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Controlled clinical trials of cell therapy in stroke: Meta-analysis at six months after treatment

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Abstract

Background: Cell therapy is promising in experimental studies and has been assessed only in a few studies on humans.

Aims: To evaluate the effect of cell therapy in humans.

Methods: We included clinical trials with a control group that reported safety and efficacy six months following treatment. Quality was evaluated and clinical scales data were extracted. Quantitative analysis was based on the standardized means difference (SMD). Among 28 trials published from 1995 to 2016, nine studies (194 patients; 191 controls) were eligible. Publication biases were assessed with the funnel plot and pre-specified explanatory variables were tested with a group analysis and a meta-regression.

Results: The overall quality was moderate. Cell therapy had a positive effect on the outcome (SMD: 0.57, 95% CI: 0.22–0.92; $p = 0.002$). The sensitivity analysis showed an upper level of effect size of 0.81 (95% CI: 0.34–1.27; $p = 0.001$) and a lower level of 0.455 (95% CI: 0.04–0.87; $p = 0.03$). None of the pre-specified explanatory variable was significantly correlated to outcome: age, ratio infarction/hemorrhage, delay from stroke to treatment, route of administration, cell type, randomization, and blinded outcome assessment. The significant heterogeneity ($p = 0.03$) was not explained by publication biases ($p = 0.09$) and was more likely due to methodological and quality differences between the trials.

Conclusions: This result suggests that cell therapy is beneficial in stroke and is expected to help in the designing of stem cells controlled clinical trials (CCT) in large populations.

Keywords

Clinical trial, intracerebral hemorrahage, ischemic stroke, stem cells, therapy, recovery

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Introduction

Effective treatments in acute ischemic stroke, i.e. reperfusion strategies with intravenous (IV) tissue plasminogen activator[1] and/or intra-arterial (IA) thrombectomy[2] have a narrow time window and a low eligibility, thereby limiting their application to a subset of patients. Therefore, despite these breakthroughs, a majority of patients is left with sensorimotor and cognitive impairments. Recently, an important research effort has been focused on the mechanisms of neural repair as these are assumed to promote recovery. In experimental studies, the surviving tissue exhibits neuro-synaptogenesis[3] and contributes to the reorganization of damaged networks[4] participating to the "structural" plasticity.[5] Neural reorganization is associated with increased neurogenesis from endogenous neural stem cells,[6] which is linked to angio-vasculogenesis and glial function, leading to the

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concept of a ''glio-neurovascular niche'' as a favorable ''stem cell niche''.[7] Cell therapy has been shown to promote endogenous neuroprotective and brain repair processes that include immunomodulation, neuronal, vascular and glial remodelling.[8] Indeed, a meta-analysis of experimental cell therapy studies reported a beneficial effect on structural and functional recovery.[9]

In this context, while several clinical studies have been run with encouraging results in humans, there is no evidence of significant clinical efficacy yet. These studies were mainly focused on safety and feasibility, had small sample sizes, which did not provide sufficient power. In a single arm meta-analysis evaluating cohort studies, cell therapy was judged effective;[10] however, as control groups were not included, no conclusion about the efficacy and effect size could be drawn, leaving these issues to be addressed. Wang et al.[11] reported the meta-analysis of mesenchymal stem cells therapy in ischemic stroke. They did not consider a unified time of follow-up after therapy. Moreover, they presented separately the effects of all the different clinical scales used and not the global effect size. Therefore, their meta-analysis did not contribute to the evaluation of the effect size.

We performed this meta-analysis to assess whether cell therapy can improve stroke outcome by selecting only clinical trials including a control group. In addition, we computed the effect size and tested a priori hypotheses about explanatory variables: type of cells, route of administration (intravenous (IV)/intra-arterial (IA)/intracerebral (IC)/intrathecal), patient age, ratio infarction/hemorrhages, delay from stroke onset to treatment, and methodology: randomized or not, blinded outcome or not.

Methods

This study was conducted according to PRISMA-P statements. We checked the published reports in English language from 1995 to June 2016. Clinical scales data were extracted, and quality of the trials was evaluated using the GRADE approach. Quantitative analysis was based on the standardized means difference (SMD) method. Publication biases were assessed with the funnel plot. The pre-specified explanatory variables were tested with group analysis and a meta-regression. The methods are detailed in the supplementary material.

Results

Clinical trials

The selection of the trials is reported in the supplementary material (supplementary Figure 1). Among 28 eligible clinical trials, nine studies representing a total of 194 patients and 191 controls were included in the meta-analysis[12–20] (supplementary Table 1). Among these nine studies, four were randomized and five were case–control studies. All the randomized studies were single blinded for outcome assessment. Overall, only one patient has been lost to follow-up for outcome assessment.[20] The trials were mainly focused on safety and feasibility. They had small sample sizes, only two of the randomized studies had 100 or more subjects. All the studies but one reported information on rehabilitation program. According to the GRADE approach, we downgraded the overall quality of the study to a moderate quality grade.

Results of the selected studies

Stem cells had a positive effect on the outcome of SMD 0.57 (95% CI: 0.22–0.92; $p = 0.002$) as reported by types of cells on forest plot (Figure 1).

As heterogeneity was significant ($p = 0.029$), we searched a publication bias using a funnel plot (supplementary Figure 2). The Egger's test was not in favor of a publication bias ($p = 0.09$).

None of the pre-specified explanatory variables was related to treatment in meta-regression.

