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REVIEW ARTICLE

Review of clinical neurorestorative strategies for spinal cord injury: Exploring history and latest progresses

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ABSTRACT

Clinical neurorestorative therapies recently made great progress for patients with spinal cord injury (SCI). This paper systemically reviews historical perspectives, recent advancements and achievements in SCI through key neurorestorative strategies. In this study, a search was performed in the PubMed, Scopus, and Scholar Google search engines using the keywords "neurorestorative strategies", "spinal cord injury", "cell therapy", "neuromodulation", and "nerve bridges". Clinical studies published in the English language were included. It is paramount for academic community involved in this field to take the initiative of a multicenter randomized, double-blind, and placebo-control clinical study with high level of evidence-based treatments for most SCI neurorestorative strategies in patient management. It is of utmost need to establish standard therapeutic methods for patients with SCI as early as possible.

1 Introduction

Currently clinical neurorestorative therapies are able to help patients with central nervous system (CNS) diseases or damage for improving their neurological function and quality of life following complete chronic spinal cord injury (SCI), stroke, amyotrophic lateral sclerosis (ALS) and many other diseases [1, 2]. Although, these advancements were made in due course of time [3, 4]; incorrect viewpoints about clinical neurorestorative treatment strategies are still noticed in this area, with special reference to SCI. This appears to be a common misunderstanding that "there are no any methods for restoring damaged neurological structure or functions so far, or even partial restoration" [5]. These viewpoints fully neglect excellent contributions and achievements in the field. On the other hand, the results in SCI are described as one of the first neurorestorative achievements or breakthrough [6] using neurorestorative therapies.

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Thus, it is needed to revisit the history, progresses and achievements of SCI using neurorestorative strategies. In this review, pioneer trials and major achievement in several neurorestorative strategies in SCI are discussed.

2 Methods

A search of the PubMed, Scopus, and Google Scholar databases for peer-reviewed papers published in the English language was performed using the keywords "neurorestorative strategies", "spinal cord injury", "cell therapy", "neuromodulation", and "nerve bridges" between 1967 and 2018, all of which display the historical events, and recent main advancements and achievements in SCI treatment.

Review articles and/or non-original papers were excluded, along with duplicate publications of the same original study and letters to the editor. Original papers reporting a definitive intervention in a stated number of patients were included in the analysis. In the case of two or three publications emanating from one study, the version with the longest follow-up and/or fullest reporting was included. All the included studies had been approved by local institutional review boards.

3 Disscussion

Neurorestorative strategies in SCI include pharmacotherapy, surgical procedures (such as intramedullary decompression and nerve bridges), neural tissue or cell transplantation, neurostimulation, neuromodulation, brain machine interface (BMI), tissue engineering, bioengineering, intensive neurorehabilitation, omental transposition, and other combined modalities.

3.1 Pharmacotherapy

Neurorestorative pharmacotherapy is used to prevent secondary neural damage through neuroprotection. This modality would attenuate cellular apoptosis or necrosis leading to neuronal and axonal survival.

3.1.1 Methylprednisolone (MP)

Bracken et al. (1990) reported that high-dose of methylprednisolone (MP) administration is an effective therapy in SCI during acute phase. The national acute spinal cord injury studies (NASCIS) II and III, have shown improvement in motor function and sensation in patients with complete or incomplete SCI. This was once considered the first effective strategy of neurological restoration at an early stage of SCI [7–9]. However, soon it became controversial because of enough evidence of serious complications compared to benefits. These complications included infection, respiratory impairment, gastrointestinal bleeding, and even death. High-dose MP therapy is no longer used routinely in acute SCI, but remains an optional therapeutic approach in certain conditions [10–15]. The current recommendation is to treat all patients with SCI according to local or regional protocol if steroids are recommended.

3.1.2 Ganglioside (GM-1)

Geisler (1991) reported that GM-1 enhanced the recovery of neurologic function in SCI after one year of follow-up [16]. However, in 2001, a multicenter randomized, double-blind, and placebo-control clinical trial did not show significant differences between treatment group and control cases [17]. Thus, GM-1 is not recommended as a routine therapy in acute SCI [12, 18–20].

