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Effectiveness of a top up transfusion programme in preventing cerebrovascular damage in a birth cohort of sickle cell disease

A single centre 10-year retrospective analysis

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Abstract

Regular transfusions are effective in managing strokes in paediatric sickle cell patients. However, there are associated risks, including alloimmunisation and iron overload. This study evaluated the efficacy of top-up transfusions in primary and secondary stroke prevention in a single tertiary paediatric centre in Central London. Forty-seven children with sickle cell disease who received transfusions in the last decade were included. No patient on a primary stroke prevention transfusion programme had a cerebrovascular event during the study period but 9.5% on secondary stroke prevention programme did. Twenty-one percent of patients in this cohort converted to exchange transfusions following transfer to adult services, of which 11% had subsequent strokes. Targeted pre-transfusion haemoglobin S % was not always met; 43% of HbS% readings in a 12- month period were above the set target of 30% and 37% were above the set target of 50%. About a third of patients had evidence of severe hepatic iron overload, but no significant cardiac iron. 25% of patients became alloimmunised, but not severe enough to warrant discontinuation of the transfusion programme. Although transfusions are effective for primary stroke prevention, iron overload remains a significant burden.

Keywords: Sickle cell disease; stroke; transfusion; iron overload; alloimmunisation

Introduction

In the United Kingdom, sickle cell disease (SCD) is one the most common genetic disorders, affecting 1 in 2000 births [1]. The risk of stroke in SCD is highest in the first decade of life [2] and can present overtly or as silent cerebral infarcts (SCIs). SCIs are more prevalent, affecting 17-35% of children, compared to 11% presenting with overt strokes [3] [4]. Within five years of having a SCI, there is a 14-fold increased risk of having an overt stroke. [5]

Without management, strokes recur in 67% of children. One of the most effective ways for prevention is transfusion therapy. In patients with a past history of stroke, maintaining a HbS concentration of less than 30% transfusions can reduce the risk of stroke recurrence to 13% [6,7]. It is unknown for how long transfusions must be maintained before it can safely be stopped without the risk of stroke recurrence, with one study showing the risk of stroke returning after 12 years of treatment [8]. Regular transfusions for primary prophylaxis reduce the risk by 92% [9].

Although transfusion therapy is effective at reducing the risk of stroke, it has its disadvantages. Alloimmunisation rates are high mainly due to antigenic differences between

blood donors and patients, as well as due to the chronic inflammatory state of SCD [10]. Additionally, excess iron from transfusions is deposited in organs leading to organ failure [11]. Iron chelation can help prevent this but is associated with high costs and problems with adherence to therapy. Consequently, alternatives to transfusion therapy have been explored such as hydroxycarbamide [12] [13].

Transfusions can be given as an additive (top-up) or via red cell exchange. Exchange transfusions can assist in reducing iron burden by removing patients' own blood at the same time as transfusing healthy red cells [14] [15]. The aim of this study is to evaluate the effectiveness of the paediatric top-up transfusion programme for stroke prevention in SCD and the extent of iron overload in the cohort.

Materials and Methods

Study Population

Paediatric SCD patients receiving two to six- weekly top-up blood transfusions for a minimum of six months in a London tertiary centre from January 2009 to February 2018 were included in this study. All patients were homozygous for haemoglobin S (HbSS). Indication for regular transfusion therapy were abnormal transcranial dopplers (TCDs), unresponsiveness to hydroxycarbamide, history of transient ischaemic attacks (TIAs) and strokes. Some patients further went on to receive exchange transfusions upon reaching adulthood. At the time of this study, automated exchange transfusions were not available for children in this centre.

Transfusion data

The total amount of blood each patient received over the course of the study and in their last year of top-up transfusions were collected. The frequency and duration of transfusion therapy were noted, as well as the HbS percentage in their last year of treatment. Alloimmunisation rates were collected.

Neuroimaging

TCD readings from the distal internal carotid, the middle cerebral and the bifurcation of the internal carotid artery were analysed; categorised as normal (<170cm/s), conditional (between 170cm/s and 200cm/s) and abnormal (>200cm/s), as defined by the STOP trial[9]. Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) were used to look for cerebral damage and vascular stenosis and categorised as normal, abnormality in the parenchyma or abnormality in the vessels [16].

Measuring Iron Overload

Liver iron concentration (LIC) was measured using R2 MRI (Ferriscan®) imaging and quantified as mg Fe/g dry tissue and cardiac iron was measured by T2* MRI imaging. Severe liver iron overload was defined as LIC >15 mg Fe/g dry tissue and cardiac iron overload was defined as below 20 msec as per published guidelines. The type and dose /kg body weight of chelation therapy each patient received during transfusions were recorded. The proportion of normal, abnormal, and conditional TCDs were measured to determine the effectiveness of the programme for primary prophylaxis. The rate of developing new strokes in children receiving transfusions for secondary stroke prevention was compared to published data.

