

Retrospective Study Regarding Objectives and Results of Upper Limb Transplant

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Rezumat

Studiu retrospectiv asupra obiectivelor și rezultatelor transplantului de membru superior

Introducere: Amputația membrului superior determină o invaliditate permanentă severă. Transplantul de membru superior este condiționat de tratamentul pentru prevenirea rejektului și influențat de factori organizatorici, socio-economici, psihologici, etici. Analiza rezultatelor obținute creează premisele continuării acestei activități în condițiile specifice din țara noastră.

Material și metodă: S-au analizat retrospectiv datele din literatură. La momentul încheierii documentării (mai 2011) în lume existau 74 de transplanturi la 53 de pacienți. S-au studiat informațiile disponibile despre intervențiile practicate și rezultatele acestora.

Rezultate: Allogrefa de membru superior are o structură complexă, cuprinzând țesuturi cu antigenicitate variabilă. Intervenția chirurgicală este efectuată de o echipă numeroasă; creșterea experienței duce la scurtarea duratei operației. Programul de urmărire și reabilitare postoperatorie este standardizat, complianța pacientului fiind esențială. Cele mai mari progrese s-au înregistrat în privința protocoalelor de imunosupresie.

Concluzii: Până în prezent transplantul de membru superior a fost efectuat în 20 centre din 12 țări. Precizarea indicațiilor și

contraindicațiilor, selecția adecvată a pacienților, experiența în creștere și noile protocoale de imunosupresie măresc șansele de reușită și calitatea rezultatului funcțional. Aplicarea acestor achiziții conceptuale permite crearea premiselor pentru integrarea țării noastre în acest efort științific convergent pe plan mondial.

Cuvinte cheie: transplant de membru superior, transplant de mână, allogrefă, transplant de țesuturi compozite, tratament imunosupresor

Abstract

Introduction: Upper limb amputation causes a severe permanent disability. Upper limb transplantation is subject to treatment to prevent rejection and influenced by organizational, socio-economic, psychological, ethical factors. Analysis of the results creates the potential for continuing this work in specific conditions in our country.

Material and methods: We retrospectively analyzed data from the literature. Upon completion of documentation (May 2011) there were 74 transplants in 53 patients worldwide. We have studied the available information on the surgical interventions and their results.

Results: Upper limb allograft has a complex structure comprising tissue with variable antigenicity. Surgery is performed by a large multidisciplinary team, whose increased experience leads to a shorter length of the operation. The post-operative follow-up and rehabilitation program are standardized, and patients' compliance is essential. The greatest advances have occurred in immunosuppression protocols.

Conclusion: The upper limb transplantation was performed in 20 centers of 12 countries so far. The specification of the

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indications and contraindications, the proper selection of patients, the increasing experience and new immunosuppression protocols provide a higher success rate and quality of functional outcome. By applying these conceptual acquisitions we will be able to create conditions for the integration of our country in this globally convergent scientific effort.

Key words: upper limb transplant, hand transplant, allograft, composite tissue transplantation, immunosuppression treatment

Introduction

Since middle of the XXth century the upper limb transplant concerned the world of surgeons. However the history of upper limb transplant is a relative short one. The procedure is still in experimental stage, so any new operation is significant. This sustained concerning for upper limb transplant comes from the great importance of the upper limb in the global economy of the human body. Thus, the loss of the dominant hand reduces the general efficiency of organism by 65%, while the loss of both hands involves a very severe permanent invalidity, similar to a blind man. In these circumstances, and taking into account that from all segments of the upper limb, the hand is the most exposed at traumas by work accidents, domestic accidents, driving accidents, i.e. and also considering the high frequency of these accidents (1,2,3), the permanent concerning for overcoming this extremely invalidant situation is more than justified.

Material and Method

The reattachment of amputated hand – also called replantation is a successfully surgical intervention carried out since middle of the last century. The surgical technique involved for hand replantation is in fact identical with one involved in hand transplantation, that's why the incoming obstacles were not necessarily on surgical matter but rather on immunologic and psychological nature matter (4). Furthermore, in case of hand transplant, there is the advantage of possibility of establishing the anatomic level of transplant and traumatically consequences are excluded.

