Efficacy of MLC601 on functional recovery after stroke: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background and purpose: Traditional Chinese medicine (TCM) MLC601 has shown promising results on functional recovery of patients after stroke. This study aimed to evaluate the pooled effect of its efficacy.

Methods: Systematic review and meta-analysis of randomized controlled trials (RCTs) assessing efficacy of MLC601 vs other TCM compounds or placebo. The pooled effect was the relative risk (RR) combined by random effects model. A prediction effect interval was estimated for new studies and a cumulative meta-analysis was performed.

Results: Four studies comprising five RCTs were included. The pooled RR was 1.64 (95% CI = 1.05–2.57; p-value = 0.031) favouring MLC601, but heterogeneity was large (I^2 = 80%; Q-test p-value = 0.0005). Therefore, the prediction interval was wide and consistent with a null effect (RR range = 0.36–7.45). The cumulative meta-analysis showed a decreasing pattern of effect size through time, with higher effects for trials comparing MLC601 vs other TCM and a systematic decrease of the pooled effect when including later trials comparing MLC601 vs placebo.

Conclusions: Evidence on the efficacy of MLC601 has decreased over time and when the comparison arm is placebo instead of other TCM compound. Current evidence suggests MLC601 does not outperform placebo on functional recovery after stroke.

Keywords

MLC601, NeuroAiD, stroke, recovery, review, meta-analysis

Introduction

Every year ~ 15 million people worldwide have a stroke, resulting in one third of deaths because of stroke progression, recurrent stroke or cardiovascular disease [1]. Half of the survivors will have a motor, cognitive or mental dependency, affecting deeply quality-of-life and making stroke one of the leading causes of disability and disease burden [2].

There have been promising reports on functional recovery after ischaemic stroke with Danqi Piantang Jiaonang (MLC601), a traditional Chinese medicine (TCM) that combines different natural components (nine herbal: Radix astragali, Radix salviae miltiorrhizae, Radix paeoniae tubae, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae and Rhizoma acori tatarinovii; and five animal: Hirudo, Eupolyphaga seu steleophaga, Calculus bovis artifactus, Buthus martensi and Cornu saiga tataricae). In Europe, for some undisclosed reason, it is only available as a simplified formulation (MLC901) including only the nine herbal components [3]. Both formulations have shown similar results in preclinical studies of cellular and animal stroke models and have shown both neuroprotective (it seems to protect the brain from ischaemic injury and to prevent neuronal death) and neuroregenerative properties (it seems to induce synaptogenesis, promote proliferation, stimulate the development of axonal and dendritic network, restore neurological and cellular function and increase cerebral blood flow velocity) [4,5] and can be prescribed as a coadjuvant treatment for stroke recovery [6]. Two systematic reviews including meta-analysis have supported the efficacy of MLC601 on stroke recovery [7,8]. However, recent multi-centric trials have reported non-significant results of MLC601 vs placebo [9,10]. The objective of this research was to update, in a systematic review and meta-analysis of randomized clinical trials (RCTs), the overall efficacy of MLC601 on the functional recovery of patients after an ischaemic stroke event.

Methods

Databases and search descriptors

The following databases were searched until December 2014: Medline through PubMed, EMBASE and PsycInfo through Ovid and CENTRAL through the Cochrane Library. The search algorithms are presented in Supplementary Appendix 1.
Selection criteria

Two researchers (EGF, JB) independently selected the trials to include. First, titles and abstracts of all retrieved records were examined to select all those that likely fitted inclusion criteria: RCTs comparing MLC601 with other TCM product or placebo and presenting outcome estimates of functional recovery after stroke. Then a full text copy was obtained and thoroughly assessed to jointly make the final decision of inclusion.

