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Targeted temperature management in deceased organ donors

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Abstract

An evaluation of a recent study by Niemann CU, Feiner J, Swain S *et al.* Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. *New England Journal of Medicine* 2015; 373 (5):405-414. PubMed PMID: 26222557. ClinicalTrials.gov number, [NCT01680744](https://clinicaltrials.gov/ct2/show/study/NCT01680744)

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Critique of:**Citation**

Niemann CU, Feiner J, Swain S, Bunting S, Friedman M, Crutchfield M, Broglio K, Hirose R, Roberts JP, Malinoski D. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. *New England Journal of Medicine* 2015; 373 (5): 405–414. PubMed PMID: 26222557. ClinicalTrials.gov number, [NCT01680744](#)

Background

There are about 16,000–17,000 renal transplants per year in the United States. Greater than 60% are deceased donor transplants. Up to 50% of these cases are complicated by delayed graft function (DGF), characterized by a requirement for dialysis in the recipient within 7 days after renal transplant. DGF is associated with an increased risk for an acute rejection episode. It is an independent risk factor for decreased graft survival and prolonged. Ischemia–reperfusion injury during the transplantation process is also a major contributing factor to subsequent poor allograft function.

Methods

Intervention was initiated after research authorization was obtained. The investigators randomized donors declared deceased by neurologic criteria (DNC) to normothermia (36.5–37.5C) versus hypothermia (34–35C). The goal was to reach the target temperature within 4 hours of enrollment and maintain temperature until transport to the operating room. The primary outcome measure was DGF. The secondary outcome measures were the rate of individual organs transplanted in each treatment group and the number of organs transplanted from each enrolled donor.

Objective

To investigate the potential benefit and safety of normothermia vs. targeted hypothermia (36.5–37.5 versus 34–35 degrees C) in donors with respect to rates of delayed graft function among transplant recipients.

Design

Prospective, randomized, controlled trial.

Setting

Patients who met DNC from two large organ-donation service areas March 20, 2012 and October 17, 2013.

Subjects

394 donors who met DNC criteria were identified by two organ-procurement organizations: Northern California and Nevada-California Transplant Donor Network and Southern California and Nevada One Legacy. Legal statutes do not require informed consent.

Analysis

The initial plan was to enroll 500 donors. This would provide a 90% power to detect a 30% relative difference in the rate of delayed graft function between the study groups. The investigators had a scheduled pre-planned interim analysis for efficacy or futility in the 5th quarter of the study period. The primary outcome subgroup comparison utilized the t test and Fisher's exact. For the secondary outcomes chi-square test was utilized. The preplanned interim analysis used a logistic-regression model for delayed graft function with adjustment for covariates including donor creatinine level at enrollment, organ-procurement agency, donor age, cold-ischemia time and donor type (Standard Criteria Donors versus Extended Criteria Donors). The primary efficacy analysis included all transplanted kidneys with known cold-ischemia time and outcome data on delayed graft function in the recipients.

Results

The interim analysis showed benefit of hypothermia, prompting early termination of the study. 370 total organ donors were enrolled. 180 were randomized to hypothermia, and 190 to normothermia. 572 patients received a kidney transplant. This included 285 kidneys from donors in the hypothermia group and 287 kidneys from donors in the normothermia group. Delayed graft function developed in 79 recipients of kidneys from donors in the hypothermia group (28%) and in 112 recipients of kidneys from donors in the normothermia group (39%). The primary efficacy analysis showed that hypothermia, as compared with normothermia, significantly reduced the odds of delayed graft function (odds ratio, 0.62; 95% confidence interval [CI], 0.43 to 0.92; P=0.02).

In an analysis involving donors who were expanded-criteria donors, hypothermia significantly reduced the odds of delayed graft function in this subgroup - 31.0% in the hypothermia group compared with 56.5% in the normothermia group with the adjusted odds ratio for the development of DGF being 0.31 (95% CI, 0.15 to 0.68; P=0.003).

Among standard-criteria donors, the rate of delayed graft function was lower in the hypothermia group than in the normothermia group (27.3% vs. 33.6%). The odds of delayed graft function were lower though not statistically significant (adjusted odds ratio, 0.71; 95% CI, 0.45 to 1.13; P=0.15).

