

Deceased Organ Donor Research: The Last Research Frontier?

Thomas Mone,⁴ John Heldens,¹ and Claus U. Niemann^{2,3*}

¹Human Research Protection Program, ²Department of Anesthesia and Perioperative Care, and

³Department of Surgery, Division of Transplantation, University of California San Francisco, San Francisco, CA; and ⁴One Legacy, Los Angeles, CA

Received August 26, 2012; accepted November 19, 2012.

See Article on Page 135

The deceased organ donor pool has been stagnant over the last 5 years and is unlikely to increase significantly in the coming years. As a result, organs are increasingly being transplanted from donors with extended criteria. The function of these organs is at particular risk for deterioration during the transplant process. Overall, there is a significant paucity of clinical trials in deceased organ donors, even though prospective, randomized clinical research is one of the major pillars of evidence-based medicine.

URGENT NEED FOR PROSPECTIVE, RANDOMIZED TRIALS IN DECEASED ORGAN DONORS

To address the growing discrepancy between available and needed organs, the US Department of Health and Human Services has launched several initiatives. One of the initiatives involves fostering prospective, randomized trials in deceased organ donors and evaluating organ donor management across different organ procurement organizations (OPOs). This is in response to the aforementioned paucity of published research into medical management practices for deceased organ donors. At this point, most studies have been retrospective in design and, therefore, suffer from well-known shortcomings inherent to that type of study. These studies have been made possible in recent years by improved collaboration between

OPOs and academic centers, and both the frequency of studies and the size of study populations have increased. The studies have clearly helped to identify management practices that need attention and improvement.¹ Several studies have investigated the impact of donor management goals and have demonstrated a significant impact on organ function when a bundle of management goals is achieved.

Although they are rare, there have been a few randomized, prospective studies in deceased organ donors helping to improve or modify organ donor management.² For example, 2 organ donor studies measured the impact of dopamine³ and solumedrol⁴ on posttransplant delayed graft function and inflammatory responses, respectively. These studies demonstrated that interventions during the donor management process had a measurable impact on organ function.

In this issue of *Liver Transplantation*, D'Amico et al.⁵ present one of the few randomized, prospective clinical studies in deceased organ donors. In this study, deceased organ donors were randomized to receive either a pretreatment with *N*-acetyl-L-cysteine (NAC) via systemic and portal vein infusions before organ recovery or standard recovery protocols. Although deceased donors were enrolled in different hospitals throughout the region, all recipients underwent transplantation at the University of Padua. Pretreatment with NAC in donors resulted in significantly improved graft survival at 3 and 12 months in comparison with controls.

Notwithstanding the scientific study design, this study points to several logistical, ethical, and

Abbreviations: IRB, institutional review board; NAC, *N*-acetyl-L-cysteine; OPO, organ procurement organization.

Address reprint requests to Claus U. Niemann, M.D., Department of Anesthesia and Perioperative Care, University of California San Francisco, 521 Parnassus Avenue, C 450, San Francisco, CA 94143-0648. Telephone: 415-502-2162; FAX: 415-502-2016; E-mail: claus.niemann@ucsf.edu

DOI 10.1002/lt.23579

View this article online at wileyonlinelibrary.com.

LIVER TRANSPLANTATION.DOI 10.1002/lt. Published on behalf of the American Association for the Study of Liver Diseases

regulatory obstacles that need to be overcome in order to conduct meaningful clinical research in deceased organ donors. In fact, D'Amico et al.'s study⁵ is notable as much for its rarity as its results, and that rarity is a reflection of the state of affairs in deceased organ donor research.

In this editorial, we highlight some of the important issues that are unique to research in deceased organ donors and matched organ recipients.⁶ It will become evident that most deceased organ donor research is performed on an ad hoc basis, is driven by individual research groups without a clearly outlined process of due diligence, and at times is conducted in a regulatory vacuum.

