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Reaching New Heights: A Comprehensive Study of Hand Transplantations in Korea after Institutionalization of Hand Transplantation Law

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Purpose: With the revision of the Organ and Transplantation Act in 2018, the hand has become legal as an area of transplantable organs in Korea. In January 2021, the first hand allotransplantation since legalization was successfully performed, and we have performed a total of three successful hand transplantation since then. By comparing and incorporating our experiences, this study aimed to provide a comprehensive reconstructive solution for hand amputation in Korea.

Materials and Methods: Recipients were selected through a structured preoperative evaluation, and hand transplantations were performed at the distal forearm level. Postoperatively, patients were treated with three-drug immunosuppressive regimen, and functional outcomes were monitored.

Results: The hand transplantations were performed without intraoperative complications. All patients had partial skin necrosis and underwent additional surgical procedures in 2 months after transplantation. After additional operations, no further severe complications were observed. Also, patients developed acute rejection within 3 months of surgery, but all resolved within 2 weeks after steroid pulse therapy. Motor and sensory function improved dramatically, and patients were very satisfied with the appearance and function of their transplanted hands.

Conclusion: Hand transplantation is a viable reconstructive option, and patients have shown positive functional and psychological outcomes. Although this study has limitations, such as the small number of patients and short follow-up period, we should focus on continued recovery of hand function, and be careful not to develop side effects from immunosuppressive drugs. Through the present study, we will continue to strive for a bright future regarding hand transplantation in Korea.

Key Words: Hand transplantation, transplantation law, vascularized composite allotransplantation, Republic of Korea

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INTRODUCTION

Since the first hand transplantation was performed in 1998, more than 150 hand transplantations have been performed worldwide.[1,2] In Korea, the first hand transplantation was performed in 2017, though the procedure was not legally recognized until 2018.[3,4] Vascularized composite tissue allotransplantation (VCA), including hand transplantation, has been widely practiced in Europe and the United States; it began relatively late in Korea due to the different perception of death

and disfigurement in the East[3] as well as the Korean healthcare system's emphasis on safety over effectiveness.

Much has been written about the satisfactory results and effectiveness of hand transplantation. The restoration of hand function allows people to overcome obstacles in their daily lives and has a very high satisfaction rate.[1,5,6] Hand transplantation can also improve psychological well-being and social relationships.[7-9] Restoring motor and sensory control of the transplanted hand is crucial to regaining function. Unlike other solid tissue transplantations, hand transplantation achieves this restoration by providing nerve connections. FK-506, an immunosuppressant, has neuroregenerative effects.[10-12] The use of FK-506 in hand transplantation has resulted in good post-operative outcomes. Sensory and motor recovery of transplanted hands is better than that resulting from replantation.[13] Although the hand is not a vital organ and hand transplantation is a new area of transplantation, it offers former amputees functional, psychological, and social recovery.

The authors aimed to study hand transplantations performed in Korea after the 2018 legislation. We examined the indications, surgical procedures, postoperative protocols, and functional results. By comparing and incorporating our experiences, this study aimed to provide a comprehensive reconstructive solution for hand amputation in Korea.

MATERIALS AND METHODS

Legal context

All hand transplantations were performed in accordance with the Korean Medical Act and the Act on Organs and Transplantation (referred to as the Organ Act).[4] The Korean healthcare system is state-run and covers all medical conditions, except cosmetic ones. All citizens are registered with the National Health Insurance System, and all hospitals accept compulsory insurance. In 2010, hand transplantation passed the New Health Technology Assessment, which determines whether a procedure is covered by the National Insurance Service.[14] In 2018, the hand was added to the Organ Act as an organ that can be donated and transplanted.[4]

Under the revised Organ Act, recipients must be at least 6 months post-injury and present a medical certificate from a psychiatrist to be eligible for hand transplantation. Donors can only be selected from brain deaths that occurred in a medical institution where the recipient is registered. Hands can be harvested simultaneously with peritoneal organ team after heart/lung removal, and the donor hand must be replaced by a prosthetic hand.[4]

Transplantation team and recipient/donor evaluation

We evaluated 3 hand transplantation patients from 2021 to 2023. This study was approved by Severance institutional review board (IRB No. 4-2023-1001). The hand transplantation team consisted of plastic surgery, orthopedic surgery, and transplantation surgery teams. Hand transplantations were managed by the Korea Network for Organ Sharing and the Korea Organ Donation Agency.

Testing for the hand transplantation included scanograms of both shoulders, magnetic resonance imaging (MRI) of the amputated hand, conventional angiography, and brain functional MRI (fMRI). We recorded the fingertip-to-elbow length, distal forearm circumference, proximal forearm circumference, presence of hair, and hand texture and color, including any damage. The size of the hand was recorded based on the size of the surgical glove. In addition, the hand and arm of the VCA team's main chief (J.W.H.) were used as a reference hand to intuitively assess the size of the hand (Fig. 1).

Brain death was confirmed by two clinical determinations of brain death separated by 6 hours followed by an electroencephalography determination and a committee determination. Then, the donor organ procurement process began.[15]

Hand transplantation operation

Three operating rooms were prepared for the transplantation. We prepared Room 1 for procuring the donor hand, Room 2 for dissecting the harvested hand, and Room 3 for hand transplantation. Donor hand procurement and the corresponding recipient procedures were performed simultaneously in adjacent operation rooms.

Donor procedures

We procured the donors' upper extremities at the distal part of the humerus for Patients 1 and 2 and at the elbow level for Patient 3. A tourniquet was not used. After procurement, a premade prosthetic hand was applied to each donor. The procured arms were packed in ice. Reserve solution (Wisconsin solution) washing (volume: 2 liters) was conducted through the brachial artery. Then, the cephalic vein, superficial radial nerve, radial artery, vena comitantes, ulnar nerve, ulnar artery, vena comitantes, and median nerve were isolated along the incision as we designed in the procured hand. Tendon dissection and carpal tunnel release were also performed (Fig. 2).

Recipient procedures

A pneumatic tourniquet was applied to the recipient, and a fish-mouth skin incision was made. The isolated cephalic vein, superficial radial nerve, radial vessel (artery and two vena comitantes), median nerve, and ulnar vessel (artery and two vena comitantes) were carefully dissected, followed by the tendon. All anatomic structures were identified and tagged with prenaming rubbers.

