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Review article

Deferoxamine in intracerebral hemorrhage: Systematic review and meta-analysis

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ABSTRACT

Background: Intracerebral hemorrhage (ICH) is a stroke with a high morbidity and mortality rate. Deferoxamine (DFX) is thought to be effective in treating Intracerebral Hemorrhage. In our study, we performed a meta-analysis to evaluate the treatment effects of DFX.

Methods: We systematically searched PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, and Chinese Biomedical Literature Database in Jan 2022 for studies on DFX for ICH patients. Outcome measures included relative hematoma volume, relative edema volume, good neurological functional outcome and adverse events. Odds risk (OR) and weighted mean difference (WMD) were used to evaluate clinical outcomes.

Results: After searching 636 articles, 4 RCTs, 2 NRCTs, and 1cohort study were included. We found that DFX was effective in hematoma absorption on day 7 after onset, but the difference was not significant on day 14. DFX could suppress edema expansion on days 3, 7, and 14 after onset. DFX did not contribute to better outcomes after 3 and 6 months when used the modified Rankin Scale and the Glasgow Outcome Scale to evaluate neurological prognosis. The pooled results showed no statistically significant difference in Serious adverse events between the experimental and control groups.

Conclusions: DFX could limit edema expansion on days 3, 7, and 14 after commencement and facilitate hematoma absorption at week 1 without significantly increasing the risk of adverse events, but it did not improve neurological prognosis.

1. Introduction

Intracerebral hemorrhage (ICH) is a common stroke accounting for approximately 15% of all strokes with a high morbidity and mortality rate [1,2]. The hematoma occupancy effect and subsequent secondary brain injury are implicated in ICH damage, which is caused mostly by apoptosis, oxidative stress, inflammation, ferroptosis, and autophagy [3–6]. As yet, no scientifically established specialized therapy or treatment (Phase III) is available [7,8]. Palliative care is still one of the primary therapeutic strategy today, while the fact that the treatment benefit for hematoma expansion and edema reduction is insignificant.

Many studies have proved that perihematomal edema (PHE) is an important factor affecting the prognosis of ICH patients [9–11]. Iron has been shown to play a key role in PHE formation and tissue damage after ICH [11–13]. Following ICH, iron in red blood cells (RBCs) causes damage to brain tissue through various mechanisms [14]. Deferoxamine (DFX) can cross the blood-brain barrier and reduce iron accumulation in nervous tissue, and it has a variety of neuroprotective functions in addition to complexing with iron ions [15,16]. Although multiple trials have found that DFX may be beneficial in ICH, there is a lack of consensus and inadequate quality data from meta-analysis to determine if DFX is useful in avoiding secondary neuronal damage. Thus, we performed a systematic review and meta-analysis to evaluate the efficacy of DFX treatment for ICH patients.

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2. Methods

2.1. Eligibility criteria

Inclusion criteria (1) age > 18; (2) patients with intracerebral hemorrhage confirmed by craniocerebral imaging examination (including patients with parenchymal hemorrhage caused by spontaneous intracerebral hemorrhage and traumatic intracerebral hemorrhage); (3) comparison of deferoxamine and placebo; (4) studies reported related outcomes; (5) studies with full text accessible (6) RCTs, non-RCTs or cohort studies.

Exclusion criteria (1) age < 18; (2) allergic to deferoxamine; (3) patients who plan to undergo surgical intervention; (4) patients with bleeding caused by tumor, aneurysm rupture or arteriovenous malformation; (5) patients with deep coma and bilateral dilated pupils; (6) use of anticoagulant drugs or abnormal coagulation function; (7) patients received iron supplements recently; (8) poor patient compliance.

2.2. Search strategy and study selection

We comprehensively searched in PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, the Chinese Biomedical Literature Database, and Clinical Trials.gov until Jan 2022. The following search terms were used: Deferoxamine, Intracerebral Hemorrhage, Cerebral Hemorrhage. The relevant articles were all screened to avoid omitting. Two independent reviewers conducted searches and literature screening (TS and YZ), and disputes were resolved by consensus after discussions with a third author (QX).

2.3. Data collection and quality assessment

All eligible studies were independently searched and extracted by three investigators (TS, YZ and MW). The following information was extracted: title, author, year and country of publication, study design, sample size, sex, age, duration of follow-up, outcome measures, and intervention details. Disagreements were resolved through a discussion with an investigator (QX).