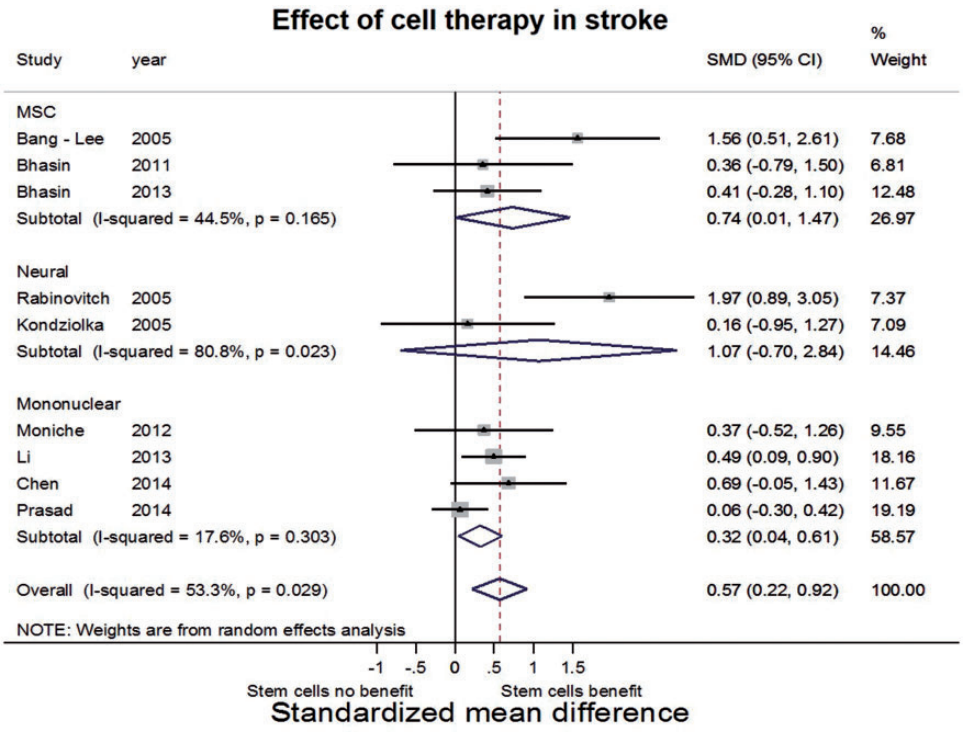
Three out of nine studies reported only one clinical assessment scale representing a total of 84 patients and 75 controls (weight: 43.1%). For sensitivity analysis, the upper level of effect size was 0.81 (95% CI: 0.34–1.27; $p = 0.001$) and the lower level was 0.45 (95% CI: 0.04–0.87; $p = 0.03$). When dropping the study with lowest quality,[13] the effect size remained significant (0.41, 95%CI: 0.14–0.68; $p = 0.003$) and heterogeneity was no more present ($p = 0.25$).

All the studies reported safety information. Safety data often did not allow to attribute for each study the reported events to the treated or control groups. There were, at six months, five deaths per group in one study.[20] One study reported development of lung cancer in one patient.[18] Three studies reported overall five seizures which were sensitive to therapy and which occurred in three patients.[14,16,20] Fever was reported in 3.8% of the patients in one study.[18] Headaches were frequent,[13,19] and one study reported a recurrent stroke.[14]

Discussion

This meta-analysis suggests an overall positive effect of cell therapy after stroke with an effect size of 0.57 that can be considered as medium. In the sensitivity analysis, the effect size boundaries were 0.81 and 0.45 and were both significant. When considering the number of treated patients and the reported adverse events, cell therapy presented a favorable safety profile.

Figure 1. Forest plot. Forest plot with group analysis according to cells types.



MSC: mesenchymal stem cells; Neural: stem cells of neural origin; Mononuclear: mononuclear cells; N treated: number of treated patients; N controls: number of control patients. Box areas are proportional to the weight for the individual studies.

The precision of the SMD measures seems correct taking into account the size of the confidence intervals and the effect sizes which are close across the studies.

However, these encouraging findings are hampered by a significant heterogeneity test which was not likely due to a publication bias. The meta-regression did not explain heterogeneity either. The low quality of the methodology of one study[13] may account for heterogeneity. When dropping this trial, the effect size remained significant and heterogeneity was absent.

The meta-regression did not support the effect of the explanatory variables: best delay for treatment, type of cell and dose, route of administration, patient's characteristics such as age, severity, and type of stroke, inclusion of infarcts and/or hemorrhages, randomization and blinding of assessments.

Likely do to the above mentioned methodological choices, the meta-analysis of Wang et al.[11] did not report a significant difference in favor of cell therapy.

In conclusion, this meta-analysis suggests that cell therapy may improve clinical outcome and presents a favorable safety profile. Due to the small number of trials, their sample sizes, design heterogeneities, and their overall moderate quality, these findings have to be considered as preliminary. Larger and well-designed studies are needed for confirmation of this positive potential. These trials should be more detailed in (1) reporting feasibility such as cell harvesting and culture issues and cells production standardization, (1) in using improved clinical trials methods such as randomization and double blind assessment, (3) in clinical tools used such as validated stroke scales, (4) in complementary information using biomarkers such as biology and imaging, (5) in multiple time points for assessing outcome, (6) in more detailed information on adverse events, (7) and on associated therapies such rehabilitation programs as brain repair needs behavioral reinforcement therapies.

Declaration of conflicting interests

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