Transplantation

The orthopedic surgery team started with bone fixation. The donor's bone was cut considering the thickness difference between the donor and recipient. As the recipients' amputation

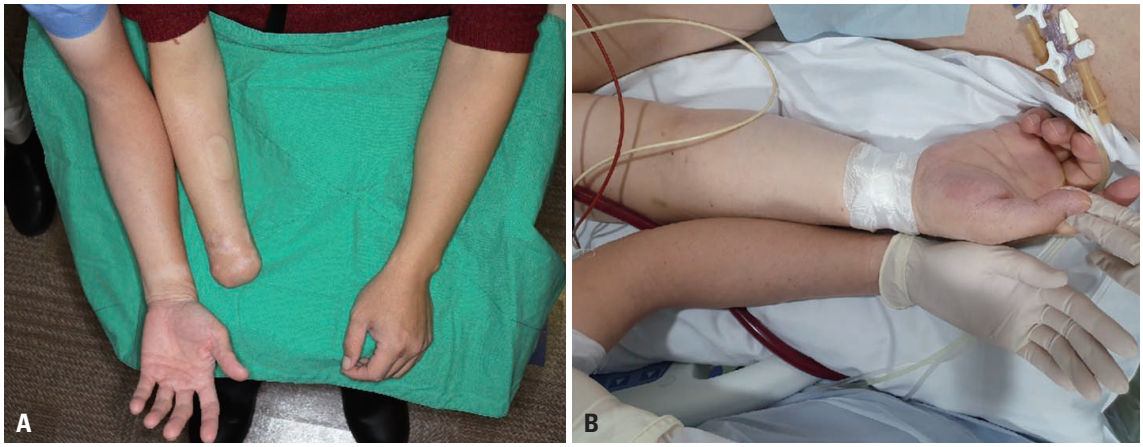

Fig. 1. Preoperative recipient and donor evaluation. Preoperative assessment was performed in the same way for all patients. (A) Preoperative photograph comparing the reference hand with the recipient hand in Patient 2. The hand and arm of the VCA team's main chief (J.W.H.) were used as a reference hand to intuitively assess the size of the hand. (B) Preoperative photograph comparing the reference hand with the donor hand in Patient 1. VCA, vascularized composite tissue allotransplantation.

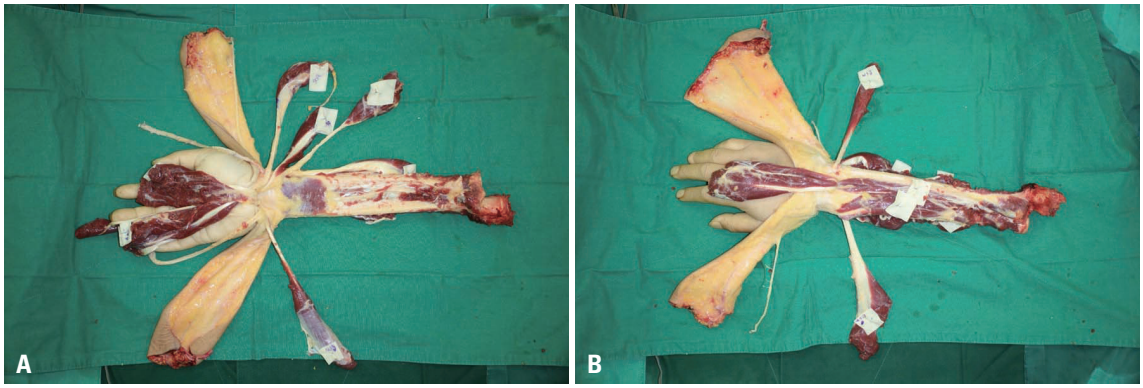

Fig. 2. Photograph of the dissected donor hand in Patient 3. (A) Photograph of the dissected donor hand on the volar side. (B) Photograph of the dissected donor hand on the dosal side.

levels were distal, the standard of bone cutting was adjusted to the distal radius level (pronator quad's proximal margin) to use as much of each recipient's bone as possible. All extensor tendon repairs were performed thereafter.

Next, the plastic surgery team came in to temporarily repair the cephalic vein, connect the radial artery, and then anastomose two vena comitantes. The orthopedic team then came back in and carried out a complete repair of the flexor tendon. Neurorrhaphy was performed on the median nerve and ulnar nerve, and the anterior interosseous nerve was connected to the motor branch of the ulnar nerve for supercharging. Next, the plastic surgery team returned and anastomosed the ulnar artery, remaining vena comitantes, ulnar cutaneous nerve, and superficial radial nerve. The skin flaps of the donor and recipient were then drawn appropriately. The temporarily connected cephalic vein was cut to fit the size of the skin flap and re-anastomosed. The basilic vein was also anastomosed.

Postoperative management and evaluation

The patients were given immunosuppressants, which are commonly used in hand and organ transplantations (Table 1),[8,16-18] as part of a three-drug regimen with high-dose steroid treatment in the event of rejection. Postoperative care and rehabilitation of the hand were carried out in accordance with the established methods for hand transplantation and forearm replantation.[19,20]

Table 1. Immunosuppressive Regimen and Infection Prophylaxis

Induction	Maintenance	Prophylaxis
Methylprednisolone	Prednisone	Piperacillin+tazobactam
Tacrolimus	Tacrolimus	Trimethoprim-sulfamethoxazole
Basiliximab	Mycophenolate mofetil	Ganciclovir

To confirm the postoperative outcome, we periodically assessed mobility, sensation, and activities of daily living and followed up with imaging tests, such as x-rays, ultrasound, and brain fMRI.

Sensory outcomes were checked by two-point discrimination. The Semmes–Weinstein monofilament test was performed to measure static and dynamic pressure. Functional outcomes were assessed using the Disabilities of the Arm, Shoulder, and Hand (DASH) score and the Hand Transplantation Scoring System (HTSS).

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RESULTS

Patients and donors

This study included three patients who received hand transplantation. Their general characteristics are provided in Table 2. The patients underwent unilateral hand allotransplantation following trauma. All were originally right-hand dominant, and the amputation state was at the distal forearm level. Two patients underwent hand transplantation within 3 years of injury, and one received the hand transplant 34 years after injury, which occurred in adolescence. All of the hand transplantations were performed 1–2 years after the first visit. All three patients used prostheses prior to transplantation; Patient 2 used a myoelectric prosthesis.

Donors were chosen considering the bone size, overall hand and arm size, and skin flap characteristics. The recipients and donors were antigen mismatched at one human leukocyte antigen (HLA)-A and two HLA-Bs in major histocompatibility complex class I. Patient 1 had mismatches in HLA-DR and HLA-DQ, and Patients 2 and 3 had one mismatch each in HLA-DR and HLA-DQ. The donor blood types were all O+; of the recipients, Patient 1 was O+ and Patients 2 and 3 were B+ (Table 3).

