Korean J Neurotrauma. 2025 Apr;21(2):124-136
https://doi.org/10.13004/kjnt.2025.21.e9
pISSN 2234-8999·eISSN 2288-2243

KJNT

Clinical Article

Check for updates

Deferoxamine for Spontaneous Intracranial Hemorrhage: A Pilot Study on Neurological and Radiological Outcomes

Mohammad Shirani [1], Masoud Sohrabiasl [2], Ali Meshkini [2], Farhad Mirzaei [2], Seyed Mohammad Mehdi Hashemi [1], Fatemeh Jafari [3], Ali Salami [2], Ebrahim Rafiei [1], and Arad Iranmehr [1,3]

[1]Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Neurosurgery, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Gamma Knife Radiosurgery Center, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: Dec 27, 2024
Revised: Feb 28, 2025
Accepted: Mar 6, 2025
Published online: Apr 14, 2025

Address for correspondence:
Arad Iranmehr
Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences, Tehran 1417613151, Iran.
Email: arad.iranmehr@gmail.com

ORCID iDs
Masoud Sohrabiasl
https://orcid.org/0000-0003-3195-3552
Arad Iranmehr
https://orcid.org/0000-0002-5932-9375

Funding
No funding was obtained for this study.

Conflict of Interest
The authors have no financial conflicts of interest.

Informed Consent
The participants were provided with detailed information about the potential benefits and

ABSTRACT

Objective: Spontaneous intracranial hemorrhage (ICH) is a catastrophic medical condition associated with significant morbidity and mortality. Because the accumulation of unbound iron following ICH contributes to secondary brain injury, deferoxamine, an approved chelation drug, has become the center of attention. However, its therapeutic effects remain a matter of dispute. This double-blind randomized controlled trial aimed to investigate the therapeutic potential of deferoxamine in terms of neurological and radiological outcomes.
Methods: The study enrolled 42 participants diagnosed with spontaneous ICH, confirmed by computed tomography, and randomly assigned them to either a deferoxamine treatment group or the placebo control group. The placebo control group received routine treatment plus a placebo, whereas the treatment group received routine treatment conjugated with 7.5 mg/kg of deferoxamine per hour intravenously over the first 3 days. The study compared the hematoma and edema volumes, Glasgow coma scale (GCS) scores, and mortality rates between the 2 groups. Our study employed rigorous randomization and blinding procedures to ensure unbiased results.
Results: There was a significant (p<0.05) improvement in the patients' GCS scores until the fourth day; however, no significant difference was noted thereafter. In addition, both the edema and hematoma volumes were significantly lower in the deferoxamine treatment group versus the placebo control group, as were the length of stay, intubation requirement, and mortality.
Conclusion: Deferoxamine administration can, at least within a short timeframe, improve neurological and radiological parameters.

Keywords: Deferoxamine; Cerebral hemorrhage; Intracranial hemorrhage; Randomized controlled trial; Neurosurgery

INTRODUCTION

Spontaneous intracranial hemorrhage (ICH) bears profound implications for public health, given its association with a high mortality rate and significant long-term morbidity. As a clinical

risks of the study, as well as their role and the study procedure. Written informed consent was obtained from each participant.

Ethics Approval

Ethical considerations were taken into account throughout the study. Both the intervention and control groups received conventional treatment following the guidelines. The safety of the treatment administered to the test group was evaluated prior to the commencement of the study. This work was completely aligned with concepts of Helsinki declaration. Data gathering and analysis were conducted with permission from the Tabriz University of Medical Sciences Ethics and Research Committee (IR.TBZMED.REC.1401.142) and the Iranian Registry of Clinical Trials (IRCT20190325043107N30). No additional financial burden or radiation exposure was imposed on the patients. Also, they were free to enter or exit the trial at any time.

entity accounting for 10%–15% of all strokes, ICH is burdened with a sobering 40%–59% mortality rate within the first month following the event, much of which occurs in the first 48 hours.[5,25] In the case of morbidity, the primary determinants of the outcome include: 1) the size of the intracerebral hemorrhage[15]; 2) the patient's degree of consciousness upon arrival; and 3) the existence or extent of intraventricular bleeding.

Those conjugated with the location of the involved area affect the severity of disabilities and sequels following the incident.[25] According to reports, the percentage of patients who have survived but will regain their functionality is less than 40%.[26]

These grave statistics not only reflect the critical nature of the condition but also the imperative for medical science to forge new paths in treatment and management.

