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Iron chelators for acute stroke (Review)

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[Intervention Review]

Iron chelators for acute stroke

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ABSTRACT

Background

Stroke is the second leading cause of death and a major cause of morbidity worldwide. Retrospective clinical and animal studies have demonstrated neuroprotective effects of iron chelators in people with haemorrhagic or ischaemic stroke. This is the first update of the original Cochrane Review published in 2012.

Objectives

To evaluate the effectiveness and safety of iron-chelating drugs in people with acute stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (2 September 2019), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2019, Issue 9; 2 September 2019), MEDLINE Ovid (2 September 2019), Embase Ovid (2 September 2019), and Science Citation Index (2 September 2019). We also searched ongoing trials registers.

Selection criteria

We included randomised controlled trials (RCTs) of iron chelators versus no iron chelators or placebo for the treatment of acute stroke, including subarachnoid haemorrhage.

Data collection and analysis

Two review authors independently screened the search results. We obtained the full texts of potentially relevant studies and evaluated them for eligibility. We assessed risk of bias using the Cochrane 'Risk of bias' tool, and the certainty of evidence using the GRADE approach.

Main results

Two RCTs (333 participants) were eligible for inclusion; both compared the iron-chelating agent deferoxamine against placebo. Both studies evaluated participants with spontaneous intracerebral haemorrhage. We assessed one study to have a low risk of bias; the other study had potential sources of bias.

The limited and heterogeneous data did not allow for meta-analysis of the outcome parameters. The evidence suggests that administration of deferoxamine may result in little to no difference in deaths (8% in placebo vs 8% in deferoxamine at 180 days; 1 RCT, 291 participants; low-certainty evidence). These RCTs suggest that there may be little to no difference in good functional outcome (modified Rankin Scale

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score 0 to 2) between groups at 30, 90 and 180 days (placebo vs deferoxamine: 67% vs 57% at 30 days and 36% vs 45% at 180 days; 2 RCTs, 333 participants; low-certainty evidence). One RCT suggests that administration of deferoxamine may not increase the number of serious adverse events or deaths (placebo vs deferoxamine: 33% vs 27% at 180 days; risk ratio 0.81, 95 % confidence interval 0.57 to 1.16; 1 RCT, 291 participants; low-certainty evidence). No data were available on any deaths within the treatment period. Deferoxamine may result in little to no difference in the evolution of National Institute of Health Stroke Scale scores from baseline to 90 days (placebo vs deferoxamine: 13 to 4 vs 13 to 3; P = 0.37; 2 RCTs, 333 participants; low-certainty evidence). Deferoxamine may slightly reduce relative oedema surrounding intracerebral haemorrhage at 15 days (placebo vs deferoxamine: 1.91 vs 10.26; P = 0.042; 2 RCTs, 333 participants; low-certainty evidence). Neither study reported quality of life.

Authors' conclusions

We identified two eligible RCTs for assessment. We could not demonstrate any benefit for the use of iron chelators in spontaneous intracerebral haemorrhage. The added value of iron-chelating therapy in people with ischaemic stroke or subarachnoid haemorrhage remains unknown.

PLAIN LANGUAGE SUMMARY

Drugs for reducing iron in people with acute stroke

Background

Brain damage after stroke is complex, and consists of both direct and delayed damage. A disturbance in local iron levels may be linked to delayed brain damage. Therefore, limiting iron toxicity is a potential target in the treatment of people with stroke. Iron-chelating drugs are able to bind excess iron in blood and in local tissue, and may reduce iron accumulation and iron-related brain injury. In animal studies, iron-chelating drugs have been shown to protect brain cells after occurrence of stroke.

Search date

The updated search was performed on 2 September 2019.

Study characteristics

We identified two trials, with 333 participants in total, which investigated the effectiveness on good clinical outcome of iron chelation therapy with deferoxamine for acute stroke. Both trials studied the effect in people who had bleeding in the brain, a subset of acute stroke.

Key results

With the limitation that studies could not be pooled, the data did not show any difference in good neurological outcome between groups. Both studies reported that administration of deferoxamine was safe. Oedema formation around the haematoma was slightly reduced in the deferoxamine group in one study, but not in the other.

Certainty of the evidence

The certainty of the evidence for the use of deferoxamine for the improvement of neurological outcome in spontaneous intracerebral haemorrhage is low. This is based on two small studies with short follow-up, and with differences in outcome measurement. Limited evidence was available regarding side effects. The added value of iron-chelating therapy in people with ischaemic stroke or subarachnoid haemorrhage remains unknown.

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SUMMARY OF FINDINGS

Summary of findings 1. Iron chelator versus placebo for adults with acute stroke

Iron chelator versus placebo for adults with acute stroke

Patients or population: adults with acute stroke

Settings: hospitals and clinical centres

Intervention: deferoxamine

Comparison: placebo

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Deferoxamine				
Death from all causes at end of scheduled follow-up	180 days		P = 0.959	291 (1 RCT)	Low[a]	Yu 2015 did not describe any deaths.
	8% (12/144)	8% (12/147)				
Good neurological outcome (mRS 0 to 2) (follow-up: 30 to 180 days)	30 days		Not estimable	333 (2 RCTs)	Low[b]	One small study had a follow-up of 30 days (Yu 2015), and one larger study had follow-up at 90 and 180 days (Selim 2019).
	67% (14/21)	57% (12/21)				
	90 days					
	33% (47/143)	34% (48/140)				
	180 days					
	36% (48/135)	45% (61/135)				
Serious adverse events (SAE)	180 days		RR 0.81 (0.57 to 1.16)	291 (1 RCT)	Low[a]	Yu 2015 found no SAEs and did not assess general adverse effects. Selim 2019 described one drug-related SAE (ARDS).
	33% (49/147)	27% (39/144)				

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Any deaths within the treatment period	No data available	-	-	-	Selim 2019 and Yu 2015 did not report on deaths within the treatment period.
Neurologic impairment scale at baseline and at the end of follow-up (NIHSS)	baseline mean (SD) to 30 days mean (SD) 8.7 (5.4) to 2.8 (4.0) 9.1 (4.6) to 3.2 (3.6)	Not estimable	333 (2 RCTs)	Low[c]	Yu 2015 reported average NIHSS and standard deviations at baseline and at 30 days. No statistical tests were performed. Selim 2019 reported median NIHSS and interquartile range at baseline and at 90 days and tested for significance.
	baseline (median (IQR) to 90 days (median (IQR) 13 (9 to 19) to 4 (2 to 7) 13 (8 to 17) to 3 (1 to 7)	P = 0.37			
Relative oedema volume	Postinfusion scan[d] median (IQR) 0.7 (0.3 to 1.2) 0.9 (0.4 to 1.3)	Not estimable	333 (2 RCTs)	Low[c]	Selim 2019 and Yu 2015 defined relative oedema volume as absolute oedema volume dived by haematoma volume. Selim 2019 reported median changes in perilesional oedema and interquartile ranges. Yu 2015 reported average changes and standard deviations at 15 days.
	15 days, mean (SD) 1.91 (1.94) 10.26 (17.54)	P = 0.042			
Quality of life	No data available	-	-	-	Selim 2019 and Yu 2015 did not report on quality of life.

*The basis for the **risk in the control group** (e.g. the median control group risk across studies) is provided in footnotes. The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ARDS: acute respiratory distress syndrome; **CI:** confidence interval; **DFO:** deferoxamine; **IQR**: interquartile range; **mRS**: Modified Rankin Scale; **NIHSS:** National Institutes of Health Stroke Scale; **RCT**: randomised controlled trial; **RR**: risk ratio; **SAE**: serious adverse event; **SD:** standard deviation.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by two levels for imprecision because of low number of studies with small sample size.
[b]Downgraded by two levels for imprecision because of low number of studies with small sample size and non-congruent follow-up times.
[c]Downgraded by two levels for imprecision because of low number of studies with low sample size, non-congruent follow-up times and non uniformity in reporting.
[d]Time of measurement varied slightly between the control group (73 h, IQR 69 to 78) and the experimental group (74 h, IQR 69 to 78).

