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A randomized 500-subject open-label phase 3 clinical trial of minimally invasive surgery plus alteplase in intracerebral hemorrhage evacuation (MISTIE III)

Wendy C Ziai¹, Nichol McBee², Karen Lane², Kennedy R Lees³, Jesse Dawson⁴, Paul Vespa⁵, Richard E Thompson⁶, A David Mendelow⁷, Carlos S Kase⁸, J Ricardo Carhuapoma¹, Carol B Thompson⁹, Steven W Mayo¹⁰, Pat Reilly^{11,12}, Scott Janis¹³, Craig S Anderson^{14,15}, Mark R Harrigan¹⁶, Paul J Camarata¹⁷, Jean-Louis Caron¹⁸, Mario Zuccarello¹⁹, Issam A Awad²⁰, Daniel F Hanley² MISTIE III investigators

¹Division of Neurosciences Critical Care, Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

²Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, MD, USA

³School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK

⁴Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

⁵Department of Neurosurgery, University of California, Los Angeles, CA, USA

⁶Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁷Department of Neurosurgery, Newcastle University, Newcastle upon Tyne, UK

⁸Department of Neurology, Emory University, Atlanta, GA, USA

⁹Biostatistics Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

¹⁰Emissary International LLC, Austin, TX, USA

¹¹Genentech Inc., San Francisco, CA, USA (retired)

¹²Jamison-Reilly LLC, Hummelstown, PA, USA

¹³National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

¹⁴The George Institute for Global Health China at Peking University Health Science Center, Beijing, China

¹⁵The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia

¹⁶Department of Neurosurgery, University of Alabama, Birmingham, AL, USA

Corresponding author: Wendy C Ziai, Department of Neurology, Johns Hopkins Hospital, 600 N. Wolfe St., Phipps 455, Baltimore, MD, USA 21231. wezai@jhmi.edu.

Author contributions

All authors contributed to study design and oversight. WCZ wrote the manuscript's first draft, which all authors reviewed and revised.

¹⁷Department of Neurosurgery, University of Kansas, Kansas City, KS, USA

¹⁸Department of Neurosurgery, University of Texas, San Antonio, TX, USA

¹⁹Department of Neurosurgery, University of Cincinnati, Cincinnati, OH, USA

²⁰Section of Neurosurgery, Neurovascular Surgery Program, University of Chicago, Chicago, IL, USA

Abstract

Rationale and hypothesis: Surgical removal of spontaneous intracerebral hemorrhage (ICH) may reduce secondary destruction of brain tissue. However, large surgical trials of craniotomy have not demonstrated definitive improvement in clinical outcomes. Minimally invasive surgery (MIS) may limit surgical tissue injury, and recent evidence supports testing these approaches in large clinical trials.

Methods and design: MISTIE III is an investigator-initiated multicenter, randomized, open-label phase 3 study investigating whether minimally invasive clot evacuation with thrombolysis improves functional outcomes at 365 days compared to conservative management. Patients with known symptom onset within 24 h of the computed tomography (CT) scan-confirmed supratentorial ICH volume ≥ 30 mL and intact brainstem reflexes were screened with a stability CT scan at least 6 h after diagnostic CT. Patients who met clinical and imaging criteria (no ongoing coagulopathy; no suspicion of aneurysm, arteriovenous malformation, or any other vascular anomaly; and stable hematoma size on consecutive scans) were randomized to either MIS plus thrombolysis or medical therapy. The sample size of 500 was based on findings of a phase 2 study.

Study outcomes: The primary outcome measure is dichotomized modified Rankin Scale 0–3 vs. 4–6 at 365 days adjusting for severity variables. Clinical secondary outcomes include dichotomized extended Glasgow Outcome Scale and all-cause mortality at 365 days; rate and extent of parenchymal blood clot removal; patient disposition at 365 days; efficacy at 180 days; type and intensity of ICU management; and quality of life measures. Safety was assessed at 30 days and throughout the study.

