LARYNGEAL TRANSPLANTATION

DRAŽEN SHEJBAL[1], MIRKO IVKIĆ[1], VLADIMIR BEDEKOVIĆ[1],
LIVIJE KALOGJERA[1] and RENATO JANUŠIĆ[2]

[1]Department of Otorhinolaryngology and Head and Neck Surgery,
«Sestre milosrdnice» University Hospital, Zagreb, Croatia
[2]Department of Head and Neck Tumors, University Hospital for Tumors, Zagreb, Croatia

Summary

Laryngeal transplantation is not a new concept. Experiments with reinnervation, revascularisation, immunosupression and preservation started in the late 1950s. The impression after the first successful transplantation was as follows: all expected complications were successfully overcome and the expected failures did not occur. This report will discuss ethical and tehnical considerations of laryngeal transplanatation and risk of cancer reccurrence due to immunosuppression. Laryngeal organ transfer holds the best promise for preserving the quality of life in patients who have lost laryngeal function.

KEY WORDS: *laryngeal transplantation, reinnervation, revascularistaion, ethical consideration*

TRANSPLANTACIJA LARINKSA

Sažetak

Transplantacija larinksa nije neka nova zamisao. Pokusi s reinervacijom, revaskularizacijom, imunosupresijom i očuvanjem započeli su još kasnih 1950-ih. Nakon prve uspješno obavljene transplantacije stekao se dojam da su sve očekivane komplikacije svladane i da se očekivani nedostatci nisu pojavili. U ovom radu razmatrit ćemo etička i tehnička pitanja transplantacije larinksa te opasnost pojave recidiva raka zbog imunosupresije. Transplantacija larinksa najviše obećava kad je riječ o očuvanju kvalitete života bolesnika koji su ostali bez funkcije larinksa.

KLJUČNE RIJEČI: *transplantacija larinksa, reinervacija, revaskularizacija, etička pitanja*

INTRODUCTION

It has been almost a hundred years since the first transplantation of a human organ, a kidney. Transplantations were initially meant to save lives, i.e. to prevent premature death. However, along with the progress in transplantation and immunosuppression techniques, organ transplantations started to be performed also in non-vital indications.

The patient after laryngectomy is speech-impaired, or speaks in an unnatural post-laryngectomy speech. The main objective of larynx transplantation is therefore to restore normal voice communication, which would relieve the laryngectomee from depression and isolation (1).

HISTORY

At the beginning of the 1960s, Boles established the criteria to be fulfilled by larynx transplantation; phonation with an agressive pulmonic airstream and motility of vocal cords, swallowing of food without aspiration, restoration of airstream in the nose, and thus restoration of smell and taste (2). Shortly afterwards Work and Boles performed larynx autotransplantation

in the dog, and Ogura, Takenouchi and Silver elaborated the technical difficulties of revascularisation and reinnervation (3,4). On the basis of those experiments, in 1969 in Belgium Klyskens and Ringoir performed the first larynx transplantation. The transplant was removed eight months later due to carcinoma recurrence; swallowing had been normal until then, and the voice had never been restored. The transplant itself was not reinnervated, and carcinoma recurrence was interpreted as an imperfection of immunosuppression (5). A twenty-year pause due to obviously unsolvable problems came to an end in 1987, when Strome et al. started a series of trials aiming at only one task: to enable larynx transplantation.

ANATOMICAL AND CLINICAL PROBLEMS

Eighty percent of larynx vascularization goes through a. thyreoideae superior, which presupposes transplantation with the thyroid gland. The most perfect animal model had the arterial inflow through a. thyreoideae superior, and the vein blood was taken through a. thyreoideae inf. of the transplant into the end-to-side attached v. cave inf. of the recipient (6). A meticulously precise elaboration of the revascularization technique was required in order to procure as many trial animals as possible for determination of an ideal type of immunosuppression.

