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RHINOSEPTOPLASTY, OUTCOMES AND PERSPECTIVES

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Under modern conditions of accelerating scientific and technological progress various injuries of the nose of domestic, military nature are becoming more common ENT pathology. In addition, the unfavorable environmental situation and modifying the human genome leads to congenital deformities of the nose, which are combined with the presence of dental pathology (cleft lip or cleft palate).

Indicated deformities in most cases are combined with a significant deformity of nasal septum, which leads to a significant change in respiratory function of the nose and consequently its other functions and thus reduce the quality of human life. Therefore, the correction of external nose defect of congenital or acquired nature and pathologies of intranasal structures are becoming more actual problem.

Under our supervision are currently 125 people with deformity of the nose and nasal septum, who underwent surgery – rhinoseptoplasty in various versions. Most often in our practice, we used open or closed type of rhinoseptoplasty. In this case, patients were removed hypertrophied or deformed sections of nasal bridge and nasal septum.

The question of using one or another form of surgical intervention was decided individually with each patient and depended on his or her preferences, as well as the severity of the deformity.

In patients with congenital genetic changes in the facial skeleton performing rhinoseptoplasty acquires additional complexity associated with the elimination of multiple malformations. In these patients there is considerable deformity not only of the pyramids of the external nose, but its such structures as the tip, nostrils. In this case, the nasal septum has a pronounced deviation, which blocks the nasal breathing from one or both sides. In such patients rhinoseptoplasty is performed in several stages: septoplasty, correcting nasal bridge and then moving the nostrils. Or vice versa, dental surgery is performed either before or after complex surgical interventions on the nasal structures.

Certain difficulties are performing rhinoseptoplasty in cases where there is a need for additional auto transplant material. These, for example are: saddle nose, soft tissue defects of external nose.

To fill in defects of tissue surgeons have to perform additional surgical interventions. This is a significant disadvantage. Moreover, such an additional trauma brings emotional pain to the patient, sometimes can be observed postoperative complications in the area of additional surgery. Transplant material can be: costal cartilage, fragment of auricle, front face of tibia.

In connection with this promising trend is the growing of bone or cartilage tissue from bone marrow cells. In this case, it is possible to program any volume and configuration of cultured tissues. This technique is introduced at the Institute for Problems of Cryobiology and Cryomedicine of National Academy of Sciences of Ukraine.

The promising direction for treatment of patients with rhinoseptoplasty is development of tissue engineering constructs of lost fragments of bone and cartilage. Tissue engineering is an interdisciplinary field dealing with the *in vitro* development of functional biosubstitutes that maintain or restore functions of damaged tissues and even whole organs after the implantation of such substitutes *in vivo*. An actual approach in modern tissue engineering involves the isolation of cells from patient tissue biopsy, expansion of cells *in vitro* and then seeding them into a three-dimensional scaffold of predefined shape and size. In this case, mesenchy-

mal stromal cells (MSCs) appeared to be the most promising cell type for generating connective tissue engineered substitutes due to high proliferation activity of MSCs, expansion and ability to differentiation into multiple cell types.

The use of scaffold should both retain the cells within the defect site and also promote tissue ingrowth and vascularization. Ideal scaffold should be biocompatible, non-immunogenic and biodegradable (in many cases, but not always), promoting optimal attachment, proliferation and differentiation of cells.

The aim of the study was the seeding of bone marrow and adipose tissue derived MSCs into macroporous scaffold and investigate cell proliferation and differentiation into osteogenic and chondrogenic lineages within the scaffold.

Osteogenic differentiation medium consisted of α -MEM supplemented with 10% FCS, 50 U/ml penicillin, 50 mg/ml streptomycin and 0,2 mM L-glutamine with osteogenic supplements, consisted of 20 mM ascorbic acid (Sigma-Aldrich), 10 mM β -glycerolphosphate (Sigma-Aldrich) and 1 μ M dexamethasone (Sigma-Aldrich).

For chondrogenic differentiation cell-seeded scaffolds were cultured in chondrogenic differentiation medium consisted of α -MEM, supplemented with 50 U/ml penicillin, 50 mg/ml streptomycin and 0,2 mM L-glutamine with chondrogenic supplements, consisted of 20 mM ascorbic acid (Sigma-Aldrich), 0.1 μ M dexamethasone (Sigma-Aldrich), 10 μ g/ml insulin and 100 μ g/mL sodium piruvate (Sigma-Aldrich), and 10 ng/mL TGF- β 3.

Adhesion and distribution of MSCs within scaffolds were confirmed by SEM observations (fig. 1). The fig. 1 shows that Cells appeared to be flattened with fibroblast-like morphology, growing and filling spaces within the outer and inner surfaces of pores.

Osteogenic differentiation capacity of MSCs after 3 weeks of induction in spongy scaffolds was confirmed by alkaline phosphatase expression (fig. 1A). After 28 days of chondrogenic differentiation, cells accumulated extracellular matrix, which was positively stained by alcian blue (fig. 2B). In the control group no alcian blue staining was observed. fig. 2 also shows that cells not only grew on the pore walls' surfaces of the scaffold, but also filled spaces between them.