Conventionally, the treatment of spontaneous ICH has been largely supportive, centered on the containment of hematoma expansion, the maintenance of cerebral perfusion, and the prevention of secondary complications.[27] Surgical intervention, an option for select cases, has grappled with inconsistent results in improving patient outcomes.[12,13] Besides, pharmaceutical agents have shown promising results in previous work of our team on some other nervous system pathologies.[19,23] Therefore, it has led to a quest for new pharmacological therapies aimed at mitigating the pathophysiological processes that govern secondary brain injury.[2,11]

Amid this backdrop, deferoxamine has garnered attention as a potential therapeutic agent in mitigating iron-mediated secondary injury. Individuals who suffer from ICH are at increased risk of experiencing secondary brain injury due to iron overload,[8] an ion known for its oxidative stress properties that increase ferroptosis and autophagy within neural cells. This problem occurs as a result of hemoglobin breakdown within the intracranial bleed and the release of blood components, including hem, iron, and thrombin.[9]

Deferoxamine, an Food and Drug Administration-approved pharmaceutical agent for the treatment of iron overload, exhibits the capacity to form a complex with iron ions through a process known as chelation. This can detoxify the brain environment and potentially decrease the oxidative damage that contributes to secondary brain damage.[1] Besides its chelation activities, it has been proposed that deferoxamine independently has neuroprotective properties, including anti-inflammatory, anti-oxidant, and anti-apoptotic effects.[17]

Despite its traditional use in conditions of iron overload, deferoxamine functions through a high-affinity binding mechanism that allows it to chelate labile iron, even in patients with normal systemic ferritin levels. In the context of spontaneous ICH, hemolysis within the hematoma results in localized iron release, independent of systemic ferritin levels.[8] The accumulation of free iron catalyzes reactive oxygen species formation, exacerbating neuronal damage via ferroptosis.[10] Deferoxamine mitigates this by forming a stable complex with $Fe3^{+}$, preventing its participation in the Fenton reaction, thereby reducing oxidative stress and secondary brain injury.[28]

Supporting this proposition, several *in vivo* and *in vitro* as well as animal model studies have been published in reputable scientific journals, which have shown that deferoxamine reduces brain edema and improves neurological functions post-ICH, providing the impetus for consideration of its application in human medicine.[3-6,20,24,28] Despite the limited number of

https://doi.org/10.13004/kjnt.2025.21.e9

human clinical trials on this matter, there is growing optimism due to clinical trial reports such as the i-DEF trial. This trial suggested safety and hinted at therapeutic efficacy in humans, which is promising for the diffusion of this potential therapy from "bench to bedside."[3,18,20]

Our investigative stance is that, through the administration of deferoxamine, we may witness a diminution in the post-ICH perihematomal edema and restraint of hematoma expansion evidenced by imaging modalities. Concomitantly, we expect enhancements in neurological function as determined by recognized clinical scoring systems (specifically GCS and Glasgow outcome scale [GOS]), thereby delivering support to our hypothesis that deferoxamine's iron-chelating prowess and other neuroprotective features can translate into tangible clinical benefits so it can be applied in routine medical practice. Our study is reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines in reporting clinical trial results.

MATERIALS AND METHODS

We employed a prospective parallel-cohort design with a 1:1 test-control ratio to investigate the aforementioned parameters.

Subjects of the study were randomly selected through a convenience sampling technique among patients admitted with spontaneous ICH diagnosis in Tabriz University Hospitals.

The inclusion criteria for this study consisted of the following: 1) patients over 22 years of age; 2) confirmed spontaneous ICH by computed tomography (CT) scan; 3) possibility of initiation of therapy within 18 hours of symptom onset; 4) being vitally stable; and 5) granting informed consent to be included in the study.

Our study employed a set of exclusion criteria, which are outlined as follows: 1) hypersensitivity to deferoxamine; 2) serum creatinine over 2 mg/dL; 3) the necessity of blood transfusion or hemoglobin less than 9 g/dL upon admission; 4) an INR greater than 1.5; 5) patients with ICH secondary to brain aneurysmal rupture; 6) patients with a GCS of less than 6; 7) thalassemia patients; 8) patients with dysregulated iron diseases; 9) patients with a history of hepatorenal disorders; 10) consumption of iron supplements; 11) history of stroke in the past 3 months; 12) patients under treatment with anticoagulant injections; and 13) patients with nervous system disease and disabilities, e.g., parkinsonism and multiple sclerosis.

Sample size

The sample size, as a surrogate for the larger population under study, must adhere stringently to statistical criteria to enable the generalization of the study results to the population as a whole. Thus, in our study, to achieve a power of at least 90% with a significance level of 0.05, we used the following formula to determine the appropriate sample size.

$$n = \frac{p(1-p)z^2_{\frac{\alpha}{2}}}{e^2}$$

p=0.05

$$Z\frac{\alpha}{2} = 1.96$$

https://doi.org/10.13004/kjnt.2025.21.e9

With reference to this formula and taking into account a predicated 10% drop rate, our final sample size was 21 for each of the test and control groups. The process of patient selection in this study is presented in **FIGURE 1**.

Randomization

We utilized block permutation randomization to ensure the balance in the sample size by means of age, gender, etc. In this method, every patient was allocated an intervention or control group, and each of them received either deferoxamine or a placebo in addition to routine treatments. Each block consisted of 4 subjects, and for 42 subjects involved in this study, we would need 7 blocks. Then, we ran our blocks through random allocation software to allocate each subject to one of the groups.

