Deferoxamine mesylate in patients with intracerebral haemorrhage (i-DEF): a multicentre, randomised, placebo-controlled, double-blind phase 2 trial

*Magdy Selim, Lydia D Foster, Claudia S Moy, Guohua Xi, Michael D Hill, Lewis B Morgenstern, Steven M Greenberg, Michael L James, Vineeta Singh, Wayne M Clark, Casey Norton, Yuko Y Palesch, Sharon D Yeatts, on behalf of the i-DEF Investigators**

Lancet Neurol 2019; 18: 428–38

Published Online March 18, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30069-9

See Comment page 416

*Members listed in the appendix.

Beth Israel Deaconess Medical Center, Boston, MA, USA (Prof M Selim MD, C Norton BS); **Harvard Medical School, Boston, MA, USA** (Prof M Selim, Prof S M Greenberg MD); **Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA** (L D Foster MS, Prof Y Y Palesch PhD, S D Yeatts PhD); **National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA** (C S Moy PhD); **Department of Neurosurgery** (Prof G Xi MD) **and Department of Neurology** (L B Morgenstern MD), **University of Michigan Medical School, Ann Arbor, MI, USA; Health Science Center, University of Calgary, Calgary, AB, Canada** (Prof M D Hill MD); **Massachusetts General Hospital, Boston, MA, USA** (Prof S M Greenberg); **Department of Anesthesiology and Neurology, Duke University, Durham, NC, USA** (M L James MD); **San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, USA** (Prof V Singh MD); **and Oregon Health and Science University Hospital, Portland, OR, USA** (Prof W M Clark MD)

Correspondence to: Prof Magdy Selim, Division of Stroke & Cerebrovascular Disease, Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue—Palmer 127, Boston, MA 02215, USA
mselim@bidmc.harvard.edu

See Online for appendix

Summary

Background Iron from haemolysed blood is implicated in secondary injury after intracerebral haemorrhage. We aimed to assess the safety of the iron chelator deferoxamine mesylate in patients with intracerebral haemorrhage and to establish whether the drug merits investigation in a phase 3 trial.

Methods We did a multicentre, futility-design, randomised, placebo-controlled, double-blind, phase 2 trial at 40 hospitals in Canada and the USA. Adults aged 18–80 years with primary, spontaneous, supratentorial intracerebral haemorrhage were randomly assigned (1:1) to receive deferoxamine mesylate (32 mg/kg per day) or placebo (saline) infusions for 3 consecutive days within 24 h of haemorrhage onset. Randomisation was done via a web-based trial-management system centrally in real time, and treatment allocation was concealed from both participants and investigators. The primary outcome was good clinical outcome, which was defined as a modified Rankin Scale score of 0–2 at day 90. We did a futility analysis: if the 90% upper confidence bound of the absolute risk difference between the two groups in the proportion of participants with a good clinical outcome was less than 12% in favour of deferoxamine mesylate, then to move to a phase 3 efficacy trial would be futile. Primary outcome and safety data were analysed in the modified intention-to-treat population, comprising only participants in whom the study infusions were initiated. This trial is registered with ClinicalTrials.gov, number NCT02175225, and is completed.

Findings We recruited 294 participants between Nov 23, 2014, and Nov 10, 2017. The modified intention-to-treat population consisted of 144 patients assigned to the deferoxamine mesylate group and 147 assigned to the placebo group. At day 90, among patients with available data for the primary outcome, 48 (34%) of 140 participants in the deferoxamine mesylate group, and 47 (33%) of 143 patients in the placebo group, had modified Rankin Scale scores of 0–2 (adjusted absolute risk difference 0·6% [90% upper confidence bound 6·8%]). By day 90, 70 serious adverse events were reported in 39 (27%) of 144 patients in the deferoxamine mesylate group, and 78 serious adverse events were reported in 49 (33%) of 147 patients in the placebo group. Ten (7%) participants in the deferoxamine mesylate and 11 (7%) in the placebo group died. None of the deaths were judged to be treatment related.

Interpretation Deferoxamine mesylate was safe. However, the primary result showed that further study of the efficacy of deferoxamine mesylate with anticipation that the drug would significantly improve the chance of good clinical outcome (ie, mRS score of 0–2) at day 90 would be futile.

Funding US National Institutes of Health and US National Institute of Neurological Disorders and Stroke.

Introduction

Intracerebral haemorrhage is a frequent cause of permanent disability and mortality and is a substantial burden on global health-care systems and societies.[1] Worldwide, the overall incidence is approximately 25 per 100 000 person-years, with some estimates as high as 2·3 million cases per year.[1] Supportive medical care remains the mainstay of treatment, and efforts to target haematoma expansion or reduction have had little effect.[2,3]

Release of iron from haemoglobin degradation products after haemolysis of red blood cells within intracerebral haematomas has been implicated in various processes that contribute to secondary neuronal injury after intracerebral haemorrhage, including apoptosis, oxidative stress, inflammation, and autophagy.[5–7] A growing body of preclinical evidence suggests that the iron chelator deferoxamine mesylate exerts neuroprotective effects after intracerebral haemorrhage[7–9] and is a promising treatment option. We previously did a phase 1 dose-finding, safety, and feasibility study[10] of deferoxamine mesylate in patients with acute intracerebral haemorrhage to translate preclinical findings into the clinical setting. On the basis of the results of that study, we designed a pilot phase 2 trial to assess the safety of deferoxamine mesylate in a larger cohort of patients and to assess whether the drug could be a viable therapy for intracerebral haemorrhage before embarking on a large phase 3 trial.

Research in context

Evidence before this study

We searched PubMed up to Jan 5, 2019, with the terms "ICH", "intracerebral haemorrhage", "haemorrhage", AND "deferoxamine" without language restrictions. Of the 123 preclinical studies and six clinical studies that we identified, 45 preclinical studies and two clinical studies were excluded because they were not related to intracerebral haemorrhage, were not in vivo experimental studies, were duplicate publications, were about non-primary or non-spontaneous intracerebral haemorrhage, or did not have prespecified outcomes. Preclinical studies suggested that iron accumulates in the brain after experimental intracerebral haemorrhage, that iron-mediated toxicity contributes to delayed cellular injury and neurological deficits, and that treatment with deferoxamine mesylate attenuates neuronal death and improves recovery after intracerebral haemorrhage in various species. We examined the studies for methodological rigour, use of blinding and randomisation, and outcome assessment to establish the risk of bias. The clinical studies were non-randomised, open-label, and small (sample sizes of 20–42 participants), and were classified as being at high risk of bias. We previously did a small phase 1 safety and dose-finding study of deferoxamine mesylate in 20 patients with intracerebral haemorrhage, which identified 62 mg/kg per day (up to a maximum dose of 6000 mg per day) as the maximum tolerated dose. However, this dose was associated with increased pulmonary toxic effects in the subsequent High Dose Deferoxamine in intracerebal haemorrhage (HI-DEF) trial. Therefore, the available evidence was insufficient to ascertain the appropriate dosage of deferoxamine mesylate or its safety in this patient population or to show the drug's effects on neurological outcomes after intracerebral haemorrhage.

Added value of this study

To our knowledge, the Intracerebral Haemorrhage Deferoxamine (i-DEF) trial is the first multicentre, randomised, double-blind, placebo-controlled trial to prospectively collect clinical, functional, and imaging outcome data from a large population of patients with intracerebral haemorrhage given deferoxamine mesylate. The intermediate dose of deferoxamine mesylate (32 mg/kg per day for 3 days) examined was well tolerated by patients with intracerebral haemorrhage and did not increase the frequency of serious adverse events, major disability, or death compared with placebo. However, compared with placebo, treatment with deferoxamine mesylate did not seem to improve the chances of good clinical outcome (ie, a modified Rankin Scale score of 0–2) 90 days after intracerebral haemorrhage.

