

# Lessons Learned From the First Quadruple Extremity Transplantation in the World

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**Background:** Limb transplantation is emerging as a promising area of surgery and is an indispensable alternative for prosthetic rehabilitation of amputees, the severity of which is increasing because of combat-related injuries. Successful unilateral and bilateral limb transplantations have already been performed before this operation.

**Methods:** We performed the first ever quadruple limb transplantation in February 2012. The limbs procured from a 40-year-old man heart-beating donor were transplanted to a 27-year-old male patient who was a quadruple amputee for the last 14 years because of an electrical injury.

**Results:** To shorten the ischemic period to a minimum, 3 separate microsurgery teams worked simultaneously. All extremities were reperfused within 8 hours of procurement, and the operation lasted for 12 hours. Metabolic load was managed by hemodialysis. One hour after the completion of the operation, cardiac arrest developed, resuscitation of which necessitated median sternotomy and temporary partial cardiopulmonary support. Despite the removal of the transplanted limbs and all efforts including continuous hemodialysis, plasmapheresis, and extracorporeal membrane oxygenation, the patient died on the fourth day after transplantation in a clinical condition of severe systemic inflammation.

**Conclusions:** The problems we faced were difficulty of vascular access for invasive monitoring and fluid replacement, and the severe systemic inflammation effects of which could not be dealt with, despite aggressive supportive treatment. We hope that our experience will enlighten the surgeons who are willing to extend the limits of limb transplantation and serve the success of future operations.

**Key Words:** quadruple extremity transplantation, composite tissue allotransplantation, face transplantation

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The world's first quadruple limb transplantation has been performed in Hacettepe University Hospital. Although bilateral upper extremity transplantation to a quadrimembral amputee was previously performed, transplantation of both upper and lower extremities was first performed in our case.<sup>1</sup> Quadruple amputees have lost either all or part of both their upper and lower extremities. Compared with single-limb amputees, they are reliant on rehabilitation and prosthetics, with fair to poor expectations and outcomes. In addition to an increasing incidence, there is a recent shift in the etiology of quadruple amputations because of increased number of combat-related injuries and high-voltage electrical damage. Patients with bilateral transfemoral amputations experience loss of balance

while sitting and rolling. They also experience a lack of propulsive and proprioceptive support in ambulation. Bilateral upper extremity amputees lose the ability to interact with and manipulate objects in their environments during activities of daily living. In contrast to unilateral or bilateral amputees, quadruple amputees are unable to compensate for the lost functionality using the remaining limbs. The potential of this operation gives them the chance to regain a certain level of independence. This increases the motivation of quadruple amputees, and they are considered as potential transplant candidates.<sup>2</sup>

A multidisciplinary team composed of specialists from the departments of psychiatry, nephrology, anesthesiology, critical care, hematology, cardiology, and microsurgery has worked closely together during the preoperative preparation, conduct of operation, and postoperative period. At the time of this operation, bilateral limb transplantations were successfully performed for both upper and lower extremities at above elbow and knee levels, respectively. Despite careful planning, attentive care for preoperative preparation, cautious conduct of the operation, and significant efforts in the postoperative care, the patient died on the fourth postoperative day. We believe that the experience we gained from this case will serve to the success of future operations.

Despite the unfortunate result of our case, we keep our enthusiasm and expectation that quadruple limb transplantation can successfully be performed, provided that we continue working on the clinical aspects of this issue and develop the required novel technologies in the light of the lessons derived from this case.

## CASE PRESENTATION

The patient was a 27-year-old man who had all 4 extremities amputated after an electrical accident, which had occurred 14 years ago. There were amputations on the right arm at shoulder level, on the left arm at the level of mid-humerus, and on the legs above the knees (Fig. 1). The patient was evaluated and extensively discussed by the composite tissue transplantation council, and their approval was granted. Preoperative evaluation was performed by a multidisciplinary team, and no contraindications or medical problems that would prohibit the operation were found. The 4 extremities procured from a 40-year-old male brain dead donor were transplanted to the quadruple limb amputee donor. The donor and the recipient were blood group compatible (O and A) and had a 0/6 HLA match. IRB and National Organization for Organ Transplantation approvals were also obtained.