To ensure allocation concealment, the randomization sequence was generated using computer-based randomization software before patient recruitment. The sequence was concealed from investigators responsible for enrollment using opaque, sealed, and sequentially numbered envelopes. This method prevented selection bias by ensuring that group assignment was unknown until the moment of allocation. Additionally, a third-party statistician, independent of the clinical team, supervised the sequence generation and allocation process to maintain the integrity of the randomization procedure.

To minimize confounding, we performed block permutation randomization, ensuring balanced allocation of key prognostic factors, including hematoma size and location. While extraventricular and intraventricular involvement were not independently randomized, *post hoc* analysis confirmed no significant baseline differences in these variables between groups.

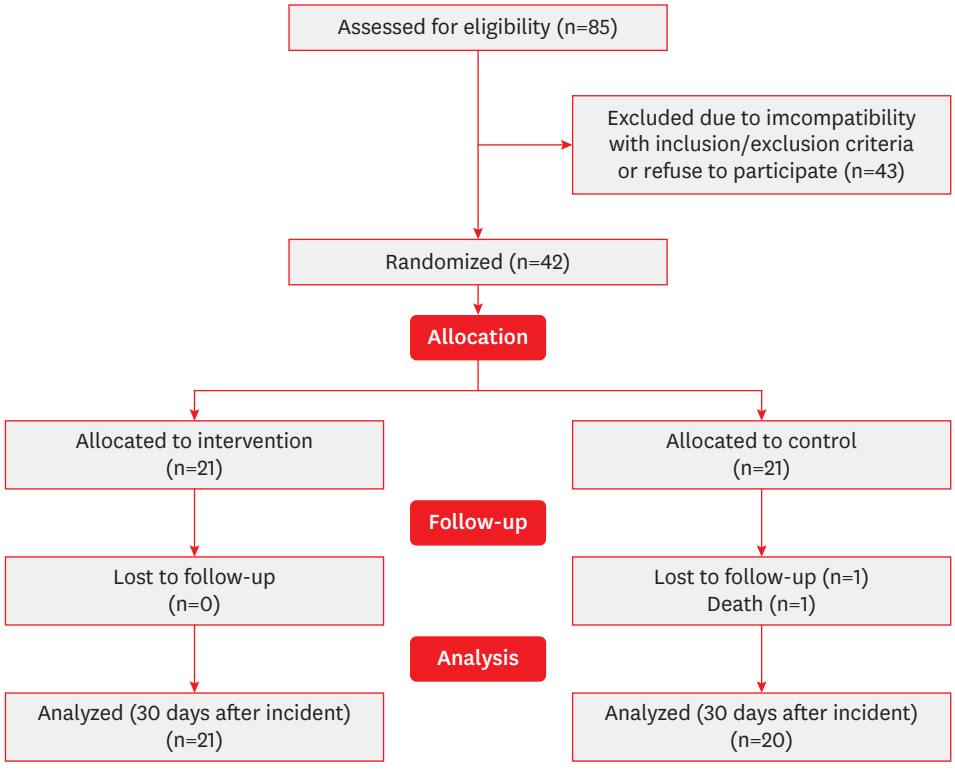

FIGURE 1. Process of patient enrollment.

https://doi.org/10.13004/kjnt.2025.21.e9

Blinding

In our study, only the specialist prescribing the drug was aware of the agent prescribed for the patient, while the clinician recording the result and the patients receiving the treatment were completely unaware of the type of treatment. Hence, our study can be categorized as a double-blinded randomized controlled trial.

Interventions

For every patient who showed clinical manifestations of a stroke, a brain CT scan was conducted. If the CT scan revealed evidence of spontaneous ICH and the patient met the inclusion and exclusion criteria for the study, they were informed of the study and its potential benefits and risks. The study was explained thoroughly to ensure the patient fully understood the implications, and informed consent was obtained. If the patient was unable to provide consent due to a low level of consciousness, the next of kin was consulted to obtain informed consent.

After the patient was enrolled in the study, their vital signs, neurological examination, and Glasgow coma scale (GCS) were evaluated and recorded. Hematoma volume and location were also recorded as a baseline for further evaluation.

After ensuring patient enrollment and carefully inspecting inclusion and exclusion criteria, patients were admitted to either the neurology or neurosurgery ward. Subsequently, a thorough examination of vital signs, GCS scoring, and neurologic condition was conducted. For patients who met the aforementioned criteria and exhibited symptoms for less than 18 hours, either a placebo or the first dose of deferoxamine was administered based on prior randomization.

According to previous studies, the patients who were assigned to the intervention group were subjected to a continuous infusion of deferoxamine at a rate of 7.5 mg/kg per hour for 3 days straight, with a maximum daily dosage of 6,000 mg to avoid toxicity. On the other hand, the control group was given normal saline as a placebo. Throughout the treatment period, the patients were monitored closely for any changes in their blood pressure and vital signs. If there was a decrease of 20 mmHg in the systolic pressure or a decrease of 10 mmHg in the diastolic pressure, the administration of the drug was halted immediately. Any side effects that were observed during the treatment were recorded diligently for further evaluation.

