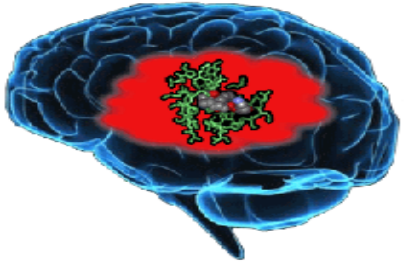

iDEF

Intracerebral Hemorrhage Deferoxamine Trial

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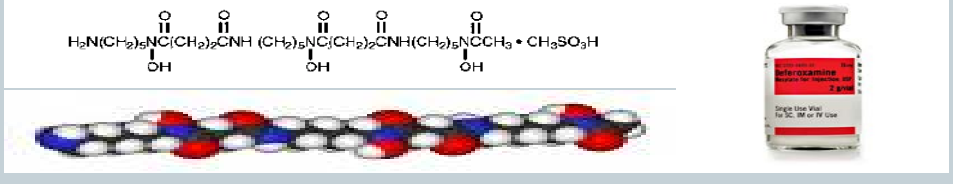
iDEF

INTRACEREBRAL HEMORRHAGE DEFEROXAMINE TRIAL

NINDS (U01 NS074425)

Deferoxamine Mesylate in hemorrhagic stroke



IND No: 77306

Trial Administration Organization

Coordination Centers

- Beth Israel Deaconess Medical Center, Boston, MA
- Data Coordination Unit, Department of Public Health Sciences, College of Medicine, Medical University of South Carolina
- Sponsor: NINDS (U01NS074425)
- → "NIH StrokeNet"

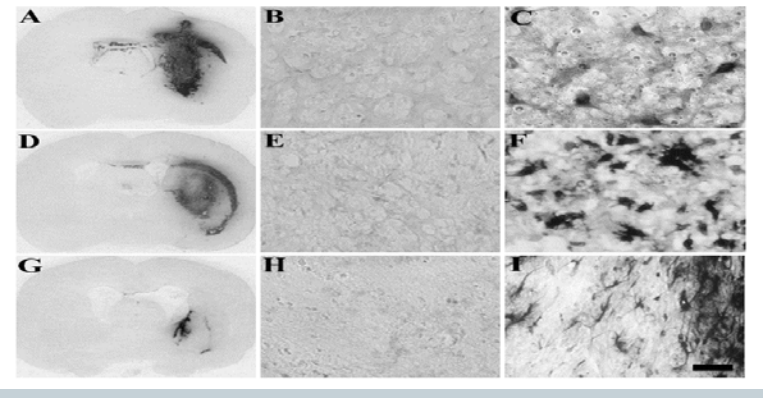
Clinical Sites

- 27 centers – 25 activated
  - 23 USA (14/25 StrokeNet sites)
  - 4 Canada
- Looking for 8-10 additional sites

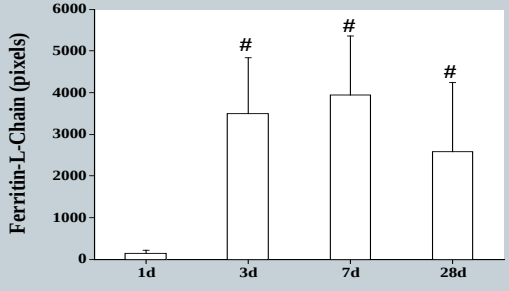
Background

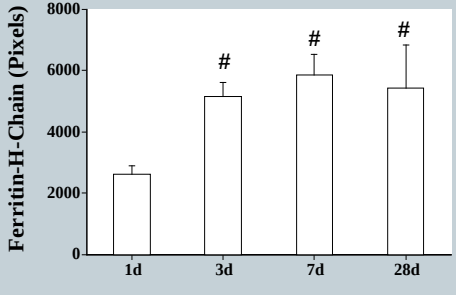
- Pre-clinical studies
- Phase I
- Early Phase II (HI-DEF)

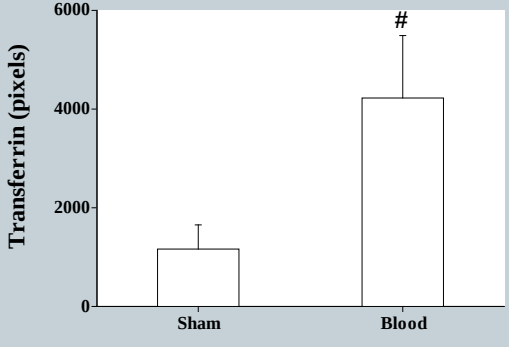
Upregulation of Iron Handling Proteins in The Brain After ICH

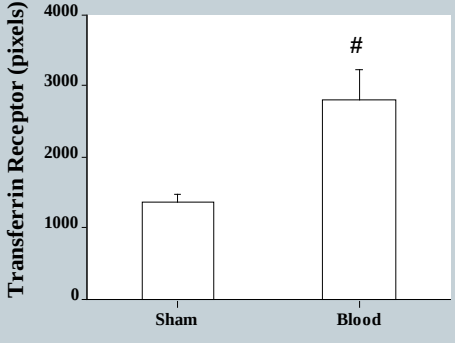


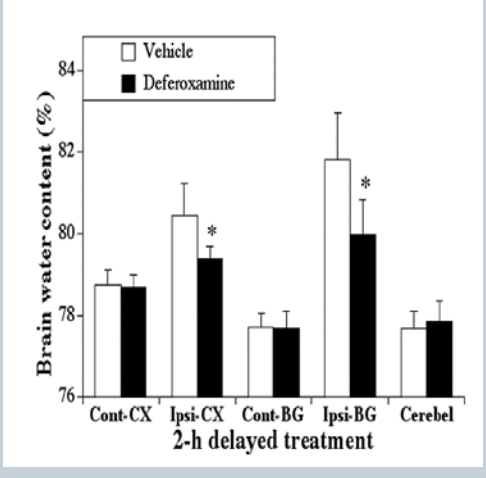
Iron histochemistry in the contralateral (B, E, H) and the ipsilateral basal ganglia (C, F, I) at day 1 (A, B, C), day 3 (D, E, F) and day 28 (G, H, I) after ICH (A, D, G).



