The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of cold (static) storage (CS) or machine (pulsatile) profusion (MP), as a means of preserving kidneys from either heart-beating donors (HBD) or non-heart-beating donors (NHBD) prior to transplantation, was studied.

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis; cost-utility analysis.

Study population
The population comprised patients who were suffering from end-stage renal failure and who were eligible for kidney transplants.

Setting
The setting was secondary care. The economic study was conducted in the UK.

Dates to which data relate
The effectiveness data related to studies published between 1973 and 1997. The dates for resource use were not explicitly given. The price year was 2002 for some resources, although it was unclear whether all the unit costs were adjusted to this date.

Source of effectiveness data
The study was based on a systematic review of the literature.

Modelling
The relative costs and clinical effects of MP versus CS for HBD and NHBD scenarios were determined through decision analytic modelling, using Excel. The final estimates were derived using univariate and multivariate proportional hazards analyses, and the Weibull baseline hazard function. Diagrammatic representations of the model(s) were not provided.

Outcomes assessed in the review
To derive input parameters for the graft loss model, the review assessed the relationship between DGF and graft loss, the relationship between DGF and long-term graft loss, and Cox models for graft loss.
Study designs and other criteria for inclusion in the review
For the relationship between DGF and graft loss, the vast majority of studies were of an observational design (although this was not a stated criterion). For the relationship between DGF and long-term graft loss, focus was placed on studies that used proportional hazards analysis. Cox models for graft loss were based finally on one observational study.

Sources searched to identify primary studies
Fifteen electronic bibliographic databases were searched. In addition, article references and sponsor submissions were handsearched.

Criteria used to ensure the validity of primary studies
As this was a systematic review it is not possible to summarise the chosen methods. Full details were reported in Chapter 3 of the study.

Methods used to judge relevance and validity, and for extracting data
As this was a systematic review it is not possible to summarise the chosen methods. Full details were reported in Chapter 3 of the study.

Number of primary studies included
Eighteen studies were included for the relationship between DGF and graft loss. Of the 7 studies reporting Cox models for graft loss that were initially found, only two presented Kaplan-Meier survival for DGF versus no DGF. One of these studies was chosen as it allowed calibration of a model of graft loss.

Methods of combining primary studies
The authors adopted both univariate and multivariate proportional hazards analyses, in conjunction with Kaplan-Meier graft survival plots, to derive graft survival estimates dependent on DGF or no DGF. For the relationship between DGF and graft loss, a narrative summary was given. A meta-analysis was used to estimate the hazard of graft loss from DGF.

Investigation of differences between primary studies
The heterogeneity in the primary studies was described, and a rationale was provided for studies that eventually contributed to the modelling.

Results of the review
For the relationship between DGF and graft loss, the results showed that DGF is associated with higher rates of graft loss.

The rate ratios of allograft failure from the multivariate proportional hazards analysis were:

- for delayed allograft function (any versus none), 1.72 (confidence interval, CI: 1.07 - 2.76; p=0.02);
- for rejection (any versus none in first 30 days), 1.99 (CI: 1.23 - 3.21; p<0.01);
- for rejection beyond 30 days, 3.53 (CI: 2.08 - 6.00; p<0.01);
- for nonwhite versus white recipient race, 2.78 (CI: 1.78 - 4.35; p<0.01); and
- prior renal transplant (any versus none), 1.38 (CI: 1.02 - 1.87; p=0.04).

The Kaplan-Meier graft survival plots for 1, 3, 5 and 10 years showed that, for MP versus CS, the survival advantage ranged from 1 to 2% (HDB) and from 2 to 3% (NHBD).
These values were not statistically significant because of the small trial sizes.

**Measure of benefits used in the economic analysis**
Two measures of health benefit were used in the economic analysis. These were cumulative graft-years lost when using CS in comparison with MP (cost-effectiveness elements), and the gain in quality-adjusted life-years (QALYs) with the use of MP. Graft-years lost were based on graft survival data derived from the systematic review. The utilities for the QALY analysis were obtained from a separate review of the literature. A score of 0.84 was assigned to a functioning transplant and a score of 0.65 to dialysis following graft failure. The health benefits were discounted at a rate of 1.5%, in accordance with UK Treasury guidelines.

