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Ethical challenges in vascularized composite allotransplantation of the lower extremity: lessons learned from hand transplantation and implications for the future

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Abstract

Vascularized composite allotransplantation (VCA) is a novel surgical practice that involves the transplantation of multiple tissue types as a functional unit without the primary purpose of extending life. While VCA of the upper extremity is becoming increasingly accepted and performed, VCA of the lower extremity remains largely unexplored despite its acknowledged potential value. There are inherent ethical concerns surrounding VCA that are dominated by a conflict between the principles of beneficence and maleficence. The primary question is whether the quality-of-life benefits to the patient outweigh the risks associated with long-term immunosuppression for a non-lifesaving procedure. In addition, the ethical conversation involves concerns regarding informed consent, donor autonomy, patient privacy and public disclosure, patient selection, and unique considerations in the pediatric patient. Lower extremity VCA has additional ethical issues compared to upper extremity VCA, as current lower limb prostheses provide excellent, near baseline function that upper limb constructs have not yet been able to achieve. In this review, we discuss the ethical challenges of lower extremity VCA using available evidence for the upper extremity. We also compare ethical considerations of VCA of the extremity with other surgical alternatives to limb loss - namely, limb salvage and replantation - and address how the conversation may be altered with further advancements in immunosuppression and prosthetic technology.

Keywords: Vascularized composite allotransplantation (VCA), lower extremity, ethics, limb salvage, replantation

INTRODUCTION

Vascularized composite allotransplantation (VCA) is the transplantation of multiple tissue types as a functional unit, usually without the primary purpose of extending life. This practice is in contrast with solid organ transplantation, which is often lifesaving in nature. Among the most widely practiced and publicized forms of VCA is transplantation of the upper extremity, including the forearm and hand. VCA of the lower extremity, conversely, is a frontier that has been only minimally explored but has potential value. The number of individuals with loss of at least one lower limb in the United States was estimated at 1,027,000 in 2005 and projected to more than double by 2050[1]. This pool may be up to three times larger than that of upper extremity amputees[1]. Amongst these individuals, 43% would be interested in VCA of the lower extremity[2]. However, compared with upper extremity VCA, VCA of the lower extremity has a higher ethical burden, as lower extremity prosthetics offer excellent function for amputees with substantial potential for enhancing the quality of life of qualified patients[3,4].

Here, we discuss the ethical considerations surrounding VCA of the lower extremity - informed largely by evidence for upper extremity transplantation - in its current state of practice as well as how new advancements in immunosuppression and technology may change the conversation. We also compare VCA with limb salvage and replantation in this context.

HISTORY OF VCA OF THE LOWER EXTREMITY

The first lower extremity transplantation occurred in 2006 between three-month-old ischiopagus twins, a unique autologous situation for which the recipient did not necessitate immunosuppression[5-7]. In 2011, the first attempt at bilateral transfemoral transplantation in an adult patient was performed after the 20-year-old recipient sustained traumatic above-knee amputations from a motor vehicle accident[8]. Unfortunately, the recipient developed brain lymphoma 15 months post-transplant and immunosuppression was ceased, resulting in rejection and the removal of both limbs[9,10]. The third and fourth attempts occurred in 2012 as part of the world's first efforts at triple and quadruple extremity allotransplantation, respectively[11,12]. Both recipients experienced rejection in the immediate postoperative period that required reamputation of the allografts. The third recipient died within 5 months and the fourth recipient within 1 week of the procedure due to complications[11,12]. Most recently, in 2018, a 32-year-old male underwent unilateral transfemoral transplantation after an above-knee amputation one year prior. Only a six-month follow-up has been published, at which point the recipient was partially weight-bearing with evidence of sensory and motor function recovery[13]. These five reports are the only known cases of VCA of the lower extremity, with none taking place in the United States.

While the evidence for lower extremity transplantation is sparse, roughly 150 patients have received hand transplantations since the first successful attempts in 1998 and 1999[14,15]. Following successful early outcomes, in 2002, the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) was established as a means of collecting and synthesizing outcomes data in a centralized manner. Over the past decade, experimental immunosuppressive protocols have been adopted by medical centers nationwide and internationally. In 2014, the U.S. Department of Health and Human Services' Organ Procurement and Transplantation Network (OPTN) Final Rule was modified to include limbs (both upper and lower extremity), faces, and other VCAs under the definition of "organs" in order to supervise the processes for identifying potential donors, requesting authorization, and safely and effectively allocating VCAs[16]. At the time of publication, 20 unique transplant programs for any type of VCA (e.g., limb, abdominal wall, face, genitourinary organ) have been approved by OPTN[17]. These include 11 centers for upper extremity and three for lower extremity transplantation: Brigham and Women's Hospital, Medstar Georgetown Transplant Institute, and University of Chicago Medical Center[17].

