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
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 alleviation
- 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 occurring

- 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

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<td>National Acute Chest Syndrome Study Group: Showed that transfusion improves oxygenation Secondary RCT data analyses of STOP, SWITCH and SIT trials</td>
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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:
  \[ v = \frac{\pi \rho r^4}{8 l \eta} \]

  velocity = \[ \frac{\pi \text{ (pressure)} \text{ (radius of tube)}^4}{8 \text{ (length of tube)} \text{ (viscosity of fluid)}} \]
Why is viscosity important

Intravital microscopy pre and post-exchange
- Improved microvascular perfusion
- Reduced flow velocity
- Reduced vessel diameter


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

Duclos et al Ther Apheresis Sciences 2013 Aug;48(2):219-22 (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

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
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!