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The role of stem cell secretome on spinal cord injury regeneration: a systematic review and meta-analysis

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ABSTRACT

Background: The treatment of spinal cord injuries (SCIs) is a controversial topic and is not yet effective. Stem cell secretome is an emerging alternative treatment that uses the paracrine effect of stem cells. Although there have been many studies on this subject, there are still differences regarding the origin, dose, route of secretome administration, type of experimental animal, phase of the SCI, and outputs evaluated. The topic needs a systematic review and meta-analysis.
Methods: This systematic review and meta-analysis were reported based on criteria from Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The authors searched PubMed, ScienceDirect, Cochrane Library, and Google Scholar with multiple electronic databases until October 2021.
Results: Twenty-eight studies that met the inclusion criteria were included in this research. The stem cell secretome was very beneficial as the axonal regeneration agent (n=12); it increases the locomotor recovery (n=28) and growth factors (n=2) and reduces the size of the cystic cavity (n=1) and lesion extension (n=14). We recognized 28 studies that met our inclusion criteria. Stem cell secretome therapies showed improvement in the locomotor score (standard mean difference [SMD]: 0.94; 95% confidence interval [CI]: 0.75–1.13, $p<0.000001$, $I^2=90\%$) and reduction in the lesion size (SMD: 5.06; 95% CI: 3.44–6.67, $p<0.00001$, $I^2=94\%$).
Conclusion: The stem cell secretome greatly affects treating SCI rodent models. Future studies should focus on chronic SCIs in the primary research, translational research, and neurological research stage of stem cell secretome.

Keywords: Regeneration, Stem Cell Secretome, Spinal Cord Injury, Treatment.
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INTRODUCTION

Spinal cord injuries (SCIs) are commonly found in active patients with complicated neurological conditions.[1-3] They can cause death and present a socioeconomic burden.[4-6] Wang H et al. state that many factors, including neuroplasticity, the microenvironment, inflammation, apoptosis, ischemia, reactive gliosis, and glial scar formation, inhibit SCI repair.[7]

Many researchers investigated how to improve SCI treatments, but neuroprotective and neuroregenerative agents are still uncertain solutions.[8–10] Stem cell therapies, in particular, are showing great promise. Several cell types have progressed to clinical trials, including neural stem cells (NSCs), bone marrow aspirate stem cells, and mesenchymal stem cells (MSCs).[5,11,12] Cunningham CJ et al. stated that after 14 days of stem cell injection in the tail vein of rats, only about 4% of stem cells were found in the brain with ischemic injury, with 10% still alive[13]. Paracrine actions mediate stem cell transplantation.[14–16] Stem cell secretomes are non-cell metabolites secreted from stem cells that contain cytokines, chemokines, growth factors, extracellular vesicles (EVs), and exosomes.[13,17,18] These EVs are membrane-bound vesicles that play an important role in intracellular signaling.[19,20] EVs can be characterized by their biogenesis: apoptotic bodies (500–4,000 nm) arise as a result of plasma membrane blebbing and cell disintegration during apoptosis; microvesicles (50–2,000 nm) bud directly from the membrane, and exosomes (30–100 nm) are released when a multivesicular body fuses with the membrane.[21,22] While EVs can contain proteins and lipids, most research into central nervous system repair therapies focuses on the mRNA and microRNA cargo.[4,23,24]

Acellular secretome therapies hold great translational potential and have several advantages over conventional cell therapies, including mitigating the risk of immune rejection, reducing the risk of tumourigenesis, and having the ability to cryopreserve treatments without needing to consider the issues of maintaining cell viability.[13] Other advantages include safety control, mass production, use in emergency cases, affordability, and practicality for neurological applications.[18] This study aims to review and analyze the therapeutic effect of the stem cell secretome on SCI repair in a rodent model.

