

The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Sickle cell disease (SCD) is a recessive genetic blood disorder, caused by a mutation in the beta-globin gene. This mutation results in an altered haemoglobin molecule that polymerises when deoxygenated and damages red cells, which adopt the characteristic sickle shape. Their abnormal shape and decreased flexibility means that they are more likely to obstruct small blood vessels, reducing the amount of oxygen delivered to lungs, brain and other tissues, and causing vascular endothelial damage. SCD occurs more commonly in people whose family origins are African, African Caribbean, Asian or Mediterranean; it is rare in people of north European origin. Sickle cell anaemia (SCA) is the most common form of SCD and may also be referred to as HbSS or SS disease. For children with SCD, the risk of stroke is estimated to be up to 250 times higher than in the general childhood population. Transcranial Doppler (TCD) ultrasonography is a non-invasive technique that measures local blood velocity in the proximal portions of large intracranial arteries. Screening with TCD ultrasonography identifies individuals with high cerebral blood velocity; these children are at the highest risk of stroke. A number of primary stroke prevention strategies are currently used in clinical practice in the UK including blood transfusion, treatment with hydroxycarbamide and bone marrow transplantation (BMT).

Objectives

The purpose of the review is to assess the clinical effectiveness and cost-effectiveness of primary stroke prevention treatments for children with SCD who are identified (by TCD ultrasonography) as being at high risk of stroke. The objectives are to systematically examine the published evidence for primary stroke prevention treatments for children with SCD, identify gaps in the current clinical and economic literature, and make recommendations for future clinical research and practice. To this end, a systematic review and economic evaluation were conducted.

Methods

Nine electronic databases [the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE), EMBASE, the Health Technology Assessment (HTA) database, ISI Web of Science Proceedings, ISI Web of Science Citation Index, the NHS Economic Evaluation Database (NHS EED) and MEDLINE] were searched, from inception to May 2011 for randomised controlled trials (RCTs), non-randomised studies and economic evaluations. Studies that compared blood transfusion, hydroxycarbamide or BMT with standard care or with each other were considered; studies of children with TCD velocities of ≥ 200 cm/second were included. Outcomes for clinical effectiveness included incidence of stroke, vasculopathy, adverse events and quality of life (QoL). Cost-effectiveness outcomes included cost per stroke avoided (CPSA) and cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts, applied inclusion criteria to relevant publications and quality assessed the included studies. The results of the data extraction and quality assessment are summarised in structured tables and as a narrative description.

A de novo economic Markov model was developed to assess the cost-effectiveness of blood transfusion for primary stroke prevention in children with high blood velocity and SCD. The Markov model estimated the change in blood velocity, the incidence of stroke and SCD-related complications. The model was run for the lifetime of a hypothetical cohort of 1000 2-year-old patients with SCD. The model was run twice: the intervention scenario, in which blood transfusion is provided as treatment for children with blood velocity of ≥ 200 cm/second and the non-intervention scenario, in which blood transfusion is not provided as treatment for children with blood velocity of ≥ 200 cm/second. The model adopted an NHS perspective and expressed outcomes in terms of cost per QALY gained.

Results

Clinical review

No papers were identified which evaluated the efficacy of BMT or hydroxycarbamide for primary stroke prevention. Two RCTs were identified which considered the efficacy of blood transfusions: the Stroke Prevention Trial in Sickle Cell Anaemia (STOP) trial and a follow-on trial, Optimising Primary Stroke Prevention in Sickle Cell Anaemia (STOP 2). The patient populations differed between the two trials. In the STOP trial, children with abnormal TCD velocities (blood flow velocity of ≥ 200 cm/second) were randomised to receive blood transfusion ($n=63$) or no transfusion ($n=67$), with a mean follow-up time of 19.6 months. In the STOP 2 trial, children whose TCD velocities had normalised after ≥ 30 months of blood transfusion were randomised to continued transfusion ($n=38$) or halted transfusion ($n=41$). No meta-analyses of these trials were undertaken.

