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Original Article

Three-dimensional changes of noses after transplantation of implant-type tissue-engineered cartilage for secondary correction of cleft lip–nose patients

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ABSTRACT

Introduction: We have developed an implant-type tissue-engineered cartilage using a poly-L-lactide scaffold. In a clinical study, it was inserted into subcutaneous areas of nasal dorsum in three patients, to correct cleft lip–nose deformity. The aim of this study was to helping evaluation on the efficacy of the regenerative cartilage.

Methods: 3D data of nasal shapes were compared between before and after surgery in computed tomography (CT) images. Morphological and qualitative changes of transplants in the body were also evaluated on MRI, for one year.

Results: The 3D data from CT images showed effective augmentation (>2 mm) of nasal dorsum in almost whole length, observed on the medial line of faces. It was maintained by 1 year post-surgery in all patients, while affected curves of nasal dorsum was not detected throughout the observation period. In magnetic resonance imaging (MRI), the images of transplanted cartilage had been observed until 1 year post-surgery. Those images were seemingly not straight when viewed from the longitudinal plain, and may have shown gentle adaptation to the surrounding nasal bones and alar cartilage tissues.

Conclusion: Those findings suggested the potential efficacy of this cartilage on improvement of cleft lip–nose deformity. A clinical trial is now being performed for industrialization.

1. Introduction

In regenerative medicine of cartilage, local cartilage defects of the knee and elbow joints have been repaired by autologous cell transplantation. Injection of suspension containing cultured articular chondrocytes suspension has been the main method of autologous chondrocyte transplantation [1], while another option was an application of mixture with collagen hydrogel [2]. In addition, bone marrow-derived [3], synovium-derived [4], and fat-derived [5] mesenchymal stem cells have been used as another cell sources. With those treatments, improvement of symptoms, such as pain, and tissue repair have been reported.

Otherwise, cartilage disease generally manifested variety in severity. It is not limited to local defects of articular cartilage, but also includes facial cartilage defects and hypoplasia that are accompanied by huge cartilage defects. Cleft lip and palate-

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associated nose deformity is one example. Its symptoms include a tilted low nose and lateral imbalance between the nasal alae [6]. This deformity has been treated by grafting autologous bone, autologous cartilage, or silicone implant into the nasal dorsum and apex. However, those treatments have disadvantages, such as that the nose becomes hard, curved, or exposed [7]. Some difficulty is derived from the point that no ideal material can be obtained among existing transplants. Introduction of innovative treatment, regenerative medicine, has been expected.

Because conventional regenerative cartilage was prepared with cell suspension [1] or mixture with gel [2], and had low mechanical strength, it was hardly applied for correction of cleft lip–nose deformity. We have developed tissue-engineered cartilage with 3D morphology and high mechanical strength using a biodegradable polymer (poly-L-lactide, PLLA) scaffold [8]. We termed it as an implant-type tissue-engineered cartilage. Using this implant-type tissue-engineered cartilage, we corrected nose deformity in cleft lip and palate patients as a clinical study [9]. In this clinical study, no serious adverse events that were associated with the tissue-engineered cartilage occurred throughout the postoperative 3 years. The efficacy was also confirmed by comparing the lateral cephalogram between before and after surgery, in which more than 2-mm augmentation was observed at 3 months after surgery and was maintained for 3 years.

However, only 2D evaluation could be made, when cephalograms were used for quantitative analyses. Since the nose is located in the center of the face and it has a protruding 3D structure, the corrected nose shape should be 3-dimensionally analyzed. Moreover, regarding information on internal properties of regenerative cartilage that used a scaffold material and was transplanted subcutaneously, few studies has been reported in which cartilage regeneration was confirmed in a biopsy specimen from patients [9]. No morphological or biochemical change in the whole transplants of regenerative cartilage has been reported, yet. Although computed tomography (CT) images hardly evaluate biological properties of cartilage in the body, magnetic resonance imaging (MRI) has been frequently used, in which, for example, a contrast agent-based MRI technique, delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC), reflects glycosaminoglycan content within cartilage [10]. In this study, we traced changes in transplanted regenerative cartilage in the body utilizing MRI images.

Thus, in a small cohort treated with implant-type tissue-engineered cartilage for nose deformity associated with cleft lip and palate (3 patients, 1 year of follow-up period), firstly, 3D data of nasal shapes were prepared from CT images and compared between before and after surgery to analyze 3D changes. Secondly, morphological and qualitative changes of transplants in the body were evaluated on MRI, aiming at helping evaluation on the efficacy of the implant-type regenerated cartilage.

