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[Intervention Review]

Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia

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ABSTRACT

Background

Beta thalassaemia is a common inherited blood disorder. The need for frequent blood transfusions in this condition poses a difficult problem to healthcare systems. The most common cause of morbidity and mortality is cardiac dysfunction from iron overload. The use of iron chelation therapy has reduced the severity of systemic iron overload but specific, non-toxic treatment is required for removal of iron from the myocardium.

Objectives

To assess the effects of calcium channel blockers combined with standard iron chelation therapy in people with transfusion-dependent beta thalassaemia on the amount of iron deposited in the myocardium, on parameters of heart function, and on the incidence of severe heart failure or arrhythmias and related morbidity and mortality.

Search methods

We searched the Cochrane Haemoglobinopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched ongoing trials databases, and the reference lists of relevant articles and reviews.

Date of last search: 24 February 2018.

Selection criteria

We included randomised controlled trials of calcium channel blockers combined with standard chelation therapy compared with standard chelation therapy alone or combined with placebo in people with transfusion-dependent beta thalassaemia.

Data collection and analysis

Two authors independently applied the inclusion criteria for the selection of trials. Two authors assessed the risk of bias of trials and extracted data and a third author verified these assessments. The authors used the GRADE system to assess the quality of the evidence.

Main results

Two randomised controlled trials (n = 74) were included in the review; there were 35 participants in the amlodipine arms and 39 in the control arms. The mean age of participants was 24.4 years with a standard deviation of 8.5 years. There was comparable participation from both genders. Overall, the risk of bias in included trials was low. The quality of the evidence ranged across outcomes from low to high, but the evidence for most outcomes was judged to be low quality.

Cardiac iron assessment, as measured by heart T2*, did not significantly improve in the amlodipine groups compared to the control groups at six or 12 months (low-quality evidence). However, myocardial iron concentration decreased significantly in the amlodipine groups compared to the control groups at both six months, mean difference -0.23 mg/g (95% confidence interval -0.07 to -0.39), and 12 months, mean difference -0.25 mg/g (95% confidence interval -0.44 to -0.05) (low-quality evidence). There were no significant differences between treatment and control groups in serum ferritin (low-quality evidence), liver T2* (low-quality evidence), liver iron content (low-quality evidence) and left ventricular ejection fraction (low-quality evidence). There were no serious adverse events reported in either trial; however, one trial (n = 59) reported mild adverse events, with no statistically significant difference between groups (low-quality evidence).

Authors' conclusions

The available evidence does not clearly suggest that the use of calcium channel blockers is associated with a reduction in myocardial iron in people with transfusion-dependent beta thalassaemia, although a potential for this was seen. There is a need for more long-term, multicentre trials to assess the efficacy and safety of calcium channel blockers for myocardial iron overload, especially in younger children. Future trials should be designed to compare commonly used iron chelation drugs with the addition of calcium channel blockers to investigate the potential interplay of these treatments. In addition, the role of baseline myocardial iron content in affecting the response to calcium channel blockers should be investigated. An analysis of the cost-effectiveness of the treatment is also required.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers for preventing heart dysfunction related with iron overload in transfusion-dependent beta thalassaemia

Review question

We reviewed the evidence on whether drugs can prevent heart dysfunction due to excessive iron deposits in the hearts of people with beta thalassaemia who receive regular blood transfusions.

Background

Beta thalassaemia is a common inherited blood disorder that causes anaemia. People with this disorder need frequent blood transfusions which result in excess iron deposited in the heart causing it to be damaged. Complications related to the heart are the most common cause of death and disability in these individuals. High levels of iron in the heart strongly predicts subsequent heart failure. It is common practice to give drugs to reduce iron in the body (known as chelators) but there is no specific treatment for reducing iron deposited in the heart and protecting it from damage. Drugs that block calcium channels in the heart have been shown to reduce iron entering into this organ. However, little is known about how effective and safe these drugs are in people with beta thalassaemia.

Search date

The evidence is current to 24 February 2018.

Trial characteristics

We included two trials (74 participants) in the review, an earlier pilot study and the later larger study. Participants had beta thalassaemia, significant iron overload, and were receiving standard chelation treatment; they had an average age of 24 years. They were randomly selected to be treated for 12 months with either amlodipine (a calcium channel blocker) in addition to their chelation drugs or with chelation drugs alone (in the earlier trial) or with chelation drugs together with a placebo (dummy drug with no active medication) in the later trial.

Key results

Although there was no significant decrease in the amount of iron in the heart (main outcome) seen after 12 months of treatment with amlodipine when measured in one way, there was a significant decrease after 12 months of treatment using another measurement. There was no difference in other outcomes such as iron levels in the blood or the liver or in a further measure of heart function. Even though no serious adverse events were noted, further trials are needed to assess the safety of this treatment. Further research with larger, long-term trials is needed.

Quality of the evidence

Overall, the trials included in this review appeared to be well run. However, the main outcome was reported differently in both trials and several other outcomes were missing details. The quality of evidence was low for all outcomes.