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[Intervention Review]

Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia

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ABSTRACT

Background

Regularly transfused people with sickle cell disease (SCD) and people with thalassaemia (who are transfusion-dependent or non-transfusion-dependent) are at risk of iron overload. Iron overload can lead to iron toxicity in vulnerable organs such as the heart, liver and endocrine glands; which can be prevented and treated with iron chelating agents. The intensive demands and uncomfortable side effects of therapy can have a negative impact on daily activities and well-being, which may affect adherence.

Objectives

To identify and assess the effectiveness of interventions (psychological and psychosocial, educational, medication interventions, or multi-component interventions) to improve adherence to iron chelation therapy in people with SCD or thalassaemia.

Search methods

We searched CENTRAL (the Cochrane Library), MEDLINE, Embase, CINAHL, PsycINFO, Psychology and Behavioral Sciences Collection, Web of Science Science & Social Sciences Conference Proceedings Indexes and ongoing trial databases (01 February 2017). We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register (12 December 2017).

Selection criteria

For trials comparing medications or medication changes, only randomised controlled trials (RCTs) were eligible for inclusion.

For studies including psychological and psychosocial interventions, educational Interventions, or multi-component interventions, non-RCTs, controlled before-after studies, and interrupted time series studies with adherence as a primary outcome were also eligible for inclusion.

Data collection and analysis

Three authors independently assessed trial eligibility, risk of bias and extracted data. The quality of the evidence was assessed using GRADE.

Main results

We included 16 RCTs (1525 participants) published between 1997 and 2017. Most participants had β-thalassaemia major; 195 had SCD and 88 had β-thalassaemia intermedia. Mean age ranged from 11 to 41 years. One trial was of medication management and 15 RCTs were of medication interventions. Medications assessed were subcutaneous deferoxamine, and two oral-chelating agents, deferiprone and deferasirox.

We rated the quality of evidence as low to very low across all outcomes identified in this review.

Three trials measured quality of life (QoL) with validated instruments, but provided no analysable data and reported no difference in QoL.

Deferiprone versus deferoxamine

We are uncertain whether deferiprone increases adherence to iron chelation therapy (four trials, very low-quality evidence). Results could not be combined due to considerable heterogeneity (participants' age and different medication regimens). Medication adherence was high (deferiprone (85% to 94.9%); deferoxamine (71.6% to 93%)).

We are uncertain whether deferiprone increases the risk of agranulocytosis, risk ratio (RR) 7.88 (99% confidence interval (CI) 0.18 to 352.39); or has any effect on all-cause mortality, RR 0.44 (95% CI 0.12 to 1.63) (one trial; 88 participants; very low-quality evidence).

Deferasirox versus deferoxamine

We are uncertain whether deferasirox increases adherence to iron chelation therapy, mean difference (MD) -1.40 (95% CI -3.66 to 0.86) (one trial; 197 participants; very-low quality evidence). Medication adherence was high (deferasirox (99%); deferoxamine (100%)). We are uncertain whether deferasirox decreases the risk of thalassaemia-related serious adverse events (SAEs), RR 0.95 (95% CI 0.41 to 2.17); or all-cause mortality, RR 0.96 (95% CI 0.06 to 15.06) (two trials; 240 participants; very low-quality evidence).

We are uncertain whether deferasirox decreases the risk of SCD-related pain crises, RR 1.05 (95% CI 0.68 to 1.62); or other SCD-related SAEs, RR 1.08 (95% CI 0.77 to 1.51) (one trial; 195 participants; very low-quality evidence).

Deferasirox film-coated tablet (FCT) versus deferasirox dispersible tablet (DT)

Deferasirox FCT may make little or no difference to adherence, RR 1.10 (95% CI 0.99 to 1.22) (one trial; 173 participants; low-quality evidence). Medication adherence was high (FCT (92.9%); DT (85.3%)).

We are uncertain if deferasirox FCT increases the incidence of SAEs, RR 1.22 (95% CI 0.62 to 2.37); or all-cause mortality, RR 2.97 (95% CI 0.12 to 71.81) (one trial; 173 participants; very low-quality evidence).

Deferiprone and deferoxamine combined versus deferiprone alone

We are uncertain if deferiprone and deferoxamine combined increases adherence to iron chelation therapy (very low-quality evidence). Medication adherence was high (deferiprone 92.7% (range 37% to 100%) to 93.6% (range 56% to 100%); deferoxamine 70.6% (range 25% to 100%).