We assessed the quality of each included study. For RCTs, we used the criteria outlined in the Cochrane Handbook [17], which includes seven domains (random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other bias). For observational studies, we used the Newcastle Ottawa Scale for quality assessment. For non-randomized controlled trials (non-RCTs), we used the Methodological Index for non-randomized studies (MINORS) [18]. All non-RCTs were propensity-matched case-control studies. Disagreements in the process of quality assessment were resolved by discussion or by a third investigator (QX).

2.4. Outcome measures

The primary objectives were to assess the efficacy of DFX for hematoma and edema absorption. The secondary objectives were to assess whether DFX can improve neurologic outcomes after ICH. Good neurological function outcome was defined as Glasgow Outcome Score (GOS)≥ 4, modified Rankin Scale (mRS) score≤ 3.

2.5. Statistical analysis

We conducted the analysis using the Review Manager 5.4 software. To evaluate the effect of deferoxamine on ICH, we calculated the weighted mean difference (WMD) for continuous variables and the odds ratio (OR) as the evaluation index for dichotomous variables, and displayed the results in a forest plot style (95% confidence interval (CI) was calculated). If there was significant heterogeneity (I2 > 50% or p < 0.10), we used the random-effects model. Otherwise, we use the fixed effects model.

3. Results

3.1. Search results, study characteristics, and quality assessment

We systematically searched articles published before Jan 2022 and identified 636 articles in total that were related to this topic. After removing the duplicate and irrelevant reports, 17 reports were included. After the full-text review, we excluded 10 records. Finally, 7 studies were selected for inclusion in the final analysis. The PRISMA flow diagram of the study selection process is plotted in Fig. 1, and the characteristics of studies included in the meta-analysis are shown in Table 1. The results of the quality evaluation of the included studies are listed in Table 2, Table 3 and Fig. 2.

3.2. Relative hematoma absorption

We define the relative absorption of hematoma to reflect the absorption of hematoma. For example, the 3rd-day relative hematoma absorption = (initial hematoma – 3rd-day hematoma)/ initial hematoma. Five of the seven studies we collected reported DFX absorption of cerebral hematoma. Among them, the relative hematoma absorption at 1 and 2 weeks could be combined. Yu Yao [10] reported that DFX could inhibit hematoma absorption. Gang Wu [19], Chengying Xiong [20], Jian Yu [21], and Fulin Xu [22] reported that DFX can promote the absorption of hematoma. After data combination analysis, we found that DFX promoted hematoma absorption at 1 week (MD, −0.17; 95%CI, −0.30 to −0.04; P = 0.01), while there was no obvious therapeutic effect at 2 weeks (MD, −0.08; 95%CI, −0.25 to 0.08; P = 0.32). Fig. 3.

3.3. Relative edema volume

We defined relative edema volume as the absolute edema volume/ hematoma volume and absolute edema volume is the volume of edema excluding the hematoma. Data of relative edema were combined at 3 days, 1 week, and 2 weeks in 5 studies [10,19–22]. We found that the relative edema of the experimental group was less than that of the control group at 3 (MD, −0.46; 95%CI, −0.67 to −0.24; P < 0.0001), 7 (MD, −0.42; 95%CI, −0.55 to −0.28; P < 0.00001) and 14 days (MD,

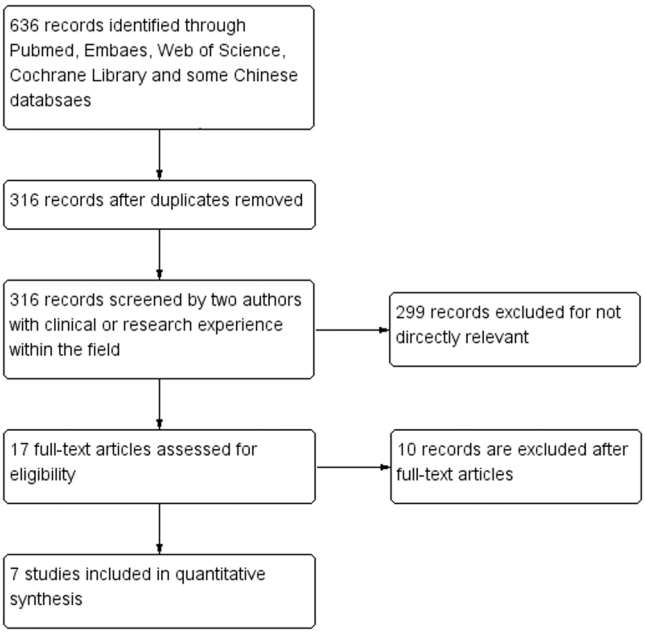

Fig. 1. PRISMA flow diagram of the study selection process.

