Pulmonary retransplantation in paediatric patients: a justified therapeutic option? A single-centre experience

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Abstract

Objective: Pulmonary retransplantation remains controversial due to the increased morbidity and mortality compared with primary lung transplantation. So far, only few data about paediatric retransplantation are available. We retrospectively analysed our experience with retransplantations in children. Methods: Since 1994, seven pulmonary retransplantations in children were performed at our institution. We analysed pretransplant characteristics, operative parameters as well as the post-transplant outcome of these recipients and compared them to 29 patients who underwent primary lung transplantation during the same period. Results: Indications for retransplantation were bronchiolitis obliterans syndrome in six patients and primary graft failure in one patient. Pretransplant characteristics, perioperative morbidity and mortality were similar in both groups. Hospital mortality was 2/7 (29%) after retransplantation and 6/29 (21%) after primary transplantation (p = 0.64). Actuarial 3-year survival was 71% and 60% after redo and primary transplantation, respectively (p = 0.50). Development of bronchiolitis obliterans syndrome did not differ between both groups (p = 0.99). Conclusions: In our small cohort of paediatric patients, pulmonary retransplantation was associated with an acceptable long-term outcome comparable to primary pulmonary transplantation. This differs from currently available data. However, further long-term studies including more patients and longer follow-up intervals are required.

Keywords: Paediatric lung transplantation; Pulmonary retransplantation; Bronchiolitis obliterans syndrome

1. Introduction

Lung transplantation (LTx) has become an established therapeutic option not only for adults but also for children with a variety of end-stage pulmonary diseases. Rising experience concerning the operative procedure itself as well as the postoperative management led to a lower in-hospital morbidity and mortality. By contrast, long-term survival is still not satisfactory. Bronchiolitis obliterans syndrome (BOS) is the main cause of late death. It occurs in about 50% of paediatric lung recipients within the first 5 years and is responsible for 43–62% of late deaths [1,2]. Despite different treatment strategies for BOS that have been reported [3,4], an effective prevention or therapeutic option does not exist. End-stage BOS may finally lead to lung failure and cause an impaired quality of life [5]. Thus, lung retransplantation (re-LTx) remains the only treatment option in many of these patients. Further indications for re-LTx are acute graft failure, severe acute rejection and, in rare cases, also major airway stenoses. Acute graft failure is the leading cause of early postoperative mortality, causing almost 30% of early deaths [1].

The use of the few available donor organs for retransplantations has to be justified in the face of patients dying on the waiting list for primary transplantation. So far, studies dealing with pulmonary retransplantation in children are rare. Most studies report a considerably worse long-term outcome compared with primary transplantation [2,6,7]. In pulmonary retransplantation with use of organs from deceased donors, median survival was approximately 1 year. By contrast, the recent paediatric LTx report of the registry of the International Society of Heart and Lung Transplantation (ISHLT) showed an improved survival after retransplantation [1].

Thus, additional data are required for a substantial judgement on this treatment option as for our advice towards our patients and the justification of the use of donor organs for this patient group. In this study, we analysed pretransplant characteristics, operative parameters, as well as post-transplant outcome of paediatric patients, who underwent
2. Patients and methods

In the observation period between October 1994 and July 2009, 38 paediatric patients underwent primary LTx at our institution. Within this group, re-LTx was performed in seven children (study group). Two patients, who were older than 18 years at the time of re-LTx, were excluded from this study. Thus, a cohort of 29 children after primary LTx was used for comparison (control group). All patients received organs from deceased donors.

Immunosuppression was the same in both groups and consisted of tacrolimus (or cyclosporine A), mycophenolate mofetil (or azathioprine) and prednisone. There was no difference in the anti-infective prophylaxis policy in both groups. Patients at risk received a prophylaxis against cytomegalovirus with ganciclovir, followed by valganciclovir, as soon as oral administration was possible, for a total of 3 months. Prophylaxis against Candida infection was performed with oral amphotericin B for 6 months, and against Pneumocystis jiroveci infection with cotrimoxazole. In case of pre-existent colonisation with Aspergillus, patients also received voriconazole for 3 months, followed by itraconazole as all other patients did from the time of transplantation.

All patients were regularly seen at our institution. Flexible bronchoscopy including broncho-alveolar lavage was routinely performed during the first 6 months after transplantation. Thereafter, bronchoscopy was only performed when clinically indicated. Pulmonary function tests were performed at least every 3 months at our institution. In the meantime, the patients used portable handheld spirometers on a daily basis at home. Acute rejection was diagnosed by pulmonary functional tests as well as bronchoscopic and radiographic findings. Additional trans-bronchial biopsies were performed if diagnosis remained unclear. BOS was defined according to the standard spirometric criteria [8] after the exclusion of infection and airway stenoses.