Statistical Analysis

Microsoft Excel 2016 and SPSS version 24.0 (IBM Statistics, Armonk, New York, USA) were used to collect and analyse the data. A Mann-Whitney U test was conducted to compare alloimmunisation rates with the total volume of blood transfused for each patient, with a p-value of 0.05 to determine significance.

Ethical approval

The study constituted a clinical audit. No patient identifiable material was used in this study and no formal ethical approval was required for this study.

Results

Study Population

Data from 47 children were analysed. The demographics of the patient population is described in Table 1. The total patient follow-up time is 341 patient years. At the time of this study, 20 patients were still being transfused on the paediatric top-up programme. Most of the population were male (75%). The most common indication was high TCDs (32%). More than half of patients started transfusions under the age of 5 years (51%). Thirty- eight percent (n=18) patients received regular transfusions for 5-9 years. 57% of patients used deferasirox film coated tablets (Exjade FCT©) for chelation and about a fifth were additionally taking hydroxycarbamide (19%, n=9). Three patients (6%) underwent bone marrow transplant.

The total volume of blood transfused during the study period, the duration of top-up transfusions and the annualised blood volume transfused per kg body weight can be seen in Figure 1. Six patients (13%) received more blood than 200ml/kg per year. The HbS percentage varied throughout the course of the top-up transfusion programme. Figure 2 shows the target HbS% in their last year of top-up transfusions. Pre-transfusion HbS% targets were not met in 43% of tests for those with a target of 30%. For those with a pre-transfusion HbS % target of 50%, 37% of tests did not meet the target.

Primary Stroke Prophylaxis

Twenty-six patients (55%) had no history of stroke or SCI before starting transfusions. Of those, 23 (89%) had TCDs annually after starting the programme. The proportion of normal, conditional, and abnormal readings in the middle cerebral artery (MCA), bifurcation of the internal carotid artery and the distal internal carotid artery (dICA) are seen in Table 2. The MCA had the highest proportion of conditional readings (9.3%) and the dICA had the highest proportion of abnormal readings (n = 12; 4.8%).

Secondary Stroke Prophylaxis

Twenty-one patients in the cohort (45%) patients had a history of stroke or SCIs. Of these, two (9.5%) had further strokes after starting transfusion programme.

Alloimmunisation Rate

Twelve patients (26%) became alloimmunised whilst receiving top-up transfusions. No significant difference was noted between the rate of alloimmunisation and the volume of blood transfused. The different antibodies that the alloimmunised patients developed can be seen in Table 3, with anti-C being the most common. None of these were severe enough to warrant withdrawal from the transfusion programme.

Iron Overload

MRI-based organ iron overload monitoring results were available in 35 (75%) patients. Of these, 12 patients (34%) had MRI estimate of liver iron concentrations above 15mg/g of dry tissue, with the highest concentration being 39.9 mg/g of dry tissue, indicating severe iron overload. In contrast, none of the patients had evidence of clinically significant cardiac iron deposition (Figure 2)

Exchange transfusions

Following the transfer of clinical care from paediatric to adult services within the same institution, 10 patients in the study went on to receive regular exchange transfusions. Of these, nine patients had a past history of strokes. Subsequent to the commencement of exchange transfusion, one patient with a past history of stroke developed a subsequent stroke. MRI assessment of organ iron overload was available for analysis in six out of 10 patients and demonstrated severe liver iron overload in three patients but no significant cardiac iron deposition.

Discussion

Regular transfusions can prevent strokes in SCD, as both primary and secondary prevention. Consequently, many services have adopted regular transfusions as a part of their stroke management programme. This study aimed to look at the effectiveness of a top-up programme in one paediatric haemoglobinopathy tertiary centre. The rate of stroke recurrence in the secondary prophylaxis group was 9.5%, similar to rates seen previously [17]. No patient on transfusions for primary prevention developed an ischaemic stroke during this study. The HbS percentage of the patients varied, and the pre-transfusion target was not always maintained. In this study, 43% HbS readings were above the set target of 30% and 37% were above the set target of 50%.