Implications of all the available evidence

Our primary results suggest that a phase 3 efficacy trial of deferoxamine mesylate, with anticipation that treatment would significantly improve the chance of good clinical outcome at 90 days in patients with intracerebral haemorrhage, would be futile. The i-DEF trial was not designed or intended to test the efficacy of deferoxamine mesylate, and thus our findings should not change standards of clinical practice. An important observation from this study is that patients with intracerebral haemorrhage seem to continue to improve past 3 months. In this regard, our secondary results suggesting the non-futility of deferoxamine mesylate at day 180 could be relevant. Future studies in patients with intracerebral haemorrhage should consider assessment of outcomes beyond this traditional timepoint to capture the full extent of recovery. Sharing the full safety and outcome data from i-DEF is likely to stimulate further investigations of therapeutic interventions targeting iron-mediated toxicity and secondary injury after intracerebral haemorrhage to improve outcome of patients.

Methods

Study design and participants

The Intracerebral Haemorrhage Deferoxamine (i-DEF) trial was a prospective, multicentre, futility-design, randomised, placebo-controlled, double-blind, phase 2 clinical trial at 40 hospitals in Canada and the USA. Eligible participants were aged 18–80 years, had spontaneous, primary, supratentorial intracerebral haemorrhage, and could start study drug within 24 h of the haemorrhage. Key exclusion criteria were suspected secondary causes for intracerebral haemorrhage, infratentorial intracerebral haemorrhage, severe iron deficiency, pregnancy, breastfeeding, serum creatinine concentration of 2 mg/dL or higher, coagulopathy (defined as activated prothrombin time >40 s, an international normalised ratio >1·3, or concurrent use of direct oral anticoagulants or low-molecular-weight heparin at presentation), pre-haemorrhage scores of 2 or more on the modified Rankin Scale (mRS), deep coma (a Glasgow Coma Scale score of 6 or less or a score of 3 on item 1A of the US National Institutes of Health Stroke Scale [NIHSS]), irreversibly impaired brainstem function, an NIHSS score of less than 6 at presentation, plans for haematoma evacuation before administration of study drug, an indication that withdrawal of care would be implemented within 72 h, and high risk of acute respiratory distress syndrome. The appendix details all other inclusion and exclusion criteria, including those pertaining to acute respiratory distress syndrome, and the rationale for the study's futility design. The trial was approved by the US Food and Drug Administration (IND #77306) and Health Canada (CTA #160713). Ethics approval was obtained at each participating site. The trial was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Good Clinical Practice Consolidated Guidelines. Written informed consent was obtained from each participant

or legally authorised representative according to local regulations.

Randomisation and masking

Participants were recruited from emergency departments and stroke units and enrolled by local investigators, who then entered randomisation covariates into the web-based trial-management system (WebDCU). Participants were randomly allocated (1:1) to deferoxamine mesylate or placebo (saline) infusion via WebDCU, which allowed randomisation to occur dynamically in real time and ensured complete concealment of treatment allocation. Balance of key covariates was controlled via a combination of minimisation (to minimise the sum of imbalances in baseline covariates) and biased-coin (to avoid deterministic assignments) methods. WebDCU confirmed eligibility, assessed treatment-group distribution within each baseline covariate, calculated the sum of the marginal imbalances, and dynamically generated the random allocation. When the imbalance measure was zero, simple randomisation was applied; otherwise, a biased-coin probability of 0·75 was applied in favour of the treatment allocation that would reduce the imbalance. The key covariates were clinical site, baseline intracerebral haemorrhage score (<3 *vs* ≥3), time to treatment (≤12 h *vs* >12 h), warfarin use at onset of intracerebral haemorrhage (yes *vs* no), NIHSS score (≤10 *vs* >10), and volume of intracerebral haemorrhage (≤10 mL *vs* >10 mL) at presentation. For randomisation purposes, haematoma volume was estimated by local investigators on the basis of the admission CT with the ABC/2 method.[11]

Study drug was reconstituted by the sites' pharmacists in the pharmacy in all cases. Reconstituted deferoxamine mesylate looked identical to saline and was provided to the investigators on the ward for blinded administration. All participants and site trial personnel, except for pharmacists, were masked to treatment assignment until completions of data analyses. Pharmacists were not involved in any other study-related assessments.

Procedures

All patients underwent brain CTs at presentation as standard practice to confirm the diagnosis of intracerebral haemorrhage. Demographic and baseline clinical characteristics of eligible participants were recorded at enrolment. Severity of the haemorrhage was measured with the Glasgow Coma Scale, the NIHSS, and the intracerebral haemorrhage score.[12] The Glasgow Coma Scale is a measure of the level of consciousness. Scores range from 3 to 15, with 3 representing deep unconsciousness and higher scores suggesting milder impairment of consciousness. The NIHSS provides a measure of neurological deficits. Scores range from 0 to 42, with 0 corresponding to no neurological deficits and higher scores suggesting increased severity of neurological deficits. The intracerebral haemorrhage score is a prognostic model used to predict disability and mortality among patients with spontaneous intracerebral haemorrhage on the basis of age, Glasgow Coma Scale score, intracerebral haemorrhage volume and location (supratentorial *vs* infratentorial), and the presence of intraventricular haemorrhage. Scores range from 0 to 5, with increasing scores corresponding to increasing probability of disability and mortality.

Deferoxamine mesylate 32 mg/kg per day (to a maximum dose of 6000 mg per day) or placebo (saline) was given by intravenous infusions at a rate of 7·5 mg/kg per h on 3 consecutive days. The first infusion was started within 24 h of the intracerebral haemorrhage. The appendix provides the rationale for dose selection, the treatment window, and the duration of treatment.

Participants were assessed in person daily until the day after the last study infusion, and then on day 7 or at discharge (whichever was earlier), on day 30, and on day 90. Assessments were measurement of NIHSS, mRS, and Glasgow Coma Scale scores, the Montreal Cognitive Assessment (MoCA), review of adverse events, and a study-specific visual and auditory assessment battery in capable participants to assess newly emerging visual or auditory changes, which have been reported with long-term use of deferoxamine mesylate.[13] Participants were contacted by telephone on day 60 to assess emerging serious adverse events and on day 180 to measure scores on the mRS.[14] The mRS provides a measure of the degree of disability or dependence in daily activities for people who have had a stroke or experienced other causes of neurological disability. Scores range from 0 to 6, with 0 corresponding to no symptoms at all, and higher scores suggesting increasing disability and dependence; a score of 6 represents death. All assessments were done by qualified investigators who were certified in mRS and NIHSS administration and masked to treatment assignment. A study-related CT was done within 24 h of completion of the last study infusion.

Outcomes

The primary outcome measure was good clinical outcome, which was defined as a dichotomised mRS score of 0–2 at day 90. Prespecified secondary outcomes were mRS scores dichotomised to 0–3 to define a good clinical outcome at day 90; mRS scores of 0–2 and 0–3 at day 180 (because of data suggesting that recovery after intracerebral haemorrhage might occur beyond 3 months[15]), ordinal distribution of mRS scores at day 90 and day 180, the effect of early versus late treatment (ie, ≤12 h *vs* >12 h from onset of intracerebral haemorrhage symptoms) on functional outcome, change in NIHSS scores from presentation to day 90, and MoCA scores at day 90.