METHODS

Study methodology

The PICOS (Population, Intervention, Comparison, Outcome, Study Design) criteria used in this study are based on the following: the population is spinal

cord injury model-rodentia; intervention is stem cell conditioned medium or secretome (mesenchymal stem cell, neural stem cell, olfactory ensheathing stem cell, embryonic stem cell, human exfoliated deciduous teeth stem cell); comparison is normal saline or placebo; outcomes are histopathologic changes, biomarker or immunologic changes, and neurologic changes (motoric, sensory, and autonomic); and study design is in vivo studies using spinal cord injury model-rodentia. We adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

The following criteria were considered for the study's eligibility: type of study, animal samples, index test, and reference standards. The type of studies included in our systematic review were original research articles, and research reports conducted using rodents as animal models were included. Narrative reviews, systematic reviews, meta-analyses, non-comparative research, in vitro studies, technical reports, editor responses, scientific posters, study protocols, conference abstracts, cross-sectional, case-control, and randomized controlled trials (RCT) were excluded. Articles without full-text availability, non-English, and irrelevant topics were also excluded. The study that used spinal cord injury models in rodents treated with stem cell secretome as study samples were included in this study. There was no limitation for the type of spinal injury method or rodent species.

After the stem cell secretome administration to the SCI rodent model, the outcome is measured by the lesion size and behavioral assessment using the Basso-Beattie-Bresnahan (BBB) locomotor rating scale. The BBB locomotor is a well-established and widely recognized ordinal scale with discrete values ranging from 0 to 21 or no observable hind limb movement to well-coordinated body movements.[3,5] Although the BBB score is a subjective observation of limb movement and walking characteristics in an open field environment originally designed for assessing rats, the adaptation of this scoring system in other rodent species (i.e., mice) using the Basso Mouse Scale (BMS) has also emerged and has been validated for observing mice locomotor functions.[12,25,26]

A positive correlation exists between spinal cord regeneration and an increased BBB scale.[27] The extent of the injury in the spinal cord and treatment efficacy could be evaluated by observing the behavioral outcomes in experimental SCI animal models. The degree of neuronal destruction in the gray matter of the injury region is related to activity levels. These behavioral outcomes have also been linked to the loss of ascending and descending axons in the white case along with the reorganization of the remaining functional nervous system.[1,5]

Studies were included evaluating the BBB or BMS score of SCI model rodents after a stem cell or secretome treatment. Studies without BBB or BMS mean difference and standard deviation (SD) were included only in the qualitative analysis. The reference standard was experimental laboratory research performed by qualified professionals by evaluating the effect of stem cell secretome treatment on histopathologic outcomes, biomarker or immunologic change outcomes, and neurologic outcomes.

Data sources and search

A literature search was carried out with multiple electronic databases, such as PubMed, ScienceDirect, Cochrane Library, and Google Scholar. The search was conducted from the inception of the database until October 2021. The keywords used in electronic databases were described using the following Boolean operators: (["Secretome" or "Secreted Factors" or "Secreted Proteins"] and ["Neuroregenerative" or "Regenerative" or "Regeneration"] and ["Spinal Injury" or "Spinal Cord Injury" or "Cervical Myelopathy"]). All the studies from these databases were stored in the authors' library in EndNote X9 (Clarivate, USA).

Study selection

After removing duplicates, retrieved articles were screened by two independent reviewers based on their titles and abstracts (INS and NMM). Potentially eligible full-text articles were thoroughly assessed using the eligibility criteria described above. Any emerging discrepancies were resolved by consensus among the review team. The study selection process was recorded in the PRISMA flow chart.

Data extraction and analysis

Selected studies were extracted with Microsoft Excel 2016 (Microsoft Corporation, USA). The following data were recorded: first author, year, region, study design, sample size, stem cell secretome type, aim, SCI type, dose, administration, assessment period, and outcome results (histopathologic, biomarker and immunologic changes, and neurologic). All statistical tests for this meta-analysis were conducted using Review Manager (RevMan) v5.3 (Cochrane Collaboration, UK).

Risk of bias in individual studies (qualitative synthesis)

The quality of each study included in this systematic review was assessed by two independent reviewers (HS and BDV) according to the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) Risk of Bias (RoB) tool, an adapted version of the highly established Cochrane RoB tool developed by the SYRCLE. We excluded studies with a high RoB from the meta-analysis to maintain the present study's robustness.

Quantitative data synthesis (meta-analysis)

Mean difference and SD with a standard mean difference (SMD), and the confidence interval (CI) of 95% were calculated in this study. To determine the effect size, either a fixed-effect model (FEM) or random-effect model (REM) was used based on the heterogeneity level. The FEM was used when the included studies were considered homogenous (low variability in studies' results or variation due to random error), indicated by an I^2 value of less than 50%. Otherwise, a REM was used. The pooled estimate was presented in a forest plot.

