An observational study of Donor Ex Vivo Lung Perfusion in UK lung transplantation: DEVELOP-UK

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Disclaimer: This report contains transcripts of interviews conducted in the course of research and contains language that may offend some readers.

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Scientific summary

Ex-vivo lung perfusion for lung transplant

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Scientific summary

Introduction

Respiratory diseases account for one in five deaths in the UK. Lung transplantation is the only realistic therapeutic option for selected patients with end-stage chronic lung disease, and provides dramatic improvements in both survival and quality of life. In younger patients with life-threatening cystic fibrosis lung disease, median survival after lung transplant now exceeds 10 years. However, 20–30% of patients waiting for lung transplantation will die before a donor organ becomes available. Although a shortage of multiorgan donors contributes, the main problem is that donor lungs are very susceptible to dysfunction, and about 80% of potential donor lungs in the UK are deemed unusable for transplantation. It has been suggested that, in addition to promoting more organ donation, better use of existing organ donors is an important way in which to increase the numbers of lung transplants performed; many centres worldwide have thus increased activity by accepting more 'extended criteria' donors. This strategy, however, is not without risks to early outcomes. The major early cause of death after lung transplantation is primary graft dysfunction (PGD), a severe lung injury akin to acute respiratory distress syndrome. Evidence that PGD has a major impact on survival comes from experience in several centres worldwide and from the International Society for Heart and Lung Transplantation: the reported incidence of PGD is up to 25%, and PGD is associated with a 30-day mortality of 50%, compared with < 10% among those without PGD. There is, therefore, an urgent clinical need to safely increase the utilisation of donor lungs from the existing donor pool without negatively impacting on early survival after lung transplant.

Ex vivo lung perfusion (EVLP) is a novel technique in which donor lungs that are unusable because of poor or uncertain function can be assessed objectively and potentially reconditioned for safe use in clinical lung transplantation, thereby increasing the donor pool. Evaluation of human donor lungs in isolated perfusion circuits offers unique advantages, as isolation of the lung may alleviate injurious factors associated with the donor or recipient haemodynamics, hormonal derangements and their proinflammatory milieu. This allows time for optimisation of the donor lung without the immediate risk associated with fully supporting the recipient. EVLP can also objectively identify lungs that are not suitable for transplantation either because poor function is a result of irreversible damage or because pre-existing lung disease, such as emphysema, is identified in the donor lung. In this respect, EVLP may provide reassurance to potential recipients that 'extended criteria' donor lungs that might have been previously considered unusable are acceptable for lung transplantation.

As of June 2011, approximately 25% of the world's early experience with EVLP, 17 out of 65 cases, had been gained in the UK. Although initial experience was promising, a large-scale trial of the procedure was felt to be required to demonstrate its effectiveness in increasing lung transplant activity in a safe and cost-effective way. The Donor Ex Vivo Lung Perfusion in UK lung transplantation (DEVELOP-UK) study was therefore designed to address this urgent clinical need by assessing how effective EVLP assessment and reconditioning of donor lungs is at safely increasing UK lung transplant activity.

Objective

The aim of DEVELOP-UK was to evaluate the clinical effectiveness and cost-effectiveness of the technique of donor EVLP in increasing UK lung transplant activity by allowing previously unusable donor lungs to be safely used in clinical lung transplantation. Furthermore, the study allowed the applicability of EVLP to lung transplant services in the UK NHS to be determined.

The study was designed as a multicentre, unblinded, non-randomised, non-inferiority observational study, with an adaptive design to evaluate the clinical and economic effectiveness of EVLP in assessing and reconditioning donor lungs for transplantation compared with standard lung transplantation. The study also included an embedded qualitative substudy to determine the experiences of, and hopes and fears around, EVLP use in patients waiting for, or after, lung transplantation.

As a UK-based multicentre study, it involved all five officially designated NHS lung transplant centres: Birmingham, Harefield (London), Manchester, Newcastle and Papworth (Cambridge). These five tertiary centres provide all adult lung transplant activity to potential recipients with end-stage chronic lung disease in England, Scotland, Wales and Northern Ireland.