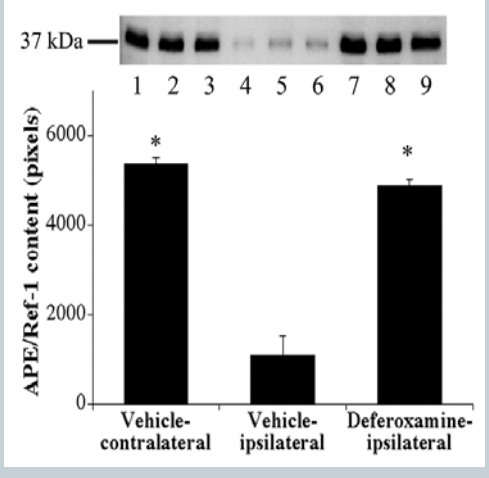




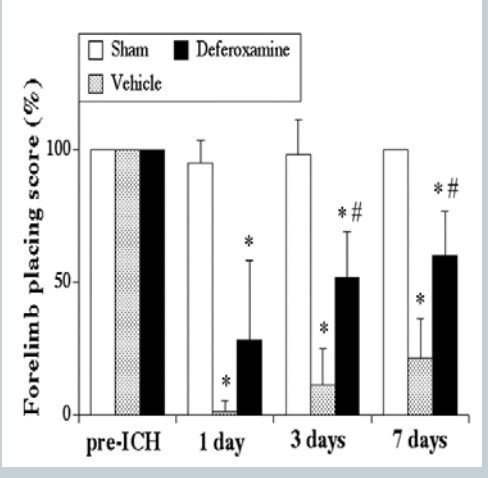




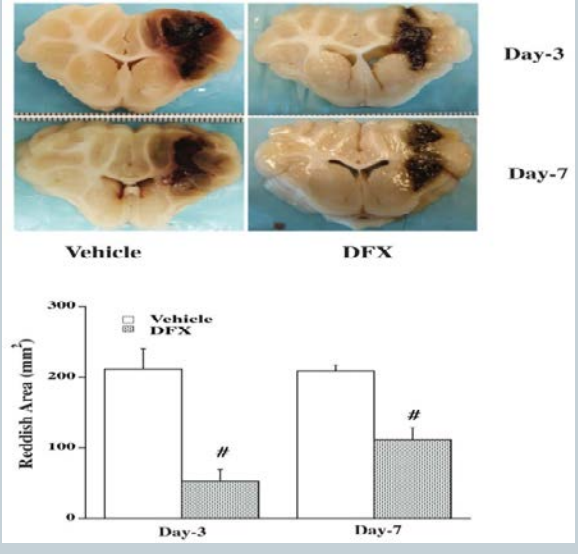
DFO attenuates brain edema after ICH



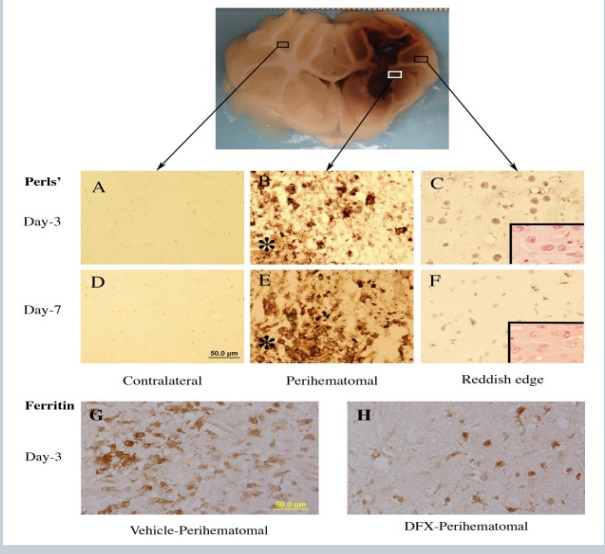
DFO prevents DNA oxidative damage (the reduction in APERef-1 repair) after ICH



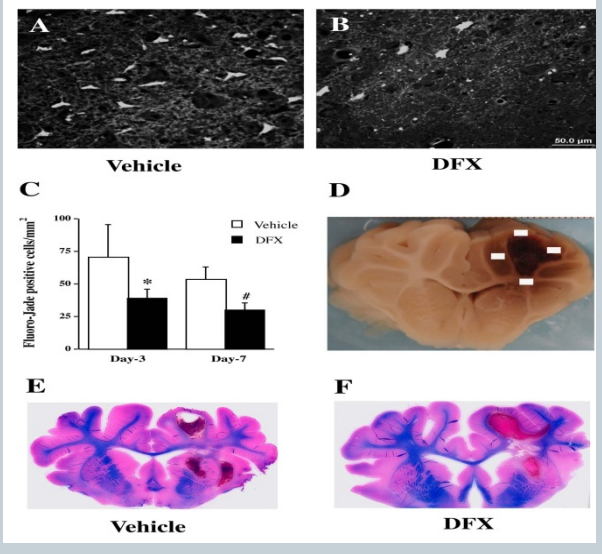
DFO reduces neurological deficits after ICH



DFO reduces reddish zone around hematoma at day 3 and 7



Ferritin positive cells were less in DFO-treated animals at day 3 and 7



DFO reduced Fluoro-Jade C + cells in the perihematomal area & Reduced Luxol fast blue-stained white matter in the ipsilateral hemisphere at day 7

Iron-mediated Neurotoxicity

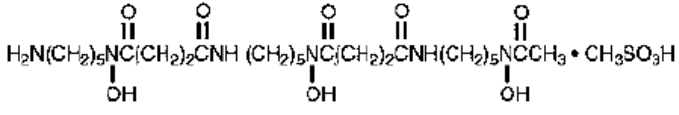
- Haber-Weiss (Fenton) reaction → hydroxyl radical formation, oxidative stress & cell death

$$Fe^{+++} + {}_oO_2^- \rightarrow Fe^{++} + O_2$$
$$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + OH^- + {}_oOH$$
$${}_oO2\text{-} + H_2O_2 \rightarrow {}_oOH + HO^- + O_2$$

- Activation of lipid peroxidation
- Inhibition of Na^+/K^+ ATPase activity
- Exacerbation of excitotoxicity

Deferoxamine Mesylate

- Chelates iron from ferritin and forms a stable complex that prevents iron from entering into further chemical reactions
- The iron chelate-complex (ferrioxamine) is primarily excreted by the kidneys
- Serum protein binding rate < 10%
- Volume of distribution = 0.8 – 1.35 L/kg
- Molecular weight = 561 (657 as mesylate)



Deferoxamine – BBB – Neuronal Uptake

- DFO brain levels between 100 & 200 μM/L peaked within 60 minutes after SC injection of 100 mg/kg and exceeded serum levels in rat models of ischemic stroke
- Radioactivity was highest in the brain & bile of dogs injected with tritrium-labeled DFO
- In vivo microdialysis probes in blood & brain show that DFO can diffuse into the brain down a concentration gradient after IV infusion
- Intraperitoneal DFO decreases CSF iron levels and ferritin-labeled cells in the brain in ICH animal models

Deferoxamine Mesylate: Neuroprotective Effects

- Decreases free iron's availability for the production of hydroxyl radicals
- Prevents apoptosis induced by glutathione depletion & oxidative stress

- Activates a signal transduction pathway leading to activation of transcription factor 1.cAMP response element-binding protein (ATF-1/CREB) and expression of genes known to compensate for oxidative stress
- Induces HIF1-α and inhibits hypoxia inducible factor prolyl hydroxylases

- Induces transcription of heme oxygenase-1, which catalyzes the degradation of heme to biliverdin and carbon monoxide
- Has anti-inflammatory effects by stimulating cyclo-oxygenase, and reducing gene expression of VCAM-1, ICAM-1, MCP-1, TNFα, and IL-6

- Inhibits glutamate excitotoxicity
- Exerts anti-autophagocytosis effects in animal models of ICH
- Has BP lowering effects (α-adrenergic blockade via mesylate)

DFO in ICH

Phase I, Feasibility, Safety, and Dose Finding Study

R01-NS 057127

Safety and Tolerability of Deferoxamine Mesylate in Patients With Acute Intracerebral Hemorrhage

Magdy Selim, MD, PhD; Sharon Yeatts, PhD; Joshua N. Goldstein, MD, PhD; Joao Gomes, MD; Steven Greenberg, MD, PhD; Lewis B. Morgenstern, MD; Gottfried Schlaug, MD, PhD; Michel Torbey, MD; Bonnie Waldman, JD; Guohua Xi, MD; Yuko Palesch, PhD; The Deferoxamine Mesylate in Intracerebral Hemorrhage Investigators

Background and Purpose—Treatment with the iron chelator, deferoxamine mesylate (DFO), improves neurological recovery in animal models of intracerebral hemorrhage (ICH). We aimed to evaluate the feasibility, safety, and tolerability of varying dose-tiers of DFO in patients with spontaneous ICH, and to determine the maximum tolerated dose to be adopted in future efficacy studies.

Methods—This was a multicenter, phase-I, dose-finding study using the Continual Reassessment Method. DFO was administered by intravenous infusion for 3 consecutive days, starting within 18 hours of ICH onset. Subjects underwent repeated clinical assessments through 90 days, and computed tomography neuroimaging pre- and post-drug-administration.

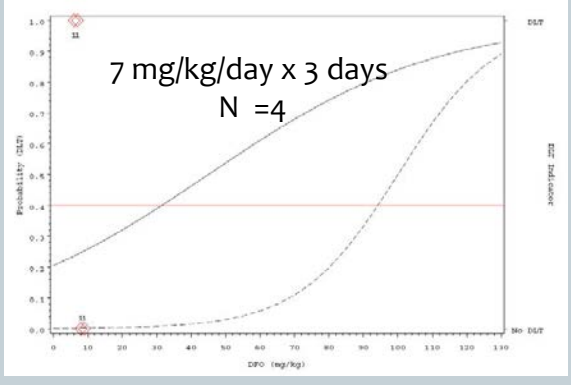
Results—Twenty subjects were enrolled onto 5 dose tiers, starting with 7 mg/kg per day and ending with 62 mg/kg per day as the maximum tolerated dose. Median age was 68 years (range, 50–90); 60% were men; and median Glasgow Coma Scale and National Institutes of Health Stroke Scale scores on admission were 15 (5–15) and 9 (0–39), respectively. ICH location was lobar in 40%, deep in 50%, and brain stem in 10%; intraventricular hemorrhage was present in 15%. DFO was discontinued because of adverse events in 2 subjects (10%). Six subjects (30%) experienced 12 serious adverse events, none of which were drug-related. DFO infusions were associated with mild blood-pressure-lowering effects. Fifty percent of patients had modified Rankin scale scores ≤ 2, and 39% had modified Rankin scale scores of 4 to 6 on day 90; 15% died.