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BACKGROUND

Description of the condition

Stroke is the second leading cause of death and a major cause of morbidity worldwide (Global Burden of Disease Study 2019). Significant research efforts have been undertaken to develop pharmaceutical therapies for stroke, but only a few have revealed drugs that improve the prognosis of people who have had an acute stroke. In ischaemic stroke, tissue plasminogen activator (tPA) resolves clots and restores blood flow, but is only safe and beneficial if administered within a short therapeutic window (Wardlaw 2014). Secondary prophylaxis with antiplatelet therapy improves the prognosis of people with acute ischaemic stroke by preventing the formation of new clots (Sandercock 2008). In subarachnoid haemorrhage (SAH), the calcium antagonist nimodipine has been shown to reduce the risk of poor outcome and secondary ischaemia (Dorhout Mees 2007). There is no pharmacological agent showing benefit in spontaneous intracerebral haemorrhage (ICH). Because of these limited therapeutic options, identification of new treatments to improve the clinical outcome of people with acute stroke is of great importance, both on a personal and public health level.

In the last two decades, disturbances in iron homeostasis have been implicated as a contributing factor to neural damage following stroke. Free iron catalyses conversion of H_2O_2 and O_2^- into highly reactive and toxic hydroxyl radicals (the Haber-Weiss reaction), leading to a cascade of oxidative stress and cell death by apoptosis (Carbonell 2007; Selim 2004). Haemoglobin degradation products resulting from thrombolysis and haemolysis after stroke cause an iron overload and catalyse the Haber-Weiss reaction sequence, with neurotoxic effects (Goldstein 2003). In ICH and SAH, haemoglobin degradation products exert the same effects.

Iron overload is also causally linked with endothelial damage (Duffy 2001), lipid peroxidation of the cell membrane (Ishimaru 1996), brain oedema (Huang 2002), larger infarct volumes (Castellanos 2002), diabetes (Salonen 1998), inflammatory response exacerbation and ischaemic reperfusion injury following stroke (Mehta 2002). Clinical research also reveals that high serum ferritin levels are independently associated with poor outcome after ischaemic stroke (Millan 2007), and after ICH (Pérez de la Ossa 2010).

Description of the intervention

Iron-chelating drugs have been widely used for more than 40 years in people with iron overload diseases, such as haemochromatosis, thalassaemia, and sickle cell disease. These drugs bind excess iron and may reduce iron-induced brain damage. Bound iron is inert and cannot perform in chemical reactions that lead to neurotoxic events (Selim 2009). The pharmacodynamics and pharmacokinetics of iron chelators are well known, since these drugs have been used safely for more than 40 years (Prabhu 2009).

Animal stroke models have demonstrated that iron chelators exert a neuroprotective effect, and preclinical research suggests that iron chelation can prevent damage from ischaemic stroke (Hanson 2009), ICH (Nakamura 2004), and SAH (Arthur 1997, Lee 2010).

How the intervention might work

Iron-chelating drugs work to bind excess iron in the blood and local tissues. The generation of hydroxyl radicals in the Haber-Weiss reaction leads to extraction of hydrogen from unsaturated lipids in the cell membrane, and initiates lipid peroxidation (Carbonell 2007; Halliwell 1984; Selim 2004). Additionally, it can exacerbate excitotoxicity by increased intracellular iron accumulation (Dávalos 2000; Regan 1996). Iron-chelating drugs can chelate ferric ion (Fe3+) and haemosiderin to form a stable and inert complex that prevents iron from entering the Haber-Weiss reaction. As such, these drugs limit iron overload and iron-mediated toxicity secondary to acute stroke (Selim 2009).

The most studied iron chelator is deferoxamine (DFO). In acute ischaemic stroke animal models, this drug has been shown to induce tolerance against cerebral ischaemia (Prass 2002), reduce brain swelling (Xing 2009), decrease ischaemic volume (Li 2008), and reduce reperfusion injury (Hatcher 2009). In acute haemorrhagic stroke animal models, DFO can reduce brain oedema (Nakamura 2004), neurologic deficits (Gu 2009), and brain atrophy (Okauchi 2010). In animal models of SAH, DFO reduces cerebral vasospasm and delayed cerebral ischaemia (Lee 2010). In addition, iron chelators (DFO and deferasirox) also have the effect of neuroprotection and neurorepair in vitro (Dexter 2011; Zaman 1999; Zhao 2011).

Why it is important to do this review

Despite the growing evidence from in vitro and animal models that has demonstrated the beneficial effect of iron-chelating therapy in acute stroke, clinical evidence is still insufficient. A systematic analysis of all randomised controlled trials (RCTs) of iron chelation therapy for acute stroke is needed. Because of the high and increasing incidence of stroke, and its associated burden of disease and excessive costs, even a small improvement in favourable outcomes could have a major impact on health care. This is the first update of the original Cochrane Review published in 2012 (Ma 2012).

OBJECTIVES

To evaluate the effectiveness and safety of iron-chelating drugs in people with acute stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished RCTs of iron chelator versus no iron chelator (or placebo) for the treatment of acute ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage were eligible for inclusion.

Types of participants

We included participants of any age or sex with clinically diagnosed acute ischaemic stroke (cerebral infarction) or haemorrhagic stroke (ICH or aneurysmal subarachnoid haemorrhage).

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Types of interventions

The intervention of interest was iron chelator versus no iron chelator or placebo, administered in any dose, by any route, for any duration and started within 48 hours after acute stroke.

Types of outcome measures

Primary outcomes

- Death from all causes at end of scheduled follow-up
- Good functional outcome: either no significant disability or slight disability with independence for assistance (dependency assessed at least one month after acute stroke)

We defined independence as not being dependent on others for activities of daily living, for example having a Glasgow Outcome Scale (GOS) score of more than four (Jennett 1975), modified Rankin Scale (mRS) score of zero to two, and Barthel Index of 60 to 100 (Sulter 1999). We used a minimum interval of one month to allow time for recovery from the initial stroke.

Secondary outcomes

- Any complications and (serious) adverse events (AEs) during the treatment and follow-up periods (e.g. death, recurrent ICH or embolism, acute respiratory distress syndrome (ARDS), anaemia, unexplained worsening of neurologic status, hepatic or renal dysfunction, allergic reactions, phlebitis and hypotension).
- Any deaths within the treatment period
- Neurologic impairment scale at follow-up periods (e.g. the National Institute of Health Stroke Scale (NIHSS), Canadian Neurological Scale, European Stroke Scale or the Scandinavian Stroke Scale; or any other scale that involves motor, sensory or other impaired neurologic function)
- Oedema volume surrounding haematoma or infarction
- Quality of life, if assessed by the included trials

Search methods for identification of studies

See the methods for the Cochrane Stroke Group Specialised register.

Electronic searches

We searched the following electronic databases.

- Cochrane Stroke Group Trials Register (last searched 2 September 2019)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 9) in the Cochrane Library (last searched 26 August 2019) (Appendix 1)
- MEDLINE Ovid (from 1950; last searched 2 September 2019) (Appendix 2)
- Embase Ovid (from 1980; last searched 2 September 2019) (Appendix 3)
- Web of Science: Science Citation Index Expanded (SCIEXPANDED) (last searched 2 September 2019) (Appendix 4)

We developed the MEDLINE search strategy using a combination of controlled vocabulary and free-text terms with the help of the Cochrane Stroke Group Information Specialist and adapted it for the other databases. Where necessary, we combined these with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials, as described in the Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019).

We also searched the following ongoing trials registers (last searched 2 September 2019):

- Clinicaltrials.gov (clinicaltrials.gov) (Appendix 5);
- ISRCTN Registry (www.isrctn.com);
- Internet Stroke Center: The Stroke Trials Registry (www.strokecenter.org/trials);
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch) (Appendix 6).

Searching other resources

In an effort to identify published, unpublished and ongoing trials, we:

- checked the reference lists of all relevant papers; and
- contacted researchers and study authors if necessary.

Data collection and analysis

Selection of studies

Two review authors (LL and RA) independently reviewed the titles, abstracts, and keywords of citations obtained from the searches of the electronic databases and excluded studies that were irrelevant (e.g. experimental stroke model, transfusion-dependent patients and people with sickle cell disease). We obtained the full text of the remaining studies and the same two review authors independently assessed which trials met the predefined inclusion criteria with no disagreement.