Table 1
Characteristics of included studies.

Study	Design	Patients	M/F	Age		Experimental Intervention	Relative hematoma absorption	Relative edema volume	Neurological outcome
				Experimental group	Control group				
Yao Yu 2015	RCT	42	NM	64.2 ± 9.5	60.1 ± 8.7	32 mg/kg/d for 3 days	8 and 15 days	1, 4, 8 and 15 days	15 and 30 days mRS and GOS, 8, 15 and 30 days NIHSS
Sharon D. Yeatts 2013	RCT	41	26/15	64 (35–77)*	64 (43–77)*	62 mg/kg/d for 5 days	NR	NR	3 months mRS
Magdy Selim 2019	RCT	291	179/112	59 (51–71)#	62 (54–70)#	32 mg/kg/d for 3 days	NR	NR	3 and 6 months mRS
Chengying Xiong 2018	RCT	113	63/50	59.7 ± 2.7	60.0 ± 3.3	20 mg/kg/d for 3 days	7 and 14 days	7 and 14 days	7 and 14 NIHSS
Gang Wu 2014	Cohort study	29	22/7	60.8	56.8	20 mg/kg/d for 3 days	7 and 14 days	1, 3 and 7 days	7, 15 days and 3 months NIHSS
Jian Yu 2017	non-RCT	94	69/25	53.4 ± 14.1	52.3 ± 17.2	20 mg/kg/d for 5 days	3, 7 and 14 days	3, 7 and 14 days	6 months GOS
Fulin Xu 2019	non-RCT	90	63/27	73.6 ± 10.0	74.5 ± 9.62	20 mg/kg/d for 5 days	7 and 14 days	7 and 14 days	6 months GOS

RCT: randomized controlled trial; non- RCT: non-randomized controlled trials; M/F=Male/Female; NR: not reported; mRS: modified Rankin scale; GOS: Glasgow Outcome Scale; NIHSS: National Institute of Health stroke scale.
* Median (Full Range); # Median (Interquartile Range);

Table 2
Quality assessment by the Newcastle Ottawa Scale (NOS) for cohort studies.

Study	Selection				Comparison	Outcome			Scores
	Exposed Cohort	Nonexposed Cohort	Ascertainment of Exposure	Outcome of Interest		Assessment of Outcome	Length of Follow-Up	Adequacy of Follow-Up	
Gang Wu 2014	1	1	1	1	1	1	1	1	8

Table 3
Quality assessment by the Methodological Index for non-randomized studies (MINORS) for non-randomized controlled studies.

Study	Item								Additional criteria in the case of comparative study				Scores
	A	B	C	D	E	F	G	H	I	J	K	L	
Jian Yu 2017	2	2	2	2	1	2	2	2	2	2	2	2	23
Fulin Xu 2019	2	2	2	1	1	2	2	1	2	2	2	2	21

A, A clearly stated aim; B, Inclusion of consecutive patients; C, Prospective collection of data; D, Endpoints appropriate to the aim of the study; E, Unbiased assessment of the study endpoint; F, Follow-up period appropriate to the aim of the study; G, Loss to follow up less than 5%; H, Prospective calculation of the study size; I, An adequate control group; J, Contemporary groups; K, Baseline equivalence of groups; L, Adequate statistical analyses.

−0.33; 95%CI, −0.61 to −0.05; P = 0.02). Fig. 4.

3.4. Favorable neurological outcomes

Neurological outcome was assessed by the modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS). We defined the favorable neurological outcome with several related rating scales (mRS≤3, GOS≥4). The outcome of the three studies [10,23,24] was evaluated by mRS at 3 months, and there was no statistical difference after combined analysis (OR, 0.83; 95%CI, 0.54–1.26; P = 0.38). Two studies [21,22] used GOS to evaluate the outcome at 6 months and one study [23] used mRS. The pooled analysis showed no statistical difference (OR, 1.13; 95%CI, 0.73–1.73; P = 0.58). Fig. 5.

3.5. Adverse events

Some adverse events were not reported consistently across the included studies. Therefore, we only analyzed certain important adverse events (such as the number of subjects experiencing Serious adverse events at any time from receiving treatment through day 90) with adequate data. Two studies [23,24], consisting of 333 patients, reported infections. The pooled results showed no statistically significant difference in Serious adverse events between the experimental and control groups (OR, 0.84; 95%CI, 0.53–1.34; P = 0.47). Fig. 6.

