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Statins for neuroprotection in spontaneous intracerebral haemorrhage (STATIC): protocol for a multicentre, prospective and randomised controlled trial

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ABSTRACT

Introduction Intracerebral haemorrhage (ICH) is a neurological emergency with high morbidity and mortality, and current treatment is limited. Emerging evidence has reported that statins can exert neuroprotective effects in cerebrovascular diseases. However, most of the published clinical studies are retrospective. Therefore, it is important to conduct a prospective randomised controlled trial to further validate the efficacy and safety of statins in patients with ICH.

Methods and analysis The present study is performed at Xuan Wu Hospital Capital Medical University, Beijing Fengtai You'anmen Hospital and Shunping County Hospital, Hebei Province. The target number of patients is 98. Eligible patients are randomly assigned in a 1:1 ratio to the statins group or the control group. The primary outcome is the perihaemorrhagic oedema to haematoma ratio at 7 days. Secondary outcomes include mortality at 30 days, haematoma resolution rate at 7 days, National Institute of Health stroke scale (NIHSS) score at 7 days or discharge, ordinal distribution of modified Rankin scale (mRS) score at 90 days, the proportion of patients with an mRS score of 0–2 on day 90, the proportion of patients with an mRS score of 0–3 on day 90, absolute haematoma volume changes between initial and 7-day follow-up CT scan, absolute perihaematomal oedema changes between initial and 7-day follow-up CT scan.

Ethics and dissemination The trial has been approved by the ethics committees of Xuan Wu Hospital Capital Medical University, Beijing Fengtai You'anmen Hospital and Shunping County Hospital, Hebei Province. The results will be disseminated in a peer-reviewed journal and in conference reports.

Trial registration number NCT04857632.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The results of this study will provide new insights and evidence for the treatment of intracerebral haemorrhage.
⇒ It may be more appropriate to employ a placebo control.
⇒ The sample size in this study is relatively small.
⇒ The open-label design may lead to a placebo effect.

INTRODUCTION

Intracerebral haemorrhage (ICH) is a commom neurological injury, which has been related to significant morbidity and mortality.[1] Despite rapid development in medicine, the treatment options of ICH still remain limited without obvious breakthroughs. Statins, which are hydroxy methyl glutaryl coenzyme A reductase depressants, are commonly used to low serum cholesterol.[2] Moreover, statins are also proven to have neuroprotective properties in subarachnoid haemorrhage, ischaemic stroke and traumatic brain injury.[3 4] Therefore, statin, as a neuroprotective agent, has aroused much interest, especially in diseases with limited treatment options, such as ICH.

In several preclinical studies, statin therapy in animal models of ICH has been validated neuroprotective effects, obtaining improved neurologic function, decreased cerebral oedema, promoted angiogenesis and neurogenesis and reduced inflammatory cell infiltration.[5–7] Clinical studies in humans have been largely limited to retrospective studies that have reported better patient outcomes associated with statins use prior to ICH, including reduced mortality, improved functional outcomes and decreased perihaematoma oedema (PHE).[8–10] PHE is a quantifiable marker of secondary brain injury formation post-ICH and is strongly related to adverse prognosis.[11 12] Therefore, PHE is considered as a promising therapeutic target of ICH. Also, several observational studies have found improved mortality and functional prognosis in patients who continue or start statins after ICH.[13–15] In addition, a previous randomised trial put forward concerns about a possible increased risk of recurrent ICH in patients with prior haemorrhagic stroke

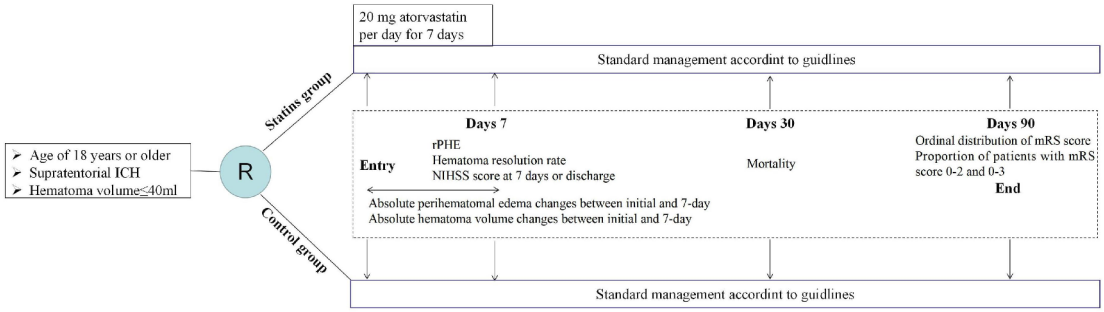

Figure 1 The study design and treatment flow chart. ICH, intracerebral haemorrhage; mRS, modified Rankin scale; NIHSS, National Institute of Health stroke scale; rPHE, perihaemorrhagic oedema to haematoma ratio.

who had previously used statins.[16] However, most studies on statins have failed to show a significant correlation between statins use and elevated risk of haemorrhagic stroke. Overall, both previously published preclinical and clinical findings support a potential neuroprotective role for statins in acute ICH. Notably, current relevant clinical studies are mostly limited to retrospective studies and lack evidence of prospective randomised controlled studies. As such, this is a study to investigate the efficacy and safety of statins in ICH by designing a prospective randomised controlled trial. The results will provide evidence-based support for statins to treat cerebral oedema after ICH and to further improve patients prognosis.