RISK-BENEFIT PROFILE OF VCA

The primary ethical conflict surrounding VCAs is whether the quality-of-life benefits to the patient outweigh the long-term risks associated with an extensive non-lifesaving procedure. In ethical terms, this is considered a conflict between beneficence and nonmaleficence. Beneficence holds that patient's best interests are paramount, while nonmaleficence refers to an obligation to avoid preventable harm. The OPTN Final Rule provides a distribution framework for organ transplantation focused on the just allocation of scarce resources, as there is more demand for traditional, lifesaving transplants (e.g., kidney, liver, heart) than available organs[18]. In contrast, the primary ethical issue in VCA is focused on whether the procedure itself is ethical, rather than fair allocation. A standardized protocol for measuring and reporting outcomes does not currently exist, but the benefits and risks of upper extremity VCA are well-documented in the literature and can be largely extrapolated to the conversation on lower extremity VCA - although key differences do exist.

Benefits

The main goal of VCA of the extremity is to improve quality of life via restoration of sensation and motor function after limb loss. All viable transplanted hands have demonstrated normal skin color and texture as well as normal hair and nail growth, arterial blood supply, and venous outflow[19]. Reports released by the IRHCTT have shown that all documented upper extremity allograft recipients have recovered protective sensibility (i.e., ability to detect pain, thermal stimuli), with 91% of patients redeveloping tactile sensibility and 82% regaining partial discriminative sensibility[20]. There is no reason to expect that VCA of the lower extremity cannot also demonstrate such successful restoration of sensory function. Importantly, the first lower extremity allograft recipient has recovered diminished but present sensation to light touch[7]. The most recent recipient demonstrated early signs of sensory recovery as well, although long-term data is not available[13]. Recovery of protective sensibility and proprioception, which contribute to effective ambulation, alone would represent a substantial benefit over available prostheses - the most common alternative to VCA of the extremity[21].

Currently, the level of functional recovery required for restoration of lower extremity gait, balance, and postural control is unknown, although these motor functions are far less intricate than those of the hand and are arguably easier to achieve. The distal intrinsic muscle reinnervation critical to restoring near baseline function for the hand is speculated to be less crucial to attaining meaningful lower extremity function[22]. This is rooted in the fact that the knee plays a greater role in ambulation than the foot and ankle, giving greater importance to proximal versus distal innervation[23]. To date, many hand transplant recipients have exhibited motor function sufficient to perform gripping and pinching actions and recovery of a number of manual skills. Patients with bilateral transplantations have also been able to achieve symmetric use of their hands[19]. In the short term, the two initial attempts at lower extremity VCA have shown a return to ambulation with assistance and a nearly normal passive range of motion with good strength throughout, although the active range of motion was markedly decreased compared to baseline[7,8]. The most recent attempt has also shown some active range of motion and partial weight-bearing at six-months postop[13]. The greater distance that must be traversed with nerve regeneration in the lower versus upper extremity must be another consideration, however, as nerves regenerate at a peak rate of 1 mm/day-3 mm/day while motor endplates remain responsive only on the scale of years after denervation, after which functional recovery is unlikely[24,25]. Accordingly, denervation muscle atrophy can present a greater challenge for motor and sensory outcomes of lower extremity VCA, and patient outcomes post-transplant may be more akin to individuals with peripheral nerve injuries (i.e., foot drop in the setting of peroneal nerve damage)[26].

Overall, the less intricate nature of lower extremity motor function may mean that allotransplantation has greater potential for restoring normal levels of function than has been shown with VCA of the hand. Yet, the more straightforward function of the lower extremity is also why lower extremity prosthetics are more effective than upper extremity prosthetics at re-approximating the functional demands of the native limb. Further, it is unclear how weight-bearing factors come into this discussion, as the upper limb is not subject to the same loads that burden the lower limb. Whether lower extremity allografts are capable of meeting the long-term demands that prosthetics are designed for has also yet to be explored. At the very least, VCA of the lower extremity may offer the possibility of converting from an above-knee to below-knee amputation, which has benefits in energy expenditure, cardiovascular strain, and independence[27].