Hand transplantation

Table 4 shows the details of the operations. In all three cases, the overall surgery time was approximately 18 hours, and procuring the hand from the donor took less than 20 minutes. After cross-clamping the donor aorta, the first reperfusion took 4 hours 14 minutes in Patient 1, approximately 7 hours in Patient 2, and 7 hours 36 minutes in Patient 3. The lengths of stay in the intensive care unit for Patients 1, 2, and 3 were 4 days, 2 days, and 3 days, respectively, and the total hospitalization periods were 28 days, 17 days, and 23 days, respectively. All patients underwent successful hand transplantation with no complications during surgery or in the immediate post-operative period (Fig. 3).

Clinical outcomes and additional operation

There were several complications after hand transplantation, although none were severe (e.g., thrombosis, flap congestion, or immediate hyperacute rejection). All three patients had partial skin necrosis and underwent additional surgical pro-

Table 2. Patient Characteristics

Characteristics	Patient 1	Patient 2	Patient 3
Age (yr)	61	47	50
Sex	Male	Male	Male
Medical history	HTN, BPH	None	None
Dominant hand	Right hand	Right hand	Right hand
Amputation cause	Crushing injury by catapult	Machine accident at factory	Crushing injury by catapult
Injury hand and level	Right distal forearm level	Right distal forearm level	Left distal forearm level
Amputation year	2018.07.13 (age 59)	2019.02.22 (age 44)	1988.12.27 (age 15)
First outpatient visit (time from first visit to hand transplantation)	2018.10.25 (2.2 years)	2021.03.22 (1 year)	2021.07.12 (1.6 years)
Transplantation date (time from amputation to transplantation)	2021.01.09 (2.5 years)	2022.03.09 (3 years)	2023.02.04 (34.1 years)
Blood type	O+	B+	B+
Use of prostheses	Yes	Yes (myoelectric prostheses)	Yes

HTN, hypertension; BPH, benign prostatic hyperplasia.

Table 3. Donor Matching

Characteristics	Patient 1 donor	Patient 2 donor	Patient 3 donor
Age (yr)	38	31	53
Sex	Male	Male	Male
Blood type (→ recipient)	O+ (→ O+)	O+ (→ B+)	O+ (→ B+)
Arm circumference of donor and recipient (proximal forearm/distal upper arm)	Donor: 31 cm, Recipient: 24 cm/ Donor: 34 cm, Recipient: 28 cm	Donor: 22 cm, Recipient: 26.4 cm/ Donor: 21.5 cm, Recipient: 26 cm	Donor: 26.5 cm, Recipient: 25 cm/ Donor: 30 cm, Recipient: 27 cm
HLA matching (donor/recipient)			
HLA-A	A2, -/A2, A24	A24, A30/A24, A33	A31, A33/A24, A31
HLA-B	B35, B38/B46, B55	B64, B52/B62,B58	B61, B44/B51, -
HLA-DR	11, 15/8, 9	4, 15/4, 13	9, 13/4, 9
HLA-DQ	7, 5/9, 6	4, 6/8, 6	9, 6/8, 9
PRA ID	I 0%, II 0%	I 0%, II 0%	I 0%, II 0%
Lymphocytotoxic crossmatch	Negative	Negative	Negative

HLA, human leukocyte antigen; PRA ID, panel-reactive antibody identification.

Table 4. Operative Procedures

	Patient 1	Patient 2	Patient 3
Total operation time	17 h 40 m	18 h 42 m	18 h 53 m
ACC time	2021.01.09 18:09	2022.03.09 17:17	2023.02.04 17:27
First reperfusion time (cold ischemic time)	2021.01.09 22:23 (4 h 14 m)	2022.03.10 00:15 (7 h)	2023.02.05 01:03 (7 h 36 m)
ICU hospitalization period	4 days	2 days	3 days
Total hospitalization period	28 days	17 days	23 days

ACC time, aortic cross-clamp time; ICU, intensive care unit.

