Hypothermic machine perfusion utilization and outcomes for deceased-donor kidneys: A retrospective cohort study

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ABSTRACT

Introduction: Hypothermic machine perfusion (HMP) has been established as an efficacious method for preserving kidney allografts from deceased donors in clinical trials, but little data are available on the effectiveness of HMP in real-world settings. We examined factors associated with HMP use and clinical outcomes in a real-world organ procurement organization setting.

Methods: We conducted a retrospective cohort study of the Lifecenter Northwest organ procurement database from 2010 to 2015, linked to the United Network of Organ Sharing outcomes database. We examined HMP utilization, and our primary outcomes were delayed graft function (DGF) and graft survival, using multivariable Poisson and Cox regression models.

Results: Among 1729 deceased-donor kidneys, 797 (46%) were preserved with HMP. Higher donor age, region of procurement, and donation type were associated with HMP use. HMP was associated with a 37% decreased risk of DGF (adjusted relative risk 0.63, 95% confidence interval [CI]: 0.51–0.78), with no effect on 1-year graft survival (adjusted hazard ratio 0.83, 95% CI: 0.38–1.80).

Conclusion: Variation exists in the utilization of HMP for deceased donor kidneys. HMP reduced the risk for DGF, but was not associated with improvements in long-term graft survival.

Key Words: Hypothermic machine perfusion, kidney, transplantation

INTRODUCTION

Hypothermic machine perfusion (HMP) is a method of organ preservation for renal allografts from deceased donors.[1] Compared to static storage, HMP provides the renal vasculature continuous cold flow of preservation solution, which theoretically provides more physiologic preservation conditions compared to static storage in iced solution. Optimizing conditions for renal allografts is important for contemporary transplant practice, as the use of kidneys from older patients and with expanded donation criteria is increasing rapidly.[2] While HMP has been available for over 40 years, recent advances in technology have allowed the development of portable devices that are user-friendly and commercially available.[3] Therefore, interest in the use of HMP in the field of renal transplantation is on the rise.

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In clinical trial, HMP improved 1 year allograft survival from 90% to 94%, and confirmed observational studies suggesting an impact on delayed graft function (DGF). While HMP has an effect, the question of effectiveness remains debatable, given significant costs and suggestions within available data that all subgroups may not benefit equally especially low-risk donors. Furthermore, little data are available on the patterns of HMP use in contemporary settings. Therefore, the aims of our study were: (1) To examine factors associated with the use of HMP and clinical outcomes in a real-world organ procurement organization setting, and (2) To examine whether donor risk modifies the association between HMP and clinical outcomes following renal transplantation.

**METHODS**

**Population and study design**

The study used data from LifeCenter Northwest (LCNW, Bellevue, WA, USA), an organ procurement organization for a 4-state region in the northern United States (Alaska, Montana, North Idaho, and Washington). The LCNW organ procurement database was examined from 2010 to 2015, containing data from all organs procured during that time frame (whether they were transplanted or not). Using a unique donor organ identification number, the database was linked to the United Network of Organ Sharing (UNOS) outcomes database. A retrospective cohort study was conducted to examine deceased donor kidneys procured at LCNW during the study period. Because deceased donors do not meet the regulatory definition of human subjects and the final linked database was fully de-identified, the study was waived from Institutional Review Board review at the University of Washington.

**Exposures, outcomes, and covariates**

In the primary analysis, among donor kidneys which were procured for transplantation, the utilization of HMP was the primary outcome. Exposures evaluated in this population included demographic variables (age, body mass index), clinical variables (donor criteria – standard, extended, donation after cardiac death; use of kidney donor profile index [KDPI] score; cold ischemia time), and regional facility characteristics. The KDPI score aims to summarize the quality of a deceased donor kidney, compared to other recovered kidneys. In a secondary analysis, among donor kidneys that were transplanted, the utilization of HMP as the exposure and the following outcomes were examined: (1) DGF, defined as the requirement for dialysis during the 1st week after transplantation; and (2) 1-year graft survival. For the secondary analysis, we also considered recipient covariates, including age, gender, and cold ischemia time.