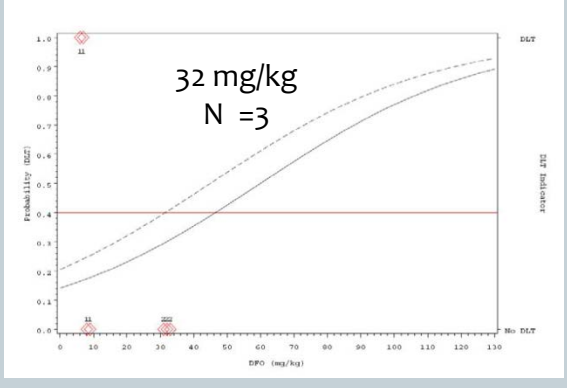
Conclusions—Consecutive daily infusions of DFO after ICH are feasible, well-tolerated, and not associated with excessive serious adverse events or mortality. Our findings lay the groundwork for future studies to evaluate the efficacy of DFO in ICH. (***Stroke*. 2011;42:3067-3074.**)

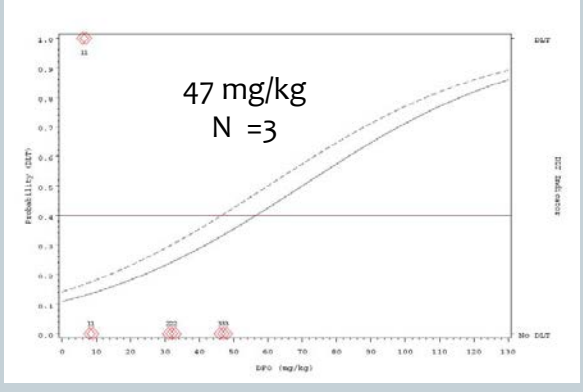
Key Words: deferoxamine mesylate ■ iron ■ ICH

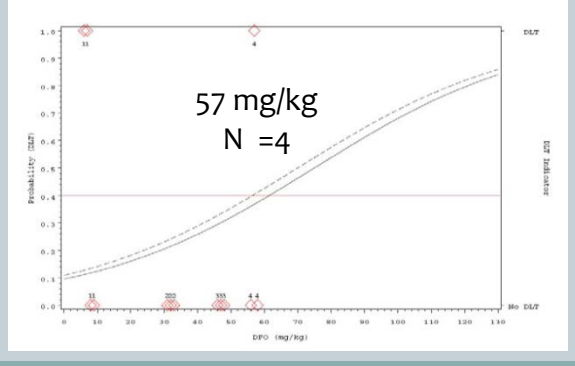
Phase I Results

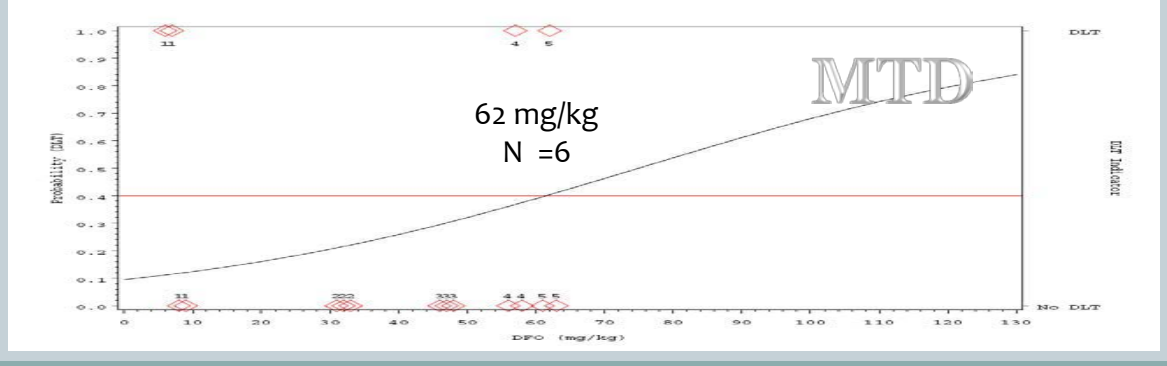
A total of 20 subjects were enrolled into 6 cohorts











Effective dose in animal models

Published in final edited form as:
Stroke. 2009 May ; 40(5): 1858–1863. doi:10.1161/STROKEAHA.108.535765.

Effects of deferoxamine on intracerebral hemorrhage-induced brain injury in aged rats

Masanobu Okauchi, MD[1], Ya Hua, MD[1], Richard F. Keep, PhD[1,2], Lewis B. Morgenstern, MD[1,2], and Guohua Xi, MD[1,2]

1*Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan*

2*Department of the Stroke Program, University of Michigan, Ann Arbor, Michigan*

Abstract

Background and Purpose—Deferoxamine (DFX) reduces brain edema, neuronal death and neurological deficits after intracerebral hemorrhage (ICH) in young rats. In the present study, we investigated whether DFX is effective on brain injury after ICH in aged rats and examined dose dependency.

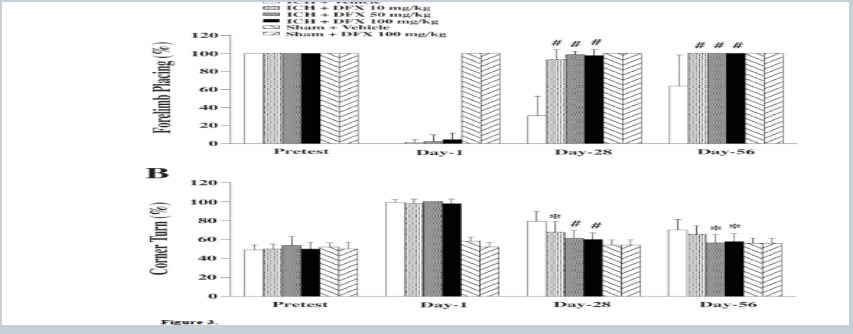
Methods—Male Fischer 344 rats (18-months old) had an intracaudate injection of 100-μL autologous whole blood and were treated with different doses of DFX (10, 50 and 100 mg/kg) or vehicle 2 and 6 hours post ICH and then every 12 h up to 7 days. Rats were sacrificed at day 3 for brain edema determination and day 56 for brain atrophy measurement. Behavioral tests were performed during the experiments.

Results—All three doses of DFX attenuated perihematomal brain edema at 3 days (e.g. at dose 50 mg/kg, 80.4±0.5 vs. 81.6±0.9% in the vehicle-treated group, $p<0.01$). 50 and 100 mg/kg DFX also reduced ICH-induced ventricle enlargement, caudate atrophy and ICH-induced neurological deficits in aged rats. However, while 10 mg/kg DFX reduced ventricle enlargement and forelimb placing deficits, it did not reduce caudate atrophy and corner turn deficits.

