Red cell exchange transfusion in sickle cell disease- an overview

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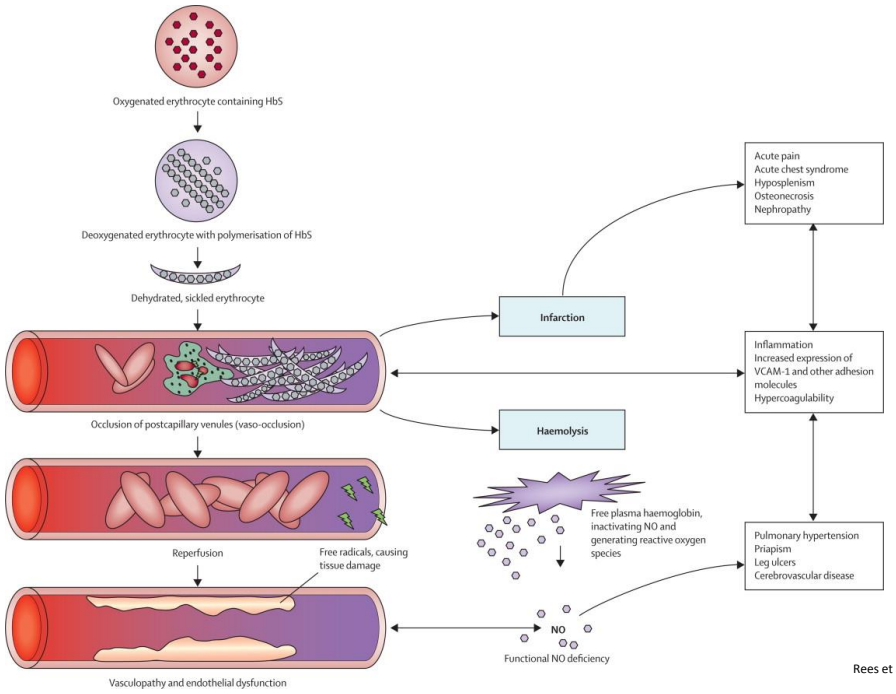
Sickle cell disease

- Monogenic disorder
- Amino acid change from glutamic acid to valine in position 6 of the beta globin chain.
- The resulting haemoglobin S tends to polymerise under reduced oxygen tension deforming the erythrocytes to become sickle shaped.
- This shape change causes excessive adhesion and rigidity of the erythrocytes leading to premature destruction and vessel occlusion which can lead to a number of complications such as tissue necrosis and organ damage



Rees et al Lancet 2010

Sickle Cell Disease – Clinical features

- Chronic haemolytic anaemia
- Painful vaso-occlusive crises
- Increased susceptibility to infection
- Chronic organ damage
- Increased mortality

Complications of SCD- acute

- Painful crisis
- Susceptibility to infection due to functional asplenia
- Dactylitis
- Sequestration crisis- hepatic/splenic
- Chest crisis
- Priapism
- Stroke

Transfusion in SCD

- Mainstay of disease allieviation
- Pivotal role established by several studies, most notably in primary stroke prevention and management of Acute Chest Syndrome (ACS)

- Reduce or dilute sickle haemoglobin containing RBCs in blood
  - Reduces chance of acute vaso-occlusive sickling occuring
- Improved haematocrit and Hb oxygen saturation
  - increases O2 delivery to tissues potentially reversing or ameliorate active sickling
- Suppression of erythropoietin release due to high Hb,
  - reducing production of new HbS containing cells

Why transfuse?

- Prevent organ damage
- Potentially reverse organ damage
- Treat episodes of acute anaemia
- Treat episodes of acute stroke, ACS, priapism and other acute complications of SCD

Indications for chronic transfusions in SCD

Indications	Evidence base
Primary stroke prevention	Stroke Prevention Study in Sickle Cell Anemia (STOP)
Secondary stroke prevention	Stroke Prevention Study in Sickle Cell Anemia 2 (STOP 2) Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)
Silent cerebral infarcts	Silent Infarct Transfusion Trial (SIT)
Pre- operative	Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS): Showed that preoperative transfusion is associated with decreased perioperative complications
Management of recurrent acute chest syndrome	National Acute Chest Syndrome Study Group: Showed that transfusion improves oxygenation Secondary RCT data analyses of STOP, SWiTCH and SIT trials

Other indications for chronic transfusion (expert opinion based)

- Sickle nephropathy
- Recurrent acute chest syndrome
- Recurrent acute painful crises, not responding to hydroxycarbamide
- Stuttering priapism
- Intolerant of hydroxycarbamide due to cytotoxicity
- Sickle hepatopathy
- Early avascular necrosis of weight-bearing joints
- Cerebral vasculopathy in the absence of high TCD velocity