Keywords

Randomized controlled trial; protocols; intracerebral hemorrhage; stroke; surgery; minimally invasive surgery; thrombolysis

Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes with an incidence of 24.6 per 100,000 person-years, and is increasing due to the rising use of anticoagulants and antiplatelet drugs and an aging population.¹ The burden of spontaneous ICH is significant, with up to 50% mortality in the first 30 days, prolonged hospital stays, and similarly poor morbidity with more than half of survivors not achieving functional independence.^{2,3} Despite substantial research demonstrating the safety of a variety of general and specific medical treatments, ICH remains a disease without a specific therapy and accounts for much of the social burden of stroke.⁴

Current guidelines state that evacuation of a supratentorial hematoma or decompressive hemicraniectomy could be life-saving for deteriorating patients, but that early hematoma evacuation is not clearly beneficial for otherwise stable patients.^{5,6} Surgical reduction of hematoma volume is appealing with theoretical advantages of easing parenchymal displacement, alleviating intracranial pressure, and mitigating the neurotoxic effects of clot components, including thrombin, hemoglobin degradation products, and inflammatory cascades.^{7,8} Yet, trials of open surgical evacuation (craniotomy) have not altered outcomes after either early surgery in all eligible patients⁹ or delayed surgery in only those who deteriorate.^{10–13} Meta-analyses of either standard craniotomy or all surgical procedures for ICH, compared to conservative medical treatment, demonstrate a small advantage for surgery, but with heterogeneity and trial quality issues. A subgroup analysis of craniotomy for lobar ICH without intraventricular extension demonstrated no significant functional benefit from surgery and only a trend toward mortality benefit.¹¹

By limiting the size of the cranial opening and minimizing incisional disruption of brain tissue, minimally invasive surgery (MIS) clinical series and trials suggest benefit, but suffer from heterogeneity of eligibility, endpoint measurement, and surgical execution issues.^{12,14–15} Large procedural variations exist in MIS techniques that combine multiple surgical elements.^{16–22} To allow for direct comparison, prospective studies should standardize targeting precision, cranial entry, mechanical removal, and surgical task endpoint. A meta-analysis reported that stereotactic aspiration within 24 or 72 h significantly decreased the odds of death or dependence at final follow-up compared to either medical management or craniotomy.¹⁵ Recently, the Minimally Invasive Surgery Plus Alteplase in Intracerebral Hemorrhage Evacuation (MISTIE) II trial showed that intraparenchymal clot can be targeted and drained safely using aspiration with a standardized, image-guided catheter procedure followed by intrahematoma delivery of alteplase over 3 days.^{22,23} Trial results reported potential improvement in clinical outcomes in surgically treated patients (10% improved function at the 0–3 modified Rankin Scale [mRS] threshold compared to the control arm at 180 days).²³ These findings support the reduction of toxic metabolic injury with MIS reported in animal models.²⁴

Minimally invasive clot evacuation with intra-hematoma thrombolysis is thus a rational therapy, with substantial data supporting its safety. However, there is insufficient evidence to recommend routine use in clinical practice. We therefore designed a multisite, explanatory, phase 3 randomized controlled trial of sufficient size to test the clinical hypothesis that parenchymal clot could be precisely targeted, via a minimal cranial opening, and drained safely, navigating with a stereotactic catheter in a standardized procedure and using serial alteplase injections. We hypothesize this specific approach to hematoma volume reduction would improve clinical outcomes in ICH patients.

Study objectives

The primary efficacy objective is to demonstrate that MIS plus alteplase improves functional outcome by a 12% increase in the proportion with mRS scores of 0–3 compared to medically treated subjects at 365 days. The primary safety objective is to demonstrate that

early management with MIS and alteplase is safe for the treatment of ICH relative to rates of mortality, rebleeding, and infection in medically treated subjects at 30 days.

