Intestinal transplantation: surgical techniques and rejection

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By

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Management of IF

**Acute**
- Intestinal stroke initiatives
  - Nutritional autonomy
    - Yes
    - No

**Chronic**
- Functional, neoplastic and vascular disorders
- Short bowel syndrome
  - Medical and surgical rehabilitation
    - Nutritional autonomy
      - Yes
      - No
    - Visceral Tx
      - No
History of Visceral Tx

1902
Alexis Carrel
Triangulation method

1959
Lillehei
1st MV Tx in dogs.

1960
Starzl
1st ISB Tx in dogs.

1967
Lillehei
1st Reported ISB Tx in Human.

1970
Worldwide n=8, ISB Tx.
Azathioprine; disappointing results

1985
n=18, visceral Tx.
Cyclosporine; refractory rejection and sepsis.

1995
n=162, visceral Tx.
Tacrolimus; improved patient and graft survival.

2000
Center for Medicare and Medicaid Services
Visceral Tx
Approved therapeutic modality for chronic IF with insurance coverage
Visceral (intestinal) Transplantation (Tx)

Types

Isolated small bowel (ISB) Tx

Liver-intestine (LI) Tx

Full MV Tx

Modified MV Tx

Intestine

Intestine

Liver

Intestine

Liver

Stomach

Duodenum

Pancreas

Stomach

Duodenum

Pancreas
Visceral Tx

Protocols of immunosuppression

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Induction agent (s)</th>
<th>Maintenance agent (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daclizumab.</td>
<td>Tacrolimus. Steroids.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol 2</th>
<th>Induction agent (s)</th>
<th>Maintenance agent (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rATG (rabbit antithymocyte globulin). Rituximab.</td>
<td>Tacrolimus.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol 3</th>
<th>Induction agent (s)</th>
<th>Maintenance agent (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alemtuzumab.</td>
<td>Tacrolimus.</td>
</tr>
</tbody>
</table>
PATIENTS AND METHODS

Setting of the study
GI Transplant Division, Miami Transplant Institute/Jackson Memorial Hospital, University of Miami Miller School of Medicine, Miami, Florida, USA

Subjects

Inclusion criteria
Failure of TPN
- Liver failure.
- Thrombosis of central veins.
- Central line-related systemic sepsis.
- Dehydration.

Conditions associated with early death
- Desmoid tumor.
- Ultra-SBS.
- Congenital mucosal disorders.
- IF with high morbidity.

Exclusion criteria
- Significant cardiopulmonary insufficiency
- Incurable malignancy
- Intraabdominal or systemic infections
- Severe immune deficiency syndromes
PATIENTS AND METHODS

TECHNICAL DESIGN

Subjects

Criteria for the donors

Inclusion criteria

• Cadaveric (Brain dead, heart beating).
• Younger than 50 years old.
• Identical and compatible ABO-blood grouping.
• BMI is less than 28 kg/m².
• ICU stay is ≤5 days.
• CIT is no longer than 9 hours.
• Good liver function, if MV allograft is being procured.
• Serum sodium level is not higher than 155 mEq/L.
• CMV and EBV positive or negative donors.

Exclusion Criteria

• Extended criteria donors.
PATIENTS AND METHODS

TECHNICAL DESIGN

Tools of the study

49 Patients

13 Patients
Group (I)
ISB transplant recipients
• SBS.
• Congenital motility disorders.
• Enterocyte absorptive capacity deficiency.
• Gardner’s syndrome.

36 Patients
Group (II)
Full MV transplant recipients
PN associated liver failure
  +
  • SBS.
  • Complex abdominal pathology.

SBS.
PATIENTS AND METHODS

OPERATIONAL DESIGN

Surgical techniques

ISB Tx (n=13)

Back-table preparation
PATIENTS AND METHODS

OPERATIONAL DESIGN

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OPERATIONAL DESIGN

ISB Tx (n=13)

Recipient procedure

Surgical techniques
PATIENTS AND METHODS

OPERATIONAL DESIGN

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Recipient procedure
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Surgical techniques

Full MV Tx (n=36)

Donor procedure
PATIENTS AND METHODS

OPERATIONAL DESIGN

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PATIENTS AND METHODS

Surgical techniques

OPERATIONAL DESIGN

Full MV Tx (n=36)

Recipient procedure
Immunosuppression protocol

Induction immunosuppression
- rATG: 2 mg/kg X5.
- Steroids (Solu-Medrol) in a tapering mode.
- Rituximab.
- Basiliximab.

