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Article

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

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Abstract: **1. Background and Objective:** Spontaneous Intracranial Hemorrhage (ICH) is a catastrophic medical condition associated with significant morbidity and mortality. As the accumulation of unbound iron following ICH contributes to secondary brain injury, deferoxamine, an approved chelation drug, has become the center of attention. At the same time, its therapeutic remains a matter of dispute. This double-blinded Randomized Controlled Trial (RCT) aims to investigate the therapeutic potential of deferoxamine in neurological and radiological aspects. **2. Methods and Materials:** The study enrolled 42 participants diagnosed with spontaneous ICH and confirmed by CT scan, randomly assigning them to either the deferoxamine treatment group or the placebo control group. While the control group received the routine treatment plus a placebo, the treatment group received routine treatment conjugated with 7.5 mg/kg of deferoxamine per hour intravenously over the first three days. The study compared hematoma and edema volume, GCS score, and mortality rates between the two groups. Our study employed rigorous randomization and blinding procedures to ensure unbiased results. **3. Results:** There was a significant ($p < 0.05$) improvement in patients' GCS up until the fourth day, but no significant difference was noted afterward. In addition, the volume of both edema and hematoma was significantly lower in the intervention group, as well as the length of stay, intubation requirement, and mortality. **4. Discussion:** Deferoxamine administration can, at least in a short timeframe, improve neurological and radiological parameters.

Keywords: deferoxamine; spontaneous intracranial hemorrhage; intracranial hemorrhage (ICH); randomized clinical trial; neurosurgery

1. 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 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.(1, 2)

In the case of morbidity, the primary determinants of the outcome include:

- The size of the intracerebral hemorrhage.(3)
- The patient's degree of consciousness upon arrival.
- 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.(2) According to reports, the percentage of patients who have survived but will regain their functionality is less than 40%.(4)

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.(5) Surgical intervention, an option for select cases, has grappled with inconsistent results in improving patient outcomes.(6, 7) Therefore, it has led to a quest for new pharmacological therapies aimed at mitigating the pathophysiological processes that govern secondary brain injury (8, 9).

Amid this backdrop, deferoxamine emerged as a beacon of hope. Individuals who suffer from ICH are at increased risk of experiencing secondary brain injury due to iron overload (10), 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(11).

Deferoxamine, an FDA-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(12). Besides its chelation activities, it has been proposed that deferoxamine independently has neuroprotective properties, including anti-inflammatory, anti-oxidant, and anti-apoptotic effects(13).

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 (1, 14-19). Despite the limited number of 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." (16, 19, 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 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 CONSORT guidelines in reporting clinical trial results.

2. 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:

- Patients over 22 years of age
- Confirmed spontaneous ICH by CT scan
- Possibility of initiation of therapy within 18 hours of symptom onset
- Being vitally stable
- Granting informed consent to be included in the study

Our study employed a set of exclusion criteria, which are outlined as follows:

- Hypersensitivity to deferoxamine
- Serum creatinine over 2 mg/dl

- The necessity of blood transfusion or hemoglobin less than 9 g/dl upon admission
- An INR greater than 1.5
- Patients with ICH secondary to brain aneurysmal rupture
- Patients with a GCS of less than 6
- Thalassemia patients
- Patients with dysregulated iron diseases
- Patients with a history of hepatorenal disorders
- Consumption of iron supplements
- History of stroke in the past three months
- Patients under treatment with anticoagulant injections
- Patients with nervous system disease and disabilities, e.g., parkinsonism and multiple sclerosis

2.1. Sample size

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

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.

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.

2.2. 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.

2.3. Binding

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 double-blinded.

2.4. 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 three days straight, with a maximum daily dosage of 6000 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.

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 Glasgow Outcome Scale, 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 Glasgow Outcome Scale, (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.

Table 1. Glasgow Outcome Scale.

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

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).

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

2.5. Statistical analysis

The compiled data were meticulously documented using IBM SPSSv.23. The results were presented using appropriate descriptive statistics such as mean and standard deviation. For examining qualitative variables, a chi-square test was employed. In contrast, for quantitative variables, a t-test was performed for comparative analysis. A p-value of less than 0.05 was considered significant.

3. Results:

3.1. Descriptive Results

The average age of the participants was 61.18±5.41 years. There were 28 males. Their initial Glasgow Coma Scale (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.

Table 3. Demographics at baseline.

p-value	Groups (n=42)		Variable
	Intervention (n=21)	Control (n=21)	
0.749	62.01±5.55	60.89±5.37	Age
0.669	n=13	n=15	Male
	n=8	n=16	Female
0.859	12.24±1.8	12.24±1.8	Primary GCS
0.653	21.54±5.85	22.02±5.59	Mean
	n=9	n=8	Less than 10
	n=10	n=11	10-30
0.885	n=2	n=2	More than 30
	n=15	n=16	Hypertension
0.693	n=12	n=14	Diabetes mellitus
0.789	n=13	n=12	Smoking
0.851	9.86±3.15	9.31±3.29	Symptom-to-needle time (h)
0.558	n=15	n=13	Anti-coagulant use

Throughout seven days following the intervention, the Glasgow Coma Scale (GCS) of patients was regularly measured and logged every eight hours. The intervention group exhibited a rapid improvement in GCS scores compared to the control group, whose improvement was significantly slower. Figure 1 illustrates the significant differences in the GCS changes between the groups at all measured time points.