Throughout the patient's hospitalization, a comprehensive evaluation of their clinical state was conducted daily. This involved a detailed neurological examination and constant monitoring of their GCS score. Moreover, in accordance with the ward's customary practice for stroke patients, a CT scan was carried out on the third and seventh day after admission. This was done to assess the intraparenchymal blood volume and determine the extent of edema surrounding the hematoma. All of these measurements were meticulously recorded.

In the event of any decrease in the GCS score or deterioration of the patient's clinical condition, an immediate CT scan was obtained, and the appropriate interventions were administered.

It is pertinent to mention that none of the participants were deprived of conventional treatment in line with the most reliable and credible guidelines available. The drug under investigation was included as an adjunct to conventional therapy.

https://doi.org/10.13004/kjnt.2025.21.e9

The ABC/2 formula was used to measure the volume of the hematoma and the volume of edema peripheral to the hematoma.

In order to assess the efficacy of interventions, we conducted a weekly observation of the GOS, Rankin scale, and mortality statistics. This procedure was conducted over 30 days post-incident, with information gathered during hospitalization, post-discharge clinic visits, or via phone consultations. To evaluate the effectiveness of the interventions, we performed a weekly monitoring of the GOS (**TABLE 1**), Rankin scale, and mortality rates. This process was carried out for 30 days following the incident, with data collected during hospitalization, clinic visits following discharge, or through phone consultations.

Beyond hematoma volume and cerebral edema, we recorded serial neurological assessments using the National Institutes of Health Stroke Scale (NIHSS) to provide additional objective functional data.[15] However, these results were not included in the final manuscript due to the limited statistical power of our sample size, which may have introduced variability in NIHSS scores. Given that our primary endpoints focused on hematoma volume, cerebral edema, and functional scales (GCS and Rankin), the inclusion of additional serial assessments without adequate power could have led to inconclusive or misleading interpretations. Future larger-scale studies should incorporate and analyze these objective measures with sufficient statistical rigor. Additionally, perfusion CT imaging was considered but not routinely performed due to resource limitations. Future studies should also integrate advanced imaging techniques, such as diffusion tensor imaging or functional magnetic resonance imaging, to assess microstructural integrity and neuroplasticity following deferoxamine administration.

During the first 7 days of admission, the Rankin scale was evaluated to ascertain the severity of the patient's disability. This scale ranges from 0, with no unusual neurological symptoms, to 5, which indicates morbid disability, and 6, which indicates death (**TABLE 2**).

Statistical analysis

The compiled data were meticulously documented using IBM SPSSv.23 (IBM Corp., Armonk, NY, USA). The results were presented using appropriate descriptive statistics such as mean and standard deviation. For examining qualitative variables, a χ^2 test was employed.

TABLE 1. Glasgow outcome scale

Grades	Description
1. Death	Severe injury or death without recovery of consciousness
2. Persistent vegetative state	Severe damage with a prolonged state of unresponsiveness and a lack of higher mental functions
3. Severe disability	Severe injury with permanent need for help with daily living
4. Moderate disability	No need for assistance in everyday life; employment is possible but may require special equipment
5. Low disability	Light damage with minor neurological and psychological deficits

TABLE 2. Modified Rankin scale for neurologic disability

Rankin score	Severity of disability
0	No abnormal neurological symptoms at all
1	No significant disability despite some symptoms, able to carry out usual activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

https://doi.org/10.13004/kjnt.2025.21.e9

In contrast, for quantitative variables, a *t*-test was performed for comparative analysis. To account for potential confounders such as comorbidities, initial GCS, and baseline hematoma volume, a multivariable linear regression model was employed. The model adjusted for these factors when analyzing GCS improvement and Rankin scale outcomes. A sensitivity analysis was also performed by excluding patients with extreme baseline characteristics (e.g., GCS <8 or hematoma volume >30 mL), confirming that the treatment effect remained consistent. A *p*-value of less than 0.05 was considered significant.

RESULTS

Descriptive results

The average age of the participants was 61.18±5.41 years. There were 28 males and 24 females. Their initial GCS score had a mean value of 8.12±1.24. The volume of bleeding was 21.29±5.96 milliliters. Most participants were using anticoagulant medication and had comorbidities, including diabetes, chronic hypertension, and smoking. The time interval between symptom onset and the initiation of medication was 9.59±3.62 hours.

Furthermore, there were no significant differences in the baseline participant information between the intervention and control groups. **TABLE 3** shows the demographic information of the study participants.

All cases in our cohort presented with supratentorial ICH, which aligns with the predominance of this subtype in spontaneous ICH cases.[13] As such, subgroup analysis based on ICH location was not feasible in this pilot study. Similarly, while age is a known prognostic factor, our study design focused on short-term functional outcomes, and both treatment and control groups were age-matched (p=0.749). Future trials with larger cohorts should explore differential responses based on age and ICH location.