Patients were recruited from December 2013 through August 2017. Data collection ended in September 2018.

Methods

Design

MISTIE III is an investigator-initiated, adaptively randomized 1:1, multicenter open-label phase 3 evaluation of MIS and ICH lysis with alteplase versus conventional medical care (Figure 1). The study (n = 500) evaluated the efficacy and safety of MIS plus 1.0 mg of alteplase every 8 h for up to nine doses as compared to medically treated subjects. Outcome assessments were performed by local certified investigators and adjudicated by central, blinded investigators. The protocol was registered with clinicaltrials.gov (NCT01827046) and approved by each site's Institutional Review Board. The complete protocol and statistical analysis plan are available at clinicaltrials.gov/ct2/show/NCT01827046.

Patient population

Functionally independent (historical mRS = 1) male and female patients, age ≥ 18 years, with spontaneous, non-traumatic ICH with or without intraventricular hemorrhage (IVH) were screened. (See supplemental Table B for complete inclusion and exclusion criteria.)

Eligible patients were identified upon ICH diagnosis. A computed tomographic angiogram (CTA) or digital subtraction angiogram was performed prior to randomization to rule out underlying cerebrovascular or brain pathology. If CTA was contraindicated due to renal impairment, magnetic resonance angiography was used. Magnetic resonance imaging (MRI) was done at baseline and repeated once between days 7 and 10 (±1 day) to assess edema and cerebral ischemia.

A CT scan was required daily on days 1–4 post randomization, and repeated approximately 24 h after removal of the ICH catheter in surgical subjects or on day 5 in medical subjects. An unscheduled CT scan was done if the subject improved or worsened by more than 2 points on the Glasgow Coma Scale (GCS) motor score for 8 h.

Randomization

Patients were randomized to MIS with alteplase or standard care according to a centralized procedure coordinated via the electronic data capture (EDC) system (VISION, Prelude Dynamics, LLC, Austin, TX, USA) using a covariate-adaptive method.²⁵ Pocock and Simon's design²⁶ was used to improve the balance across study arms in the number of subjects with certain variables strongly predictive of functional outcomes (mRS) at 365 days post stroke, including age, pre-randomization clot volume, and baseline severity of impairment as measured by GCS.²⁷ Prior to randomization, for each incoming patient, the imbalance between treatment arms was determined using the accumulated available data on age, clot volume, and GCS. The patient was then randomized with high probability (e.g. weighted coin toss) to the treatment arm that would lower the imbalance. Patients were not

considered for adaptive randomization until their site had enrolled two patients into each treatment arm by within-site block randomization.

Intervention

Standard care

Subjects were followed daily for six days post randomization and returned for follow-up at days 30, 180, and 365. Telephone follow-up occurred at days 90 and 270. All subjects were treated medically using published intracerebral hemorrhage treatment guidelines and standard intensive care unit (ICU) protocols such as intracranial pressure (ICP) management, neurological status, cardiovascular management, respiratory care, nutritional support, venous thromboembolism prophylaxis, and withdrawal of life support decisions (supplemental Table C). Intraventricular hemorrhage fibrinolysis was prohibited, although normal saline flushes were permitted to clear an obstructed extraventricular drain. Trial center selection was standardized using assessment of the site team (e.g. surgeon, intensivist, study coordinator), facilities, target population census, and equipoise for the proposed trial design.

Surgery and alteplase therapy

In individuals randomized to receive MIS plus alteplase, after administration of the appropriate anesthetic, we used an image-guided stylet or real-time imaging to place a rigid cannula within the middle two-thirds of the overall hematoma diameter. Careful hematoma aspiration was performed freehand using a 10 mL syringe until there was no longer any fluid component of the clot in the aspirate or until first resistance. We then passed a soft ventriculostomy catheter through the outer sheath of the cannula, also with image-guided stylet or real-time imaging, leaving the soft catheter with all its perforations in the center of the distal portion of the residual hematoma. The catheter was tunneled subcutaneously away from the incision and connected to a three-way stopcock and closed drainage system. A CT scan was done to confirm correct placement and measure clot size reduction.

