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Engineered autologous nasal cartilage for repair of nasal septal perforations: a case series

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Objective: This phase I clinical trial assessed the use of autologous nasal chondrocyte tissue-engineered cartilage (N-TEC) for functional repair of nasal septal perforations (NSP).

Background: The most widely used technique to treat NSP, namely interposition grafting with a polydioxanone (PDS) plate combined with a deep temporal fascia (DTF) graft, is still suboptimal towards patient satisfaction and revision rates.

Methods: Patients ($n = 5$, all female, age range: 23–54 years) had a 0.5–2.0 cm diameter NSP. N-TEC was manufactured by expansion and 3D culture of autologous nasal septum chondrocytes into Chondro-Gide collagen membranes. N-TEC was then shaped intraoperatively and enveloped in the harvested DTF before suturing it into the NSP. Safety (primary outcome) was assessed by the number of serious adverse reactions (SAR) until 12 months. Secondary outcomes included feasibility, assessed by surgical graft manipulation, and efficacy, assessed using subjective scoring (nasal obstruction symptom evaluation, NOSE, and visual analog scale, VAS, scores) and objective breathing function tests. Structural closure of NSP after 12 months was defined using endoscopy and computed tomography (CT) scans.

Results: NSP treatment by N-TEC implantation was safe and feasible, as no SAR and no challenge in graft manipulation was recorded for any of the patients. One year postoperative, subjective scoring improved in all patients, unless already optimal (average improvement of 23 and 28.6 points out of 100, respectively, for NOSE and VAS scores). Objective respiratory function overall confirmed – with the exception of one case – the observations above (average improvement of 172 ml/s). NSP were closed and the mucosae completely healed in three patients.

Conclusion: Autologous N-TEC is a valid treatment for NSP and warrants further clinical tests.

Keywords: autologous nasal chondrocyte tissue engineered cartilage, case series, nasal septal perforations, N-TEC, regenerative medicine, tissue engineered cartilage, tissue engineering

Introduction

Nasal septal perforation (NSP) is a medical condition characterized by the loss of cartilage and/or bony structures of the nasal septum, together with the mucoperichondrium and mucoperiosteum[1]. The prevalence of NSP is ~1–2%[2]. There are many causes of NSP, such as a history of nasal surgery (iatrogenic), trauma, self-infliction, drugs, chemical irritants, neoplastic causes, inflammatory causes (vasculitides and Wegener's granulomatosis), or infections (syphilis and tuberculosis)[3]. Perforation of the nasal septum creates pathological turbulence in the nasal airflow, resulting in a decrease in the normal humidification process[4]. Depending on the size and location of the septal perforation, patients have symptoms more or less severe such as epistaxis, rhinorrhea, crusting, whistling, nasal obstruction, pain, and saddle nose deformity[3]. Nasal septal perforations can be classified by size as small (maximal diameter <0.5 cm), medium (0.5–2 cm), or large (>2 cm)[5]. Surgical treatment of NSP is technically challenging and requires

HIGHLIGHTS

- Nasal septal perforation (NSP) can lead to nasal instability, obstruction, and pain.
- Standard treatment with alloplastic implant leads to suboptimal revisions rates.
- Engineered cartilage is an alternative implant for repair of medium-sized NSP.
- First implantations in patients demonstrated safety and closure of perforations.

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training and experience from surgeons. Numerous techniques have been developed for the repair and reconstruction of the nasal septum, including the use of local intranasal flaps with closure of the mucoperichondrium[6], alloplasts[7], pericranial flaps[8], and grafting with acellular human dermal allograft[9].

The generally accepted technique for the repair of medium septal perforations is interposition grafting with a polydioxanone (PDS) plate as an alloplastic implant, combined with a temporoparietal fascia (TPF), a deep temporal fascia (DTF) graft or a fascia graft. In this technique, closure or approximation of the mucosal edges across the perforation is usually not performed, because the sandwich graft provides a scaffold of mesenchymal origin for revascularization and mucosal regrowth[10]. However, there is no prospective, high-level evidence available for this approach, and most reported experiences with the use of a PDS plate for repair in NSP are based on a small case series with a level of evidence of 4[5,10–12]. In most studies, no comparator group was used (except one retrospective study), and a short postoperative follow-up of ~6 months was applied. Standard questionnaires, such as the Nasal Obstruction Symptom Evaluation (NOSE) score, are not consistently used to describe and assess patients' symptoms as the main efficacy criteria preoperative and postoperative. The PDS plate, as a synthetic material for repair in NSP, is a foreign material that can lead to infection, extrusion of the plate, and possibly an increase in thickness at the site of perforation repair with consecutive nasal obstruction. The success rate of this technique is sometimes reported to range from 86 to 100%, but only based on retrospective analysis at short observation times. Levin *et al.*[13] published in 2022 a systematic review of NSP reconstruction with a PDS plate, reporting reperforation in about 20% cases. The surgical site infection of PDS plates is also described to be at around 10% of cases[14].

Autologous septal cartilage in rhinoplasty is also widely used for nasal cartilage reconstruction because of its excellent biotolerance, elasticity, resistance, ease of shape, and viability, combined with minimal resorption rate and low infection and extrusion rates[15,16]. Additionally, patients generally prefer to receive biological autologous grafts. The major drawback on using autologous septal cartilage is that often insufficient healthy tissue is available. Alternative strategies, consisting on the grafting of cartilage from the auricular concha or rib[17], suffer from others disadvantages, such as additional surgery and associated donor-site morbidity.

