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Application of olfactory ensheathing cells in clinical treatment of spinal cord injury: meta-analysis and prospect

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1 Introduction

Spinal cord injury (SCI) is the most serious complication of spinal injury and often leads to severe neurological dysfunction below the lesioned segment. The incidence of SCI is increasing year by year, and the annual increase of SCI patients is about 500,000 worldwide [1]. It has been previously thought that in the sequela of SCI, the nerve self-repair function disappears, leading to permanent neurological dysfunction.

Fortunately, after years of unrelenting efforts by researchers and clinicians, neurorestoration has become a reality. In 2014, 31 experts from 20 countries reached a consensus [2]: neurorestorative strategies with positive preclinical results have been translated into clinical studies, and cell therapy has emerged as one of the most highly regarded neurorestorative strategies.

In 2017, Assinck et al. [3] proposed that olfactory ensheathing cells (OECs) are one of the ideal cells for repairing SCI. OECs are a class of mature functionally differentiated glial cells that functions between Schwann cells and oligodendrocytes. These OECs have many
neurorestorative functions including neurotrophic effects [4], ability to inhibit gliosis and scar formation [5], ensheathing capacity [6], immune regulation [7], and strong mobility [8]. Huang first began the clinical study of OECs transplantation for the treatment of SCI in the world as early as 2001. Subsequently, various countries and regions have successively carried out clinical researches on the OECs therapy.

Clinical Cell Therapy Guidelines for Neurorestoration published in 2016 and 2018 [9, 10] have recommended the safe doses of olfactory ensheathing cell and the transplantation methods. However, there is no detailed instruction for these factors provided in these two guidelines.

In order to further understand the precise treatment of SCI by OECs treatment, this study was based on the source, dose and transplantation methods of OECs in order to systematically evaluate the treatment strategies of chronic SCI with OECs.

## 2 SCI clinical trials of OECs transportation

### 2.1 Search strategy

In July 2018, we searched for related clinical trials in PubMed, Cochrane Library, EMBASE, CNKI, and Wanfang Data. The search language is not limited. After all possible studies were identified, their references were screened for potential articles. The English database search terms and retrieval methods are shown in Table 1.

### 2.2 Trial identification and features

PubMed, EMBASE and Cochrane Library databases were searched and 328 papers were included in this study. After excluding duplicate literatures, retrospective literatures, case reports, reviews, animal experiments and irrelevant literatures, a total of 30 clinical trials on OECs transplantation for SCI published during 2002–2014 were selected, which include 6 Chinese and English literatures by manual searching. The publication peaked in 2006 and declined after 2011 (Fig. 1).

These 30 articles are from 4 different countries, including 25 from China, 2 from Portugal, 2 from Australia, and 1 from Poland. In addition, there is only one RCT trial from China [11]. In the aspect of source of OECs, fetal OECs were used in all the Chinese literatures except Rao’s. Autologous olfactory mucosa (OMAs) were used in 2 trials from Portugal. Autologous OECs were used in Australia and Poland.

### 2.3 Data extraction

Two researchers extracted data from 30 articles including source, injection site, dose, maximum volume of injection, injection target (Table 2).

### 2.4 Typical clinical trials

From 2001 to 2006, Lima et al. [34, 35] performed partial scar repair and OMAs transplantation of SCI in 27 patients with chronic SCI. The results indicated that OMA is feasible, relatively safe, and may be beneficial for patients with chronic SCI when combined with postoperative rehabilitation. They believe that one of the keys to OMAs transplantation for chronic SCI is that OMAs contain NSCs which repair nerve function other than Schwann cells or OECs. But the fact is that Lima currently reports a small sample size to prove its safety. Moreover, from the data of the efficacy evaluation, the degree of improvement of neurological function of OMAs transplantation showed no advantages compared with the transplantation of OECs alone.

In 2013, Tabakow et al. [38] conducted a phase I clinical trial of autologous OECs transplantation in patients with complete SCI. A total of 6 SCI patients were included, 3 of which were in the transplantation group. The cell cultures that Tabakow isolated from the patient’s autologous olfactory mucosa were mainly OECs and ONFs. Without further purification, the percentage of S100 positive cells in the cultures was only 10%~25.7%. Tabakow et al. [39] then obtained olfactory bulbs from a patient with sinus disease who underwent an intracranial surgery. The OEC concentration was 16%, and the autologous spinal cord transplantation was performed in combination with peripheral nerve bridging materials. The patient’s neurological function was significantly enhanced compared to the 3 OEC transplant recipients who received this from mucosal origin. In the transplant operation, the researchers used a micro pump and a microscopic operating system to inject multiple points in the Matrix 1. This may cause secondary damage to the spinal cord. In addition, the number of cases in the
Tabakow’s experiment is very small, and there is no further large-scale study. Thus, the conclusions drawn are still not repeatable.