Table 1. Demographic data, indications for transplantation, preoperative characteristics and kind of transplantation. LTx, lung transplantation; HLTx, heart/lung transplantation.

<table>
<thead>
<tr>
<th>Study group at re-LTx (n = 7)</th>
<th>Study group at primary LTx (n = 7)</th>
<th>Control group (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplantation [years], median (range)</td>
<td>17.1 (14.0–17.9)</td>
<td>14.1 (12.0–17.8)</td>
</tr>
<tr>
<td>Indications for transplantation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>5 (71)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1 (14)</td>
<td></td>
</tr>
<tr>
<td>Acute interstitial pneumonia</td>
<td>1 (14)</td>
<td></td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>3 (10)</td>
<td></td>
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<tr>
<td>BOS after primary transplantation</td>
<td>6 (86)</td>
<td></td>
</tr>
<tr>
<td>Primary graft failure</td>
<td>1 (14)</td>
<td></td>
</tr>
<tr>
<td>Preoperative characteristics, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedridden patients</td>
<td>4 (57)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Ventilator-dependent at time of transplantation</td>
<td>3 (43)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>ECMO dependent at time of transplantation</td>
<td>1 (14)</td>
<td>1 (14)</td>
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<tr>
<td>Kind of transplantation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral LTx</td>
<td>6 (86)</td>
<td>5 (71)</td>
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<tr>
<td>Single LTx</td>
<td>1 (14)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>HLTx</td>
<td>0 (0)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Among them, reduced-size LTx</td>
<td>2 (29)</td>
<td>3 (43)</td>
</tr>
</tbody>
</table>

2.1. Statistical analysis

All data were prospectively recorded and retrospectively analysed. Categoric variables were analysed by using Fisher’s exact test. Continuous variables with Gaussian’s (normal) distribution were expressed as mean ± SD. Differences between two groups were analysed with the Student’s unpaired t-test. Parameters with non-normal distribution were expressed as median and range. Differences were analysed using the Mann—Whitney U-test. Survival and time to BOS analysis was performed using the Kaplan—Meier method, and differences between groups were calculated by the Mantel—Cox log-rank test. SPSS for Windows (version 16.0.2, SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. All analyses were two-tailed with a p-value of less than 0.05 considered statistically significant.

The Hannover Medical School Ethics Committee granted approval for this research.

3. Results

3.1. Pretransplant characteristics, morbidity and mortality

Patient characteristics, indications for transplantation and kind of transplantation are summarised in Table 1. There were no significant differences between the groups (p > 0.10, except indications for retransplantation). Table 2 demonstrates donor-specific and perioperative data, as well as hospital morbidity and mortality that were similar in both groups. Median survival was 4.6 years after retransplantation and 3.8 years after primary transplantation (p = 0.91, Fig. 1). One-year actuarial survival was 71% in the study group and 65% in the control group. Three-year survival was 71% and 60% (standard error 17% and 10%), respectively. Four of the seven patients (57%) after pulmonary retransplantation are still alive 1.5, 3.2, 3.3 and 12.6 years after retransplantation (Table 3). One cystic fibrosis (CF) patient died 4.6 years after retransplantation because of BOS. The two other patients died during the early postoperative
course. The first child was on extracorporeal membrane oxygenation (ECMO) due to acute interstitial pneumonia and underwent single LTx. Retransplantation was performed 17 days later because of acute graft failure. He died 5 days after re-LTx because of respiratory failure combined with multiple-organ failure. The second patient underwent retransplantation after ECMO for end-stage BOS and died 14 days later because of septic multiple-organ failure.

In the control group, 17 of 29 patients (59%) are still alive. Causes of deaths were BOS in three patients, early graft failure, multiple-organ failure and infection ($n = 2$ each), and recurrence of cancer, post-transplant lymphoproliferative disorder and drug abuse ($n = 1$ each).

### 3.2. Best lung function after retransplantation

In four of the five patients, who were discharged after retransplantation, forced expiratory volume in 1 s (FEV$_1$) (%) predicted, best value that was achieved after LTx was better after retransplantation than after primary transplantation (Table 3). The FEV$_1$ of the study group was comparable to that of the control group ($88 \pm 25\%$ vs $83 \pm 14\%$, study group vs control group, $p = 0.60$).