Safety outcomes were adverse events of special interest (ie, anaphylaxis at any time during the study infusion, hypotension requiring medical intervention at any time during the study infusion that could not be explained by other causes, development of new and unexplained visual

or auditory changes after initiation of the study infusion, and respiratory compromise of any cause, including acute respiratory distress syndrome, in hospital until day 7 or discharge [whichever was earlier]), all serious adverse events up to day 90, deaths (both all-cause deaths and intracerebral haemorrhage-related deaths) up to day 180, and any adverse event up to day 7 or hospital discharge (whichever was earlier).

Statistical analysis

The primary hypothesis specified that if the between-group difference in the proportion of participants with a good clinical outcome at day 90 is less than 12% in favour of deferoxamine mesylate, then moving forward with a phase 3 assessment would be futile. We estimated that 254 participants (127 in each group) were needed to test the futility hypothesis with 80% power, assuming that approximately 28% of participants in the placebo group would have mRS scores of 0–2 at 90 days on the basis of the weighted average of the proportions of patients with good clinical outcome reported in the literature.[16–18] Final sample size was then increased to 294 to account for possible dilution of treatment effect associated with loss to follow-up, withdrawal of consent, and randomly assigned participants not receiving their assigned treatment because of deteriorating neurological status. Additionally, the trial was adequately powered to assess the futility hypothesis with mRS scores of 0–3 as a secondary outcome based on an absolute risk difference of less than 13% in favour of deferoxamine mesylate.

We followed a prespecified statistical analysis plan, which was finalised before the database was locked and the final data analysis was done. In accordance with the futility design, the primary analysis plan specified that if the one-sided 90% upper confidence bound (90% UCB) of the treatment effect (absolute adjusted risk difference [AARD]) was less than 12% in favour of deferoxamine mesylate compared with placebo, then to move to a phase 3 trial would be futile. The hypothesis was tested via a generalised linear model relating the probability of good clinical outcome to treatment after adjustment for the randomisation covariates as specified in the statistical analysis plan. The choice of 12% as the futility threshold was to some extent arbitrary. Previous phase 3 trials in intracerebral haemorrhage were powered to detect a minimum clinically important difference of 10%.[19] Taking into consideration this minimum clinically important difference, that no available treatments prevent disability after intracerebral haemorrhage, and that effect sizes tend to be overestimated in pre-phase-3 trials, we set the futility threshold for the primary outcome in i-DEF at 12%.[20] The prespecified futility threshold for an mRS score of 0–3 was set at 13% (not 12%) to maintain statistical power for this dichotomisation.

The generalised linear model we detailed was also used for secondary analyses of mRS outcomes (0–3 at days 90 and 180, and 0–2 at day 180) and was expanded to include an interaction between treatment and time to treatment initiation (≤12 h *vs* >12 h). We did a shift analysis of the full distribution of the mRS at days 90 and 180 via a proportional odds model. We did Wilcoxon rank-sum tests to assess NIHSS and MoCA scores at day 90. The primary outcome was also assessed for treatment differences in prespecified subgroups (time to treatment ≤12 h *vs* >12 h, intracerebral haemorrhage score 0–2 *vs* 3–5, sex, race, age <60 years *vs* ≥60 years, and intraventricular haemorrhage *vs* no intraventricular haemorrhage), whereby each covariate was assessed individually with a model that includes treatment, subgroup, and the corresponding interaction effect to derive subgroup-specific treatment effect estimates and assess heterogeneity across the subgroups.

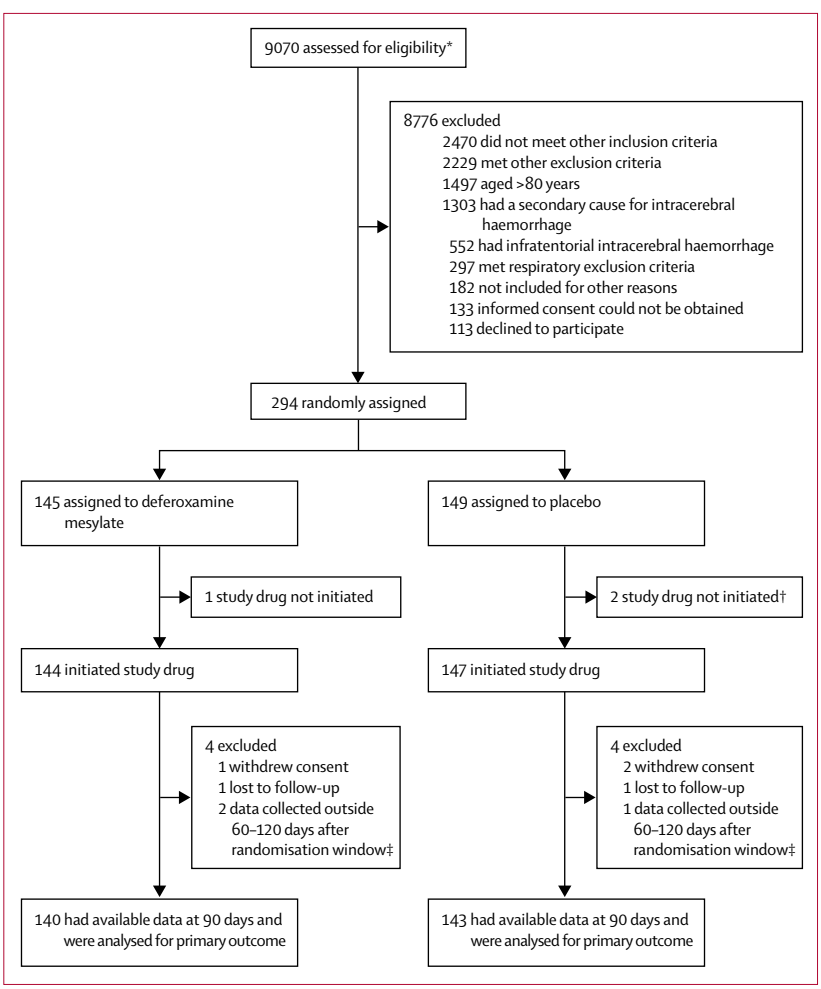

Figure 1: **Trial profile**
There were three crossovers in the placebo group and one in the deferoxamine mesylate group. *Screen failure logs were entered into the WebDCU web-based randomisation system on a monthly basis by each site. †Informed consent documentation was missing for one of these participants, who was subsequently removed from the database; this occurrence was classified as a post-randomisation exclusion. ‡The statistical analysis plan specified that only data collected no sooner than 60 days and no later than 120 days after randomisation would be included in the primary analysis.

Adverse events were classified according to terminology from the Medical Dictionary for Regulatory Activities combined with principal-investigator-preferred adjustments. Treatment differences in the cumulative incidences of mortality and adverse events of special interest were assessed via relative risk with corresponding 95% CIs.

