The Efficacy and Safety of Granulocyte Colony-Stimulating Factor for Patients with Stroke

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Background: Granulocyte colony-stimulating factor (G-CSF) has been shown to reduce lesion volume and improve functional outcome in experimental stroke models. However, whether G-CSF plays a role currently in patients with stroke remains uncertain. Our study aimed at examining the efficacy and safety of G-CSF in patients with acute ischemic stroke. *Methods:* A comprehensive search was conducted in 5 online databases up to April 2014, and 10 studies with 711 patients met the criteria. *Results:* The results showed that G-CSF was beneficial in improving the National Institutes of Health Stroke Scale (standardized mean difference [SMD], .43; 95% confidence interval [CI], .03-.82; $P = .04$) and modified Rankin Scale (mRS) scores (SMD, .72; 95% CI, .51-.93; $P = .01$), and elevating $CD34^+$ count ($P < .001$). No treatment effects were found in Barthel Index scores (SMD, −.13; 95% CI, −.61 to .35; $P = .59$), serious adverse events (relative ratio [RR], 1.12; 95% CI, .91-1.38; $P = .28$), or the death of serious adverse events (RR, 1.25; 95% CI, .82-1.91; $P = .30$) between groups at day 90. Adverse effect on vascular complications was not detected to be increased although G-CSF produced a marked elevation in the total leukocyte count (SMD, 3.52; 95% CI, 2.54-4.49; $P < .001$). *Conclusions:* In conclusion, G-CSF is effective at mobilizing bone marrow–derived $CD34^+$ stem cells to the peripheral blood. It also seems to improve the National Institutes of Health Stroke Scale and mRS scores. The administration of G-CSF appears to be safe and well tolerated. Further studies need to be done on a large sample to verify or fully characterize the results. **Key Words:** Stroke—granulocyte colony-stimulating factor (G-CSF)—hematopoietic stem cell—meta-analysis.

Introduction

As one of the major causes of death and disability in the world, stroke exerts a profound influence on individuals and their families.[1] Accounting for approximately 80% of all strokes, ischemic stroke kills 2.9 million people annually and leads to 3.4 million people living with disability worldwide. With the growing aging population, the number of patients tormented with stroke may achieve a higher increase in the future.[2,3] As one of the main treatments, intravenous tissue plasminogen activator is the only Food and Drug Administration–approved thrombolytic agent currently available for acute ischemic stroke.[4] However, its narrow therapeutic time window makes it a limitation to apply in clinical practice.[5,6] Other treatments such as antiplatelet (aspirin and clopidogrel), anticoagulant,

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fibrinolytic, and neuroprotective therapy do not achieve an ideal effect. A potential approach to combat stroke is probably the transplantation of bone marrow stem cells. Of which, the growth factors are the ones that made it.[7-9]

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor of 20 kDa,[10] which acts on hematopoietic ($CD34^+$) stem cells to modulate neutrophil precursor proliferation and differentiation.[11] It is typically used to counteract human neutropenia and hematologic malignancy.[12] Recently, the role and properties of G-CSF in stroke have been disclosed. Meta-analysis of G-CSF in stroke animals confirmed the infarct size reduction and functional enhancement.[12,13] Currently, some well-designed studies have investigated the efficacy of G-CSF in stroke patients. However, the conclusions among studies are still controversial. Some studies[14,15] supported the application of G-CSF, whereas others[14,16] found no differences between the G-CSF and placebo groups.

Therefore, we performed this meta-analysis of all available randomized controlled trials (RCTs) to clarify the role of G-CSF in patients with stroke.

Methods

We did this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.[17]

Study Search and Identification

We conducted a literature search of the PubMed, EMBASE, Web of Science, Cochrane Library and the Chinese Biomedical Literature Database for all RCTs that evaluated G-CSF in patients with stroke. The strategy used the following key words: "G-CSF," "granulocyte-colony stimulating factor," "stroke," and "cerebral infarction." The search was done up to April 2014 without language restrictions. The bibliographies of included articles and reviews were further cross checked independently by 2 investigators to search for articles not referred to in the previously noted databases. If there was division regarding eligibility, a third investigator resolved.

Inclusion Criteria and Study Selection

Inclusion criteria: (1) the design of included study was an RCT; (2) the intervention involves intravenous or subcutaneous recombinant human G-CSF in acute ischemic stroke; (3) published in adult population; and (4) reported 1 or more outcome measures including clinical efficacy for National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) score and Barthel Index (BI) scores, security indicators for serious adverse event (SAE) and death of SAE, and laboratory values for $CD34^+$ and leukocyte counts at 90 days.

Assessment of Study Quality

The methodological quality of included RCTs was assessed critically by 2 reviewers according to the Cochrane Handbook 5.2.[18] Each study was rigorously appraised in accordance with the following 5 points: (1) random generation; (2) proper concealment of the allocation sequence; (3) blinding of the patient and the investigator; (4) complete follow-up for therapeutic effect; and (5) intention-to-treat analysis.

Data Extraction and Outcome Measures

All data from available trials were separately extracted by 2 independent investigators according to the standard data extraction sheet. The safety outcomes included SAE and the death of SAE; the efficacy outcomes consisted of NIHSS, mRS, and BI scores. In addition, laboratory parameters for $CD34^+$ count and leukocyte count at day 90 were also reported.

Statistical Analysis

We calculated the relative ratio (RR) and the standardized mean difference (SMD) and their respective 95% confidence interval (CI) as measures of the relationship between G-CSF and outcomes. RR was calculated for dichotomous variables and SMD for continuous variables. Q statistic and I^2 statistic were applied to determine heterogeneity and measure its degree, respectively, among studies. We performed meta-analysis using a fixed effects model to achieve the pooled RR and SMD within included studies, a random-effects model was used when statistically significant heterogeneity was existent ($P < .10$ or $I^2 > 50\%$). If the heterogeneity was still not eliminated, the sensitivity analysis was performed to ensure the findings. A P value less than .05 was considered statistically significant.

Results

Search Results and Characteristics of Included Studies

Of the 609 articles filtered out by using keyword-based search, 10 RCTs[14,19-27] involving 711 individuals were eventually included in our meta-analysis (Fig 1).

Among all the included studies, 356 (50.1%) participants were randomly divided into G-CSF–treated group and 355 (49.9%) to placebo group. The sample sizes ranged from 10 to 324 subjects, and all participants were recruited within 7 days after stroke. Of 10 articles, 9 studies were designed to receive G-CSF in a fixed-dose regimen, whereas only 1 study in a dose-escalation manner[27] via subcutaneous or intravenous infusion. The follow-up time varied from 3 months to 12 months. The design, recruitment, and baseline characteristics of individual studies are shown in the Table 1.