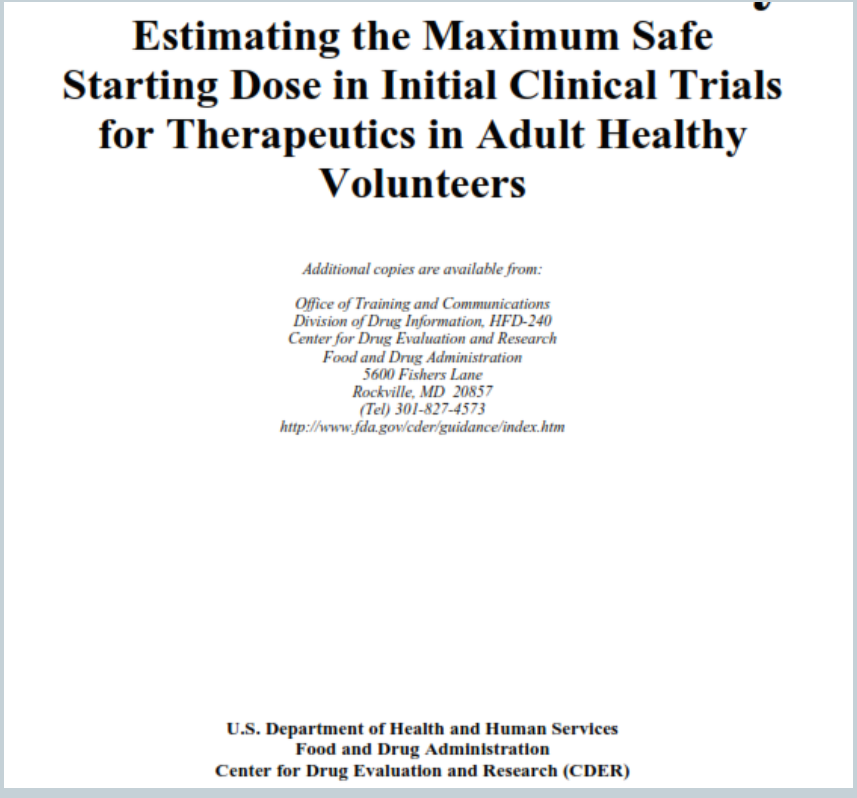
Conclusions—These results indicate that DFX can reduce ICH-induced brain injury in aged as well as young rats and that a dose higher than 10 mg/kg is the optimal dose of DFX in this model.

Keywords

brain atrophy; cerebral hemorrhage; deferoxamine; iron



Effective HED = 16-32 mg/kg/day



Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

- 100 mg/kg in rats = 100 x 0.16 = 16 mg/kg in humans
- 200 mg/kg in rats = 200 x 0.16 = 32 mg/kg in humans

What is the optimal duration of treatment?

Published in final edited form as:
Stroke. 2010 February ; 41(2): 375–382. doi:10.1161/STROKEAHA.109.569830.

Deferoxamine treatment for intracerebral hemorrhage in aged rats: therapeutic time window and optimal duration

Masanobu Okauchi, MD[1], Ya Hua, MD[1], Richard F. Keep, PhD[1,2], Lewis B. Morgenstern, MD[1,2], Timothy Schallert, PhD[1,3], and Guohua Xi, MD[1,2]

[1]Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan

[2]the Stroke Program, University of Michigan, Ann Arbor, Michigan

[3]Department of Psychology, University of Texas at Austin

Abstract

Background and Purpose—Deferoxamine (DFX) reduces brain edema, neurological deficits and brain atrophy after intracerebral hemorrhage (ICH) in aged as well as young rats. Our previous study found that 50 mg/kg is an effective dose in aged rats. In the present study, we explored potential therapeutic time windows and optimal therapeutic durations.

Methods—Aged male Fischer 344 rats (18-month old) sustained an intra-caudate injection of 100-μL autologous whole blood, followed by intramuscular DFX or vehicle beginning at different time points, or continuing for different durations. Subgroups of rats were sacrificed at day 3 for brain edema measurement and day 56 for brain atrophy determination. Behavioral tests were carried out on days 1, 28 and 56 post-ICH.

Results—Systemic administration of DFX, when begun within 12 hours after ICH, reduced brain edema. DFX treatment started 2 hours after ICH and administered for 7 days or more attenuated ICH-induced ventricle enlargement, caudate atrophy and neurological deficits. DFX attenuated ICH-induced brain atrophy and neurological deficits without detectable side effects when begun within 24 hours and administered for 7 days.

Conclusions—To the extent that these results can be translated to humans, the therapeutic time window and the optimal duration for DFX in this aged rat model of ICH may provide useful information for an ongoing DFX-ICH clinical trial.

Keywords

behavior; brain atrophy; brain edema; cerebral hemorrhage; deferoxamine; iron

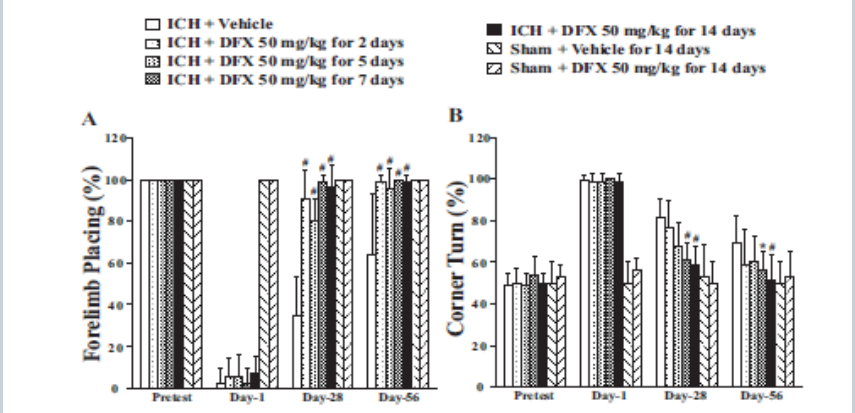
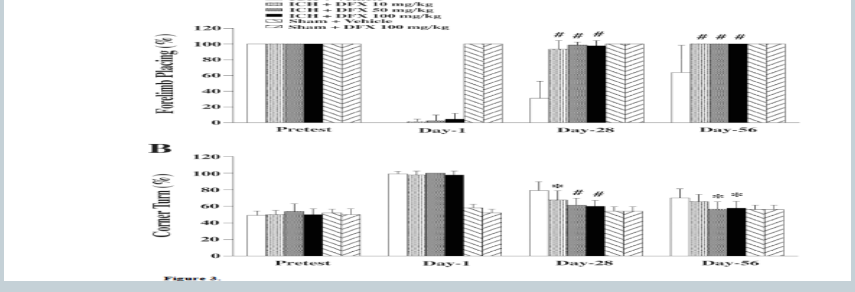


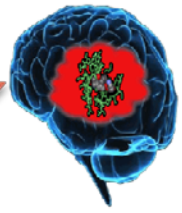
Figure 2. Forelimb placing (A) and corner turn (B) scores before ICH and 1, 28, and 56 days after ICH. Values are expressed as the means±SD. *P<0.05, #P<0.01 vs ICH+vehicle group. For forelimb placing, 100%=no deficit, 0%=maximal deficit. For corner turn, 50%=no deficit, 100%=maximal deficit.



Is there supportive evidence that Deferoxamine is of sufficient promise to improve outcome prior to embarking on a large-scale phase III study of DFO as a treatment for ICH patients?

HI-DEF

High Dose Deferoxamine in Intracerebral Hemorrhage



iDEF

Intracerebral Hemorrhage Deferoxamine Trial

Futility Study of Deferoxamine Mesylate in Intracerebral Hemorrhage

A prospective, multi-center, randomized, double-blind, placebo-controlled, Futility design study

NINDS (U01-NS074425)

HI-DEF

High Dose Deferoxamine in Intracerebral Hemorrhage

Primary Objectives

1. To assess whether it is futile to move deferoxamine forward as a therapeutic intervention for ICH into Phase III evaluation by comparing the outcome of deferoxamine-treated subjects to placebo-treated subjects with respect to good outcome (defined as mRS score of 0-2 at 90 days) in a futility analysis

2. To assess the safety of deferoxamine infusions (at a dose of 62 mg/kg/day, up to a maximum dose of 6000 mg/day), given for 5 consecutive days, in a large cohort of ICH patients

Secondary Objectives

1. To explore the differences between early (≤12h) and late (>12h-to-24h) time windows in deferoxamine treatment effect on functional outcome

2. To perform a dichotomized analysis considering the proportion of deferoxamine- and placebo-treated subjects with mRS score of 0-3