TABLE 3. Demographics at baseline

Variables	Groups (n=42)		*p*-value
	Control (n=21)	Intervention (n=21)	
Age (year)	60.89±5.37	62.01±5.55	0.749
Sex			0.669
Male	15	13	
Female	16	8	
Primary GCS	12.24±1.80	12.24±1.80	0.859
Hematoma volume (mm^3)			
Mean	22.02±5.59	21.54±5.85	0.653
Less than 10	8	9	0.885
10–30	11	10	
More than 30	2	2	
Comorbidities			
Hypertension	16	15	0.859
Diabetes mellitus	14	12	0.693
Smoking	12	13	0.789
Symptom-to-needle time (hour)	9.31±3.29	9.86±3.15	0.851
History of the anti-coagulation use	13	15	0.558

Values are presented as number or mean ± standard deviation.
GCS: Glasgow coma scale.

https://doi.org/10.13004/kjnt.2025.21.e9

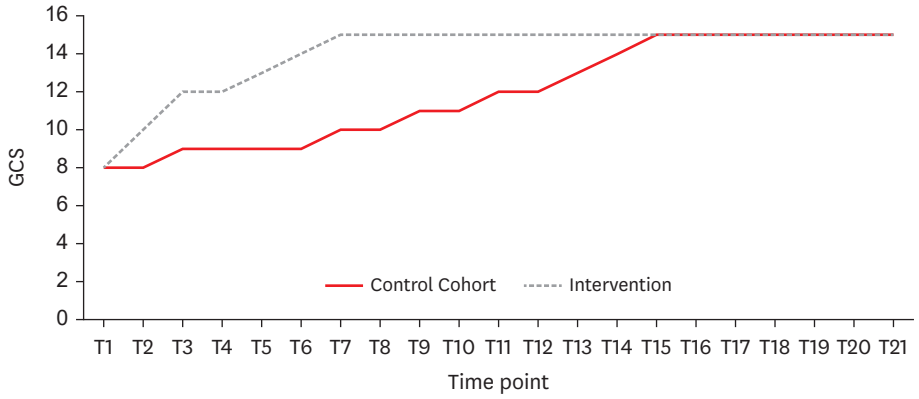

FIGURE 2. The trend of Glasgow coma scale changes over time.
GCS: Glasgow coma scale.

Throughout 7 days following the intervention, the GCS of patients was regularly measured and logged every 8 hours. The intervention group exhibited a rapid improvement in GCS scores compared to the control group, whose improvement was significantly slower. **FIGURE 2** illustrates the significant differences in the GCS changes between the groups at all measured time points.

TABLE 4 presents the mean differences in the GCS at baseline and on a daily basis post-intervention. The findings suggest that the intervention group had significantly more GCS changes than the control group in the first 4 days. However, there was no significant difference in the mean changes from the fourth day onwards.

Upon analyzing the hemorrhage volume on the third and seventh days, it was discovered that the intervention group exhibited significantly lower bleeding than the control group. Furthermore, the intervention group showed significantly lower levels of cerebral edema than the control group during both measured time points. **TABLE 5** presents a detailed comparison of the hemorrhage volume and cerebral edema at different measurement times between the 2 groups.

Based on the Rankin scale, disability status was assessed, revealing no significant differences in scores between the groups on the first and second days following the intervention. However, from the third to the seventh days, the intervention group showed significantly better scores than the control group. The comparison of Rankin scale results for both groups can be found in **TABLE 6**.

TABLE 4. Trend of GCS over 7 days of treatment in the 2 groups

Variables	Groups (n=42)		*p*-value
	Control (n=21)	Intervention (n=21)	
Baseline GCS	8.10±1.68	8.40±1.41	0.859
GCS on day 2	9.18±1.96	12.41±1.29	0.001
GCS on day 3	10.29±1.19	15	0.003
GCS on day 4	13.50±1.10	15	0.009
GCS on day 5	15	15	0.999
GCS on day 6	15	15	0.999
GCS on day 7	15	15	0.999

Values are presented as number or mean ± standard deviation.
GCS: Glasgow coma scale.

https://doi.org/10.13004/kjnt.2025.21.e9

TABLE 5. Comparison of bleeding volume and brain edema between the 2 groups

Variables	Groups (n=42)		*p*-value
	Control (n=21)	Intervention (n=21)	
Primary bleeding volume	21.54±5.85	22.02±5.59	0.653
Bleeding volume on day 3	19.28±3.45	12.41±3.29	0.012
Bleeding volume on day 7	14.27±3.12	5.29±1.36	0.005
Primary brain edema	8.33±1.14	8.27±1.29	0.659
Brain edema on day 3	6.28±1.33	4.27±1.03	0.005
Brain edema on day 7	4.52±0.66	2.18±0.29	0.002

TABLE 6. Changes in the Rankin scale between control and intervention subgroups

Variables	Groups (n=42)		*p*-value
	Control (n=21)	Intervention (n=21)	
Day 1	3.11±0.96	3.15±0.15	0.859
Day 2	3.49±0.63	3.01±0.54	0.001
Day 3	4.32±0.85	2.15±0.63	0.003
Day 4	3.85±0.74	2.01±0.67	0.009
Day 5	3.66±0.56	1.95±0.85	0.999
Day 6	3.52±0.63	1.66±0.96	0.999
Day 7	3.26±0.96	1.33±0.37	0.999

Statistical analysis to determine the *p*-value was the sample *t*-test.