Main outcome and data extraction

Data were extracted on functional recovery, attained by patients as the most clinically relevant outcome to assess the efficacy of the treatment on post-stroke rehabilitation. Functional recovery was expressed as a dichotomous outcome according to appropriate cut-off points on functional independence scales and indexes—a score ≥ 65 in the Barthel index [5], a modified Rankin scale (mRS) score of 0/1 [9,10], a Diagnostic Therapeutic Effects of Apoplexy Scoring System (DTER) item #8 score of 0 (that is approximately equal to a mRS score of 0/1) [6]. Data extraction was performed in duplicate following an intention-to-treat approach (all subjects randomly allocated to arms were included in the efficacy analysis assuming a negative outcome for patients lost to follow-up).

Statistical analysis

Trials were grouped by (i) type of comparator (other TCM or placebo) and (ii) study time (1 or 3 months). Effect size was the relative risk (RR), with values > 1 meaning MLC601 was better than the comparator. Effect sizes were combined by the Mantel-Haenszel method according to the random effects model—with the DerSimonian-Laird between-groups heterogeneity estimate—and a prediction RR was estimated [11]. Sensitivity analysis of the pooled estimate was conducted by leaving out one study from the full meta-analysis set. Also a cumulative meta-analysis was done to assess changes in the overall evidence of efficacy throughout time. A small study bias analysis was planned only in case enough studies for the meta-analysis (~ 10) were retrieved.

Analyses were done with the R package [12] using the _meta_ library [13].

Results

Eleven published RCTs were selected, but only four, including five RCTs, provided appropriate data to be included in the meta-analysis [5,6,9,10] (see Supplementary Appendix 2 for a flow-chart of the review and Supplementary Appendix 3 for excluded trials and reasons for exclusion); Chen et al. [6] report two previously unpublished Chinese RCTs that record the efficacy of MLC601 vs other TCM compound at 1 month of treatment. The rest of the trials report the efficacy of MLC601 vs placebo at 3 months. The study of Bavarsad Shahripour et al. [5] imputed efficacy data assuming a 44.5% improvement following Chen et al. [9] and no differences between arms was reported in the paper. Overall, 1065 subjects were randomized to MLC601 and 871 to control (205 to other TCM, 666 to placebo). Table I shows a summary of the included studies.

Figure 1 shows the results by treatment time and comparator (1 month and other TCM; 3 months and placebo). The overall RR was 1.64 (95% CI = 1.05–2.57; p-value = 0.031) favouring MLC601 over the comparators, but between trials heterogeneity was extremely large ($I^2 = 80%$; Q-test p-value = 0.0005), which makes the interpretation of the pooled effect estimate unreliable. Yet, with all the up-to-date combined evidence, the prediction interval for the results of a new

| Table I. Summary of studies. |
|--------------------------------|
| **Study and countries** | **Population** | **Interventions and dosages** | **Follow-up & outcome measures** |
|---------------------------|----------------|-------------------------------|---------------------------------|
| Chen et al. [6] 2009*; Singapore | 605 adult subjects (18–70 years) with recent ischaemic stroke (since 10 days to 6 months before randomization), recruited from 6 centres | MLC601 vs Buchang Naonixitong Jiaonang, randomized according to 1:1 ratio (200 subjects) or 3:1 ratio (405 subjects) 4 capsules, 3 times per day for 4 weeks | 4 weeks DTER |
| Bavarsad Shahripour et al. [5] 2011; Iran | 80 adult subjects (60–80 years) with acute ischaemic stroke (within 1 week of randomization) from a single centre | MLC601 vs placebo (talc), randomized in 1:1 ratio 4 capsules, 3 times per day for 12 weeks All subjects received standard anti-platelet (aspirin) treatment (80 mg twice a day) | 12 weeks Barthel index, mRS |
| Chen et al. [9] 2013; Singapore, Philippines, Thailand, China, Malaysia | 1100 adult subjects (mean age 61.4 years) with acute ischaemic stroke (randomization within 72 hours of onset) from 21 centres | MLC601 vs placebo (barley, dried ripe fruit, noodle fish and citric acid), randomized in 1:1 ratio according to block randomization 4 capsules, 3 times per day for 12 weeks All subjects received standard stroke care (anti-platelet therapy, control of vascular risk factors and appropriate rehabilitation) | 10 days, 1 week and 12 weeks mRS, Barthel index, NIHSS |
| Bavarsad Shahripour et al. [10] 2014; Iran | 190 adult subjects (55–90 years) with acute ischaemic stroke (randomization within 1 week of onset) from 3 centres | MLC601 vs placebo, randomized in 1:1 ratio 4 capsules, 3 times per day for 12 weeks All subjects received standard stroke care (anti-trombotic therapy, statin, blood pressure control and any other treatment deemed appropriate) | 12 weeks NIHSS, mRS |

