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[Intervention Review]

Vitamin D supplementation for sickle cell disease

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ABSTRACT

Background

Sickle cell disease is a genetic chronic haemolytic and pro-inflammatory disorder. The clinical manifestations of sickle cell disease result from the presence of mutations on the beta globin genes that generate an abnormal haemoglobin product (called haemoglobin S) within the red blood cell. Sickle cell disease can lead to many complications such as acute chest syndrome, stroke, acute and chronic bone complications (including painful vaso-occlusive crisis, osteomyelitis, osteonecrosis and osteoporosis). With increased catabolism and deficits in energy and nutrient intake, individuals with sickle cell disease suffer multiple macro- and micro-nutritional deficiencies, including vitamin D deficiency. Since vitamin D maintains calcium homeostasis and is essential for bone mineralisation, its deficiency may worsen musculoskeletal health problems encountered in sickle cell disease. Therefore, there is a need to review the effects and the safety of vitamin D supplementation in sickle cell disease.

Objectives

To investigate the hypothesis that vitamin D supplementation increases serum 25-hydroxyvitamin D level in children and adults with sickle cell disease.

To determine the effects of vitamin D supplementation on general health such as growth status and health-related quality of life; on musculoskeletal health including bone mineral density, pain crises, bone fracture and muscle health; on respiratory health which includes lung function tests, acute chest syndrome, acute exacerbation of asthma and respiratory infections; and the safety of vitamin D supplementation in children and adults with sickle cell disease.

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 database such as PubMed, clinical trial registries and the reference lists of relevant articles and reviews.

Date of last search: 15 December 2016.

Selection criteria

Randomised controlled studies and quasi-randomised controlled studies (controlled clinical studies) comparing oral administration of any form of vitamin D supplementation to another type of vitamin D or placebo or no supplementation at any dose and for any duration, in people with sickle cell disease, of all ages, gender, and phenotypes including sickle cell anaemia, haemoglobin sickle cell disease and sickle beta-thalassaemia diseases.

Data collection and analysis

Two authors independently extracted the data and assessed the risk of bias of the included study. They used the GRADE guidelines to assess the quality of the evidence.

Main results

One double-blind randomised controlled study including 46 people with sickle cell disease (HbSS, HbSC, HbSβ+thal and HbSβ0thal) was eligible for inclusion in this review. Of the 46 enrolled participants, seven withdrew before randomisation leaving 39 participants who were randomised. Only 25 participants completed the full six months of follow up. Participants were randomised to receive oral vitamin D3 (cholecalciferol) (n = 20) or placebo (n = 19) for six weeks and were followed up to six months. Two participants from the treatment group have missing values of baseline serum 25-hydroxyvitamin D, therefore the number of samples analysed was 37 (vitamin D n = 18, placebo n = 19).

The included study had a high risk of bias with regards to incomplete outcome data (high dropout rate in the placebo group), but a low risk of bias for other domains such as random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, selective outcome reporting; and an unclear risk of other biases.

Compared to the placebo group, the vitamin D group had significantly higher serum 25-hydroxyvitamin D (25(OH)D) levels at eight weeks, mean difference 29.79 (95% confidence interval 26.63 to 32.95); at 16 weeks, mean difference 12.67 (95% confidence interval 10.43 to 14.90); and at 24 weeks, mean difference 15.52 (95% confidence interval 13.50 to 17.54). We determined the quality of the evidence for this outcome to be moderate. There was no significant difference of adverse events (tingling of lips or hands) between the vitamin D and placebo groups, risk ratio 3.16 (95% confidence interval 0.14 to 72.84), but the quality of the evidence was low. Regarding the frequency of pain, the vitamin D group had significantly fewer pain days compared to the placebo group, mean difference -10.00 (95% confidence interval -16.47 to -3.53), but again the quality of the evidence was low. Furthermore, the review included physical functioning PedsQL scores which was reported as absolute change from baseline. The vitamin D group had a lower (worse) health-related quality of life score than the placebo group but this was not significant at eight weeks, mean difference -2.02 (95% confidence interval -6.34 to 2.30). However, the difference was significant at both 16 weeks, mean difference -12.56 (95% confidence interval -16.44 to -8.69) and 24 weeks, mean difference -12.59 (95% confidence interval -17.43 to -7.76). We determined the quality of evidence for this outcome to be low.