Clinical research in general requires a series of steps that include a proposed intervention; a detailed review of the study protocols by institutional review boards (IRBs)/ethics committees; a well-established informed consent process; complete transparency of the proposed intervention; well-defined primary study endpoints; close communication with all health care providers involved in the care of the study subjects; and, lastly, detailed documentation of the study intervention within each study subject's medical chart and the study database. Additionally, the establishment of a safety monitoring board is frequently required so that it can serve as the guardian for each study subject enrolled in the clinical study.

As for most clinical studies, the type of intervention dictates the study protocol and subject safety guards. In the case of deceased organ donor research, the subjects include deceased organ donors and organ recipients.

As a result, the evaluation of intervention-related risks must include recipients of organs from deceased donors who were enrolled in clinical studies. According to a somewhat arbitrary categorization, interventions can range from donor management evaluations (eg, compliance with donor management goals or novel fluid resuscitation algorithms) to minimal-risk interventions (eg, mild hypothermia or remote ischemic preconditioning) to low-risk interventions (approved drugs/devices with known toxicity and safety profiles) to, lastly, moderate- to high-risk interventions using investigational drugs or devices. The last category is naturally the most contentious one.

Many experimental animal studies have successfully examined potential interventions that are aimed at protecting organs during the transplant process, yet very few translational studies have been performed. This is in part because many of these experimental studies have used investigational drugs or devices that have a limited or nonexistent track record in clinical studies and, therefore, can be considered moderate- or high-risk interventions. As the history of medicine has shown, however, an investigational drug or device may ultimately lead to a paradigm shift in clinical therapeutic management. Unless there is a concerted effort by the transplant community and regulatory bodies to resolve the logistical, legal, and ethical issues surrounding deceased organ donor

research with subsequent substantial change in research environment and the regulatory framework, it is unlikely that high-risk interventions will be conducted in the near future.

In D'Amico et al.'s study,⁵ deceased donors were treated systemically with NAC. NAC has been used for a long time and has a good safety track record, so it may be considered a low-risk intervention. The authors correctly point this out; however, it is certainly of interest whether the NAC treatment had any effect on additional organs that were transplanted.

Although it is controversial, NAC may have protective effects on renal function in some clinical settings.^{7,8} We have no information about whether the NAC treatment could have affected other organs recovered from the enrolled donors and whether the allograft function of all transplanted organs was post-operatively monitored.

This leads to the next set of questions regarding communication between different transplant centers. Were all additional accepting transplant centers/teams (ie, those involved in kidney, heart, lung, and pancreas transplantation) informed about the study before the enrollment of donors and provided sufficient information to determine whether the intervention would pose a benefit or risk to the recovered organs? The same centers may be concerned that a randomized controlled trial of a deceased donor intervention could confound recipient-focused randomized controlled trials. Does an active intervention such as an NAC infusion in the deceased donor interfere with research in the recipient? It is equally important whether a potential conflict of research interest exists that encourages individual transplant centers to opt out of a donor intervention trial simply to protect the recipient research study subject pool. Although initial objections from transplant centers could include any trials in donors, upon reflection, this problem may be significant only when the donor and recipient trials use identical endpoints or when an investigational drug is used. Certainly in transplantation, endpoints such as organ function and patient survival, regardless of their crudeness, may be identical, and possible interference between studies must be evaluated on an individual basis.

Overall, transplant centers are frequently ill informed about standard organ donor management protocols and ongoing studies in deceased organ donors. This can result in expressed concern from transplant centers serving different organ systems that clinical interventions in organ donor management may have unknown and potentially harmful effects on organ function and survival after transplantation.

For example, at OneLegacy (an OPO that serves most of Southern California), an attempt was made to replicate and advance the solumedrol study through a comparison of slow-bolus administration and continuous infusion. This certainly qualifies as a donor management evaluation because solumedrol is given to almost all donors at OneLegacy, and the mode of

administration was investigated. A number of transplant health care providers were unaware that solumedrol was a commonly used medication in donor management, and they brought up scientifically unproven and mostly discredited arguments that it might be harmful to pancreas function. The concern was also raised that a continuous infusion might result in excessive levels at the time of transplantation, which in turn might lead to unanticipated interactions with recipient medications. In this particular attempt, these issues were successfully addressed with the 12 local transplant centers, and the study proceeded, but these issues that were unearthed can serve as examples of obstacles that hamper donation science research.

