Are current interventions for preventing silent cerebral infarcts in people with sickle cell disease effective and safe? A Cochrane Review summary with commentary

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The aim of this commentary is to discuss from a rehabilitation perspective the published Cochrane Review 'Interventions for preventing silent cerebral infarcts in people with sickle cell disease' by Estcourt et al.,[1] under the direct supervision of the Cochrane Cystic Fibrosis and Genetic Disorders Group. This Cochrane Corner is produced in agreement with *Developmental Medicine & Child Neurology* by Cochrane Rehabilitation.

BACKGROUND

Sickle cell disease (SCD) is one of the most common genetic disorders and is linked to the inheritance of two abnormal beta globin genes. Silent cerebral infarcts (SCIs) are a common neurological complication in children with SCD defined as the 'abnormal magnetic resonance imaging (MRI) of the brain in the setting of a normal neurologic examination without a history or physical findings associated with an overt stroke'.[2] SCIs seem to increase cognitive impairment and therefore affect academic performance.[2]

Determining if there are any safe and effective interventions for preventing SCIs in people with SCD is of prominent importance for physiatrists and other rehabilitation professionals.

INTERVENTIONS FOR PREVENTING SILENT CEREBRAL INFARCTS IN PEOPLE WITH SICKLE CELL DISEASE[1]

What is the aim of this Cochrane Review?

The aim of this Cochrane Review[1] was to assess the effectiveness of interventions to reduce or prevent SCIs in people with SCD.

What was studied in the Cochrane Review?

The population addressed in this review was people with homozygous SCD, sickle beta thalassaemia, and sickle haemoglobin C disease, including children and adults of both sexes, with or without evidence of SCIs. The interventions studied were red blood cells (RBC) transfusions, haematopoietic stem cell transplantation, hydroxyurea alone, or RBC transfusions combined with hydroxyurea. The interventions were compared to each other or to standard care or placebo. Primary outcomes were: the proportion of people with SCD developing new or progressive SCIs lesions on MRI, all-cause mortality, and serious adverse events. Secondary outcomes were: clinical stroke, changes in cognitive function from baseline and at least 6 months, changes in quality of life from baseline and at least 6 months, and any adverse events.

Up-to-dateness of the Cochrane Review

The authors searched for published and unpublished studies in the Cochrane Library, MEDLINE, Embase, CINAHL, the Transfusion Evidence Library, LILACS, Web of Science, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, up to April 2020.

What are the main results of the Cochrane Review?

The review analysed five trials including 660 children and adolescents (2–20y) with HbSS disease and HbSβ^0 thalassaemia. In particular, three trials compared RBC transfusion versus standard care and the other two compared hydroxyurea and phlebotomy versus RBC transfusions and chelation.

RBC transfusions compared with standard care

One trial[3] compared long-term RBC transfusions with standard care in 196 children with SCD and normal transcranial doppler (TCD) velocities, reporting that the intervention may make little or no difference in the incidence of SCIs, mortality, and clinical stroke and in improving cognitive functions. However, it may reduce the incidence of serious adverse events, including pain crisis, and it may slightly improve quality of life (low-certainty evidence).

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A further trial[4] compared long-term RBC transfusions with standard care in 124 children with SCD and abnormal TCD velocities, reporting that the intervention may reduce the incidence of SCIs, serious adverse events, and clinical stroke (low-certainty evidence); while it is uncertain whether it makes any difference in mortality rates and incidence of pain crisis (very low-certainty evidence).

These two trials[3,4] also compared long-term RBC transfusions with standard care in 326 children with SCD at risk of stroke who had not received previous long-term RBC transfusions, reporting that the intervention may reduce the incidence of serious adverse events, including pain crisis (low-certainty evidence), and it probably reduces the incidence of clinical stroke (moderate-certainty evidence).

Continued RBC transfusions versus halted transfusions

One trial[5] compared transfusions continued with transfusions halted in 79 children and adolescents with SCD and normalized TCD velocities, reporting that the continued intervention may reduce the incidence of SCIs (low-certainty evidence); while it is uncertain whether it makes any difference in mortality rates and incidence of clinical stroke (very low-certainty evidence).

Hydroxyurea versus RBC transfusions

One trial[6] compared hydroxyurea with RBC transfusions in 121 children with SCD who have not had a stroke, reporting that it is uncertain whether it makes any difference in any of the investigated outcomes (incidence of SCIs, mortality, serious adverse events including pain crisis, and clinical stroke; very low-certainty evidence).

One trial[7] compared hydroxyurea with RBC transfusions in 133 children and adolescents with SCD who had a stroke, reporting that it is uncertain whether it makes any difference in the incidence of SCIs, mortality, serious adverse events, and clinical stroke (very low-certainty evidence), and it may increase the risk of pain crisis (low-certainty evidence).

How did the authors conclude on the evidence?

The authors concluded that long-term RBC transfusions may reduce the incidence of SCIs in people with SCD and abnormal TCD velocities, but may have little or no effect in children with normal TCD velocities. In children at higher risk of stroke and who have not received long-term transfusions, long-term RBC transfusions probably reduce the risk of stroke and other adverse events. In children and adolescents at high risk of stroke with normalized TCD velocities, continued RBC transfusions may reduce the risk of SCIs. Switching to hydroxyurea may increase the risk of SCIs and serious adverse events in secondary stroke prevention. It is uncertain if it has any effect on other outcomes.

What are the implications of the Cochrane evidence for practice in rehabilitation?

This Cochrane Review aimed to study effectiveness and safety of interventions to reduce or prevent SCIs in people with SCD. The paucity (only five studies and 660 people), lack of generalizability (all studies included only children and adolescents with HbSS disease and HbSβ^0 thalassaemia), and overall low to very low quality of the available evidence, prevented the authors from making recommendations for the optimal use of interventions to prevent SCIs.

From a rehabilitative perspective, SCD is a health condition affecting several aspects of functioning, including activity limitations and participation restrictions.[8] It is very important to prevent SCIs and stroke that would worsen functioning and increase rehabilitation needs.[9]

Future research should consider the effectiveness and safety of interventions with a focus on functioning and use outcome measures based on the International Classification of Functioning, Disability and Health framework.[10]

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