4. Discussion

In this meta-analysis, we evaluated the clinical efficacy of DFX for the treatment of ICH. A total of 4 RCTs, 2 non-RCTs, and 1 observational study were included. All the non-RCTs used "propensity score matching". Based on this, we found that: 1) edema in ICH patients treated with DFX was well controlled within 2 weeks compared to placebo. 2) Meanwhile, no obvious effect of DFX increases the risk of serious adverse events. 3) The presence or absence of DXF has no effect on neurological function.

After ICH, hemoglobin is released into the brain during the breakdown of red blood cells, and cell-free hemoglobin and its breakdown products are neurotoxic and induce secondary brain damage [6,25,26]. The toxicity of hemoglobin is multifactorial and mainly seems to be mediated by four factors: oxidation, inflammation, nitric oxide scavenging, and edema. Iron, a major hemoglobin degradation product, plays a key role in edema formation and cell death after ICH [27,28]. Prominently, the mechanism of iron toxicity includes generating free radicals and directly compromising the neighboring brain cells [3,29]. Reactive oxygen species (ROS) can directly or indirectly damage all biomolecules, including proteins, lipids, deoxyribonucleic acid, and

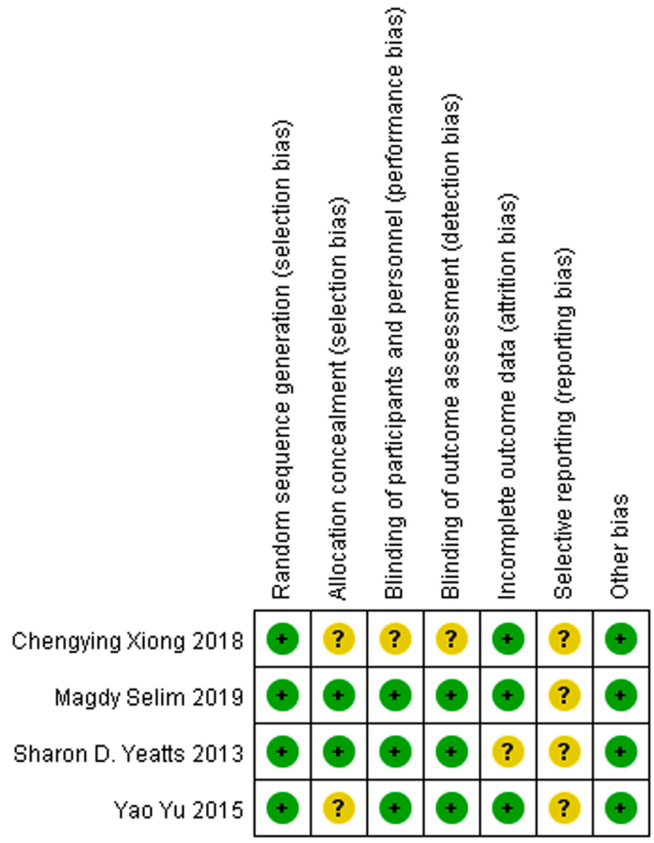

Fig. 2. Risk of bias summary.

carbohydrates [29]. Thus, the quest for routes that regulate iron absorption and facilitate iron elimination could have significant clinical ramifications. DFX, a Food and Drug Administration-approved drug for the treatment of acute iron intoxication and chronic iron overload due to transfusion-dependent anemias, has been proven to mitigate the neurotoxic effects of hemoglobin [30,31], which acts primarily through crossing the blood-brain barrier and chelating iron ions to decrease of iron accumulation in nerve tissue.

In the present study, DFX promoted the absorption of hematoma on day 7 after ICH onset, but not on day 14. According to our analysis, Y Yu [10] showed that DFX promoted hematoma absorption both on day 7 and day 14. However, Chy Xiong [20], Fl Xu [22], and G Wu [19] have reported that DFX can promote hematoma absorption. J Yu [21] reported statistically showed significant difference in hematoma absorption at 7 days, while there was no significant difference between the experiment and the control group at 14 days. This meta-analysis was significantly heterogeneous due to differences in dosage, duration, and other factors involved in the study. Due to limited studies, we were unable to conduct sensitivity analysis. Therefore, further studies are required to be included in future meta-analyses. In his research, Fulin Xu used the method of propensity matching (PSM). Propensity matching can control the influence of confounding factors to achieve the effect of randomized control. The propensity score matching (PSM) could mimic a randomized clinical trial (RCT) in which the effect of a therapy is evaluated by comparing the outcomes of treated and control subjects belonging to the matched sample [32]. In summary, we believe that DFX may promote hematoma absorption on day 7, while DFX treatment has no obvious advantage on day 14. In addition, the dosage and duration of DFX were different in the included studies. Therefore, further studies are needed to verify whether DFX with different doses and duration has different effects on hematoma absorption.