It is certainly appropriate for centers that will be offered organs to be informed of the standard of practice in donor management at an OPO and about any systematic changes to that standard that are being studied. However, communication is often locally focused and neglects the fact that organs are routinely offered to and transplanted in other donation service areas across the country. In an attempt to address this issue, it has become apparent that speaking of a standard of practice in organ donor management starts with the faulty assumption that there is in fact a standard across different service areas or regions of the country. There is certainly a range of practices and interventions that are used according to the individual clinical circumstances of each donor, but the medications, ventilator settings, time of management, and interventional procedures can vary dramatically between donors, procurement coordinators, and OPOs.

From a research perspective, this variation has allowed the retrospective evaluation of different treatment modalities, as seen with donor management goal-related studies, which have generated hypotheses for prospective trials. Conversely, the proposal of an entirely new treatment that is outside the broad range of OPO donor management practices can be expected to run into resistance from transplant teams because of the concern that the treatment modality may have a negative impact on organs that are considered for transplantation.

INFORMED CONSENT IN DECEASED ORGAN DONOR RESEARCH

The need for informed consent by study subjects is trial-dependent and is regulated by IRBs, state/national regulatory bodies, or both. In the United States, deceased donor management studies do not require IRB/ethics review committee approval. Brain-dead organ donors are not considered human subjects by federal definition: "human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."⁹ Research consent (more properly called authorization

in deceased donation because the research subject is unable to consent) from donors or families is not legally required for deceased donor research when no additional tissue, blood, or organs are recovered solely for research.

However, the involvement of an IRB/ethics review committees (or a national regulatory equivalent) at a minimum is advisable to ensure institutional and public trust. Regardless of the regulatory oversight, it is readily apparent that multiple IRBs and regulatory bodies potentially need to be involved during the planning of interventional deceased organ donor research that may require recipient consent. In the extreme, such a study may include a local review at each potential donor hospital (for the determination of granting a waiver for deceased organ donor research), a review at the principal investigator's institution, and, lastly, a review at each transplant center that may receive organs from deceased organ donors enrolled in the study. The complexity of this process can quickly become staggering because organs are allocated and distributed across counties, states/provinces, and even nations.

If the introduced risk stratification is used for proposed interventions, recipient consent may not always be necessary because much organ donor research falls within the broad range of the standard of practice. The implementation of standard-of-care protocols in deceased donors and in minimal-risk research studies of deceased organ donors may not need the informed consent of recipients. In general, in these types of studies, the care of the organ recipients is not altered, and the benefits of the intervention in the deceased donor (ie, better preserved organ function and more organs transplanted) far outweigh the risks to the recipient.

However, it is reasonable to argue that studies in which recipients are subjected to a low-risk intervention that clearly does not fall within the minimal-risk category should require a full IRB review, ideally first at the principal investigator's institution or the responsible regulatory body and on an ad hoc basis at receiving transplant centers. The early involvement of bioethicists and health care providers with deep expertise in the field is strongly recommended. Currently, most decisions about recipient consent requirements are based on ad hoc working groups and rely on the willingness of deceased organ donor researchers to share the information.

In the current study, D'Amico et al.⁵ report that the study was reviewed by the local ethics review committee, presumably at the University of Padua. Not surprisingly, the ethics review committee determined that informed consent was not necessary from the families of the deceased organ donors but should be obtained from the organ recipients.

All recipients underwent transplantation at a single center. This simplified issues of informed consent and ethical review. However, we do not know at what time the recipients were asked to participate in the study. It is hard to imagine a more coercive situation for

informed consent than the one that arises when a transplant recipient is told that there is a matching organ available but it has been obtained after a research intervention. Informed consent could be obtained at an earlier point in time, but the patient is still left with the choice of potentially turning down an available organ. Of course, transplant recipients make choices and indicate their preferences about acceptable organs for other situations (ie, high-risk donors), and some centers incorporate consent for donor research into the initial consent process long before organ offers.