In 2005, Feron et al. [36] performed a single-blind phase I clinical trial of autologous OECs transplantation in 6 patients with SCI, and 3 patients in the transplantation group. The results indicated that it was safe for autologous OECs transplantation within 1 year. In the grafts prepared in this clinical trial, the positive
cells of S100 and glial fibrillary acidic protein (GFAP) were > 95%, and the p75NTR positive cells ranged from 76% to 88%. In the transplant operation, the cells were injected at a depth of 4 mm by means of Matrix 2. Mackay-Sim [37] has followed the patients for 3 years. Clinical assessments included medical, psychosocial, radiological, as well as specialized tests of neurological and functional deficits. Unfortunately, except for 1 patient with improved sensory function, the remaining patients had no significant neurological recovery.

The above tests are all clinical trials of autologous olfactory mucosa-derived OECs for the treatment of chronic SCI. OECs from autologous sources have no immunological rejection defects. Thus, they are considered to be one of the best sources of cells for spinal cord restoration. However, there is no uniform standard of autologous OECs culture preparation and transplantation procedures. The sample size is only 58 cases in total, which shows no significant neurological restoration.

Most Chinese clinical trials use human fetal OECs with large sample sizes. Several clinical trials showed the efficacy of those fetal OECs. These clinical studies use standard fetal OECs, unified transplantation methods and pathways that are in line with the recommendations of The Chinese Clinical Guidelines for Neurorestoration Cell Therapy [9] and The Clinical Cell Therapy Guidelines for Neurorestoration [10].

### 3 Clinical efficacy of fetal OECs in the treatment of chronic SCI

#### 3.1 Eligibility criteria

To further understand the efficacy of fetal OECs for

| Reference | Source | Injection site | Dose | Volume, points |
|-----------|--------|----------------|------|----------------|
| Wu, J et al. [12] | fetal OECs | rostral and caudal ends of the lesions | $5 \times 10^5$ | 25 μL/point, 2 |
| Zhang, Z C et al. [13] | fetal OECs | Group A: the border of the superior part of lesions and normal spinal cord | NA | Group A: 50 μL/point, 1 |
| | | Group B: the either sites of the lesions | Group B: 50 μL/2-4 points, 2-5 |
| Liu, C et al. [14] | fetal OECs | the border of lesions and normal spinal cord | $10^6$ | 100 μL (total), multiple |
| Zheng, Z C et al. [16-18] | fetal OECs | upper or lower injured region and left or right normal spinal cord | $(1-4) \times 10^6$ | 50 μL/2-5 points, 2-5 |
| Huang, H et al. [19-26] | fetal OECs | rostral and caudal ends of the lesion | $10^6$ | 25 μL/point, 2 |
| Chen, L et al. [11, 27, 28] | fetal OECs | both posterior horns of spinal cord 0.5 cm distal and proximal to SCI area | $8 \times 10^6$ | 10 μL/point, 4 |
| Bao, G F et al. [30] | fetal OECs | multiple points of the cross between spinal cord injury and normal spinal cord | $5 \times 10^6$ | 25 μL (total), multiple |
| Rao, Y et al. [31] | fetal OECs | the border between lesions and normal spinal cord | $(2-5) \times 10^6$ | 50 μL/2-5 points, 2-5 |
| Rao, Y et al. [32] | autologous OECs | local anesthesia, MR-guided injection to the lesion tail | $8 \times 10^6$ | 2 mL/6 points*, 6 |
| Rao, Y et al. [33] | autologous OECs | the border between lesions and normal spinal cord | $2 \times 10^6$ | 40-50 μL/4-5 points, 4-5 |
| Lima, C et al. [34, 35] | OMA$s$ | parenchyma | NA | NA |
| Feron, F et al. [36] | autologous OECs | Matrix 1 | $(1.2-2.8) \times 10^9$ | 1.1 μL, 270-630 |
| Mackay-Sim, A et al. [37] | autologous OECs | Matrix 2 | $1.8 \times 10^9 - 2.12 \times 10^9$ | 60-106 μL/20-46 points, 20-46 |