	Deferoxamine mesylate group (n=144)	Placebo group (n=147)
Age, years	59 (51–71)	62 (54–70)
Sex		
Female	56 (39%)	56 (38%)
Male	88 (61%)	91 (62%)
Race		
White	81 (56%)	100 (68%)
Black	31 (22%)	33 (22%)
Asian	25 (17%)	12 (8%)
Native American or Alaskan	2 (1%)	0
Native Hawaiian or other Pacific Islander	3 (2%)	1 (1%)
Unknown	2 (1%)	1 (1%)
Ethnicity		
Hispanic or Latino	21 (15%)	27 (18%)
Not Hispanic or Latino	123 (85%)	120 (82%)
Glasgow Coma Scale Score	14 (13–15; 8–15)	14 (11–15; 7–15)
US National Institutes of Health Stroke Scale score	13 (8–17; 6–33)	13 (9–19; 6–32)
Intracerebral haemorrhage score		
Median (IQR)	1 (0–1)	1 (0–2)
≤2	139 (97%)	138 (94%)
>2	5 (3%)	9 (6%)
Medical history		
Hypertension	113 (78%)	124 (84%)
Diabetes mellitus	32 (22%)	43 (29%)
Cardiac disease	14 (10%)	15 (10%)
Pulmonary disease	31 (22%)	26 (18%)
Previous ischaemic stroke or transient ischaemic attack	10 (7%)	16 (11%)
Previous intracerebral haemorrhage	7 (5%)	3 (2%)
Previous drug use		
Antiplatelet agents	42 (29%)	49 (33%)
Warfarin	1 (1%)	1 (1%)
Antihypertensives	119 (83%)	125 (85%)
Statins	38 (26%)	36 (24%)
Modified Rankin Scale score (before intracerebral haemorrhage)		
0	130 (90%)	130 (88%)
1	14 (10%)	17 (12%)
Blood pressure, mm Hg		
Systolic	134·9 (16·0)	136·8 (15·0)
Diastolic	71·4 (13·9)	70·5 (13·2)
Blood glucose, mg/dL	133·5 (113·2–153·5)	138·0 (118·0–164·0)
Time from intracerebral haemorrhage to treatment, h		
Median	17·4 (10·8–22·4)	19·5 (11·2–22·9)
≤ 12	44 (31%)	46 (31%)
>12	100 (69%)	101 (69%)

(Table 1 continues on next page)

The log-rank test was used to compare the survival curves for each treatment group.

The protocol specified that participants who significantly deteriorated (ie, development of fixed and dilated pupils or a decrease in Glasgow Coma Scale score to ≤6) after randomisation and before initiation of the study infusion should be classified as post-randomisation exclusions and thus were excluded from subsequent study-related procedures. The target population for the futility analysis and safety outcomes was the modified intention-to-treat population comprising only participants in whom the study infusions were initiated.

Prespecified sensitivity analyses of dichotomised mRS outcomes at day 90 and day 180 were also done in the intention-to-treat, as-treated, and per-protocol populations. Complete case analysis was planned as the primary analytic approach, with prespecified sensitivity analyses with last-observation-carried-forward, best-and-worst-case-scenario (whereby a favourable outcome [ie, best case scenario] is imputed for the placebo group, and an unfavourable outcome [ie, worst case scenario] is imputed for the deferoxamine mesylate group), and multiple imputation approaches (appendix). Briefly, an imputation for each missing outcome was generated on the basis of observed relationships between the outcome and covariates. This process was repeated to create 100 sample datasets with complete outcomes, each of which was analysed as described. We compiled the results to yield a single statistical inference about treatment effect. We used multivariable models adjusted for additional prognostic baseline variables (including volume of intraventricular haemorrhage, thalamic *vs* non-thalamic intracerebral haemorrhage, and severity index quartiles;[21] appendix) to do additional post-hoc analyses of dichotomised mRS outcomes.

We did a post-hoc exploratory analysis to examine the interaction between deferoxamine mesylate treatment, time to treatment after onset of intracerebral haemorrhage (≤12 h *vs* >12 h), and baseline relative perihaematomal oedema, and their effects on post-infusion relative perihaematomal oedema, after adjustment for baseline serum glucose, concomitant use of anti-oedema drug, and oedema volume.

All CTs were sent to the i-DEF core imaging laboratory (Beth Israel Deaconess Medical Center, Boston, MA, USA) for further review by experienced raters, who were masked to clinical data and treatment assignment, to confirm location of the intracerebral haemorrhage and the presence or absence of intraventricular haemorrhage, and to do volumetric measurements of intracerebral haemorrhages and perihaematomal oedema. Areas of the haematoma and perihaematomal oedema were automatically delineated with imaging analysis software (Analyze 11.0 Visualization and Analysis Software for Medical Imaging; AnalyzeDirect, Overland Park, KS, USA), and density thresholds were used on each slice followed by manual correction. The software provided

total volume measurements for intracerebral haemorrhage, intraventricular haemorrhage, and perihaematomal oedema by summing the volumes from all respective slices. We previously validated the inter-rater and intra-rater reliability of this approach.[22]

SDY and LDF did all statistical analyses in SAS (version 9.4). The trial is registered with ClinicalTrials.gov, number NCT02175225. It was overseen by an executive committee and monitored by an independent data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke. Study data were centrally monitored and analysed by the Data Coordination Unit in the Department of Public Health Sciences at the Medical University of South Carolina (Charleston, SC, USA).

Role of the funding source

The study funder had roles in study design but did not contribute to data collection, analysis, or interpretation, or writing of the report. MS, LDF, and SDY had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between Nov 23, 2014, and Nov 10, 2017, 9070 patients were assessed for eligibility and 294 were recruited (figure 1). 145 patients were assigned to the deferoxamine mesylate group and 149 patients to the placebo group, but three patients were subsequently classified as post-randomisation exclusions and excluded from the analysis. Thus, the modified intention-to-treat population comprised 291 patients, 144 in the deferoxamine mesylate group and 147 in the placebo group.

Median age was 59 years (IQR 51–71) in the deferoxamine mesylate group and 62 years (54–70) in the placebo group (table 1). 81 (56%) patients in the deferoxamine mesylate group were white compared with 100 (68%) in the placebo group. More patients in the placebo group than in the deferoxamine mesylate group had thalamic intracerebral haemorrhage, intraventricular haemorrhage, and a history of previous ischaemic strokes (table 1). Conversely, more patients in the deferoxamine mesylate group than in the placebo group had non-thalamic deep intracerebral haemorrhage and a history of previous intracerebral haemorrhage (table 1). Other characteristics were broadly similar between groups (table 1).

Data for the primary outcome at day 90 were available for 140 (97%) participants in the deferoxamine mesylate group and 143 (97%) in the placebo group (figure 1). Data for outcomes at 180 days were available for 135 participants in both groups. At day 90, 48 (34%) of 140 patients in the deferoxamine mesylate group and 47 (33%) of 143 in the placebo group had mRS scores of 0–2 (AARD 0·6%; 90% UCB 6·8%), which fell below the prespecified 12% futility threshold (figure 2). In secondary analyses, 61 (45%) of 135 patients in the deferoxamine mesylate group and 48 (36%) of 135 in the placebo group had mRS scores of 0–2 at day 180 (AARD 8·6%; 90% UCB 15·6%, which exceeded the futility threshold). 91 (65%) of 140 patients in the deferoxamine mesylate group and 82 (57%) of 143 patients in the placebo group had mRS scores of 0–3 (AARD 6·2%; 90% UCB 12·1%) at day 90, and 97 (72%) of 135 and 92 (68%) of 135, respectively, had mRS scores of 0–3 at day 180 (AARD –1·8%; 90% UCB 2·9%), between-group differences that fell below the corresponding futility thresholds (figure 2). Figure 3 shows ordinal distribution of mRS scores at days 90 and 180. The adjusted odds ratio of a good clinical outcome, defined at

	Deferoxamine mesylate group (n=144)	Placebo group (n=147)
(Continued from previous page)		
Intracerebral haemorrhage location		
Lobar	26 (18%)	33 (22%)
Deep (thalamic)	45 (31%)	61 (41%)
Deep (non-thalamic)	73 (51%)	53 (36%)
Intracerebral haemorrhage volume, mL	12·1 (6·1–23·8)	13·0 (6·7–27·3)
Intraventricular haemorrhage		
n	47 (33%)	62 (42%)
Volume, mL*	0·0 (0·0–2·1)	0·0 (0·0–5·4)
Relative perihaematomal oedema volume*	1·2 (1·0–1·6)	1·1 (0·9–1·5)

Data are median (IQR), n (%), median (IQR; range), or mean (SD). *Based on volumetric measurements by a central reader.