The larynx is immunogenic like other tissues – an immune response being produced by the mucous membrane; the biopsy and histological examinations of which give us a clue about the level of rejection. The cartilage itself is of medium immunogeneicity. In a number of trials, the best combination proved to be the therapy with Munoronab CD3 antibodies, cyclosporine, methylprednisolone and mycophelonate mofetil (7,8). Examinations of the above mentioned combination for carcinoma recurrence have not been performed. Clinical experience has shown that the development *of de nuovo* neoplasms in immunosuppressed patients after kidney, heart or lung transplantations is more frequent than in control populations that do not receive immunosuppression (9,10). The most frequent are skin carcinoma, then lymphomas and lung carcinoma in the third place (11). Malignant tumors are the third most frequent cause of death in those patients, after rejection of grafts and infection (12). Due to vital indications, the risk is considered acceptable. According to a study by Pollard et al., who have studied a population with heart or lung transplants, or with both, 11.5 % of patients developed nonlymphatic malignant tumors, half of which in the head or neck. Ninety-six percent of those tumors were cutaneous, and 80 % of them squamous cell carcinoma. Fifty-five percent of the total number of patients with malignant tumors died as a direct consequence of tumor development (13). Liver carcinoma is for the time being the only indication for transplantation of an organ affected by malignant tumor. Although the recurrence rate is high, from 15 to 50% depending on age, spread and type of tumor, the risk is also considered acceptable (14,15). HIV infection is not a contraindication for transplantation and immunosuppression (16).

Reinnervation should enable normal mobility and sensitivity of the larynx, which would in turn enable the patient to breath, phonate and swallow without aspiration. The biggest obstacle to phonation and breathing after the connection of donor and acceptor recurrence is synkinesis. Due to unspecific, random connection of the abductor with adductor threads it comes to inappropriate, paradoxical movement of vocal cords. Therefore reinnervation of the larynx should be approached after separation of anterior and posterior branches of the n. recurrens, which means a surgical area of one square centimetre for the surgeon, with nerve threads about 0.5 cm long and with 0.5 mm in diameter (17,18). The basis for further improvement of the model was provided by Tucker's reinnervation of vocal cords in humans, by transplantation of the nervous-muscular transplant directly onto the adductor muscles of the larynx (19). A further step toward the future was improvement of nerve preservation in the recipient. Upon laryngectomy it is necessary to preserve both nervus recurrens for the future transplantation. Two options have been developed: connection of anterior and posterior branches to the branches of ansa cervicalis, and connection of the n. recurrens with the corresponding part of the muscles to the newly created muscular pocket of the remaining strap

musculature of the neck. The method is called "nerve banking", and the selected option depends on the spread of the laryngeal tumor itself (20).

Preservation of the larynx from the moment of discontinuation of the donor circulation to the transplantation is a special problem, as the larynx remains vital for about 45 minutes upon discontinuation of blood supply. By combination of cold keeping in heparinized physiological solution, the vitality may be extended to three hours. The technique of continued hypothermic perfusion can extend the vitality to 48 hours; however the procedure itself is very complicated and increases the risk of mechanical damage and infection. The best option proved to be the larynx preservation in the University of Wisconsin solution, by means of which the laryngeal vitality was maintained for about 20 hours. This solution is used also for preservation of other transplants. Glucose in it is replaced with raffinose and lactobionate. Hydroxyethyl starch reduces the cell swelling by reduction of transcapillary and osmotic fluid transport. Cytotoxic oxidants, appearing after reperfusion, are diminshed with glutation, and dexamethasone stabilizes the cell membranes. The solution reduced the adherence of leucocytes to the endothelium, which reduces the graft injury (21).