## Tissue Procurement

We have procured the extremities and full face working simultaneously with solid organ procurement teams. Extremities were perfused with Wisconsin solution.

## Irradiation of the Procured Extremities

Based on the promising results of an experimental study performed by our radiation oncology team, which points to the advantage of preoperative irradiation to reduce the antigenic load of the transplanted extremities,<sup>3</sup> we irradiated the extremities preoperatively.

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**FIGURE 1.** Preoperative view of amputation levels.

### Immunotherapy

The immunosuppressive treatment included induction with ATG and standard triple therapy with tacrolimus, mycophenolate mofetil, and corticosteroids 1 hour before surgery.

### Operative Period

Our major aim was to shorten the cold ischemia of procured extremities. We devised 2 strategies, first, to perform simultaneous transplantation of the extremities by 3 different microsurgery teams (Fig. 2 A,B) and, second, to reestablish circulation of the lower extremities by inserting temporary shunts between stumps of femoral arteries and veins while performing transplantation of upper extremities (Fig. 3). To prevent bleeding from the muscle tissue, we applied Surgicell to raw surfaces. Because our first team was performing the total face transplantation procured from the same donor to another recipient, we started extremity transplantation with the 2 teams. The third team joined the operation after completing the total face transplantation, which is the second face transplantation in Turkey. The total cold ischemic time for all extremities was around 8 hours. The total duration of the surgery for all 4 extremities was approximately 12 hours (Fig. 4).

All anastomoses were performed satisfactorily, and there were no problems regarding microsurgical technique. The injury pattern necessitated unconventional strategies to achieve satisfactory vascular access for both monitoring and fluid resuscitation and anastomosis of one of the vascular stumps.

Because the subclavian and femoral vessels were to be used for anastomoses, they were not available to use for fluid resuscitation and monitoring. The left internal jugular vein was used for fluid resuscitation. For invasive blood pressure monitoring, the right inferior epigastric artery was dissected and used but occluded within 3 hours. Based on this result, we believe that the use of any vessel proximal to the femoral artery is inappropriate during lower extremity transplantation. We opted to place a cannula in the right internal iliac

artery, which caused spasm in distal circulation that was relieved upon removal of the catheter.

Because the amputation was due to an electrical injury, the injured segment in the right subclavian vein was quite long, and its stump was located at the thoracic inlet just below the costoclavicular ligament, rendering it useless for anastomosis. To solve this problem, the right external jugular vein was dissected, transected, and reversed under the clavicle to be used for anastomoses with the donor's right subclavian vein.

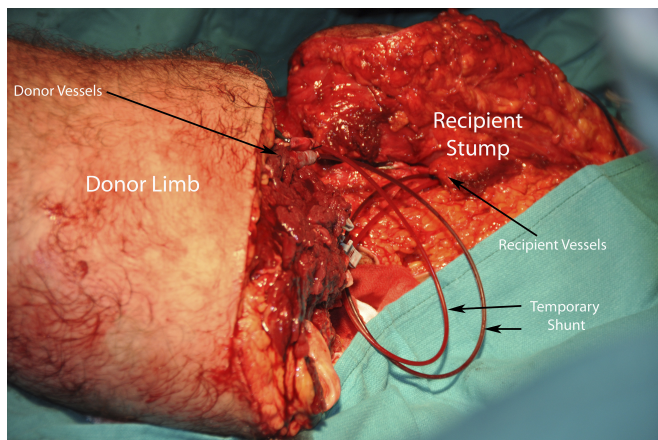
Both hemodynamic and metabolic parameters were closely monitored during the operation. Despite a trend toward metabolic acidosis and mild hyperkalemia, which were manageable, the patient was stable during the initial phases of the operation. Close to the time of completion of the anastomoses, the acidosis worsened despite all supportive efforts and therapies. One hour after the last extremity was transplanted, progressive bradycardia occurred, which was followed by cardiac arrest. Spontaneous circulation was reestablished after a short period of resuscitation, which required sternotomy and temporary partial cardiopulmonary support. The metabolic evaluation revealed metabolic acidosis, hyperkalemia, and hyperphosphatemia. Continuous hemodialysis and intermittent plasmapheresis ensued. Despite all supportive treatments, the patient's metabolic state could not be improved, and transfusion requirements increased. Blood and blood product transfusion requirements totaled 200 units over 4 days. The extremities were sequentially amputated. Despite all supportive treatments and interventions, the patient died on the fourth day.