The beneficence argument for VCA of the extremity is further strengthened when the psychosocial components of quality of life are also considered. Improvement in motor skills allows recipients to resume their previous jobs, perform activities of daily living, and have a normal social life[28,29]. VCA also offers the benefit of aesthetic restoration of body image that exceeds what can be achieved with prosthetics, salvage procedures, and replantation. An important and increasingly recognized consequence of severe disfigurements, such as limb loss, is that of "social death" - a construct constituting social isolation, loneliness, ostracism, loss of personhood, altered role and identity, and personal harm - which has been associated with physical pain and increased risk of mortality[30-33]. VCA carries the potential for the treatment of social death - admittedly more applicable to upper versus lower extremity amputees, as the former is more visible - that cannot be attained through alternatives. In fact, both functional and psychosocial outcomes following hand transplantation have been shown to be superior to those associated with the use of alternatives after limb amputation[34-37]. At up to 18 years post-transplantation, patients have shown decreasing disability with excellent and improving outcomes per appearance, sensibility, mobility, psychological and social acceptance, daily activities and work status, and patient satisfaction and general well-being[38]. Similar observations can likely be anticipated for patients after lower extremity transplantation. By centering perspective around the whole person, VCA has been proposed as "lifesaving" in recent literature[30,33]. This thereby negates the argument against the procedure as only life-enhancing and demonstrates how VCA of the extremity can promote the best interests of the patient on multiple dimensions.

Risks

While the potential benefits of VCA of the extremity are evident, there are substantial risks. First, postoperative complications are an inherent risk for any extensive surgical procedure. Reported complications for hand transplantation have included postoperative vessel thromboses, skin necrosis, ischemic reperfusion injury, surgical site infections, pneumonia, sepsis, and acute limb loss[38-40]. Similar complications would be expected for procedures involving the lower extremity, but the larger operative area carries a greater risk for considerable blood loss - especially for proximal or bilateral transplants - than for upper extremity VCA.

The primary concern surrounding VCA is recipients' susceptibility to allograft rejection and a requirement for long-term immunosuppression. Almost all hand transplant recipients experience at least one episode of acute rejection within the first posttransplant year, and additional episodes beyond this point are not rare[29,38,41]. Chronic rejection is an emerging threat that has been reported in nine cases to date, with graft loss occurring in four. Despite the high documented rejection rate, graft survival rates hold at approximately 70% in patients with > 10 years of follow-up[38]. A complex immunosuppressive regimen is necessary for VCA that follows protocols well-established for solid organ transplantation. They typically involve induction with mono- or poly-clonal antibody therapy followed by lifelong maintenance with triple-drug combinations[19,42]. Such extensive immunosuppression can cause complications, including but not limited to metabolic disturbances, opportunistic infections, malignancies, and thromboses - thereby carrying risks for shortening life and creating harm for the recipients[38]. These risks are exemplified by two of the four cases of true lower extremity allotransplantation, which were complicated by the development of a primary central nervous system lymphoma and disseminated aspergillosis with multi-organ failure and early death[26]. Interestingly, however, immunosuppressive medications have been shown to accelerate the rate of nerve regeneration - although the implications for functional recovery are unclear[43,44]. Centers have also reported using similar dosage and serum level requirements as those widely accepted for solid organ transplantation[45]. Other than medical consequences, the necessity for immunosuppression, along with physiotherapy specific for limb transplantation, further generate substantial time and financial costs that may create a burden on the patient's behalf.

Additionally, the psychosocial burden for recipients and families must be considered. Experts note that candidates often underestimate the difficulties experienced in the posttransplant period, especially since the quality of life tends to decrease in the first three months after the procedure before improvement is seen, not reaching baseline reported quality of life until approximately one year after hand transplantation[46-48]. Recipients frequently develop mood changes and anxiety in this perioperative period and during episodes of acute rejection[46]. Moreover, a psychosocial challenge of extremity transplantation involves assimilation of the new limb into the recipient's body image. The visible nature of VCA of the extremity can result in body image distortion and a disrupted sense of bodily integrity, leading to negative self-evaluation and a reduced sense of well-being[49,50]. Inability to psychologically integrate the allograft may then lead to nonadherence with medications and subsequent rejection. This process can exacerbate recipients' emotional and physical distress, as they would be faced with not only reexperiencing loss of a limb but also potential lesser function than before the transplant from further amputation of the preexisting stump. Visibility of the transplant may also lead to psychological regression, negative responses from family and friends, and acute distress[33]. Furthermore, caregivers of recipients must endure substantial burdens from balancing employment and other responsibilities with the demands of long-term care, which are only amplified for family members who are untrained and unprepared to perform the skilled medical tasks required of them[51].