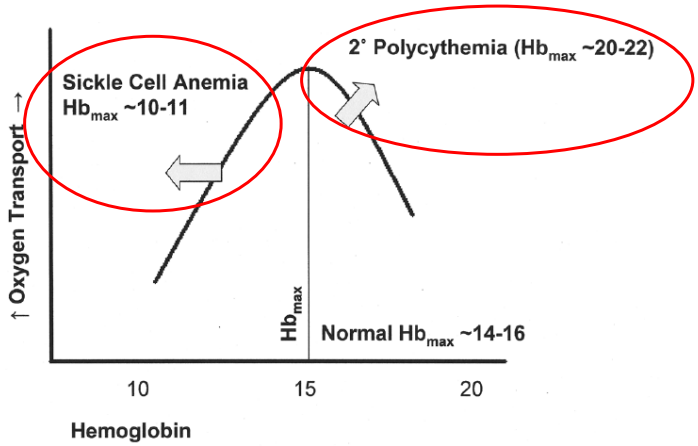
Transfusion considerations: Blood viscosity and flow velocity

- Laminar flow of fluid through a tube:

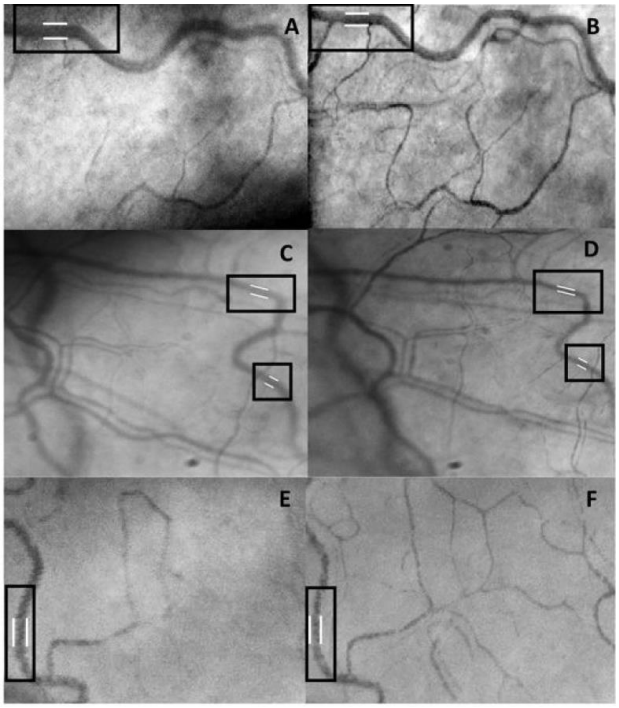
$$v = \frac{\pi p r^4}{8 l \eta}$$

$$\text{velocity} = \frac{\pi \text{ (pressure) (radius of tube)}^4}{8 \text{ (length of tube) (viscosity of fluid)}}$$

Why is viscosity important



Swerdlow PS.Hematology Am Soc Hematol Educ Program. 2006:48-53. Review.



Intravital microscopy pre and post-exchange

- Improved microvascular perfusion
- Reduced flow velocity
- Reduced vessel diameter

Cheung et al J Pediatr Hematol Oncol. 2012 April ; 34(3): 169–174

Limitations of top up transfusion

- Top up transfusions not feasible in patients with high Hb or haematocrit
- Inevitable iron overload, mandating the need for iron chelation, with associated concerns regarding compliance, cost and adverse effects

Benefits of apheresis

- Avoid hypervolemia and hyperviscosity
- Achieve greater reduction in the post-procedure sickle haemoglobin
- Maintain euvolemia throughout and therefore suitable for very low or very high starting haemoglobin
- Achieve neutral or negative iron balance

Pitfalls of Apheresis

- Venous access
- Donor exposure per procedure
- Allo-immunisation*
- Required expertise & Logistical support
- Pathological intolerance to exchange procedure (e.g. in children with significant cerebral vasculopathy)

*Despite higher donor RBC consumption, exchange transfusion has been shown to exhibit a good immunohematologic safety profile relative to conventional transfusion in a large SCD cohort

Michot et al Transfusion. 2015 Feb;55(2):357-63

Automated vs manual exchange

- More consistently achieve desired post procedure HbS%,
  - hence more effective in stroke prevention where S% has to be<30
- More precise control of Haematocrit
- Less dramatic fluid shifts during procedure
- Reduced procedure time
- Less frequent procedures required
  - though more donor blood each time
- No difference in adverse effects or use of iron chelation
- Much more use of central venous access in the automated exchange group, particularly in adults

Kuo KH et al Br J Haematol. 2015 Aug;170(3):425-8 (adult)
Duclos et al Ther Apheresis Sciences 2013 Aug;48(2):219-222 (children)
Quirolo et al Transfusion 2015;55:775–781