Data extraction and management

Two review authors (LL and RA) independently extracted the following data from the included studies.

- Stroke type: ischaemic or haemorrhagic stroke (ICH or SAH)
- Methodological quality of each identified trial: sequence generation, allocation concealment, loss to follow-up, blinding of outcome assessment
- Types of participants: inclusion and exclusion criteria, age, sex, similarity of groups at baseline, severity of stroke
- Interventions: type of iron chelator, duration, route of administration, with or without other combined treatment
- Types of outcomes
- Methods of analysis (intention-to-treat analysis or per-protocol analysis, or both)
- Statistical methods used

Assessment of risk of bias in included studies

Two review authors (LL and RA) assessed included RCTs using the 'Risk of bias' assessment tool as described in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We independently evaluated risk of bias through assessing: sequence generation, allocation concealment, blinding (we assessed each main outcome or class of outcomes), incomplete outcome data (we assessed each main outcome or class of

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outcomes), selective outcome reporting and other sources of bias. We created 'Risk of bias' tables including a judgement of 'low risk', 'high risk' or 'unclear risk' of bias for each domain.

Measures of treatment effect

We intended to calculate the risk ratio (RR) and 95% confidence interval (CI) for dichotomous data, and the mean difference (MD) or standardised mean difference (SMD) and 95% CI for continuous outcomes.

Unit of analysis issues

We excluded non-standard designs, including cross-over trials and cluster-randomised trials.

Dealing with missing data

We planned to contact study authors to obtain any information missing from published reports.

Assessment of heterogeneity

We intended to examine statistical heterogeneity with the I^2 statistic. We considered substantial heterogeneity existed if $I^2 > 50\%$. If there was substantial heterogeneity, we would look for the potential sources of the heterogeneity using preplanned subgroup analyses.

Assessment of reporting biases

We planned to undertake funnel plots to detect the existence of possible publication bias, as described in chapter 13 of the *Cochrane Handbook* (Higgins 2019), if the number of included studies was sufficient (defined as 10 or more included studies).

Data synthesis

We intended to calculate the RRs and 95% CIs for dichotomous outcomes and calculate the MD or SMD and 95% CIs for continuous outcomes using a fixed-effect model if there was no evidence of statistical heterogeneity. Otherwise, we would use the random-effects model. We intended to perform all analyses using the Review Manager software RevMan Web (RevMan Web 2020).

Subgroup analysis and investigation of heterogeneity

We intended to perform the following subgroup analyses, where possible:

- stroke subtypes: ischaemic stroke participants only, ICH participants only; SAH only;
- type and dose of iron chelator; and
- the route of medication administration.

Sensitivity analysis

We planned to carry out sensitivity analysis to explore the influence of study design and to determine the impact of studies with lower methodological quality, while excluding:

- studies at high risk of bias for blinding; and
- unpublished data.

Summary of findings and assessment of the certainty of the evidence

We summarised the findings in Summary of findings 1 using the GRADE approach as described in chapter 14 of the *Cochrane Handbook* (Higgins 2019). We included the following outcomes:

- death from all causes at end of scheduled follow-up;
- good neurological outcome (follow-up: 30 to 180 months);
- serious adverse events;
- any deaths within the treatment period;
- neurologic impairment scale at baseline and at the end of follow-up;
- relative oedema volume; and
- quality of life.

We downgraded the certainty of evidence using the five GRADE domains: study limitations, imprecision, inconsistency, indirectness, and publication bias. We justified all decisions to downgrade the certainty of evidence using footnotes.

RESULTS

Description of studies

Results of the search

The updated electronic search strategies identified 452 records from English and other language databases, as well as cross-references of included trials and other systematic reviews. At the end of our search, we had 390 records after duplicates were removed. We discarded 376 and requested full-text copies of 14 references. Eight of these were trial protocols (of which six were Characteristics of ongoing studies), so we excluded them. Of the remaining five studies, we excluded four. We identified two studies (with 333 participants) that met the inclusion criteria and included them in this review (Figure 1). For details of the studies we examined and the reasons we included or excluded them, see the Characteristics of included studies and Characteristics of excluded studies tables.

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Figure 1. Study flow diagram

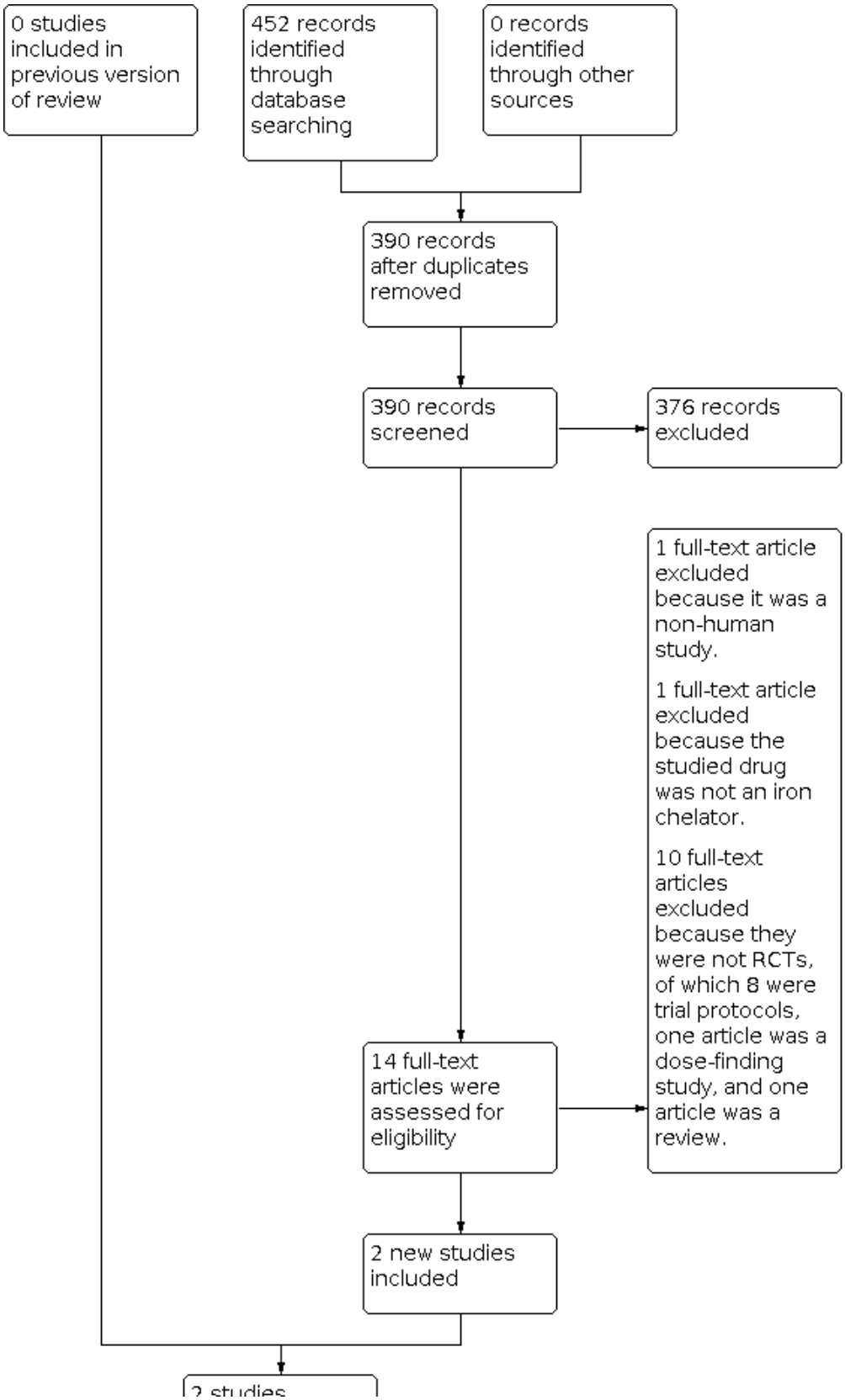

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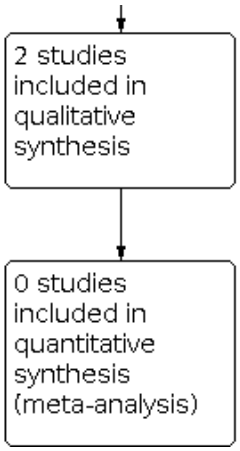
Figure 1. (Continued)



In the original review, two studies were included (NCT00777140; Selim 2011). In the initial selection phase, we excluded these two studies because they did not meet the inclusion criteria. We reported our exclusion criteria in the Characteristics of excluded studies section.