Besides, our study shows that DFX inhibited edema expansion on days 3, 7, and 14 after ICH. There are three stages of cerebral edema after intracerebral hemorrhage. The first stage is the early hydrostatic pressure and clot retraction, and the blood from the clot enters the surrounding tissues. The second stage is related to coagulation cascade reaction and thrombin production. The third stage is associated with erythrocyte lysis and hemoglobin toxicity. Meanwhile, another important cause of cerebral edema after intracerebral hemorrhage is the

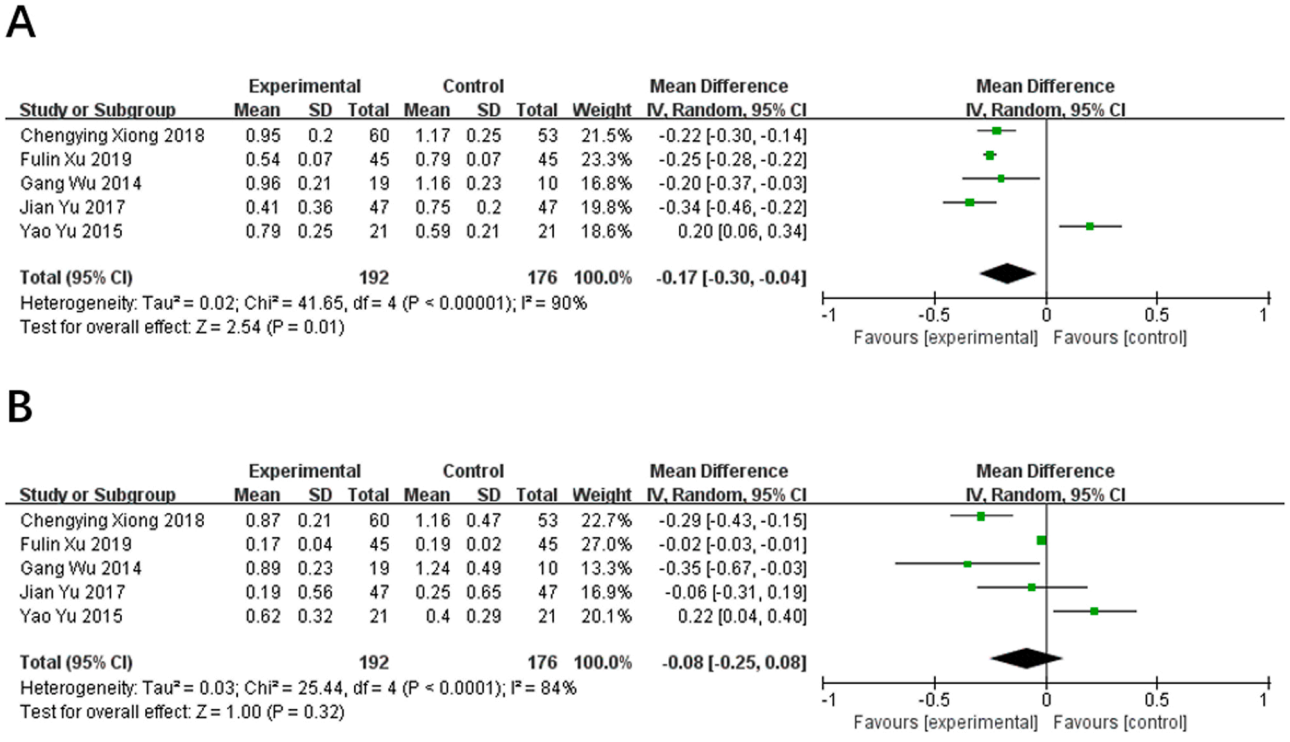

Fig. 3. Forest plot of relative hematoma absorption. (A) 7 days after onset. (B) 14 days after onset.