The results indicate that stem cell-based bone and cartilage tissue engineering is promising for treatment of patients with rhinoseptoplasty.

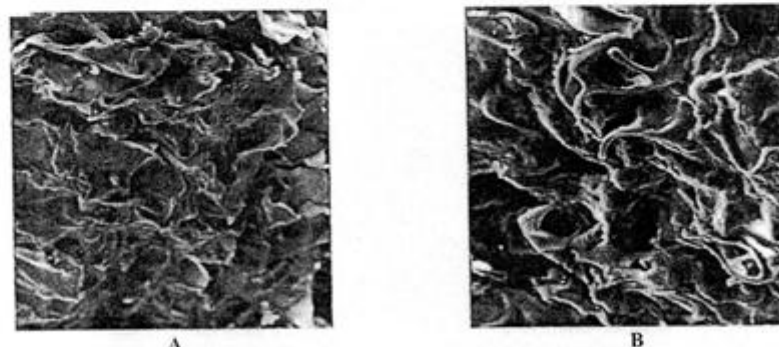


Fig. 1. Scanning electron microscopy of unseeded scaffold (A) and MSCs-seeded wide-porous scaffold on the 7th day of culture (B)

Osteogenic differentiation capacity of MSCs after 3 weeks of induction in spongy scaffolds was confirmed by alkaline phosphatase expression (fig. 2A). After 28 days of chondrogenic differentiation, cells accumulated extracellular matrix, which was positively stained by alcian blue (fig. 2B). In the control group no alcian blue staining was observed.

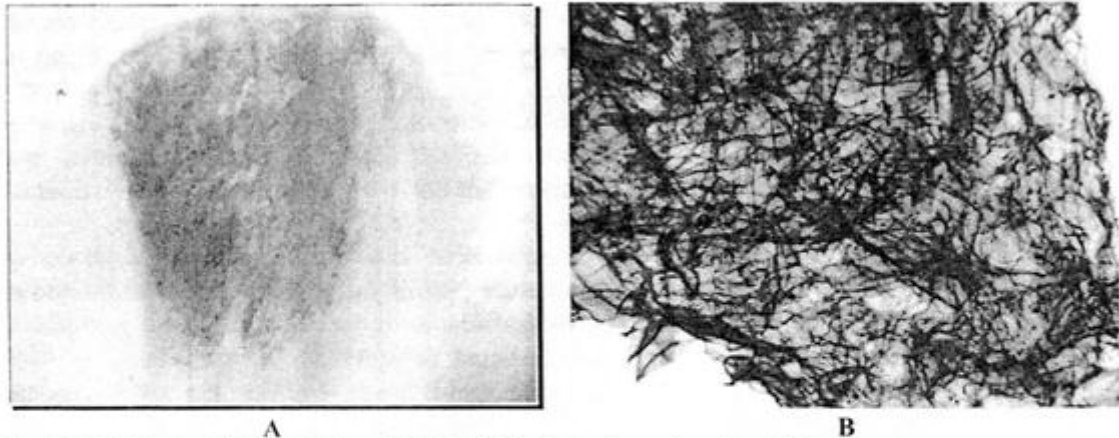


Fig. 2. Multilineage differentiation of MSCs within three-dimensional scaffold:
 A – osteogenic differentiation (alkaline phosphatase expression);
 B – chondrogenic differentiation (alcian blue / safranin staining)

However, the introduction of this method is hampered by the high cost of reagents.

It is very important to assess the results of surgical intervention. It must be comprehensive and consist of functional and aesthetic results. The aesthetic outcome of surgery is determined by the patient's opinion of it. Even if the surgeon is not always satisfied with the result of performed operation, the final word rests with the patient. However, it must be said that the result of surgery should be, assessed by the patient no earlier than 1 or 2 months after discharge from hospital.

Functional results of rhinoplasty are estimated based on the results of rhinomanometry diagnosis. With rhinomanometry we study the dependence of the airflow passing through the nasal cavity caused by the pressure differential between the inner outlet of the nasal cavity (Hoan) and atmospheric pressure. It was used the technique of rear active rhinomanometry using the developed device for measuring overfall-discharge characteristics TNDA-PRH (certificate of state metrological certification № 05-0102 of 01.04.2010).