Due to its complex structure, which consist of a lot of tissues with variable antigenicity (28 muscles, 27 bones, 3 main nerves, 2 important arteries, and also skin, joints, cartilages, fats and may nervous fibers and small and big blood vessels of which the skin shows the highest antigenicity, the human hand allograft belongs to composite tissue allografts. The first transplant of composite tissues described by history is the so called "Legend of black leg" (Legenda Aurea), which reveals the story of two twin brothers: The Cosma and Damian Saints ("doctors without silver") which, in the third century, had transplanted the lower limb prevailed from a black deceased slave to a white man with a sick lower limb requiring amputation (5,6). This



Figure 1. Legend of the black leg

well known legend was transposed in images, in many paintings inspired by this theme, most of that realized in 15th century (7) (Fig. 1).

At the time of concluding this documentation (may 2011) there already were 74 hand transplants performed in 53 patients around the World and their number increases continuously (see Table 1). At the global scale there are 20 medical centers in 12 countries where upper limb transplantation already was proceeded (Fig. 2). It was proved the importance of partnerships in generating and implementing standard protocols for immunosuppression and recovery.

The most important moments in hand transplant history are presented in what follows. The available information



Figure 2. The map of centers where hand and composite tissue transplant are performed

Source: IRHCTT - International Registry on Hand and Composite Tissue Transplantation

Table 1.

Nr.	Type ⁽¹⁾	Date	Location	Institution	Receiver ⁽²⁾
1	Single	Feb-1963	Guayaquil, Ecuador	(*)	28 ♂
2	Single	1964	Lyon, France	(*)	(*)
3	Single	Sep-1998	Lyon, France	Hopital Edouard Herriot	48 ♂
4	Single	Jan-1999	Louisville, USA	Jewish Hospital	37 ♂
5	Single	Sep-1999	Guangzhou, China	Nanfang Hospital	39 ♂
6	Single	Sep-1999	Guangzhou, China	Nanfang Hospital	27 ♂
7	Single	Jan-2000	Guangxi, China	First Affiliated Hospital of Guangxi University	27 ♂
8	Single	Jan-2000	Nanjing, China	(*)	(*)
9	Double	Jan-2000	Lyon, France	Hopital Edouard Herriot	33 ♂
10	digital	Jan-2000	Yantai, China	Shandong Provincial Hospital	18 ♂
11	Double	Mar-2000	Innsbruck, Austria	Universitätsklinik für Chirurgie	45 ♂
12	Single	May-2000	Kuala-Lumpur, Malaysia	Selayang Hospital	1 month ♀
13	Double	Sep-2000	Guangzhou, China	Nanfang Hospital	(*)
14	Single	Oct-2000	Milan, Italy	Milano-Biocca University	35 ♂
15	Single	Nov-2000	Harbin, China	First Affiliated Hospital of Harbin Medical University	(*) ♂
16	Single	Nov-2000	Harbin, China	First Affiliated Hospital of Harbin Medical University	(*) ♂
17	Double	Jan-2001	Harbin, China	First Affiliated Hospital of Harbin Medical University	(*)
18	Single	Feb-2001	Louisville, SUA	Jewish Hospital	36 ♂
19	Single	Oct-2001	Milano-Italy	Milano-Biocca University	(*)
20	Single	Jan-2002	Brussels, Belgium	Erasmus University Hospital	(*)
21	Single	Jun-2002	Harbin, China	First Affiliated Hospital of Harbin Medical University	(*)
22	Single	Jul-2002	Nanjing, China	(*)	(*)
23	Double	Oct-2002	Harbin, China	First Affiliated Hospital of Harbin Medical University	(*)
24	Single	Nov-2002	Milan, Italy	Milano-Biocca University	(*)
25	Double	Feb-2003	Innsbruck, Austria	Universitätsklinik für Chirurgie	(*)
26	Single	May-2003	Lyon, France	Hopital Edouard Herriot	(*)
27	digital	Feb-2005	Nanjing, China	(*)	(*)
28	Double	Feb-2006	Wroclaw, Poland	(*)	32 ♂
29	Double	Jun-2006	Innsbruck, Austria	Universitätsklinik für Chirurgie	(*) ♂
30	Single	Nov-2006	Louisville, SUA	Jewish Hospital	54 ♂
31	Double	Dec-2006	Valencia, Spain	Clinica Cavados	47 ♀
32	Single	2007	Wroclaw, Poland	(*)	42 ♂
33	Double	Feb-2007	Lyon, France	Hopital Edouard Herriot	(*)
34	Double	Nov-2007	Valencia, Spain	Clinica Cavados	(*)
35	Single	Jan-2008	Wroclaw, Poland	(*)	30 ♂
36	Double	Jul-2008	Münich, Germany	(*)	(*)
37	Single	Jul-2008	Louisville, SUA	Jewish Hospital	32 ♂
38	Single	Nov-2008	Louisville, SUA	Jewish Hospital	(*) ♂
39	Single	Mar-2009	Pittsburg, SUA	Pittsburg University	24 ♂
40 ⁽³⁾	Double	Apr-2009	Paris, France	Henri Mondor Hospital	30 ♂
41	Double	May-2009	Pittsburg, SUA	Pittsburg University	57 ♂
42	Double	Jul-2009	Lyon, France	Hopital Edouard Herriot	(*) ♂
43	Double	Feb-2010	Pittsburg, SUA	Pittsburg University	41 ♂
44	Single	Feb-2010	Texas, SUA	Wilford Hall Medical Center	(*) ♀
45	Double	Jun-2010	Wroclaw, Poland	(*)	(*) ♂
46	Double	Aug-2010	Louisville, SUA	Jewish Hospital	55 ♂
47	Single	Sep-2010	Pittsburg, SUA	Pittsburg University	27 ♂
48	Double	Sep-2010	Pittsburg, SUA	Pittsburg University	(*) ♀
49	Double	Nov-2010	Monza, Italy	Ospedale San Gerardo	52 ♀
50	Single	Mar-2011	California, SUA	Ronald Reagan UCLA Medical Center	26 ♀
51	Double	Mar-2011	Melbourne, Australia	St. Vincent Hospital	65 ♂
52	Single	Mar-2011	Atlanta, SUA	emory University in Atlanta	21 ♀
53 ⁽³⁾	Double	May-2011	Boston, SUA	Brigham and Women's Hospital	57 ♀