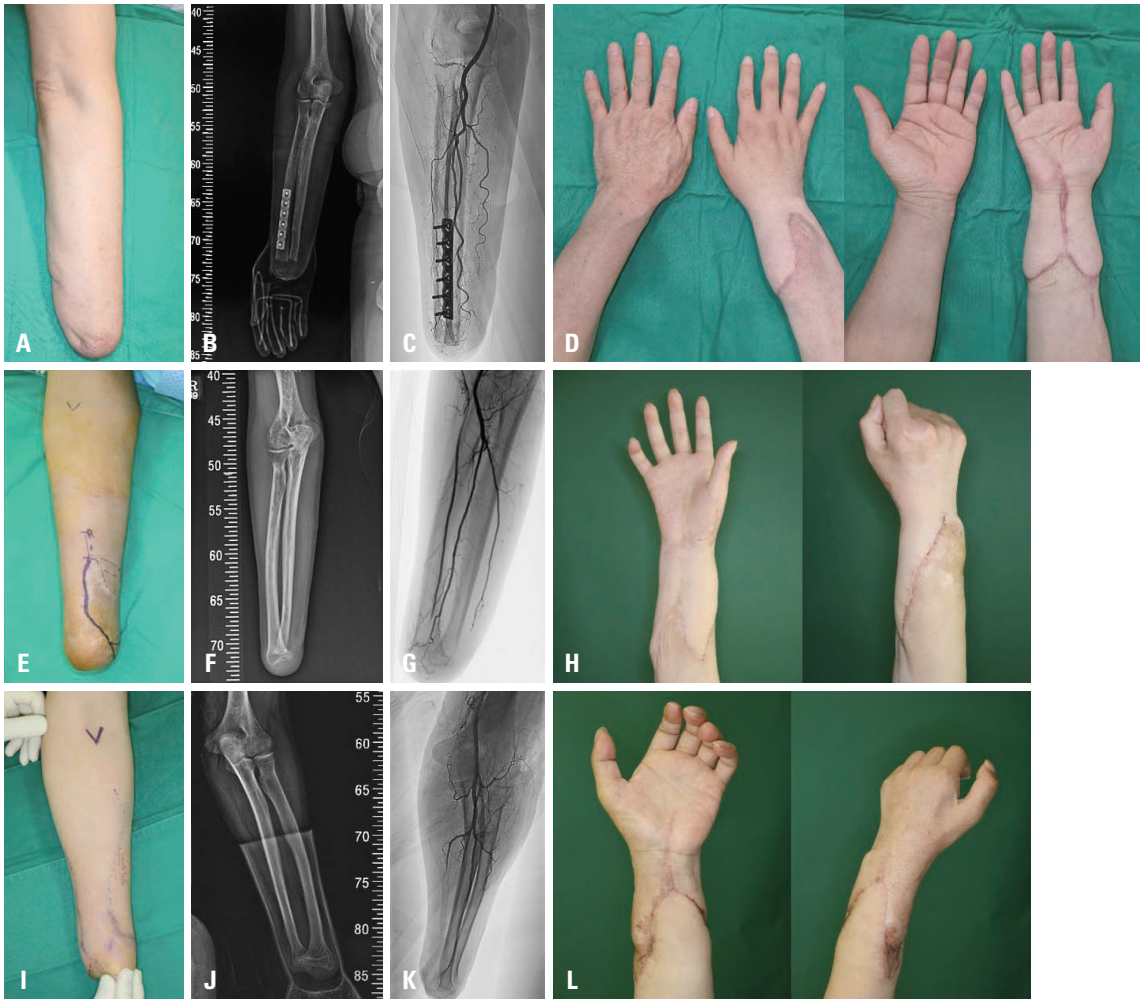

Fig. 3. Serial progression photographs from preoperative gross and imaging photographs to the most recent postoperative photographs. (A) Preoperative photograph of Patient 1. (B) Image of the preoperative scanogram of Patient 1. (C) Image of the preoperative angiography of Patient 1. (D) Postoperative photographs of Patient 1 (POD 2Y). (E) Preoperative photograph of Patient 2. (F) Image of the preoperative scanogram of Patient 2. (G) Image of the preoperative angiography of Patient 2. (H) Postoperative photopraphs of Patient 2 (POD 1Y 6M). (I) Preoperative photograph of Patient 3. (J) Image of the preoperative scanogram of Patient 3. (K) Image of the preoperative angiography of Patient 3. (L) Postoperative photographs of Patient 3 (POD 6M).

cedures (Table 5 and Fig. 4) .

One year after surgery, Patient 1 had difficulty with the pinch motion due to a decreased ability to extend and abduct the thumb as a result of thumb medial collateral ligament insufficiency. Tenolysis was performed for the adhesions around multiple tendons in the flexor compartment.

Acute rejection

Acute rejection occurred in all patients within 3 months. Patient 1 experienced rejection again during recovery from the first acute rejection (Table 6).

In Patient 1, acute rejection was suspected due to asymptomatic erythema 33 days after surgery, and a skin biopsy revealed acute rejection with superficial perivenular lymphocytic infiltration and basal vacuolization (Banff grade I) (Fig.

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5).[16,21,22] We administered steroid pulse therapy (Methysol 500 mg with normal saline, intravenous injection) for 2 hours during 3 days, and topical tacrolimus cream. The patient's symptoms improved and the steroid dose was tapered, but the symptoms worsened again. Skin biopsy showed Banff grade III, so steroid pulse therapy was repeated. This time, after 3 days of in-

Table 5. Additional Surgical Interventions

	Complications	Additional surgical procedures
Patient 1	Hematoma	Incision and drainage (POD 2)
	Partial skin necrosis (recipient side)	Debridement and primary repair (POD 41)
	Thumb ligament instability, tendon adhesion, and redundant skin	Thumb metacarpophalangeal joint arthrodesis, tenolysis, and debulking procedure (1 year 19 days post-op)
Patient 2	Partial skin necrosis (recipient side)	Debridement (POD 37) Debridement and coverage with STSG (POD 49)
	Bulky flap and redundant skin	Debulking procedure (1 year 4 months 7 days post-op)
Patient 3	Partial skin necrosis (donor side)	Debridement and coverage with STSG (POD 31)

POD, postoperative day; STSG, split-thickness skin graft.