Table 1: **Baseline demographic and clinical characteristics**

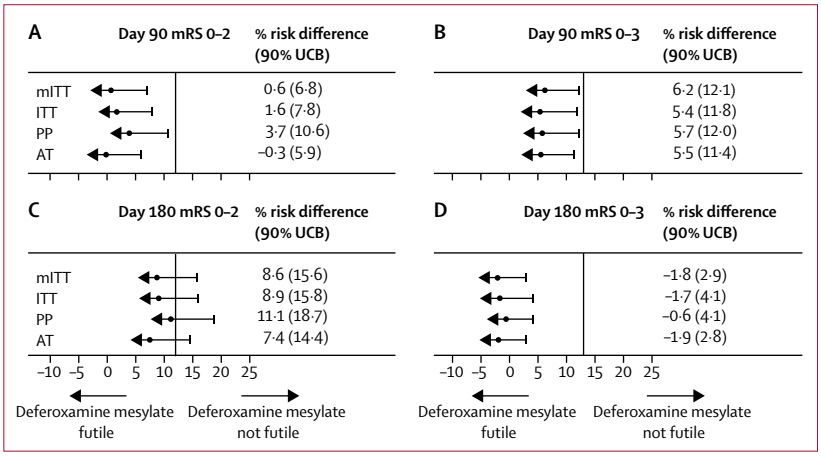

Figure 2: **Futility analyses of mRS score in patients receiving deferoxamine mesylate or placebo at days 90 (A, B) and 180 (C, D)**

Black circles represent adjusted point estimates, and the endcaps are the one-sided 90% UCBs derived from the model. The arrow indicates that the lower confidence bound is not shown, in keeping with the one-sided alternative hypothesis. To declare futility, the entire confidence interval had to lie to the left of the vertical reference line. The mITT population included all randomly assigned participants in whom the study infusion was started, irrespective of whether or not the infusion was prematurely discontinued. The ITT population comprised all randomly assigned participants, irrespective of whether or not they received study infusion. In the AT analysis, participants were analysed according to the administered treatment, which could differ from the treatment to which they were randomly assigned. The PP population included all participants who underwent at least one post-treatment assessment and had no major protocol violations that affected the analysis (appendix). mRS=modified Rankin Scale. 90% UCB=90% upper confidence bound. mITT=modified intention to treat. ITT=intention to treat. PP=per protocol. AT=as treated.

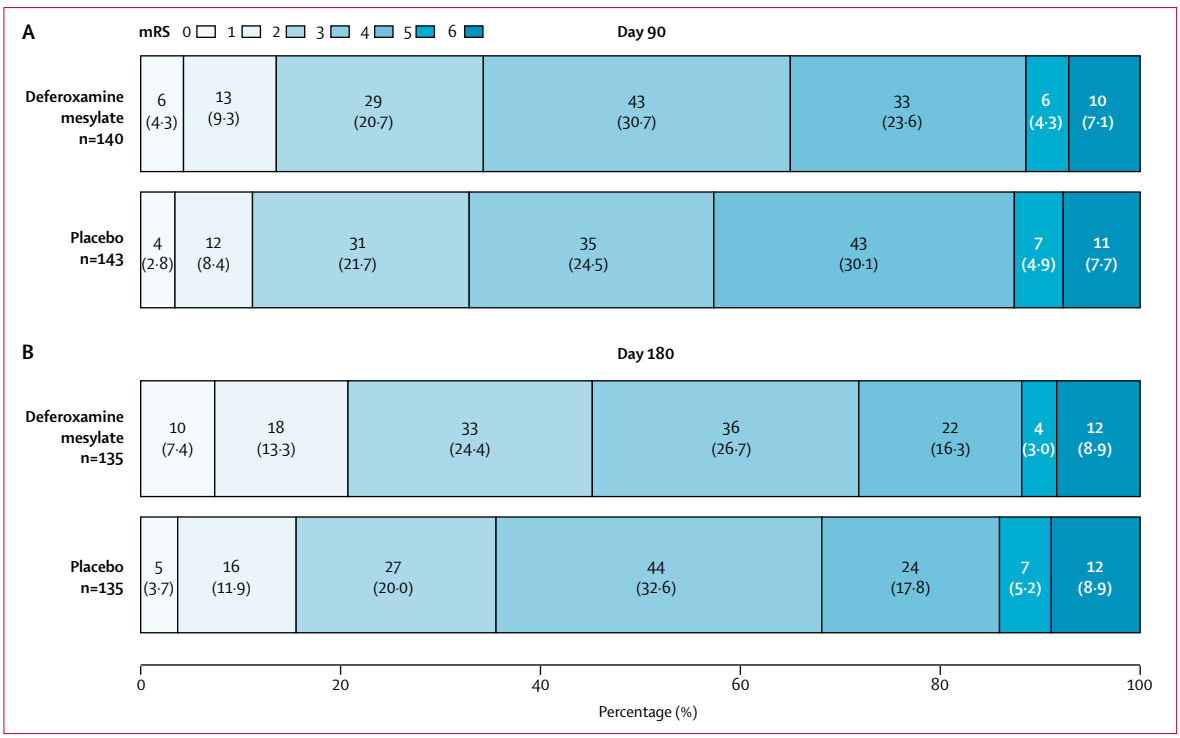

Figure 3: **Ordinal distribution of mRS scores in patients receiving deferoxamine mesylate or placebo at days 90 (A) and 180 (B)**
Data are presented only for patients in whom an mRS score was obtained. Percentages might not sum to 100 because of rounding. mRS=modified Rankin Scale.

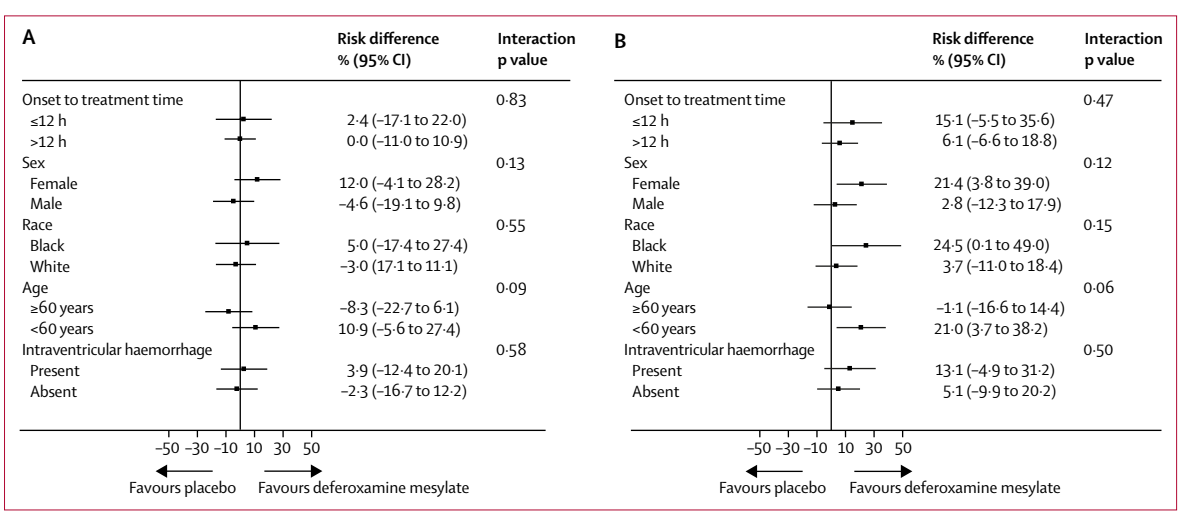

Figure 4: **Good clinical outcome by prespecified subgroups at days 90 (A) and 180 (B)**
A good clinical outcome was defined as a modified Rankin Scale score of 0–2.

all dichotomisations of mRS scores, was 1·10 (95% CI 0·72–1·67) at day 90 and 1·26 (0·82–1·93) at day 180 in the deferoxamine mesylate versus the placebo group. The proportion of patients with mRS scores of 0–2 and 0–3 seemed to increase between day 90 and day 180 in both the deferoxamine mesylate and placebo groups (figure 3). Furthermore, the proportion of patients in the placebo group with mRS scores of 4–5 seemed to decrease between these timepoints (figure 3). Analysis of the primary outcome in prespecified subgroups showed no evidence of differences between groups (figure 4). Median NIHSS (3 [IQR 1–7] *vs* 4 [2–7]; p=0·37) and MoCA (24 [IQR 18–27] *vs* 24 [18–27]; p=0·83) scores did not differ between groups at day 90.