Risk of bias across studies (publication bias)

When a minimum of 10 studies were available for meta-analysis, publication bias would be evaluated by generating

a funnel plot with RevMan v5.3. An asymmetrical shape indicates the presence of publication bias potential, whereas a symmetrical shape indicates the absence of publication bias.

Additional analysis

When we encountered unclear decisions, a sensitivity analysis was planned by repeating the meta-analysis using alternative decisions.

RESULTS

Study selection

Our search yielded 4,182 articles. Seventy-two duplicates were removed. Then, the authors read the titles and abstracts of the remaining 4,110 articles for preliminary screening. The authors excluded the articles that did not fulfill the eligibility criteria. Full texts were retrieved for 46 articles, and 16 studies were excluded with reasons (six in vitro studies, four studies with different outcomes, three irrelevant studies, two review articles, and one study protocol). Other than that, there was one study with a different intervention, and one study was an updated version of another study. Finally, 28 studies were included for qualitative analysis. Our study selection process was presented in the PRISMA diagram, as depicted in Figure 1.

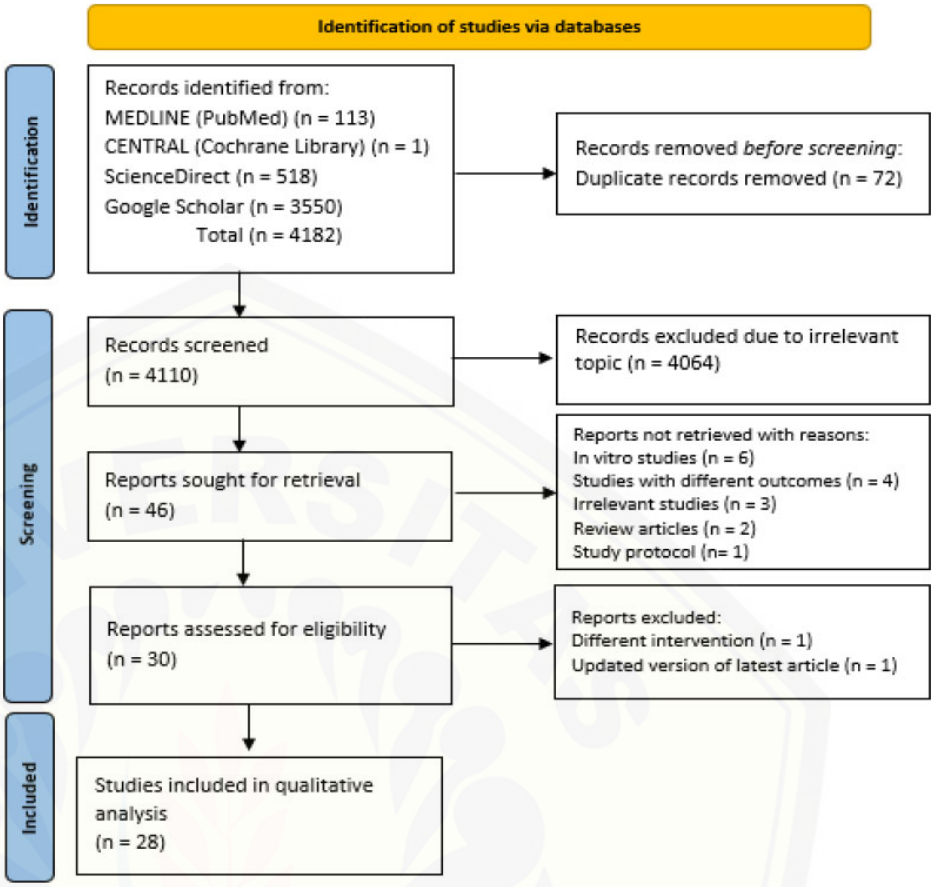

Figure 1. PRISMA flow chart summarizing the literature search and number of included studies.