3.1.3 Other pharmacotherapeutic trials

Neither naloxone nor tirilazad mesylate therapy showed therapeutic benefits in patients with SCI in clinical trials [21]. Administration of human erythropoietin did not improve the functional outcome of patients with traumatic injuries to cervical spinal cord [22]. Although minocycline (Casha) showed a tendency towards improvement in several functional parameters in SCI, it failed to show restoring efficacy in SCI [23]. Acidic fibroblast growth factor (aFGF) [24] and granulocyte-colony stimulating factor (GCSF) have shown some benefits in cases of incomplete SCI [25], but more evidences and further studies are required.

Neurorestorative pharmacotherapy managment in SCI is still a long way to achieve progress in SCI treatment. It is worth mentioning that a small progress of restoring neurological functions by pharmacotherapy should be valued and explored further.

3.2 Neurorestorative surgery

There are two kinds of neurorestorative surgery for

SCI namely intramedullary decompression and nerve bridges.

3.2.1 Intramedullary decompression or myelotomy

Galanda (1974) and Yamada (1976) reported that myelotomy could help patients with spasticity or spasms in chronic SCI to improve their walking ability [26, 27]. Whereas, Borovich (1978) reported that myelotomy didn't improve patients' neurological functions in acute cervical cord injury [28]. Wu (1981) suggested that necrotic tissue should be washed out by saline or gently sucked in acute SCI [29] for better results. Tachibana (1984) and Koyanagi (1989) reported that myelotomy was effective in preventing secondary neurological damages in SCI [30, 31]. So far it remains controversial whether myelotomy or removing necrotic tissue in the central gray matter can be effective to prevent secondary damage in SCI and restore patients' neurological functions. Therefore, multicenter, randomized, double-blind, placebo-controlled clinical studies should be done to confirm evidence of neurorestorative effects.

3.2.2 Nerve bridges

Carlsson (1967) was the first to report that reconstructing efferent pathways to the urinary bladder for a paraplegic child resulted in urine control improvement [32]. Twenty years later, more experts started to perform similar surgical procedures for SCI, and showed partial neurological functional improvements [33–36]. Due to the nature of the invasive procedures, it is difficult to perform control clinical studies, hence nerve bridges are not routinely used methods in SCI. Larger randomized clinical studies are necessary to make this procedure a standardized treatment method for SCI.

3.3 Neural tissue or cell transplantation

3.3.1 Neural tissue transplantation

Iumashev (1989) reported that peripheral nerve transplant in SCI resulted in improvement of sensation and movement [37]. He (1995) transplanted fetal brain tissue and Falci (1997) transplanted embryonic spinal cord grafts in SCI for functional improvements [38, 39]. Afterward there were few reports of fetal or embryonic tissue transplantation in SCI.

3.3.2 Cell transplantation

Huang (2003) and Rabinovich (2003) reported that olfactory ensheathing cell (OEC) transplantation could restore some neurological functions for chronic SCI [40, 41]. Later on several other kinds of cells, such as bone marrow, mononuclear cell (BMMC), mesenchymal stromal cells (MSC) and etc., were used for SCI therapy through different transplanting ways and various kinds of other cells were used as combined therapy to treat SCI patients [42–47]. The majority of those cell therapy reports could help patients with SCI in recovering partial lost functions and improve their quality of life. But all these cell therapies did not become a routine treatment for SCI. The reason for no advancement in this area is the lack of clinical cell therapy trials in SCI through multicenter, randomized, double-blind placebo-control studies. Thus, the clinical trials of high level of evidence-based medical evidence is the key issue in this field.

3.4 Neurostimulation or neuromodulation and brain machine interface

3.4.1 Neurostimulation or neuromodulation

von Wild (2002) reported that computer added locomotion by implanted electrical stimulation in paraplegic patients showed some functional recovery [48]. Minassian (2004) found that stepping-like movements could be induced by epidural stimulation in humans with complete SCI [49] as shown in similar studies later [50–53]. Recently, more reports using this method showed positive results in patients with complete chronic SCI by partially restoring their standing and walking abilities [54, 55]

3.4.2 Brain machine interface

Simeral (2011) reported that implanting an intracortical microelectrode array could help a tetraplegic patient in neural control of cursor trajectory and click [56]. Hochberg (2012) showed that patients with tetraplegia using a neurally controlled robotic arm initiate function and grasp [57]. Onose (2012) reported that using motor imagery EEG-based brain-computer interface (BCI) could help chronic tetraplegics to do robotic arm control [58]. Collinger (2012) showed that a patient with tetraplegia is able to guide a robotic

arm with thoughts through high-performance neuroprosthetic control [59]. Mignardot (2017) reported that the multidirectional gravity-assist enabled natural walking in non-ambulatory individuals with SCI and enhanced skilled locomotor control [60].

