LITERATURE REVIEW

The role of cartilage and bone allografts in nasal reconstruction

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ABSTRACT

Nasal reconstruction is challenging, considering surgical techniques complexity and difficulties in remodelling a tridimensional structure. Reconstructive requirements are: correct deformity evaluation, selecting the most suitable treatment option, respecting the principle of aesthetic subunit, appropriate reconstruction of each affected nasal layer, long-term stabile functional and aesthetic results. Reconstructive procedures range from simple to very complex. Conventional techniques can fail in restoring a satisfactory appearance in severely disfigured patients, for whom a new possibility arises: Vascularized Composite Allografts (VCA) transplantation.

In this paper, we focus on nasal skeletal framework restoration. Structural defects may require a large amount of reconstructive material obtained usually from cartilage or bone autografts. Autologous cartilage is the gold standard in nasal architectural recovery, but in some cases, autologous graft sources are not available, imposing the necessity to use alternative solutions represented by the allografts or alloplastic materials. We analysed the specific features of skeletal allografts used in nasal reconstruction.

With current clinical experience, the use of cartilage and bone allografts (especially irradiated cartilage homografts) shows a promising reconstructive option for nasal structural defects. For extensive facial defects, including midface deformities, impossible to restore with traditional surgical techniques, a new reconstructive era was open through the development of the VCA field.

KEYWORDS: nasal reconstruction, cartilage allografts, bone allografts, VCA, antigenicity

INTRODUCTION

Of all the aesthetic units of the face, the nose has a great importance because of its essential roles in respiration, olfactory senses and phonation and its central location on the face, which influences the physiognomy decisively; the aesthetic consideration is an important part of the psychosocial integration and influences the patients' life quality. Nasal tissue defects may interest normal respiratory and olfactory functions, as well as face aesthetics; therefore, there is a great interest in refining the reconstructive possibilities for this anatomic segment. There are a lot of possible etiologies for the nasal defects: trauma including burns, tumors both benign and malignant, congenital malformations, infections, autoimmune disease and other rare ailments that may affect the nasal region[1].

Nasal pyramid reconstruction is quite a challenge considering the surgical techniques because of the difficulties determined by having to remodel tridimensional structures and the complexity of the reconstructive methods that do not always have the expected results[2]. The following aspects are important and must be acknowledged in nasal reconstruction: correct assessment of the defect - extension and depth of the affected structures and functional involvement, the adjacent anatomical regions, careful elaboration of a therapeutic plan considering the defect, the patient's general status (possible comorbidities) and his/ her

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wishes, long term follow-up, in order to achieve a normal quality of life and socio-professional integration[3].

Extensive defects imply using a complex surgical treatment, following several steps in order to achieve structural and, most importantly, functional restoration of the nasal region. The main objectives are: restoration of the support mechanisms - bone and cartilage structures, nasal mucosa and skin, anticipating a high standard healing, with normal aspect tissues, minimal scars and a stable result in time[4]. Not only must the tissues be similar to those that they replace, but they must have certain characteristics, such as: the covering skin must have normal aspect, be slim, congruous and vascular, the lining must be slim, supple and vascular, and it must not affect the airway, nor deform the shape of the nose because of too much bulk or rigidity. In order to prevent collapse and deformity, the skeletal framework must support, shape and strengthen the restoration against gravity, tension and/ or scar contraction[5].

The principles of facial reconstruction have changed from traditional defect assessment to a visual perspective. The principle of aesthetic units is an important concept in facial reconstruction and it implies that the human eye captures images only as a sequence of blocks more than a series of confluent lines, which are eventually put together into a single picture. The shape of the defect may be modified so as to determine the shape of the flap and control the resulting scars, proving that the morphology of the defect does not set limits to the surgeon's possibilities. The final scars can be forced to line between two adjacent aesthetic subunits, and thereby be more inconspicuous[5,6]. Millard and Burget separated the nose into "subunits" based on skin quality, border outline, and tridimensional delineation[6-8]. In the nasal region, each subunit is defined by a change in surface outline, a breach in the natural plane, or reflections of light. The nasal unit is made out of the tip, dorsum, columella, and paired alae, sidewalls and soft triangle subunits[6]. The reconstructive goal implies that the character of the units must be restored, instead of filling the defects without taking into account the unit outline, and risking that the tissue replacement may become a distracting scrap within the subunit[5].