Study characteristics and results of individual studies

These studies' subjects were rodents with SCIs receiving stem cell secretome treatment. We focused on the outcome (histopathologic, biomarker and immunologic changes, and neurologic factors). The studies were conducted in rats (n=23), with the remainder utilizing mice (n=5), using SCI models: contusion (n=16); compression (n=8); hemisection (n=3); and complete transection (n=1). The injury level of 28 studies is thoracic (T7–12). The secretomes were derived from MSCs (n=19) and NSCs (n=5), whereas the routes of administration were intravenous (n=16), intrathecal (n=9), and intraperitoneal (n=3). The stem cell secretome was very beneficial, as the axonal regeneration agent (n=12) increases the locomotor recovery (n=28) and growth factors (n=3) but reduces the size of cystic cavities (n=4) and lesion extension (n=14).

Five of the 28 studies included in the qualitative synthesis did not provide the BBB/BMS score. In two studies, we could not extract the BBB/BMS score as the mean, and SD data was unavailable in both groups and the control group.[28,29] Of the 10 studies that provided a BBB score, four were excluded from the meta-analysis, as the treatment was administered one to two weeks after SCI induction surgery. In contrast, the remaining studies administered the treatment within 24 hours after SCI induction.[30,31-34] Recent literature shows that the secretome administration's timing plays a crucial role in neuro-generative effects, having the most promising effects in acute treatment (48 hours post-SCI).[35] Thus, including these studies in the meta-analysis will induce a bias (intervention bias). In addition, the study by Munter JP et al. used T-cell deficient rats, making a difference in the baseline characteristics.[32] This study was judged as having a high RoB and excluded from the meta-analysis.

Risk of bias in individual studies (qualitative synthesis)

We critically assessed the quality of each study with the SYRCLE tool. Most studies did not provide adequate information regarding the bias domains' judgment, leading to an unclear (moderate) RoB. Three studies had a high selection bias caused by the difference in baseline characteristics, as they either administered immunosuppressive agents for the rats or used immunocompromised rats.[32] The study by Lu Y et al. did not report adequate follow-up data or the loss of participants.[28] Eight studies had a high bias in other categories arising from different outcome measurement scoring systems and a different intervention administration timeline.[29,30]

Quantitative data synthesis (meta-analysis)

We compared the pooled effect size of stem cell secretome treatment on rodents with SCI to trigger neuro-generative progress based on the BBB/BMS scale's