The novelty of VCA means candidates must assume an inherent risk of uncertainty regarding outcomes and complications of the procedure. Long-term data, while expanding for VCA of the hand, does not yet exist for VCA of the lower extremity. Therefore, limb transplantation can cause harm to the patient that may or may not be superseded by the benefits discussed earlier.

Finally, as previously discussed, there are differences in the functionality of upper and lower limb prostheses and hence, distinctions in the ethical considerations for VCA. While upper extremity prosthetics provide acceptable function, they have not yet been able to provide the dexterity needed to attain function similar to baseline[52]. Meanwhile, lower extremity constructs have shown an excellent return to the limb's less complex range of motion, with many patients able to achieve independent ambulation[3,4]. Accordingly, the risk for potential harm is higher for lower extremity VCA, as a meaningful alternative exists without the risks of immunosuppression.

INFORMED CONSENT

Given the complexity and high-risk profile of VCA, issues surrounding patient autonomy are central to the ethical conversation. Candidates must understand the implications of their decision and receive sufficient education to provide informed consent. The discussion should thoroughly address the burdens, commitments, and demands of VCA - including but not limited to adherence with and complications of long-term immunosuppression, potential initial decreases in quality of life, and psychosocial challenges. Benefits are likely easily imaginable for candidates, whereas the extent of risks assumed is less transparent. This discrepancy in knowledge is further worsened by the publicity surrounding extremity transplantation. Media coverage unsurprisingly tends to focus on the positives of the procedure and on patients with the best outcomes, thereby creating misunderstanding regarding the true risk-benefit profile amongst potential candidates and compromising informed consent[53].

It is pertinent to note that VCA candidates, especially bilateral amputees, may be particularly vulnerable to accepting the substantial risk involved with the experimental nature of limb transplantation[54,55]. This may further contribute to the agreement without appropriate consideration of the risks involved. Thus, while patient autonomy must be prioritized and recipients have a right to choose, the decision for VCA must also be approached with a caution that requires scrutiny from providers.

DONOR AUTONOMY

In contrast with solid organs, VCAs are not currently a routine part of first-person or family authorization for organ donation[56]. The Uniform Anatomical Gift Act creates the option to register as an organ donor when applying for a driver's license and is thereby the most appropriate means for ensuring donor consent. However, the existing law does not currently cover VCAs[57]. In 2018, Pennsylvania became the first state to modify its adaptation of the law to include VCAs[58]. As such, the question of autonomy largely remains unaddressed for donors in the extremity transplantation process. VCA donation currently requires separate and explicit authorization by the donor prior to death or, more commonly, by family as surrogate decision-makers after death. Surrogate consent, while better than no consent, is not equivalent to first-person consent. The current practice of asking for VCA separately also carries the concern about negatively influencing the willingness to donate solid organs, which can further decrease an already insufficient supply[59].

Furthermore, limb transplantation is tied to a social significance that can make donation especially difficult for donor families. The potential for post-transplantation rejection and discarding of the allograft(s) may be difficult for donor families to accept but a realistic consequence about which they must be informed[60]. If explantation were to occur, they may learn of the event through the media. An additional psychological deterrent would be knowing another person has the attributes of a loved one, especially if there are markings that are unique or recognizable on the allograft. In these cases, limbs may not be eligible for donation. If the allograft is deemed to be an otherwise excellent match, the recipient must also agree to accept the potential identifiability of the markings. Therefore, discussion of the potential consequences and possibility of failure should be considered when obtaining informed consent from donor families.

