Liver transplantation in infants weighing under 7 kilograms: Management and outcome of PICU


Abstract: Liver transplantation (LT) is an established treatment for children with acute and chronic liver failure. Some reports suggest that infants under the age of 1 yr and children weighing under 13 kg are high-risk groups associated with less satisfactory results. This report describes our experience during the pediatric intensive care unit stay of 16 infants weighing < 7 kg who received LT. We reviewed the records of 16 infants with median age 7.4 months and median weight 5.8 kg, who received 18 liver allografts, nine whole and nine reduced. We also reviewed the use of adrenergic agonist agents, anti-infectious agents, antihypertensive agents, diuretics, immunosuppression protocol, sedation-analgesia agents, others agents (prostaglandin E1, heparin and dipyridamole), diagnosis and management of rejection episodes, follow-up examination, nutrition and outcome. Mean peri-operative blood transfusions were 204 mL/kg, 188 mL/kg of plasma and 36 mL/kg of platelets; mean operative time was 5 h. Primary abdominal wound closure was possible in nine patients. Median initial intensive care unit stay was 18 days. Reasons for an initial stay of more than 18 days were retransplantation (1), gastrointestinal bleeding (2), paralytic ileus and atelectasis (2), septic shock (2), diaphragmatic paralysis, renal impairment and acute respiratory distress syndrome (2). Mean requirement for artificial ventilation was 168 h. Mean use of dobutamine, prostaglandin E1 and dopamine was 3.3, 7.5 and 8.8 days, respectively. Parenteral nutrition was started at a mean of 48 h and oral food intake was started at a mean of 72 h. The most frequent complications were infection, atelectasis, gastrointestinal bleeding, acute renal failure and hepatic artery thrombosis. Four children required six re-explorations and two received retransplantation. Mean overall survival rate was 82% and graft survival was 72%. Weight alone (under 7 kg) should not be considered as a contraindication for LT. The survival rate of children post-LT is excellent regardless of graft type.

LT is an established treatment for children with acute and chronic liver failure. Although some reports suggest that infants under the age of 1 yr and children with body weight below 13 kg are high-risk groups associated with less satisfactory results (1), more recent reports show the results of LT in these children to be comparable with those of others undergoing LT (2–5).

The development of reduced-size LT and living-related LT has extended LT to many small infants who would otherwise have died while waiting for a size-matched graft (6–8).

This report describes our experience during the PICU stay of 16 infants weighing < 7 kg (normal
weight of infant about 6 months, and technically more difficult to transplant) who received a liver transplant. A total of 13 of our patients were under 1 yr of age when they underwent initial LT.

Patients and methods
Between June 1992 and December 2002, 89 children under the age of 17 yr received 100 LTs performed at our center. Of the 89 patients, 16 infants (18%) under 7 kg were referred for assessment for LT. Median age was 7.4 months (range 1–14) and median weight 5.8 kg (2.6–6.95). The infants (10 girls, six boys) received 18 liver allografts, nine whole and nine reduced. Indications for transplantation were biliary atresia (12), neonatal hepatitis (2), fulminant viral hepatitis (1), undetermined-cause fulminant liver failure (1) and cirrhosis (not specified) (1). We used the PELD 3 score (9) in children awaiting LT Table 1.

Adrenergic agonist agents
Dobutamine or adrenaline were used when an inotropic effect was required and dopamine or noradrenaline were used in the case of hypotension, depending upon tachycardia, existed.

Anti-infectious agents
Initial antimicrobial therapy included amoxicillin-clavulanic acid and aztreonam, and was later altered or stopped after the results of peri-operative cultures became known.
Sulfamethoxazole/trimethoprim was used as prophylaxis against *Pneumocystis carinii* pneumonia at a dose of 5–10 mg/kg/day. Ganciclovir was used in CMV-negative recipients at a dose of 10 mg/kg/day over 21 days and nystatin as required.