Exploratory Objectives

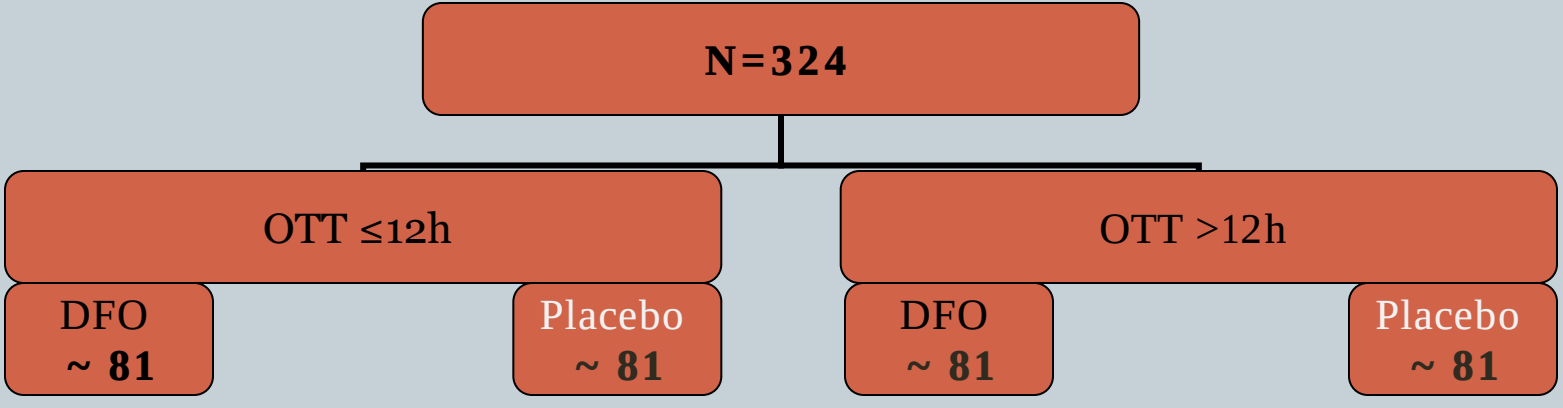
1. To determine the overall distribution of scores on mRS and mortality at 3 months in DFO-treated subjects
2. To obtain data on MoCA & SIS-16 scores at 3 months, and the change in NIHSS between presentation and day-90 to explore the effects of treatment on neurological, functional, and cognitive functions
3. To explore the effects of treatment on relative PHE volume progression as a potential marker of DFO's biological activity on brain tissue
4. To explore the effects of DFO on the size of ventricular enlargement in patients with intraventricular extension of ICH
5. To explore the effects of DFO on the incidence of symptomatic cerebral edema up to day-7 or discharge (whichever is earlier)
6. To explore whether the effect of DFO on outcome is dependent on the initial ICH volume to determine if specific limits for ICH volume should be specified as inclusion/exclusion criteria in future studies

HI-DEF Study Design

- Prospective, multi-center, double-blind, randomized, placebo-controlled clinical trial
- Total sample size = 324 patients with spontaneous ICH
- Study Drugs:
  - Active: DFO (62 mg/kg/day, up to a maximum of 6000 mg/day)
  - Placebo: Matching normal saline
  - Given by continuous IV infusion for 5 consecutive days
  - Initiated within 24h of ICH symptom onset

HI-DEF Study Design

- Randomization:
  - 1:1 (targeted n=162 active drug & 162 placebo)
  - Control for baseline ICH score (0-2 vs. 3-5); ICH onset-to-treatment time (≤12h vs. >12-24h); and concurrent use of anticoagulants at ICH onset



Status

- Funding began in September 2012
- 42 Subjects enrolled
  - 16 sites
  - First: March 18, 2013
  - Last: October 15, 2013
  - Enrollment suspended on October 18, 2013

- Mean age = 62.5 $\pm$ 11.1 years
  - Median = 64
  - Range = 35 – 77
  - 16 women – 26 men
- Mean hematoma volume (ABC/2 method) = 25.78 $\pm$ 26.3 cm^3
  - Median = 15.6
  - Range = 0.7 – 103
- Mean baseline GCS score = 13 $\pm$ 2.2
  - Median = 14
  - Range = 9 -15
- IVH present in 33.3%

Safety Data

- 5 cases of ARDS
  - 3 unrelated
  - 2 possibly related
- Deaths = 3 (7%)
  - All had ARDS
  - 1 due to neurological deterioration
  - 2 due to ARDS and multi-system failure

Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning

MILTON TENENBEIN STEPHEN KOWALSKI ANNA SIENKO
DRUMMOND H. BOWDEN IAN Y. R. ADAMSON

The drug of choice for the treatment of iron poisoning is desferrioxamine, though the best route of administration, dose, and duration of treatment are unclear. We report fatal lung injury in four patients who were treated with continuous intravenous infusions.

The patients, aged 19–26 years, had received desferrioxamine infusions of 15 mg/kg per h for 65–92 h. Respiratory distress developed after 32–72 h. The patients met clinical, physiological, and necropsy criteria for the diagnosis of adult respiratory distress syndrome (ARDS); none had any of the known risk factors for the development of this disorder. We reviewed the records of forty-three iron-poisoned patients treated with desferrioxamine infusions. No patient treated for less than 24 h had pulmonary complications; however, of the fourteen treated for longer than 24 h, four were the patients with ARDS and four others had pulmonary oedema of other causes.

We suggest that the pulmonary complications are caused by continuous infusion of desferrioxamine and that the ARDS in these patients was a consequence of free-radical generation. We recommend that desferrioxamine infusion should not be administered for longer than 24 h.

Lancet 1992; **339**: 699–701.

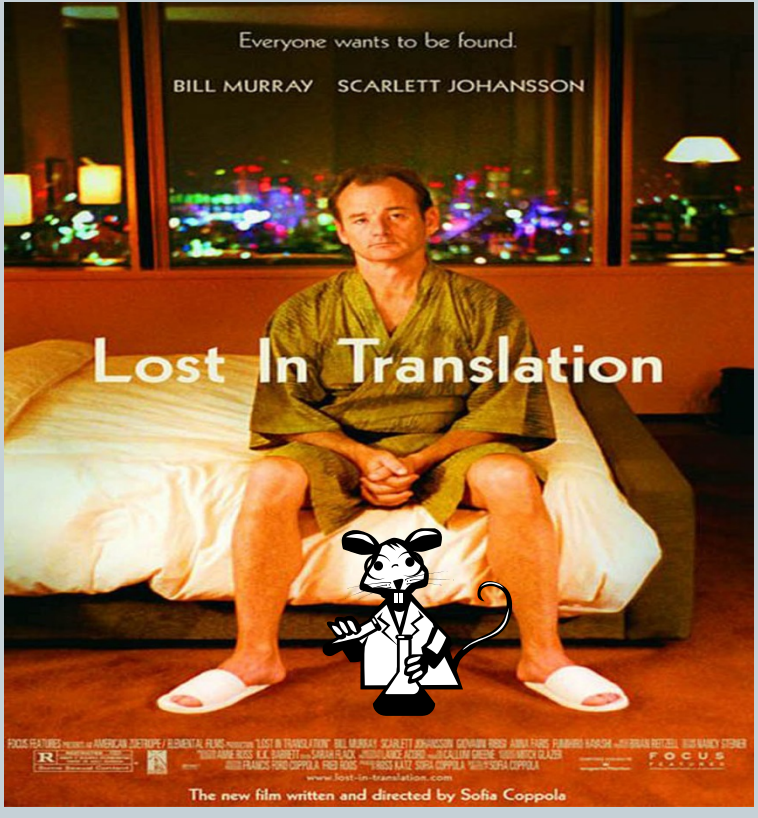
ADDRESSES **Departments of Pediatrics, Pharmacology, and Medicine** (M. Tenenbein, FRCPC), **Anesthesia** (S Kowalski, FRCPC) **and Pathology** (A. Sienko, MD, D. H. Bowden, MD, I. Y. R. Adamson, PhD), **University of Manitoba; and Manitoba Poison Control Centre** (M. Tenenbein), **Winnipeg, Manitoba, Canada.** Correspondence to Dr Milton Tenenbein, Children's Hospital, 840 Sherbrook Street, Winnipeg, Manitoba R3A 1S1, Canada.

