.

Author	Nation	Year	Case (*n*)	Cell type	Route of transplant
Huang H, et al.	China	2003	171	OEC	cord parenchyma
Rabinovich SS, et al.	Russia	2003	15	hemopoietic tissues+OEC	subarachnoidally
Féron F, et al.	Australia	2005	3	OEC	cord parenchyma
Guest J, et al.	United States	2006	1	OEC	cord parenchyma
Lima C, et al.	Portugal	2006	7	olfactory mucosa	cord parenchyma
Huang H, et al.	China	2006	222	OEC	cord parenchyma
Mackay-Sim A, et al.	Australia	2008	6	OEC	cord parenchyma
Lima C, et al.	Portugal	2010	20	olfactory mucosal autografts	cord parenchyma
Zheng ZC, et al.	China	2010	213	OEC	cord parenchyma
Huang H, et al.	China	2012	108	OEC	cord parenchyma
Wu J, et al.	China	2012	11	OEC	cord parenchyma
Wang D, et al.	China	2012	24	OEC	cord parenchyma
Rao Y, et al.	China	2013	8	OEC	cord parenchyma
Tabakow P, et al.	Poland+UK	2013	6	autologous mucosal olfactoryensheathing cells and olfactory nerve fibroblasts	cord parenchyma

Table 2 Comparison of surgical parameters and clinical efficacy of spinal cord parenchyma transplantation using olfactory ensheathing cells.

Author	Case (*n*)	Incision size	Transplant site	Cell concentration	Total amount of cells	Transplant device	Average operation time	Postoperative management	Follow-up time	Complication	Clinical efficacy
Huang H, et al. [7]	171	4 cm	The upper and lower boundary areas of the damaged area and the normal area, 2-4 injection points	10,000 single cells /μL	500,000 cells / 50 μL	4.5# syringe needle (approved by the Food and Drug Administration)	1.5 h	Postoperative rehabilitation training	2–8 weeks	No serious complications	Improved
Wang D, et al. [11]	24	4–6 cm	Spinal gray matter at a distance of 0.5 cm from the distal and proximal ends of the spinal cord injury zone, 4 injection points	10,000/μL	500,000/ 40 μL	5# syringe needle (approved by the Food and Drug Administration)	1.7 h (1.5 – 2.5 h)	Postoperative rehabilitation training	3.2 yr (0.5–5.2 yr)	No serious complications	Nine of the 10 patients had a 1 to 2 spinal cord segment with a sensory level of injury. There was no change in motor function. There was no change in the sensory level of injury in 1 patient, but his limb spasm was significantly relieved after surgery.
Féron F and Mackay-Sim A, et al. [15,16]	3	4–6 cm	1μL per injections, spinal cord injury zone, one vertebral body segment at the distal end and the proximal end. number of injection points: Case 1: 270 Case 2: 545 Case 3: 630	80,000 cells/μL	Patient 1 297μl (12 million) Patient 2 599.5μl (24 million) Patient 1 693μl (28 million)	Self-made microinjection instruments	4 h	Postoperative rehabilitation training	3 yr	No serious complications	In 1# patients, touch and pinprick improved on both sides of the body, decreased more than 3 dermatodes
Tabakow P, et al. [14]	3	6–8 cm	Spinal cord injury zone, one vertebral body segment at the distal and proximal ends, 0.5 μl per injections, Case 1: 20 sites (120 injections), case 2: 40 sites (128 injections), case 3: 46 sites (212 injections)	30,000–200,000 cells/μL	Case 1: 60 μL (1,800,000), Case 2: 64 μL (1,920,000), Case 3: 106 μL (21,200,000)	Self-made microinjection instruments	9–11 h	Postoperative rehabilitation training	1 yr	Long-term no complications. Recent complications include: fever (T1, T2, T3) Urinary tract infection (T1, T2) Mild anemia (T1, T2) Anemia requiring blood transfusion (T3) Systemic hypotension (T3) Pressure sore ulcer (T1) Temporary loss of musculocutaneous nerve (T1)	The first 2 surgical patients ASIA A to ASIA C and ASIA B. Diffusion tensor imaging showed that the spinal cord injury in these patients focused on the continuity of some white matter bundles throughout the process. The third surgical patient, although maintaining ASIA A, showed a segment of motion and sensory function below the degree of injury. Neurophysiological examination showed improvement in spinal cord conduction and lower limb muscle activity.

(Continued)

Author	Case (*n*)	Incision size	Transplant site	Cell concentration	Total amount of cells	Transplant device	Average operation time	Postoperative management	Follow-up time	Complication	Clinical efficacy
Huang H, et al. [10]	108 (79 cases in rehabilitation group; 29 cases in poor rehabilitation training)	2–3 cm keyhole surgery	The upper and lower boundary areas of the damaged area and the normal area, 2–4 injection points	10,000 single cells /μL	500,000 cells / 50μL	4.5# syringe needle (approved by the Food and Drug Administration)	1 h	Postoperative rehabilitation training	3.47 ± 1.12 yr	None	The average ASIA motor score of 108 cases increased from 37.79±18.45 to 41.25±18.18, the light touch score was from 50.32±24.71 to 55.90±24.46, the pinprick score was from 50.53±24.92 to 54.53±24.62; the IANR-SCIFRS score increased from 19.32±9.98 to 23.12±10.30. Sufficient rehabilitation training has a significant impact on the improvement of motor scores. 14 cases (12.96%) improved ASIA A to ASIA B; 18 cases (16.67%) improved ASIA A to ASIA C, 9 of which (8.33%) improved walking ability or they used walking device with or without help Walking; 12 of 14. males (14.29%) improved sexual function. Electromyography was performed on 31 patients; 29 patients showed improvement and the other 2 did not change significantly. PVSEP test: of the 31 patients, 28 showed improvement and the remaining 3 did not change.

