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Short Report

Distinct patterns of response to transfusion therapy for different chronic complications of sickle cell disease: A useful insight

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ABSTRACT

Two main sub-phenotypes have been described in sickle cell disease: one with higher baseline haemoglobin and a higher rate of painful crises and one with lower baseline haemoglobin, increased markers of haemolysis and a higher incidence of pulmonary hypertension, priapism and leg ulcers. We compared the patterns of response to regular automated red cell exchange transfusion over a five-year period of 21 patients with recurrent painful crises from the first group and 3 patients with pulmonary hypertension and 5 with recurrent severe stuttering priapism form the second and found them to be distinctly different. Response for pain is slow and increases gradually over years. The most pronounced clinical benefit and the one that appears first is a reduction in the severity rather than the frequency of painful crises. In contrast to the slow and gradual response we see for pain, response of patients with pulmonary hypertension and priapism is immediate with significant clinical improvement even after the first transfusion. The response appears to be directly correlated to the HbS level as the symptoms of both conditions invariably recur rapidly when transfusions are delayed or discontinued but resolve again once they are re-instituted.

1. Introduction

Sickle cell disease (SCD) is characterised by significant phenotypic variability. Two main subgroups have been described: the first characterised by higher baseline haemoglobin (Hb) and a propensity to recurrent painful crises (RPC) [1,2] whereas the second is characterised by lower baseline Hb, higher markers of haemolysis such as bilirubin and lactic dehydrogenase (LDH) and an association with pulmonary arterial hypertension (PAH), priapism, leg ulcers and renal involvement [3]. We report here our five-year experience offering automated red cell exchange transfusions (ARCET) for RPC, PAH and priapism and the different patterns of response observed between the two groups.

2. Methods

Since June 2011, 21 patients have entered at different times a regular ARCET programme in our institution for management of RPC and have completed at least one year. Over the same period, we have also treated 3 patients with PAH and 5 patients who suffered of severe stuttering priapism. The Spectra Optia apheresis system was used by nurses trained and signed competent in the haematology day unit. The same apheresis parameters and settings were used for both groups including draw and return rates and ACDA (citrate) anticoagulant. The procedure, irrespective of indication, was scheduled for every eight weeks but for patients not responding or whose symptoms recurred within that period the interval was reduced to every six weeks. Depending on body weight, all patients received between 10 and 14 units of red blood cells per procedure with a target post-ARCET HbS of $\ll$10%. The aim for the pre-ARCET HbS level was 30–40% but that varied and adjusted according to clinical response. None of these patients was or had been recently treated with hydroxycarbamide as this was declined or contraindicated. Of the patients treated for RPC, 14 completed at least 2 years, 12 patients 3 years, 10 patients 4 years and 4 patients completed at least 5 years (Table 1). Data have been retrospectively analysed and their response was compared to that seen in the 3 patients with PAH and the 5 patients with priapism. Response to treatment for RPC was assessed by the reduction in the number of emergency hospital attendances (EA) for management of pain compared to the year before commencing ARCET. EA were sub-divided in: (a) EA to the emergency department or the haematology day unit with discharge in less than 24 h after analgesia administration (EA $\ll$ 24 h), (b) number of in-patient episodes lasting up to 7 days (IE $\leq$ 7), (c)

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number of in-patient episodes lasting longer than 7 days (IE ≫> 7) and (d) total number of in-patient days in excess of 7 (IPD ≫> 7). Assessing response to treatment was at the discretion of the treating clinician but in general, patients not achieving a ≥25% reduction in EA after the first year of ARCET were considered non-responders (NR).

3. Results

From the 21 patients treated for RPC, 4 were discontinued after a mean of 16 months (14–18) as they were considered NRs. Mean pre-transfusion HbS achieved was 41% (32–57) and did not differ between responding patients and NRs (Table 1). Responding patients showed a 25% reduction in their EA ≪ 24 h 1 year after starting ARCET, 43% after 2 years, 65% after 3 years, 74% after 4 years and 80% after 5 years when compared to their attendances the year prior to ARCET. IE ≤ 7 were essentially unchanged after 1 year. Subsequently, a reduction of 31%, 20%, 30% and 76% was observed 2, 3, 4 and 5 years after starting ARCET respectively. IE ≫> 7 were reduced by 25%, 38%, 44%, 65% and 76% after 1, 2, 3, 4 and 5 years after commencing ARCET respectively. Finally, IPD ≫> 7 were reduced by 48%, 62%, 76%, 83% and 92% after 1, 2, 3, 4 and 5 years of ARCET respectively (Fig. 1). For the 4 patients that ARCET was discontinued as they were deemed as NR, EA ≪ 24 h 1 year after starting ARCET increased by 5% and IE ≤ 7 increased by 96%. At the same time, their IE ≫> 7 reduced by 21% and their IPD ≫> 7 showed a 58% reduction.