**Direct costs**
As a health service perspective was chosen, only the direct costs were included. The costs and the quantities were reported separately. The direct costs covered graft loss, the short-term cost of DGF, and the machine preservation system. The cost of graft loss included hospitalisation, annual technician costs, and annual immunosuppressive maintenance therapy. The cost of the machine preservation system included maintenance, cassette, solution, purchase cost, machine plus starter pack, and personnel.

Discounting was appropriately applied at a rate of 6%. The dialysis costs were derived from the UK Prospective Diabetes Study Group and were adjusted to 2002 values. Continuous ambulatory peritoneal dialysis costs were derived from a study in the Trent Region. The costs associated with transplant maintenance were derived from a Trent Institute Guidance Note and the UK Medicines Information Service. The costs associated with the machine preservation system were based on the use of a Waters Corporation Medical System RM3 renal preservation system (actual system used by the Leicester General Hospital). The cost per transplant was based on data from the Renal and Liver Transplant Unit of the Freeman Hospital in Newcastle Upon Tyne.

**Statistical analysis of costs**
Uncertainty in the data was addressed in the sensitivity analysis.

**Indirect Costs**
The indirect costs were not assessed.

**Currency**
UK pounds sterling ( ).

**Sensitivity analysis**
The sensitivity of the long-term survival model was assessed by introducing random errors of the order of +/- 3% into each of the 12-month interval hazard estimates. The Weibull model was then refitted to obtain new baseline parameter estimates. A sensitivity analysis, using lower and upper limits from the meta-analysis, was also performed to assess the error in estimating the hazard of graft loss from DGF. Uncertainty in the kidney preservation system model was addressed by means of probabilistic sensitivity analyses. Mean values and standard errors were derived from the literature, or assumed in some cases, and were applied to all parameters used in the model. Where prior distributions were unknown, uniform distributions based on minimum and maximum values were used. Standard errors for parameters with normal or log normal distributions were chosen to allow for wide uncertainty in the model. An Expected Value of Perfect Information (EVPI) analysis was also conducted on the model as a whole, and on individual parameters.

**Estimated benefits used in the economic analysis**
Cumulative graft-years lost using CS compared with MP for HBD were 0.01 (after 1 year), 0.03 (after 2 years), 0.06
The results for NHBD were 0.01 (after 1 year), 0.04 (after 2 years), 0.08 (after 5 years) and 0.2 (after 10 years), respectively.

The expected gain in QALYs from MP were 0.05 (CI: 0 - 0.13) for NHBD and 0.03 (CI: 0 - 0.09) for HBD.

**Cost results**
The expected marginal cost per patient of MP was -1,900 per transplant (CI: -7,000 - +1,500) for NHBD and -600 (CI: -4,900 - +1,800) for HBD. As such, both were non significant cost-savings.

**Synthesis of costs and benefits**
The baseline results indicated that MP has the potential to be cost-saving and more effective than CS (dominant). However, uncertainty in the results indicated that, in some instances, this could be reversed. Therefore, the costs and benefits were combined using the incremental net benefit approach and cost-effectiveness acceptability curves (CEACs) for MP compared with CS. The results were presented for both NHBD and HBD.

For NHBD, MP would have a probability of 80% of being the dominant strategy over CS. At a cost-effectiveness acceptability threshold of 20,000 per QALY, MP would have an expected net benefit of approximately 1,200 per transplant recipient.

For HBD, MP would have a probability of 50 to 60% of being the dominant strategy over CS. At a cost-effectiveness acceptability threshold of 20,000 per QALY, MP would have an expected net benefit of approximately 1,200 per transplant recipient. However, there is a 10% chance that it will cost more and be less effective.

The sensitivity analysis on the range of Weibull baseline parameters showed that the model was insensitive to errors in the estimation of the survival function (graft-years lost remained at 0.15 years over the range tested).

The sensitivity analysis for long-term graft survival and graft-years lost showed that the estimated benefit for MP is stable under the range of estimates for DGF provided by the meta-analysis.