**Statistical analysis**

Descriptive statistics were used to examine clinical, demographic, and facility-level features of the deceased-donor kidney cohort, stratified by HMP utilization status. For the primary analysis, factors associated with HMP utilization for deceased-donor kidneys were examined using univariate and multivariable Poisson regression models, taking into account clustering at the donor kidney level. For the secondary analyses, univariate and multivariable Poisson regression models were used to analyze the association of HMP utilization with DGF; and univariate and multivariable Cox proportional hazards regression models were used to analyze the association of HMP utilization with 1-year graft survival. Given that the cohort size was fixed, a formal sample size calculation was not performed. All analyses were performed using Stata 15.0 (College Station, TX).

**RESULTS**

**Demographic and clinical characteristics**

During the study, 1729 deceased-donor kidneys were procured and linked to the UNOS outcomes database; among these kidneys, 797 (46%) were preserved with HMP. Table 1 describes demographic, clinical, and facility-level characteristics in of the deceased-donor kidneys, stratified by HMP status. The median (interquartile range, IQR) age of the cohort was 36 years (24, 50 years), and higher in pumped kidneys (43 years [28, 53]) compared to the non-pumped kidneys (31 years [22, 45]). In this cohort, 1416 (92%) of deceased-donor kidneys were transplanted locally. The majority of kidneys (1114 [64%]) were from standard criteria donors, although 168 (9.7%) were from extended criteria donors and 447 (26%) were donated after cardiac death. The median (IQR) cold ischemia time was 16.3 h (11.9, 22 h), and was longer in the pumped kidneys (17 h [12.3, 21.9]) compared to the nonpumped kidneys (15.8 h [11.0, 22.1]).

**Factors associated with hypothermic machine perfusion utilization**

Table 2 shows factors associated with HMP utilization in the deceased-donor kidney cohort. On multivariable analysis, higher donor age, region of procurement, and donation type were all significantly associated with the utilization of HMP. Compared to kidneys procured in western Washington, kidneys procured in eastern Washington had a 15% decreased risk of utilizing HMP (adjusted relative risk [aRR] 0.85, 95% confidence interval [CI]: 0.73–0.99) and kidneys procured in Alaska had a 27% decreased risk of utilizing HMP (aRR 0.73, 95% CI: 0.60–0.90). Compared to standard criteria kidneys, kidneys procured after cardiac death had a 152% increased risk of HMP utilization (aRR 2.52, 95% CI: 2.23–2.84) and extended criteria kidneys had a 52%
Table 2: Factors associated with hypothermic machine perfusion utilization

| Characteristic                      | Relative risk* | 95% CI       | P     |
|-------------------------------------|----------------|--------------|-------|
| Age                                 | 1.02           | 1.01-1.02    | <.0001|
| BMI                                 | 1.01           | 1.00-1.01    | 0.08  |
| Region                              |                |              |       |
| Western Washington                  | Ref            |              |       |
| Montana                             | 0.86           | 0.72-1.03    | 0.1   |
| Eastern Washington                  | 0.85           | 0.73-0.99    | 0.03  |
| Alaska                              | 0.73           | 0.60-0.90    | 0.003 |
| Presence of KDPI Score              | 0.91           | 0.81-1.02    | 0.11  |
| Donation type                       | Ref            |              |       |
| Standard criteria donation          | 2.52           | 2.23-2.84    | <.0001|
| Extended criteria donation          | 1.52           | 1.25-1.85    | <.0001|

*Multivariable poisson regression model adjusted for all variables reported. KDPI: Kidney donor profile index, BMI: Body mass index, CI: Confidence interval

These data are for the entire cohort. Continuous data are presented as medians (25th-75th percentile) and categorical data are indicated as total for the entire cohort (percentages). *Cold ischemia time: 49 out of 797 (6.2%) missing for pumped kidneys; 132 out of 932 (14.2%) missing for nonpumped kidneys. BMI: Body mass index.

increased risk for HMP utilization (aRR 1.52, 95% CI: 1.25–1.85). The KDPI score was not associated with the use of HMP for deceased-donor kidneys (P = 0.11).