NA, not applicable. *, two sets of injections per week, lasted for 4 weeks. OMA$s$, contain neural stem cells (NSCs) and OECs. ONFs, olfactory nerve fibroblasts. Matrix 1, a five by three grid of injection sites was regularly arrayed rostral and caudal to the injured spinal cord and less regularly than shown through the damaged cord. Rows were 5 mm apart and columns were 1 mm apart where possible. Matrix 2, consisted of four to five rows, 2 mm apart. The posterolateral sulcus was chosen as the main entry point for cell microinjection.
the treatment of chronic SCI, the investigators included clinical studies that met the two guidelines: (1) patients with chronic SCI were enrolled in the study and received fetal OECs for transplantation; (2) reported American Spinal Injury Association (ASIA) motor score, light score, and pinprick score; (3) the transplantation method is parenchymal injection at the junction of the lesion and/or the upper and lower normal tissues; (4) single dose is \((1-2) \times 10^6\) OECs; (5) single injection volume is less than 25 μL.

Two researchers carefully reviewed all the literatures to determine the relevant clinical trials. In order to avoid duplication of statistics, the researchers confirmed the time of the clinical trial, the research unit and the follow-up periods, and avoided the literature containing the duplicate data. Finally, these data was verified by a third party. For different literatures from a same clinical trial, we included the largest sample size or the latest published literature (Table 2 and Table 3).

### 3.2 Document quality evaluation

The included literatures recorded the ASIA scores before and after the transplantation. The pre-transplant neurological status was classified as the exposed group, and the neurological status after transplantation was classified as non-exposed group. All literatures were evaluated by two investigators using the modified Newcastle-Ottawa Scale (NOS). The quality of the literatures were determined after the two researchers reached a unanimous agreement (Table 3).

### 3.3 Meta analysis

The first author was responsible for data statistics. The AISA motor score, the light touch score and the pinprick score were analyzed using the Review Manager 5.3 program for the two follow-up phases. Since the ASIA score is a measurement data, the weighted mean difference (WMD; 95% CI) was used as the statistical analysis amount. When \(F < 50\%\) and \(P > 0.1\), the results were considered to be homogenous, and the fixed effect model was selected. If \(F > 50\%, P < 0.1\), it was considered no homogeneity in each study, then a random effects model was used. If the source of heterogeneity could not be judged, no meta-analysis was performed.

### 3.4 Results

#### 3.4.1 Short-term efficacy outcome

Heterogeneity test showed that the short-term functional changes of motor, light touch and pinprick scores were homogenous in each study after transplantation (motor score, \(F = 0\%, P = 0.61\); light touch score, \(F = 24\%, P = 0.26\); pinprick score, \(F = 0\%, P = 0.45\)). Analysis using a fixed effect model suggested that the differences in the functional scores before and after OECs transplantation were statistically significant [motor score, WMD = 4.52, 95% CI (2.00, 7.03), \(P = 0.0004\); light touch score, WMD = 8.56, 95% CI (5.84, 11.28), \(P < 0.00001\); pinprick score, WMD = 9.54, 95% CI (6.81, 12.27), \(P < 0.00001\)]. This indicated that fetal OECs

| Author, Year | Operation time | Sample size | SCI to implant | Follow up | Object selection | Comparator | Result evaluation | Score |
|--------------|----------------|-------------|----------------|-----------|-----------------|------------|------------------|-------|
| Wu, J et al., 2012 [12] | 1/2004–12/2004 | 11 | 6~42 months | 12~18 months | 0 0 1 1 | 1 | 0 1 1 5 |
| Zheng, Z C et al., 2008 [17] | 6/2004–6/2007 | 114 | > 6 months | 2~4 weeks | 1 1 1 1 | 1 | 0 0 1 6 |
| Zheng, Z C et al., 2013 [18] | 7/2009–7/2010 | 43 | > 6 months | 3~8 weeks | 1 1 1 1 | 1 | 0 0 1 6 |
| Huang, H et al., 2006 [23] | 11/2001–1/2004 | 300 | 6 months–18 years | 2~8 weeks | 1 1 1 1 | 1 | 0 0 1 6 |
| Huang, H et al., 2012 [22]* | NA | 108 | NA | 3.47 ± 1.12 years | 1 1 1 1 | 1 | 0 1 1 7 |
| Dong, W et al., 2013 [29] | 9/2005–3/2010 | 24 | > 6 months | average of 3.2 years | 0 0 1 1 | 1 | 0 1 1 5 |