PATIENT PRIVACY & PUBLIC DISCLOSURE

Loss of patient privacy is a risk that should be assumed with modern-day VCA, as the procedure is commonly reported on through print, social, and visual media[61]. The novelty of VCA creates a conflict between physician and institution excitement for publicity and recipient/donor right to privacy and confidentiality. Outside of medicine, the success of VCA is largely judged by the general public on aesthetic outcomes and media depictions of transformation. Such perceptions can influence willingness to donate allografts, funding, and general support for or against future procedures[33]. To date, media reports have largely focused on the benefits of VCA for the recipient, which may increase the availability of allografts but lack an accurate portrayal of the difficult course to recovery[61]. Transplant centers have an ethical obligation to develop public trust by reporting on both positive and negative outcomes, and data-sharing is essential for continued improvement in the field[62]. However, these duties come at the cost of donors and recipients who may be subjected to unwanted media scrutiny. In order to achieve sufficient informed consent, both recipients and donor families should be cautioned that their identities will likely be revealed[63]. With the rise in social media, patient privacy and confidentiality are at increased risk of compromise, and institutions should continue to aid potential candidates in understanding these possibilities.

PATIENT SELECTION

The fairness of candidate selection for extremity transplantation has been questioned due to its strict criteria. Maximum clinical success requires selection based on anatomic, medical, and psychosocial factors. Contraindications have been outlined and include age > 65 years, serious coexisting medical or psychological conditions (i.e., coronary artery disease, diabetes, alcoholism), history of malignancy within five years of remission, human immunodeficiency virus infection, positive crossmatch with the donor, and positive pregnancy test in female candidates - although these are becoming less stringent with evolution of the field[64]. Surgical indications remain undefined, and standardized criteria for inclusion and exclusion of recipients are lacking[65].

Given the experimental nature of the procedure, institutions and providers may choose the “easier” patient to avoid negative outcomes and bypass those with the greatest need. Patients with better social support and less significant psychological complications are considered more suitable, as adaptive coping styles, supportive family and friends, stable finances, and logistical factors have been shown to be predictors of successful outcomes[66]. However, substantial differences exist in the already subjective mental health evaluation of candidates[49], thereby leaving room for biases to act. In optimizing outcomes, decisions may be indirectly colored by discrimination based on disability, criminal history, suicidal behavior, or socioeconomic status. Issues regarding access to and disparities in VCA are further complicated by some institutions considering certain causes of limb loss as contraindications to VCA, as a history of risky behavior can reflect a non-psychologically ideal candidate[67,68]. As a result, less psychosocially ideal patients are often passed over as candidates. While these selection methods are not equitable, their restrictions may be non-negotiable given the necessity of long-term medical appointments, a complex immunosuppressive regimen, and physical rehabilitation for successful outcomes. It must be noted that currently, the field of VCA remains experimental and most reported patients are enrolled in review board-approved clinical trials with institution-dependent inclusion criteria. Therefore, the concept of “need” is still under study. Equitable allocation of care and fair patient selection will become more central to the ethical conversation if extremity transplantation utilization increases.

ETHICAL CHALLENGES OF PEDIATRIC VCA

As discussed previously, the first case of lower extremity transplantation occurred between three-month-old ischiopagus twins. In 2000, a 28-day-old infant with congenital absence of the hand was the first pediatric recipient of an upper extremity allograft from her monozygotic twin[69]. The first attempt at pediatric extremity VCA with a non-biologically identical donor was performed in 2010 outside the United States. The recipient was a 17-year-old female with bilateral proximal-third arm amputations who underwent bilateral transplantation and expired in the immediate postoperative period[70]. The first successful bilateral hand transplantation in a pediatric patient was performed in 2015 at the University of Pennsylvania[71]. The 8-year-old recipient was already immunosuppressed because he had previously received a kidney transplant at age 4. To date, these remain the only examples of pediatric VCA of the extremity, but most are not reflective of true allotransplantation or its associated risks. Expansion of VCA access to the pediatric population - where lifelong immunosuppression is required and patients cannot provide autonomous consent - raises even more ethical issues.