Defects are adequately approached through a large panel of surgical procedures from skin grafts, local or regional flaps, tissue expansion, to more complex procedures involving use of biomaterials or tissue transfers (avascular bone or cartilage grafts, microsurgical free tissue transfer flaps for large defects, prefabricated and prelaminated flaps)[9]. Augmentation (like in secondary rhinoplasty), nasal valve abnormalities assessment or reconstruction after achieved defects of nasal skeleton may require a large amount of structural material obtained usually from cartilage autografts; but in some cases, when donor sites are not available or surgical indication may impose, allografts (cartilage and bone cadaveric homografts) or alloplastic materials (silicone, polyethylene) can be used[10, 11].

Traditional reconstructive methods can fail in achieving a satisfactory appearance in patients with severe disfigurements (after burns, severe high-energy trauma like gunshots, congenital facial malformations), often necessitating numerous, staged, surgical interventions and providing unsatisfactory results. Vascularized composite allotransplantation represents a new emergent field, offering a unique reconstructive opportunity for injuries and defects that involve multiple layers of functional tissue that are impossible to repair using conventional surgical techniques. Transplantation of human partial or total face allografts enables an entirely different level of cranio-facial reconstructive surgery, permitting restoration of extensive defects in just a one-stage procedure with good functional and aesthetic results. Limitation in a rapid expansion of vascularized composite allotransplants as standard reconstructive procedures is posed by the side effects of the immunosuppressive drugs that patients must take to prevent rejection and graft loss, those procedures serving for quality of life and functional recovery, rather than life-saving indications. In order to improve Vascularized Composite Allografts (VCA) outcomes, translational studies are needed to develop less toxic immunosuppressive regimens and possibly achieve donor-specific tolerance (the ideal situation in transplantation)[12-15].

BONE AND CARTILAGE GRAFTS FOR STRUCTURAL NASAL RECONSTRUCTION

For adequate three-dimensional structural reconstruction we need good-quality, well-vascularized soft tissues, with appropriate texture and stabile structural support in order to obtain the best size, conformation and function of the lost nasal tissue. Structural reconstruction is mandatory for nasal contour and respiration[16-18].

In order to restore the nasal framework, cartilage grafts are usually needed, but in some cases bone grafts are also required[19]. Grafts have to meet some conditions for providing the best functional and aesthetic result: adequate intrinsic strength to restore the contour, also shape and texture similar with the missing part of the nasal skeleton[17].

Grafts used in reconstruction of the nose have three major goals: restoration, support and contour. Restoration grafts replace nasal skeleton defects and they are represented by bone or cartilage depending on the type of defected tissue. Support grafts confer strengthening of the existing skeleton. Contour grafts

Table 1
Grafts Classification

Type	Description
Biological material	Autograft: from the same individual Isograft: from univiteline twins Allograft/Homograft: from another individual from the same species Xenograft: from another species
Non-biological material/ synthetic	Alloplastic materials
Tissue-engineered	Scaffolds + cell cultures

are used to model the tip of the nose or for correcting topographic deformities[17].

Grafts can be biologic (autografts, homografts, xenografts) or synthetic (different alloplastic implants). Also, tissue-engineered structures were obtained combining synthetic scaffolds seeded with different cell cultures. Table 1 describes the classification of the grafts usually used in reconstructive procedures[20, 21].

A. Autologous cartilage and bone grafts

Autografts are the first choice in any reconstruction, surviving as living tissue with very good long-term outcomes and does not elicit any immune response[19]. Autologous cartilage grafts are recognized as gold standard in nasal reconstruction. Nasal septum, concha of the ear and rib cartilages are the main sources for prelevation of autologous cartilage. The optimal donor site is the septal cartilage, because it is stiff and maintains its shape after inset in defect area. For curved defects the conchal cartilage is more suitable[18,22].

Unfortunately, the septal and auricular sources are less accessible as quantity and, in the cases with extensive defects and higher reconstructive necessities, the use of the rib cartilage is needed[18,22]. Prelevation of rib cartilage can be associated with donor-site morbidity as: pain, clicking of the thoracic wall, vicious scars, contour deformity[23]. Another problem regarding rib cartilage grafts is the risk of postoperative warping[24].