Serious adverse events, both overall and within the first 7 days of treatment, and adverse events of special interest were balanced between the two groups (table 2). The appendix lists all adverse events that were recorded. Only

two (1%) cases of acute respiratory distress syndrome were reported in the deferoxamine mesylate group. One case was adjudicated to be possibly related to study drug, whereas the other was unlikely to be related to, or was unrelated to, the study drug according to the safety monitors. Ten (7%) of 144 patients in the deferoxamine mesylate group and 11 (7%) of 147 in the placebo group had died by day 90 (figure 5). Four deaths in the deferoxamine mesylate group and two in the placebo group occurred within 7 days of randomisation. By day 180, two more patients died in deferoxamine mesylate group and one more in the placebo group. Intracerebral-haemorrhage-related deaths occurred in seven (5%) patients in the deferoxamine mesylate group and eight (5%) in the placebo group. None of the deaths were judged to be treatment related.

In exploratory analyses, median changes in intracerebral haemorrhage (–0·2 mL [IQR –1·4 to 1·0] *vs* –0·2 mL [–1·7 to 0·8]), intraventricular haemorrhage (0·0 [–0·6 to 0·0] *vs* 0 [–1·9 to 0·0]), and relative perihaematomal oedema (0·9 [0·4 to 1·3] *vs* 0·7 [0·3 to 1·2]) volumes between baseline and the final post-infusion scan were similar between the deferoxamine mesylate group and the placebo group. Median time from randomisation to the last post-infusion scan was 74 h (IQR 69 to 78) in the deferoxamine mesylate group and 73 h (71 to 76) in the placebo group. The interaction between baseline relative perihaematomal oedema and time from haemorrhage onset to treatment varied by the treatment arm (p=0·0022). Up to 12 h, for every one unit increase in baseline relative perihaematomal oedema, relative perihaematomal oedema after the last infusion of study drug increased by 0·28 (95% CI 0·03 to 0·53) in patients in the deferoxamine mesylate group and 0·83 (0·43 to 1·24) in those in the placebo group. After 12 h, the corresponding increases were 0·87 (0·64 to 1·11) in the deferoxamine mesylate group and 0·52 (0·24 to 0·79) in the placebo group.

	Deferoxamine mesylate group (n=144)	Placebo group (n=147)	Relative risk (95% CI)
Serious adverse events			
At any time	39 (27%)	49 (33%)	0·81 (0·57–1·16)
Within 7 days	24 (17%)	26 (18%)	0·94 (0·57–1·56)
Adverse events of special interest			
Allergic reactions (during infusion of study drugs)*	3 (2%)	0	..
Hypotension*	1 (1%)	2 (1%)	..
New visual or auditory changes†	3 (2%)	4 (3%)	0·77 (0·00–14·97)
Respiratory compromise			
All cause	20 (14%)	23 (16%)	0·89 (0·51–1·54)
Caused by acute respiratory distress syndrome*	2 (1%)	1 (1%)	..
Symptomatic cerebral oedema‡	9 (6%)	5 (3%)	1·84 (0·63–5·35)

*Relative risk and 95% CIs were not calculated because of the small number of events. †Exact 95% CIs provided (95% CIs not specified as exact are asymptotic CIs). ‡Defined as oedema accompanied by an unexplained increase of more than 4 points on the US National Institutes of Health Stroke Scale or a decrease of more than 2 points in Glasgow Coma Scale score during the first week after intracerebral haemorrhage.

Table 2: **Safety outcomes at day 90**

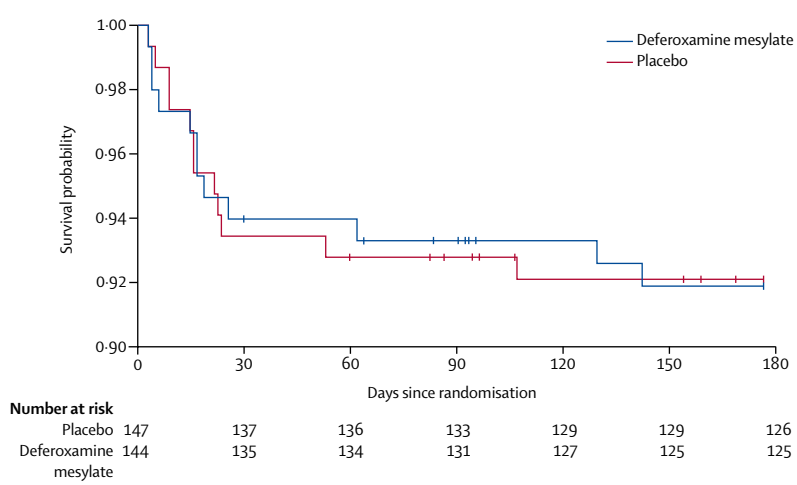

Figure 5: **Kaplan-Meier curves of mortality at 180 days**
Crosses represented censored patients. Log-rank test statistic for between-group difference 0·0026 (p=0·9591).

Discussion

In the i-DEF trial, treatment of patients with intracerebral haemorrhage with deferoxamine mesylate was not sufficiently promising to warrant phase 3 investigation of efficacy with anticipation that the drug would improve the chance of good outcome (ie, an mRS score of 0–2) at 90 days. At day 180, the AARD in the proportion of patients in each group with an mRS score of 0–2 was 8·6% in favour of the deferoxamine mesylate group—a difference above the specified futility threshold.

Treatment with deferoxamine mesylate was safe in this trial. The frequency of serious adverse events, major disability, and death was similar in the deferoxamine mesylate and placebo groups. The dose, regimen, and duration of treatment with deferoxamine mesylate have important safety implications. Unlike in the HI-DEF trial,[23] in which continuous intravenous infusion of high-dose deferoxamine mesylate (62 mg/kg per day for 5 consecutive days) was associated with increased pulmonary toxicity and acute respiratory distress syndrome, interrupted daily intravenous infusions of deferoxamine mesylate at 32 mg/kg per day for 3 days in i-DEF were not associated with an increase in all-cause respiratory compromise, including acute respiratory distress syndrome.