### DISCUSSION

Our group is one of the 3 composite tissue allotransplantation teams in Turkey. Over the last decade, we have performed many microsurgical operations as well as conducted various experimental studies on composite tissue transplantation. The senior author worked on experimental composite allotransplantation and permanent immunotolerance using different therapeutic methods.<sup>3</sup> The aim of our experimental studies is to achieve permanent immune tolerance without the use of immunosuppressive drugs and develop novel clinical composite tissue allotransplantations in the future.<sup>4,5</sup>

Nerve allotransplantations in replanted arms have been performed by the authors on 2 children, the younger of whom had total motor and sensorial recovery. To our knowledge, this report on clinical nerve allotransplantation was the second published article in the literature.<sup>6</sup>

We have performed the sixth full face transplantation in the world simultaneously with the reported quadruple transplantation.



**FIGURE 2.** Temporary shunts between the femoral artery and veins of lower extremities.





**FIGURE 3.** A and B, Three microsurgical teams performed all surgery procedures simultaneously.

Full face procured from the same donor was transplanted to another patient. At the sixth postoperative month, the patient gained full face mimic muscle movements and sensorial innervations.<sup>7-9</sup>

As the success of allotransplantation has increased, an accompanying trend toward performing multiple simultaneous vascularized composite tissue allotransplantation procedures has developed. Although it is hypothetically promising, controversy on multiple simultaneous vascularized composite tissue allotransplantations persists, and clinical experience is limited.<sup>10,11</sup> As reported in a recent article, 2 cases of simultaneous face and bilateral hand allotransplantations, one performed in France and the other in the United States, were the only simultaneous vascularized composite tissue allotransplantations to date.<sup>11</sup> The practice of concomitant vascularized composite tissue

allotransplantation is at the early stage of development, with more work to be done as this article states “providing authors’ collective experience in the interest of advancing the debate concerning simultaneous vascularized composite tissue allotransplantation and to provide insights as to how such procedures may be approached more successfully in the future.”<sup>11</sup>

The most important technical difference of quadruple limb transplantation from extremity replantation is the need to obtain a satisfactory length of the vascular stumps. Because the amputation was due to an electrical injury, which resulted in long segment vessel injury, unlike the cases we experienced in acute traumatic amputations, the level of the stumps of vessels to be anastomosed could not be estimated based on the level of amputation. Fortunately, we had already dissected long segments of vessel stumps on the donor extremities in case we encountered such a difficulty. Therefore, it might be beneficial to ensure that the vascular stumps are long enough while procuring the extremities from the donor.

Based on our experience, we suggest that iliac vessels should be harvested for use as vessel grafts in case the primary vascular anastomoses are difficult or impossible because of longer gaps than estimated.

Currently, there are 3 major questions to be answered in extremity transplantation: (1) What are the indications? (2) How we can reduce ischemia? (3) How can the impact of a large antigenic load be minimized?

**Differences in Extremity Transplantation Indications Among Different Countries**

The International Registry on Hand and Composite Tissue Transplantation has reviewed hand transplants performed over an 11-year period and reported on the outcomes.<sup>12</sup>

They accounted for 49 transplanted hands, 17 unilateral and 16 bilateral. It should be mentioned that because of the inability to obtain complete patient information, a subset of transplants in China and in some other centers have not been included in the review. In China, from September 1999 to March 2009, 15 hand/forearm/palm/digit allotransplantations (5 unilateral and 1 bilateral hand transplantations, 3 unilateral and 2 bilateral forearm transplantations, 1 palm transplantation, and 1 thumb transplantation) have been performed on 12 patients.<sup>12</sup>

Furthermore, Biemer<sup>13</sup> has performed the world’s first bilateral arm transplantation in Germany. His patient had lost both arms at