⁽¹⁾Single hand transplant or double hand transplant; ⁽²⁾age in years/gender; ⁽³⁾double hand transplant simultaneously with face transplant; (*) unknown / unpublished data

regarding hand transplant until nowadays was analyzed by focusing on: surgical technique, antireject theory, short term and long term postoperative results, ethical and psychological

issues, postoperative recovery, organizational and social – economic factors.

The analysis of objectives and results achieved at interna-

tional level creates the premises of implementation of this activity in our country.

The early hand transplants were proceeded in the age of modern immunosuppression (Lyon – 1963 and South America – Ecuador - 1964), (8) reason for which, despite the fact that technically the operations faced certain success, eventually rejection was installed and amputation was required in about 2 weeks postoperatively (9). At the time, immunosuppression was made to what current standards would call primitive immunosuppression agents (azathioprine, 6-mercaptopurine, steroids) accordingly with present standards.

After the 2 unfavorable attempts a relatively long break installed until the 90's when a great number of studies and researches took place but no surgical hand transplant intervention was proceeded.

In the following years, the consistent studies regarding immunosuppression led toward a significant increase of surviving rate of transplanted organs, by introducing the Cyclosporine at early 80's. This prevents transplant rejection by suppressing the humanbody immune system (10,11). Also in that period Jan Dausset founded the idea of HLA (Human Leukocyte Antigens) and his experiences showed that transplants are better tolerated in situation where HLA groups of donor and recipient are identical or they differ very little (12). Serious concernings regarding hand transplant arose in 1996, when a research partnership was established between University of Louisville, Kleinert Institute (Kleinert, Kutz and co) and Jewish Hospital looking for coordinating the research projects and resources.

Thus, in 1997 the researches started in the following projects: the effect of cryopreservation on allogenicity and tissue conservation; epidemiological study regarding hand transplant – risk/profit ratio analysis; local perfusion.

On the other hand the effort of researchers focused on the study of hand transplant and transplant of composite tissues on big animals. The experiments were conducted with and without immunosuppressors, with comparative results notification (13,14). In November 1997 took place the International Allotransplant Symposium of Composite Tissues and it could be considered an important moment. The event was hosted by Jewish Hospital Foundation and brought together experts in immunology, transplant surgery, plastic and reconstructive surgery and also in medical ethics. They concluded that hand transplant should be tried on humans (15).

The protocol for hand transplant was elaborated and finalized in January – May 1998 and included: informed patient confirming, selection criteria of patients, surgical technique, postoperative monitoring, rehabilitation and recovery procedures and immunosuppression.