Methods

The target population for the study was adult patients (aged ≥ 18 years) with advanced lung disease who had already been accepted (at study inception) onto an active lung transplant waiting list in one of the five UK centres, plus any new adult patients who were added to the active waiting list during the course of the study recruitment from 1 April 2012 to 9 July 2014. The experimental intervention was EVLP. EVLP was performed outside the donor and recipient bodies by connecting the lungs to a semiautomated EVLP machine (Vivoline Medical AB, Lund, Sweden), which warmed lungs to body temperature and circulated a specialised perfusate solution through their vasculature. Following slow rewarming to 32 °C, the lungs were ventilated with supplementary oxygen by connecting them to a standard intensive therapy unit (ITU) ventilator. EVLP provides the opportunity to carefully assess donor lung function, including gas exchange, over a number of hours before making a decision on their usability for transplantation. The study was commenced using a hybrid EVLP protocol, combining elements of the EVLP protocols previously developed in Toronto and Lund. After 22 EVLP assessments using the hybrid protocol and following an interim evaluation of some early adverse events after the first eight EVLP transplants, the protocol was changed entirely to the Lund protocol for the remaining 31 EVLP assessments and subsequent 10 transplants.

When a lung suitable for potential transplantation became available, the NHS Blood and Transplant organ retrieval team was dispatched to the donor hospital to assess the donor lungs. After careful assessment, a decision was made using study criteria whether the lungs could be used immediately for standard transplantation, should undergo EVLP assessment and reconditioning, or were unsuitable for transplantation.

The primary outcome measure was survival during the first 12 months following lung transplantation. Secondary outcomes were clinically relevant patient-centred outcomes that are influenced by the effectiveness of lung transplantation, and that contribute to the health-care costs, impact on recipients' quality of life and cost-effectiveness.

Results

A total of 487 patients from the UK lung transplant waiting list either completed an expression of interest (EOI) form, or fully consented to participate in the study. EOI forms allowed those living a significant distance from the transplant centre to confirm their interest in participating without the need for face-to-face interaction with the research team.

Donor lungs from 53 donors deemed unsuitable for standard transplantation were assessed with EVLP, of which 18 (34%) were transplanted, constituting the EVLP arm of the study. A total of 184 patients received standard donor lungs and constitute the control arm of the study. Other than a higher proportion of donation after circulatory death and of male donors in the EVLP arm, there were no differences in the donor or recipient characteristics between the two arms.

The study did not reach target recruitment: only 184 standard transplants out of a target of 206 (60.1%), and only 18 EVLP transplants out of a target of 102 (17.6%), were achieved before the independent Trial Steering Committee advised that the study should be stopped early. This was because of poor enrolment in the EVLP arm, and because there was no indication that the rate of EVLP assessments was increasing sufficiently. In addition, there was a signal of a higher rate of serious adverse events, mainly requirement for unplanned extracorporeal membrane oxygenation (ECMO) support in the EVLP arm. The final EVLP sample size limited the subsequent comparisons to mainly descriptive statistics.

The Kaplan–Meier estimate of survival at 12 months was 0.67 [95% confidence interval (CI) 0.40 to 0.83] for the EVLP arm and 0.80 (95% CI 0.74 to 0.85) for the standard arm. Based on Cox regression, the hazard ratio for overall survival in the EVLP arm relative to the standard arm over the 12-month follow-up was 1.96 (95% CI 0.83 to 4.67).

The median duration of invasive ventilation in the EVLP arm was 72 hours, and the median ITU stay was 14.5 days. In the standard arm, the corresponding values were 38 hours and 4.3 days. Overall, post-operative hospital stay was similar in the two arms. The rate of grade 3 PGD at 24 hours was 44.4% in the EVLP arm and 17.8% in the standard arm. The rates decreased in both arms by 72 hours, to 27.8% versus 22.5%. ECMO support was required in 7 of 18 (38.8%) transplant recipients in the EVLP arm, and in 6 of 184 (3.2%) recipients in the standard arm.

There were no anastomotic complications in the EVLP arm, but 14 of 146 (9.5%) transplants in the standard arm exhibited anastomotic complications by 12 months, including two instances of bronchial dehiscence. Rates of chest radiograph abnormalities over the 12-month follow-up period were similar in the two arms, and there was a trend towards lower rates of infection in the EVLP arm. Lung function tests were similar between the groups during 12 months of follow-up. The risk of rejection was highest in the first 3 months, but there was no difference between rates of A2 rejection in the two arms of the study.