Depletion versus conventional exchange: when to deplete

- No direct comparative studies exist, however depletion exchanges can be undertaken in patients with persistently high starting Hct and HbS%
- Depletion exchanges are more likely to achieve negative iron balance
- Depletion exchange required 11% fewer RBC units and increased inter-procedure interval from 37 to 53 days compared to conventional exchange.
  - Estimated savings of more than $4.5 million over 10 years for 20 patients while providing improved care.
- Depletion exchanges are not always tolerated in patients and therefore needs to be chosen carefully

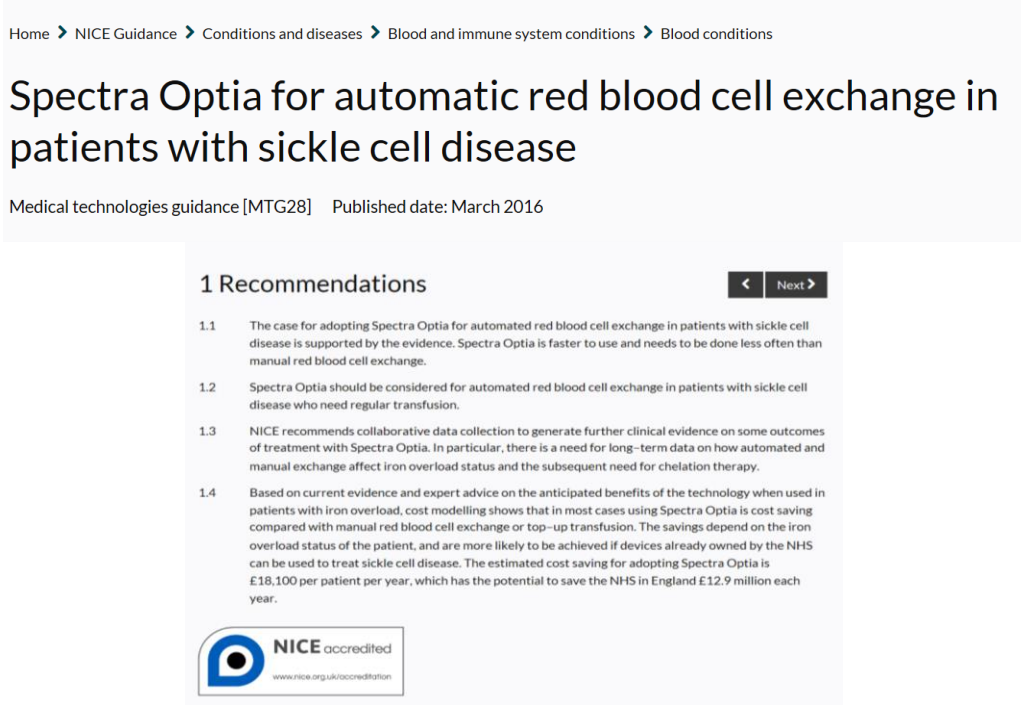
Sarode R et al J Clin Apher. 2011;26(4):200-7

Requirements of an exchange

- RH CcDEe and K compatible <7days old Sickle negative blood
- Reliable venous access x2
- Nursing expertise
- Machinery
- Individualised targets for HbS and haematocrit.

Cost effectiveness of an apheresis service

- Expensive initial outlay
  - may be minimal if centre already has expertise and facilities in therapeutic apheresis for stem cell collection, plasma exchange or platelet donation
- Specific expertise is needed for obtaining peripheral venous access in paediatric services
- Ability to achieve negative iron balance may obviate the need for iron chelation
- Reduced procedure time, reduced frequency of procedure and ability for 1 nurse to potentially run two procedures simultaneously represent significant efficiencies



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Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease

Medical technologies guidance [MTG28] Published date: March 2016

1 Recommendations

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1.1 The case for adopting Spectra Optia for automated red blood cell exchange in patients with sickle cell disease is supported by the evidence. Spectra Optia is faster to use and needs to be done less often than manual red blood cell exchange.

1.2 Spectra Optia should be considered for automated red blood cell exchange in patients with sickle cell disease who need regular transfusion.

1.3 NICE recommends collaborative data collection to generate further clinical evidence on some outcomes of treatment with Spectra Optia. In particular, there is a need for long-term data on how automated and manual exchange affect iron overload status and the subsequent need for chelation therapy.

1.4 Based on current evidence and expert advice on the anticipated benefits of the technology when used in patients with iron overload, cost modelling shows that in most cases using Spectra Optia is cost saving compared with manual red blood cell exchange or top-up transfusion. The savings depend on the iron overload status of the patient, and are more likely to be achieved if devices already owned by the NHS can be used to treat sickle cell disease. The estimated cost saving for adopting Spectra Optia is £18,100 per patient per year, which has the potential to save the NHS in England £12.9 million each year.

NICE accredited
www.nice.org.uk/accreditation

Summary

- Therapeutic apheresis is feasible, safe and effective
- Peripheral access can be successfully used, but needs operator expertise
- Financial case in favour of erythrocytapheresis is strong
- Offers an alternative to simple top up transfusions to the physicians and patients

- Now NICE recommended!