The protocol was approved in June 1998 by University of Louisville, Human Studies Committee and by Jewish Hospital Institutional Review Board (10). The subject proved to be of great interest in medical circles and beyond of it, it was also much discussed by media. In newspapers specific items were published and on radio and television the specialists participated at round tables and answer at interviews in order to inform the population about hand transplant aspects.

The first hand transplant was performed in Lyon – France in September 1998. The patient's name is Clint Hallam. The surgical team was led by J.M. Dubernard and the intervention needed 13 hours. The patient (from New Zealand) lost his right hand 2 years before due to an accident while he was imprisoned (15,16,17). After 2 and half years, more precisely on 2nd February 2001, in London, the transplanted hand was amputated at patient's request. The intervention was justified by the fact that the patient was unable to follow strict anti-reject and physical therapy (16,18,19). After the surgery, Hallam felt uncomfortable with idea of having a dead person's hand transplanted. Moreover, his expectations proved to be unrealistic in terms of postoperative outcome.

These situations alerted the medical world about the undeniable necessity for strict selection of patients for this type of intervention and the need for a pre and postoperative care complex monitorizing the patients which included sustained psycho and psychiatric therapy (20).

On 25th January 1999 took place the first hand transplant in United States of America. The patient's name is Matthew Scott din Absecon – New Jersey and who had a transplanted left hand. The intervention was carried out at Jewish Hospital from Louisville, Kentucky, where the patient remained for 3 months (15,17).

After that he returned home, and after another month he went back to his job. At postoperative consultation 6 month after surgery, laboratory tests were performed and also a biopsy of the transplanted segment (21,22).

On 21st September 1999, 2 hand transplants were realized simultaneously in Orthopedic and Traumatology Department in Nanfang Hospital from Guangzhou – Peoples Republic of China (18). The recipients were 2 men – one of 39 years old and the other one of 27 years old (23). For unpublished and unknown reasons, the evolution of 39 years old patient was unfavorable involving a rejection and need amputation at one year and 8 months posttransplant (24).

In the rank of upper limb transplantations proceeded around the world, the followings should be mentioned:

On 12th January 2000 a surgical team of 50 surgeons was built up and led by Professor Jean Michel Dubernard in order to realize the first ever double handtransplant, at Edouard Hospital from Lyon – France. The intervention lasted 17 hours. The patient – a 33 years old male, Denis Chatelier, a professional painter and father of 2 children, lost both his hands after a premature explosion of an artisanal petard (18, 25,26,27,28,29).

On 25th January 2000 was the anniversary of the first successful hand transplant. The patient, Matthew Scott returned at Jewish Hospital for checking. The results of the tests and the patient himself confirmed the success of the intervention and therapy. At that time he managed to open doors, keep a glass, tie his shoelaces and use his left hand for daily activities. The prevailed biopsy showed no sign of rejection, but the patient continued the rehabilitation and physical therapy 3 days per week (21,30).

Another noteworthy upper limb transplant is the one on 18th May 2000, in Kuala-Lumpur, Malaysia where took place

the first ever transplant of arm, forearm and hand. The patient, a one month old girl, named Chong Li Ying, was born with a severe malformation of upper left limb. The intervention was made by a surgical team led by dr. V. Pathmanathan and took place at Selayang Hospital. Besides the youthness of the patient, the breakthrough consisted in the fact that the donor was nobody else but her sister, so no rejection therapy was conducted (15,18,31).

While Malaysia faced the mentioned premiership, at Jewish Hospital from Louisville – Kentucky, physicians and specialists from all over the World met in the Second International Symposium of Compound Tissues Allotransplant (15). It lasted 2 days and included highly valuable achievements of the three surgeons who performed 5 out of 6 hand transplants made in the World at that time, as follows:

- Warren C. Breidenbach, III, M.D., Kleinert, Kutz and Associated Hand Care Center P.L.L.C., who realized the first hand transplant in United States of America (32);
- Professor Jean Michel Dubernard, Edouard Herriot Hospital, Lyon, France, who operated a single hand transplant care and the first ever double hand transplant and
- Iguoxian Pei, M.D. Ph.D., First military University, Guangzhou, Peoples Republic of China, who carried out the first hand transplant in China.

There was also presented: Matthew Scott – the first patient from United States of America who was the recipient of a hand transplant and works and research studies regarding immunologic therapy, rejection, tolerance, new medicines and various experimental models on laboratory animals.