In the STOP trial, one patient in the transfusion group had a stroke (primary end point) compared with 11 children in the standard care group. In the STOP 2 trial, the primary composite end point was stroke or reversion to abnormal TCD velocity. In the transfusion-halted group, 16 patients experienced an event (two had a stroke and 14 reverted to abnormal TCD velocities), whereas there were no events in the continued-transfusion group. Both the STOP and STOP 2 trials were halted prematurely due to the number of events that occurred in the standard-care arms.

Economic evaluation

No relevant economic evaluations were identified for inclusion in the review. The de novo modelling suggests that the intervention (blood transfusions plus TCD scans for patients with SCD at high risk of stroke, aged ≥ 2 years) may be good value for money compared with TCD scans only. The intervention has an incremental cost-effectiveness ratio (ICER) of £24,075 per QALY gained, and helps avoid 68 strokes over the lifetime of a population of 1000 patients. The intervention costs an additional £13,751 per patient and generates 0.6 extra years of life in full health per patient.

Discussion

The two STOP trials clearly show the benefit of initiating and continuing chronic prophylactic blood transfusion in children with SCD who are identified to be at high risk of stroke using TCD ultrasonography. Annual TCD scans from the age of 2 years for children with SCD and the initiation of blood transfusion in children whose TCD velocity is ≥ 200 cm/second now form routine clinical practice. However, both STOP trials were prematurely halted owing to large

numbers of events in the non-transfusion arms. A recent meta-analysis by Bassler reported large differences in treatment effect size between trials that were stopped early and similar trials that ran their full course (Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, *et al.* Stopping randomised trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA* 2010;**303**:1180–7). It is therefore unclear what the long-term outcomes of these trials would have been as treatment effects of continued blood transfusion may have been overestimated. It is also unclear for how long prophylactic blood transfusion should continue in order to provide benefits in terms of primary stroke prevention in children with abnormal TCD velocities. Research suggests that 60% of children with high TCD velocities do not go on to suffer a stroke, and there is no method by which to predict which children will not have a stroke and therefore would not benefit from receiving long-term blood transfusion. In addition, there are few data on the pattern of iron overload in children with SCD and the mortality effects of long-term blood transfusion. No published data regarding the efficacy of other primary stroke prevention strategies except blood transfusion were identified. One trial is ongoing to assess the potential role of hydroxycarbamide in reducing TCD velocities in children aged <2 years but results are not yet available.

The ICERs produced by the de novo model are subject to significant uncertainty owing to a number of limitations in the clinical effectiveness and cost-effectiveness data available. Estimates of costs and benefits for individuals with SCD are subject to substantial uncertainty. Sensitivity analyses and validation against existing data and expert opinion have provided some reassurance that the conclusion of the model is reliable; however, it is possible that the conclusion that blood transfusions are cost-effective may be influenced by uncertainty in a small number of model parameters. Further research is thus required to verify the results reported here.

Conclusions

The use of TCD ultrasonography to identify children at high risk of stroke and treating these children with prophylactic blood transfusions appears to be both clinically effective and cost-effective when compared with TCD ultrasonography only. However, given the limitations in the data available, further research is required to verify this conclusion.

Recommendations for future research

Several research recommendations can be proposed from this review. Clinically, more research is needed to assess the effects of long-term blood transfusion on both the QoL and mortality rates of children, the effects of chelation and iron overload in patients with SCD who are receiving blood transfusion, and the length of time for which transfusion should be continued. More data are also needed on the prevalence of SCD in the UK and primary stroke prevention treatment pathways and outcomes, as well as research to identify which children will go on to have a stroke following abnormal TCD results. It is likely that the National Haemoglobinopathy Register will prove useful in obtaining these data. It is also important to assess the potential role of hydroxycarbamide in primary stroke prevention.

From an economic perspective, further research is required to generate more robust data on which to base estimates of cost-effectiveness or against which model outputs can be calibrated. More data are required to explain how utility weights vary with age, transfusions and strokes. Research is also needed around the cost of paediatric stroke in the UK, which also considers indirect costs and the cost of informal care, research around post-stroke outcome data and research into survival rates for children with SCD.

Study registration

This study is registered as PROSPERO CRD42011001496.

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Publication

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NIHR Health Technology Assessment programme

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