2. Patients and methods

2.1. Patients and procedures

This study conformed with the Declaration of Helsinki. It followed the guidelines for clinical research using human stem cells formulated by the Ministry of Health, Labour and Welfare of Japan, and was approved by the Ethics Committee of the University of Tokyo and Minister of Health, Labour and Welfare of Japan. We recruited three patients with a nasal deformity caused by cleft lip and palate at the University of Tokyo Hospital (Tokyo, Japan). All patients gave written informed consent.

Detailed procedures were described in the previous paper [9]. 390 mL of autologous serum and 0.1 g of auricular cartilage were obtained from a patient. In the cell processing center of the University of Tokyo Hospital, chondrocytes were isolated from the auricular cartilage after collagenase digestion, and were cultured for 4 weeks in the medium containing the autologous serum with insulin and fibroblast growth factor 2 [11]. The chondrocytes were finally expanded to 240 million in cell number. Cultured chondrocytes were mixed with atelocollagen hydrogel (Atelocollagen implant, Koken, Tokyo, Japan) at the density of 10^8 cells/mL [12], and were then administered into the PLLA scaffold (pore size: approximately 200 μm, porosity: approximately 95%) with the dome-like shape of 50-mm long, 6-mm wide and 3-mm thick (KRI, Kyoto, Japan) [8], to make an implant-type tissue-engineered cartilage (Fig. 1a). All processes were recorded by traceability system.

In the transplantation of the implant-type tissue-engineered cartilage, the marginal incision of the bilateral nostrils was connected by a transcolumellar incision (gull-in-flight incision). A pocket was dissected over the nasal dorsum through the gull-flight-incision. The open method allowed direct vision of the cartilaginous and bony vault. The periosteum over the nasal bones was raised to enable a transplant to lie in close contact with the bones. The tissue-engineered cartilage was inserted into a subcutaneous pocket formed in the nasal dorsum (Fig. 1b). The curved nasal septum cartilage was removed and retransplanted into columella [13].

One woman and two men who presented with cleft lip–nose deformity were enrolled between December 13, 2010 and February 6, 2012. A twenty-five year old female (patient #1) was suffering from a right cleft lip (Fig. 2). The second patient (#2) was the twenty-one year old male, who was suffering from a bilateral cleft lip and palate. In this patient, a lip switch flap was also performed, in addition to the transplantation of tissue-engineered cartilage (Fig. 3). Patient #3 was a 22-year old male suffering from a left cleft lip and palate (Fig. 4). In this patient, we observed calcification in the area of the tissue-engineered cartilage (Fig. 4 bottom).

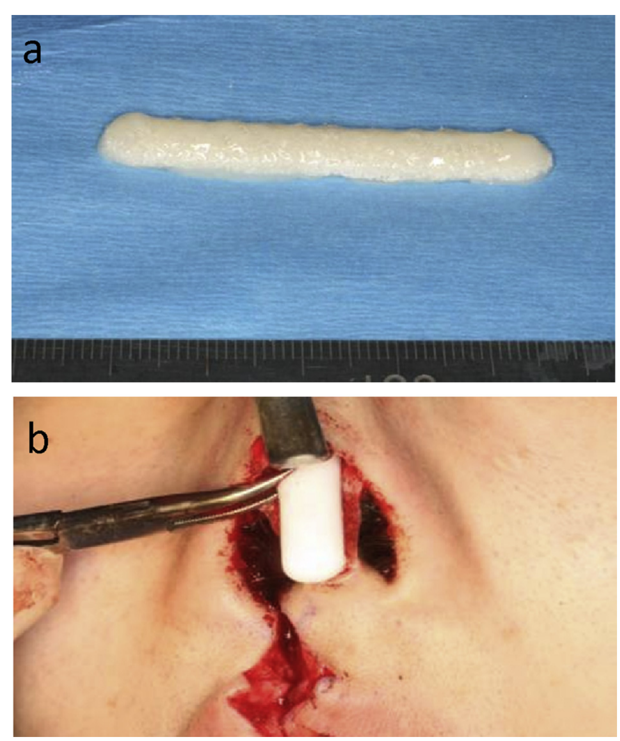

Fig. 1. Implant-type tissue-engineered cartilage. The tissue-engineered cartilage was dome-shaped with 5 cm long, 6 mm wide and 3 mm thick (a). It was carefully inserted into the nasal dorsum (b).