**FIGURE 4.** Quadruple transplantations were completed in approximately 12 hours.

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proximal and middle humeral levels. He had an advanced functional recovery and continued to perform his daily activities years after the operation.<sup>14</sup> Cavadas et al<sup>15</sup> from Spain have reported another bilateral arm transplantation. The patient had amputations at the level of the distal third of the humerus. Five months after the surgery, both allografts functionally recovered to a level to perform powerful flexion and extension at elbow level. The same surgical team has performed the world's first double leg transplantation on a man whose legs were amputated above the knee after an accident.<sup>16</sup>

We believe that the total number of extremities transplanted to this date may well be over 70 worldwide.

We think that the indications of reported case of finger and hand transplantations at the palmar level and unilateral upper extremity transplantations have to be discussed extensively. A single functional upper extremity is enough to meet most daily activities in a lifetime. The same applies to lower extremities, where a patient with a single functional lower extremity may walk with orthopedic walker or prosthetics. We think that composite tissue transplantation is an overtreatment for these patients. In our case, the patient did not have any capability of movement because of the high levels of amputation. The theoretical indication for upper extremity transplantation above the elbow has typically been questioned.<sup>17</sup> However, Cavadas et al<sup>15</sup> demonstrated excellent functional results of allotransplanted arms within the two-year postoperative period.

We performed bilateral lower extremity transplantation above the knee level simultaneously with bilateral upper extremity transplantation above the elbow level. Our aim was to enable the patient to gain ambulation with the aid of external knee stabilizers and a walker. One of our bilateral above knee leg replantation patients, who was operated about 15 years ago, currently walks using the same strategy.

Significant controversy exists regarding the indications for quadruple extremity transplantation. However, it is an undisputed reality that many patients, especially military personnel, need quadruple extremity transplantations to regain their daily activities. The potential to improve the quality of life of these patients is a significant motivation for transplant surgeons to turn to these challenging operations.

### Problem of Ischemia in the Transplanted Extremity

Ischemia is a major problem both affecting the overall success of the operation and also creating a significant metabolic load for the patient because of ischemia reperfusion injury. The problem begins at the time of procurement of extremities and continues during the operative and postoperative period.<sup>18</sup>

The performance of simultaneous multi-organ procurement by multiple teams is an important technical problem because the composite tissue procurement team has to work in a confined space in the operating theater, a situation to which the transplantation teams are unaccustomed. Thus, they must be well prepared for this difficulty and review and revise the procurement plan with the solid organ procurement teams.

Within our strategy, to revascularize the donated extremities as soon as possible and shorten the ischemic period, we prepared 3 microsurgery teams, which worked simultaneously. As the first team was performing a full face transplantation on a separate patient, and joined the operation later, the other teams started to transplant upper extremities, while circulation of the lower extremities were reestablished via temporary shunts. Total operative time for transplantation of 4 extremities was 12 hours.

Despite all technical precautions, transplantation of extremities caused a significant metabolic load that exceeded our expectations. In the early phases of the operation, hyperkalemia and acidosis were manageable by hemodialysis. However, 1 hour after revascularization of all 4 extremities, the metabolic acidosis increased, and hyperkalemia worsened, despite continuing hemodialysis and intermittent

plasmapheresis. We speculate that simultaneous revascularization of the four extremities caused a sudden increase in the metabolic load.

The hemodynamic and metabolic scenario was similar to clinical syndromes characterized by severe systemic inflammation and increased vascular permeability. To prevent and/or deal with this common problem, which resembles Crush syndrome, the following precautions must be taken into consideration:

1. Shortening the ischemic period must be a major aim but is not enough to prevent major metabolic problems. The main principle of multiple extremity transplantation should be to achieve zero ischemia. Currently, this can only be achieved by selecting heart-beating donors and sequentially performing procurement and transplantation of each extremity in a stepwise manner. However, this approach is not practical in the setting of multi-organ procurement. Novel strategies are needed to solve this problem.
2. Transport of procured extremities between different institutions is a major factor extending the ischemic period and is the reason why performance of donor and recipient operations in the same institution is preferable.
3. One extracorporeal perfusion machine is intended to provide oxygen and nutrition at physiological flow rates and at normal body temperature for solid organ allotransplantation.<sup>19</sup> In a recent study, Constantinescu et al<sup>20</sup> have reported an extracorporeal perfusion model for porcine extremity before replantation, and they have reported minor tissue damage in perfused group. If limbs are procured from a distant hospital, extracorporeal perfusion must be used for the procured extremity during transport. In case of interinstitutional transport of procured extremities, required novel technologies for extracorporeal perfusion and oxygenation, as well as removal of metabolic products, must be engineered and used.
4. Although no scientific data are published related to continuous hemodialysis during extremity transplantation, hemodialysis must be started prophylactically before the conventional hemodialysis indications appear and continued during the operation and early postoperative period until the patient becomes metabolically stable.

### Problem of High Antigenic Load Problem

Antigenic load of multiple composite allografts were previously criticized as a major concern.<sup>9</sup>

We demonstrated experimentally<sup>4,21</sup> that the amount of the transplanted tissue may have a major influence on transplant antigenic load as well as on the induction and maintenance of chimerism.

More recently, Gordon et al<sup>22</sup> quantified the amount of skin surface area for some composite tissue allotransplantations. Using this study as a reference, the total skin surface area of procured extremities was estimated to be 4000 to 5000 cm<sup>2</sup>.

Although this is a significant antigenic burden, no significant immunologic challenges were reported for earlier composite tissue allotransplantations like bilateral lower extremity transplantation at above-knee level, having quite high antigenic loads.<sup>15,23</sup> There is little evidence to suggest that the antigenic burden of concomitant vascularized composite allotransplantation procedures is prohibitive from a safety aspect.

Hematopoietic cells are transferred with the bone marrow component of transplanted tissues into the recipient's body. Risk of graft-versus-host disease is usually an expected morbidity after hematopoietic cell transplantation.<sup>24</sup> Total lymphoid irradiation of transferred bone marrow used in hematopoietic malignancies to prevent graft-versus-host disease may also be used for composite tissue allotransplantation. However, the important issue is the irradiation dosage to avoid vascular damage in the extremities. In one experimental study, the safe irradiation dosage for vascular network was determined.<sup>25</sup> In an experimental study, our coworkers reported



the safe irradiation dosage that does not cause vascular damage in endothelial layer of the thoracic aorta of rats, measured at the 21st day of irradiation, as single dose of 8 Gy. In that experimental study, single dose of 15 Gy applied to rats, which corresponds to 48 to 54 Gy of irradiation applied to human, caused permanent endothelial damage. Based on these findings, we have applied 6 Gy of irradiation for 15 minutes, which seems to be quite safe even in long term, to reduce the antigenic load from all extremities. We think that this dosage provided bone marrow suppression without causing vascular damage in extremities.

Because the patient was supported by hemodialysis, laboratory measures of GFR were not reliable. Before cardiac arrest, hyperkalemia developed despite hemodialysis and serum K levels increased to 7 mg/dL. This clearly points to a metabolic load. Although an intraoperative echocardiography was not performed, the need for extracorporeal pump support indicates a decline in cardiac functions. Unfortunately, an autopsy was not performed. As far as the underlying cause of mortality is considered, taking into account the high blood and blood product infusion requirements and similarity of hemodynamic profile to distributive shock, we propose that the major problem that led to mortality was a severe systemic inflammatory response, which we believe was immunologically triggered. Additionally, blood loss from raw surfaces alone does not explain the magnitude of blood transfusion. We believe that disseminated intravascular coagulation triggered as a component of severe systemic inflammation was the underlying cause of intravascular hemolysis, which also contributed to increased metabolic load.

**CONCLUSIONS**

Considering the changing etiologies and increasing incidence of quadruple amputations because of extensive injuries such as electrical and combat-related injuries, achieving successful quadruple limb transplantation is an important issue for surgeons dealing with composite tissue transplantation. Based on our experience, we believe that quadruple extremity transplantation is an achievable goal, provided that ischemic period is shortened as much as possible to decrease the severity of metabolic problems.

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