Meta-analysis of Statin Use for the Acute Therapy of Spontaneous Intracerebral Hemorrhage

J. Humberto Tapia Pérez, MD,* O. Can Yildiz, MD,† Thomas Schneider, PhD, MD,† and Christopher Nimsky, PhD, MD*

Background: Growing evidence demonstrates the neuroprotective effects of statins, and the risk to develop an intracerebral hemorrhage (ICH) using statins has been refuted. However, some controversy remains regarding their role in the acute phase after ICH onset. Therefore, we performed a systematic review to investigate this issue. *Methods:* We searched in MEDLINE, Web of Knowledge, and Scopus databases for studies examining the outcome in patients with spontaneous ICH and statin use. The analysis was performed for short-term (≤3 months) and long-term outcome (≥6 months) and a further subanalysis considered studies seeking for the effects of the discontinuation of statin after ICH onset. A random-effect model was applied, and country was used as a cofactor for meta-regression; odds ratios (ORs) with 95% confidence intervals (CIs) are offered. *Results:* A total of 17 studies were included, only 1 pseudo cohort trial assessed the new use of statin after ICH onset and 3 studies evaluated the suspension of statin after ICH onset, the rest of the studies focused on the effect of the regular use of statin before ICH onset. The number of patients with an ICH exposed and not exposed to statins were 3455 and 11,821, respectively. The absolute short-term mortality was 27.3% in statin users and 33% in nonusers that represented a significant risk reduction of mortality (OR, .73; 95% CI, .54-.97). For long-term mortality, the effect was less evident (OR, .71; 95% CI, .43-1.15). The analysis of the 3 studies assessing the discontinuation of statins suggested a reduction of mortality risk by continuing statin (OR, .14; 95% CI, .1-.20). *Conclusions:* The current evidence suggests that continuing statin after ICH onset might be highly related to improvement of the outcome of patients with ICH. Despite this strong suggestion, randomized controlled trials should be performed to further investigate this association. **Key Words:** Intracerebral hemorrhage—meta-analysis—mortality—statins.

Introduction

Despite much marvelous advancement in the field of medicine in recent years, only minor, if any, progress could be achieved regarding the mortality and morbidity rates of intracerebral hemorrhage (ICH),[1-3] although the results of most recent studies look promising. One example of these advantages are the results of the second trial from the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial study group, where the aggressive blood pressure reduction prevented not only the hematoma expansion but also resulted in a modest improvement of the 90-day functional outcome.[4]

Statins display several independent effects of cholesterol reduction, such as GTPases regulation, through which a number of pathways could be modulated and lead to a neuroprotective action.[5] Because of these denominated pleiotropic effects, statins are attractive candidates for the development of a neuroprotective

From the *Klinik für Neurochirurgie, Philipps-University Marburg, Marburg; and †Klinik für Neurochirurgie, Universitätsklinik Otto von Guericke Magdeburg, Magdeburg, Germany.
Received May 24, 2015; accepted June 27, 2015.
Address correspondence to J. Humberto Tapia Pérez, MD, Universitätsklinikum Marburg, Klinik für Neurochirurgie, Baldingerstrasse, 35033 Marburg, Germany. E-mail: jhtapiap@gmail.com.
1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.06.036

strategy.[6] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels suggested that an increased risk of ICH in patients treated with high-dose atorvastatin, especially in those with a previous hemorrhagic stroke, in men, and in those with increased age. Patients with stage II of hypertension before the ICH also have an increased risk.[7] However, the existence of such risk was refuted by 2 larger meta-analyses.[8,9] Moreover, an improvement of neurologic recovery has been shown in animal models of ICH sometimes ago.[10] Although no randomized controlled trial (RCT) has been fully executed till this date, a number of observational studies were conducted trying to find a correlate between statin use and the outcome after ICH. Two meta-analyses have been published regarding this question with controversial results; although a clear favorable outcome by statin exposure was demonstrated by Biffi et al,[11] the most recent meta-analysis of Lei et al[12] showed no significant positive or negative effect in outcome. These studies considered the 30- and 90-day mortality, and they did not discriminate between continued and discontinued statin use after ICH onset. Trying to clear the issue, we performed a systemic review of the literature analyzing the effects of statin exposure on both the short-term and the long-term outcomes and the effects of discontinuation of statins after ICH.

Methods

Study Identification

Two reviewers (J.H.T.P. and O.C.Y.) independently identified studies by searching the following databases through December 2014: MEDLINE (1966-2014), Elsevier Scopus (1980-2014), and ISI Web of Knowledge by Reuters (1999-2014). No language restriction was applied. The key words "intracerebral hemorrhage" or "intracranial hemorrhage" and "statins" were used.

Study Selection

For our meta-analysis, we included studies on patients with spontaneous ICH, which assessed morbidity and mortality as main objective. All such studies were considered regardless of the duration or dose of statin therapy. We excluded studies restricting the evaluation of localization (eg, only ICH infratentorial). Studies analyzing ICH because of trauma, vascular malformations, thrombolysis, or hemorrhagic ischemic stroke were also excluded. Articles analyzing the risk to develop an ICH using statins were not considered in our review because it was not our end point.

Data Extraction and Study Quality

The 2 independent reviewers evaluated the studies (J.H.T.P. and O.C.Y.). Study quality was assessed using a modified version of the Newcastle–Ottawa Quality Assessment Scale (NOS). An NOS score was assigned to each study based on the quality of group selection, comparability of groups, and assessment of outcomes. The details of sample size, setting, statin treatment, mortality, and functional outcome were extracted from the studies.

Data Analyses

Studies were classified into groups according to the evaluation time of the outcomes. Studies assessing mortality inhospital and up to 3 months were considered as short-term mortality and studies with results after 6 months as long-term mortality. In a first analysis, all studies were included and statin therapy was defined as the exposition to statin at any time (eg, usual statin users, new users). Additionally, we sought after the effect of statins discontinuation, and an analysis of the studies providing this information was performed. The effect of statin on functional outcome was explored in terms of the definition of good outcome used in the articles, where this information was available (eg, Glasgow Outcome Score score 4-5, Rankin score). Results for dichotomous data were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Heterogeneity between the studies was assessed using a standard I^2 test. All calculations were carried out with the free statistical software OpenMetaAnalyst (Center for Evidence-based Medicine (CEBM), Providence, RI, USA).[13]

Sensitivity Analyses

We searched potential sources of heterogeneity in several forms. We performed primary analyses using fixed-effects and random-effects models. Second, we performed an analysis removing 1 study at a time and recalculating the results in an iterative form. We tested the setting country as cofactor (classified as America, Asia, and Europe); the reason of that was to explore the possible influence of the different therapy in the different countries.

Results

Description and Quality Evaluation of Studies

We identified 653 records from searches of electronic databases. After review of titles and abstracts, 22 articles were read. Of these studies, 6 were excluded because they did not satisfy the inclusion criteria. We included another articles in press from our group, so we kept 17 studies into analysis (Fig 1, Table 1). The median value of NOS for the included studies was 6.

We did not found any RCT and 1 pseudo trial assessed the new application of statin in patients with ICH and without previous use (statin exposed 18 and controls 57). Three studies provided enough information about the previous use of statin and its continuation or discontinuation (statin continued 1190 and statin discontinued