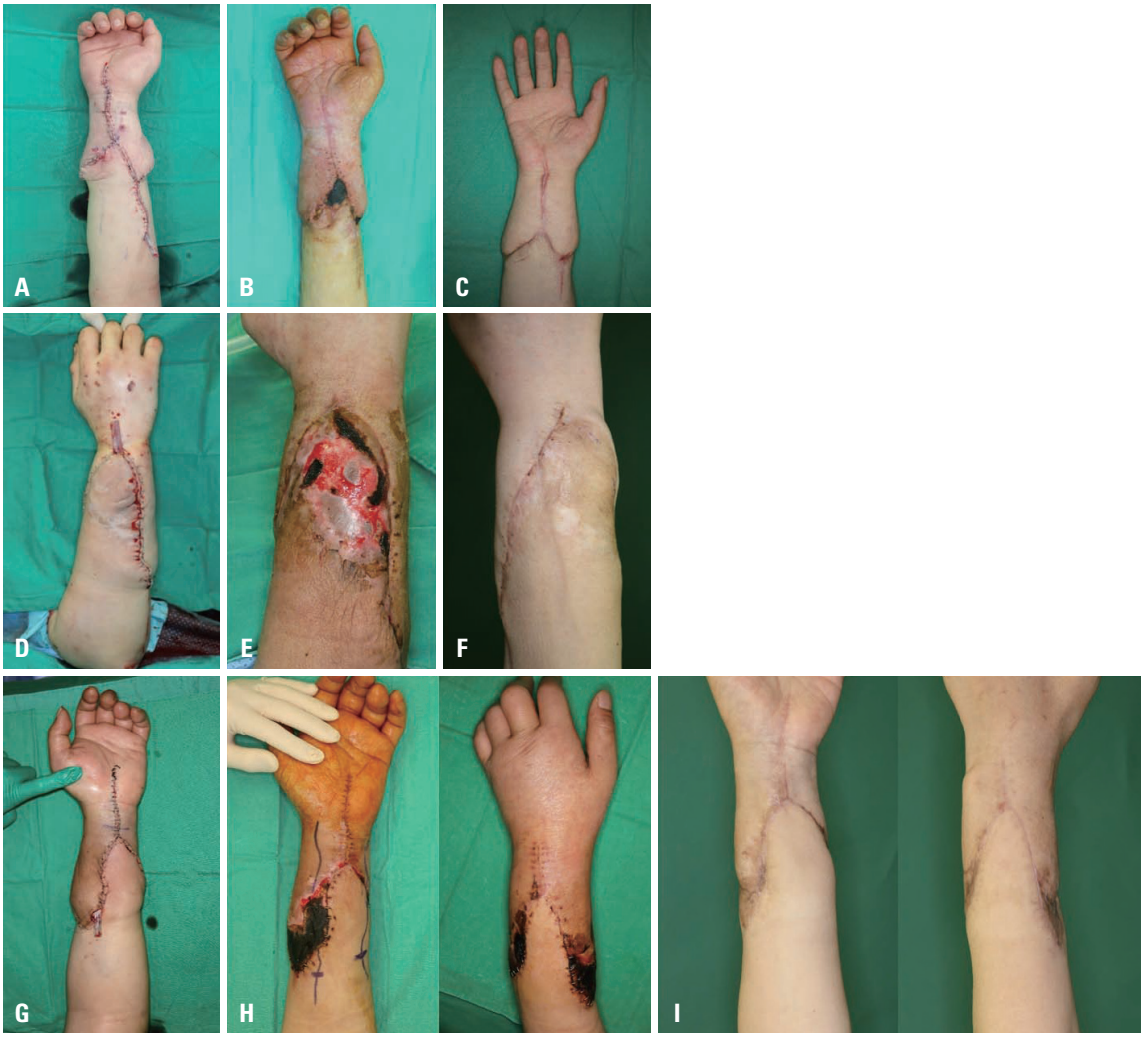

Fig. 4. Photographs of patients immediately after hand transplantation; photographs with partial skin necrosis and recent photographs of well-healed patients after additional surgical interventions. (A) Photograph immediately after hand transplantation in Patient 1. (B) Photograph of partial skin necrosis in Patient 1 (POD 41). (C) Most recent postoperative photograph of Patient 1 (POD 2Y). (D) Photograph immediately after hand transplantation in Patient 2. (E) Photograph of partial skin necrosis in Patient 2 (POD 49). (F) Most recent postoperative photograph of Patient 2 (POD 1Y 6M). (G) Photograph immediately after hand transplantation in Patient 3. (H) Photographs of partial skin necrosis in Patient 3 (POD 31). (I) Most recent postoperative photographs of Patient 3 (POD 6M). Patients 1 and 2 had skin necrosis on the distal region of their previous trauma scar lesion. Patient 3 had skin necrosis on the distal part of the donor skin flap; this necrosis may have been far from the wrist level of the perforator cluster, although we attached the distal perforator cluster of the pedicle to the skin at the wrist level. POD, postoperative day.

Table 6. Characteristics of Acute Rejection Episodes

	Acute rejection	Rescue therapy
Patient 1	POD 33 Sx: diffuse swelling and erythema Banff grade I	Steroid pulse therapy for 3 days (methylprednisolone 500 mg with N/S, IV for 2 h) Topical tacrolimus cream
	POD 41 Sx: diffuse asymptomatic erythema Banff grade III	Steroid pulse therapy for 3 days (methylprednisolone 500 mg with N/S, IV for 2 h) Topical steroid cream+tacrolimus cream
Patient 2	POD 60 Sx: Maculopapular rash Banff grade I	Steroid pulse therapy for 3 days (methylprednisolone 500 mg with N/S, IV for 2 h) Topical tacrolimus cream
Patient 3	POD 66 Sx: maculopapular rash and erythema Banff grade II	Steroid pulse therapy for 3 days (methylprednisolone 500 mg with N/S, IV for 2 h) Topical tacrolimus cream

Sx, symptoms; POD, postoperative day; N/S, normal saline; IV, intravenous injection.

travenous steroid pulse therapy, the steroid dose was tapered more slowly. A topical steroid was additionally applied, alternating with topical tacrolimus.

Patients 2 and 3 each had a single episode of acute rejection, which developed at 60 and 66 days after surgery, respectively. The same rescue therapy (steroid pulse therapy) used for Patient 1 was administered to Patients 2 and 3. The erythema and rash resolved within approximately 2 weeks of treatment.

Sensation

Patient 1 acquired a protective sensation to heat and cold at 4 months postoperatively, whereas Patients 2 and 3 were able to perceive hot and cold at 3 months postoperatively. Patient 1 had sensation in the tips of all five fingers at 5 months postoperatively, and Patient 2 regained sensation in each digit at 4 months postoperatively. By 5 months after surgery, all patients had palmar/dorsal discrimination and positional awareness.

To measure static and dynamic pressure, the Semmes–Weinstein monofilament test was performed on Patient 2 at 11 months postoperatively. The sensory evaluation measured 2.83 on all areas of the palm and dorsum of the hand and was the same for all fingers. However, during the follow-up period, the patients were unable to discriminate between the two points in the two-point discrimination test and perceived only one pressing sensation.

Functional outcomes

The DASH and HTSS scores showed improvements in the patients' activities of daily living and satisfaction levels (Fig. 6). Postoperatively, the patients' DASH scores showed progressive, valuable improvement. In particular, there was a significant improvement after stabilization (1 year after surgery). HTSS scores showed that the patients became increasingly satisfied with their lives after surgery. The patients were also very satisfied with the appearance and function of their transplanted hands and noted no significant interference with their daily activities.

