INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Stem cell therapy for peripheral nerve injury: An up-to-date meta-analysis of 55 preclinical researches

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Review question / Objective: **It has been the gold standard for decades to reconstruct a large peripheral nerve injury with a nerve autograft, and this remains true today as well. In addition to nerve autografts, biological conduits and vessels can also be applied. A fair amount of studies have examined the benefits of adding stem cells to the lumen of a nerve conduit. The aim of this meta-analysis was to summarize animal experiments related to the utilization of stem cells as a luminal additive when rebuilding a peripheral nerve injury using nerve grafts.**
Eligibility criteria: **The inclusion criteria were as following: 1.Reconstruction of peripheral nerve injury; 2.Complete nerve transection with gap defect created; 3.Animal in-vivo models; 4.Experimental comparisons between nerve conduits containing and not containing one type of stem cell; 5.Functional testing and electrophysiology evaluations are performed. The exclusion criteria were as following: 1.Repair of central nervous system; 2.Nerve repair is accomplished by end-to-end anastomosis; 3.Animal models of entrapment injuries, frostbite, traction injuries and electric injuries; 4.Nerve conduits made from autologous epineurium; 5.Clinical trials, reviews, letters, conference papers, meta-analyses or commentaries; 6.Same studies have been published in different journals under the same or a different title.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 October 2022 and was last updated on 20 October 2022 (registration number INPLASY2022100083).

INTRODUCTION

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Rationale: Research on stem cells' potential to enhance peripheral nerve regeneration has been met with enthusiasm and has been followed up by further research. The majority of such studies, however, were single-center and small-sized. It is costly and difficult to conduct large-scale or multi-centre experiments in the meantime. For years, only one previous meta-analysis was conducted eight years ago, and therefore numerous researches undertaken in recent years were not included. In order to provide one more comprehensiveand rigorous assessment of the effectiveness of different types of stem cells in enhancing regeneration after peripheral nerve injury, up-to-date meta-analysis is warranted.

Condition being studied: The aim of this meta-analysis was to summarize animal experiments related to the utilization of stem cells as a luminal additive when rebuilding a peripheral nerve injury using nerve grafts.

METHODS

Search strategy: A systematic search of PubMed, Cochrane, Embase, and Web of Science was conducted from January 1, 2000 to September 21, 2022. Here is a combination of Medical Subject Headings (MeSH) terms and free words we used: ("peripheral nerve injuries" OR "peripheral nerve defect") AND ("nerve regeneration" OR "nerve tissue regeneration" OR "neural tissue regeneration" OR "nervous tissue regeneration" OR "nerve reconstruction" OR "nerve repair") AND ("stem cells" OR "progenitor cells"OR "mother cells"OR "colony-forming unit"). Merely original English-language research papers were searched. The final eligibility of retrieved papers was determined by two adjudicators separately scrutinizing their titles and abstracts.

Participant or population: Animal models of peripheral nerve injury.

Intervention: Nerve conduit filled with stem cells.

Comparator: Empty nerve conduit (without stem cells).

Study designs to be included: No special restrictions.

Eligibility criteria: The inclusion criteria were as following: 1.Reconstruction of peripheral nerve injury; 2.Complete nerve transection with gap defect created; 3.Animal in-vivo models; 4.Experimental comparisons between nerve conduits containing and not containing one type of stem cell; 5.Functional testing and electrophysiology evaluations are performed. The exclusion criteria were as following: 1.Repair of central nervous system; 2.Nerve repair is accomplished by end-to-end anastomosis; 3.Animal models of entrapment injuries, frostbite, traction injuries and electric injuries; 4.Nerve conduits made from autologous epineurium; 5.Clinical trials, reviews, letters, conference papers, meta-analyses or commentaries; 6.Same studies have been published in different journals under the same or a different title.

Information sources: A systematic search of PubMed, Cochrane, Embase, and Web of Science was conducted from January 1, 2000 to September 21, 2022. Here is a combination of Medical Subject Headings (MeSH) terms and free words we used: ("peripheral nerve injuries" OR "peripheral nerve defect") AND ("nerve regeneration" OR "nerve tissue regeneration" OR "neural tissue regeneration" OR "nervous tissue regeneration" OR "nerve reconstruction" OR "nerve repair") AND ("stem cells" OR "progenitor cells"OR "mother cells"OR "colony-forming unit"). Merely original English-language research papers were searched. The final eligibility of retrieved papers was determined by two

adjudicators separately scrutinizing their titles and abstracts.

Main outcome(s): Sciatic Functional Index (SFI), muscle mass ratio (MM), and electrophysiological parameters (amplitude, latency, and nerve conduction velocity) were the main outcomes of this study.

Quality assessment / Risk of bias analysis: The literature quality evaluation was performed independently by two researchers employing the Review Manager software risk assessment tool (RevMan 5.3; Cochrane Collaboration, Oxford, UK), in accordance with the SYRCLE's risk of bias tool; third parties were consulted when opinions were inconsistent to reach a consensus. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines were followed for reporting this meta-analysis. Version 15.1 of STATA (Stata Corp, Texas, USA) was used to perform statistical analyses.An overall pooled estimate [with a 95% confidence interval (CI)] was calculated for every study included. A random-effects model and sensitivity analysis were used if there was heterogeneity among studies; otherwise, a fixed-effects model was used. Heterogeneity of effect sizes was computed using the I2 index, which evaluated the degree of heterogeneity of individual results. An I2 statistic greater than 75% suggested considerable heterogeneity among the studies. Forest plots were used to visually display the results of the individual studies and pooled estimates. Egger's and Begg's tests were used to assess publication bias. The p-value of a value was considered statistically significant when it was less than 0.05 ($p < 0.05$).

Strategy of data synthesis: Stata 15.1 (Stata Corp, Texas, USA) was used to analyze the data. SMD (95%CI) combined effect size was used as the continuous variable. I2 is used to evaluate heterogeneity. If the heterogeneity test is $p \geq 0.1$ and $I2 \leq 50\%$, it indicates that there is homogeneity between studies, and the fixed effects model is used for combined analysis; if $p<0.1$ and $I2>50\%$, it indicates that the study If there is heterogeneity, use sensitivity analysis or subgroup analysis to find the source of heterogeneity. If the heterogeneity is still large, use the random effects model or give up the combination of results and use descriptive analysis.

Subgroup analysis: Based on different follow-up durations, subgroup analyses were conducted.

Sensitivity analysis: Sensitivity analysis was carried out by STATA 15.1 (Stata Corp, Texas, USA) to test the stability of the meta-analysis results.

Language restriction: English.

Country(ies) involved: China.

Keywords: stem cells; peripheral nerve injury; animal experiments; meta-analysis.

Contributions of each author:

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