More than a third of patients in this study had evidence of severe iron overload and a significant proportion of patients who converted to exchange transfusions remained severely iron overloaded. Adherence to chelation therapy was significant problem in the cohort and persisted beyond childhood. Over a quarter of the cohort became alloimmunised, similar to previous studies [18,19] . The most common alloantibodies were for the Rh and Kell systems, despite the presence of routine matching for ABO, Rh and Kell systems. This apparent disparity may be due to the presence of genotypic differences in blood groups due to the ethnic mismatch between blood donors and recipients in the UK [20]. In contrast to previous studies, the rate of alloimmunisation was not associated the total amount of blood transfused[21]. This may be due to the majority of patients starting transfusions under the age of 5 years which can affect alloimmunisation rates [18].

In conclusion, this study provides real world evidence of the efficacy of top-up transfusions in primary stroke prevention for SCD in a 10-year retrospective analysis of a

single tertiary centre in the UK. Iron overload is still a significant disadvantage for both top-up and exchange transfusions despite regular chelation.

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Table 1 Demographic data of the transfused patients

Parameter	*n* =47		Percentage (%)
Sex	Male	35	75
	Female	12	25
Indication			
High TCD	15		32
Stroke	12		26
SCI	9		19
Vasculopathy	4		9
Symptom control	7		15
Age starting Transfusion			
1-5	24		51
6-10	12		26
11-15	9		19
16-19	2		4
Duration of Transfusion (years)			
0.5-4	15		32
5-9	18		38
10-14	10		21
15-19	4		9
Chelation during top-up transfusion			
Deferasirox	15		32
Exjade FCT	27		57
None	5		11
Hydroxycarbamide (as part of dual therapy)			
	Yes	9	19
	No	38	81
Bone Marrow Transplant			
	Yes	3	6
	No	44	94

TCD: transcranial doppler; SCI: Silent cerebral infarction; Exjade FCT: Deferasirox Film Coated Tablet

Table 2 showing the total number of normal, conditional, and abnormal TCD readings for the middle cerebral artery (MCA), bifurcation of internal carotid artery and the distal internal carotid artery (distal ICA) in children on transfusions for primary stroke prevention.

	Normal n (%)	**Conditional n (%)**	**Abnormal n (%)**	**Total readings**
MCA	222 (86.7%)	24 (9.3%)	10 (3.9%)	256 (100%)
Bifurcation	230 (93.1%)	14 (5.7%)	3 (1.2%)	247 (100%)
Distal ICA	225 (90.7%)	11 (4.4%)	12 (4.8%)	248 (100%)

Table 3 Number of patients who became alloimmunised during the study period and details of antibodies developed

Alloimmunised	n (%)
No	35 (74.5)
Yes	12 (25.5)
Type of antibody n (%)	
C	8 (67)
Cw	1 (8)
e	1 (8)
Kp[a]	5 (42)
Lu[a]	2 (17)

Figure 1. Comparison of the total amount the blood transfused and the duration of transfusion therapy in years (A) and the total amount transfused per kilo in the last year of the patients' top-up transfusion (B).

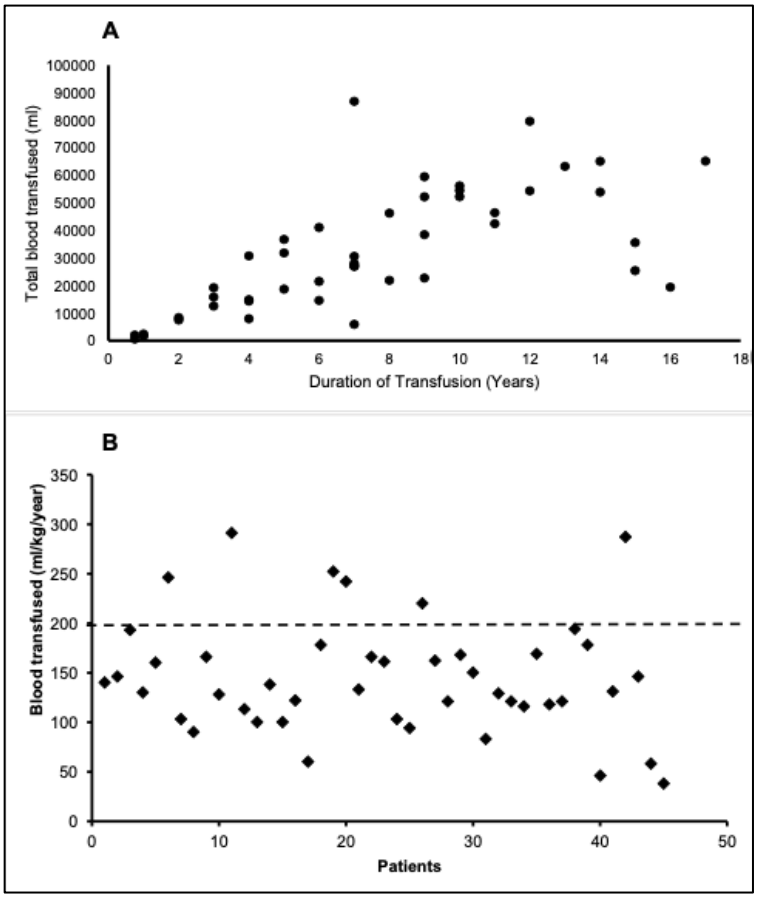

Figure 2. Target HbS% in the last 12 months of top-up transfusions in the study. 43% of the total number of HbS% readings were above the 30% target (2A) and 36.6% of HbS% readings were above 50% (2B)