Other Respiratory Complications

- Pulmonary edema in 5 patients (2 ARDS; 1 fluid overload)
- Respiratory failure in 3 patients
- Respiratory failure in 2 patients in phase I

- 2 cases possible/probable ARDS
- 1 case was ARDS

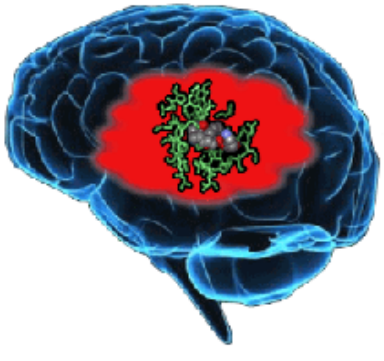
Almost


Everyone wants to be found.
BILL MURRAY SCARLETT JOHANSSON
Lost In Translation
www.lost-in-translation.com
The new film written and directed by Sofia Coppola

Status Update

- DSMB terminated enrollment into HI-DEF on February 12, 2014
  - Imbalance in the frequency of ARDS cases between the deferoxamine- and placebo-treated groups
  - No other safety concerns

- Protocol amended and approved by DSMB on May 14, 2014 → iDEF.....



iDEF

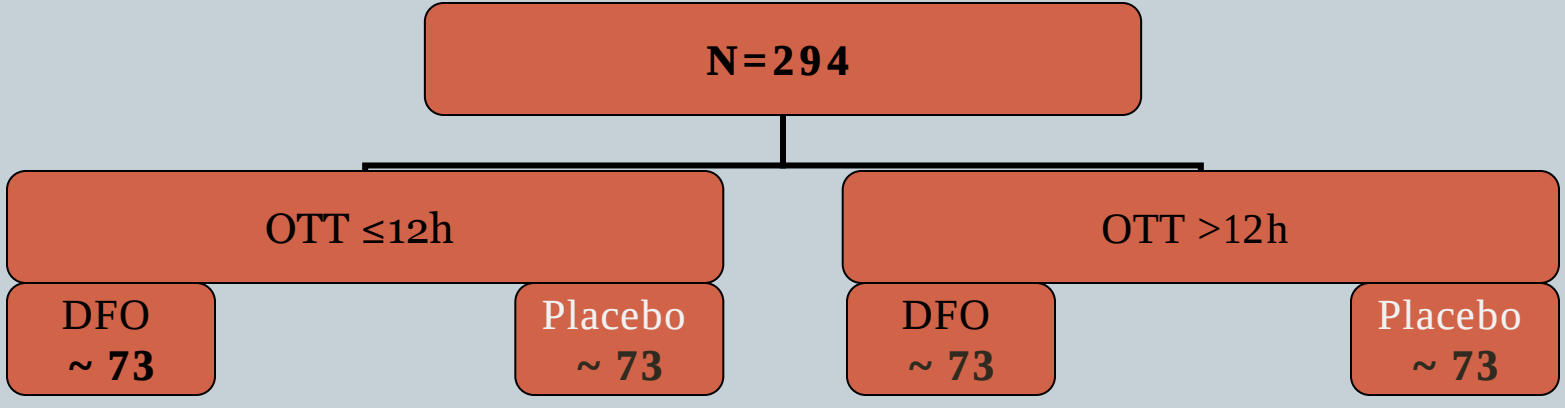
Intracerebral Hemorrhage Deferoxamine Trial

Protocol Overview

- Same objectives
- Lower dose (32 mg/kg/day) – shorter duration (3 days)
- More restrictive exclusion criteria to exclude patients at high risk for developing ARDS
- More oversight of respiratory complications
- Standardized ventilator management (ARDSNet) and definition for ARDS (Berlin criteria)
- Stopping rule
- Improved randomization process
- Extended follow-up to 6 months instead of 3
- Sample size = 294

iDEF Study Design

- Randomization:
  - 1:1 (targeted n=147 active drug & 147 placebo)
  - Control for baseline ICH score; ICH onset-to-treatment time; baseline ICH volume; baseline NIHSS; and concurrent use of anticoagulants at ICH onset



Inclusion Criteria

1. Age ≥ 18 and ≤ 80 years
2. The diagnosis of ICH is confirmed by brain CT scan
3. NIHSS score ≥6 and GCS >6 upon presentation
4. The first dose of the study drug can be administered within 24h of ICH symptom onset
5. Functional independence prior to ICH, defined as pre-ICH mRS ≤1
6. Signed and dated informed consent is obtained

Main Exclusion Criteria

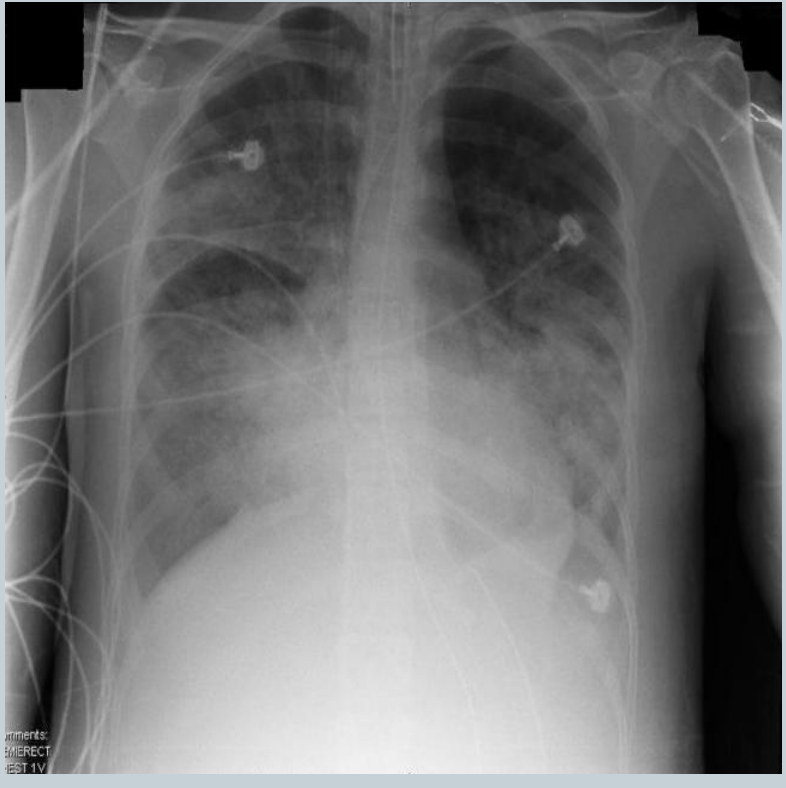
- Known severe iron deficiency anemia (defined as hemoglobin concentration <7g/dL or requiring blood transfusions)
- Pre-existing disability, defined as pre-ICH mRS score ≥2
- Taking iron supplements containing ≥ 325 mg of ferrous iron, or prochlorperazine (compazine)
- Known pregnancy, or positive pregnancy test, or breastfeeding
- Indication that a new DNR or Comfort Measures Only (CMO) order will be implemented within the first 72 hours of hospitalization
- Abnormal renal function, defined as serum creatinine >2mg/dL
- Coagulopathy
  - Elevated aPTT or INR >1.3 upon presentation
  - Concurrent use of direct thrombin inhibitors (such as dabigatran), direct factor Xa inhibitors (such as rivaroxaban or apixaban), or low-molecular-weight heparin

Exclusion Criteria

- Irreversibly impaired brainstem function (bilateral fixed and dilated pupils and extensor motor posturing)
- Complete unconsciousness, defined as a score of 3 on item 1a of the NIHSS (Responds only with reflex motor or autonomic effects or totally unresponsive, and flaccid)
- Planned surgical evacuation of ICH prior to administration of study drug (*placement of EVD is not an exclusion criterion*)
- Suspected secondary ICH
- Infratentorial hemorrhage
- Alcohol or drug use
- Patients with heart failure taking > 500 mg of vitamin C daily
- Known severe hearing loss

Exclusion Criteria

- Patients with confirmed aspiration, pneumonia, or evident bilateral pulmonary infiltrates on chest x-ray or CT scan prior to enrollment
- Patients with significant respiratory disease such as chronic obstructive pulmonary disease, pulmonary fibrosis, or any use (chronic or intermittent) of inhaled O_2 at home
- FiO_2 >0.35 (>4 L/min) prior to enrollment
- Shock (SBP <90 mmHg) at presentation



Exclusion Criteria

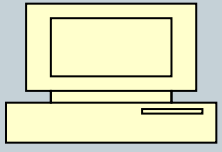
- Sepsis (present source of infection ± lactic acidosis) or Systemic Inflammatory Response Syndrome (Temp >100.4F or <96.8F; Heart rate >90; Respiratory rate >20 or $PaCo_2$ <32 mmHg; WBC >12, <4, or bands >10%)
- The presence of 4 or more of the following risk modifiers for ARDS prior to enrollment:
  - Tachypnea (respiratory rate >30)
  - SpO_2 <95%
  - Obesity (BMI >30)
  - Acidosis (pH <7.35)
  - Serum albumin <3.5 g/dL
  - Concurrent use of chemotherapy