revealed different degrees of improvement in neurological status such as sensory and motor function after the treatment. Early results were confirmed by long-term follow-up. The results further show that multiple injections with large volume of the cell solution may lead to iatrogenic spinal cord injury and ineffectiveness of the treatment. This situation may be observed in the two patients of the Australian team who injected 300 μL (545 injection points into the spinal cord in one case, and 24 million cells), 350 μL (630 injection points, 28 million cells) in the second case.

4 Discussions

The biological properties of olfactory ensheathing cells (OECs) make them suitable for promoting neurorestoration including axonal regeneration, neuroplasticity, myelination repair, stimulating angiogenesis, changing local microenvironment through releasing cytokines or secreting neurotropic or growth factors and more other neurorestrorative mechanisms in the injured spinal cord. OECs can interact with glial scars and improve functional outcomes with rehabilitation for SCI [10, 17, 18]. Although intrathecal injection is

a less invasive option, most researchers still believe that OECs can be directly transplanted into the adjacent segment of spinal cord by injecting micro-uploaded cell suspensions using fine needles or glass capillaries. Actually intramedullary injection seems to be the best route for cell transplantation [8]. After intramedullary injection the transplanted cells can interact directly with the host environment.

However, it is worth noting that the intramedullary injection of the OECs may be associated with the following risks: damaging spinal cord by needle injection, possible spinal cord ischemia due to high pressure gradient and hydrodynamic separation in the spinal cord parenchyma with large injection volumes [19]. Therefore, the location of cell transplantation, the concentration of cells, the total amount of cells, injection devices, and transplantation surgical techniques are very important for safety and efficacy.

In theory, more tiny microinjections may promote the integration of transplanted cells with the host tissue, which has certain benefits. In experimental animals, very fine multi-point small volume injections could be performed for long periods of time. However, the human spinal cord is completely different from experimental animals (including primates). Human spinal cord movement or floating range is larger, associated with breathing, and heartbeat. From a clinical perspective, clinical practical needs are the first choice and consideration rather than animal experiments. In order to reduce needle damage, fewer hand-held injections may be the best choice at present time (the failure of patients 2# and 3# in Australian studies provides evidence). Especially in the cervical spine and T11-L1 segments, any secondary damage to the incompletely injured spinal cord and the patient's existing neurological function is unacceptable and should be avoided.

Regarding the choice of incision size, the spinal cord segment that needs to be transplanted should generally be exposed, but the keyhole surgery used by Dr. Huang's team appears to be an option for patients without adhesion and cystic abnormality, with an average operation time about 1 hour. Compared with the long operation time of 9 to 11 hours in Europe, and longer incision length, this method's complications related with anesthesia and surgery were greatly reduced, and the recovery time after surgery was also shortened. In particular, 2 hours are the prime time from the lab until the end of the cell transplantation [20].

Reducing the total injection volume and appropriately increasing the concentration of the cell suspension is an aspect to be considered. However, the inner diameter of the needle of the applied syringe is of utmost importance. Actually excessive cell concentration, or the resistance to flow of the cell suspension through the needle, can crush and damage the cells. Therefore, a moderate concentration, a moderate total volume, and an appropriate number of injection points are items to be determined in the future studies.

Finally, through the comparison of the results from multiple centers in this paper, a global consensus can be considered that association of strong rehabilitation program is essential for the recovery of the patients' motor function. Simple cell transplantation, if not combined with rehabilitation training, cannot trigger or promote neuromuscular activity [10].

5 Conclusions

The cell implantation into the spinal cord parenchyma has a certain effect on the functional recovery for chronic complete SCI. Concise surgery that meets clinical practice may have advantages over seemingly precise and complex surgical procedures: saving surgery time, reducing iatrogenic secondary damage, reducing associated complications, and similar or better clinical outcomes. Excessive transplant capacity per unit volume may be an important cause of poor surgical outcomes. Excessive operative time, excessive cell population and numerous punctures points may adversely affect the surgical outcome.

Preliminary recommendations for surgical parameters include: (1) cell concentration: moderate (10,000–30,000/μL); (2) total cells: moderate (>1 million/50–100 μL); (3) incision selection: minimally invasive, keyhole; (4) transplanted site: junction zone between normal and abnormal segment can be implanted; (5) number of transplant sites: 4–8; (6) excellent transplantation equipment should be suitable for sterilization and freehand coordination; (7) intraoperative adhesions and cysts are better to be surgically released or removed; (8) postoperative rehabilitation should be instituted early with adequate target-oriented intensive program.

Disclosure

The authors declare that they have no competing interests.

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