There are unique concerns of VCA in a growing child[72,73]. The young age at initiation of immunosuppression means greater life years at risk and near-certain development of serious adverse effects, including malignancy, shortened life expectancy, and eventual loss of the graft to rejection[74,75]. A key risk demonstrated for pediatric solid organ transplantation is the higher susceptibility for end-stage renal disease and subsequent need for a kidney transplant as well[76]. Such adverse events are enhanced by the association of young age, especially adolescence, with decreases in adherence to immunosuppression[77]. In fact, the incidence of poor adherence in pediatric transplantation ranges from 30% to 76%, with contributing factors across multiple dimensions related to adjustment difficulties during these transitional years[78,79]. Further, the use of corticosteroids and early transplantation has been shown to negatively impact skeletal growth and neurocognitive function, resulting in delay and more psychiatric difficulties[73]. All the above can have deleterious effects on quality-of-life measures across the lifespan. Interestingly, despite avid concern that grafts may not grow at appropriate rates, follow-up from the first pediatric hand transplant recipients demonstrated allograft growth rates comparable to established nontransplant norms[69,71]. However, this encouraging finding also brings attention to another area of concern for pediatric VCA. Limited long-term data exists for all pediatric transplantation - not only VCA. This is mainly due to a lack of randomized clinical trials in the pediatric population plus the small number of cases each year[74,80]. Thus, the uncertainty surrounding pediatric extremity transplantation is substantial.

Moreover, the decision for pediatric VCA calls into question whether parental consent is adequate for complex, elective procedures with lasting implications for the child. Pediatric care typically requires informed consent from the recipient's parent/guardian with assent of the child playing a larger role as they age[81]. This model focuses on the idea of the "best interests of the child" rather than autonomy[82]. However, it is unclear if VCA meets those best interests. Consent in VCA must be held to a higher standard because the procedure is non-lifesaving, and patient cooperation is necessary. Nevertheless, even when discussed in depth, the long-term, active participation in therapy and immunosuppression required of recipients is unlikely to be understood by younger individuals. Rather, the option to wait and involve the child in the decision when they are older may be preferred, given the current state of the science.

VCA VERSUS LIMB SALVAGE AND REPLANTATION

Other than amputation and use of prostheses, traditional surgical treatment modalities for limb loss include limb salvage and replantation of the detached extremity. While replantation - like VCA - is more conventionally seen for the upper extremity, an increasing number of cases involving the lower extremity have been reported in recent years[83-91]. For VCA to be ethically pursued, it must at least be in a state of clinical equipoise; that is, not clearly worse than these available treatment options.

At present, decision-making in limb-threatening lower extremity trauma has been grounded in the results of two clinical trials: the Lower Extremity Assessment Project (LEAP) and the Major Extremity Trauma Research Consortium (METRC). Evidence from LEAP revealed similar functional outcomes for limb salvage versus amputation, with a substantial proportion of patients in both groups experiencing significant disability and being limited in or unable to work[92-97]. Outcomes were also more affected by a patient's economic, social, and personal resources than the treatment option pursued or the level of injury[92,93,96]. METRC produced similar findings, reporting that patients who underwent limb salvage would have had small differences in most outcomes had they undergone amputation[98,99]. Importantly, mobility scores would have been significantly improved for amputation[98,99]. No strong evidence currently exists for replantation or VCA of the lower extremity.

Inherent differences in the circumstances surrounding limb salvage and replantation versus allotransplantation may favor the latter in terms of patient benefit. Limb salvage and replantation make use of the injured extremity in acute, urgent operations that must occur shortly after trauma. Consequently, they involve little predictability, minimal preoperative planning, and greater ischemia time. In VCA, the allograft tissues are less damaged, the procedure is better controlled given its more elective nature, and the recipient is more clinically stable at the time of surgery and able to begin rehabilitation earlier[37]. Importantly, VCA of the lower extremity is not mutually exclusive from limb salvage, replantation or amputation, as VCA could still be performed in the future if another option is initially pursued.

As discussed above, the argument for VCA involves its recovery of sensory and motor function, decreased disability, and psychosocial benefits - although existing data is from upper extremity, not lower extremity VCA. Both limb salvage and replantation procedures also offer the key benefit of restoration of sensation, but hand transplantation has demonstrated higher rates of recovery for tactile and discriminative sensibility (80%-90% *vs.* 30%-60% for replantation)[20,100]. Transplanted hands also exhibit finer two-point discrimination than replanted hands, although this measure is not an essential goal for the lower extremity[28,101,102]. Otherwise, replants have shown superior strength, perhaps due to greater muscle atrophy in transplant recipients secondary to extended time between limb loss and VCA, but lesser recovery of intrinsic muscle use[28,103]. Further, salvage and replantation are associated with a higher degree of scarring and a greater risk of unequal lower extremity lengths due to bone-shortening from the inciting trauma[104,105]. VCA has the benefit of having excess tissues available for procurement to maximize cosmetic results. Per overall quality of life, limb salvage has demonstrated psychological results near equivalent to amputation, with substantial postoperative rates of depression, anxiety, substance abuse, and suicidal ideation[96]. In contrast, replantation and allotransplantation have reduced concerns related to body image, independence, and social reintegration[106,107]. Patients undergoing both procedures have been able to resume suitable work, with transplant recipients reporting higher satisfaction[108,109]. It must also be mentioned that while physical rehabilitation is required for all three options, VCA was initially thought to require the additional burden of cognitive therapy to gain control of the allograft. Yet, evidence suggests that this may not be necessary, as immediate cortical integration has been demonstrated in upper extremity VCA recipients long after amputation, and a substantial concern has been removed from the argument against allotransplantation[110].