Authors' conclusions

We included only one low-quality clinical study which had a high risk of bias with regards to incomplete outcome data. Therefore, we consider that the evidence is not of sufficient quality to guide clinical practice. Until further evidence becomes available, clinicians should consider the relevant existing guidelines for vitamin D supplementation (e.g. the Endocrine Society Clinical Practice Guidelines) and dietary reference intakes for calcium and vitamin D (e.g. from the USA Institute of Medicine). Evidence of vitamin D supplementation in sickle cell disease from high quality studies is needed. Well-designed, randomised, placebo-controlled studies of parallel design, are required to determine the effects and the safety of vitamin D supplementation in children and adults with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for sickle cell disease

Review question

We reviewed the evidence about the effect of giving vitamin D supplements to people with sickle cell disease.

Background

Sickle cell disease is an inherited red blood cell disorder affecting millions of people worldwide. In sickle cell disease, the red blood cells become crescent-shaped and hard so that they block small blood vessels resulting in a lack of oxygen supplied to tissues and organs.

This blockage causes episodes of pain, short-term and long-term organ damage, acute chest syndrome and stroke. Sickle cell disease can also lead to bone complications in both the short and long term. Pain and musculoskeletal complications are the most common reasons for people with sickle cell disease seeking medical treatment; even though they do not greatly contribute to mortality, they remain an important cause of illness in the short and long term.

Vitamin D deficiency is common in people with sickle cell disease regardless of age and season. Since vitamin D regulates calcium levels and supports bone health, its deficiency may worsen musculoskeletal health problems already present in people with sickle cell disease. Therefore we wanted to discover whether giving vitamin D supplements to people with sickle cell disease was better or worse than giving either placebo (substance which contains no medication) or no vitamin D supplements.

Search date

The evidence is current to: 15 December 2016.

Study characteristics

The review included one study which recruited 46 people with sickle cell disease aged between seven and 21 years; of these 39 people in the study were randomly selected to take vitamin D tablets or placebo tablets for six weeks and then followed up for six months. The study reported results from 37 people.

Key results

People taking a vitamin D supplement had higher levels of vitamin D in their blood when it was measured after eight, 16 and 24 weeks. There were no differences in the number of people reporting side effects, such as tingling in the lips or hands between the vitamin D group and the placebo group. The vitamin D group had fewer days of pain compared to the placebo group. The study also reported on health-related quality of life (physical functioning scores). After eight weeks the vitamin D group had a slightly worse score than the placebo group, but the difference was much greater after 16 and 24 weeks.

Given these results from this small single study with moderate to low quality of the evidence, we do not think the results of our review are of sufficient quality to guide clinical practice. Until further evidence becomes available, clinicians should consider relevant existing guidelines for vitamin D supplementation (e.g. the Endocrine Society Clinical Practice Guidelines), and recommendations for calcium and vitamin D intake (from e.g. the USA Institute of Medicine). High-quality studies looking at the effects of supplementing vitamin D in children and adults with sickle cell disease are needed.

Quality of the evidence

We do not think there are risks of bias in the way people were put into the different groups and we do not think anyone (either the participant or the doctor) could guess which group they were in once the study started. Even though the adverse events were not reported in the original report, the study author provided the information upon request. More people dropped out of the placebo group (68.4%) than the vitamin D group (5%), and two people assigned to vitamin D group but not included in the analysis. We considered there was a high risk of bias in the way the study reported results. The evidence is only applicable to people with sickle cell disease when they are in a steady state, i.e. at least 30 days from blood transfusion and at least 14 days from any acute sickle complication. The quality of evidence for the outcomes ranged from moderate to low. We considered the quality of the evidence for vitamin D blood levels to be moderate, and for adverse events, days of pain and health-related quality of life, the quality of the evidence was low.