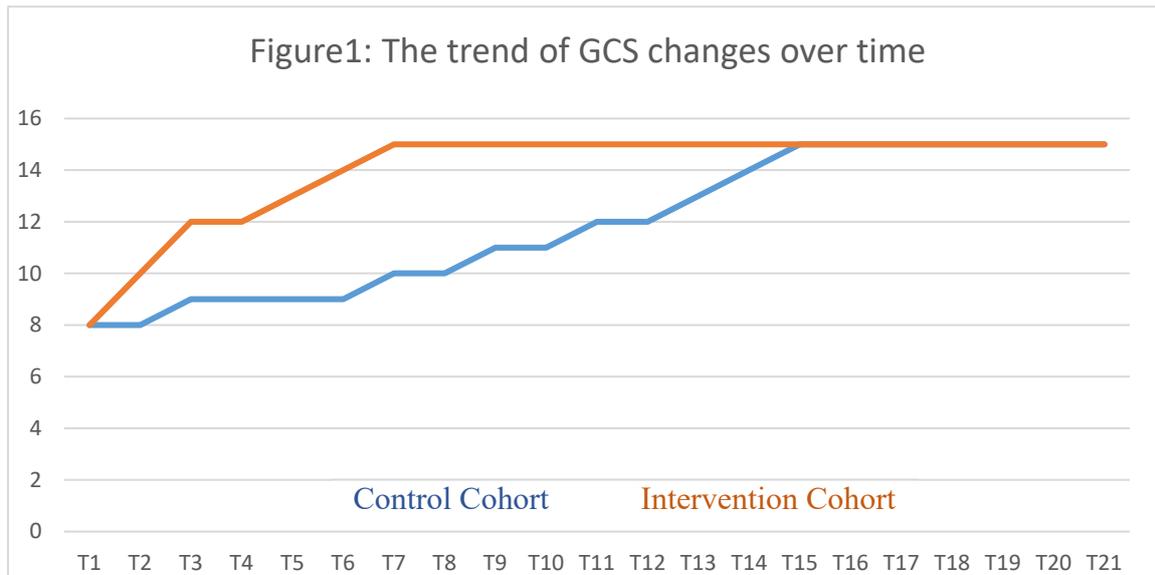


Figure 1. The trend of GCS changes over time.

Table 4 presents the mean differences in the Glasgow Coma Scale (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 four days. However, there was no significant difference in the mean changes from the fourth day onwards.

Table 4. Trend of GCS over 7 days of treatment in the two groups.

p-value	Groups (n=42)		Variable
	Control (n=21)	Intervention (n=21)	
0.859	8.1±1.68	8.4±1.41	Baseline GCS
0.001	9.18±1.96	12.41±1.29	GCS on day 2
0.003	10.29±1.19	15	GCS on day 3
0.009	13.50±1.10	15	GCS on day 4
0.999	15	15	GCS on day 5
0.999	15	15	GCS on day 6
0.999	15	15	GCS on day 7

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 two 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.

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 four in the control group, and this difference was statistically significant ($p=0.033$).

Table 5. Comparison of bleeding volume and brain edema between the two groups.

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

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

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

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

4. Discussion

Our research has yielded valuable insights into the impact of deferoxamine on the treatment of spontaneous Intracerebral Hemorrhage (ICH). 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. (21), Foster et al. (22), and the authors of the i-DEF trial (3) acknowledge the safety and tolerability of deferoxamine mesylate in patients suffering from acute ICH. Furthermore, Keep et al. (11) 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 (CSF) following ICH (14). 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.

Animal models, in particular, have been instrumental in demonstrating that deferoxamine may attenuate brain swelling and neurological deficits. Nakamura et al. (23) 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.

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. (24), 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 (24), 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. (22) 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 (3).

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 (25-27). Moreover, it is essential to monitor serious adverse events (SAEs) that might not be solely attributable to deferoxamine but could also be related to the normal evolution of stroke pathology, such as symptomatic intracranial hemorrhage, early neurological worsening, and mortality (28). In addition, earlier trials, as reported by Selim et al. [3], 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 (29).

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.

5. 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 6000 mg had a significant impact on the short-term radiological and neurological outcomes of spontaneous intracranial hemorrhage. Thus, deferoxamine can be a promising therapeutic option for improving outcomes in patients with spontaneous intracranial hemorrhage.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare that they have no competing interests.

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