The most important issue regarding justification of this surgery is the potential benefit versus the acceptable risk. A non-vital organ is being transplanted; the patient undergoes immunosuppression with all its side effects (22). In the USA, approx. 2,000 laryngectomies are performed in the treatment of laryngeal carcinoma every year. According to a study conducted in Great Britain, 75% of the laryngectomees would consent to the surgery if normal voice could be guaranteed to them, whereas the percentage drops to 50% for the option "minimum chance of voice restoration". Only 20 % of the respondents would consent to transplantation in case that they are to be subjected to a long-term immunosuppression (23). The authors of the first larynx transplantation in the USA establish three indications for this surgery: benign tumors of the larynx, laryngectomy after a trauma, and patients who have undergone laryngectomy for cancer and who remain disease-free after five years (8). The price of this surgery is US$ 100,000 and it is not covered by medical insurance in the USA. The algorithm of ethical dimension of the larynx transplantation can be followed right from the present-day two opposing concepts of the treatment of larynx carcinoma: surgery or radiotherapy? Which of the options guarantees a longer survival – radiotherapy or laryngectomy, which is then followed by transplantation? An important role is that of the patient's psychosocial status and motivation for a new and demanding intervention but also for a better quality of life.

SUCCESSFUL LARYNX TRANSPLANTATION, OR HOW LITTLE WE KNOW ABOUT THE LARYNX

In 1998, larynx transplantation was performed in a 40-year-old male, who lost the larynx after a motorcycle fall twenty years earlier. He was aphonic, lost the sense of taste and smell, and used an external device to speak. After consultations with the psychiatrist, speech therapist and a surgical team, he decided to undergo a surgery. The donor was a 40-year-old male, who died after the rupture of a cerebral aneurism. The HLA compatibility was complete. The transplant comprised the larynx and 75% of the pharynx, a small part of the oesophagus, the thyroid gland and the parathyroid gland, as well as six tracheal rings, without the left interior jugular vein, which was damaged during taking of the transplant. Until implantation, the transplant was kept in the University of Wisconsin solution for ten hours.

The donor's right a. thyreoideae superior was connected to the patient's a. thyreoideae superior, and the donor's right jugular vein to the patient's right facial vein. The left a. thyreoidaea sup. was connected end-to-end, and the left a. thyreoidea media end-to-side to the left interior jugular vein. The larynx was attached through the patient's hyoid bone and the donor's thyroid cartilage with three circumferential suture, the medium one going through the epiglottis. Both n. laryngeus sup. and the right n. recurrens were connected. The left n. recurrens was not connected, as it could not be identified in the patient. The patient's thyroid gland was not removed.

The postsurgical status was as follows: all expected complications were successfully overcome and the expected failures did not occur. Rejection of the transplant and infection were successfully solved. The patient uttered "hello" three days after the surgery, in a breathy voice, and phonated by means of aryepiglottic folds. Six months after the surgery, both vocal folds were in the medial plane. The authors believe that "the patient's left n. recurrens was reinnervated with small regional motor fibres". The reinnervation on both sides has also been confirmed electromiographically. The planned laser cordectomy was not performed. Three months after the surgery, the patient started to take food, the senses of taste and smell were restored. Eighty-three percent of the total activity of the thyroid was taken over by the transplanted thyroid gland, and despite of 10-hour ischemia the donor's parathyroid glands were also active. Thirty-six months after the surgery, the voice was normal in all phonatory characteristics.

The patient described his life after the surgery as immeasurably improved (8).

CONCLUSION

The voice is a unique expression of the human mind, a weapon that brought us victory in the last evolutional battle, that against the Neanderthal. The battle for the quality of life is a logical evolutional sequence, in which larynx transplantation has its place. We are witnesses of its first steps. The number of people without the larynx on one side and the progress of larynx surgery on the other should provide a solid argumentation that larynx transplantations become spread worldwide.

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Author's address: Dražen Shejbal, M.D., Dept. of Otorhinolaryngology and Head and Neck Surgery, «Sestre milosrdnice» University Hospital, Vinogradska c. 29, 10 000 Zagreb, Croatia, E-mail: dr.azen@vip.hr