Maintenance immunosuppression
- Tacrolimus.
- Everolimus.
PATIENTS AND METHODS

OPERATIONAL DESIGN

Graft monitoring

- Frequent endoscopies.
- Serum level of citrulline.
- Clinical examination and hand-held Doppler US.
## RESULTS

<table>
<thead>
<tr>
<th>Recipient Baseline Variables</th>
<th>ISB Tx (n=13)</th>
<th>Full MV Tx (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Age (year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Adult (≥18 year)</td>
<td>69.2% (n=9/13)</td>
<td>50.0% (n=18/36)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>B. Gender</strong></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>1. Female</td>
<td>46.2% (n=6/13)</td>
<td>50.0% (n=18/36)</td>
<td></td>
</tr>
<tr>
<td>2. Male</td>
<td>53.8% (n=7/13)</td>
<td>50.0% (n=18/36)</td>
<td></td>
</tr>
<tr>
<td><strong>C. Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>1. White (non-Hispanic)</td>
<td>53.8% (n=7/13)</td>
<td>52.8% (n=19/36)</td>
<td></td>
</tr>
<tr>
<td>2. Black (non-Hispanic)</td>
<td>23.1% (n=3/13)</td>
<td>16.7% (n=16/36)</td>
<td></td>
</tr>
<tr>
<td>3. Hispanic</td>
<td>23.1% (n=3/13)</td>
<td>30.6% (n=11/36)</td>
<td></td>
</tr>
<tr>
<td><strong>D. Pre-transplant BMI</strong></td>
<td>21.2 ± 1.1</td>
<td>21.8 ± 1.0</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>E. ABO-Blood Group</strong></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>1. A</td>
<td>15.4% (n=2/13)</td>
<td>33.3% (n=12/36)</td>
<td></td>
</tr>
<tr>
<td>2. B</td>
<td>23.1% (n=3/13)</td>
<td>8.3% (n=3/36)</td>
<td></td>
</tr>
<tr>
<td>3. O</td>
<td>61.5% (n=8/13)</td>
<td>58.3% (n=21/36)</td>
<td></td>
</tr>
<tr>
<td><strong>F. Type of Transplant</strong></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>1. Primary Transplant</td>
<td>84.6% (n=11/13)</td>
<td>91.7% (n=33/36)</td>
<td></td>
</tr>
<tr>
<td>2. Secondary Transplant</td>
<td>15.4% (n=2/13)</td>
<td>8.3% (n=3/36)</td>
<td></td>
</tr>
</tbody>
</table>
## RESULTS

<table>
<thead>
<tr>
<th>Other Baseline Variables</th>
<th>ISB Tx (n=13) Mean ± SE</th>
<th>Full MV Tx (n=36) Mean ± SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Donor Age (years)</td>
<td>15.4 ± 3.7</td>
<td>18.3 ± 2.8</td>
<td>0.58</td>
</tr>
<tr>
<td>1. Adult (≥18 years)</td>
<td>23.1% (n=3/13)</td>
<td>52.8% (n=19/36)</td>
<td>0.06</td>
</tr>
<tr>
<td>B. Donor BMI (Kg/m²)</td>
<td>20.6 ± 0.9</td>
<td>20.9 ± 0.7</td>
<td>0.43</td>
</tr>
<tr>
<td>C. Ischemia times</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Cold ischemia time (CIT) (hours)</td>
<td>6.7 ± 0.32</td>
<td>7.8 ± 0.27</td>
<td>0.04</td>
</tr>
<tr>
<td>2. Warm ischemia time (WIT) (minutes)</td>
<td>25.2 ± 1.5</td>
<td>29.4 ± 1.4</td>
<td>0.11</td>
</tr>
<tr>
<td>D. T/B Cell Cross-match</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>1. T-/B-</td>
<td>83.3% (n=10/12)</td>
<td>85.7% (n=30/35)</td>
<td></td>
</tr>
<tr>
<td>2. T-/B+</td>
<td>0% (n=0/12)</td>
<td>2.9% (n=1/35)</td>
<td></td>
</tr>
<tr>
<td>3. T+/B+</td>
<td>16.7% (n=2/12)</td>
<td>11.4% (n=4/35)</td>
<td></td>
</tr>
<tr>
<td>E. Abdominal Wall Closure</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>1. Primary Abdominal Wall Closure</td>
<td>*53.8% (n=7/13)</td>
<td>47.2% (n=17/36)</td>
<td></td>
</tr>
<tr>
<td>2. Vacuum Assisted Closure</td>
<td>46.2% (n=6/13)</td>
<td>52.8 (n=19/36)</td>
<td></td>
</tr>
<tr>
<td>F. Stoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ileostomy</td>
<td>53.8% (n=7/13)</td>
<td>13.9% (n=5/36)</td>
<td>0.005</td>
</tr>
<tr>
<td>2. Colostomy</td>
<td>38.5% (n=5/13)</td>
<td>36.1% (n=13/36)</td>
<td></td>
</tr>
<tr>
<td>3. No Stoma</td>
<td>7.7% (n=1/13)</td>
<td>50.0% (n=18/36)</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS

Indications for ISB Tx

- Congenital: 8%
- Dysmotility: 15%
- Vascular: 15%
- Traumatic: 8%
- Infectious: 8%
- Inflammatory: 46%