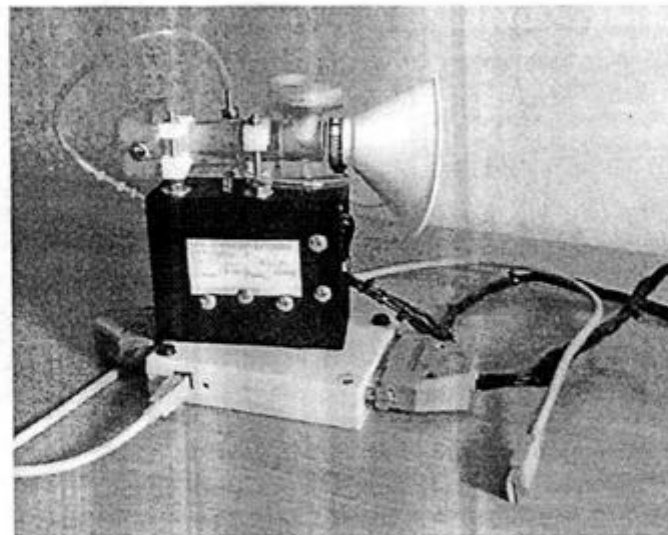


Fig. 3. Device for measuring overfall-discharge characteristics

The composition of this unit (fig. 3) includes a measuring unit, containing a differential sensor of air pressure differential between the pressure in the outlet of nasal cavity and atmospheric, and sensor of air flow through the nasal passages during breathing (in the phase

of inspiration). The latter is based on the principle of the Venturi meter. Signals from the sensors come into converting unit controller based on multi-channel measurement module L-Card E14-140, the main components of which are managing microcontroller AVR At-Mega8515, 14-bit analog-digital converter (ADC) LTC1416 and PDIUSB12D interface module to communicate with the PC via USB-port. The digitized signals from sensors of pressure and flow rate with a sampling frequency of 500 Hz are transmitted via USB-interface to PC for further processing and analysis. The main diagnostic indicator of the degree of violation of nasal breathing at a standard rhinomanometry is a coefficient K_R of generalized assessment of nasal resistance $K_R = \frac{\Delta p}{Q}$, $\frac{kPa}{l/s}$ which is the ratio of the measured values of pressure drop ΔP to air flow Q .

Obviously, the higher the coefficient K_R of the generalized evaluation of nasal resistance – the worse the performance of nasal breathing. Fig. 4. shows the plots obtained in the preoperative (1) period and 2 months after endonasal rhinoplasty (2) with the correction of curvature of the nasal septum (the dots denote the experimental data, solid lines – their linear approximation). It is obvious that before the operation coefficient of nasal resistance was

$$K_{R1} = 8,2 \frac{kPa}{l/s}$$

at the maximum of air flow when breathing through the nose less than 2 l/s

and after nasal rhinoplasty was $K_{R2} = 2,6 \frac{kPa}{l/s}$ with an increase in air flow up to 3,3 l/s

which made it possible to evaluate functional outcome of rhinoplasty as $K_{R1}/K_{R2} = 2,3$, i.e. coefficient of resistance of nasal breathing decreased in 2,3 times. It should be borne in mind that the indicators of pressure drop and airflow through nasal cavity depend on individual features of patient (age, physical condition, etc.).

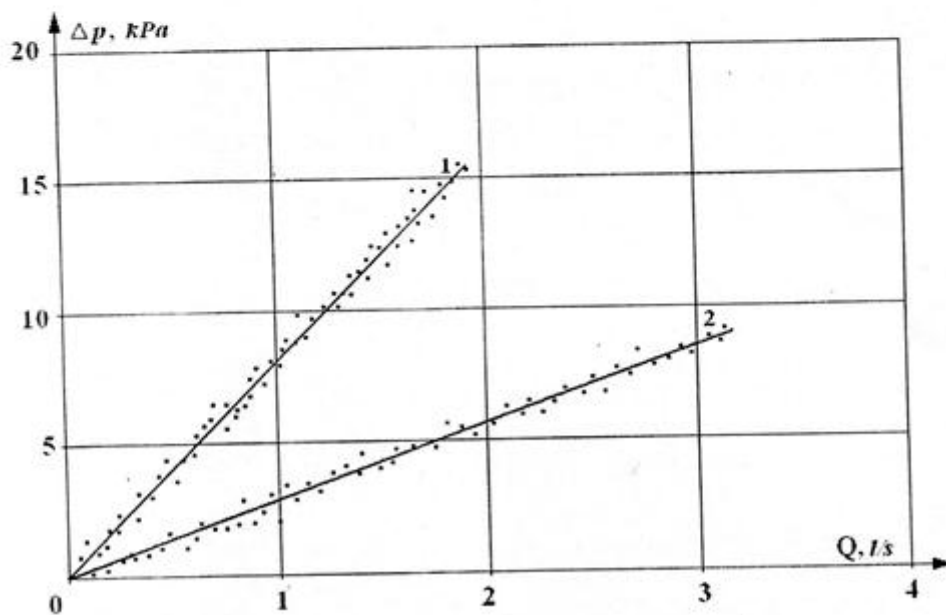


Fig. 4. Results of treatment of 125 patient: beautiful – 102; good – 21; without effect – 2

Thus performing rhinoseptoplasty in practice is frequent operative intrusion. Providing operation with transplant material is a complicated issue which nowadays involves performing extra operative intrusions. However there are prospects of relieving the patients from excessive sufferings by implementing methodic of growing tissue from mesenchymal stromal cells. An important issue is assessing of obtained both esthetic and functional outcomes in rhinoseptoplasty.

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