Autologous bone grafts are also used in nasal reconstruction in selected cases when the goal is to achieve very good strength and support of the recreated framework. Bone grafts do not have wider indications due to their morbidity of the donor areas and rigid consistency, unnatural at palpation. Common donor sites for bone autografts are: calvarial bone, iliac crest and costal bone[18]. In extensive defects, requiring subtotal or total nasal reconstruction, free microsurgical transferred osteomiocutaneous flaps may be the best approach for the patient, conferring satisfactory tissue coverage. Moore et al. illustrated that the radial forearm osteocutaneous flap is a good option for nasal lining and bony support in subtotal nasal defects reconstruction[25]. Also, osteocutaneous fibula free flap can be used for nose reconstruction, like Nakayama reported with a female patient having a squamous cell carcinoma of the right ethmoid sinus, requiring subtotal nasal reconstruction after tumor resection[26].

Vascularized bone has great advantages compared with the avascular graft in nasal reconstruction: less infections, lower resorption, long-term stability of the reconstructive and aesthetic results[26].

Other methods using autologous components to restore tissue defects are based on cell therapies and tissue-engineered constructs, when appropriate donor sites are not available. Yanaga reported a clinical study using of human autologous chondrocytes, prelevated from auricular conchal cartilage (a cartilaginous piece around 1 cm), cultured with autologous serum and injected in a gel form in contact with the periosteum, with good, stabile results in complicated architectonic defects of the nose and the craniofacial region[27]. Fulco et al. also developed a trial including patients with two-layer alar defect resulted after resection of non-melanic tumors. The defect was reconstructed using engineered cartilage substitutes composed by collagen membranes and chondrocytes isolated from the nasal septum and cultured with autologous serum. The team had satisfactory functional and aesthetic outcomes at the 1-year follow-up with structural stability and appropriate respiratory function. Histological assessment in this study at the 6-month follow-up observed the replacement of the engineered cartilage matrix by fibro-muscular fatty tissue but with preserved stability[28].

There are also other ongoing research trying to obtain tissue-engineered product able to restore the normal aspect and function of lost tissues, but many of these approaches have practical limitations regarding reconstruction of large defects, availability, financial and administrative requirements (necessitating complex infrastructure including cell biology laboratory and appropriate materials), making a more difficult translation from basic to clinical research[29].

B. Cartilage and Bone Allografts

a. Indications

As we see above, autografts remain the priority in the majority of cases of nasal reconstruction. There are some situations when autologous sources are not available or do not have indications for the patient. Limits of autografts use are: not enough reconstructive autologous material (reduced availability or inappropriate quality), donor-site morbidity, necessity of seriate, multiple surgical interventions increasing the duration and costs of hospitalization, long and complex surgical interventions involving more than one operatory site (a problem in elderly patients or with associated comorbidities), patients desires and expectations, reconstructive experience of the surgical team[30,31]. In those cases, the use of an allograft can provide a satisfactory reconstructive solution.

b. Immunological features of cartilage and bone allografts

Wide-scale utilization of human allografts would offer an unbelievable reconstructive potential, the only limits from this point of view being the immunologic effects that must be taken into consideration in any organ/ tissue transplant[32]. In order to avoid the immune complications (rejection with allograft dysfunction and local and systemic reaction), different strategies have been developed according to the transplant type in the interest of acceptance of the transplanted component:

- processing tissues for reducing antigenicity (in bone and cartilage allografts different strategies are used, like freezing and thawing, irradiation),
- administration of immunosuppressive therapy,
- developing immunomodulatory and immunologic tolerance induction protocols[32,33].

Bone and cartilage allografts are used both as free (non-vascular) and vascularized[34].

Once the development of transplant medicine was initiated, a special interest was born for the study of specific immunogenicity of each organ and tissue. There were also many studies conducted regarding the utilization of bone and cartilage allografts and the immunogenicity of nonvascular grafts, but a lot of new information has gathered concerning the development of the vascularized composite allotransplantation field[34-36].

Vascularized composite tissue allografts pose immunologic challenges compared with organ transplants, due to their structural components derived from all three germinal layers (ectoderm, mesoderm and endoderm): skin, subcutaneous tissue, bone, bone marrow, cartilage, tendons, muscle, blood vessels, nerves, mucosa[37,38].