Patients in the intervention group had a significantly shorter hospitalization duration of 5.62±1.29 days than the control group with 9.14±2.63 days (p=0.001). Additionally, the intervention group had a zero mortality rate at 30 days, whereas the control group had one deceased patient, and this difference was statistically significant (p=0.015). The intervention group also had fewer individuals requiring intubation during the intervention, with only one patient compared to 4 in the control group, and this difference was statistically significant (p=0.033).

DISCUSSION

Our research has yielded valuable insights into the impact of deferoxamine on the treatment of spontaneous intracerebral hemorrhage. Our findings demonstrate that administering deferoxamine is effective in enhancing early neurological outcomes in patients with non-traumatic ICH and notably improves radiological indicators compared to the control group. This observation is of utmost significance, as it opens the door to potential therapeutic interventions that may significantly alter the course of recovery following such a devastating event.

Comparing our findings with the existing literature, we see a noteworthy alignment. The efficacy of deferoxamine as a treatment modality in ICH is well-established within the scientific community. Selim et al.,[22] Foster et al.,[7] and the authors of the i-DEF trial[15] acknowledge the safety and tolerability of deferoxamine mesylate in patients suffering from acute ICH. Furthermore, Keep et al.[9] demonstrated the agent's ability to reduce brain edema, a critical factor in the recovery from ICH.

Deferoxamine has been posited to reduce cerebral edema by facilitating the reduction of free iron levels within the cerebrospinal fluid following ICH.[28] This is a vital consideration, as elevated iron levels post-ICH have been strongly associated with secondary brain injury, as discussed earlier in this article.

https://doi.org/10.13004/kjnt.2025.21.e9

Animal models, in particular, have been instrumental in demonstrating that deferoxamine may attenuate brain swelling and neurological deficits. Nakamura et al.[16] found that deferoxamine-induced attenuation of brain edema and neurological deficits were evident in a rat model of intracerebral hemorrhage. This aligns with our findings regarding the improvements in early neurological outcomes.

Our findings indicate that deferoxamine significantly improves GCS and Rankin scale outcomes within the first 3 days. However, given that oxidative stress and neuroinflammation persist beyond this period, prolonging deferoxamine infusion may offer extended neuroprotection.[30] Studies in animal models suggest that longer deferoxamine courses further mitigate iron-mediated toxicity and cerebral edema.[16] Future trials conducted after this pilot study should explore whether a 6–7-day infusion regime could sustain neurological recovery and reduce long-term disability.[7]

However, while literature largely supports the use of deferoxamine, some counterarguments need to be acknowledged. There appears to be a concern regarding the optimal dosing and timing of deferoxamine administration, which could induce varying therapeutic outcomes. As detailed in the study protocol by Woo et al.,[29] complexities involved in the balance between therapeutic and potentially harmful doses of deferoxamine must be taken into account. Additionally, the ethnic and racial variations in the presentation and severity of ICH, as outlined in the ERICH study,[29] suggest that the response to treatment with deferoxamine might also vary across different patient demographics, posing a limitation to the generalization of results.

One of the most promising aspects noted in recent studies, consistent with our findings, is the potential of deferoxamine for improving recovery trajectories post-ICH. Foster et al.[7] conducted a post hoc analysis of the i-DEF Trial and concluded that deferoxamine may positively affect the trajectory of recovery after ICH. This evidence is congruent with the radiological improvements noted in our research.

Indeed, the literature presents a spectrum of results. The consensus tilts toward a positive effect of deferoxamine, yet the degree and consistency of its efficacy seem to vary. For instance, the phase 2 trial included in *Lancet Neurology* indicates a measured yet substantial optimism for deferoxamine use in an acute setting.[15]

From the wealth of data reviewed, the majority seems to support the potential of deferoxamine in mitigating the consequences of spontaneous ICH, which mirrors the conclusions drawn from our investigation. However, it is crucial to address the challenges in terms of dosage and patient-specific factors, which may influence the success of this treatment, as well as potential side effects.[10,30,31] Moreover, it is essential to monitor serious adverse events that might not be solely attributable to deferoxamine but could also be related to the normal evolution of stroke pathology, such as symptomatic ICH, early neurological worsening, and mortality.[14] In addition, earlier trials, as reported by Selim et al.,[15] have noted specific adverse effects following deferoxamine administration, particularly at a dosage of 32 mg/kg/day. These effects, observed within 90 days of treatment onset, included anemia, erythema around the administration site, injection extravasation, hypotension, headache, and delirium tremens, occurring in all patients who received this high dosage.[21]

While our study primarily focused on short-term outcomes, including GCS changes, 7-day Rankin scale assessments, and 30-day mortality, ICH-related disability often persists for

https://doi.org/10.13004/kjnt.2025.21.e9

months to years. Existing literature suggests that long-term follow-up (≥90 days) can provide deeper insights into functional recovery.[21] Future studies should assess whether the initial benefits observed with deferoxamine translate into sustained improvements beyond 30 days, particularly in terms of cognitive function and reintegration into daily activities.

