Blood Group Incompatible Renal Transplantation and Apheresis

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Background

• There is growing interest in transplantation across the blood group barrier to widen the pool of donor kidneys available.

• This can be achieved using a two-pronged approach of
  
  • desensitisation by either antigen-specific immunoabsorption (IA) or plasmapheresis (PP)
  • and by B-cell depletion therapy
Session Outline

This session will cover:

• A brief review of the theory of ABOi

• Outline of types of apheresis used in ABOi

• Review of the practical aspects of ABO-incompatible renal transplantation in three paediatric case studies
Background

- The greatest barrier to solid organ transplantation is the blood group ABO system.

- If an organ is transplanted which contains non-self A/B antigens, hyperacute rejection will occur causing loss of the graft.
Background

• 1955 - unsuccessful attempt to transplant across the ABO barrier
• 1987 - Alexandre et al, reported successful ABOi, using splenectomy
• Adopted by Japanese to increase living related transplants, in adults and children; heavy immunosuppression used
• Tydén et al in 2003 reported good outcomes in adults using monoclonal antibody (rituximab) rather than splenectomy, immunoadsorption and IVIG.
• First paediatric cases followed in 2005
Antigens

• Nearly all cell plasma membranes express highly specific glycoproteins on their surfaces which act as antigens.
• The antigens expressed on red cell plasma membranes are called agglutinogens (or isoagglutinogens) as they cause agglutination of mismatched red blood cells.
• Plasma also contains preformed antibodies called agglutinins (or isoagglutinins), and individuals possess antibodies against agglutinogens that they do not contain.
# Blood Groups

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Antigen (agglutinogen)</th>
<th>Antibody (agglutinin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (A1, A2*)</td>
<td>A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>none</td>
</tr>
<tr>
<td>O</td>
<td>O</td>
<td>Anti-A, anti-B</td>
</tr>
</tbody>
</table>

*A2 cases have lower antigen expression, and are easier to transplant*
Antibody Production

- Antibodies are not present in newborns and develop during the first year of life in response to exposure to food and environmental factors.
- Children express lower titres than adults
  - 46% of children on deceased donor list had titres < 1:16
ABO-Mismatching

• If there is an ABO-mismatch preformed antibody binds to blood group antigen structures on the endothelial cells of the transplanted kidney.

• This leads to fixation, binding and activation of complement, leading to endothelial cell inflammation and damage, resulting in microthrombi and micro haemorrhages and possible graft infarction.
Titres

• Antibody titres are measured by direct agglutination (saline method) for IgM and IgG levels by the indirect agglutination method.

• These assays are prone to subjective interpretation as it is a semi-quantitative technique and variation between laboratories occurs.

• Titre measurements by flow cytometry, an alternative newer technique, are associated with greater accuracy and reliability.

• Results are expressed in dilutions, with 1:4, 1:8 or 1:16 being considered safe levels at which to proceed with transplantation (British Transplantation Society, 2011).
Disadvantages of ABOi

- Increased risk of PTLD as increased immunosuppression
- Increased risk of opportunistic infections as increased immunosuppression
- Unknown long-term effects of monoclonal antibody use in transplantation
- Only for planned donation as requires work-up period
- Cost of apheresis?
- Increased risk of bleeding peri-operatively?
Benefits of ABOi

• Increases the donor pool by approx. 40%

• Allows living related donation from ABOi parent
Desensitisation

• Transplantation across the ABO barrier is made possible by the process of desensitisation.

• Firstly, formation of B-cell lymphocytes, which would form antibodies against the donor graft, are inhibited by the infusion of an anti-CD 20 monoclonal antibody, such as rituximab, four weeks before transplantation. This supersedes splenectomy.

• Secondly, circulating existing pre-formed antibodies against the donor’s antigens are removed by apheresis techniques such as plasma exchange or immunoadsorption.

• The need for a planned, pre-emptive desensitization programme currently restricts ABOi transplantation to living donation, excluding deceased donor programmes.
Accommodation

• Following ABOi transplantation, most people seem to develop an immunotolerance to the incompatible antigens in the graft and neither reject the graft or develop antibodies against it.

• Those who do develop antibodies against the donor antigens can lose the graft through the processes of rejection.

• There is another group, however, who develop anti-A or anti-B antibodies yet do not experience rejection and this is referred to as accommodation.

• Accommodation - the absence of an antigen-antibody reaction, although antigen is present on the vascular endothelial cells in the graft and there are circulating antibodies.