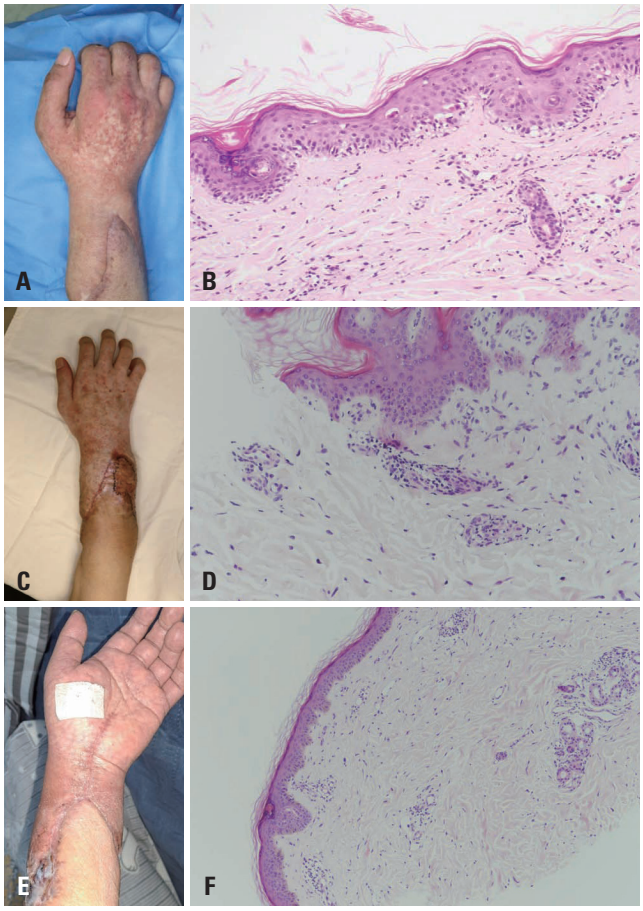

Fig. 5. Photographs of acute rejection after surgery in patients. (A) Photograph of acute rejection after surgery in Patient 1 (POD 41). (B) Pathology picture of a skin biopsy in Patient 1 at the time of acute rejection (Banff grade III). (C) Photograph of the first acute rejection after surgery in Patient 2 (POD 60). (D) Pathology picture of a skin biopsy in Patient 2 at the time of acute rejection (Banff grade I). (E) Photograph of the first acute rejection after surgery in Patient 3 (POD 66). (F) Pathology picture of a skin biopsy in Patient 3 at the time of acute rejection (Banff grade I). POD, postoperative day.

DISCUSSION

Hand/arm amputation is a high-level trauma that must be triaged and managed quickly. Those who are caring for a traumatic amputee must work quickly and efficiently to halt life- and limb-threatening processes resulting from the injury.[23] Hand/arm amputations cause disabilities that are not comparable to those of finger amputations. Psychologically and socially, hand/arm amputations can be more debilitating and limiting than any other disability, not to mention inconvenient in everyday

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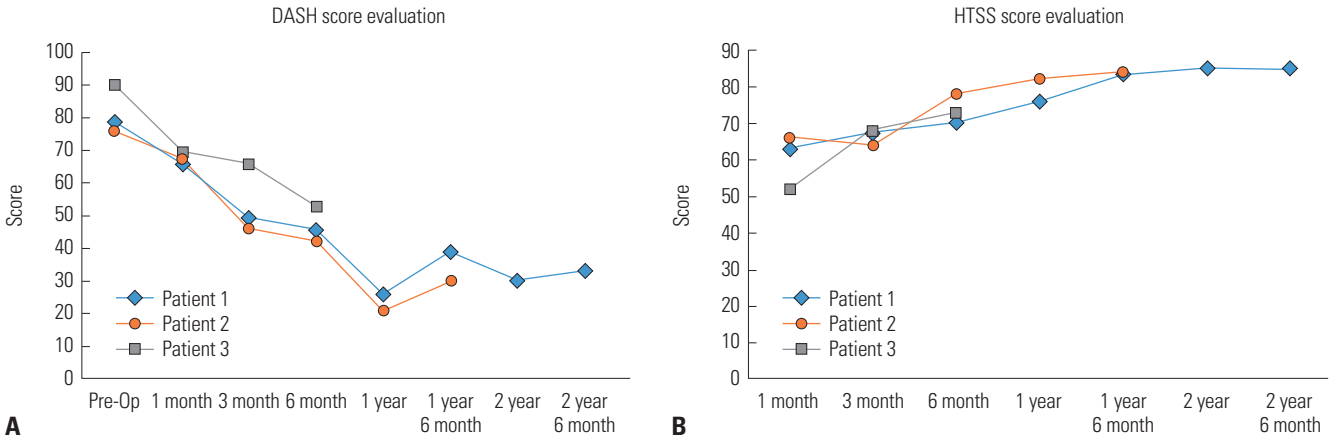

Fig. 6. Functional outcomes. (A) Disabilities of the Arm, Shoulder, and Hand (DASH) score evaluation. (B) Hand Transplantation Score System (HTSS) evaluation.

life.[9,24-32] However, hand/arm transplantation has drawn little medical interest as there is an alternative (prosthetic limbs) and the procedure has often been underestimated or ignored, especially in the field of transplantation, since the hand is not a vital organ.[29]

Hand transplantation was first performed in 1964, but the first successful hand transplantation took place in 1999.[1,5,7,33-36] The hand transplantation surgical technique is similar to–but distinct from–that of replantation. VCA is a combination medical procedure consisting of, e.g., microsurgery, reconstruction, transplantation, immunosuppression, brain death, and donation.[37] As microsurgery, replantation, and organ transplantation are common procedures in different medical fields, many professionals across fields mistakenly thought that hand transplantations would be quick to institutionalize. However, it took time to establish hand transplantation as a viable procedure.[1,36,37]

In Europe and the United States, where hand transplantations were first introduced, well-designed clinical trials were conducted prior to institutionalization. To do this, the researchers had to make many preparations–including persuading the donor's family, receiving permissions, preparing the institutions, and securing funds–within each country's environment and institutions.[1,9,38] Hand transplantation was then institutionalized after proving its stability and effectiveness. Although the United States has performed many hand transplantations since 1999, VCAs were only added to the definition of organs covered by federal regulations in 2014.[1,39,40]

In Korea, hand transplantation was institutionalized differently. We were able to perform hand transplantation only after the law and insurance system were adjusted to account for the procedure. If the hand was not registered in the transplantation law, we would not be able to perform clinical trials of hand transplantation. Korea has a national health system for all Korean nationals, and all diseases are covered by the National Health Insurance,[41] including hand amputation. For the procedure to be covered, the patient, doctor, and hospital must be within the National Insurance System. If the disease is registered in the National Insurance System, the doctor or hospital cannot charge a medical fee. If the law did not allow hand transplantation, a doctor or hospital would not be able to perform the operation even if the doctor or hospital offered financial support.

In 2010, hand transplantation passed the new medical technology assessment.[14] However, since the Organ Act defined the hand as a tissue rather than an organ, hand transplantation could not be performed officially. The first hand transplantation was unofficially performed in Korea in 2017.[3] This operation achieved good results for the patient, improving public opinion of the procedure, and hand transplantation was finally included in the Organ Act in 2018.[4] With this amendment and the finalization of the Implementing Rules in 2019, hand transplantation was officially covered by the national insurance of Korea since 2019. After institutionalization, the first legal hand transplantation, in fact the second in Korea, was performed in 2021.[21]

Currently, in Korea, hand transplantation cannot be performed alone, and the procedure must be performed with other organs such as the heart and lungs from a donor. The hand is not a vital organ, but the need and importance of hand transplantation for patients who require it cannot be overstated. It is believed that if hand transplantation can be performed independently, it may be possible to further reduce the ischemic time, leading to better postoperative outcomes. Of course, hand transplantation and VCA have made tremendous progress in Korea so far; therefore, we expect that there will be more advances, such as face transplantation, in Korea in the future based on our experience.