Included studies

Selim 2019 was a multicentre, randomised, placebo-controlled, double-blind phase 2 trial to assess the efficacy and safety of DFO in participants with ICH and to establish whether the drug merits investigation in a phase 3 trial. The trial randomised a total of 294 participants with spontaneous supratentorial ICH as confirmed by computed tomography (CT): 145 in the DFO group and 149 in the placebo group. Treatment was initiated in 144 participants in the DFO group and in 147 participants in the placebo group and all these 291 patients were included in analysis. DFO dose was 32 mg/kg for three consecutive days. Treatment was initiated within 24 hours. Participants in both groups received the same supportive treatment. The primary endpoint was mRS of 0 to 2 at day 90. Secondary endpoints were mRS 0 to 3 at day 90, mRS 0 to 2 and 0 to 3 at day 180, effect of treatment ≤ 12 hours vs > 12 hours from onset, change in NIHSS from presentation to day 90, and Montreal Cognitive Assessment (MoCA) scores at day 90. At day 90, 97% of all participants in both groups had available data.

Yu 2015 was a single-centre, double-blind, randomised, placebo-controlled clinical trial to assess the efficacy of DFO for oedema resolution and haematoma absorption after ICH. This study randomised 42 people with spontaneous ICH as confirmed by CT: 21 participants in the DFO group and 21 in the placebo group. Participants in the DFO group received intravenous injection of DFO 32 mg/kg daily from the first admission day for three consecutive days (based on the dose-finding study Selim 2011). Participants in both groups received the same supportive treatment. The primary endpoint was relative oedema volume on the fifteenth day (or discharge), calculated using the ABC/2 method where relative oedema volume = absolute oedema volume/haematoma volume. Secondary endpoints were mRS on the fifteenth and the thirtieth day.

Excluded studies

Cook 1995 is a review article describing the role of different pathophysiological factors that contribute to cerebral vasospasm, including the role oxyhaemoglobin and various intracellular processes.

Harada 1993 compared DFO with two antioxidants without iron-chelating properties (ascorbic acid and U74389F) in rats. We excluded this study because it was a non-human study.

Papadakis 2008 was a phase 3 study investigating the neuroprotective compound NXY-059, which is not an iron-chelating drug. Although NXY-059 showed positive results in this phase 3 study, a larger scale phase 3 study revealed that the efficacy of NXY-059 is not better than placebo in treating people with acute stroke (ischaemic and ICH). Hence, NXY-059 failed to materialize as an effective acute stroke treatment. We excluded this study because it did not investigate iron-chelating drugs.

Yeats 2013 was the trial protocol of the Hi-DEF trial in which people with spontaneous ICH were randomised in high-dose DFO or placebo.

Selim 2011 was a multicentre, phase 1, dose-finding study to assess the tolerability and safety of DFO in people with ICH, and to determine the maximum tolerated dose to be investigated in future studies. We excluded this study because the control group was varying doses of DFO.

NCT00777140 (TANDEM-1 trial) was a double-blind, randomised, placebo-controlled, dose-finding phase 2 clinical trial that intended to enrol 60 participants to evaluate the safety and tolerability of intravenous infusion of DFO in people with acute ischaemic stroke treated with tPA. This dose-finding study investigated three different doses of DFO (10 mg/kg intravenous bolus followed by a 72-hour continuous intravenous infusion) in three steps:

- first step: bolus 10 mg/kg plus 20 mg/kg/day versus placebo (20 participants: 15 actives versus five placebo);
- second step: bolus 10 mg/kg plus 40 mg/kg/day versus placebo (20 participants: 15 actives versus five placebo); and
- third step: bolus 10 mg/kg plus 60 mg/kg/day versus placebo (20 participants: 15 actives versus five placebo).

The TANDEM-1 trial has not been updated since 2012. We excluded this study because this was a trial protocol of a dose-finding study using varying doses of DFO.

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Ongoing studies

NCT02216513, NCT02875262, and NCT03754725 are ongoing trials investigating the effect of iron chelators after subarachnoid haemorrhage.

ChiCTR-TRC-14004979 is an ongoing trial investigating the clinical effect of DFO on oedema after intracerebral haemorrhage.

EUCTR2007-006731-31-ES and IRCT2013111915444N2 are trials investigating the effect of iron chelators after ischaemic stroke.

Risk of bias in included studies

We documented the risk of bias for included studies based on the full-text articles. Wherever there was a need for clarification, we tried contacting the authors. Based on the available data, we assessed the risk of bias as low, high or unclear. We assessed one trial to be at low risk of bias (Selim 2019), and the other one to be at high risk of bias (Yu 2015). See 'Risk of bias' tables within Characteristics of included studies for further details. For a graphical summary, see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across the included studies

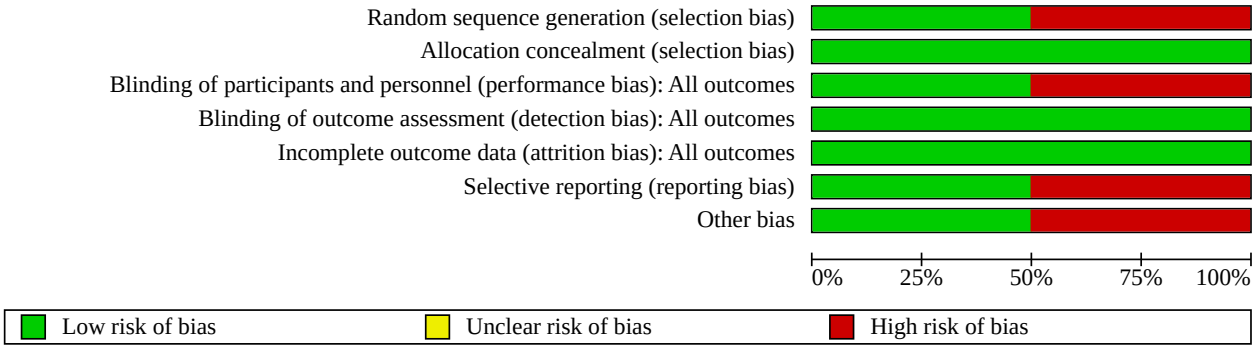

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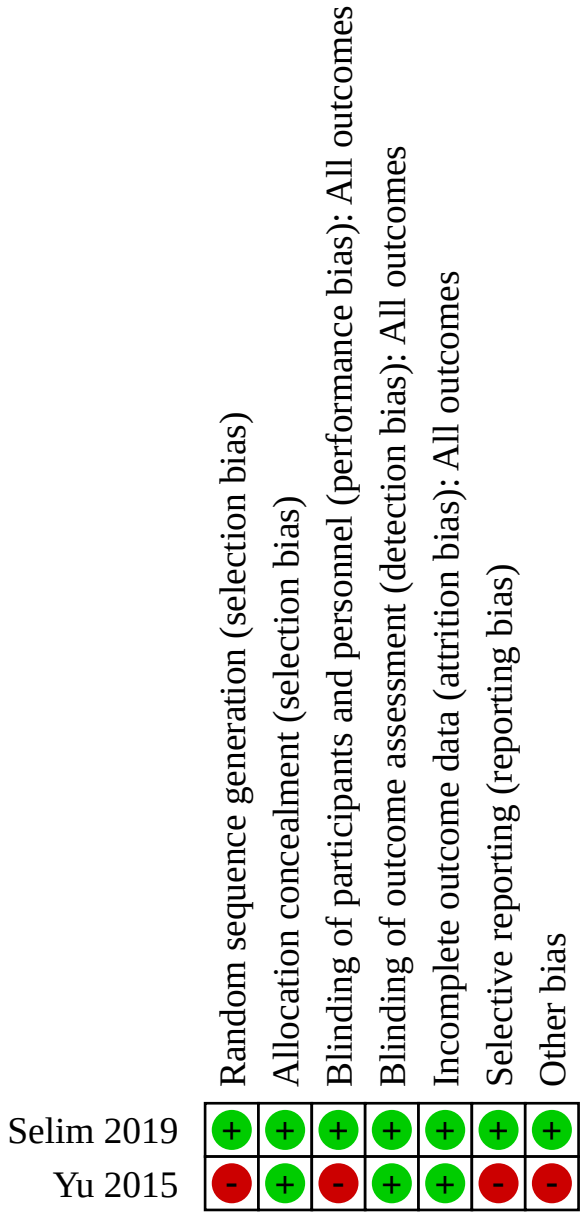
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Selim 2019 adequately reported the method of sequence generation and concealment of allocation, through a combination of minimisation and biased coin methods. Participants were enrolled by a web-based trial management system and randomly allocated (1:1) to the intervention or the control group. We assessed this as a low risk of bias.