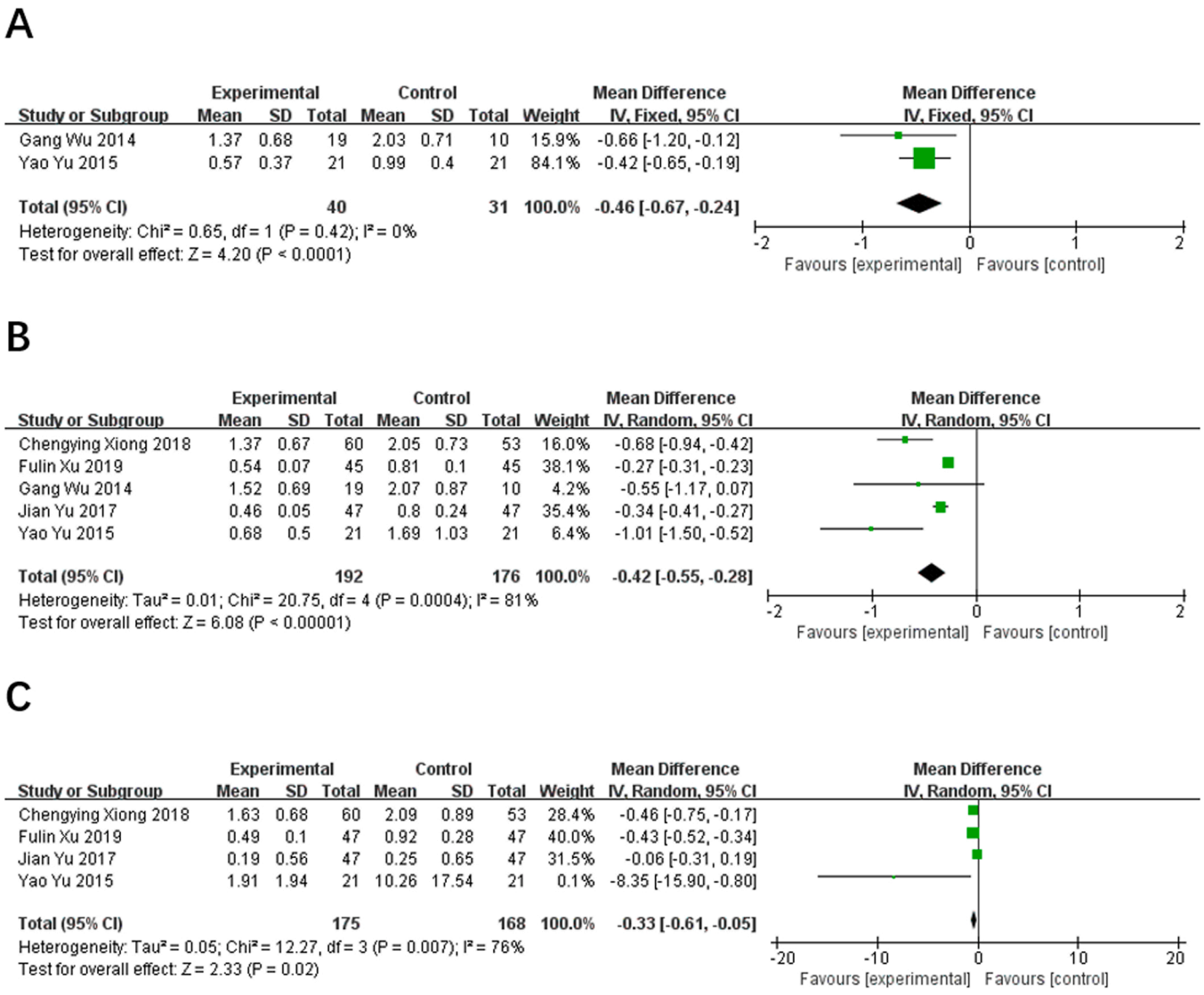

Fig. 4. Forest plot of relative edema volume. (A) 3 days after onset. (B) 7 days after onset. (C) 14 days after onset.

destruction of the blood-brain barrier and the increase of permeability [33]. The breakdown product of hemoglobin, heme, is degraded in the brain by the enzyme heme oxygenase to iron, carbon monoxide, and bilirubin, which can cause brain damage. In addition, the degradation of hemoglobin can damage the blood-brain barrier, causing brain edema. Therefore, DFX can reduce brain damage by reducing the amount of iron in brain tissue [11,33]. All of the studies we included reported DFX for the control of cerebral edema after ICH. In summary, our meta-analysis showed that DFX controlled the expansion of cerebral edema on days 3, 7, and 14 after ICH.