Table 1: The Lung Injury Prediction Score (LIPS). *(Gajic O, et al. Early identification of patients at risk of acute lung injury: Evaluation of lung injury prediction score in a multicenter cohort study. Am. J. Respir. Crit. Care Med. 2011;183(4):462-70).*

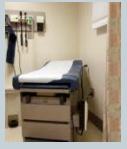
Predisposing Conditions		LIPS Points
Shock		2
Aspiration		2
Sepsis		1
Pneumonia		1.5
High risk surgery*		
	Orthopedic spine	1
	Acute abdomen	2
	Cardiac	2.5
	Aortic vascular	3.5
High risk trauma		
	Traumatic brain injury	2
	Smoke inhalation	2
	Near drowning	2
	Lung contusion	1.5
	Multiple fractures	1.5
Risk modifiers		
Alcohol abuse		1
Obesity (BMI >30)		1
Hypoalbuminemia		1
Chemotherapy		1
FiO_2 >0.35 (>4 L/min)		2
Tachypnea (RR >30)		1.5
SpO2 <95%		1
Acidosis (pH <7.35)		1.5
Diabetes mellitus**		-1

*Add 1.5 points if emergency surgery.
**Only if sepsis.

Schedule of Assessments

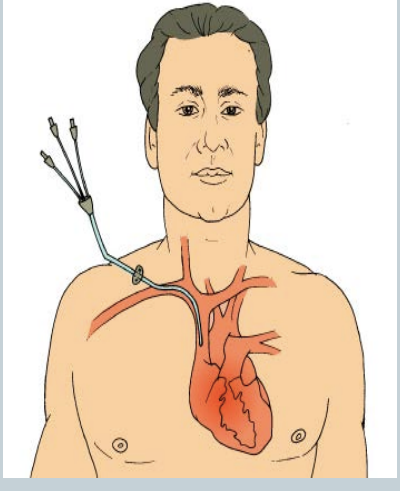




Screening	Randomization/ Baseline	Day 1	Day 2	Day 3	24h post infusion	Day7 D/C	Day 30	Day 60	Day 90	Day 180
✓ CT ✓ CXR ✓ Inclusion ✓ Exclusion	✓ ICH score ✓ NIHSS ✓ ICH volume ✓ GCS GCS ≤ 6 Fixed & dilated pupils	✓ GCS/NIHSS ✓ Visual auditory assessment ✓ AEs ✓ I/O			✓ CT ✓ GCS ✓ NIHS ✓ VAA ✓ Labs	✓ SAEs ✓ mRS ✓ SIS-16 ✓ MoCA ✓ Visual & auditory assessment				


Study Drug Administration

- The drug is supplied in vials containing 2 g of sterile, lyophilized, powdered deferoxamine mesylate
- Dissolved in 20 ml of sterile water and added to normal saline (0.9% sodium chloride) in an IV bag to achieve a final concentration of 7.5 mg per ml for IV administration.
- The infusion rate ~ 7.5 mg/kg/hour
- Maintain a dedicated line/port for the study drug infusion



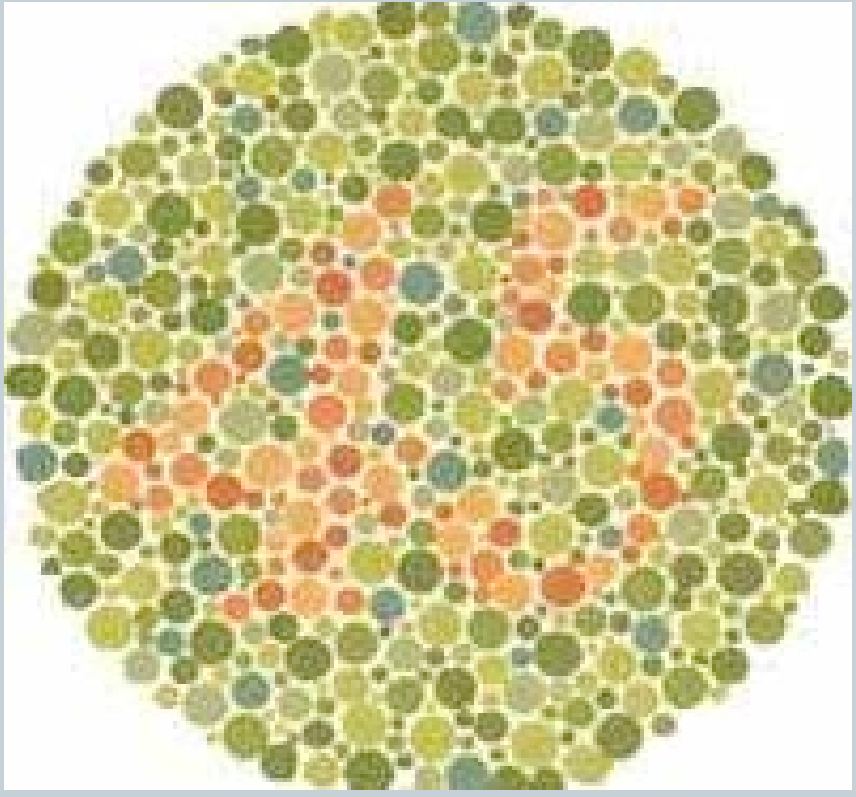
The drug is administered via a central line or IV cannula, inserted into an antecubital vein

Monitoring During The Infusion Period

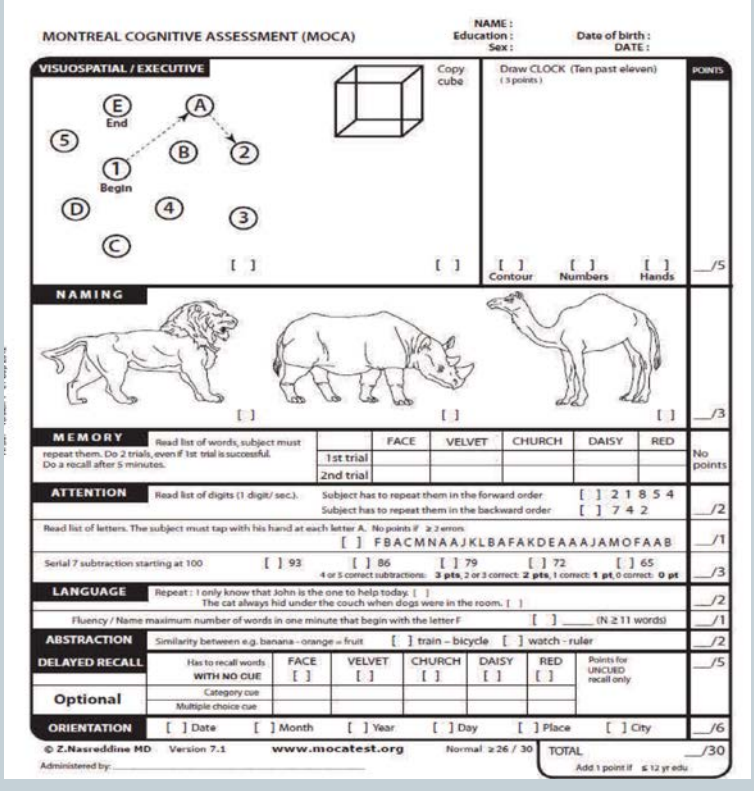
- Initial 30 minutes:
  - Allergic/anaphylactic reaction
  - Symptomatic bradycardia or hypotension
- Every 4 hours:
  - Vital signs
  - Neurological status
    - NIHSS
    - GCS
- Every Day
  - I/O_s
  - NIHSS
  - GCS
  - Visual & auditory assessment
- In intubated patients
  - PaO_2/FiO_2 ratio
  - Plateau and peak pressures
  - CXR is required if the PaO_2/FiO_2 ratio is <300

Visual & Auditory Assessment

- Visual loss or field cut
- Cataract
- Color blindness (Ishihara)
- Tinnitus
- Hearing loss



Montreal Cognitive Assessment



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	FACE	VELVET	CHURCH	DAISY	RED
Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]
Optional: Category cue					
Optional: Multiple choice cue					