• The risk of developing acute rejection of the transplanted kidney is greatest immediately following transplantation.
Types of Apheresis

- PP
- DFPP
- Immunoadsorption
Plasmapheresis

- Plasmapheresis (PP) - the removal of plasma from the blood with the replacement of a suitable substitution fluid such as plasma, albumin or colloid (Kumlien, 2008). The term plasmapheresis is used synonymously with plasma exchange (PE).

- Each session of plasmapheresis results in a 20% reduction in antibody levels. When albumin is the replacement fluid, many important physiological substances are not replaced, such as complement, coagulation factors and immunoglobulins; it takes 4-72 hours to return to pre-apheresis levels.

- The indication for plasmapheresis in ABOi renal transplantation is graded category II, grade 1B by the American Society for Apheresis (ASFA) giving it a strong recommendation with moderate quality evidence.
Double Filtration Plasmapheresis

• Double filtration plasmapheresis (DFPP) - plasma is separated from the blood and filtered through a second plasma fractionator to remove specific blood components, such as antibodies and complement factors.

• It is also referred to as cascade filtration. The pore sizes in the membrane determine the selectivity of the process: if the pore size is smaller than that of IgM, then IgM will be retained in the fractionator and not returned to the patient.

• Only a small volume of albumin is removed, therefore only a small amount of substitution fluid is required; coagulation factors are also retained.
Immunoadsorption

- Immunoadsorption (IA) - involves passing the plasma across an immunoglobulin column which removes donor specific anti-A or anti-B IgM and IgG.

- For example, Glycosorb columns (Glycorex, Sweden) contain a synthetic blood group A or B trisaccharides bound to sepharose (a bead-like polysaccharide polymer matrix) and can remove more than 90% of the target isohaemagglutinin without affecting the plasma concentration of albumin, IgG, IgA, IgM or coagulation factors.
Case Study

Double Filtration Plasmapheresis
Case Study DFPP

• 13 year old girl; 34kg
• Diagnosis of dyplasia following twin-twin transfusion
• Creatinine 450 µmol/l, pre-emptive second transplant
• Recipient blood group is O
• Donor (father) blood group is A
• Access via dual lumen tunnelled CVL
Case Study DFPP cont.

- Day -28 - Rituximab
- Day -5 - MMF and tacrolimus commenced
- Day -3 - day -1 – daily DFPP using Evaflux plasma fractionator
- Day 0 - transplant
Case Study DFPP cont.

• Spectra Optia with secondary plasma device – Evaflux 2A10 fractionator, DFPP

• 3 sessions, on consecutive days prior to transplant

• Volumes:
  • circuit = 145-185 mls
  • blood warmer tubing = 40mls
  • plus plasma prime of secondary circuit approx. 50mls

• HF’s weight 34kg, ECV 217-272mls.

• Circuit primed with saline, and blood warmer used on return line
DFPP
DFPP Plasma Volumes

• 1.5-2 plasma volumes processed:
  • Day 1 - 1.5; 164 mins
  • Day 2 - 2.0; 194 mins
  • Day 3 - 1.5; 130 mins
• ACD-A anticoagulant

• Calcium gluconate 10% infused IV via 3-way tap into distal end of circuit
  • 0.04 mmol/kg/hour; made up to 50-100mls.

• Ionised calcium checked pre and post-procedure
Albumin Replacement

- 20% used to replace plasma proteins lost when the fractionator is flushed
- Aiming for 100mls over the session
- Infused via 3-way tap into venous return line
DFPP - Rinsing the Fractionator

• Max pressures of fractionator are <450mmHg

• Fractionator can be flushed to remove accumulated proteins
• 100mls 4.5% albumin used for each flush
• 3 flushes required for first session and then only 2
DFPP - Serum Albumin levels

<table>
<thead>
<tr>
<th></th>
<th>Day -3</th>
<th>Day -2</th>
<th>Day -1</th>
<th>Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin g/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>42</td>
<td>39</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Post</td>
<td>33</td>
<td>33</td>
<td>31</td>
<td>33</td>
</tr>
</tbody>
</table>