Table 1. Recipient, graft characteristics and PICU outcome

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Sex/age (months)</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>PELD score</th>
<th>Graft</th>
<th>Outcome (months)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F/14</td>
<td>6.95</td>
<td>Biliary atresia</td>
<td>33.68</td>
<td>Segmental (left lobe)</td>
<td>Alive 131</td>
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<td>2</td>
<td>F/7</td>
<td>6.5</td>
<td>Biliary atresia</td>
<td>36.44</td>
<td>Segmental (left lobe)</td>
<td>Alive 88</td>
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<tr>
<td>3</td>
<td>F/4</td>
<td>5.6</td>
<td>Cirrhosis (not specified)</td>
<td>38.55</td>
<td>Whole</td>
<td></td>
</tr>
<tr>
<td>Retransplantation (18 days) HAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alive 87</td>
</tr>
<tr>
<td>4</td>
<td>M/7</td>
<td>6.22</td>
<td>Biliary atresia</td>
<td>36.8</td>
<td>Whole</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>M/14</td>
<td>6.4</td>
<td>Biliary atresia</td>
<td>46.2</td>
<td>Whole</td>
<td>Alive 94</td>
</tr>
<tr>
<td>6</td>
<td>M/9</td>
<td>6.95</td>
<td>FHF</td>
<td>32.16</td>
<td>Segmental (left lobe)</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>M/10</td>
<td>5.8</td>
<td>Biliary atresia</td>
<td>47.63</td>
<td>Whole</td>
<td></td>
</tr>
<tr>
<td>Retransplantation (11 days) HAT</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>8</td>
<td>M/12</td>
<td>6.5</td>
<td>Biliary atresia</td>
<td>47.69</td>
<td>Segmental (II–III)</td>
<td>Alive 48</td>
</tr>
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<td>9</td>
<td>F/6</td>
<td>5.4</td>
<td>Biliary atresia</td>
<td>33.38</td>
<td>Segmental (left lobe)</td>
<td>Alive 43</td>
</tr>
<tr>
<td>10</td>
<td>F/1.5</td>
<td>2.7</td>
<td>Neonatal hepatitis</td>
<td>37.43</td>
<td>Whole</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>M/4</td>
<td>6.95</td>
<td>FHF</td>
<td>52.5</td>
<td>Segmental (I, II, III, IV, V, VIII)</td>
<td>Alive 26</td>
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<tr>
<td>12</td>
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<td>Biliary atresia</td>
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<td>Whole</td>
<td>Alive 22</td>
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<tr>
<td>13</td>
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<td>Biliary atresia</td>
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<td>Segmental (II–III)</td>
<td>Alive 11</td>
</tr>
<tr>
<td>14</td>
<td>F/2</td>
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<td>Neonatal hepatitis</td>
<td>54.53</td>
<td>Segmental (II–III)</td>
<td>Alive 9</td>
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<td>15</td>
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<td>Whole</td>
<td>Alive 7</td>
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<td>F/14</td>
<td>6.3</td>
<td>Biliary atresia</td>
<td>42.78</td>
<td>Whole</td>
<td>Alive 6</td>
</tr>
</tbody>
</table>

Antihypertensive agents
Clonidine or hydralazine are given for systemic hypertension, depending on whether symptoms of sympathetic overactivity occur. Others as nifedipine and captopril (ACE inhibitor) if necessary.

Diuretics
Dopamine is administered at 2.5 mcg/kg/min in continuous infusion to achieve a urine output of 1–1.5 mL/kg/h. If necessary, we use furosemide, spironolactone and chlorothiazide are given as required. When renal impairment appears, we use mannitol or dialysis.

Immunosuppression
TCL has been used at an initial oral dose of 0.15–0.20 mg/kg/day, and subsequent doses adjusted on the basis of recommended trough blood TCL concentrations at different stages: 0–1 post-transplant month, 10–15 ng/mL; 1–3 months, 8–12 ng/mL; 3–12 months, 8–10 ng/mL; >12 months, 5–8 ng/mL. Fluconazole is co-administered in cases of very low trough blood TCL concentrations because of a marked increase in TCL bioavailability by local inhibitory effect. If we cannot reach the trough blood TCL recommended concentration with a two-time daily schedule, we switch to a three-time daily schedule.
Methylprednisolone was used in the post-operative period as follows: 10 mg/kg/day in two doses, then 8, 6, 4, 2 mg and eventual discontinuation over 3–6 months. Since February 2000, basiliximab (Simulect™; Novartis Pharmaceutical Corporation, Hanover, NJ, USA), a chimeric anti-IL-2 receptor monoclonal antibody, has been used with the first dose administered on day 0 at 12 mg/m² and the second on day 4 post-transplantation if CD25 lymphocytes are over 2%.
Sedation-analgesia agents

Sedation with midazolam or propofol is administered depending on whether hypotension and/or bradycardia exist or not. Analgesia consists of fentanyl or remifentanil. Rocuronium or vecuronium are used as a skeletal muscle relaxant and cisatracurium when altered liver function exist.