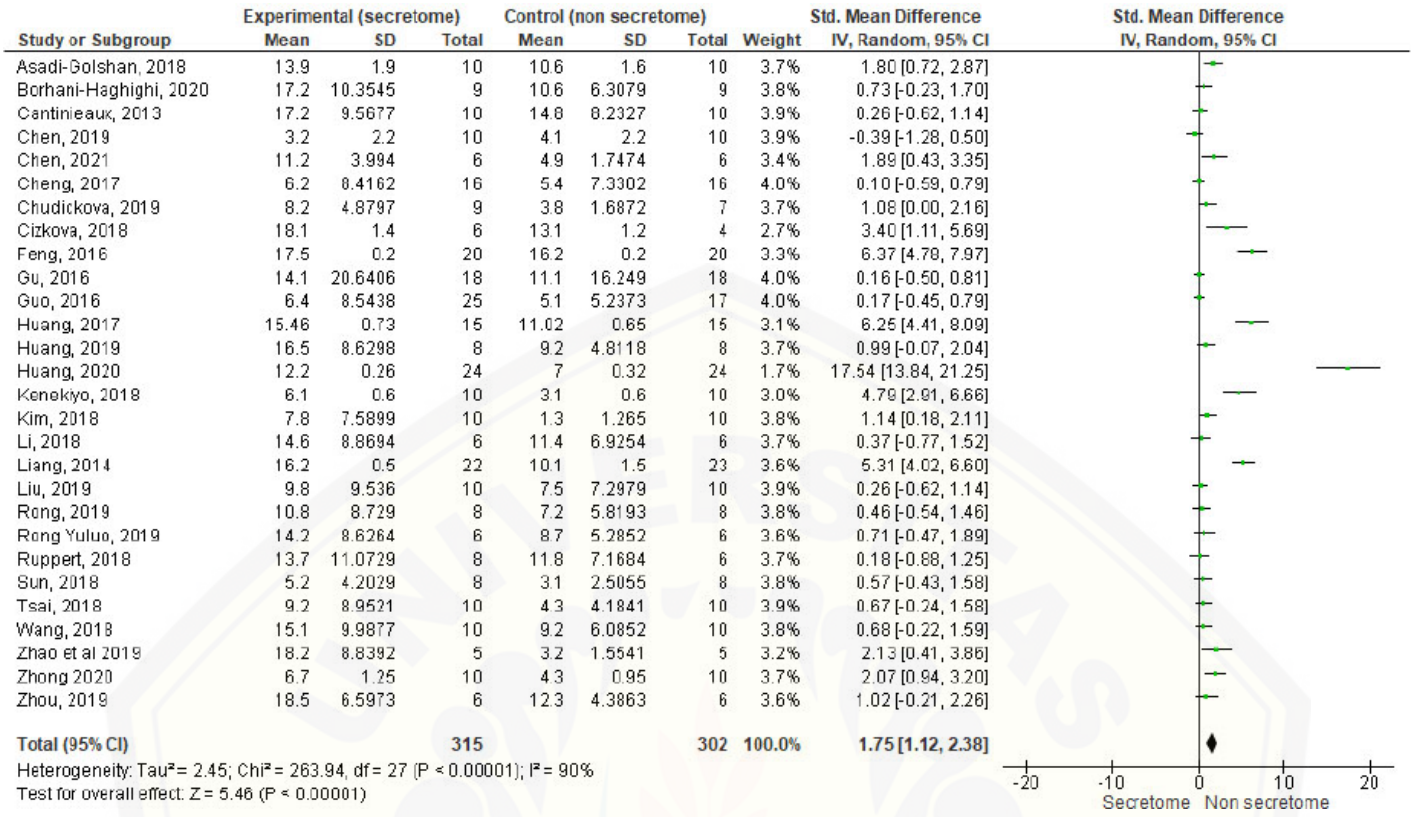

Figure 2. Forest plot showing random effect models of stem cell secretome therapies on the locomotor score. A positive SMD represents an improvement in locomotor score. Points indicate effect size estimates for each comparison, and error bars are 95% CIs. Point size indicates the relative weight of each estimate. The diamond represents the overall effect size, and the diamond width is 95% CI.

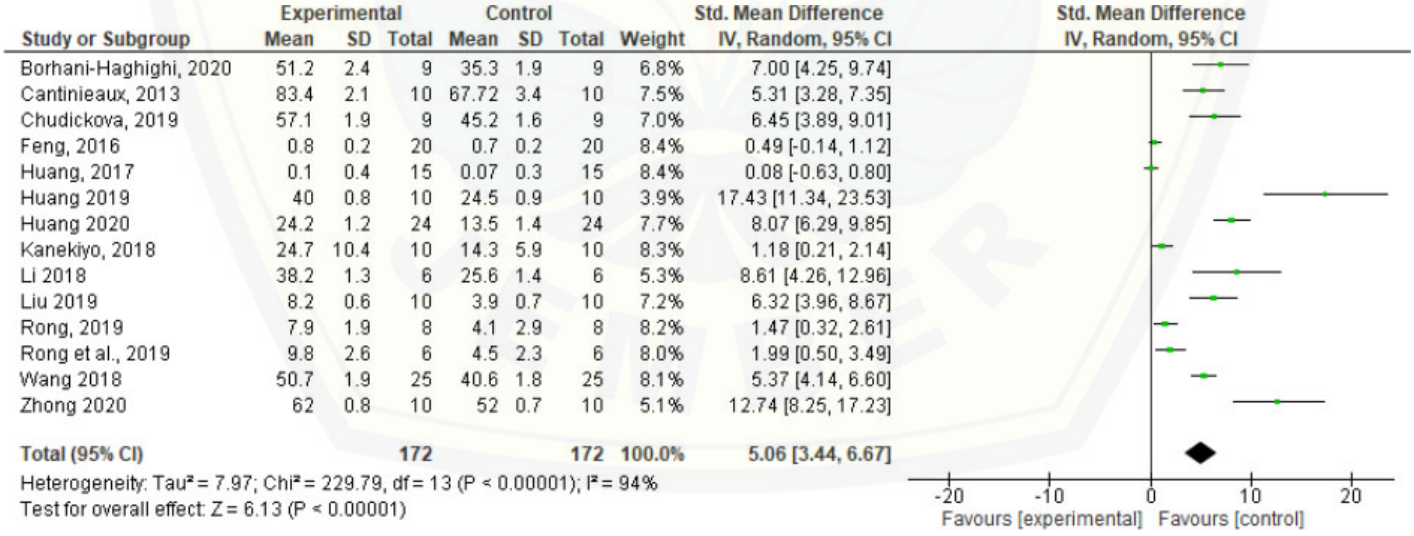

Figure 3. Forest plots showing random effect models of stem cell secretome therapies on secondary outcome measure lesion size. Positive SMDs demonstrate a reduction in lesion volume. The dots indicate effect size estimates for each comparison, and the error bars are 95% CIs. The dot size indicates the relative weight of each estimate. The diamond shape represents the overall effect size, and the diamond width is 95% CI.