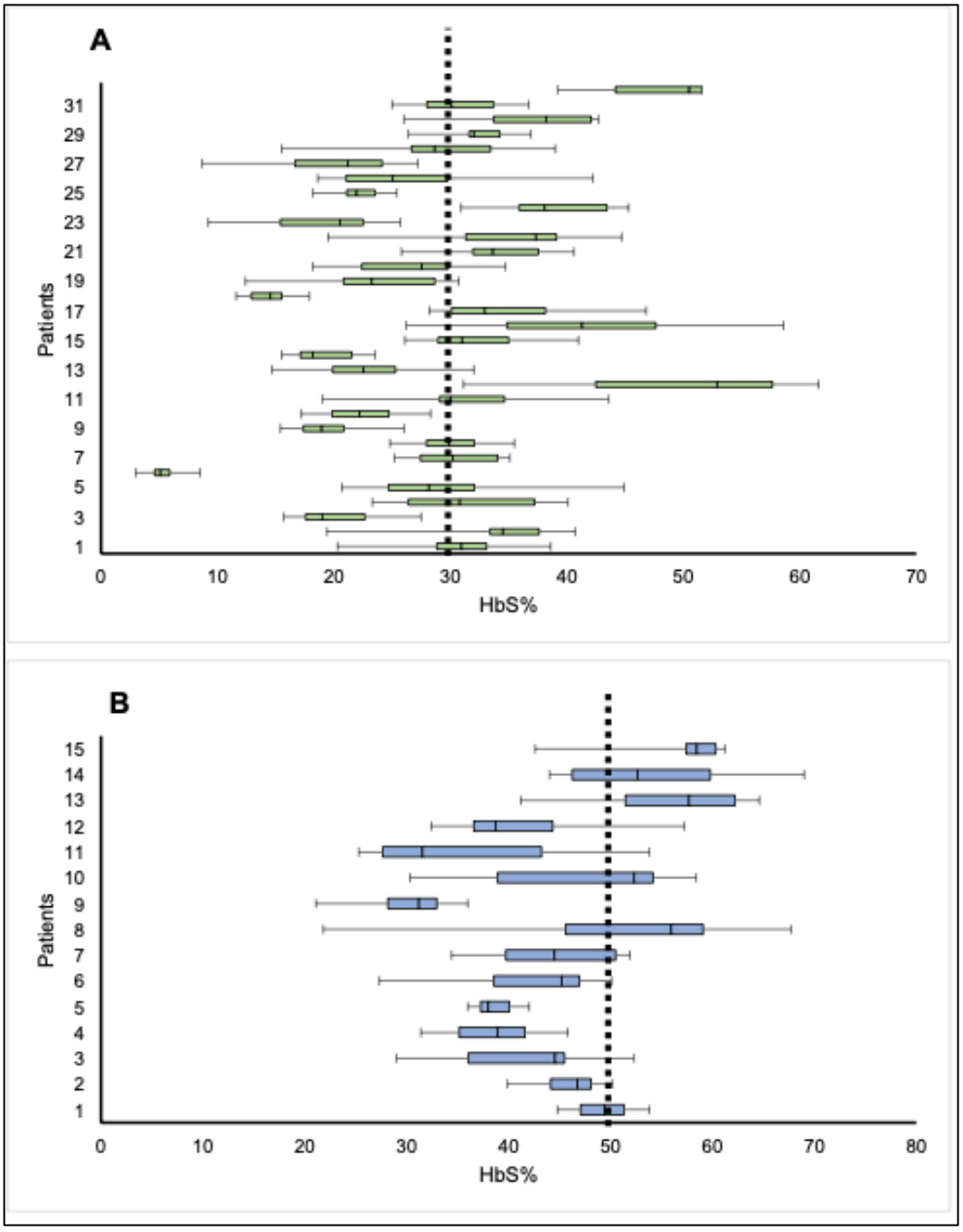

Figure 3 Liver iron concentration (A) and cardiac iron concentration (B) during the top-up transfusion programme. Ferritin levels of the patients during the transfusion programme are displayed in Figure 3C.