Others

Prostaglandin E₁ (0.1–0.6 mcg/kg/min) was used to maintain splanchic circulation. Prophylactic heparin was administered if prothrombin time (PT) > 60% (in two consecutive determinations). Normal PT (78–110%), international normalized ratio (INR): 100% (1), 75% (1.5), 50% (2), 37.5% (2.5), 25% (3), 18.7% (3.5), 12.4% (4), activated partial thromboplastin time (APTT) ratio < 2 (normal APTT ratio: 0.8–1.2) and antithrombin III (ATIII) > 80%; and for 2 wk after transplantation followed by anti-aggregants (dipyridamole) if platelet count was > 100 000/mm².

Diagnosis and management of rejection episodes

The diagnosis of rejection was based on clinical, biologic and, on occasions, histologic criteria (some episodes were treated without confirmation by liver biopsy). Acute graft rejection episodes were treated with 10 mg/kg/day steroid bolus over 3 days. If graft dysfunction persisted, MMF was introduced. If the acute graft rejection episode persisted, a trial switch of immunosuppressant was required.

Monitoring of intra-abdominal pressure

Bladder pressure was our method of choice to monitorize the intra-abdominal pressure, especially when patients were mechanically ventilated. The cut-off of a too high pressure was 15–20 mmHg. The therapeutic measure to correct a too high pressure was the use of temporary silastic patches.

Follow-up examination

Liver ultrasound was performed daily for the first 5 days, then twice a week for 2 wk and then once a week until discharge at home.

Nutrition

Oral food intake was allowed as soon as possible in the absence of a surgical contraindication. Supplementary nasogastric feeding or parenteral nutrition, or both, were provided to restore nutrition. We start with casein hydrolysate formulas. Ranitidine and/or sucralfate were always used as gastric protection. Omeprazole was occasionally used.

Statistical methods

The means of anthropometric before and after transplant were compared by the paired t-test.

Results

Twelve infants had evidence of severe decompensated liver disease at the time of transplant, and two required ventilatory support (two had acute encephalopathy). Eleven infants were severely malnourished (mean standard deviation score was −2.65 for weight and −2.32 for height). One year after LT, the mean standard deviation score was −0.99 for weight and −1.39 for height: differences were significant (p < 0.05).

Medical follow-up

The median initial intensive care unit stay for 16 patients (18 transplants) was 18 days (range: 1–180). Reasons for an initial stay of more than 18 days were retransplantation (2), gastrointestinal bleeding (1), paralytic ileus and atelectasis (1), septic shock (1), diaphragmatic paralysis, renal impairment and ARDS (1).

The mean requirement for artificial ventilation for 16 transplantations was 168 ± 158 h (range: 24–456). Mean use of dobutamine, prostaglandin E₁ and dopamine was 3.3 ± 2.8, 7.5 ± 1.94 and 8.8 ± 3.4 days, respectively. Parenteral nutrition was started at a mean of 48 h, lasting 12.3 ± 6.8 days; oral food intake was started at a mean of 72 h.

Complications

The most frequent complications were infection [31 episodes in 10 (62%) patients], atelectasis [seven episodes in six (37%) patients], gastrointestinal bleeding [seven episodes in five (31%) patients], acute renal failure [six episodes in six (37%) patients], hepatic artery thrombosis [five episodes in four (25%) patients], hypertension [five episodes in five (31%) patients] and gastroenteritis [four episodes in four (25%) patients]. Other complications which occurred in three cases with time were acute rejection episodes, portal vein thrombosis, thrombocytopenia and leucopenia; complications which occurred in two cases with time were anemia, ARDS, biliary stricture, hyperglycemia, hypogammaglobulinemia; and other complications which occurred in one case with time were bronchitis, chylothorax, diaphragmatic paralysis, pleural effusion, pneumothorax, acute tubular necrosis, nephrotic syndrome, ascites, biliary peritonitis, paralytic
ileus, pneumoperitoneum, and disseminated intravascular coagulation.

However, four children required six re-explorations because of the following complications: pneumoperitoneum, intra-abdominal hematoma, biliary peritonitis, diaphragmatic paralysis, hepatic artery thrombosis and portal vein thrombosis.

Retransplantation

Two of 16 patients (12%) received more than one graft. Reasons for retransplantation are given in Table 1.