improvement and lesion size. We used the last BBB/BMS scale improvement assessment for each study that compared the stem cell secretome and control groups. Overall, stem cell secretome therapies improved locomotor scores compared with the control group (SMD: 0.94; 95% CI: 0.75–1.13, p<0.000001, I^2=90%). A moderate pooled effect size was observed and presented on the forest plot in Figure 2. It was also found that stem cell secretome therapies reduce the lesion size compared with the control group (SMD: 5.06; 95% CI: 3.44–6.67, p<0.00001, I^2=94%). A moderate pooled

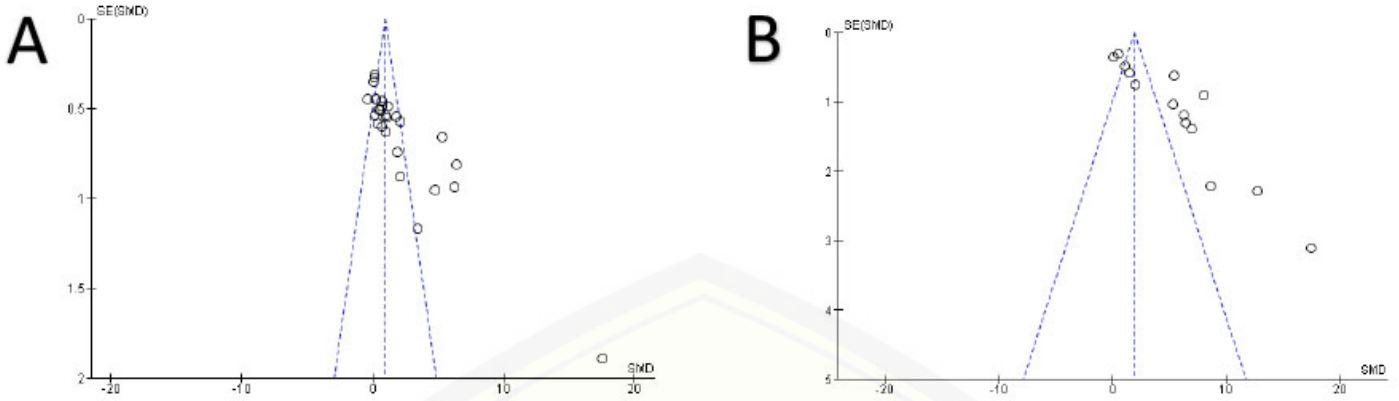

Figure 4. Assessment of publication bias: (A) Funnel plots show pronounced asymmetry in the locomotor score and (B) lesion size. White funnels show 95% CIs.

effect size was observed and presented on the forest plot in Figure 3.

Risk of bias across studies (publication bias)

A publication bias analysis with a funnel plot was conducted in 28 studies for locomotorius score and 14 for lesion size. Generating a funnel plot analysis when more than 10 studies are included will raise the test's power, and thus, the result will not be questionable, as seen in Figure 4.

Additional analysis

As the study focused on BBB/BMS scale improvement after stem cell secretome treatment, the researchers also performed a descriptive analysis based on different BBB/BMS evaluation times. The mean and standard errors from each study were summarized. The development of locomotor recovery post-stem cell secretome treatment was mainly significant in the first 28 days (four weeks) in three included studies and 56 days (eight weeks) in seven.

We also performed a sensitivity analysis by repeating the meta-analysis using all 10 studies that provided a BBB/BMS score. It yielded a heterogeneity as high as 98% (not presented) upon inclusion. High heterogeneity may cause inaccurate estimate effects; therefore, only moderate or better scores were included in the quality studies in the meta-analysis.[5,36] Nevertheless, this finding proved that the difference in treatment administration timeline and baseline characteristics might play a role in the overall effects.