Since hand transplantation is still in its infancy compared to other transplantation fields, the law has defined certain restrictions for hand donors. Only brain deaths that occur in hospitals where the hand transplant recipients are registered qualify as donors. In other words, seeking out hand donors from other hospitals is not allowed. However, the current system does have some advantages: it facilitates support from other medical specialties within the same institution, enables the use of

the same infrastructure in the operation room for both procurement and transplantation, and especially, reduces the ischemic time.

Hand procurement and transplantation in this study were performed similarly to many previous experiences.[3,7,18,19] There are varying opinions on the order of hand procurement within the organ procurement process.[42] However, in Korea, the law stipulates that hand procurement can be performed simultaneously with intraperitoneal organ procurement after an intrathoracic organ is procured. This reflects the opinion that ischemic time is important for functional recovery of the hand, given that it consists of muscle.

We composed the hand transplantation team mainly of essential personnel so it could move swiftly. The plastic surgery and orthopedic surgery departments were in charge of the surgery, and the transplantation surgery department was in charge of the transplantation procedure and immunosuppression. When each patient first visited the hospital, the plastic surgeon and orthopedic surgeon took turns performing the same evaluation. To maintain tension of the team until a donor appeared, the patients visited the hospital every 2–3 months. This visitation schedule helped familiarize the patients with the hospital system and the hand transplantation process.

The plastic surgery team focused on the flaps, blood vessels, and nerves; and the orthopedic surgery team focused on the bone, muscle, tendon, and nerves. Each team participated in the procurement and transplantation following a planned order. Each team was also familiar with all the surgical procedures so they could complete any procedure, if necessary.

The hands for Patients 1 and 2 were procured at the level of the humerus shaft, and the hand for Patient 3 was procured at the level of the elbow. A tourniquet was not used for the donors. First, we wanted to use the space efficiently to avoid disturbing the general surgery team. Second, there was not much bleeding during the procurement preparation. Only the brachial artery, cephalic vein, and basilar vein required dissection, and muscles were cut using an energy device to minimize bleeding. Furthermore, the tourniquet was not necessary since the osteotomy was performed after aortic clamping. After hand procurement, as stipulated by the Organ Act, the donor's hand was replaced with a pre-customized prosthesis.

The donor and recipient dissections and operations were similar to the procedures performed by other groups.[16,20,42] However, we extended the donor volar forearm incision to the midpalm for carpal tunnel release. The dorsal sensory nerve was covered by the superficial radial nerve and the dorsal branch of the ulnar nerve at the wrist level. To discriminate these nerves from the wrist, we had to dissect near the wrist crease level. We were careful not to dissect too much from the distal perforator cluster to the skin. We supercharged the anterior interosseous nerve from the median nerve of the donor to the motor branch of the ulnar nerve to enforce the motor nerve (Fig. 2).

Though the ischemic time was over 6 hours for Patients 2 and 3, there were no complications related to long ischemic time. The warm ischemic time allowed for arm amputation is usually 6 hours;[31] over 6 hours is allowed for cold ischemia.[43,44] As the procured donor hand was cooled by ice and washed with cold reserve solution, we considered that the cold ischemic time of over 6 hours would be allowed.

Since blood flow, e.g., in the flaps, is important immediately after surgery, the plastic surgery team mainly cared for the patient in the early period after the operation, and the transplant surgery team performed immunosuppression and vital care. When the patient was in stable condition, the orthopedic surgery team took the lead for exercise and rehabilitation.

To evaluate blood flow in the transplanted hand, we compared the readings from two O_2 pulse oximeters: one on the patient's toe or finger, and the other on the transplanted finger. The difference was approximately 1%–2%. We also checked the capillary nail refill time, which allows for an easier assessment of blood flow and refilling compared with the skin.

Acute rejection occurs in 87.8% of hand transplantations within 1 year.[8,22] Patient 1 first developed acute rejection on postoperative day 33, and Patients 2 and 3 developed a rash on postoperative days 60 and 66, respectively. All of the acute rejections were resolved with steroid pulse therapy (Fig. 7).

In Patient 1, the immediate postoperative tacrolimus blood level was maintained at 10–12 ng/mL and then lowered to 6 ng/mL after 2 weeks, but acute rejection occurred on postoperative day 33. Rescue therapy (intravenous steroid pulse therapy and topical tacrolimus) was started and tacrolimus blood levels were maintained, and the symptoms resolved. However, during recovery from the first acute rejection episode and tapering of the intravenous steroid pulse therapy to oral medication, acute rejection reoccurred on postoperative day 41 with the skin rash. Intravenous steroid pulse therapy was immediately resumed, and the tacrolimus level was elevated to 10–12 ng/mL and maintained. Steroid therapy was also tapered more slowly than before by adding 2 days of intravenous infusion. The tacrolimus target level was then maintained at 10 ng/mL until 3 months after surgery, when it was reduced to 6–8 ng/mL.

Patients 2 and 3 each had an acute rejection episode approximately 2 months after surgery and were started on the same rescue therapy as that used for Patient 1. Their tacrolimus levels were elevated to 10 ng/mL based on previous experience. The acute rejection symptoms resolved within approximately 2 weeks of rescue therapy.

As the skin is the first line of defense against foreign antigens, the current protocol recommends that the tacrolimus level be maintained at 10 ng/mL for the first year after hand transplantation, similar to lung transplantation, and then reduced thereafter. Thus, the tacrolimus levels of Patients 1 and 2 were reduced to 6 ng/mL after 1 year and maintained.

We carefully checked the patients' hemoglobin levels to detect anemia caused by passenger lymphocyte syndrome. Al-

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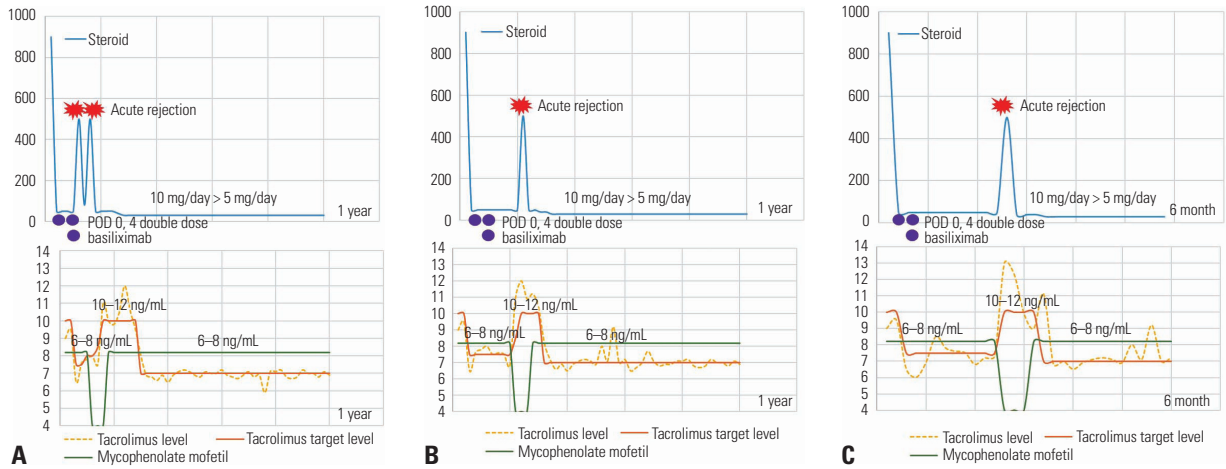