3.5 Tissue engineering

Bryukhovetskiy（2015）reported that biodegradable polymers SpheroGel used to fill into a cavity of spinal cord for patients with SCI helped them in improving some of their neurological functions [61]. Zhao et al. reported NeuroRegen scaffold with human umbilical cord blood-mesenchymal stromal cells was effective in improving neurological functions for patients with chronic SCI [62]. This tissue engineering therapy did not fully clarify whether injured spinal tissue should be totally resected two months after injury and whether the procedure "totally resecting injured spinal cord tissue" is beneficial or harmful for SCI patients. It is known that patients with complete SCI have a potential to restore some neurological functions spontaneously or through neurorestorative therapies several years late [1, 2]. Tissue engineering should have a clear indication and contraindication for patients with complete SCI. Total excision of injured spinal cord must be carefully managed.

3.6 Bioengineering

Kucher (2018) reported that human anti-Nogo-A antibody was well tolerated in patients with acute complete SCI through intrathecal administration and showed some efficacy [63]. This antibody therapy still needs multicenter, randomized, double-blind placebo-controlled clinical trials.

3.7 Intense neurorehabilitation

McDonald (2002) reported that a patient with complete chronic SCI recovered from ASIA_A to ASIA-C through intense neurorehabilitation [64]. Later, more similar reports were published [65, 66]. Unfortunately, there are no multicenter, randomized, double-blind placebo-control trials for this method yet.

3.8 Omental transposition

Goldsmith (1986) reported that omental transposition treating patients with chronic SCI showed some functional recovery [67]. Following his study, some researchers reported similar results. However, this method did not show any further progress in the last ten years.

3.9 Other methods

3.9.1 Sural nerve graft

Cheng (2004) reported that sural nerve graft bridged and reconnected specific pathways of spinal cord from white to gray matter helped the patient recover some functions [68]. On the other hand Barros (2004) did not achieve similar results using the same method [69].

3.9.2 Hypothermic treatment

Negrin J (1973) showed that hypothermia was helpful for acute and chronic post-traumatic paraplegic patient [70]; yet this method is not employed to treat patients with SCI.

3.9.3 Acupuncture for spinal cord injury

Gao (1996) and Cheng (1998) reported that acupuncture treatment was helpful in complete SCI [71, 72]. Even though this therapy showed some help in SCI, it needs further evidence based evaluation.

3.10 Combined therapies

3.10.1 Different cell combination

Rabinovich (2003), Moviglia (2006) and Seledtsova (2010) reported that transplantation of OEC or/and BMMC combination in patients with SCI, showed some functional recovery [41, 73, 74].

3.10.2 Multiple routes of cell administration

Moviglia (2006) reported that combined protocol of cell therapy for chronic SCI by intravenous (IV) and intra-arterial (IA) showed electrical and functional recovery [46]. Geffner(2008) reported that autologous BMMCs via multiple routes was safe for patients with SCI and improve their quality of life [75].

3.10.3 Combined cell therapy and Laserponcture

Bohbot (2010) reported that olfactory ensheathing glia transplantation combined with LASERPONCTURE in human SCI showed improvement as measured by electromyography monitoring [76].

3.10.4 Cell therapy combination with neurorehabilitation

Huang (2012) reported that patients with chronic complete SCI following OEC transplantation in combination with intensive neurorehabilitation exercises showed better outcome compared to patients with minimal neurorehabilitation exercise [47].

4 Summary

It is very hard to make any progress in restoring neurological functions for SCI patients, particularly for chronic complete SCI; hence any scientific work or progress in this field should be highly welcomed. Currently these individuals with chronic complete SCI have chances to partially restore their neurological structure and functions through cell therapy, neuromodulation/neurostimulation, nerve bridges, intensive rehabilitation exercise and other related procedures [2]. It is likely that future neurorestorative therapies can result in a big breakthrough for patients suffering from chronic complete SCI and restore more functions. Researchers in the field of Neurorestoratology should respect pioneers' contribution and achievements in relation to their own work. The future of neurorestoratology relies on multicenter, randomized, double-blind, and placebo-control clinical studies to obtain higher level of evidence-based results. This would allow most SCI neurorestorative strategies to become standard treatment methods for patients with SCI.

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Disclosure

The authors declare no conflict of interests for this paper.

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