DFX had little effect on the favorable neurological outcome in the short term. We defined the favorable neurological outcome with several related rating scales (mRS≤3, GOS≥4). The mRS ranges from 0 to 6, with higher scores indicating worse outcome. We defined the good functional outcome as mRS 0–3 using a dichotomy. The GOS scale is from 1 to 5, with a higher score indicating better results. We defined good functional outcome as GOS≥ 4 using dichotomy. The meta-analysis showed that DFX did not improve neurological outcome in ICH patients at either 3 or 6 months. DFX has been shown to improve neurological outcomes in many animal studies [34,35]. Therefore, we believe that there may be the following reasons for the difference in therapeutic effect between clinical trials and animal trials: (1) The location of intracerebral hemorrhage may have a greater impact on the prognosis of the patient's neurological function. In animal experiments, the interference of the bleeding site can be excluded because of the same hematoma site. However, in clinical trials, the location of patients' hematoma is uncertain, which may obscure the therapeutic effect of DFX. (2) Differences in DFX dose, time, and route of administration may result in differences. In animal-model experiments, it is usually given intramuscularly or intraperitoneally. The clinical trial was administered intravenously with DFX. It may be that BEFORE iron is produced in brain tissue, DFX has already been metabolized by the kidney, which reduces the therapeutic effect of DFX chelate iron.

Deferoxamine (DFX) is a potentially nonsurgical effective drug for the treatment of cerebral hemorrhage. However, the efficacy and safety of DFX as a therapy for intracerebral hemorrhage were not identical among the existing literature. Iron, as a metabolite produced by erythrocyte lysis after cerebral hemorrhage, may play a significant role in the etiology and disease progression of intracerebral hemorrhage. It is a metabolite produced by erythrocyte lysis after cerebral hemorrhage. Preclinical studies suggested that iron accumulates in the brain after experimental ICH, which iron-mediated toxicity leads to delayed cellular injury and neurological deficits through iron-mediated toxicity, and then treatment with deferoxamine (DFX) attenuates neuronal death and improves recovery after ICH in different species. In the present study, we found that DFX has shown favorable efficacy in reducing