In Yu 2015, a random table of group information was established in the design phase before participant enrolment according to the sequence of the participants enrolled. We assessed this as a high risk of bias.

Blinding

Selim 2019 reported blinding of participants and personnel. The trial medication and the placebo were matched to look identical. The only person not blinded was the pharmacist, who was not

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involved in any study-related assessments. All assessors were blinded. We assessed this as low risk of both performance and detection bias.

Yu 2015 reported blinding participants and relatives, but did not explicitly report on blinding of caregivers. This introduces a high risk of performance bias, because participants in the intervention group received intravenous injections whereas participants in the control group did not. The outcome assessment and all assessors were blinded. Therefore, we deemed the risk of detection bias to be low.

Incomplete outcome data

Both Selim 2019 and Yu 2015 adequately described participants' attrition. Selim 2019 classified three participants as postrandomisation exclusions and excluded them from the analysis. This led to a modified intention-to-treat population of 291 instead of 294 participants. In the DFO group, the trialists excluded four participants (one withdrew consent, one was lost to follow-up and two had data collected outside the prespecified data collection window). In the control group, the trialists excluded four participants (two withdrew consent, one was lost to follow-up and one had data collected outside the window). We considered this to be a low loss to follow-up (2.7%).

Yu 2015 randomised 42 participants, and all of them completed the 30 day follow-up. The trial did not report any dropouts, and reported outcomes for all randomised participants.

We assessed risk of attrition bias to be low in both studies.

Selective reporting

Both Selim 2019 and Yu 2015 reported on all outcomes specified in the methods section of the manuscripts, either in the results section or the supplementary files. Selim 2019 was a registered study. All outcome parameters mentioned in the manuscript had also been mentioned in the protocol. We assessed the risk of reporting bias to be low. Yu 2015 was a registered study; however, the protocol did not specify any outcome measures. This introduced a high risk of reporting bias. We also considered the retrospective registration of the trial protocol to introduce a risk of reporting bias.

Other potential sources of bias

We have no reason to assume other sources of bias in the study by Selim 2019. The registered trial protocol for the Yu 2015 study was updated after the paper was received by the publishing journal. This retrospective registration introduced a high risk of bias.

Effects of interventions

See: **Summary of findings 1** Iron chelator versus placebo for adults with acute stroke

Please see Summary of findings 1 for an overview of results.

Deaths

Selim 2019 reported that 10 of 144 (6.9%) participants in the DFO group and 11 of 147 (7.5%) in the placebo group had died by day 90, and by day 180 total mortality was 12 of 144 (8.3%) in the DFO group and 12 of 147 (8.2%) in the control group (P = 0.956); none of the deaths were judged to be treatment related. Selim 2019 described four deaths in the DFO group and two in the placebo group in the first seven days. The treatment period was three days and no assumptions can be made about the fraction of participants that died in the treatment period.

Yu 2015 did not report any deaths in either the DFO and the placebo group.

Clinical outcome

Both Selim 2019 and Yu 2015 investigated clinical outcome, with the same definition of good clinical outcome (mRS 0 to 2). As a secondary endpoint, Selim 2019 also investigated the proportion of participants with a mRS score 0 to 3. However, the timing of this endpoint was different in the two studies (15 and 30 days in Yu 2015, and 90 and 180 days in Selim 2019). This precluded quantitative analysis.

Yu 2015 found no difference in good clinical outcome between the DFO and the placebo group at 15 days (mRS 0-2: DFO group 47.6%, control group 52.4%, P = 0.758). There was also no difference between the two groups at 30 days (mRS 0-2: DFO group 57.1%, control group 66.7%; P = 0.525). Glasgow Outcome Score (GOS) improved from 3.0 ± 0.2 at baseline to 4.3 ± 0.9 at 30 days in the DFO group and from 3.1 ± 0.3 to 4.5 ± 0.9 in the placebo group. Barthel Index (BI) score improved from 60.7 ± 32.8 at baseline to 79.5 ± 28.1 at 30 days in the DFO group and from 66.9 ± 31.6 to 80.5 ± 31.9 in the placebo group. No statistical tests were done on GOS and BI scores.

Selim 2019 found no difference in good clinical outcome between the DFO and placebo group at both 90 and 180 days, regardless of the definition of good clinical outcome (mRS 0 to 2 or mRS 0 to 3). At 90 days, 34% (48 of 140) of patients in the DFO group had mRS scores of 0 to 2, and this score was reported for 33% (47 of 143) in the placebo group. This difference fell below the prespecified 12% futility threshold. In secondary analysis, 45% (61 of 135) of participants in the DFO group and 36% (48 of 135) in the placebo group had mRS scores of 0 to 2 at day 180. Sixty-five per cent (91 of 140) of participants in the DFO mesylate group and 57% (82 of 143) of participants in the placebo group had mRS scores of 0 to 3 at day 90. Seventy-two per cent (97 of 135) of participants in the DFO group and 68% (92 of 135) of participants in the placebo group had mRS scores of 0 to 3 at day 180. The results of Selim 2019 suggest that a large phase 3 trial would be futile (in terms of the proportion of participants with good clinical outcome (mRS 0 to 2 at day 90). Secondary analysis left open the possibility that DFO might not be futile in terms of good clinical outcome at day 180 and should be investigated further.

Safety and tolerability

In Yu 2015, there were no SAEs related to DFO use. General adverse events were not reported. Selim 2019 reported all AEs and SAEs. In the placebo group, 49 of 147 participants (33%) suffered serious adverse events (SAEs), compared with 39 of 144 (27%) in the DFO group (relative risk 0.81 (95% CI 0.57 to 1.16). A special mention of ARDS is made, and two cases (1%) were reported in the DFO group. One of these cases was possibly related to the study drug. Both studies concluded that the administration of DFO was safe.

Neurologic impairment

Selim 2019 reported no difference in NIHSS scores at 90 days. Median NIHSS scores improved from 13 (interquartile range (IQR) 8

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to 17) at baseline to 3 (IQR 1 to 7) at 90 days in the DFO group and from 13 (IQR 9 to 19) at baseline to 4 (IQR 2 to 7) in the placebo group (P = 0.37).

Yu 2015 reported average NIHSS and standard deviation at baseline (9.1 ± 4.6 in the DFO group and 8.7 ± 5.4 in the placebo group) and at 30 days (3.2 ± 3.6 in the DFO group and 2.8 ± 4.0 in the placebo group). The trialists did not report any statistical tests.

Oedema formation and absorption of the haematoma

Yu 2015 reported higher haematoma absorption in the placebo group than in the DFO group from day one to day eight (relative absorption DFO group 0.21, control group 0.41; P = 0.006), and from day eight to day 15 (relative absorption DFO group 0.55, control group 0.79; P = 0.004). The relative oedema volume on the fifteenth day (or discharge) in the placebo group was higher than the relative oedema volume in the DFO group (mean ± standard deviation was 10.26 ± 17.54 vs. 1.91 ± 1.94, P = 0.042). The results of Yu 2015 suggest that DFO can slow down the absorption of haematoma after ICH and prevent the formation of oedema.