Fig. 7. Immunosuppressive regimen for postoperative management. (A) Postoperative immunosuppressive regimen used in Patient 1. (B) Postoperative immunosuppressive regimen used in Patient 2. (C) Postoperative immunosuppressive regimen used in Patient 3. POD, postoperative day.

though passenger lymphocyte syndrome is a rare complication resulting from ABO-mismatched organ transplantation, we were concerned about the possibility.[45,46]

All patients experienced postoperative necrosis of the periapical skin (Fig. 4). All underwent debridement or revision or received a split-thickness skin graft in the 2 months after surgery. Patients 1 and 2 had skin necrosis on the distal region of their previous trauma scar lesion. The previous trauma wound scar must be carefully evaluated to decide whether to include the skin flap for skin closure. Patient 3 had skin necrosis on the distal part of the donor skin flap; this necrosis may have been far from the wrist level of the perforator cluster, although we attached the distal perforator cluster of the pedicle to the skin at the wrist level. In any case, when there is less skin available for hand transplantation, it is better to cover first and revise later to protect the internal structure. Patient 2 received an autoskin graft from their skin to the recipient-side skin defect. Patient 3 received an alloskin graft from their skin to the donor skin defect. Additional operations were performed based on the hand condition and were similar to those performed following hand replantation. Thumb joint arthrodesis, tenolysis, or debulking surgery was performed 1 year later if needed.

The patients' motor and sensory recovery and return to normal activities of daily living were satisfactory. Their DASH scores and HTSS results improved significantly after surgery. The patients were particularly satisfied in areas that we, as doctors, had not considered. In Korea, people often use umbrellas, even in light rain, as well as public transport and buses. After the hand transplantation, the actions of opening and folding an umbrella and paying transit fare came naturally, so the patients were very satisfied that they were not conscious of their surroundings.

Patient 3 had an amputation at the carpal level of the wrist at the age of 16. Hand transplantation was performed approximately 34 years later. Since he was an adolescent, his hand growth was almost complete and he was already using the remaining arm well, so the basic anatomic structure of the forearm was considered reliable for hand transplantation. However, although the muscle belly was relatively intact, the tendon atrophy was severe.

As the hand is not a vital organ, the ethical question of lifelong immunosuppression after transplantation has been consistently raised in the past. For this reason, it has been suggested that bilateral and dominant hand amputations should be targeted first.[7,18] However, in reality, when the dominant hand is transplanted, it may not be able to perform well as the dominant hand. It may perhaps be better to help amputees with a remaining dominant hand by performing non-dominant hand transplantations. Although the guidelines suggest prioritizing dominant hand transplantation, we selected our recipients considering all the relevant factors, and Patient 3 underwent non-dominant hand transplantation.

Aside from functional problems, depression and psychosocial weakness can be quite distressing for amputees.[25,26,47] Of course, the importance of an extremity cannot compare to that of a vital organ, but amputation is no less painful than vital organ failure. The development of immunosuppressive drugs has reduced and improved the side effects of transplantation.[48,49] Although the lifelong use of immunosuppressive drugs should be thoroughly reviewed from a medical perspective, we should also consider whether it is ethical to oppose hand transplantation due to immunosuppression.

Active research is currently examining targeted muscle reinnervation and 3D-printed dynamic prostheses for hand reconstruction.[50-53] Hand transplantation is considered to be in the same phase of institutionalization as these reconstruction methods. These methods may also evolve, but if immunosuppressive drugs with fewer side effects are developed, hand transplantation may become a more competitive option.

Although hand transplantation in Korea is catching on later than it has in other countries, this long initiation has resolved many of the issues that can arise with hand transplantation,

such as insurance, procurement sequencing, and donor restoration. Other studies have made claims that these transplants are more difficult in Eastern countries. The process of adapting and settling into a new medicine can be quite challenging, regardless of the patient's healthcare environment, social system, and culture. It is a mistake to attribute the cause of such difficulties to the Eastern culture or to look only at the ethics. Some aspects of the procedures were surprisingly difficult, and others were easy. The order of procurement and donor restoration are set and regulated by law. The compulsory insurance coverage has also made the cost significantly more favorable than in other countries.

The limitations of this study include the authors' limited experiences with hand transplantation and the short follow-up period. However, since hand transplantation is uncommon and it takes a long time to accumulate related data, this study will add to the existing body of knowledge, helping to build an understanding of hand transplantation in Korea and the process of setting up new medical procedures in different environments.

In conclusion, hand transplantation is a viable reconstructive option for restoring hand function, and patients have shown positive functional and psychological outcomes. However, as the newness of hand transplantation currently allows us to study only a few transplantations with limited follow-up periods, more research is needed on the recovery of hand function, chronic rejection, and the side effects of immunosuppressive drugs. Nevertheless, the future of hand transplantation in Korea is bright.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jong Won Hong. Data curation: Yo Han Kim and Jong Won Hong. Formal analysis: Yo Han Kim and Jong Won Hong. Funding acquisition: Jong Won Hong. Investigation: all authors. Methodology: Jong Won Hong, Yun Rak Choi, and Dong Jin Joo. Project administration: Jong Won Hong, Yun Rak Choi, Dong Jin Joo, and Kyung Ock Jeon. Resources: all authors. Software: Jong Won Hong and Kyung Ock Jeon. Supervision: Jong Won Hong, Yun Rak Choi, and Dong Jin Joo. Validation: Jong Won Hong. Visualization: Yo Han Kim. Writing—original draft: Yo Han Kim and Jong Won Hong. Writing—review & editing: Jong Won Hong. Approval of final manuscript: all authors.

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