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The Application of Stem Cell Sheets for Neuronal Regeneration after Spinal Cord Injury: A Systematic Review of Pre-Clinical Studies

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 July 2023 and was last updated on 08 July 2023.

INTRODUCTION

Review question / Objective Does the application of stem cell sheets improve the treatment of spinal cord injuries in animal models?

Condition being studied Spinal cord injury (SCI) is a kind of central nervous system disease with high morbidity and disability rate. At present, the commonly used clinical treatment methods such as surgery, glucocorticoid, hyperbaric oxygen therapy can only slightly delay the aggravation of secondary injury, but can not solve the problem of nerve regeneration. Therefore, finding an effective way of nerve regeneration after SCI has become a research hotspot in SCI in recent years. Stem cell sheets technology can effectively promote nerve repair and regeneration after SCI by continuously cultivating high-density cells in vitro and promoting extracellular matrix secretion to form a membrane composed of cells and extracellular matrix. This study will evaluate the effects of the application of stem cell sheets to treat spinal cord injuries in animal models. It can pave the way for further preclinical study and, ultimately, clinical study to treat spinal cord injuries.

METHODS

Participant or population All animal models with spinal cord injury are included without restriction on animal species and modeling methods.

Intervention Stem cell sheets.

Comparator Stem cell suspension injection, blank, Gelatin sponge, normal saline, PBS, vehicle, cultural medium.

Study designs to be included control studies.

Eligibility criteria The following criteria were used to determine eligibility for inclusion in this study: (1) use of stem cell sheets; (2) in vivo studies utilizing the SCI animal model; (3) manuscripts written in English. The following types of studies were excluded: (1) manuscript designs including reviews, systematic reviews, meta-analyses, case reports, guidelines, clinical studies, conference

proceedings; (2) studies without a separate control group; (3) non-available full-text.

Information sources A thorough literature search of electronic databases was performed, including PubMed–MEDLINE, EMBASE, and Web of Science. The search terms used for exhaustive searches against the three databases were: “cell sheet OR cell sheets OR cell aggregates OR scaffold-free” AND “spinal cord injury OR spinal cord injuries OR spinal injury OR spinal injuries OR spinal cord trauma OR spinal cord transection OR post-traumatic myelopathy OR spinal cord laceration OR spinal cord contusion.” Only studies published in English were included. We screened the reference lists of included studies for additional eligible studies not retrieved by our search.

Main outcome(s) The outcome measures for this systematic review were as follows: (1)improvement of locomotor function measured by Basso-Beattie-Bresnahan (BBB) scale or grip strength test in SCI-induced animal models observed after the application of stem cell sheets; (2)improvement of sensory function measured by Von Frey test in SCI-induced animal models observed after the application of stem cell sheets; (3) axonal regeneration in the lesion site of spinal cord assessed by histological analysis.

Quality assessment / Risk of bias analysis Using SYRCLE's Risk of Bias tool for animal research, two reviewers conducted independent assessments of the quality of the articles that were included in the analysis. The following ten criteria were used to assess possible bias in the enrolled studies: (1) sequence generation, (2) baseline characteristics, (3) allocation concealment, (4) random housing, (5) blinded animal intervention, (6) random outcome assessment, (7) blinded outcome assessment, (8) incomplete outcome data, (9) selective outcome reporting, and (10) other types of bias. A third reviewer was consulted to settle any disagreements of opinion that may have arisen. Each study was graded to either be of “low,” “high,” or “unclear” risk.

Strategy of data synthesis The data extracted from each eligible study were qualitatively synthesized in the main text of the article. A meta-analysis could not be conducted due to the high heterogeneity of available data. The data categories extracted from each eligible article were as follows: (1) 1st author; (2) year; (3) type of stem cell; (4) type of Graft; (5) donors; (6) stem cells characterization; (7) cell sheets characterization; (8) cell differentiation at application; (9) type of animals; (10) animal model; (11) study cohorts; (12) follow-up; (13) outcomes. When pertinent studies were identified but the required information was not found in the published article, we would attempt to contact the original authors if necessary.

Subgroup analysis None planned.

Sensitivity analysis None planned.

Country(ies) involved China.

Keywords Spinal cord Injury, stem cells, cell sheets, regenerative Medicine, tissue engineering, systematic Review, animal experiments.

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