Selim 2019 reported that there was there was no difference in changes in relative perilesional oedema: DFO group 0.7 (0.3 to 1.2); control group 0.9 (0.4 to 1.3). Up to 12 hours, relative perilesional oedema increased by 0.28 in the DFO group and 0.83 in the placebo group. Meta-analysis was not possible.

Quality of life

Neither Selim 2019 nor Yu 2015 reported on quality of life measurements.

DISCUSSION

Summary of main results

In addition to the first edition of this review (Ma 2012), we have included two new RCTs that compare the effect of DFO with placebo in participants with spontaneous intracerebral haemorrhage (Selim 2019; Yu 2015). We have excluded the two studies analysed qualitatively in the first edition (Selim 2011; NCT00777140). The limited number of studies and their heterogeneity precluded meta-analysis. Neither of the studies demonstrated difference in good clinical outcome between groups. Both studies concluded that administration of DFO was safe. Yu 2015 demonstrated higher oedema absorption after 15 days, but Selim 2019 found no difference in changes in relative perilesional oedema

There were no studies investigating the effect of iron chelation therapy in acute ischaemic stroke or subarachnoid haemorrhage.

Overall completeness and applicability of evidence

The limited evidence presented in this review does not allow us to draw any conclusions about the effect of DFO in people with stroke in general. Insufficient data also restricted potential subgroup analyses in participants with spontaneous intracerebral haemorrhage. In light of all the information provided above, the applicability of our findings is limited.

Quality of the evidence

We assessed the certainty of the evidence presented in this review using the GRADE approach, and have presented this information in Summary of findings 1. We graded the certainty of evidence to be low across outcomes. The limited number of studies and their heterogeneity precluded meta-analysis. We assessed the risk of bias in Selim 2019 to be 'low'. In Yu 2015, there were potential sources of bias leading to selection bias, performance bias and reporting bias. We assessed attrition and detection bias to be low.

We assessed the evidence about death from all causes to be of low certainty. Case fatality was very low in the two included studies, suggesting that they excluded people with ICH who had severe signs at stroke onset (both Selim 2019 and Yu 2015 excluded people with GCS scores < 5, and Selim 2019 also excluded people with NIHSS scores < 6). The certainty of evidence was downgraded because of this possible indirectness.

We assessed the evidence for good neurological outcome to be of low certainty. Follow-up duration varied greatly between 30 and 180 days, and we only included two studies. The certainty of evidence was downgraded because of this inconsistency and the small number of studies included.

We assessed the evidence for serious adverse events to be of low certainty. Yu 2015 found no serious adverse events and Selim 2019 reported one event. The certainty of evidence was downgraded because of the small number of studies and events reported.

We assessed the evidence for neurological impairment to be of low certainty. Both included studies reported on this outcome parameter, but there was no uniformity in reporting, precluding meta-analysis. The certainty of evidence was lowered because of inconsistency and the small number of studies included.

We assessed the evidence for perilesional oedema to be of low certainty. Both included studies reported on this outcome parameter, but there was no uniformity in reporting. The certainty of evidence was downgraded because of inconsistency and the small number of studies included.

We did not assess the certainty of evidence for the quality of life outcome, as no study reported this.

Potential biases in the review process

We conducted this review in accordance with established Cochrane standards. Two review authors independently assessed the search results and resolved any discrepancies by discussion or by consultation with a third review author. We did not restrict the search by language. Two review authors extracted data from all included studies and resolved any discrepancies by discussion or by consultation with a third review author. We may have missed some unpublished data, owing to a relatively large number of ongoing trials where we could not contact study authors.

Agreements and disagreements with other studies or reviews

The two included studies were the only RCTs in which DFO and placebo were compared in people.

In animal studies, DFO was found to decrease perilesional oedema (Nakamura 2004; Xing 2009), and neurological deficits (Gu 2009). One of the included RCTs showed that the perilesional oedema volume was lower in the DFO group (Yu 2015), but a difference in

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neurological deficit could not be demonstrated. Selim 2019 did not find a clear effect of DFO on the growth of relative oedema.

The use of iron chelators for SAH has been subject of animal studies with promising results on reduced vasospasm, oxidative stress, neuronal cell death and mortality (Arthur 1997; Harada 1992; Lee 2010; Vollmer 1991). No clinical study for the use of DFO in aneurysmal subarachnoid haemorrhage has been performed, although several trials are proposed (NCT02216513; NCT02875262; NCT03754725). Hatcher 2009 and Li 2008 described animal studies investigating ischaemic stroke, but we did not identify any studies in humans.

A safety study for the use of DFO in people with intracerebral haemorrhage (ICH) has been performed (Selim 2011). This study revealed the tolerability and safety of DFO in doses up to 62 mg/kg/day and up to a maximal dose of 6000 mg/day in people with ICH administered for three days. The included study by Selim 2019 built upon this earlier work.

AUTHORS' CONCLUSIONS

Implications for practice

There is limited evidence for the administration of iron chelators in acute stroke. We could not demonstrate any benefit for the use of iron chelators in spontaneous intracranial haemorrhage (ICH) with regards to good clinical outcome. The added value of iron-chelating therapy in people with ischaemic stroke or subarachnoid haemorrhage remains unknown.

Implications for research

There are only two completed randomised controlled trials (RCTs) that compare the effect of any iron chelator with placebo or no intervention in people with ICH. Selim 2019 indicated that, while treatment with deferoxamine was safe, any effects of iron chelators would be modest and would require a large RCT to exclude such a modest effect. The value of such a trial is uncertain.

The design and performance of future research should ensure:

- appropriate methods of randomisation with adequate concealment of allocation;
- double-blinding (blinding investigators, participants and outcome assessors);
- standard dichotomous functional outcome measurement;
- evaluation of therapeutic effect and adverse events;
- completed follow-up of all randomised participants with long-term follow-up (at least 180 days).

Finally, the RCTs identified for this review investigated the effect of iron-chelation therapy in spontaneous ICH. The effect of iron chelation in ischaemic stroke and subarachnoid haemorrhage remains to be determined.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Selim 2019

Study characteristics

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Selim 2019 *(Continued)*

Methods	Multicentre, randomised, placebo-controlled, double-blind phase 2 trial
Participants	**Inclusion criteria:** participants aged 18 to 80 years with spontaneous primary supratentorial ICH confirmed by CT; inclusion possible within 24 hours of the haemorrhage **Exclusion criteria:** suspected secondary causes, infratentorial localisation, severe iron deficiency, pregnancy or lactation, renal failure, coagulopathy, pre-haemorrhage mRS ≥ 2, GCS < 6, NIHSS < 6, planned or suspected need for surgical therapy **Number of participants randomised:** experimental group n = 145, control group n = 149 **Number of participants evaluated:** experimental group n = 140, control group n = 143
Interventions	**Intervention:** DFO 32 mg/kg intravenous daily from the admission day for 3 consecutive days. Maximum daily dose 6000 mg **Control:** matched placebo
Outcomes	**Intervention:** DFO 32 mg/kg intravenous daily from the admission day for 3 consecutive days. Maximum daily dose 6000 mg. Initiation within 24 hours **Control:** matched placebo **Primary endpoint:** mRS 0 to 2 at day 90 **Secondary endpoints:** mRS 0 to 3 at day 90, mRS 0 to 2 and 0 to 3 at day 180, distribution of mRS scores at day 90 and day 180, effect of treatment ≤ 12 hours vs > 12 hours from onset, change in NIHSS from presentation to day 90, MoCA scores at day 90. All adverse events and serious adverse events **Duration of follow-up:** 180 days
Notes	**Language:** English **Funded by:** National Institute of Neurological Disorders and Stroke (U01 NS074425) **Conducted in:** USA **Author contact information:** Magdy Selim, mselim@bidmc.harvard.edu

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using a web-based trial-management system in a 1:1 ratio by balancing of key covariates.
Allocation concealment (selection bias)	Low risk	Participants were recruited and enrolled by local investigators. Participants were randomly allocated (1:1) to deferoxamine mesylate or placebo (saline) infusion via a web-based trial management system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded, except for the pharmacists (who were not involved in any other study-related assessments). DFO and saline placebo were matched to look alike.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All assessments were made by qualified investigators who were masked to treatment assignment.