The results of our prespecified secondary analyses of the proportion of patients with mRS scores of 0–3 at day 90 and mRS scores of 0–2 at day 180, and the changes in ordinal analysis of mRS scores between days 90 and 180, could be relevant in view of the pathophysiology of intracerebral haemorrhage and known pattern of late recovery. These results raise important and challenging questions about the appropriate effect size and timing of outcome assessments in trials of treatments for

intracerebral haemorrhage, and about interpretation of i-DEF results. Establishing the smallest clinically meaningful effect size that would have an effect on clinical practice is challenging, and a lower futility threshold would have necessitated a much larger sample size. The Hemorrhagic Stroke Academia Industry roundtable recommended that a realistic absolute effect size for an acute intervention in patients with intracerebral haemorrhage should be 3–10% (average 5%), and that acceptance of a small effect size might depend on the safety, nature, and cost of the intervention.[24] Deferoxamine mesylate could be such a candidate. It is off-patent and low cost (roughly US$100–150 per infusion), and experience from our trial suggests that the intermediate dose regimen we studied is safe, simple to administer, and does not require highly specialised skills or facilities. Future studies with a small effect size will require a large number of patients (probably 2000–3000) and global collaboration.

The timing of endpoints (3 months *vs* 6–12 months) in stroke trials has been debated.[25] It has been argued[24,25] that patients with intracerebral haemorrhage, who tend to have severe morbidity as a result of the haematoma, associated oedema, and intraventricular haemorrhage often require substantial time for these secondary effects to resolve and to show improvement on measures of functional disability.[15,25–28] Differences in outcome between treatment groups might thus not be maximal at the traditional 3-month timepoint. Accumulating evidence suggests that patients with haemorrhagic stroke continually improve past 3 months and up to 1 year.[15,26–28] Our results are consistent with these observations.

Increases in the proportion of patients with mRS scores of 0–2 and 0–3 between the 90-day and 180-day timepoints in both groups, and decreases in the number of patients in the placebo group with mRS scores of 4–6, suggest that the differences between the deferoxamine mesylate and placebo groups at day 180 were not related to interim worsening or death of participants in the placebo group.

Because perihaematomal oedema is thought to be a radiological marker of secondary injury in intracerebral haemorrhage, we explored the effect of deferoxamine mesylate on growth of relative perihaematomal oedema as a potential surrogate marker of the drug's biological activity in the brain. By contrast with findings from other clinical studies,[29,30] deferoxamine mesylate did not seem to have a clear effect on growth of relative perihaematomal oedema. This finding could be attributed to other effects of deferoxamine mesylate independent of relative perihaematomal oedema,[7,10] a too-short interval between baseline and post-infusion scans to capture the peak of perihaematomal oedema, or insensitivities and crude nature of relative perihaematomal oedema measurements,[31] or could show that deferoxamine mesylate does not have an effect on growth of perihaematomal oedema. The rate of perihaematomal oedema growth and oedema extension distance are emerging parameters that might be better measures than relative perihaematomal oedema, and require further assessment in our cohort. Animal studies showed that the optimal therapeutic window for deferoxamine mesylate to reduce perihaematomal oedema was within 12 h of intracerebral haemorrhage (but the correlation between oedema and neurological deficits weeks to months later was weak),[9] and that administration of deferoxamine mesylate after 24 h did not reduce brain oedema but improved neurological function.[7] The results of our post-hoc analyses suggest that deferoxamine mesylate's effect on perihaematomal oedema varies according to time to treatment after onset of intracerebral haemorrhage, and are in line with animal data.[7,9] We did not power the trial to examine deferoxamine mesylate's effect on perihaematomal oedema, which might have affected our ability to detect any potential effects. Overall, 90 (31%) of 291 patients in our trial received treatment within 12 h of intracerebral haemorrhage, and we found no evidence of significant heterogeneity in the effect of deferoxamine mesylate on good clinical outcome in any prespecified subgroup, including that relating to time to treatment (≤12 h *vs* >12 h).

The putative beneficial effects of deferoxamine mesylate might not necessarily be dependent on effects on perihaematomal oedema, and might be related to iron-chelating properties, which decrease the amount of free iron available for the production of hydroxyl radicals and protects against oxidative stress, apoptosis, ferroptosis, and the cascade of events involved in secondary injury.[7,9,10] We posit that deferoxamine mesylate primes this machinery, that the severity of injury after intracerebral haemorrhage might mask some of the benefits of therapy early on, and that the benefit of treatment gradually accumulates but does not become fully apparent until adverse consequences of haematomal mass effect and intraventricular haemorrhage are resolved. The findings that the AARD was 6·2% in favour of deferoxamine mesylate for mRS scores of 0–3 at day 90, and 8·6% in favour of deferoxamine mesylate for mRS scores of 0–2 at day 180, could support this hypothesis.

We caution against misinterpretation of our secondary results to conclude that deferoxamine mesylate is more efficacious than placebo. i-DEF was a phase 2 futility-design trial that was intentionally not designed to test efficacy.[32] Additionally, several confounders could have affected our findings. A higher proportion of patients in the placebo group than in the deferoxamine mesylate group had thalamic intracerebral and intraventricular haemorrhages. These unfavourable baseline prognostic characteristics could have contributed to poorer outcomes in the placebo group, although sensitivity analyses adjusting for these prognostic confounders did not substantively alter the overall interpretation of results. The proportion of patients with mRS scores of 0–2 in the placebo group (33% at day 90 and 36% at day 180) were higher than the proportions that we anticipated during the trial design (28% based on outcomes at 90 days),

which could be attributed to use of different eligibility criteria from other trials, less severe intracerebral haemorrhages in our cohort, or temporal changes in management of intracerebral haemorrhage. The increased proportion of patients in the placebo group with good clinical outcome could have slightly decreased our power to declare futility (from 80% to 76%). However, the power of the primary endpoint is not of concern because futility was declared, and the point estimates of the risk difference between treatments at day 180 are not consistent with futility. We also did multiple secondary analyses of mRS scores, which yields concern over increased type I error. However, the futility hypothesis differs from hypotheses specified in traditional phase 3 efficacy trials and the probabilities of type I and type II errors are interpreted differently.[32] Because the null hypothesis in futility design is that the active intervention (deferoxamine mesylate) improves outcome (ie, mRS score) relative to the control (placebo) intervention by a prespecified threshold, and the rejection of this hypothesis implies futility, increased type I error (ie, incorrect rejection of a true null hypothesis) because of multiple testing cannot account for the non-futile results of mRS scores of 0–2 at day 180. We cannot, however, rule out the possibility that the non-futility of mRS scores of 0–2 at day 180 was a type II error, although i-DEF was designed to achieve 80% power when treatment outcomes are identical. Our study also has other limitations. We excluded patients with clinically significant respiratory conditions who were at high risk of acute respiratory distress syndrome (roughly 3% of screened people) and those older than 80 years. Furthermore, our patients had mild deficits, small (ie, <15 mL) intracerebral haemorrhage volumes, and a high frequency of deep intracerebral haemorrhage. Thus, the generalisability of our results to the overall population with intracerebral haemorrhage could be limited.

In conclusion, our results suggest that treatment with deferoxamine mesylate for 3 consecutive days was safe in patients with intracerebral haemorrhage, but that a large phase 3 trial of deferoxamine mesylate efficacy (in terms of the proportion of patients with good clinical outcome—ie, mRS scores 0–2 at day 90) would be futile. Our prespecified secondary analyses leave open the possibility that deferoxamine mesylate might not be futile in terms of good clinical outcome at day 180, and should be further scrutinised. These findings have important implications for the design of future trials in patients with intracerebral haemorrhage and future studies of deferoxamine mesylate.

Contributors

MS devised the trial hypotheses, designed the trial, provided guidance for data analysis, interpretation, and presentation, and drafted most of the Article. LDF had roles in statistical analysis and data interpretation, and contributed to the development of, and revisions to, the Article. CSM oversaw trial conduct and progress. GX was involved in trial design and critically revised the Article. MDH, MLJ, VS, and WMC recruited and randomly assigned trial participants, and critically revised the Article. LBM and SMG were involved in trial design and critically revised the Article. CN provided volumetric measurements of imaging data. YYP devised the trial, had roles in statistical analysis and data interpretation, and critically revised the Article. SDY devised the trial, had roles in statistical analysis and data interpretation, and contributed to the development of, and revisions to, the Article.