On 26th January 2001, Mathew Scott, the recipient of the first hand transplant from United States of America went through a series of medical examinations and assessment tests, at 2 years after the surgical intervention. These took place at Jewish Hospital and Kleinert, Kutz and Associated Hand Care Center.

Warren C. Breidenbach, III, M.D. declared that both the sensitive and motor function of the transplanted hand is better than at the last check made. Moreover, the prevailed biopsy showed no sign of rejection and recorded no rejection episode in the last 17 months (30). Thus, the curative physicians were satisfied with local and general evolution. The patient continued the recovering therapy twice per week (22).

In December 2006, in Valencia, Spain at Cavadas Clinique performed the first hand transplant to a woman. It was a double transplant, and the patient aged 47 years suffered 28 years before a bilateral amputation at radiocarpian level (33).

In 2007 and January 2008 2 more hand transplants were held under “Polish Program”, for 2 males of 42 and respectively 30 years old, in Wroclaw (34).

In July 2008, in Munchen, Germany, took place the first double arm transplant. The patient Karl Merk, 54 years old and the intervention lasted 15 hours (35).

On 12th July 2008, in United States of America, at Jewish Hospital was performed the next hand transplant for Dave Armstrong, 32 years old from Upland, California. The surgical

intervention lasted 14 hours and was proceeded by a team of 18 surgeons and 2 anesthetists. The team leader Warren Breidenbach, M.D. stated after the operation that it was the easiest intervention of hand transplant so far, due to amputation level and to the fact that the remaining tissues of amputation stump weren't crushed or sclerotized (15,17). Despite all of this, on 16th April 2009, at less than one year, the transplanted hand was amputated due to an incoming complication.

In the autumn of the same year (24 November 2008) United States of America supplied the fifth hand transplant, again at Jewish Hospital. The patient, Jan Erik Hondusky from Massena, New York faced a surgical intervention carried out in a record time: 9 hours. The team leader, surgeon Warren Breidenbach M.D. stated that physicians' efforts were canalized on two directions: improving the surgical techniques and lowering the immunosuppression. As regarding the immunosuppressants, 2 steroid type drugs were given up at the last 2 transplants, while only one immunosuppressive drug was used for Hondusky (15,17,31).

Between 14 and 15 March 2009 a surgical team from Pittsburg University performed a hand transplant for a 24 year old male, victim of a training accident. It was the sixth hand transplant in United States of America. The novelty consisted in administration of an infusion of donor bone marrow in order to reduce the immune response and respectively to reduce the need for traditional immunosuppressive medicines. Before the surgical intervention antibodies had been administrated to the patient to modulate the immune response and it was treated with tacrolimus. The new therapeutical steps are known under the name of Pittsburg Protocol (15,36).

On 4th April 2009, at Henri Mondor Hospital from Creteil (Paris suburb) took place a very complex surgical transplant. The 30 years old patient was the victim of a fire. The procedure consisted of transplanting of both hands simultaneously with partial transplant of face. The duration exceeded 30 hours and involved a team made by 40 professionals. Although it was about the sixth face transplant in the World, it was a premiere because of simultaneously with the double hand transplant (15).

On 4th May 2009 a 10 surgeons team from Pittsburg University performed the first double hand transplant in United States of America. The patient, 57 years old Jeff Kepner, from Augusta, Georgia, received a 9 hours lasting surgical intervention, despite of initial estimation for 20 hours (15,16).

An unhappy event was produced on 8th June 2009 when, during a surgical reintervention to treat an infection, the 30 years old patient, beneficiary of hand and face transplant performed at Henri Mondor Hospital from Creteil (Paris) two months before, died due to a heart attack (15,27).

On 22nd July 2009 was made the annual evaluation for patient Karl Merk, the first patient in the World with double hand transplant. A good evolution was reported with a faster than expected progress. After the physical therapy and electrostimulation, the motric acquisitions estimated at 2 years were made 1 year after the surgical intervention.

On 17th February 2010 the physicians from Wilford Hall Medical Center of Lackland Airforce Base from Texas, accom-

plished a handtransplant from a donor to a female receiver patient. It was the first woman, out of 9 handtransplant beneficiary patients in United States of America (15,16).

On 22nd June 2010 a Polish soldier has undergone a double hand transplant from a female donor. The patient had lost both hands in 3 years while he was rescuing a young recruit from a bomb explosion (7,16).