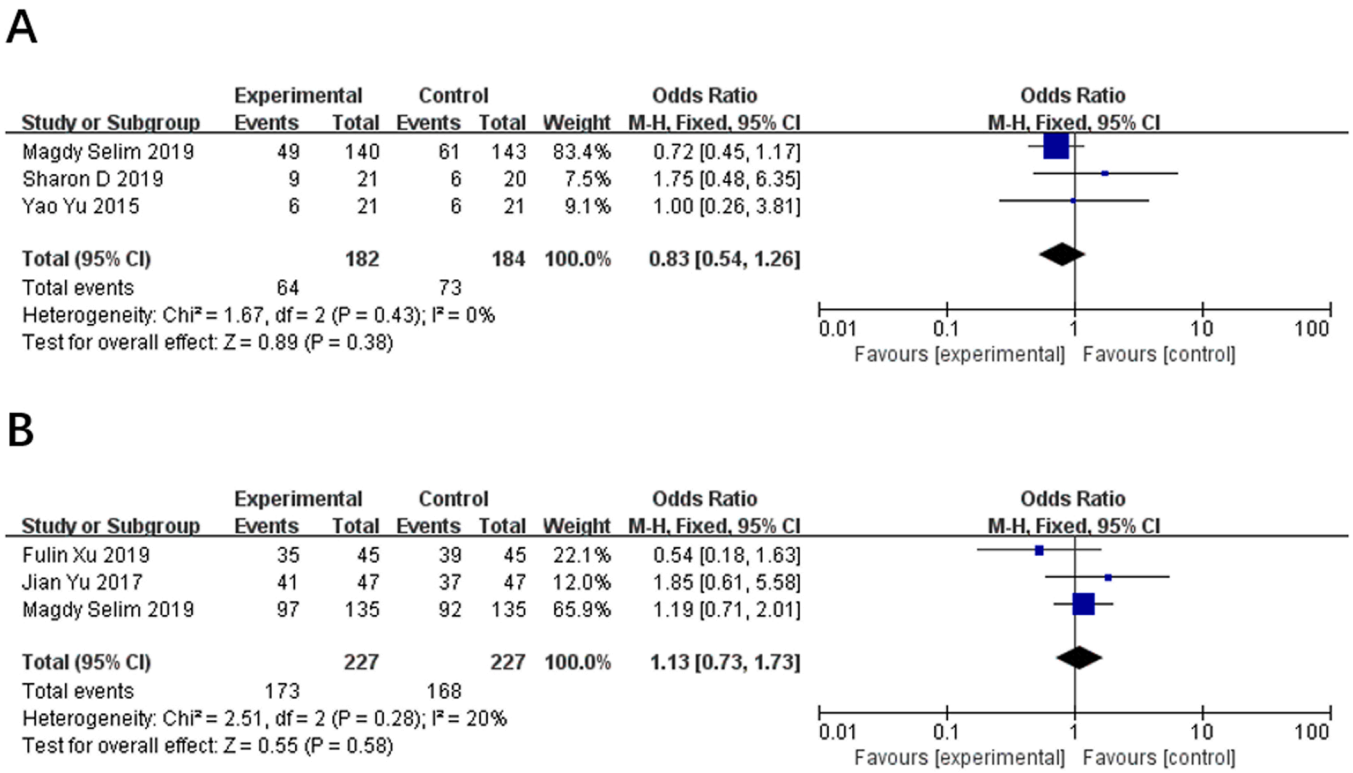

Fig. 5. Forest plot of favorable neurological outcomes. (A) 3 months after onset. (B) 6 months after onset.

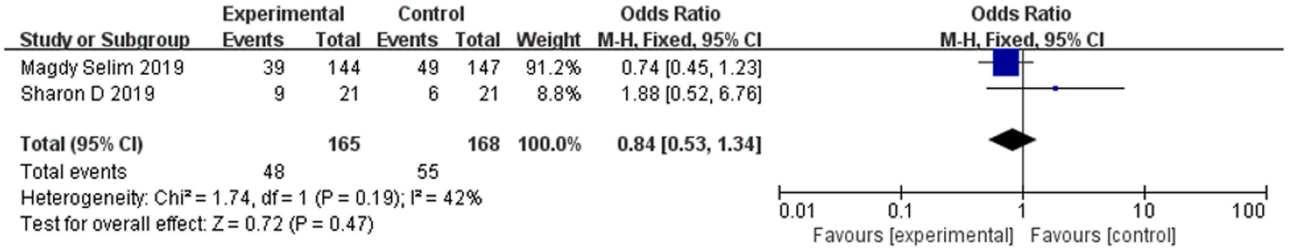

Fig. 6. Forest plot of adverse Events.

hematoma and edema, while it may not act satisfactorily on neurological function. Nowadays, there are several differences exist in current studies: 1) Drug dose; 2) Duration of medication; 3) Unified criteria for evaluating drug effectiveness. It is hoped that future studies will address these questions and determine the effectiveness of the drug. While DFX has been shown to be effective in laboratory animals, the road ahead is long and hard in the efficacy for all patients with ICH.

We believe that the impairment of neurological functions is related to the hemorrhage and edema after ICH, but the hemorrhagic portion of the brain appears to have a stronger impact on patient prognosis. If the hemorrhage is located in the basal ganglia region, especially on the left side, it will have much worse effect on the patient's neural function, including language and motor function, than other part hemorrhage. If the hemorrhage is located in the frontal lobe, the patient may only show symptoms such as headache, dizziness and personality changes, which will not cause serious consequences for the patients' later life. In different patients, the hemorrhage location in the brain is not fixed, so these may hide the treatment effect of DFX. We are wondering if we can design subgroups in clinical trials to differentiate between different hemorrhage sites. This would be used to exclude the prognostic impact of differences in the site of cerebral hemorrhage. This would provide more clarity on whether DFX would provide a benefit to the patient.

4.1. Limitations

Our research still has several limitations. First, not all included studies were randomized controlled studies, which may increase the risk of bias and reduce the veracity of the results. Second, DFX is administered at different doses and durations, which may skew the results. In the end, the number of studies included was small, which would lead to statistical deviation. Therefore, larger, multicenter, high-quality randomized controlled trials are needed to validate our results.

5. Conclusion

DFX could limit edema expansion on days 3, 7, and 14 after commencement and facilitate hematoma absorption at week 1 without significantly increasing the risk of adverse events, but it did not improve neurological prognosis.

Ethics approval

Not applicable.

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CRediT authorship contribution statement

T Sun, YY Zhao, MY Luo, QX Xiao, M Wu were major contributors in conceiving and writing the manuscript. T Sun, YY Zhao wrote the paper with input from all authors. T Sun, YY Zhao and MY Luo conceived the study and were in charge of overall direction and planning. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Consent to participate

Not applicable.

Consent for publication

Not applicable.

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