Combination therapy may make little or no difference to the risk of SAEs, RR 0.15 (95% CI 0.01 to 2.81) (one trial; 213 participants; low-quality evidence).

We are uncertain if combination therapy decreases all-cause mortality, RR 0.77 (95% CI 0.18 to 3.35) (two trials; 237 participants; very low-quality evidence).

Deferiprone and deferoxamine combined versus deferoxamine alone

Deferiprone and deferoxamine combined may have little or no effect on adherence to iron chelation therapy (four trials; 216 participants; low-quality evidence). Medication adherence was high (deferoxamine 91.4% to 96.1%; deferiprone: 82.4%)

Deferiprone and deferoxamine combined, may have little or no difference in SAEs or mortality (low-quality evidence). No SAEs occurred in three trials and were not reported in one trial. No deaths occurred in two trials and were not reported in two trials.

Deferiprone and deferoxamine combined versus deferiprone and deferasirox combined

Deferiprone and deferasirox combined may improve adherence to iron chelation therapy, RR 0.84 (95% CI 0.72 to 0.99) (one trial; 96 participants; low-quality evidence). Medication adherence was high (deferiprone and deferoxamine: 80%; deferiprone and deferasirox: 95%).

We are uncertain if deferiprone and deferasirox decreases the incidence of SAEs, RR 1.00 (95% CI 0.06 to 15.53) (one trial; 96 participants; very low-quality evidence).

There were no deaths in the trial (low-quality evidence).

Medication management versus standard care

We are uncertain if medication management improves health-related QoL (one trial; 48 participants; very low-quality evidence). Adherence was only measured in one arm of the trial.

Authors' conclusions

The medication comparisons included in this review had higher than average adherence rates not accounted for by differences in medication administration or side effects.

Participants may have been selected based on higher adherence to trial medications at baseline. Also, within the clinical trial context, there is increased attention and involvement of clinicians, thus high adherence rates may be an artefact of trial participation.

Real-world, pragmatic trials in community and clinic settings are needed that examine both confirmed or unconfirmed adherence strategies that may increase adherence to iron chelation therapy.

Due to lack of evidence this review cannot comment on intervention strategies for different age groups.

PLAIN LANGUAGE SUMMARY

Strategies to increase adherence to iron chelation therapy in people with sickle cell disease or thalassaemia

Review question

We wanted to determine if there are any interventions (medication, psychological or educational) that would help people adhere to their iron chelation therapy.

Background

People with sickle cell disease or thalassaemia who receive regular transfusions, are exposed to iron overload which can result in toxicity to organs and death. Iron chelation therapy is used to prevent or treat iron overload, but it can be a demanding regimen, and have unwanted side effects. There are three types of iron chelators being used to treat iron overload: deferoxamine given subcutaneously (by injecting a drug into the tissue layer between the skin and the muscle); and two agents that are taken orally, deferiprone and deferasirox.

Search date

The evidence is current to 12 December 2017.

Study characteristics

We searched the literature for both randomised and non-randomised studies, and found 16 randomised trials with 1525 participants, published between 1997 and 2017. Most people had β-thalassaemia major; one trial included people with SCD and one included people with a milder form of thalassaemia (thalassaemia intermedia). Mean age ranged from 11 years to 41 years. We included one trial of medication management and 15 trials comparing different drug treatments.

Key results

Trials included comparisons of individual agents to each other or a combination of drugs compared to one drug alone or to other combinations of drugs.

We were uncertain if single agents or combined agents made any difference in adherence rates, serious adverse events or mortality. Quality of life, measured using validated questionnaires, was only reported in two trials, but not enough data were reported to determine any differences between treatments.

There was no evidence on intervention strategies for different age groups.

We found that there was an unusually high adherence rate to all drugs and combinations of drugs in all the trials. This may be because participants may have been selected based on their ability to stick to medication regimens. Also, adherence may increase in trial participants when there is a higher level of clinician involvement in care.

We concluded that real-world randomised and non-randomised trials, run in both the community and in clinics, are needed to examine a variety of proven and unproven strategies that may be useful for increasing adherence to iron chelation therapy.

Quality of evidence

We rated the quality of evidence as low to very low across all of the outcomes in this review. This was due to trials being at serious or very serious risk of bias; outcome estimates being imprecise (wide confidence intervals); and not widely applicable (with some trials conducted only in children of a specific age and meeting specific criteria).