* Pooled data from two independents studies.

DTER, Diagnostic Therapeutic Effects of Apoplexy Scoring System; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination.
trial would be consistent with the null effect (RR range = 0.36–7.45).

The results of the comparison of MLC601 vs other TCM at 1 month of treatment were homogeneous ($I^2 = 8\%$) and favoured significantly MLC601 (RR = 2.40; 95% CI = 1.28–4.51). The results of the comparison of MLC601 vs placebo at 3 months were highly heterogeneous ($I^2 = 84\%$) and non-significant (RR = 1.37, 95% CI = 0.85–2.21). In this analysis the main source of heterogeneity was the study of Bavarsad Shahripour et al. [10]. Its elimination from the analysis set reduced the heterogeneity to 0% and the RR to 1.05 (95% CI = 0.93–1.18). The prediction interval for a new study comparing MLC601 vs placebo was extremely large (RR range = 0.005–370.4).

The cumulative meta-analysis (see Figure 2) shows a decreasing pattern of effect size through time, with higher effects for the first trials comparing MLC601 vs other TCM and a systematic decrease of the pooled effect when including the later trials comparing MLC601 vs placebo.

### Discussion

The former promising results of the efficacy of MLC601 on the functional recovery of patients after suffering a stroke do not seem to be supported as new evidence has been included in the systematic review. According to this analysis the efficacy of MLC601 has decreased over time and this decrease matches the change in the comparison arm. The significant and clinically relevant results obtained in the first Chinese trials [6] were obtained comparing MLC601 vs another TCM compound and, thus, supposedly active treatment. Yet in later studies when the comparison arm was placebo instead of other TCM compound, the efficacy decreased [5,9,10]. This issue is at least unusual and difficult to explain since the expectation would have been exactly the opposite: larger effect estimates from the comparison of MLC601 vs placebo than from the comparison of MLC601 vs another TCM compound.

The results do not agree with those reported in previous reviews and meta-analyses [7,8], probably because of (i) more...
strict inclusion criteria and (ii) updating evidence in the analysis. Li et al. [8] meta-analysed not only RCTs, but also observational trials without randomization of patients to treatments, which was not permitted in the meta-analysis. This study has also updated the previous analysis of Siddiqui et al. [7] by including two more recent RCTs whose results are at odds with former trials [5,10].

The evidence on the efficacy of MLC601 provides a very large prediction estimate of effect size, with values centred at the null effect but spread over a wide interval and, thus, compatible with important effects in both positive and negative directions. Currently the authors know of one ongoing RCT (ClinicalTrials.gov Identifier: NCT01847924), whose results—jointly with other planned but not yet registered trials—should be included in a future meta-analysis to update current results and provide a more precise effect size estimate. However, current evidence does not support MLC601 over placebo regarding functional recovery of patients after stroke.

Supplementary Material

The following supplemental data for this article can be accessed on the publisher’s website at http://tandfonline.com/doi/10.3109/02699052.2015.1118764:
Data supplement #1: Search algorithms.
Data supplement #2: Flow chart.
Data supplement #3: List of excluded trials and reasons for exclusion.

Declaration of interest

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