After introduction of the concept of different organs and tissues antigenicity by Murray, Lee proposed a relative scale of antigenicity of the components of vascularized composite allografts, with skin being the most antigenic tissue[39,40]. In the antigenic hierarchy, cartilage and tendons are the least antigenic structures, bone has lower immunogenicity and muscle has an intermediate position[35,40]. Each of these components expresses different antigenicity, but may elicit a varying and non-synchronized immune response in composite tissue allotransplantation[41,42]. Due to its highest antigenicity, skin is used as sentinel marker for monitoring graft rejection in vascularized composite allografts[41].

Cartilage allografts antigenicity

Cartilage is different to other tissue do to its lack of vascularisation and innervation, having minimal ability for lesion repair[43]. Histologically, cartilages are composed by cells included in the cartilage matrix consisting of ground substance and collagen and elastin fibers (consistence in those fibers varies in different types of cartilaginous tissues) and enclosed in the perichondrium. Chondrocytes are situated in lacunae of the extracellular matrix[44]. Avascularity was thought to determine the "immune privilege" of the cartilage, based on the observations that the immune system is limited in recognizing and rejecting cartilage allografts[45].

The antigenicity of the cartilage is determined by the expression of major histocompatibility complex (MHC) antigens on structural components of cartilaginous tissues. The perichondrium has relative less immunogenicity, determined by its cellular components. The perichondrium is involved in the initiation of the allorecognition in non-vascularized cartilage allografts[44].

The cartilage matrix does not express antigens MHC and it does not provoke an immunologic reaction, due to its immunologic inaction. The chondrocytes, on the other hand, express antigens, MHC I and to some extent MHC II, which makes them susceptible to being recognized and provoking an important immune response. The particularity is their location in the lacunae surrounded by a non-antigenic matrix, which means that if the transplanted cartilage is intact, it is protected from immunologic recognition and graft destruction[44].

Histopathological findings in both experimental and clinical experience confirmed the low antigenicity of the cartilaginous tissue[44].

Bone allografts antigenicity

Bone allografts can be the target of rejection by the recipient after recognizing the proteins and glycoproteins express on cell surface, mainly through a cellular immune response, but also a low humoral immune response was observed[40,44].

For the non-vascular allograft, a reduction of the antigenicity is obtained by freeze-drying the bone graft before transplantation[46].

A correlation was observed between the antigenicity of bone allografts and Major Histocompatibility Complex barriers, with lower immunogenicity levels in cases of MHC antigen matching[44].

The bone allograft also transfers the bone marrow component, which is involved in immunological processes.

With vascularized bone marrow allotransplantation, we saw that the bone marrow stromal microenvironment is preserved, representing also a continuous source of donor hematopoietic cells inducing microchimerism (detected in the host blood and lymphoid organs) with immunomodulatory and tolerance-inducing properties[47].

c. Clinical use of cartilage and bone homografts

Cartilage homografts

There is a large clinical experience so far (more than five decades) with the use of the irradiated cartilage allografts in craniofacial reconstruction[48]. Irradiation of the cadaveric rib cartilage with gamma rays eliminates cellular components, avoiding immunological recognition and also the risk of transmissible pathogens[31].

The irradiated homografts are easily carved and sculpted, providing a good source of cartilage in different nasal reconstructions. Very good results were obtained in augmentation of the dorsum nasi region[10]. Variable resorption rates were reported, the incidence of resorption increasing in long-term follow-up, with highest levels around 75%. In 66 patients studied by Menger, which received a total of 177 irradiated homologous rib cartilage grafts, 121 (68%) grafts maintained their properties, with moderate resorption encountered in 55 patients (31%) and complete resorption in just one patient. Regarding the resorption process, a support function diminution rather than a reducing of volume of the reconstructed area was noted. The authors noted low complication rates and good functional and aesthetic results[49]. Another important aspect is the risk of cartilage warping. Experimental studies revealed a similar warping rate in non-irradiated and irradiated cartilage grafts[31]. Cartilage physical properties can be influenced by the irradiation dose, high-dose irradiation being associated with considerably less stiffness and increased resorption rates[50].

An extensive clinical study was reported by Kridel et al., during 24 years, including 357 patients who beneficiated of a number of 386 rhinoplasties using 1025 irradiated homologous costal cartilage grafts. The favourable result of this extensive study encourages the use of irradiated cartilage homografts in nasal surgery, due to their stabile long term-results in preserving structural nasal framework, low complication rates (including infection, resorption) similar with conventional rhinoplastic interventions, no need for donor areas, higher efficiency in decreasing duration and complexity of procedures, anaesthetic risk, hospital stay and cost[51].