METHODS AND ANALYSIS

Design

The STATIC is a multicentre, prospective, randomised, open-label, blinded endpoint study investigating the efficacy and safety of statins in ICH patients. The first patient was enrolled on 6 August 2021. The anticipated completion date is June 2024. The study design flow chart is shown in figure 1. This study is performed at Xuan Wu Hospital Capital Medical University, Beijing Fengtai You'anmen Hospital and Shunping County Hospital, Hebei Province. Patients who provide consent to participate, fulfil the inclusion criteria and do not meet the exclusion criteria are randomly assigned to the statins group or the control group. These two groups are treated with standard management according to the guidelines. The trial was approved by the ethics committee of every centre and was registered at ClinicalTrials.gov with NCT04857632.

Patient population

Inclusion criteria

1. ≥18 years old.
2. Obtained informed consent.
3. Haematoma size 40 mL or less in order to to minimise surgical intervention's impact on drug effect following the Chinese Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage (2019).
4. Supratentorial ICH is demonstrated via cerebral CT.
5. The first dose of atorvastatin is given to patients assigned to the statins group within 24 hours after ICH symptoms onset.

Exclusion criteria

1. Previous modified Rankin scale (mRS) score ≥2.
2. Life expectancy <7 days.
3. Prior use of statins within 1 month before ICH.
4. Positive pregnancy test, pregnancy or breast feeding.
5. Occurrence of subarachnoid haemorrhage or intraventricular haemorrhage.
6. Involved in another clinical study within 1 month before screening for this trial.
7. Inability to swallow statins and contraindication to the placement of a nasogastric tube.
8. Other diseases or abnormalities that the researchers think may be harmful to the patients' safety during the study.
9. Haematoma removal by craniotomy is planned prior to randomisation to subgroups (the planned minimally invasive surgery is not a contraindication for inclusion).
10. Liver dysfunction or active liver disease is evidenced by levels of alanine aminotransferase or aspartate aminotransferase that are twice the upper limit of normal.
11. Suspected secondary ICH related to trauma, arteriovenous malformation or ruptured aneurysm, tumour, venous sinus thrombosis or haemorrhagic transformation of an ischaemic cerebral infarction.

Randomisation

All recruited patients are randomised in a 1:1 ratio to either the statins group or the control group (N=39 each). The randomisation is immediately performed by a real-time, dynamic internet based once patients' eligibility is verified. Stratification is performed via the participating centres. Subjects are assigned a random serial number based on the time of allocation. Patients in the statin group receive statin therapy while those in the control group do not. Outcome assessors are blinded to treatment allocations.

Intervention

After screening for eligibility registration, patients randomised to the statins groups are treated orally with 20 mg atorvastatin per day for 7 days. For patients randomised to the control groups, no statins are received. Patients in both groups are hospitalised in an acute stroke

unit (or neurointensive care unit if needed) and treated according to the latest Chinese guidelines for the management of ICH (which are similar to those of the American Heart Association/American Stroke Association).

Primary outcome

The primary outcome is the rPHE at 7 days±12 hours. CT scans are performed using a 64-row CT scanner with a standard localised protocol. PHE and haematoma volumes are measured using ImageJ 1.52a (National Institutes of Health) on CT images of 5 mm slice thickness. PHE threshold set between 5 and 33 Hounsfeld units. All volume measurements are conducted using a semiautomated procedure that tracks the perimeter of the appropriate high and low attenuation regions and calculates the lesion area of each slice multiplied by the slice thickness to generate the lesion volume. All images will be analysed by two independent radiologists who are blinded to treatment assignment, and any disagreements will be resolved through consensus between them. If the results differ by less than 5 mL, the average will be taken as the final result. If the difference exceeds 5 mL, a third experienced radiologist will be consulted to calculate the final result. For patients with small ICH that are mild enough to be discharged early, we will take the results of their last head CT prior to discharge as a reference.

Secondary outcomes

Secondary outcomes are as follows: (1) mortality at 30 days; (2) haematoma resolution rate at 7 days±12 hours; (3) NIHSS score at 7 days or discharge; (4) ordinal distribution of mRS score at 90 days; (5) the proportion of patients with an mRS score of 0–2 on day 90; (6) the proportion of patients with an mRS score of 0–3 on day 90; (7) absolute haematoma volume changes between initial and 7 days±12 hours follow-up CT scan and (8) absolute perihaematomal oedema changes between initial and 7 days±12 hours follow-up CT scan.