On 24th August 2010 the medics from Louisville University made the third double hand transplant in United States of America. The patient, dr. Rich Eduards, 55 years old, from Edmond, Oklahoma, had a serious postcombustional functional disability of both hands. The surgical intervention of transplant was a particularly one due to the fact that the surgeon succeeded to preserve the nerves and innervated structures at receiver hand level and attach its to the donor hand, in hope for a faster and even better recovery, with superior functional outcomes (15,16,17).

The end of the year 2010 brought surgical interventions of transplant for women.

On 18th September 2010, also at Pittsburg University, Sheila Adventa became the first female recipient of a double hand transplant in United States of America. Her hands were amputated 7 years earlier because of an infection. The surgical intervention lasted 12 hours. Sheila Adventa is the fifth patient who was administrated by Pittsburg Protocol (27).

In March 2011 took place the first hand transplant in Australia and was performed at St. Vicent's Hospital in Melbourne for a 65 years old male who lost both hands and both legs after a septicemia (15,27).

At the end of May 2011 at Brigham and Women's Hospital in Boston, United States of America took place a double hand transplant performed simultaneously with a face transplant for a 57 years old woman from Connecticut, who was mutilated by a chimpanzee. Unfortunately, due to severe septic complications and pneumonia, both hands were amputated later, but the face transplant remained viable (15,27).

Results

The increasing number of hand transplants successfully performed led to experience enrichment, with the acquisition of sophisticated surgical techniques achievements, selected anti-reject therapies with minimal side effects and recovering and maintaining therapies which generated amazing functional results.

The impossibility of gaining information about patients with hand transplant carried out in China and the unpublished results excluded them from taking into consideration in all studies and analyses developed.

Around the World 74 upper limb transplants were performed until May 2011 for 53 patients out of which 16 were carried out in China as follows: 5 unilateral hand transplants and 1 bilateral hand transplant, 3 unilateral forearm transplants and 2 bilateral forearm transplants, one palm transplant and 2 thumb transplants regarding 13 patients (11 males and 1 female). Of the other 40 patients, 21 received unilateral transplants and 19 bilateral transplants (27). The monitoring and

control postoperative period is less than 12 years.

Most of patients who faced upper limb transplant (45%) had amputations at radiocarpian level and, the time passed after the amputation varies between 2 months to 35 years. The order of anatomical elements reconstruction, in most cases, was as follows: fixing bone axis, arterial anastomosis and then venous anastomosis, the reconstruction of median and ulnar nerve – in all cases, and of radial nerve for 45% of patients, suture of joints: individual (53%), group or mixed. For all patients the surgical intervention was followed by a rehabilitation program (between 3 and 5 days per week for one year post-operative, then with smaller frequency accordingly with the functional outcome) which included: psychotherapy, electrostimulations, and occupational therapy (37).

The immunosuppressive treatment evolved over time from primitive immunosuppressive agents to the combination of 3 modern immunosuppressive agents and after that, due to the desire of reducing complications and side effects: in monotherapy (Pittsburg Protocol). The induction was done mostly with monoclonal and polyclonal antibodies (antithymocyte globulins or alemtuzumab or basiliximab) associated with tacrolimus, mycophenolate mofetil, steroids and, in some cases a local topic immunosuppressive was used. Only 2 patients hadn't received induction therapy. The most common maintenance treatment was the combination of steroids with tacrolimus and mycophenolat mofetil $\pm$ local immunosuppressive topics. In the first 3 months all patients received tacrolimus. Also, in postoperative period all patients received large spectrum antibiotics.

In recent years, the therapeutical scheme was adjusted using tacrolimus in monotherapy, and even replacement of it with sirolimus. The Pittsburg Protocol includes the administration shortly after handtransplant, of bone marrow infusion from donor in order to modulate the immune response, in combination with tacrolimus (36, 38). Regarding the side effects, most patients (85%) developed opportunistic infections (bacterial, mycotic and viral including cytomegalovirus (39), clostridium, and herpes virus), more than 50% of patients presented metabolic complications: Cushing's syndrome, weight gain, hypertension, diabetes, renal and hepatic insufficiency and also dermatitis, increased risk of developing various types of cancer. Most of these side effects were reversible and transient. Only 2 patients developed irreversible complications namely aseptic necrosis of femoral head, after treatment with corticosteroids, requiring bilateral prosthetic device of coxofemoral joint and respectively chronic renal insufficiency requiring dialysis at 8 years after the transplant (40).