* confirmed with the author, this document is the final long-term follow-up data. A, selection of exposed group; B, selection of non-exposed group; C, determination of subject acceptance fetal OECs transplantation; D, the patient did not show the expected test results before the start of the trial; E, the exposed group is comparable to the non-exposed group; F, blind method; G: follow-up time (> 6 months);H, loss of visit rate < 10%.
transplantation significantly improved the movement and tactile function of SCI patients (Fig. 2).

3.4.2 Long-term efficacy outcome

Heterogeneity test showed that long-term changes of motor function, light touch and pinprick were homogenous in each study after transplantation (motor score, $I^2 = 0\%$, $P = 0.90$; light touch score, $I^2 = 0\%$, $P = 0.79$; pinprick score, $I^2 = 0\%$, $P = 0.71$). Analysis using a fixed effect model suggested that the scores of light touch and pinprick functional scores in patients with chronic SCI before and after OECs transplantation were statistically significant [light touch score, WMD = 6.92, 95% CI (1.33, 12.52), $P = 0.02$; pinprick score, WMD = 7.48, 95% CI (2.01,12.96), $P = 0.007$]. This shows that OECs transplantation significantly improved the long-term light touch and pinprick functions in SCI patients.

There was no statistically significant differences in motor function scores [WMD = 2.53, 95% CI (–1.20, 6.25), $P = 0.18$], indicating that OECs did not significantly improve long-term motor function in patients with chronic SCI. A meta-analysis of exercise, light touch and pinprick functions in patients with chronic OECs after long-term follow-up is shown in Fig. 3.

4 Discussion

Up till now, there are 4 countries in the world to carry out clinical trials of OECs transplantation for chronic SCI patients. The OECs’ sources include: fetal OECs which are obtained from human fetal olfactory bulbs, OMAS and/or autologous OECs obtained from autologous nasal mucosa. Since the transplantation methods and observation of efficacy indicators are different in these clinical trials, it is impossible to compare the efficacy of three different kinds of OECs.

The morphological and immunohistochemical properties of OECs from the olfactory mucosa and the

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Fig. 2  Short-term ASIA score of motor (A), light touch (B) and pinprick (C). (1) Complete paraplegia group; (2) incomplete paralysis group; (3) injured for 6 months to 2 years; (4) injured for > 2 years.
olfactory bulb are consistent. Moreover, OECs derived from their own sources have no defects in immune rejection and are thought to be the best cells for restoring the spinal cord function. However, these OECs in previous clinical trials have no uniform culture standards and transplantation specification. The trials have low reproducibility due to a small number of sample cases resulting in a lack of the efficacy of credible results. Perhaps due to these reasons, the guidelines do not recommend their protocols.

Fetal OECs derived from allogeneic sources are the first neurorestorative cells to be used in clinical trials. After rigorous screening and eliminating the repeated data, this study concluded that the total sample of clinical trials of fetal OECs in the treatment of chronic SCI reached 512, which basically met the sample requirements to prove the safety of clinical application. For the preparation and quality control of fetal OECs, Chinese Association of Neurorestoratology recommended the culture method and quality control standards of fetal OECs based on the previous clinical investigations [40]. By applying the standard protocol, the activity and purity of OECs could reach 95% and 90%, respectively. This is the only standard set for the OECs in the world that not only provides the basis for strict regulation of cell culture preparation in previous clinical studies, but also promotes the safety, efficacy and reproducibility of fetal OECs for clinical neurorestorative therapy for the future.

The investigators performed an analysis of six standard-compliant clinically studies of fetal OECs in the treatment of chronic SCI. The results showed that the short-term neurological function was significantly improved as evident by the motor score increased by 4.52 points (2.00, 7.03), the light touch score increased by 8.56 points (5.84, 11.28), and the pinprick score increased by 9.54 points (6.81, 12.27). Huang et al. [23] have hypothesized that the rapid functional recovery may be due to the mechanism of unmasking the quiescent axons that are still alive but not functioning.