Sessions

Pre vs. Post
## Case Study DFPP - Fluid Balance

<table>
<thead>
<tr>
<th>DFPP Session</th>
<th>Weight Pre-DFPP (kg)</th>
<th>Weight Post DFPP (kg)</th>
<th>End Procedure Balance</th>
<th>Actual Gain (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34.1</td>
<td>34.6</td>
<td>645mls</td>
<td>0.5kg</td>
</tr>
<tr>
<td>2</td>
<td>34.0</td>
<td>34.7</td>
<td>754mls</td>
<td>0.7kg</td>
</tr>
<tr>
<td>3</td>
<td>34.9</td>
<td>35.1</td>
<td>577mls</td>
<td>0.2kg</td>
</tr>
</tbody>
</table>
DFPP Anti-A Titres

Day -3  | Day -2  | Day -1  | Day 0
---     | ---     | ---     | ---
8       | 8       | 4       | 4

Anti-A titres

Axis Title: Pre vs Post
DFPP - Hb Levels

<table>
<thead>
<tr>
<th>Day</th>
<th>Hb g/l Pre</th>
<th>Hb g/l Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day -3</td>
<td>103</td>
<td>99</td>
</tr>
<tr>
<td>Day -2</td>
<td>103</td>
<td>89</td>
</tr>
<tr>
<td>Day -1</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>Day 0</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>
Case Study DFPP - Outcomes

- No further apheresis
- Immediate graft function
- Fall in Hb to 4.5 g/dl; blood transfusion required
- Current creatinine is 70-130 µmol/l
- Anti-A titres remain undetectable
Case Study

Immunoadsorption
Case Study IA

• 9 year old girl; 21kg
• Atypical HUS; 1 failed deceased donor transplant
• On HHD using AVF; on call for several years

• Recipient is group O
• Donor (father) is group A
• Anti-A titres as high as 1:128
Case Study IA cont.

- Day -28 - Rituximab
- Day -5 - MMF and tacrolimus commenced
- Day -4 - day -1 – daily immunoadsorption using anti-A column
- Day 0 - transplant
IA procedure

• Spectra Optia with secondary plasma device – Glycosorb anti-A column

• Volumes:
  • circuit = 145-185 mls
  • blood warmer tubing = 40mls
  • plus plasma prime of secondary circuit approx. 50mls

• MA’s weight 21kg, ECV 135-168mls.

• Circuit primed with 4.5% albumin, and blood warmer not used
Immunoadsorption
IA procedure

• ACD-A anticoagulant
• Calcium gluconate 10% infused IV via 3-way tap into distal end of circuit
  • 0.04 mmol/kg/hour; made up to 50-100mls.
• Ionised calcium checked pre and post-procedure

• 2.5 plasma volumes treated each day
• 4 hours per session
Titres – pre/post IA

Days Pre Transplant

Day -4: Pre 64, Post 8
Day -3: Pre 32, Post 2
Day -2: Pre 16, Post 2
Day -1: Pre 8, Post 4
Day 0: Pre 8
## Fluid Balance

<table>
<thead>
<tr>
<th>IA Session</th>
<th>Weight Pre-IA (kg)</th>
<th>Weight Post IA (kg)</th>
<th>End Procedure Balance</th>
<th>Actual Gain (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.5</td>
<td>22.15</td>
<td>491ml</td>
<td>0.65</td>
</tr>
<tr>
<td>2</td>
<td>21.4</td>
<td>22.1</td>
<td>381ml</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>21.6</td>
<td>22.2</td>
<td>404ml</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>21.5</td>
<td>22.25</td>
<td>554ml</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Hb - pre/post IA

HB pre/post

Session Days

Hb g/L

Pre
Post
Case Study IA - Outcomes

• Immediate disease recurrence
  • Rise in creatinine
  • Fragments on blood film
  • Drop in platelets/Hb

• Commenced eculuzimab

• No further apheresis

• Blood transfusion

• Creatinine now stable
Case Study IA - titres

• Titres post-operatively between negative and 1:8
Case Study

Rituximab only
No Apheresis?

• If titres are < 1:8 no apheresis is necessary
• B cell ablation using Rituximab only
Case Study

• 14 year old boy
• Steroid resistant nephrotic syndrome, FSGS
• Previous failed living related transplant from father, at age 12

• Recipient is blood group A
• Donor (mother) is blood group B
Case Study  cont.

• Antibody anti-B titres ranged from 1:4 to 1:8 pre-transplant
• Decision to proceed with B cell ablation only

• Day -28 - Rituximab
• Day -7 - MMF and tacrolimus commenced
• Day 0 and Day 4 – basiliximab
• Plus corticosteroids
Case Study cont.

• Immediate graft function
• Creatinine at 3 years – 100-140 µmol/l
• No disease recurrence
• Negative anti-B titres
Any questions?

Thank you.