Sample size estimation

Applying PASS software for sample size estimation, this study is a randomised controlled study of two independent samples mean comparison, set the test level α=0.05, test efficacy 1−β=90%, β is two sided, the ratio of the sample size of the two groups is set as 1:1. Referring to the results of a clinical trial study published by our research group,[17] the mean rPHE of ICH patients in the control group was 2.02 at 7 days after enrolment, and the variance was 0.27. In this study, assuming that the mean rPHE in the statin treatment group decreased by about 10%, the PASS software estimated N1=39, N2=39 and N=78. As such, the minimum sample size was 78 patients. Considering a dropout rate of 20% or less, the overall sample size was estimated to be 98 cases.

Statistical analyses

The analyses are undertaken based on the intention-to-treat principle, including all patients involved in this study. As a complement to the intention-to-treat analysis, a per-protocol analysis, excluding participants who can not complete follow-up, is performed to further confirm the results. All data in this study are statistically analysed by using SPSS V.20.0 (IBM). Continuous variables are expressed as mean±SD or median (IQR). Depending on whether the continuous variables conform to normal distribution, the independent t-test or the Mann-Whitney U test is applied for between-group comparisons as necessary. Categorical variables are reported as percentage. The χ^2 test, continuity correction or Fisher's exact test was used for between-group comparisons of the categorical variables. The multivariate logistic analysis is used to evaluate various confounding factors associated with the primary outcome variable. The identification of confounding variables in this protocol originates from two primary sources: (1) We identify some conventional potential confounders correlated with the primary outcome—namely, age, diabetes mellitus, hypertension, ICH volume, anticoagulant use, and time of imaging—through our expertise and comprehensive literature review. (2) Additionally, we select indicators with a significance level of p<0.1 for inclusion as confounding variables in the univariate analysis. Furthermore, certain confounding variables will be incorporated into the model regardless of their significance in the univariate analysis.

DISCUSSION

Secondary brain injury after ICH has been shown to be a vital factor contributing to the poor prognosis of patients. Intriguingly, statins may be neuroprotective against ICH by targeting secondary brain injury pathways.[18]

Some studies producing experimental ICH animal models have demonstrated that statins can promote the neurological recovery after ICH.[19 20] However, clinical studies evaluating the efficacy of statins in the treatment of ICH have yielded mixed and even conflicting results. Some studies have reported that statins can reduce platelet aggregation and thrombogenesis, thereby increasing haematoma expansion, enhancing the risk of recurrent bleeding and worsening ICH mortality or functional prognosis.[21 22] In contrast, some studies have indicated that statin use is related to decreased mortality and improved functional prognosis after ICH.[23 24] With different studies presenting various effects of statins on ICH, there is a need to further clarify the efficacy of statins in patients with ICH. Importantly, most of the clinical studies mentioned above are retrospective. In addition, the relevant description in the Chinese Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage (2019) is that the effect of statin on cerebral haemorrhage is currently not uniformly studied. To sum up, a randomised controlled trial is highly warranted. Thus, this study aimed to validate the efficacy and safety of statins performed on ICH patients in a multicentre, prospective, randomised controlled trial. The results of the current trial may bring new concepts and challenges for the treatment of ICH in the future, and changes in

treatment concepts and measures are of great significance in reducing the death rate and improving the quality of patients' life. Meanwhile, the medication protocol for statins in the treatment group beyond the initial 7 days is at the discretion of the researchers, encompassing decisions regarding continuation and duration. This also facilitates subsequent subgroup analyses aimed at identifying the most effective statin treatment regimen. In brief, these achievements may help to fill the gaps in the current guidelines in this field, furnishing future medical research and practice with more comprehensive and precise guidance.

Ethics and dissemination

The trial has been approved by the ethics committees of all participating centres, and written informed consents of all patients were also obtained before enrolment. The results will be disseminated in a peer-reviewed journal and in conference reports.

Data safety monitoring board

The members of data safety monitoring board (DSMB) were appointed in 2021. The members monitor the safety of the trial and ensure the safety of patients during the study, but they do not participate in the trial or in any other way in the research. The DSMB's responsibility is to make recommendations to the steering committee for modifying the protocol or terminating the trial based on safety problems. Original data can be obtained from the corresponding author on reasonable request

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Contributors CW contributed to the trial design and originated the study idea. XJiang offered expert guidance on the study's direction. YZ, HY and LN contributed to the study design based on their respective areas of expertise. SB and XJi assisted in implementing certain procedures. DG and XC collaborated on the design, implementation, writing and revision of the protocol. All authors reviewed and approved the final manuscript.

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Competing interests None declared.

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