With the use of autologous tissues for salvage and replantation, the harms related to allogeneic tissue are no longer relevant. There is no requirement for long-term immunosuppression and thus no assumption of its associated risks. However, limb salvage does require extensive debridement, fasciotomies, revascularization, and fixation and is known to be associated with a high rate of complications, including infection, thrombosis, necrosis, impaired bone healing, and the need for secondary procedures[111,112]. It must be noted that lower extremity replantation has been associated with a high rate of complications as well, with up to 86% of patients requiring secondary surgeries and a low rate of autograft survival at 45%, albeit available data is sparse[85]. Using an individual's own tissues also precludes the development of psychosocial issues with limb assimilation and body integrity that can cause critical consequences for VCA of the extremity. Finally, at present, the acceptance and continued practice of limb salvage and replantation means less uncertainty and more access to long-term data relative to allotransplantation.

Ultimately, the ethical considerations surrounding limb salvage, replantation, and VCA of the lower extremity are profoundly nuanced. It must be reinforced that the data discussed above are from available evidence on the upper extremity. Lower extremity alternatives to amputation carry more substantial burdens relative to upper extremity equivalents, given the higher and excellent level of function that available prosthetics provide for the lower extremity. With increasingly effective prosthetics, this ethical discussion must be revisited based on the latest science.

HOW MEDICAL INNOVATION CHANGES THE CONVERSATION

Prosthetic alternatives

Specific to VCA of the extremity, the function and benefits provided by the allograft must be weighed against those of prosthetics. A recent survey found that for hand transplantation, recipients experience increased satisfaction driven by social and aesthetic values and a greater sense of independence with the allograft compared with available prosthetic options. Caregivers similarly report less unease with leaving transplanted patients alone due to the superior functionality provided[113]. Again, contrary to options for the upper extremity, lower extremity prosthetic devices are more effective constructs that have demonstrated excellent outcomes with a high rate of return to independent ambulation[3,4]. Yet, patients still often reject them due to discomfort, weight, or limited usefulness - especially for above-knee amputees[114-116]. Rejection rates are as high as 1 in 3 for lower limb prostheses, compared with over 1 in 2 for upper limb constructs[117,118].

Ongoing research has been focused on enhancing the functionality and applicability of prosthetic devices. In addition to technological innovations that address socket, interface, and alignment concerns, advanced options include targeted sensory and muscle innervation, bionics, and bone-anchored prostheses[119]. The use of microprocessor-controlled components has enabled greater functional achievements in above-knee amputees, allowing real-time dynamic gait and ambulation management that permits adjustments with advancing progress during postoperative rehabilitation. Potential merits include reduced effort during ambulation, improved symmetry and natural gait, and a lower risk of falls[120,121]. Targeted sensory innervation transfers peripheral sensory nerves to denervated proximal skin and allows restoration of tactile feedback, pain, temperature, and proprioception, thus addressing a key pitfall of traditional prosthetic constructs[52,122,123]. Similarly, targeted muscle innervation, which involves the transfer of functioning nerves that have lost their operational target to intact proximal muscles, can confer additional degrees of active motion to myoelectric prostheses and has gained considerable momentum in recent years[124]. This technique also has the added benefit of reduced phantom limb pain[125], considerable morbidity in patients with lower extremity amputations. Moreover, actively powered prosthetic joints (i.e., bionics) have become more sophisticated, with new technology allowing a wider range of movements and easier transition between ambulation modes[126-128]. Osseointegration, which involves the attachment of titanium implants to the residual bone as an anchor for prostheses, has further been explored as a solution to complications regarding socket fit and comfort with encouraging early results[129,130]. More than functional benefits, recipients have reported that osseointegrated prostheses have strengthened their sense of body integrity[131]. However, despite these improvements, cosmetic values have not been a major focus of current research initiatives, especially for the lower extremity. Despite being less visible than upper extremity prostheses, studies have shown that having a lower limb device with an appearance in line with one’s body perception induces prosthesis embodiment and satisfaction[132,133]. Advanced constructs are also costly, and patients’ accessibility to these newer technologies is questionable[134]. As prosthetics become more advanced and able to meet the goal of a replacement with near-identical function and appearance as the missing limb, indications for VCA may shift out of favor due to its higher risk profile.