The median waiting time from listing was 197 days [interquartile range (IQR) 95–373 days] for a standard transplant and 142 days (IQR 60–199 days) for those receiving an EVLP-evaluated donor.

Owing to the small numbers in the EVLP arm of the study, the economic analysis was limited to a within-trial analysis, and the two transplant procedures were not compared directly in terms of their cost-effectiveness. The total cost of lung transplant in the EVLP arm was estimated to be around £98,186 [standard deviation (SD) £60,231]. The cost of a standard transplant was £63,637 (SD £44,047). The mean cost of the EVLP procedure itself was £14,066. The variability in the total EVLP cost is marked, with a SD in costs of £60,231. This is because of the increased use of ECMO and the increased length of ITU stay after EVLP transplant. The total quality-adjusted life-years (QALYs) gained per EVLP recipient were estimated to be 0.527 and 0.533 in the standard arm. A regression model on cost identified three statistically significant predictors of increased total cost: (1) higher quality of life when the person joined the waiting list; (2) use of EVLP procedure; and (3) transplanting two lungs (as opposed to one). An exploratory model compared a NHS lung transplant service that included both EVLP and standard lung transplants with one that included only standard lung transplants. The incremental cost per QALY was £73,000, well above values normally considered acceptable to the NHS. There was, however, considerable uncertainty around these results.

A total of 44 interviews were conducted with 24 men and 20 women, aged 21–69 years. The qualitative study suggests that patients had a good understanding of the need for, and the processes of, EVLP, although clinicians may want to consider exploring different ways and modes of providing information, depending on patient preferences. Overall, this work suggests that if EVLP can increase the number of suitable donor lungs available and reduce waiting times, then it is likely to be regarded as an acceptable technology to patients waiting for lung transplantation in the UK.

Conclusions

Overall, one-third of the donor lungs found unsuitable for standard transplantation that were subjected to EVLP in the study were subsequently deemed suitable for transplant. Estimated survival over 12 months in this EVLP group was lower than in the standard lung transplant group, but the data were also consistent with no difference in survival between groups. These additional EVLP transplants were associated with a higher rate of early severe graft injury and need for unplanned ECMO support, and were, on average, more costly. However, limited data mean that comparisons should be treated cautiously; the small number of participants in the EVLP arm (17.8% of the target), owing to slow enrolment in the EVLP arm and early study termination, limits the robustness of conclusions drawn, and results must be interpreted with caution.

Implications for practice

The DEVELOP-UK study is the first to report poorer outcomes in a group of EVLP transplants than in a contemporaneous standard lung transplant group, but few data were available for comparison. The study is the first non-commercial, multicentre EVLP study performed, and relied on a small number of centres in a single country to deliver a substantial target of EVLP assessments and subsequent EVLP transplants. To date, two commercially funded multicentre EVLP studies have been performed but have not yet fully published their results.

The slow enrolment into the EVLP arm of the study was because of a combination of the low number of EVLP assessments performed and the low conversion rate from EVLP assessment to transplant. This demonstrates the challenge of running an EVLP assessment service alongside an active clinical transplant programme when logistics and staff availability, due to competing transplant activity, can significantly affect units' ability to perform EVLP assessments.

The higher rate of early PGD grade 3 and need for ECMO support in the EVLP arm has raised issues about the selection of the best lungs on which to perform EVLP. Although there was a much higher ECMO rate, it was not associated with a higher mortality risk in the recipients undergoing ECMO, which, in most cases, was limited to a few days of support. The almost uniform use of cardiopulmonary bypass in recipients of EVLP donor lungs (89%) may also have contributed to the high early PGD grade 3 rates and the frequent use of ECMO as a second hit to donor lungs that already have disrupted vascular integrity.

Implications for research

The findings of the DEVELOP-UK study will help to direct further research in the area of EVLP. The high rate of early severe PGD and need for ECMO in this study makes it necessary to further investigate whether or not a combination of EVLP followed by transplant surgery on cardiopulmonary bypass causes a second hit that increases vascular leak and early reperfusion injury.

There is also work to be done to explore why only 30–40% of the lungs perfused in this study satisfied transplant criteria, and whether this was a problem with donor organ selection for EVLP or a result of the rigidity of following a multicentre prospective study protocol, which imposes stricter decision-making than would happen in a single centre outside of a formal study setting.

Trial registration

This trial is registered as ISRCTN44922411.

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