DISCUSSION

Our systematic review suggested a beneficial effect of stem cell secretome in the SCI animal model. This review used individual participant-level data to examine the effects of stem cell secretome on SCI treatment. The researchers found that most studies reported that all samples treated with stem cell secretome reduced lesion size and developed significant locomotor recovery improvement based on the increase of the mean BBB/BMS score post-SCI. This implied that stem cell secretome transplantation on the spinal cord effectively increased the development of axons in the spinal cord. This neuroregeneration was significantly increased in 28 days and 56 days following SCI treatment with stem cell secretome.

Bone marrow and adipose tissue are the long-established sources of MSCs in clinical stem cell research.[37,38] Although bone marrow-derived MSCs remain the gold standard and are most thoroughly identified in the literature, other sources of MSCs are believed to share unique characteristics of morphology, plastic adherence, and differentiation potential. In other words, various types of stem cells can be used to treat SCIs.[5,36] As a result, a new paradigm was proposed regarding the transplanted stem cells' ability to secrete bioactive molecules crucial for promoting restorative endogenous responses.[39,40] These molecules are released at the level of the injured tissue's microenvironment, including the spinal cord.[1,25]

Despite the unclear association between locomotor recovery and stem cell secretome isolated from specific tissues, the researchers suggest that this treatment has a promising beneficial effect on treating SCIs.[41,42] Stem cell secretome application in regenerative medicine has now unlocked new perimeters capable of tackling many neurological disorders.[36,43,44] Stem cell secretome acts on different pathways to preserve degenerating neural tissue.[45,46] The anti-inflammatory effects of stem cell secretome are at least partially mediated by the soluble immunoregulatory molecule.[47,48] The anti-inflammatory cytokines present in stem cell secretome are tumor necrosis factor 1, interleukin (IL) 10, IL13, IL27, IL18-binding protein, IL1 receptor antagonist, IL17E, IL12p70, ciliary neurotrophic factor, and neurotrophin 2. In contrast, the pro-inflammatory cytokines within stem cell secretome are IL1b, IL6, IL8, and IL9.[13,49]

The neuro-generative effects of stem cell secretome were shown with the beneficial effects of the secretome-based approach on nerve injury models. These effects include inflammatory environment modulation at the site of the lesion, increased vascularization of the regeneration site, increased myelin sheath thickness, Wallerian degeneration stage modulation, fibrotic tissue modulation, and accelerated fiber regeneration.[17,18]

The key role of stem cell secretome as a neurogenic modulator has also been reported recently. Both NSCs and MSCs release a growth factor panel.[9,10] A combination of various strategies to prevent secondary injuries utilizing diverse cell therapies is considered multi-protective. It,

therefore, serves as a promising treatment modality for SCI injury, as shown in pre-clinical SCI model research.[50-53] However, we could not detect the associations between locomotor recovery and cell dose for each administration route because of the wide variety of sample cells and administration.[1,21] Therefore, the result of this meta-analysis should be interpreted with caution.

We performed an extensive RoB analysis to critically appraise the studies included in this review as an attempt to provide the most credible evidence. Therefore, the results of this paper are still considerable evidence of the positive effects of stem cell secretome as an alternative treatment for SCI. The limitations of this meta-analysis, researchers did not perform a quantitative analysis of the indicators of changes in the number of vascular (angiogenesis), axon regeneration, neural relay formation, and myelin regeneration as success variables of spinal cord injury regeneration. Future reviews and meta-analyses are expected to be more complete so that the next research can be continued in clinical trials.

CONCLUSION

This systematic review and meta-analysis revealed that stem cell secretome treatment for SCIs has excellent potential. At the same time, this treatment is associated with lesion size and locomotor recovery, as shown by the improvement of the BBB/BMS scale. The present study also demonstrates that stem cell secretome treatment has a favorable sensitivity for developing neuro-generative activity of the spinal cord. Hence, this systematic review and meta-analysis provide valuable evidence for using stem cell secretome as a potential treatment for SCIs.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ETHICAL CONSIDERATIONS

None.

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AUTHOR CONTRIBUTION

INS contributed to literature searching, data acquisition, data and statistical analysis, manuscript preparation and editing. DU and HS contributed to the concept, design, definition of intellectual content, data and statistical analysis, and manuscript review.

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