A 6 h post-surgical stabilization period with an open-drainage system was required prior to first alteplase administration to reduce the possibility of secondary hemorrhage. If new bleeding or bleeding expansion was seen on the post-operative CT scan, another was done after a 12 h wait. When the bleeding was stable, dosing could be initiated.

Unless an endpoint of clot lysis was reached or an adverse treatment endpoint occurred (e.g. symptomatic hemorrhage), subjects received 1.0 mg of alteplase through the intrahematoma catheter every 8 h for up to nine doses. This was followed by a 3 mL flush of sterile saline to ensure clearance of alteplase from the catheter and delivery to the clot. After each dose, we clamped the catheter for 1 h and then re-opened it to gravity drainage for 7 h.

Treatment success was clot volume reduced to 15 mL or less (by ABC/2) on a CT scan. Dosing was permitted to continue until the clot volume was reduced further to 10 mL. After the endpoint was reached, the catheter was kept open to drain for 24 to 36 h and then removed. Infection was monitored through culture of the tip of the intra-hematoma catheter on removal. Neurosurgical clinical judgment guided replacement of catheters. The Surgical Center, located at the University of Chicago, reviewed all trajectory planning, catheter

placements and monitored clot removal assessments, catheter discontinuation protocols, and the safety and efficacy of the surgical procedure (supplemental Table D).

Blinding

The 30-, 180-, and 365-day mRS assessments were recorded and transferred to the University of Glasgow (Glasgow, UK) for scoring by trained and blinded reviewers.

Outcomes

The primary outcome measure is the adjudicated mRS, dichotomized as mRS 0–3 vs. 4–6 at 365 days post ictus. Secondary outcome measures include: dichotomized extended Glasgow Outcome Scale good (4–8) vs. poor (1–3) outcomes at 365 days; all-cause mortality longitudinally from ictus to 365 days; relationship between clot removal and functional outcome using area under the curve (AUC) methods; patient disposition as home days and discharge location; 180-day efficacy; type and intensity of ICU management; and EuroQol 5-Dimension (EQ-5D) and visual analogue scale (EQ-VAS).

Data and safety monitoring

Interim safety analyses were prepared for the external Data Safety and Monitoring Board (DSMB) every six months. Measures monitored included the incidence of symptomatic and asymptomatic intracranial bleeding events through daily CT scans for four days after randomization and 24 h after catheter removal, and the incidence of confirmed and suspected infection and in-hospital mortality. The DSMB had access to pooled data and data grouped by treatment assignment (A:B).

Pre-specified thresholds triggering DSMB review were: 30-day mortality >60%; symptomatic bleeding rate >25% (events identified within first 30 days and assessed as occurring during treatment or within 72 h after treatment were monitored); first-week operative death rate >10%; and procedure-related infection rate >15% (over the initial 30 days). Any serious adverse events (SAE) above threshold would trigger study suspension for a safety and efficacy review. Additionally, the number and proportion of all SAEs in the respective randomized groups was evaluated. Interim analyses based on O'Brien-Fleming stopping boundaries for efficacy occurred after 375 subjects were enrolled and 180-day outcomes were available.

Sample size

The trial enrolled 500 eligible patients, approximately 250 to each treatment arm. The power to detect the effect size of 13% across all clot locations with this sample size is 88%. The power to detect the conservatively estimated effect size of 11% in this patient population is 81%. All randomized patients were included in the safety analysis sample. The sample size was based on MISTIE II, which provided evidence of increasing frequency of mRS scores in the 0–2 categories between 180 and 365 days with an unadjusted proportion of mRS 0–3 increasing to 14%. We based the primary outcome on 365-day outcomes because of the lack of a plateau in good functional outcome at 180 days.