The complications occurred after the surgical intervention were: 2 patients with arterial thrombosis and one patient with venous thrombosis, showed on the first postoperative day, 6 patients with minor tegument necrosis and one patient with arterial – venous fistulas. All were treated successfully.

85% of patients experienced at least one episode of acute rejection after the transplant in the first year (41). This reveals by the appearance of the skin type and lichenin dermatitis at tegument level and, at biopsy lymphocytic infiltrate is evident. Most rejection episodes were controlled with systemic cortico-

steroids administrated (60% intravenously and 30% oral) or topical and with topical tacrolimus administrated. No damage was demonstrated in functionality after the rejection episodes.

Only one single episode of chronic rejection was recorded, manifested by hyperplasia intima at transplanted hand level and acute consecutive ischemia requiring amputation in a 275th day of evolution. This took place after 4 episodes of acute rejection untreated.

Only one patient beneficiary of a double hand transplant simultaneously with face transplant died of cerebral ischemia because of aerial ways obstruction in the 65th postoperative day.

The surviving rate in the long term run transplant is approximately 94% excluding the cases in China. Four patients suffered the amputation of transplanted hand: a patient at 29 months postoperatively because of incompliance with immunosuppressive therapy; another patient at 275 days postoperatively because of hyperplasia intima and chronic acute ischemia, another patient with bilateral transplant in the 45th postoperative day, following a bacterial infection, lost his right hand and, the last one is a female with bilateral hand and face transplant who had both hands amputated because of septic complications, less than a month after the transplant. In China, 7 transplanted hands were amputated until September 2009 and, in all cases the reason was the incompliance with the immunosuppressive therapy (36).

Considering the functional results, all patients recovered the pain sensitivity, 90% recovered the touching sensitivity and 84% recovered the discriminatory sensitivity. Regarding the motor recovery, it starts early, with muscle flexion and extension extrinsic allowing the patients to perform prehension and clip moves. The intrinsic muscles recovery takes place later between the 9th and 15th postoperative month. This thing was confirmed also by electromyographic studies (42). Moreover, the functional magnetically resonance proved that the hand regains its cortical representation at sensitive and sensorial level of cortex (43,44,45). Most of acquisitions aiming the recovery take place in the first 3 postoperative years. In the next period occur only minor acquisitions.

The quality of life was improved for more than 75% of patients who were able to do most of daily duties and managed to resume the professional activity (36,38).

Discussions

Although the results are promising there are a lot of discussions on risk/benefit regarding the hand transplant. These issues are generated mostly by side effects involved by immunosuppressant therapy, mostly because the hand transplant procedure is one of life quality improving and not of life rescuing like in the case of other organs (kidney, heart, liver, i.e.) where the risk is assumed (46,47). Therefore the transformation of an individual healthy patient (amputated but still healthy) into a chronically ill, one continuously dependent of anti reject treatment and recovery treatment is questionable (48).

Also, unlike the other organs, the hand is a permanent exposed segment, with whose image the patient has to live day

by day, fact that could be difficult for some patients considering the origin of transplanted hand. There are opinions accordingly with the hand transplant is justified only in active period from socio – professional point of view and, after 55 – 65 years of age, the more and more harming side effects should be eliminated by the amputation of transplanted segment.

In our country the objectives are as follows: reducing the discrepancy of medical practice and science versus the other European countries, intensifying the research work and generating new knowledge and transplant surgery development.

The need for performing hand transplant in Romania has at least 3 proved reasons: - clinically, by high number of amputations; - economically, for socio – professional integration of active aged patients; - not at last scientifically, for integration of Romania into European and global trend.

There are premises for performing hand transplant in our country due to the existence of the necessary framework to undergo this intervention: - the professional experience and existing surgery centers with replanting of upper limb and functional rehabilitation; - organizational environment, the establishing of National Agency for Transplant; - legal environment, the Law of Organs and Tissues Prelevation and also the Order of Ministry no. 534/2006, article 1: “Emergency Clinical Hospital from Bucharest, Department of Plastic Surgery and Reconstructive Microsurgery, led by Prof. Dr. Ioan Lascar, is accredited for performing hand transplant.

The future of hand transplant depends on the new acquisitions of the modern medical science such as: genetic therapy by genetic and genetical engineering manipulation, primordial cells using (stem cells), humanized xenografts (49).

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