Hence, despite the robust collection of data supporting the use of deferoxamine in spontaneous ICH, long-term investigations remain sparse. Our study, along with most available studies, shows promising results. Nevertheless, to recommend deferoxamine as a standard regimen for spontaneous ICH, the scientific community must engage in more extensive, long-term investigational studies. This will help better understand the optimal use of this drug and its long-term implications on patient's health and recovery. In conclusion, while the path forward is illuminated with encouraging findings, the declaration of deferoxamine as a definitive standard care treatment requires a deeper exploration of its long-term benefits and risks.

Despite promising findings, our study has certain limitations. The small sample size (n=42) restricts the generalizability of results, and the lack of long-term follow-up prevents definitive conclusions about deferoxamine's sustained impact. Additionally, while randomization balanced baseline characteristics, unmeasured confounders such as rehabilitation intensity and nutritional status may have influenced outcomes.[13] Future large-scale trials with extended follow-up are necessary to confirm the clinical utility of deferoxamine in spontaneous ICH.

CONCLUSION

In this rigorous double-blinded randomized clinical trial, we observed that the administration of deferoxamine at a rate of 7.5 mg/kg per hour with a maximum daily dose of 6,000 mg had a significant impact on the short-term radiological and neurological outcomes of spontaneous ICH. Thus, deferoxamine can be a promising therapeutic option for improving outcomes in patients with spontaneous ICH.

REFERENCES

1. Bellotti D, Remelli M. Deferoxamine B: a natural, excellent and versatile metal chelator. **Molecules 26:**3255, 2021 PUBMED | CROSSREF
2. Belur PK, Chang JJ, He S, Emanuel BA, Mack WJ. Emerging experimental therapies for intracerebral hemorrhage: targeting mechanisms of secondary brain injury. **Neurosurg Focus 34:**E9, 2013 PUBMED | CROSSREF
3. Cui HJ, He HY, Yang AL, Zhou HJ, Wang C, Luo JK, et al. Efficacy of deferoxamine in animal models of intracerebral hemorrhage: a systematic review and stratified meta-analysis. **PLoS One 10:**e0127256, 2015 PUBMED | CROSSREF
4. Dayani PN, Bishop MC, Black K, Zeltzer PM. Desferoxamine (DFO)--mediated iron chelation: rationale for a novel approach to therapy for brain cancer. **J Neurooncol 67:**367-377, 2004 PUBMED | CROSSREF
5. de Oliveira Manoel AL, Goffi A, Zampieri FG, Turkel-Parrella D, Duggal A, Marotta TR, et al. The critical care management of spontaneous intracranial hemorrhage: a contemporary review. **Crit Care 20:**272, 2016 PUBMED | CROSSREF
6. Farr AC, Xiong MP. Challenges and opportunities of deferoxamine delivery for treatment of Alzheimer's disease, Parkinson's disease, and intracerebral hemorrhage. **Mol Pharm 18:**593-609, 2021 PUBMED | CROSSREF