Statistical analyses

For the primary analyses for all efficacy measures, a modified intention-to-treat paradigm was employed in which all eligible, exposed subjects were analyzed according to their randomized assignment. Missing covariate data will be handled through multiple imputation procedures subject to the validity of missing-at-randomness assumptions. To estimate the average treatment effect, we will use the targeted maximum likelihood estimator (TMLE) of Van der Laan and Gruber.²⁸ For this primary outcome analysis, the proportions of mRS 0–3 outcomes will be compared between surgical and medical treatment arms, adjusted for baseline (pre-randomization) variables used in the covariate adaptive randomization (i.e. clot volume, age, and severity of impairment as measured by GCS) and for clinically established severity variables IVH size and ICH clot location (lobar vs. deep).

Additional, exploratory analyses of mRS at 365 days include: adjusting for other baseline variables; ordinal analysis; longitudinal analysis at 90, 180, and 270 days; severity subgroups; demographic and clinically specific subgroups (including for gender, race, and ethnicity); and random effects for hospital sites. Efficacy analyses of the ordinal shift in mRS will be undertaken on the full range (0–6) of the adjudicated mRS using Cochran-Mantel-Haenszel shift test and proportional odds logistic regression subject to the validity of shift analysis model assumptions. Other secondary outcome analyses will be carried out according to standard statistical principles for comparison of parametric or nonparametric distributions as appropriate.

Study organization and funding

Supported by the National Institutes of Health/National Institute of Neurological Disorders and Stroke (grant 1U01NS080824), MISTIE III is directed by the Division of Brain Injury Outcomes in the Johns Hopkins University, with data management by the Johns Hopkins Bloomberg School of Public Health. Alteplase was donated by Genentech in North America and purchased commercially in all other countries.

Summary

MISTIE III, an explanatory trial, is the first randomized, multicenter, controlled phase 3 trial assessing the efficacy of MIS plus alteplase therapy in ICH patients. The allowance for catheter placement, dosing, and removal decisions by non-study-team physicians reflects the practical nature and generalizability of this study. If the study outcome is positive, it will significantly improve the therapeutic options for acute hemorrhagic stroke treatment. A negative outcome could provide information needed to improve MIS or to limit its future use. Based on available screening data, we estimate that 10–15% of all ICH, or between 10,000 and 15,000 subjects in the United States yearly and 150,000 to 200,000 worldwide, would be eligible for this therapy. It is an important step toward reducing the burden of ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KRL has consulted for and received honoraria from Boehringer Ingelheim. JD has received honoraria from Bayer, Pfizer, BMS, Daiichi Sankyo, and Boehringer Ingelheim, and is an investigator in a Servier and MicroTransponder trial. PV is an InTouch Health adviser with stock equity and an adviser for M Dialysis and Moberg Medical. ADM is a director of the Newcastle Neurosurgery Foundation. CSK has been a consultant to Boehringer Ingelheim, Bayer, and GORE. CSA has received funding from the National Health and Medical Research Council of Australia and Takeda, consultancy fees from Amgen, and honoraria from Takeda. MRH is a consultant for Scientia Vascular and an investigator in the NICO Corporation-sponsored ENRICH study. IAA is funded by the NIH and has rendered expert medico-legal opinions on hemorrhagic stroke. DFH is a consultant for BrainScope, Neurotrope, Portola Pharmaceuticals, Op2Lysis, HeadSense, and Medtronic and serves on the International Journal of Stroke editorial board. The other authors declare no conflicts of interest.

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Figure 1.
MISTIE III study assessment flow chart.

AE: adverse event; CT: computed tomography; eGOS: extended Glasgow Outcome Scale; EQ-5D: EuroQol 5-Dimension; ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; MIS: minimally invasive surgery; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PBSI: Preference-Based Stroke Index; SAE: serious adverse event.