Immunosuppression

The main argument against VCA is its requirement for lifelong immunosuppression that places recipients at risk of adverse events, graft loss, and a shortened lifespan. Traditionally, extremity transplants have been maintained with a triple-drug immunosuppressive regimen after antibody-based lymphocyte depleting induction therapy - most commonly involving the use of polyclonal or monoclonal antibodies, tacrolimus, mycophenolate mofetil and steroids, all of which have significant long-term side effects[19,42].

Recent initiatives have sought to determine regimens that cause less morbidity with equal or greater effectiveness in reducing the risk of rejection, to reduce or eliminate the need for lifelong immunosuppression. At the forefront is an effort to induce donor-specific transplantation tolerance and achieve chimerism, which refers to the coexistence of donor and recipient immune cells. Multiple strategies have been proposed, including hematopoietic stem cell transplantation, costimulation blockade and cell-based therapies[135]. Topical immunosuppression may also help prevent rejection without the substantial risks implicated with systemic immunosuppression. While tolerance has been induced in various protocols for small animal models, large animal studies have largely been unsuccessful[136]. Without consistent evidence supporting immunomodulation in non-human models, the transition from bench to bedside remains limited. Nevertheless, some centers have attempted the adoption of minimal immunosuppression protocols. Of note, a joint team at the Johns Hopkins University School of Medicine and University of Pittsburgh has achieved lower rates of morbidity with the use of hematopoietic stem cell transplantation with low-dose tacrolimus monotherapy - although chimerism was not realized with this regimen[137,138]. At two years follow-up, their five-patient cohort had no signs of chronic rejection, infrequent acute rejection episodes, and an acceptable side effect profile. Elsewhere, the application of a minimal immunosuppression protocol resulted in acute rejection necessitating explantation within one year of initial hand transplantation[136]. Therefore, the advent of more effective, less toxic immunosuppressive therapies has the potential to reduce some of the ethical controversy surrounding VCA and create a more favorable risk-benefit profile.

General advancements

Another key ethical consideration of VCA of the extremity is that it is a novel procedure, which limits the data currently supporting decision-making. As time passes, a greater number of procedures will be performed, transplant facilities will have more experience with allotransplantation, and more long-term data will be available. Eventually, there will likely also be greater supervision and management of the allocation process as well as fading media scrutiny. Correspondingly, compared with the current state of VCA, future candidates may assume a lower risk of uncertainty regarding outcomes and complications of the procedure. The concerns discussed previously surrounding patient selection, understanding, and privacy may also be lessened with further development of the field.

CONCLUSION

VCA of the lower extremity is an emerging field with considerable ethical challenges, given it is being a life-enhancing rather than lifesaving procedure. The primary ethical tension is between the principles of beneficence and nonmaleficence, though there are also relevant concerns about informed consent. Experts have been increasingly in favor of the ethicality of hand transplantation[139,140], a shift in opinion which may be partially influenced by advancements in immunosuppression that alter the risk-benefit profile[19,138]. However, lower extremity transplantation is likely to remain controversial given the high function and technological innovations of lower limb prosthetics - where a shortcoming for upper extremity alternatives exists. Both are not currently and will unlikely become the best option for the majority of amputees, but VCA is a good alternative for patients who fail other reconstructive treatments. Overall, the ethical considerations surrounding VCA will continue to evolve with the data, particularly if advancements in immunosuppression decrease associated morbidities.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Xu AL, Humbyrd CJ

Performed data acquisition, as well as provided administrative, technical, and material support: Xu AL, Humbyrd CJ

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Both authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication

Not applicable.

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