### 3.3. Functional status and development of BOS after retransplantation

Three of the seven patients after re-LTx follow normal daily activities and are free of BOS (stages 1–3). 1.5, 3.2 and 12.3 years after retransplantation after ECMO for end-stage BOS and died 14 days later because of septic multiple-organ failure.

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#### 4. Discussion

Our small series of seven patients demonstrates that survival after pulmonary retransplantation was similar to that after primary transplantation. Perioperative morbidity and mortality as well as post-transplant functional outcome were comparable in patients after primary and redo transplantation.

So far, only few data on pulmonary retransplantation in children are available. According to published results, the use of organs from deceased donors for paediatric retransplantation remains controversial [1,2,6,7]. Most corresponding publications report a substantially worse outcome after re-LTx compared with primary transplantation.

Huddleston et al. reported a median survival of approximately 1 year [2]. Starnes et al. calculated an even worse outcome of less than 1 year in a smaller cohort of seven...
patients after living donor lobar re-LTx [7]. For this procedure, Kozower et al. reported a better median survival of approximately 3.5 years, but the median survival in patients receiving organs from deceased donors ranged below 1 year [6]. Aurora et al. analysed the database of the ISHLT and reported a much improved 5-year survival of 41% [1].

The median survival in our small patient cohort was 4.6 years and therefore comparable to the ISHLT data. All our patients received organs from deceased donors.

Evaluating the outcome of our patients and that of other groups, primary diagnoses, pretransplant characteristics, perioperative adverse events, as well as long-term morbidity and causes of death, have to be compared. The only study that mentions these variables in detail was published by Kozower et al. [6] In comparison to our study group, primary diagnoses, indications for retransplantation and pretransplant characteristics, such as O$_2$ support and rate of ventilated patients, were similar. Nevertheless, the rate of perioperative adverse events was lower in our patient cohort. While the incidence of early graft failure (using the same definition for early graft failure as Kozower [6]) was comparable, less patients required re-exploration (29% vs 46%) and re-intubation (0% vs 62%). These differences might partly explain the lower rate of hospital mortality in our patients (29% vs 42%). However, the better survival of our small group compared with the cited publications might be coincidental.

In general, leading causes of death within the first year after primary LTx are early graft failure and infections, in both children [1,6] and adults [9]. Among our patients, both early deaths after re-LTx were caused by graft failure combined with multiple-organ failure, at least in one case with septic aetiology. Indication for retransplantation in one of these patients was primary graft failure, a well-known risk factor for high early mortality [10]. Both patients were ECMO- and ventilator-dependent. Mechanical ventilation is also an identified risk factor for perioperative mortality [11,12]. The development of BOS was not different between both groups. In the study group, two of the six patients, after pulmonary retransplantation for BOS, developed BOS of the
second graft as early as after primary LTx (Table 3); but further progression of BOS was remarkably more decelerated after re-LTx. Two other patients were BOS-free for at least twice as long as after primary LTx. In adults, patients who were retransplanted for BOS, had a very high risk for early development of BOS soon after re-LTx [13]. Corresponding data for paediatric patients are missing.

To our knowledge, this is the first study on paediatric pulmonary retransplantation demonstrating a comparable outcome in terms of perioperative morbidity and mortality, development of BOS and survival in paediatric patients after primary and redo LTx. In parallel, recently published studies from Vienna and our group on pulmonary retransplantation in adult patients report 5-year survival rates that were comparable to survival rates after primary LTx (62% and 61%) [9,10]. Both groups did not differentiate between the era of transplantation. However, the rising experience in retransplantation in recent years and improvements in lung preservation may result in less incidence of early graft failure and therefore in better survival data [10]. The use of the few available donor organs for patients on mechanical ventilation should be considered carefully due to the higher perioperative mortality of this patient group [11,12].

4.1. Limitations of the study

The presented data have to be interpreted with respect to the very small cohort. The better survival compared with the cited publications might be coincidental. However, the functional status of all surviving patients after pulmonary retransplantation is very good, indicating a promising long-term follow-up of this group.

4.2. Conclusion

Pulmonary retransplantation in children can be performed with results that are comparable to those after primary LTx. It can be considered an effective treatment option for paediatric patients suffering from chronic graft failure. Based on the comparable outcome data, a restriction of pulmonary retransplantation does not seem to be justified. However, if these favourable results can be confirmed by other studies including more patients over a longer period of time, the need for donor organs will probably increase and thus the shortage of donor organs. Alternative surgical techniques, such as reduced-size LTx, as well as other sources of donor organs, such as living related donation, must be considered.

References