7. Foster L, Robinson L, Yeatts SD, Conwit RA, Shehadah A, Lioutas V, et al. Effect of deferoxamine on trajectory of recovery after intracerebral hemorrhage: a post hoc analysis of the i-DEF trial. **Stroke 53:**2204-2210, 2022 PUBMED | CROSSREF
8. Helbok R, Rass V, Kofler M, Talasz H, Schiefecker A, Gaasch M, et al. Intracerebral iron accumulation may be associated with secondary brain injury in patients with poor grade subarachnoid hemorrhage. **Neurocrit Care 36:**171-179, 2022 PUBMED | CROSSREF
9. Keep RF, Zhou N, Xiang J, Andjelkovic AV, Hua Y, Xi G. Vascular disruption and blood-brain barrier dysfunction in intracerebral hemorrhage. **Fluids Barriers CNS 11:**18, 2014 PUBMED | CROSSREF
10. Li Z, Liu Y, Wei R, Khan S, Zhang R, Zhang Y, et al. Iron neurotoxicity and protection by deferoxamine in intracerebral hemorrhage. **Front Mol Neurosci 15:**927334, 2022 PUBMED | CROSSREF
11. McIntosh TK. Novel pharmacologic therapies in the treatment of experimental traumatic brain injury: a review. **J Neurotrauma 10:**215-261, 1993 PUBMED | CROSSREF
12. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. **Lancet 365:**387-397, 2005 PUBMED | CROSSREF
13. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. **Lancet 382:**397-408, 2013 PUBMED | CROSSREF
14. Millán M, DeGregorio-Rocasolano N, Pérez de la Ossa N, Reverté S, Costa J, Giner P, et al. Targeting pro-oxidant iron with deferoxamine as a treatment for ischemic stroke: safety and optimal dose selection in a randomized clinical trial. **Antioxidants (Basel) 10:**1270, 2021 PUBMED | CROSSREF
15. Murthy SB, Cho SM, Gupta A, Shoamanesh A, Navi BB, Avadhani R, et al. A pooled analysis of diffusion-weighted imaging lesions in patients with acute intracerebral hemorrhage. **JAMA Neurol 77:**1390-1397, 2020 PUBMED | CROSSREF
16. 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 hemorrhage. **J Neurosurg 100:**672-678, 2004 PUBMED | CROSSREF
17. Rakshit J, Priyam A, Gowrishetty KK, Mishra S, Bandyopadhyay J. Iron chelator deferoxamine protects human neuroblastoma cell line SH-SY5Y from 6-hydroxydopamine-induced apoptosis and autophagy dysfunction. **J Trace Elem Med Biol 57:**126406, 2020 PUBMED | CROSSREF
18. Ramadhan MIA, Sitanaya SN, Hakim AHW, Ramli Y. The role of iron-chelating therapy in improving neurological outcome in patients with intracerebral hemorrhage: evidence-based case report. **Medicina (Kaunas) 59:**453, 2023 PUBMED | CROSSREF
19. Sarpolaki MK, Vafaei A, Fattahi MR, Iranmehr A. Mini-review: role of drugs affecting renin-angiotensin system (RAS) in traumatic brain injury (TBI): what we know and what we should know. **Korean J Neurotrauma 19:**195-203, 2023 PUBMED | CROSSREF
20. Selim M. Deferoxamine mesylate: a new hope for intracerebral hemorrhage: from bench to clinical trials. **Stroke 40:**S90-S91, 2009 PUBMED | CROSSREF
21. Selim M, Foster LD, Moy CS, Xi G, Hill MD, Morgenstern LB, et al. Deferoxamine mesylate in patients with intracerebral haemorrhage (i-DEF): a multicentre, randomised, placebo-controlled, double-blind phase 2 trial. **Lancet Neurol 18:**428-438, 2019 PUBMED | CROSSREF
22. Selim M, Yeatts S, Goldstein JN, Gomes J, Greenberg S, Morgenstern LB, et al. Safety and tolerability of deferoxamine mesylate in patients with acute intracerebral hemorrhage. **Stroke 42:**3067-3074, 2011 PUBMED | CROSSREF
23. Shimia M, Iranmehr A, Valizadeh A, Mirzaei F, Namvar M, Rafiei E, et al. A placebo-controlled randomized clinical trial of amantadine hydrochloride for evaluating the functional improvement of patients following severe acute traumatic brain injury. **J Neurosurg Sci 67:**598-604, 2023 PUBMED | CROSSREF
24. Shin JA, Kim YA, Kim HW, Kim HS, Lee KE, Kang JL, et al. Iron released from reactive microglia by noggin improves myelin repair in the ischemic brain. **Neuropharmacology 133:**202-215, 2018 PUBMED | CROSSREF
25. Togha M, Bakhtavar K. Factors associated with in-hospital mortality following intracerebral hemorrhage: a three-year study in Tehran, Iran. **BMC Neurol 4:**9, 2004 PUBMED | CROSSREF
26. Velasquez F, Chada D, Kellner CP, Majidi S, Sheth KN, Dams O'Connor K, et al. Abstract TP**76:** lost to follow up as a missed opportunity in ICH survivors. **Stroke 54:**ATP76, 2023 CROSSREF
27. Veltkamp R, Purrucker J. Management of Spontaneous Intracerebral Hemorrhage. **Curr Neurol Neurosci Rep 17:**80, 2017 PUBMED | CROSSREF

28. Wan S, Hua Y, Keep RF, Hoff JT, Xi G. Deferoxamine reduces CSF free iron levels following intracerebral hemorrhage. **Acta Neurochir Suppl 96:**199-202, 2006 PUBMED | CROSSREF

29. Woo D, Rosand J, Kidwell C, McCauley JL, Osborne J, Brown MW, et al. The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study protocol. **Stroke 44:**e120-e125, 2013 PUBMED | CROSSREF

30. Yu J, Yuan Q, Sun YR, Wu X, Du ZY, Li ZQ, et al. Effects of deferoxamine mesylate on hematoma and perihematoma edema after traumatic intracerebral hemorrhage. **J Neurotrauma 34:**2753-2759, 2017 PUBMED | CROSSREF

31. Yu Y, Zhao W, Zhu C, Kong Z, Xu Y, Liu G, et al. The clinical effect of deferoxamine mesylate on edema after intracerebral hemorrhage. **PLoS One 10:**e0122371, 2015 PUBMED | CROSSREF