In the long-term efficacy analysis, the light touch score increased by 6.92 points (1.33, 12.52) and the pinprick score increased by 7.48 points (2.01, 12.96). However, the motor score increased by an average of

![Fig. 3 Long-term ASIA score of motor (A), light touch (B) and pinprick (C). (1) Complete paraplegic group; (2) incomplete paralysis group; (3) foreign group; (4) good domestic rehabilitation group; (5) poor domestic rehabilitation group.](image-url)
2.53 points (−1.20, 6.25), suggesting that there was no significant difference in efficacy compared with the cell pre-operation. There are no experimental studies or systematic reviews available so far to identify this problem and analyze the cause of the decline in motor functions except Huang’s study [24].

Huang et al. [24] found that the group of poor rehabilitation had lower scores of neurological functions compared with the group of good rehabilitation ($P < 0.01$). One of the reasons is that intensive neurorehabilitation can enhance the neurological functional recovery including motor function after OEC therapy. This suggests that it is necessary to combine with long-term rehabilitation exercise after cell transplantation or other neurorestorative therapies to improve the neurological functions. Tabakow et al. [38] said that a combination of rehabilitation efforts after cell transplantation is beneficial for chronic SCI, and future controlled trials need to include a lengthy and intensive rehabilitation protocol to enhance the efficacy of the cell therapy. It appears that when OECs are gradually inactivated, the structure of nerves may not be restored any further. Thus, if the patients don’t maintain enough rehabilitation exercise, their motor function performance will decrease.

In addition, the immunological problems of fetal OECs cannot be ignored either. Chronic immune rejection may also lead to poor long-term efficacy. In order to improve the survival rate of transplanted cells and reduce the graft host response, Chen et al. [41] had performed human leukocyte antigen (HLA) matching and transplanted OECs in a group of patients with amyotrophic lateral sclerosis (ALS) and compared them with unmatched patients. HLA matching can further delay the progressive deterioration of ALS patients. However, due to the small sample size or lack of long-term follow-up, there was no significant difference found between these groups.

In terms of transplantation, except Rao’s trial [32] which used MR-guidance for injections, the other trials were performed by spinal surgery which is traumatic and requires high physical status of the patients. Several trials on assessing safety have found that adverse events in OECs transplantation are closely related to spinal surgery. In order to reduce the adverse reactions, future clinical research should carefully grasp the preoperative indications and try to explore a minimally invasive and effective transplantation method. A large number of animal studies have shown that intranasal delivery is a safe, minimally invasive and effective method for cell transplantation [42–45]. However, it has not been reported in clinical practices. Recently, the multi-center randomized controlled clinical trial of OECs intranasal delivery, led by the Chinese Association of Neurorestoratology, is carried out in China. The results of relevant research are awaited.

The clinical trials in this systematic review are self-controlled. Time window of these trails is chronic or squaledge. Therefore, the interference of spinal nerve self-repair can be ruled out, and the clinical efficacy of OECs is confirmed. On the other hand, many scholars consider that, in the chronic phase, a large number of neurons are atrophied and more scars are present in the traumatized spinal cord area. In such cases, the time for transplantation and the time window could be advanced. Khankan et al. [7] found that, in the acute phase, OECs can survive in SCI area for 8 weeks and prevents the acute inflammatory responses to reduce further damage of neurons. In other experiments, Resnick et al. [46] indicated that transplantation of OECs is not effective immediately after spinal cord contusion. Plant et al. [47] believed that the transplant effects in rats 7 days after injury was better than that of 30 minutes after injury. In summary, the best time window for OECs transplantation needs to be further explored.

In the design of the treatment, Huang et al. [24] proposed that if the neurological function is stable for 1.5 to 2 years, the patient could receive the transplantation again. For the patients with progressive deterioration a year after transplantation, a secondary transplantation is an optimal choice. A design of fractional injection therapy was also used in Rao’s trial [32]. However, since the above two studies are not RCT tests, it is still necessary to explore the design of the treatment further to improve the techniques.

In conclusion, this study systematically reviewed the sources of cell, path of transplantation, the doses, the time window, and the design of the treatment in the clinical studies of OECs transplantation for chronic SCI. In all circumstances, OEC or other neurorestorative therapies should combine with intensive neurorehabilitation. It is hoped that this review could reduce
the gap between the two major guidelines. However, there are still many more problems and bottle necks to be solved for the OECs clinical transplantation in the future.

**Disclosure**

The authors declare no conflict of interests for this paper.

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