Does simultaneous lung–liver transplantation provide an immunologic advantage compared with isolated lung transplantation?

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Simultaneous lung–liver transplantation (SLLT) is an uncommon procedure that is limited to patients unable to tolerate transplantation of either organ alone. It has been postulated that same-donor liver transplantation might provide an immunologic advantage to other simultaneously transplanted organs. We present our experience with SLLT comparing immunologic outcomes with those of patients receiving only lung transplantation to determine whether such a clinical benefit exists.

CLINICAL SUMMARY

Approval for retrospective review of our transplantation database was obtained from the University of Pittsburgh Medical Center Total Quality Control Council. Simultaneous lung–liver or heart–lung–liver transplantation was performed in 4 adults between 2003 and 2006. A control group was selected based on age, underlying diagnosis, date of transplantation, and immunosuppressive regimen.

All patients received induction therapy with rabbit antithymocyte globulin, alemtuzumab, or daclizumab. Our protocols for immunosuppression management, diagnosis/treatment of acute rejection, and infection prophylaxis have been described previously.¹

Fisher's exact test and an independent *t* test were used for qualitative and quantitative variable analysis, respectively. Values are reported as means $\pm$ standard deviations. Actuarial survival and freedom from rejection were calculated by using the Kaplan–Meier method ($P < .05$, log-rank test).

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TABLE 1. Demographics and perioperative data for the control and study groups

Characteristic	Control group (n = 16)	Study group (n = 4)	P value
Preoperative			
Age (y)	34.9 $\pm$ 9.7	30.7 $\pm$ 4.9	.420
Sex			
Male	8 (50%)	3 (75%)	.591
Female	8 (50%)	1 (25%)	.591
Weight (kg)	57.1 $\pm$ 11.5	56.7 $\pm$ 3.6	.918
Height (in)	65.1 $\pm$ 3.7	66.0 $\pm$ 2.9	.641
Lung wait time (d)	529 $\pm$ 525	363 $\pm$ 428	.569
Diagnosis			
CF	12 (75%)	3 (75%)	.751
PPH	4 (25%)	1 (25%)	.751
Operative			
Lung ischemic time (min)			
First lung	284 $\pm$ 68	258 $\pm$ 105	.541
Second lung	381 $\pm$ 91	334 $\pm$ 160	.432
CPB use	8 (50%)	2 (50%)	.708
Postoperative			
Complications			
Tracheostomy	3 (19%)	3 (75%)	.061
Bleeding	1 (6%)	0 (0%)	.800
Renal insufficiency	4 (25%)	1 (25%)	.751
Pneumonia	5 (31%)	2 (50%)	.439
LOS			
ICU (d)	20 $\pm$ 40	37 $\pm$ 42	.458
Total (d)	39 $\pm$ 36	65 $\pm$ 43	.230
No. of TBB in first year	6.5 $\pm$ 2.6	5.0 $\pm$ 1.6	.283
No. of ACR >2 in first year	11 (69%)	0 (0%)	.026
BOS $\geq$ grade 1	3 (19%)	1 (25%)	.837
Mean tacrolimus levels			
0–1 mo	12.0 $\pm$ 1.4	11.9 $\pm$ 1.5	.849
2–3 mo	13.6 $\pm$ 1.8	10.8 $\pm$ 1.6	.012
4–6 mo	12.8 $\pm$ 2.4	11.7 $\pm$ 2.3	.435
7–12 mo	12.1 $\pm$ 2.9	11.5 $\pm$ 3.4	.774
13–24 mo	12.5 $\pm$ 1.9	10.8 $\pm$ 1.6	.115
25–36 mo	10.7 $\pm$ 2.4	12.1 $\pm$ 2.9	.337

CF, Cystic fibrosis; PPH, primary pulmonary hypertension; CPB, cardiopulmonary bypass; LOS, length of stay; ICU, intensive care unit; TBB, transbronchial biopsy; ACR, acute cellular rejection; BOS, bronchiolitis obliterans syndrome.

FIGURE 1. Kaplan–Meier survival plots comparing rejection-free survival (A) and patient survival (B) for the control and study groups.

Demographic and perioperative characteristics for the study and control groups are described in Table 1. The incidence of acute cellular rejection (grade >2) in the first year after transplantation was significantly higher in the control group compared with that seen in the study group (68.8% vs 0%, $P = .026$). One patient in the study group had bronchiolitis obliterans syndrome at 18 months necessitating repeat double-lung transplantation after 2.3 years. Both groups had similar mean tacrolimus levels postoperatively, although the study group had significantly lower tacrolimus levels during months 1 to 3. Rejection-free survival was better in the study group compared with the control group during the first year, but by the third year, there was no difference between the 2 groups (Figure 1, A). There were no operative mortalities in either group, and Kaplan–Meier survival estimates were similar (Figure 1, B).

DISCUSSION

Despite the encouraging results observed in recent years with lung transplantation, coexisting severe hepatic dysfunction remains a contraindication. The challenge associated with management of multiorgan disease coupled with the shortage of organs has led to a disinterest in SLLT. However, for some patients, this remains the only option for extending life and improving quality of life.

Previous experience with this tour de force of transplantation has been limited to small case series.^{2–4} The report by Faro and colleagues³ in 5 children with SLLT demonstrated lower rates of acute rejection and bronchiolitis obliterans syndrome compared with those seen in children receiving isolated lung transplantation. However, no study in adults has provided a similar comparison.

In our experience a potent early immunologic advantage was noted in patients who received SLLT compared

with those undergoing isolated lung transplantation. This effect was noted despite both groups having similar tacrolimus levels. Interestingly, during months 2 to 3 after transplantation, lung–liver transplants were able to be maintained rejection free with significantly lower levels of tacrolimus compared with patients receiving isolated lung transplantation. Unfortunately, this effect was transient, and by the third year, there was no difference in the incidence of acute rejection between the groups.

Previous studies by Calne⁵ described the phenomenon of donor-specific immunologic protection provided by the liver. This has been attributed to numerous mechanisms, including the release of soluble histocompatibility antigens by the liver that are capable of inducing a state of tolerance and induction of microchimerism by passenger leukocytes within the liver. A similar immunologic privilege has been noted in multiorgan transplantation, including combined heart–kidney and heart–lung transplantation in which acute rejection of the heart has been lower than with isolated heart transplantation. This explanation exploits the potential for a large burden of foreign tissue to create a state of anergy within the recipient.

The clinical success noted in this and other studies augmented by a potential immunologic advantage creates an attractive option for patients with end-stage liver and lung disease. Unfortunately, our limited understanding of immunologic tolerance and the transient nature of this effect remain formidable obstacles. An additional obstacle is surviving to transplantation. Although no patients died while awaiting transplantation, other studies have reported wait-list mortalities.³

In conclusion, SLLT can be performed safely, with good early to midterm outcome. Same-donor liver transplantation might offer an immunologic advantage to simultaneously

performed lung transplantation. Further clinical and experimental studies are warranted to better understand the potential benefits, as well as the mechanisms by which they are mediated.

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