The EVPI analysis showed that the value of information for each transplant was 125 for NHBD and 240 for HBD recipients. In terms of individual model parameters, the key parameters were those associated with the long-term effectiveness of MP. More specifically, the risk factor for graft loss associated with DGF, the impact of MP on DGF and for BHD recipients, and the probability of experiencing DGF under current CS techniques. For HBD recipients, if DGF rates under 30% can be achieved with CS, then CS could be economically the preferable option over MP.

**Authors’ conclusions**
The authors produced several conclusions. However, in general terms they concluded that it is unlikely, in the UK context, that complete cost recovery would be obtained from a reduction in the incidence of delayed graft function (DGF), although this would be more likely in non heart-beating donor (NHBD) transplants. There was strong evidence of a link between DGF and graft survival. In addition, small improvements of 1% at one year and 2 to 3% at 10 years would result with machine perfusion (MP). However, this was based on studies with small samples and the difference was non significant. The baseline economic analysis showed that MP would be expected to be cheaper and more effective than cold storage (CS) for both HBD and NHBD recipients, although this result may switch because of the uncertainty in the data. There were key economic uncertainties related to the impact of MP on long-term graft survival.

**CRD COMMENTARY - Selection of comparators**
The authors clearly provided the rationale for their choice of the comparator (CS). Due to increasing demands for kidneys suitable for transplant, there is a need to consider older and NHBDs as sources. This has led to a resurgence of interest in the use of MP to preserve kidneys. Although both techniques appear to be in common use, CS may be considered as current practice and is therefore a valid comparator.
Validity of estimate of measure of effectiveness
The effectiveness data were derived from a systematic review of the literature and should, therefore, have high validity. The authors adopted a wide range of valid summary and synthesis techniques to derive inputs for the decision analytic modelling, and explained their methods comprehensively. In addition, probabilistic sensitivity analyses were conducted to assess uncertainty in the estimates. The choice of distributions and associated parameters was clearly described. However, the principal estimates related to graft survival were based on non significant differences and this weakens the internal and external validity of the study's findings, as the authors acknowledged. In terms of model transparency, the reader would have benefited from a schematic representation in order to quickly identify those estimates that were probabilities and those that were terminal node parameters.

Validity of estimate of measure of benefit
The authors provided both condition-specific (graft-years lost) and aggregated (QALY) estimates of health benefit. The utilities for the QALY calculations were derived from one study from the literature survey, but no further details of elicitation methods and the chosen perspective were given. The use of QALYs enhances the comparability of the study's results with other health care programmes that use QALYs.

Validity of estimate of costs
The direct cost analysis reflected the chosen perspective of the study (health care provider), and all relevant cost items appear to have been included. The chosen perspective reflects the methodology used in the UK, but the reader should note that other countries or researchers may wish to adopt a societal perspective and include productivity losses, as they would clearly be relevant to this patient domain. Discounting was appropriately applied as the time horizon was up to 10 years. The costs and the quantities were reported separately, and the sources of the unit costs were clearly reported. The authors provided details of refiation exercises for some cost data (dialysis) but it was unclear whether all the cost data related to the same year (2002), although this was likely to have been the case.

Other issues
The authors did not compare their results with those from other studies, although the studies forming the review of economic evaluations were appropriately summarised. The issue of generalisability was addressed through discussion of the validity and limitations of studies from other settings or countries (principally the USA), and extensive sensitivity analyses were undertaken. The authors utilised state-of-the-art techniques (net benefits, CEACs and EVPI) and clearly stated the limitations of the results and requirements for further research. The principal limitation related to the small (non significant) differences in graft survival associated with MP.

Implications of the study
In terms of clinical practice, the principal finding that MP is both more effective and less costly than CS needs to be treated with caution, owing to uncertainty in the estimates used in the modelling. For future research, the major concern relates to the small predicted improvement in graft survival associated with MP, and very large sample sizes would be needed to produce statistically significant results. The authors concluded "in addition to seeking better direct evidence on the impact of MP on DGF rates, further research on quantifying the predicted impact of DGF on graft survival would be warranted".

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