Bone allografts

The use of autologous bone grafts is associated with increased donor-site morbidity; therefore, alternative reconstructive methods were explored including the use of bone homografts. Non-vascular allografts used for bone reconstruction are obtained from cadavers and can be preserved in tissue banks, with standard requirements in procurement and testing of the grafts. There are three types of bone allografts that can be used in reconstruction: Fresh or fresh-frozen bone, FDBA: Freeze-dried bone allograft, DFDBA: Demineralized Freeze Dried Bone Allograft[52]. Deep freezing in sterile conditions of the bone grafts at -80°C reduces the antigenicity of the graft, but concerns exist regarding the hypotheses that freezing affects the properties of the graft. Experimental work suggests there are no significant differences in long-term graft incorporation in deep-freeze bone compared with fresh autologous bone graft[33]. Shaw et al. demonstrated that human cadaveric fibula grafts can be repetitively refrozen (even up to eight times) and still preserve their morphologic and biomechanical characteristics, data confirmed by the histological analysis of the bone sections[53].

In craniofacial surgery, there are some clinical data reported regarding the use of fresh-frozen allografts (like iliac crest fresh-frozen allografts) in reconstruction of the maxillary sinuses and of the atrophic edentulous alveolar ridges, with promising results[54,55].

NOSE AS COMPONENT OF VASCULARIZED COMPOSITE FACIAL ALLOGRAFTS

Since the first hand transplant performed in France in 1998, transplantation of vascularized composite allografts opened a new, promising era in reconstructive surgery. The first partial facial transplant was performed in France in 2005 by Devauchelle et al. and the first full face transplant in the world took place in Spain in 2010[56-58].

To date, 29 partial and total facial transplants were performed worldwide. The majority of the recipients are male (23 men and 6 women), young (ages ranging between 19 and 59 years, mean age 34 years), with the cause of deformity dominated by trauma (16 cases) and burns (8 cases). The deficit included, in the larger majority of the cases, the central part of the face (23 patients having their midface affected, including the nose), with severe impairment of important functions of swallowing, eating, speaking, with 22 of patients having a tracheostomy[59,60].

Recipients of face transplants require life-long immunosuppressive therapy. Standard immunosuppressive protocols include an induction phase and the maintenance period. Induction therapy consists of infusing anti-lymphocyte antibodies or anti-T-cell therapy shortly after transplant. Triple maintenance therapy with steroids, Tacrolimus and Mycophenolate mofetil is usually utilized. In case of rejection episodes, a more aggressive immunosuppressive regimen is temporary administered[32,61].

The Boston transplant team performed an analysis of upper airway recovery in face transplant patients. They had four patients, one with midface and three with full facial allotransplantation. A thorough evaluation was made for each patient prior transplantation and also in the follow-up transplant program, including: clinical examination, imagistic assessment of the airways using Dolphin Imaging software, volumetric tests and histopathological analysis of biopsy specimens prelevated from the nasal cavity trough nasopharyngoscopy. After face transplantation procedures, which also restored the upper airway, the study revealed clinical benefits on patient respiration, a significant increase of airway volume in all four patients, good nose breathing, allowing the remove of tracheostomy tubes. Respiratory mucosa histological findings were functional epithelial cells and absence of inflammation[62].

CONCLUSIONS

As is sustained by a large clinical experience, homografts have found their roles in reconstruction of the nasal skeletal framework, with good outcomes in structural, functional and aesthetic results.

Although cartilage autograft remains the gold standard in structural reconstruction of the nose, for selected cases, allografts can be favoured due to their large availability of resolving the continuous growing reconstructive demand and the necessity of a more simple surgical procedure in some patients.

Concerning the immunological aspects, they can be overcome by different strategies of physical processing of the tissues and reduction of the level of immune response after transplantation in the recipient. In particular, cartilage has its unique structural features conferring an immune privileged status compared with other tissues.

Current findings suggest that composite tissue allotransplantation may be the elective option for reconstruction of the extensive defects with associated architectural and functional deficits in the midface region, impossible to approach by conventional surgical techniques. Future research in the VCA field is necessary to develop improved immunosuppressive and immunomodulatory strategies, with the supreme goal to induce donor-specific tolerance in order to avoid the toxicity of the immunosuppressant therapy.

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