Indications for full MV Tx

- Vascular: 30%
- Congenital: 28%
- Dysmotility: 19%
- Traumatic: 6%
- Post-surgery: 6%
- Neoplastic: 11%
- Inflammatory: 46%
RESULTS

Length of hospital stay and readmissions

**Median length of hospital stay**
- **ISB TX**: 39 (14 - 140) days
- **MV TX**: 47 (0 - 270) days
- **P = 0.5**

**Median number of hospital readmissions**
- **ISB TX**: 3.5 (0 - 9) times
- **MV TX**: 2 (0 - 9) times
- **P = 0.2**
RESULTS

Rejection

Kaplan-Meier curve: any biopsy-proven acute rejection free survival by the type of transplant (ISB Tx vs. full MV Tx)

P = 0.01, Log-Rank test
RESULTS

Rejection

- Median time to develop a biopsy proven acute rejection (BPAR)
  - 2.4 (0.6-15.7) months ISB Tx
  - 0.7 (0.1-8.4) months Full MV Tx

Sites of first rejection

<table>
<thead>
<tr>
<th>Site of first rejection</th>
<th>ISB Tx (n=9)</th>
<th>Full MV Tx (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel</td>
<td>n=9</td>
<td>n=7</td>
</tr>
<tr>
<td>Colon</td>
<td>n=4</td>
<td>n=6</td>
</tr>
<tr>
<td>Colostomy</td>
<td></td>
<td>n=2</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td>n=2</td>
</tr>
</tbody>
</table>

Grades of rejection

<table>
<thead>
<tr>
<th>Grade of BPAR</th>
<th>ISB Tx (n=9)</th>
<th>Full MV Tx (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>n=7</td>
<td>n=4</td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
<td>n=4</td>
</tr>
<tr>
<td>Grade III</td>
<td>n=2</td>
<td>n=2</td>
</tr>
</tbody>
</table>
RESULTS

Rejection

Kaplan-Meier curve: severe rejection free survival by the type of transplant (ISB Tx vs. full MV Tx)

Survival Probability

0.95

0.83

ISB TX (n= 13, 2 events).
MV TX (n= 36, 2 events).
P= 0.24, Log-Rank test
RESULTS

Rejection

• Median time to develop an episode of severe rejection
  - 5.7 (1.5-9.9) months ISB Tx
  - 2 (1.5-2.4) months Full MV Tx

• Sites of severe rejection
  - ISB Tx Both the small bowel and the colon in the 2 cases.
  - Full MV Tx The small bowel in one case and the colon in the other case.
### RESULTS

**Rejection**

Stepwise Cox regression results for the hazard rate of developing BPAR during the first 36 post-transplant months (n=49, 19 events)

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Univariable P-value</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>Transplant Type (ISB Tx)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Systemic Drainage</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Citrulline Level at 1st month</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Cox regression model for the hazard rate of developing BPAR during the first 36 months post-transplant (49 cases, 19 events) that includes the 2 variables transplant type, and citrulline level at the 1st month (n=43, 17 events)

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>Transplant Type (ISB transplant)</td>
<td>0.09</td>
</tr>
<tr>
<td>Citrulline Level at 1st month</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Causes of intestinal graft failure among ISB transplant recipients

- Rejection (n=1).
- Volvulus (n=1).

Causes of intestinal graft failure among the full MV recipients

- Rejection (n=2).
- Enterocutaneous fistulas (n=1).
RESULTS

Patient survival

Kaplan Meier curve: patient survival during the first 36 post-transplant months by the type of transplant (ISB Tx vs. full MV Tx)

- ISB TX (n= 13, 0 events).
- MV TX (n= 36, 10 events).

P= 0.04, Log-Rank test
RESULTS

Patient survival

Full MV transplant recipients

- Median time to patient death within the first 3 post-transplant months
  - 1.3 (0-2.7) months

- Median time to patient death during the first 36 months
  - 2.7 (0-7.4) months

- Causes of patient death
  - GVHD (n=4).
  - Sepsis (n=2).
  - Intra-operative coagulopathy (n=1).
  - Intra-operative cardiac thrombosis (n=1).
  - Superior vena cava syndrome (n=1).
  - Rejection (n=1).
RESULTS

Graft survival

Kaplan Meier curve: freedom from graft failure or patient death from any cause (death-uncensored graft survival) during the first 36 post-transplant months by the type of transplant (ISB Tx vs. full MV Tx)

P= 0.26, Log-Rank test
CONCLUSION

• The results of our study support the worldwide agreement about the advantage of the visceral Tx either ISB Tx or full MV Tx in the management of patients with chronic IF.

• Early surgical intervention provides an efficient solution, compatible survival rate and satisfactory quality of life in the management of chronic IF in patients who cannot tolerate the life-long PN.
Thank you