In terms of secondary outcomes, the overall number of organs transplanted from each donor and the rate of organs transplanted in each treatment group. There were four adverse events in organ donors: one episode of dysrhythmia and one episode of systemic hypertension in the hypothermia group and two episodes of cardiac arrest before organ recovery in the normothermia group.

Conclusions

Targeted temperature control in donors had a statistically and clinically significant protective effect on renal-graft outcomes in recipients.

Abstract adapted from the original provided courtesy of PubMed: A service of the National Library of Medicine and the National Institutes of Health.

Commentary

Renal transplantation accounts for the majority of organ transplanted in the United States each year. Delayed graft function (DGF) incurs a significant negative impact of organ recipients and the health care system¹. The frequency of DGF varies from 4 to 10% in living donor transplants and 5 to 50% in deceased donor kidney transplants². In 1995, Terasaki *et al.*³ showed that graft survival for living unrelated donation is superior compared to deceased donation. This thought to be due to numerous pathophysiologic changes that occur in brain death that potentially contribute to DGF in the transplanted kidney⁴.

In this randomized controlled trial, subjects were either warmed to 36.5–37.5 or cooled to 34–35°C with the goal of reaching the target temperature within 4 hours of enrollment. Temperature was maintained until transport to the operating room. The average time between declaration of death and organ recovery was approximately 30 hours. Based on cardiac arrest literature the goal duration of mild hypothermia (34°C) was at least 12 hours with median duration of hypothermia turning out to be 16.9 hours⁵.

Recipients were not randomly assigned but recipient characteristics that were known to affect kidney-graft survival were balanced between the two treatment groups. The primary analysis adjusted for factors that were known to be associated with DGF such as the creatinine level at the time of consent, age, and cold-ischemia time were all significantly associated with delayed graft function. Hypothermia significantly decreased the rate of DGF (38% lower when compared to the normothermia group). The trial demonstrated that noninvasive temperature-management aimed at hypothermia in donors decreased the rate of DGF in recipients.

This study is the first randomized controlled trial to employ hypothermia in potential renal donors. The data was collected in a prospective manner. The study investigators were not involved in the outcome assessment process. In the interim analysis the factors associated with DGF such as cold ischemia time, age and baseline creatinine were taken into account making this a well-designed randomized controlled trial.

There are a number of limitations to this study. Health care providers who were caring for the donors were aware of the group

assignments which could have introduced bias into care for the donors. Transplant surgeons had the opportunity to contact the PI or Co PI if there were questions concerning donor enrollment. No information on acute rejection or the potential long term effects on graft survival can be deduced currently. In addition, outcomes with respect to other organs were not stated. The investigators excluded hemodynamically unstable and coagulopathic donors which impacts the generalizability of the study. Recipients' ethnicities are not stated in the analysis. It is known that African –American ethnicity is a risk factor for DGF⁶. No data is provided on adherence to intervention and how temperature variations were dealt with. The authors did not include details of the fluid management of donors or recipients, for example, chloride liberal versus restrictive⁷.

The study protocol mentions that subjects were warmed to 36.5–37.5. The method and duration of warming was not included in the protocol. In hypothermia trials passive rewarming was utilized since active rewarming is associated with worse reperfusion injury.

This study was terminated prematurely. A systematic review of randomized trials (RCT) stopped early for benefit by Montori *et al.* 2005⁸ showed that RCTs that stopped early show implausibly large treatment effects, particularly when the number of events is small. A Systematic Review and Meta-regression Analysis on stopping RCTs early for benefit and the estimation of treatment effects by Bassler *et al.*⁹ in 2010 showed that truncated RCTs were associated with greater effect sizes than RCTs not stopped early. This difference was independent of the presence of statistical stopping rules and was greatest in smaller studies. This renders the current results of this study preliminary. Further trials are therefore required prior to utilizing hypothermia as a standard of practice in this specific patient population.

Recommendation

This is the first RCT to investigate hypothermia in renal donors and measure recipient outcomes. The results of this study must be interpreted with caution based on the aforementioned reasons.

However, therapeutic hypothermia is both simple and incurred no adverse events. It may be applicable in donors who are relatively hemodynamically stable and not coagulopathic. From a practical view point, in the absence of another RCT addressing this issue, one may consider therapeutic hypothermia in potential renal transplant donors.

Competing interests

The authors declare that they have no competing interests.

Grant information

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