Points for UNCUED recall only

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

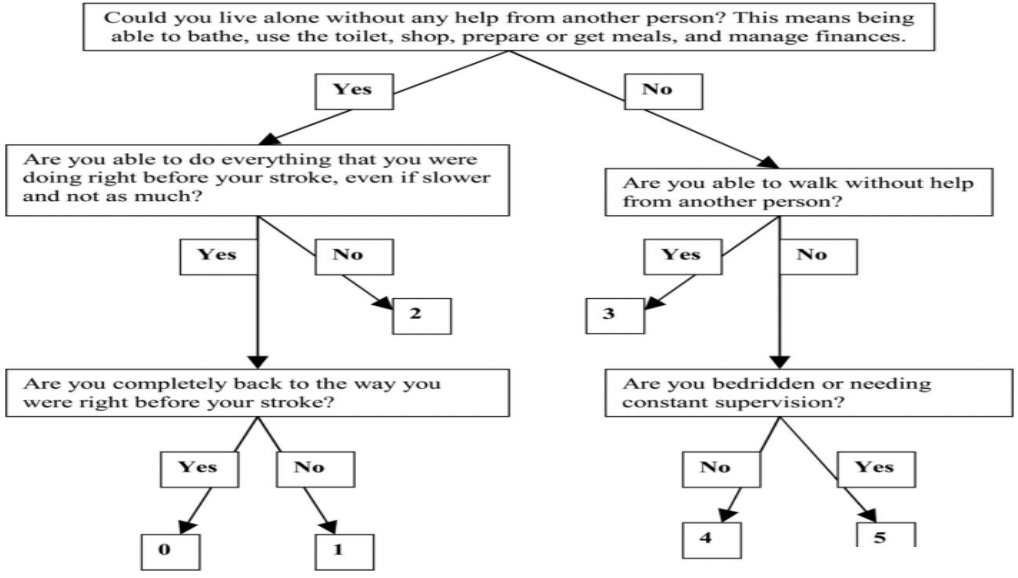
© Z.Nasreddine MD Version 7.1 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by:

mRS



Stroke 2010;41:1048-1050

Stroke Impact Scale 16

In the past two weeks, how difficult was it to...		Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a.	Dress the top part of your body	5	4	3	2	1
b.	Bathe yourself?	5	4	3	2	1
c.	Get to the toilet on time?	5	4	3	2	1
d.	Control your bladder (not have an accident)?	5	4	3	2	1
e.	Control your bowels (not have an accident)?	5	4	3	2	1
f.	Stand without losing balance?	5	4	3	2	1
g.	Go shopping?	5	4	3	2	1
h.	Do heave household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1
i.	Stay sitting without losing your balance?	5	4	3	2	1
j.	Walk without losing your balance?	5	4	3	2	1
k.	Move from a bed to a chair?	5	4	3	2	1
l.	Walk fast?	5	4	3	2	1
m.	Climb one flight of stairs?	5	4	3	2	1
n.	Walk one block?	5	4	3	2	1
o.	Get in and out of a car?	5	4	3	2	1
p.	Carry heavy objects (e.g. bag of groceries) with your affected hand?	5	4	3	2	1

P.W. Duncan, S.M. Lai, R.K. bode, S. Perera and J. DeRosa. "Stroke Impact Scale-16: A brief assessment of physical function." Neurology 2003;60:291-296.

Efficacy Endpoints

- The primary efficacy outcome measure is mRS, dichotomized to define good functional outcome as mRS score of 0-2 at 90 days
  - The futility hypothesis specifies that if the difference in good outcome proportions is less than 12% in favor of deferoxamine, then it would be futile to move deferoxamine forward to Phase III evaluation.
- A dichotomized analysis considering the proportion of deferoxamine- and placebo-treated subjects with mRS score of 0-3 will also be performed
  - The trial is adequately powered to assess the futility hypothesis using mRS 0-3 as the outcome based on a difference in treatment effect ≤ 13% in favor of deferoxamine

Efficacy Endpoints

- Ordinal analysis across all mRS scores
- The magnitude of the treatment effect, and corresponding confidence interval, will be estimated for each time window (≤12h vs. >12-24h)
- Similar analyses at 180 days

THE FUTILITY ANALYSIS

- The primary futility hypothesis, H0: (πDFO-πplacebo) ≥0.12, will be tested at one-sided alpha (the probability that an effective intervention will be called ineffective, or futile) 0.10

- The futility analysis will be conducted using a one-sided 90% upper confidence bound on the risk difference

- To declare futility, the entire interval must lie below the value 0.12, indicating that the true difference in risk of good outcome is less than 0.12 with 90% confidence

Safety Endpoints

- All AEs will be assessed until day-7 or discharge (whichever is earlier)
- New SAEs* until day-90 or resolution
- Continuing SAEs and mortality until day-180
- Adverse events of special interest (until day-7 or discharge)
  - Anaphylaxis during study drug infusion
  - Unexplained decrease in BP requiring medical intervention during infusions
  - New & unexplained visual or auditory changes after initiation of infusions
  - Respiratory compromise of any cause*

* Requires reporting within 24h

Stopping Rule

Recruitment will be stopped if the difference in the number of confirmed ARDS cases between the groups is

- 5 at any time during the recruitment of the first 40 subjects
- 10 at any time during the recruitment of subjects 41-80
- 12 at any time during the recruitment of patients 81-120
- or if the difference in the number of confirmed ARDS cases between the groups is statistically significant after 40, 80, or 120 subjects have completed the in-hospital phase based on a Pocock-adjusted, one-sided, 0.05 alpha level.

Acute Respiratory Distress Syndrome

The Berlin Definition

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

THE BERLIN DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME

Table 1. The AECC Definition[3]—Limitations and Methods to Address These in the Berlin Definition

	AECC Definition	AECC Limitations	Addressed in Berlin Definition
Timing	Acute onset	No definition of acute[4]	Acute time frame specified
ALI category	All patients with Pao_2/Fio_2 <300 mm Hg	Misinterpreted as Pao_2/Fio_2 = 201-300, leading to confusing ALI/ARDS term	3 Mutually exclusive subgroups of ARDS by severity ALI term removed
Oxygenation	Pao_2/Fio_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of Pao_2/Fio_2 ratio due to the effect of PEEP and/or Fio_2[5-7]	Minimal PEEP level added across subgroups Fio_2 effect less relevant in severe ARDS group
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor interobserver reliability of chest radiograph interpretation[8,9]	Chest radiograph criteria clarified Example radiographs created[a]
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist[10,11] Poor interobserver reliability of PAWP and clinical assesments of left atrial hypertension[12]	PAWP requirement removed Hydrostatic edema not the primary cause of respiratory failure Clinical vignettes created[a] to help exclude hydrostatic edema
Risk factor	None	Not formally included in definition[4]	Included When none identified, need to objectively rule out hydrostatic edema

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; Pao_2, arterial partial pressure of oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.

[a] Available on request.

JAMA. 2012;307(23):2526-2533

Precautions During the Infusions

- There are few restrictions on the use of concomitant medications during the study:
  - The use of prochloroperazine (compazine), is not allowed before treatment, during treatment, or up to 72 hours after the last dose of the study drug
  - Concurrent use of other experimental therapy is not allowed
  - Vitamin C supplements will not be allowed in patients with heart failure during treatment with DFO

- The established criteria for pre-mature discontinuation of the study drug are:
  - Severe allergic reaction or anaphylaxis
  - Worsening of renal function tests (creatinine >2 mg/dl)
  - ARDS
  - If the investigator feels that continued administration of the drug poses harm to the patient's medical condition
  - If the patient or his proxy voluntarily withdraws consent

NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial V_T = 8 ml/kg PBW
4. Reduce V_T by 1 ml/kg at intervals ≤ 2 hours until V_T = 6ml/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

---

pH GOAL: 7.30-7.45

Acidosis Management: (pH < 7.30)

If pH 7.15-7.30: Increase RR until pH > 7.30 or $PaCO_2$ < 25 (Maximum set RR = 35).

.

If pH < 7.15: Increase RR to 35.

If pH remains < 7.15, V_T may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).

May give $NaHCO_3$

Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%

Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O

Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T.

If Pplat > 30 cm H_2O: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).

If Pplat < 25 cm H_2O and V_T< 6 ml/kg, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or V_T = 6 ml/kg.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains ≤ 30 cm H_2O.

Thank You

Questions:
mselim@bidmc.harvard.edu