The association of HMP utilization with transplantation outcomes

Recipient characteristics are shown in Table 1. The median (IQR) age of recipients was 55 years (42, 64) and 1032 (60%) were male. Among the recipients, 430 (25%) developed DGF. The use of HMP was associated with a 37% decreased risk of DGF in the entire cohort (aRR 0.63, 95% CI: 0.51–0.78). Among kidneys with an available KDPI score (n = 546), the risk for DGF was only decreased among kidneys with a KDPI score >30 (aRR 0.52, 95% CI: 0.36–0.75) and not in kidneys with a KDPI score <30 (aRR 0.93, 95% CI: 0.56–1.53). Figure 1 shows 1-year graft survival in the cohort, stratified by HMP utilization. On multivariable analysis, there was no association of HMP utilization on 1-year graft survival (adjusted hazard ratio 0.83, 95% CI: 0.38–1.80).

**DISCUSSION**

In this large, real-world study examining the practice of HMP for deceased-donor kidneys, we found: (1) Marked variation exists in the utilization of HMP by patient, facility, and regional characteristics; (2) HMP reduced the risk for DGF in kidneys with a KDPI >30, but not in lower-risk kidneys; and (3) HMP was not associated with improvements in intermediate-term graft survival.

HMP has been enthusiastically incorporated into the workflow of transplantation, as it offers (a) the possibility of organ reconditioning, (b) assessment of renal vascular...
flow resistance, and (c) more latitude on surgical timing of implantation. A large, multicenter trial[3] found that the use of HMP was associated with benefit to DGF and graft survival; however, a consequent assumption that all kidneys may benefit from this intervention remains unproven. Differences have been detected between outcomes of kidneys from donors following death by neurologic criteria (DBD) and those from donors after death by circulatory criteria (DCD).[4] As importantly, no differences in graft survival were apparent in that same systematic review of available randomized control studies, which is consistent with the results of our own real world analysis.

A reduction in the incidence of DGF has to be considered as significant, in reducing requirements for both dialysis and prolonged hospitalization, and could be considered cost efficient. Our study was initiated by the question of whether subgroups could be identified within the pool of donor kidneys that may afford a more targeted approach to the use of HMP. The development of the KDPI was seen as offering some objective classification of risk, and consequently, benefit of HMP intervention. We have established that the benefits of HMP are not equally distributed through the pool of donor kidneys and appear to be relevant in those with a KDPI or >30. This may allow a considered discrimination in the application of HMP with conservation of resources, and a reduction in the number needed to treat to avoid DGF.

Our study had limitations. First, our study was observational and treatment assignment was nonrandom; thus, despite multivariable analyses being employed, our analysis may still be at risk for confounding by indication. Second, due to the nature of this registry database, detailed granularity of clinical information (such as drugs administered, vital signs, and laboratory parameters) was not available. Third, additional unmeasured factors may have driven the observed associations, such as socioeconomic factors. Fourth, observed variation in HMP utilization may have been driven by specific regional factors (such as population density and number of hospitals) rather than the region itself. Finally, primarily due to the issues laid out above, the analysis is at risk for residual confounding; thus, our findings require confirmation in additional databases.

CONCLUSION

This large, real-world study examining the practice of HMP for deceased-donor kidneys found: (1) marked variation exists in the utilization of HMP, (2) HMP reduced the risk for DGF in kidneys with a KDPI > 30, but not in lower-risk kidneys, and (3) HMP was not associated with improvements in a long-term graft survival. Future studies should aim to establish objective clinical markers to guide the use of HMP for deceased donor kidneys.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Ethics Committee, Research Cell, King George’s Medical University, Lucknow and appropriate approval (84th ECM II-B-Thesis) was granted by the Research Cell, King George’s Medical University, Lucknow.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Ethical conduct of research

This study was approved by the Institutional Review Board / Ethics Committee. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the conduct of this research project.

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