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Selim 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Some loss to follow-up (3% in both groups), unlikely to introduce bias because of sample size correction. All outcome measures have been reported in the results section.
Selective reporting (reporting bias)	Low risk	The study is registered and all outcome parameters mentioned in the manuscript have been mentioned in the protocol as well. However, there was a slight shift in primary/secondary outcome measures; this was unlikely to introduce bias.
Other bias	Low risk	The study funder had roles in study design but did not contribute to the study.

Yu 2015

Study characteristics	
Methods	Single-centre, double-blind, randomised, placebo-controlled clinical trial
Participants	**Inclusion criteria:** participants aged over 22 years with spontaneous ICH confirmed by CT; onset within 18 hours; clinical status of a stable condition **Exclusion criteria:** 1) allergic to DFO, 2) renal failure, 3) iron deficiency anaemia, 4) planned surgical intervention, 5) ICH secondary to tumours, aneurysms, AVMs or venous thrombosis, 6) herniation on CT, 7) GCS < 5, 8) taking iron supplements, 9) need to take vitamin C > 500 mg daily, 10) hearing impaired, 11) SBP 100 mmHg, 12) pregnant or lactating women, 13) alcoholism or drug dependence, 14) existence of any condition increasing individual's risk, 15) participation in another clinical trial, 16) refusal to accept CPR during hospitalisation **Number of participants randomised:** experimental group n = 21, control group n = 21 **Number of participants evaluated:** experimental group n = 21, control group n = 21
Interventions	**Intervention:** DFO 32 mg/kg intravenous daily from the admission day for 3 consecutive days. Maximum daily dose 6000 mg **Control:** standard medical treatment
Outcomes	**Primary endpoint:** relative oedema volume on 15th day **Secondary endpoints:** mRS on 15th and 30th day **Duration of follow-up:** 30 days
Notes	**Language:** English **Funded by:** no specific funding **Conducted in:** China **Author contact information:** Xuguang Gao, gxg56@tom.com

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation was performed using SPSS 13.0 in a 1:1 ratio using random tables designed before participant enrolment, according to the sequence of the participants enrolled.

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Yu 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation was performed using a random number table by one researcher who was not involved in recruiting participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The caregivers knew which treatment was given to the participants, because the experimental group received an intravenous injection of deferoxamine, while the controls did not. Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators evaluating the neurological scale and CT data and the statistician were blinded. Blinding methods were followed by the ethics committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up. Outcome data for relative oedema volume and the secondary outcome measures are provided in either the results section or the supplementary files.
Selective reporting (reporting bias)	High risk	The study is registered, however no outcome measures have been specified in the protocol. Serious adverse events were reported, but no general adverse events.
Other bias	High risk	The trial protocol was updated retrospectively, after submission of the manuscript to the publishing journal. This retrospective registration hints at other sources of bias.

AVM: arteriovenous malformation
CPR: cardiopulmonary resuscitation
CT: computed tomography
DFO: deferoxamine
GCS: Glasgow Coma Scale
ICH: intracerebral haemorrhage
MoCa: Montreal Cognitive Assessment
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
SBP: systolic blood pressure
SPSS: Statistical Product and Service Solutions

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cook 1995	This research is a review elaborating on the role of different pathophysiological factors contributing to cerebral vasospasm.
Harada 1993	This study compared DFO with 2 antioxidants without iron-chelating properties (ascorbic acid and U74389F) in rats.
NCT00777140	The TANDEM-1 trial has not been updated since 2012. We excluded this study because this was a trial protocol of a dose-finding study using varying doses of DFO
Papadakis 2008	This study was a phase 3 study investigating the neuroprotective compound NXY-059, which is not an iron-chelating drug.
Selim 2011	A multicentre, phase 2, dose-finding study using the Continual Reassessment Method. The control group was varying doses of DFO.

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Study	Reason for exclusion
Yeats 2013	This study is a trial protocol for the Hi-DEF trial in which participants with spontaneous intracerebral haemorrhage receive high-dose DFO therapy.

DFO: deferoxamine

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-TRC-14004979

Study name	The clinical effect of deferoxamine mesylate on edema after intracerebral haemorrhage
Methods	RCT
Participants	50 participants with spontaneous intracerebral haematoma
Interventions	**Intervention group:** intravenous injection of deferoxamine mesylate **Control group:** standardised treatment
Outcomes	**Primary outcome measure:** oedema
Starting date	October 2014
Contact information	Xuguang Gao (Peking University People's Hospital), gxg56ster@gmail.com
Notes	

EUCTR2007-006731-31-ES

Study name	Double-blind, randomised, placebo-controlled, dose-finding phase 2 clinical trial of intravenous deferoxamine in people with acute ischaemic stroke treated with tissue plasminogen activator
Methods	Double-blind, randomised, placebo-controlled, dose-finding phase 2 clinical trial
Participants	62 participants with acute ischaemic stroke of the middle cerebral artery territory, treated with iv tPA in the first 3 hours from symptoms onset
Interventions	**Intervention group:** intravenous deferoxamine bolus of 10 mg/kg (initiated during tPA infusion) and perfusion of 20/40/60 mg/kg/day during 72 hours. 3 different doses (3 steps) **Control group:** saline solution
Outcomes	**Primary outcome measure:** safety and tolerability **Secondary outcome measure:** pharmacokinetic properties, clinical benefit on functional recovery, volume of the infarct and the development of cerebral oedema and haemorrhagic transformation
Starting date	May 2008
Contact information	Unavailable
Notes	

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IRCT2013111915444N2

Study name	Effect of deferoxamine on hemorrhagic transformation of middle cerebral artery stroke
Methods	RCT
Participants	64 participants with acute ischaemic stroke in middle cerebral artery territory.
Interventions	**Intervention group:** deferoxamine, vial 500 mg, dose of 40 mg/kg/day, venous transfusion for 3 days **Control group:** no intervention
Outcomes	**Primary outcome measure:** serum ferritin at first and fourth day of admission **Secondary outcome measure:** haemorrhagic transformation on fourth and seventh day
Starting date	5 May 2014
Contact information	Ahmad Maghuli (Ahvaz Jondishapur University of Medical Sciences), a.maghuli@ajums.ac.ir
Notes	

NCT02216513

Study name	Deferoxamine to prevent delayed cerebral ischemia after subarachnoid haemorrhage
Methods	RCT
Participants	People with spontaneous subarachnoid haemorrhage.
Interventions	**Intervention group:** deferoxamine (20 mg/kg/hour) in normal saline iv for 4 hours for 5 consecutive days **Control group:** normal saline IV for 4 hours for 5 consecutive days
Outcomes	**Primary outcome measure:** delayed cerebral ischemia **Secondary outcome measure:** clinical outcome at discharge
Starting date	September 2014
Contact information	Farzaneh A Sorond, MD, PhD (Brigham and Women's Hospital)
Notes	

NCT02875262

Study name	Deferoxamine in Aneurysmal Subarachnoid Hemorrhage Trial (DASH)
Methods	Randomised placebo-controlled trial
Participants	40 participants with subarachnoid haemorrhage

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NCT02875262 *(Continued)*

Interventions	**Intervention group:** deferoxamine 32 mg/kg/day (dose adjusted to serum ferritin levels) **Control group:** NaCl 0.9% in similar doses to treatment arm
Outcomes	**Primary outcome measure:** safety (drug related adverse events; i.e. renal and hepatic dysfunction, ARDS) **Secondary outcome measure:** efficacy (number of participants with delayed cerebral ischaemia, which is defined by new, not treatment related cerebral ischaemia as registered on CT or MR imaging)
Starting date	1 December 2017
Contact information	Jeroen Boogaarts, MD, PhD (Radboud University Medical Center), jeroen.boogaarts@radboudumc.nl
Notes	

NCT03754725

Study name	Deferiprone for ruptured brain aneurysm
Methods	RCT
Participants	60 participants with aneurysmal subarachnoid haemorrhage
Interventions	**Intervention group:** 1000 mg of deferiprone (oral) 2 times a day (15 mg/kg) **Control group:** participants will receive placebo orally (sugar pill)
Outcomes	**Primary outcome measure:** ferritin levels in cerebrospinal fluid **Secondary outcome measure:** change in cognition on MoCa
Starting date	1 September 2020
Contact information	David Hasan, MD (University of Iowa), david-hasan@uiowa.edu
Notes	