CONCLUSIONS

Well-controlled deceased donor research is essential for identifying superior clinical practices that improve organ utilization and transplant outcomes. Approved donor management research protocols should be shared as broadly as possible to ensure that transplant teams are aware of and understand the potential impact of the research on recipients. Research studies should continue to focus on interventions performed as part of management protocols and evaluate whether inconsistencies in the critical care management of deceased organ donors affect organ recovery rates and organ function.

The majority of interventional trials in deceased organ donors necessarily will involve multiple transplant sites in order to track allograft outcomes. As previously stated, this can present significant additional challenges but also an interesting opportunity to think about an appropriate model for ethical and regulatory overview. Does every transplant center need to review the research protocols that are considered experimental and constitute more than a minimal risk to the donor and recipient on only the chance that a single organ might be sent to it? It is certainly each institution's right to do so, especially in the absence of clearly formulated federal regulations and guidelines.

The logistical and legal implications are mind-boggling, and it is obvious that meaningful, well-conducted research is exceedingly difficult. Furthermore, consider the impact of organ refusal (by a patient or a transplant center) due to the fact that the deceased organ donor was enrolled in a research study. Organ allocation and distribution could be substantially influenced, and this possibly could lead to increased morbidity and mortality.

Lastly, the possibility of competing trials of donors and recipients is very real because organ function and lifespan are the ultimate outcomes of transplantation. With many active transplant centers and thousands of transplant researchers, it seems impossible to avoid donor and recipient research studies that might share outcomes. However, to defer all donor management research studies to recipient studies would do a disservice to transplantation and the opportunities for improved outcomes based on donor management.

In order to provide a sound ethical and legal framework for all stakeholders involved in the transplant process (organ donors, recipients, health care providers, and transplant centers), a much broader approach is required that provides adequate review and oversight of organ donor research. Under the leadership of the appropriate governmental entities and with all stakeholders at the table, guidelines need to be established that provide strict review and oversight policies that by law supersede institutional and local regulations.

Meaningful deceased organ donor research will be successful only if the current regulatory and legal vacuum is filled.

We sincerely hope that we can help to start a constructive dialogue that is so desperately needed among all stakeholders.

REFERENCES

1. Malinoski DJ, Patel MS, Daly MC, Oley-Graybill C, Salim A; for UNOS Region 5 DMG Workgroup. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing region 5 prospective donor management goals study. *Crit Care Med* 2012;40:2773-2780.
2. Dikdan GS, Mora-Esteves C, Koneru B. Review of randomized clinical trials of donor management and organ preservation in deceased donors: opportunities and issues. *Transplantation* 2012;94:425-441.
3. Schnuelle P, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, Weiss C, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA* 2009;302:1067-1075.
4. Kotsch K, Ulrich F, Reutzel-Selke A, Pascher A, Faber W, Warnick P, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg* 2008;248:1042-1050.
5. D'Amico F, Vitale A, Frigo AC, Piovon D, Bertacco A, Bassi D, et al. Use of *N*-acetylcysteine during liver procurement: a prospective randomized controlled study. *Liver Transpl* 2013;18:135-144.
6. Feng S. Donor intervention and organ preservation: where is the science and what are the obstacles? *Am J Transplant* 2010;10:1155-1162.
7. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT). *Circulation* 2011;124:1250-1259.
8. Birck R, Krzossok S, Markowitz F, Schnülle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003;362:598-603.
9. National Science Foundation. 45 CFR part 690: federal policy for the protection of human subjects (same as 45 CFR part 46, which pertains to HHS). Subpart A: the common rule for the protection of human subjects. <http://www.nsf.gov/bfa/dias/policy/docs/45cfr690.pdf>. Accessed November 2012.