Infection

The number of infection episodes was 10 in one, five in one, three in two, two in four and one in two patients. The most frequent pathogens causing two or more infection episode were Candida species (eight episodes), Staphylococcus coagulase-negative (five episodes), Pseudomonas aeruginosa (five episodes), P. cepacia (three episodes), Enterococcus faecium (two episodes), Flavobacterium meningosepticum (two episodes), CMV (two episodes). Any of our infants found to have Epstein–Barr virus. Septicemia was the most frequent infection episode.

Deaths

Causes of death were MOF, 24 h after transplantation in one patient, poor graft function secondary to hepatic artery and portal vein thrombosis and MOF, 5 days after transplantation in one and adenovirus pneumonia and MOF, 6 months after transplantation in another.

Discussion

In this series of 16 patients weighing <7 kg at the time of transplantation, biliary atresia continued to be the most frequent indication, as in older children (10, 11). All but one had previously undergone hepatic portoenterostomy (Kasai procedure) in the early weeks of life.

LT in infants represents a major medical and technical challenge particularly in babies weighing <5 kg (2, 12). Further reduction of the left lateral segment is possible to provide a single segment graft (segment III) (13). LT was not considered by some groups in infants weighing under 3 kg (14). However, some groups have reported their experience with LT in infants during the first 3 months of life, with mean weight at the time of transplantation of 3.4 ± 1 kg (13, 15). Median peri-operative blood loss was similar to that reported by other authors (11, 16). The size of the donor is an important consideration. In our series, the mean weight ratio between donor and recipient was 5.27. It is important to avoid compression of the graft or right lung, and temporary abdominal closure (using a silastic patch if necessary) is advisable in cases where there is any degree of tightness. We have not experienced problems with delayed closure and have not seen an increase in wound infection in these patients, in common with other authors (16). Any patient who stays in the PICU after LT should be intra-abdominal pressure-monitored by direct or indirect methods, especially if mechanically ventilated. Bladder pressure is considered the method of choice (17).

In common with other groups, infection was a major problem in 10 (62%) of our patients (2, 3, 10). Sepsis was the most frequent infection, affecting five (31%) of the infants but causing no deaths. Hepatic artery thrombosis is a major complication which frequently leads to loss of graft and death of the patient; the mortality rate is approximately 50% (2, 4, 11, 18). Hepatic artery thrombosis occurred in four (25%) patients, in one twice, and all in full-size livers, in accordance with the observation of a lower rate of this complication in reduced livers (18). Two deaths occurred. The retransplantation rate in infants under 1 yr of age has been reported to range from 9.5 to 41%, often as a result of hepatic artery thrombosis, primary non-function, or rejection (4). In our series, two of 13 (15%) patients under 1 yr needed retransplantation, performed for hepatic artery thrombosis, 11 and 18 days, respectively, after the initial successful LT. Both patients made an uneventful recovery and have remained well.

Previous reports suggest that the survival of children under 1 yr after LT is lower than that of older children (18, 19). Factors associated with reduced survival rates include age under 5 and 12 months in recipients receiving full-size grafts, development of vascular thrombosis and donor weight under 6 kg (20). In the earliest report on infants under 1 yr of age undergoing LT, survival in 20 infants was 60% (19). With improved preservative solutions and surgical techniques and advances in immunosuppression and treatment of infections, a steady improvement ranging from 64 to 100% has been observed in small patient survival (2, 4, 5, 10, 11, 13, 18, 20). The mean overall survival rate for these infants was 82%. Mean follow-up was 46.3 months (range: 6–131). All survivors have normal liver function. Graft survival has been reported to range from 57 to 80% in infants undergoing LT (10, 11, 19). In our series, graft survival was 72%. The mean
overall survival rate of our group of 73 bigger/older children was 78%, and graft survival was 70%. The significant improvement of weight and height at 1 yr post-transplant was similar to that reported by other authors (2, 10).

Conclusions

LT in infants weighing < 7 kg is technically demanding but feasible and can still be performed with good outcome. Weight alone (under 7 kg) should not be considered a contraindication for LT. The improvement in survival rates in this group of very sick infants is related not only to the development of reduction hepatectomy but also to advances in medical and nursing expertise. Surgical techniques must be adapted for adequate graft preparation, vascular reconstruction and abdominal closure. The survival rate of children post-LT is excellent regardless of graft type.

Acknowledgment

We appreciate the help of Miss Christine O’Hara for useful manuscript corrections.

References