ARDS: acute respiratory distress syndrome
CT: computed tomography
iv: intravenous
MoCa: Montreal Cognitive Assessment
MR: magnetic resonance
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial
tPA: tissue plasminogen activator

APPENDICES

Appendix 1. CENTRAL search strategy

Cochrane Central Register of Controlled Trials (CENTRAL)

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#1 [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"stroke, lacunar"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"]
#2 stroke or poststroke or "post-stroke" or cerebrovasc* or brain next vasc* or cerebral next vasc* or cva* or apoplex* or SAH:ti,ab,kw (Word variations have been searched)
#3 (brain* or cerebr* or cerebell* or intracran* or intracerebral) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus*):ti,ab,kw (Word variations have been searched)
#4 (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*):ti,ab,kw (Word variations have been searched)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Chelating Agents] this term only
#7 MeSH descriptor: [Iron Chelating Agents] explode all trees
#8 MeSH descriptor: [Chelation Therapy] this term only
#9 MeSH descriptor: [Iron] this term only
#10 MeSH descriptor: [Iron Overload] this term only and with qualifier(s): [Drug therapy - DT]
#11 (iron near/6 (chelat* or chelant* or sequest* or remov*)):ti,ab,kw (Word variations have been searched)
#12 iron-chelat*:ti,ab,kw (Word variations have been searched)
#13 (deferoxamine or deferriox* or desferriox* or desferiox* or desferox* or desferal or desferin or desferol or DFO or deferasirox or Exjade or deferiprone or ferriprox or tachpyridine or desferrithiocin or DFT or thiosemicarbazone or dexrazoxane or siderophores or siderochromes):ti,ab,kw (Word variations have been searched)
#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 2857
#15 #5 and #14

Appendix 2. MEDLINE (Ovid) search strategy

MEDLINE (Ovid) (1950 to 2 September 2019)

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
5. or/1-4
6. chelating agents/ or exp iron chelating agents/
7. Chelation Therapy/8. Iron/ai [Antagonists & Inhibitors]
9. Iron Overload/dt [Drug Therapy]
10. (iron adj6 (chelat$ or chelant$ or sequest$ or remov$)).tw.
11. iron-chelat$.tw.
12. (deferoxamine or deferriox$ or desferriox$ or desferiox$ or desferox$ or desferal or desferin or desferol or DFO or deferasirox or Exjade or deferiprone or ferriprox or tachpyridine or desferrithiocin or DFT or thiosemicarbazone or dexrazoxane or siderophores or siderochromes).tw.
13. or/6-12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/14-20
22. 5 and 13 and 21

Appendix 3. Embase (Ovid) search strategy

Embase (Ovid) (1980 to 2 September 2019)

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1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke/ or stroke unit/ or stroke patient/
2. (stroke or poststroke or post-stroke).tw
3. ((brain$ or cerebr$ or cerebell$ or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm)).tw
4. (cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$).tw.
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed $)).tw.
6. 1 or 2 or 3 or 4 or 5
7. Iron chelating agent/ or iron chelation/ or iron chelate/ or deferasirox/ or deferiprone/ or deferitrin/ or deferoxamine/ or deferriferrithiocin/ or ferrozine/ or iron overload/dt
8. iron-chelat$.tw.
9. ((iron adj6 (chelat$ or chelant$ or sequest$ or remov$)).tw.
10. (deferoxamine or deferriox$ or desferriox$ or desferiox$ or desferox$ or desferal or desferin or desferol or DFO or deferasirox or Exjade or deferiprone or ferriprox or tachpyridine or desferrithiocin or DFT or thiosemicarbazone or dexrazoxane or siderophores or siderochromes).tw.
11. 7 or 8 or 9 or 10
12. 6 and 11
13. (animal/ or nonhuman/ or animal experiment/) and human.
14. (animal/ or nonhuman/ or animal experiment/)
15. 14 not 13
16. 12 not 15.

Appendix 4. Science Citation Index Expanded search strategy

Science Citation Index Expanded (SCI-EXPANDED) (from 1980 to 2 September 2019)

#1. TS=(stroke)
#2. TS=(poststroke or post-stroke)
#3. TS=(cerebrovascular disorders)
#4. TS=(intracranial embolism or intracranial thrombosis)
#5. TS=(intracranial hemorrhage or intracranial haemorrhage)
#6. TS=(brain infarction or brain hemorrhage)
#7. TS=(intracerebral hemorrhage or intracerebral haemorrhage)
#8. #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#9. TS =(Iron chelating agent)
#10. TS=(iron chelator)
#11. TS=(iron chelation or iron chelate)
#12. TS=(iron overload)
#13. TS=(deferasirox or deferiprone or deferitrin or deferoxamine or deferriferrithiocin or ferrozine or deferoxamine or deferriox* or desferriox* or desferiox* or desferox* or desferal or desferin or desferol or DFO or deferasirox or Exjade or deferiprone or ferriprox or tachpyridine or desferrithiocin or DFT or thiosemicarbazone or dexrazoxane or siderophores or siderochromes)
#14. #13 OR #12 OR #11 OR #10 OR #9
#15. #14 AND #8

Appendix 5. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

(Iron chelators OR Chelation OR Deferoxamine OR Enterobactin OR Ferrozine OR Pentetic Acid) AND (Brain Infarction OR Intracranial Hemorrhages OR Carotid Artery Diseases OR Brain Ischemia OR Cerebral Hemorrhage OR Cerebrovascular Disorders OR Stroke) [DISEASE]

Appendix 6. World Health Organization International Clinical Trials Registry Platform search strategy

Iron chelators AND STROKE OR Chelation AND STROKE OR Deferoxamine AND STROKE OR Enterobactin AND STROKE OR Ferrozine AND STROKE OR Pentetic Acid AND STROKE

WHAT'S NEW

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Date	Event	Description
25 November 2020	Amended	Author affiliation corrected

HISTORY

Protocol first published: Issue 8, 2011
Review first published: Issue 9, 2012

Date	Event	Description
13 December 2019	New citation required and conclusions have changed	The two studies that were included in the original review were excluded in this update. Two new studies were included in the update, with a total of 333 participants. In this update, We could not demonstrate any benefit for the use of iron chelators in spontaneous intracerebral haemorrhage. The added value of iron-chelating therapy in people with ischaemic stroke or subarachnoid haemorrhage remains unknown.
2 September 2019	New search has been performed	Final preparation of update started. The updated review was done by a new author team. The methodology was the same as in the original review. The search strategy was updated to specifically include subarachnoid haemorrhage as a subset of stroke.

CONTRIBUTIONS OF AUTHORS

LL conceived and designed the review, co-ordinated the review, screened the citations for eligibility, assessed the papers, managed, analysed and interpreted the data, and wrote the updated review.

RA undertook the searches, screened the citations for eligibility, assessed the papers, and analysed and interpreted the data

OT helped with analysis and interpretation of data (providing a clinical perspective), and provided general advice on the review.

KK helped with analysis and interpretation of data (providing a clinical perspective), and provided general advice on the review.

TM helped with analysis and interpretation of data (providing a clinical perspective), and provided general advice on the review.

MD helped with analysis and interpretation of data (providing a clinical perspective), and provided general advice on the review.

RB helped with analysis and interpretation of data (providing a clinical and methodological perspective), and provided general advice on the review.

HB conceived and designed the review and helped to write the updated review.

DECLARATIONS OF INTEREST

Lars van der Loo: none known.

René Aquarius: none known.

Onno Teernstra: none known.

Karin Klijn: none known.

Thomas Menovsky: none known.

Marc van Dijk: none known.

Ronald Bartels: none known.

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Hieronymus Boogaarts: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the search strategy to specifically include subarachnoid haemorrhage as a subset of stroke.

We added oedema volume surrounding haematoma or infarction as a secondary outcome measure.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Bias; Deferoxamine [adverse effects] [*therapeutic use]; Hemorrhagic Stroke [*drug therapy] [mortality]; Iron Chelating Agents [adverse effects] [*therapeutic use]; Neuroprotective Agents [adverse effects] [*therapeutic use]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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