The effect of ARCET on PAH and priapism we observed was immediate. We previously reported on two patients with HbSS and right heart catheter proven moderate-severe PAH that were heavily symptomatic despite being on regular simple transfusions to maintain Hb levels between 90 and 100 g/l. Institution of ARCET led to dramatic improvement of their symptoms after their first cycle while a significant improvement in their tricuspid regurgitant jet velocity (TRVmax) and amino-terminal pro-B natriuretic peptide (NT-PBNP) was noted in subsequent assessments. In the intervals between cycles they reported recurrence of their symptoms after the first three to five weeks, an effect we overcame by intensifying the ARCET programme and reducing the inter-procedure interval from eight to six weeks [4]. One of these patients decided to discontinue ARCET in May 2015, 26 months after starting. At that time, she was asymptomatic with no evidence of PAH by echocardiography. Within two months and with her HbS level having risen to 75%, she became increasingly breathless and an echocardiogram in August 2015 showed a TRVmax of 3.6 m/s. She re-started ARCET in September 2015 which led to immediate resolution of her symptoms while a repeat echocardiogram at the end of the same month did not show any evidence of PAH. One year on, she remains on treatment and free of symptoms. More recently, a 62 year old female patient with HbSS, sickle cell nephropathy and established chronic kidney disease became progressively breathless over the space of few months and presented acutely with severe breathlessness and hypoxia (SaO_2 88% on room air). An urgent echocardiogram showed a TRVmax of 3.5 m/s. Pulmonary embolism was excluded. At that point, when asked to describe in her own words her overall sense of health, she described it as"1 out of 10". She underwent ARCET the following day which led to a post transfusion Hb of 101 g/l, and HbS of 6% (pre-transfusion 61 g/l, and 79% respectively) and rapid resolution of her symptoms; she now rated her sense of health as "9 out of 10". Her pre-transfusion NT-PBNP was ≫>25,000 pg/ml (NR 0–120) and post-transfusion reduced to 2460 pg/ml. A repeat echocardiogram the following day (48 h after the first) showed her TRVmax to have reduced to 2.5 m/s.

We reported an identical pattern of response in five patients with HbSS and severe drug-resistant stuttering priapism who used to experience multiple episodes most nights of the week. The primary indication for ARCET was other than priapism for 4 of them (3 secondary stroke prevention and 1 recurrent leg ulcers) but it was noticed that the episodes of priapism ceased immediately after commencing ARCET. Based on this observation, a fifth patient with very troublesome priapism was started on ARCET for that reason with immediate benefit. Like the patients with PAH, these patients also reported recurrence in between cycles and immediate resolution after the next procedure, a phenomenon that diminished as they established on a regular programme and their HbS stabilised at low levels [5].

The procedures were overall well tolerated with no evidence of iron loading and a low allo-immunisation rate of 0.065/100 units of red cells [6].

Table 1
Recurrent painful crises, patient characteristics.

Age	Gender	Genotype	HbS% pre	HbS% post	Years
46	F	SS	67	46 (29–50)	5
49	F	SS	61	49 (30–66)	5
42	F	SS	82	42 (32–58)	5
32	M	SS	58	32 (28–55)	5
45	M	SC	86	45 (42–55)	4
41	M	$S\beta^0$	80	41 (29–65)	4
38	F	SS	52	38 (18–74)	4
45	M	SS	54	45 (40–54)	4
28	M	SS	48	28 (16–37)	4
41	F	SS	81	41 (36–58)	4
27	F	SC	90	27 (21–36)	3
46	M	SS	55	46 (36–57)	3
52	M	SS	81	52 (47–69)	2
48	F	SS	82	48 (34–67)	2
32	M	SS	65	32 (27–34)	1
31	M	SS	84	31 (25–58)	1
55	M	$S\beta^0$	88	55 (46–72)	1
			71	**41 (32–57)**	
NR					
39	M	M	55	39 (35–47)	1
55	F	SC	90	55 (44–62)	1
29	F	SC	77	29 (28–42)	1
50	M	SS	91	30 (44–66)	1
			78	**43 (38–54)**	

HbS% pre = mean pre-transfusion HbS level the year before commencing ARCET, HbS% post = mean pre-transfusion HbS level (and range) after commencing ARCET, years = minimum number of full years on ARCET, NR = non-responders. Figures in bold: Mean values per group.

4. Discussion

This is a single-centre retrospective analysis of the response to ARCET observed in different sub-phenotypes of SCD. Even though the number of patients is small to allow firm conclusions, different patterns of response can be discerned and given the paucity of similar published data, this observation can be useful both in clinical practice and to further help understanding the pathophysiology of different complications of SCD.

Patients on ARCET for RPC were looked at as a group and their response was assessed by comparing their hospital attendances for management of pain after ARCET to those one year prior to commencing the intervention but no formal tools such as pain diaries or quality of life questionnaires were used. Another weakness of this analysis is that other factors that may have influenced individual patients' pattern of attendance have not been taken under consideration. Since these patients have been treated at the same centre in a rather homogenous way we have no reason to believe that would significantly influence the results.

Our data suggest that overall, clinical response for RPC is gradual and builds progressively over time. A more detailed analysis shows that the first sign of response is a reduction in the length of hospitalisation even if the overall number of hospital visits remains

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