Declaration of interests

MS has received personal fees for serving on the advisory board of CSL Behring. SDY reports personal fees from Genentech and other fees from CR Bard. MDH reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada, and grants from Covidien, Boehringer Ingleheim, Stryker Inc, Medtronic, NoNO, and Alberta Innovates Health Solutions. MDH has a patent, Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients, pending with the US Patent Office (62/086,077), is a shareholder in Calgary Scientific, and is a director of the Canadian Federation of Neurological Sciences. All other authors declare no competing interests.

Data sharing

The study will follow the US National Institutes of Health policies on data sharing. The complete deidentified dataset will be made available via the National Institutes of Health's Archived Clinical Research Datasets within 1 year of publication. The dataset will be made available for limited use to researchers whose proposed use of the data is approved by the National Institutes of Health and the US National Institute of Neurological Disorders and Stroke in accordance with the terms and conditions of the National Institute of Neurological Disorders and Stroke data request form.

For the **US National Institutes of Health policies on data sharing** see http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm

For the **National Institutes of Health's Archived Clinical Research Datasets** see https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets

For the **National Institute of Neurological Disorders and Stroke data request form** see https://www.ninds.nih.gov/sites/default/files/NINDS_Data_Request_Form_508C.pdf

Acknowledgments

This investigator-initiated study was funded by the National Institute of Neurological Disorders and Stroke (U01 NS074425). Deferoxamine mesylate is a generic drug, and there was no commercial or industrial support for the trial. MS, LDF, GX, MDH, SMG, YYP, and SDY report grants from the National Institutes of Health or the National Institute of Neurological Disorders and Stroke, or both. MS has also received grants from the American Heart Association. MDH has received grant support from the Canadian Institutes of Health Research and the Heart & Stroke Foundation of Canada.

References

1 Krishnamurthi RV, Moran AE, Forouzanfar MH, et al. The global burden of hemorrhagic stroke: a summary of findings from the GBD 2010 study. *Glob Heart* 2014; **9:** 101–06.

2 Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; **358:** 2127–37.

3 Hanley DF, Thompson RE, Rosenblum M, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet* 2019; published online Feb 7. https://doi.org/10.1016/S0140-6736(19)30195-3.

4 He Y, Wan S, Hua Y, Keep RF, Xi G. Autophagy after experimental intracerebral haemorrhage. *J Cereb Blood Flow Metab* 2008; **28:** 897–905.

5 Huang FP, Xi G, Keep RF, Hua Y, Nemoianu A, Hoff JT. Brain edema after experimental intracerebral haemorrhage: role of hemoglobin degradation products. *J Neurosurg* 2002; **96:** 287–93.

6 Wagner KR, Sharp FR, Ardizzone TD, Lu A, Clark JF. Heme and iron metabolism: role in cerebral haemorrhage. *J Cereb Blood Flow Metab* 2003; **23:** 629–52.

7 Nakamura T, Keep RF, Hua Y, Schallert T, Hoff JT, Xi G. Deferoxamine-induced attenuation of brain edema and neurological deficits in a rat model of intracerebral haemorrhage. *J Neurosurg* 2004; **100:** 672–78.

8 Gu Y, Hua Y, Keep RF, Morgenstern LB, Xi G. Deferoxamine reduces intracerebral haematoma induced iron accumulation and neuronal death in piglets. *Stroke* 2009; **40:** 2241–43.

9 Okauchi M, Hua Y, Keep RF, Morgenstern LB, Schallert T, Xi G. Deferoxamine treatment for intracerebral haemorrhage in aged rats: therapeutic time window and optimal duration. *Stroke* 2010; **41:** 375–82.

10 Selim M, Yeatts S, Goldstein JN, et al. Safety and tolerability of deferoxamine mesylate in patients with acute intracerebral haemorrhage. *Stroke* 2011; **42:** 3067–74.

11 Kothari R, Brott T, Broderick J, et al. The ABCs of measuring intracerebral haemorrhage volumes. *Stroke* 1996; **27:** 1304–05.

12 Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral haemorrhage. *Stroke* 2001; **32:** 891–97.

13 Cases A, Kelly J, Sabater J, et al. Acute visual and auditory neurotoxicity in patients with end-stage renal disease receiving desferrioxamine. *Clin Nephrol* 1988; **29:** 176–78.

14 Savio K, Pietra GLD, Oddone E, Reggiani M, Leone MA. Reliability of the modified Rankin Scale applied by telephone. *Neurol Int* 2013; **5:** e2.

15 Hanley DF, Thompson RE, Muschelli J, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol* 2016; **15:** 1228–37.

16 Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352:** 777–85.

17 Lyden PD, Shuaib A, Lees KR, et al. Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT trial. *Stroke* 2007; **38:** 2262–69.

18 Haley EC Jr, Thompson JL, Levin B, et al. Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. *Stroke* 2005; **36:** 1006–10.

19 Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; **375:** 1033–43.

20 Yeatts SD, Palesch YY, Moy CS, Selim M. High dose deferoxamine in intracerebral haemorrhage (Hi-Def) trial: rationale, design, and methods. *Neurocrit Care* 2013; **19:** 257–66.

21 Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet* 2017; **389:** 603–11.

22 Mehdiratta M, Kumar S, Hackney D, Schlaug G, Selim M. Association between serum ferritin level and perihematoma edema volume in patients with spontaneous intracerebral hemorrhage. *Stroke* 2008; **39:** 1165–70.

23 Tenenbein M, Kowalski S, Sienko A, Bowden DH, Adamson IY. Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; **339:** 699–701.

24 Hemorrhagic Stroke Academia Industry (HEADS) Roundtable Participants. Unmet needs and challenges in clinical research of intracerebral haemorrhage. *Stroke* 2018; **49:** 1299–307.

25 Lees KR, Selim MH, Molina CA, Broderick JP. Early versus late assessment of stroke outcome. *Stroke* 2016; **47:** 1416–19.

26 Wilson DA, Nakaji P, Albuquerque FC, McDougall CG, Zabramski JM, Spetzler RF. Time course of recovery following poor-grade SAH: the incidence of delayed improvement and implications for SAH outcome study design. *J Neurosurg* 2013; **119:** 606–12.

27 Lee KB, Kim JS, Hong BY, Kim YD, Hwang BY, Lim SH. The motor recovery related with brain lesions in patients with intracranial haemorrhage. *Behav Neurol* 2015; **2015:** 258161.

28 Sreekrishnan A, Leasure AC, Shi FD, et al. Functional improvement among intracerebral haemorrhage survivors up to 12 months post-injury. *Neurocrit Care* 2017; **27:** 326–33.

29 Yu J, Yuan Q, Sun YR, et al. Effects of deferoxamine mesylate on haematoma and perihaematoma edema after traumatic intracerebral haemorrhage. *J Neurotrauma* 2017; **34:** 2753–59.

30 Yu Y, Zhao W, Zhu C, et al. The clinical effect of deferoxamine mesylate on edema after intracerebral haemorrhage. *PLoS One* 2015; **10:** e0122371

31 Staykov D, Wagner I, Volbers B, et al. Natural course of perihemorrhagic edema after intracerebral haemorrhage. *Stroke* 2011; **42:** 2625–29.

32 Palesch Y, Tilley B, Sackett D, Johnston K, Woolson R. Applying a phase II futility study design to therapeutic stroke trials. *Stroke* 2005; **36:** 2410–14.