SCIENTIFIC ARTICLE

The Ethics of Hand Transplantation: A Systematic Review

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Purpose We conducted a systematic review to document ethical concerns regarding human upper extremity (UE) allotransplantation and how these concerns have changed over time.

Methods We performed a systematic review of 5 databases to find manuscripts addressing ethical concerns related to UE allotransplantation. Inclusion criteria were papers that were on the topic of UE allotransplantation, and related ethical concerns, written in English. We extracted and categorized ethical themes under the 4 principles of bioethics: Autonomy, Beneficence, Nonmaleficence, and Justice. We assessed theme frequency by publication year using Joinpoint regression, analyzing temporal trends, and estimating annual percent change.

Results We identified 474 citations; 49 articles were included in the final analysis. Publication years were 1998 to 2015 (mean, 3 publications/y; range, 0–7 publications/y). Nonmaleficence was most often addressed (46 of 49 papers; 94%) followed by autonomy (36 of 49; 74%), beneficence (35 of 49; 71%), and justice (31 of 49; 63%). Of the 14 most common themes, only "Need for More Research/Data" (nonmaleficence) demonstrated a significant increase from 1998 to 2002.

Conclusions Upper extremity transplantation is an appealing reconstructive option for patients and physicians. Its life-enhancing (vs life-saving) nature and requirement for long-term immunosuppression have generated much ethical debate. Availability of human data has influenced ethical concerns over time. Our results indicate that discussion of ethical issues in the literature increased following publication of UE transplants and outcomes as well as after meetings of national societies and policy decisions by regulatory agencies.

Clinical relevance Because UE transplantation is not a life-saving procedure, much ethical debate has accompanied its evolution. It is important for UE surgeons considering referring patients for evaluation to be aware of this discussion to fully educate patients and help them make informed treatment decisions. *(J Hand Surg Am. 2017;■(■):1.e1-e15. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Ethics, hand transplantation, VCA, composite tissue allotransplantation, upper extremity allotransplantation.

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Opinions on the ethics of upper extremity (UE) allotransplantation and whether it should be performed in human subjects have evolved over the past 25 years. Open discussions were initiated at the 1991 conference on the clinical use of composite tissue allotransplantation. Held in conjunction with the Rehabilitation Research & Development Service of the Department of Veterans Affairs in Washington, DC, this conference's determination was that more preclinical data were needed prior to being able to ethically perform hand transplants in human subjects.[1] In November 1997, the conversation continued at the First International Symposium on composite tissue allotransplantation held in Louisville, KY. A controversial conclusion there was that it was time to "just do it" (human hand transplantation).[2] Outside ethicist-observer Mark Siegler, MD, agreed, stating that, based on data presented at the meeting and preparatory steps taken by presenting programs, it was "ethically defensible" to perform cadaveric human hand transplantation under an institutional review board–approved research protocol.[3] Within the next 2 years, the first 2 human patients were transplanted: the first in Lyon, France (1998),[4] and the second in Louisville, KY (1999).[5]

Following the publication of data from these and 2 other early patients, which included the amputation of the first patient's graft 28 months after transplant,[4–9] the International Federation of Societies for Surgery of the Hand and the American Society for Surgery of the Hand (ASSH) released their position statement in 2001 strongly advising caution on the further expansion of hand transplantation until more human data were available.[10] Whereas the hand transplant community heeded the call to return to the laboratory to conduct more basic research into rejection mechanisms and improved immunosuppression,[11–13] clinical UE transplants continued in parallel. In 2002, the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) was established to facilitate pooled reporting of outcomes on the world experience.[14] In 2003, the ASSH revisited its position statement, maintaining its strong cautionary stance. However, transplants continued and the hand transplantation community was widely encouraged to publish or share all data available on patient outcomes.[10–12,14,15]

In the meantime, advances in solid organ transplantation immunosuppression protocols were being made, which some researchers thought could improve hand transplantation.[16–18] By 2009, these experimental strategies were successfully adopted by the University of Pittsburgh Medical Center for hand/UE transplantation, enabling vascularized composite allotransplantation (VCA) to be performed and maintained on a single-drug immunosuppression regimen, thus further favoring the risk-benefit ratio for hand transplant recipients.[19] Inspired by these advances, several other academic institutions across the United States including the University of California Los Angeles, Harvard Medical School/Massachusetts General and Brigham and Women's Hospital, University of Pennsylvania, Emory University, Duke University, and others, established active hand transplantation programs.[20]

The data regarding improved methods of immunosuppression appeared to have disseminated into the hand surgery community during the next several years. In 2009, Mathes et al[21] published an article on North American hand surgeons' attitudes toward hand transplantation. Their study found that 78% of respondents thought that bilateral amputation and 32% that dominant hand amputation were appropriate indications for hand transplantation, whereas only 16% were in favor of performing transplants with the immunosuppression regimen available at the time.[21] Importantly, 71% of respondents believed hand transplantation was an ethical procedure when performed in carefully selected patients.[21] Bertrand et al[22] revisited this topic in 2014 and opinions were slightly more favorable toward hand transplantation—80% of respondents stated that bilateral amputation and 36% that dominant hand amputation were appropriate indications. Opinions were much more favorable when considering its required immunosuppression: 56% of respondents stated they were in favor of performing transplants with the currently available immunosuppression.[22] Despite potential selection bias, this change in opinion may have been influenced by the ASSH's 2013 revised position on hand transplantation[23] in which the procedure is acknowledged as an alternative to prosthetics but should be undertaken only by experienced centers and in carefully selected patients. This was followed by the implementation of the U.S. Department of Health and Human Services (DHHS) Organ Procurement and Transplantation Network Final Rule (42 CFR part 121) which included vascularized composite allografts as covered human organs effective July 3, 2014, and subjected programs to minimum membership requirements.[24]

Hand/UE transplant programs continue to be established in the United States and worldwide. Currently, 15 U.S. programs are listed on the American Society for Reconstructive Transplantation Web site.[20] However, concerns regarding the ethics of the