To overcome the drawbacks of the currently available techniques in reconstructive surgery, the use of autologous Nasal chondrocyte Tissue-Engineered Cartilage (N-TEC) was proposed as an alternative graft material[18]. In a first-in-human trial with five patients, we already demonstrated that N-TEC can be engineered and safely used for successful functional restoration of alar lobules after tumor resection in patients[19]. Subsequently, N-TEC was also used for the repair of focal cartilage defects in the knee in phase I[20] and phase II trials.

In the current study, we assessed the use of N-TEC for functional repair of nasal septal perforations (NSP) as a new indication.

Methods

Study design and participants

In a prospective consecutive single-center case series (phase I clinical trial) at our university hospital, we treated between 7 May 2021 and 17 November 2021 five patients (all female, age range: 23–54 years) with a nasal septum perforation of medium size, that is, diameter comprised between 0.5 and 2.0 cm as measured by endoscopy. Patients with smaller or larger perforations, smokers (>10 cigarettes per day), or current cocaine abusers were excluded. The full list of inclusion and exclusion criteria are reported in Table 1.

All participants provided written informed consent before the initial screening procedures, including CT scans and blood tests. Follow-ups were performed 6 weeks, 3, 6, and 12 months postoperative. At these times, patients were examined clinically, assessed using endoscopy (to evaluate the closures of the wound) and rhinomanometry (to evaluate the air flow). In addition, patient-reported outcomes were collected using validated questionnaires, namely the visual analog scale (VAS)-Score (Table 2) and the validated NOSE-Score[21,22] . Patients were enrolled in the trial for 1 year and all adverse events were recorded throughout this time. At the last follow-up, an additional CT scan was performed.

This study conformed to the Declaration of Helsinki and was approved by the local ethical committee (Project ID: 2020-02431) and by the Swiss Agency for Therapeutic Products (Swissmedic, 701074 (previously 2020TpP1016). The grafts were produced at University Hospital Würzburg (manufacturing authorization number DE_BY_05_MIA_2017_0021/55.2-2678.4-19-8-21) and University Hospital Basel (manufacturing authorization number 511617). The clinical trial and production of Advanced Therapy Medicinal Products (ATMP) followed national and international guidelines. This study has been registered at ClinicalTrials.gov (NCT04633928, https://clinicaltrials.gov/study/NCT04633928?cond=nasal%20septal%20perforation&rank=3.This case series has been reported in line with the Preferred Reporting Of Case Series in Surgery (PROCESS) 2020 criteria[23].

Procedures

N-TEC manufacturing was performed according as described in Fulco *et al.* (2014) and Mumme *et al.* (2016)[19,20]. To avoid harvesting blood from patients, autologous serum was replaced with human platelet lysate (hPL) using a modified process[24].

The harvesting of a cartilage biopsy (0.49 cm^2 size) from the nasal septum was performed under local anesthesia by two plastic surgeons (one junior trainee with 3 years of surgical specialty training in Plastic Surgery and one consultant with more 25 years' experience in rhinosurgery) in the vicinity of the existing perforation. At the cephalic border of the septal perforation, preparation in the subperichondrial plane was performed on both sides to extract the biopsy specimen. The mucosa was closed with resorbable sutures, and tamponade was placed for 1–2 days.

The cartilage biopsy was transported in a transport medium (Dulbecco's modified Eagle's high glucose medium supplemented with 100 U/ml Penicillin and 100 µg/ml streptomycin) at 2–8° C via validated overnight transport procedures to a Good Manufacturing Practice (GMP) facility for engineering cartilage tissue according to GMP guidelines. After enzymatic digestion of the cartilage biopsy, chondrocytes were plated into culture dishes, expanded for 2 weeks in an established expansion medium, seeded on a collagen I/III membrane (Chondro-Gide, Geistlich), and cultured for an additional 2 weeks in a chondrogenic medium[19,20,24].

Table 1

Full list of inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Informed consent as documented by signature. • Age ≥ 18 years. • Nasal septal perforation of a medium size (diameter 0.5–2.0 cm), measured by endoscopy. • Patient willingness and ability to give written informed consent to the study and to comply with all study requirements, including attending all follow-up visits and assessments	• Pregnancy or breast feeding. • Intention to become pregnant. • Known or suspected noncompliance, drug (especially cocaine abuse unless stopped more than 6 months ago) or alcohol abuse • Smoking (more than 10 cigarettes/day). • Diabetes. • Inability to follow the procedures of the study, for example, due to language problems, psychological disorders, dementia, etc. of the participant. • Nasal septal perforation of a small (< 0.5 cm) or large size (> 2.0 cm). • Evidence of active infection with HIV, HBV or HCV, syphilis. • Known allergies to porcine collagen, penicillin, or streptomycin. • Chronic treatment with steroids or immunomodulatory drugs. • Patient is the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol or in a dependency or employment with the sponsor. • Patient is unable to understand the patient information. • Known systemic connective tissue disease. • Known autoimmune disease. • Known immunological suppressive disorder or is taking immunosuppressive. • Patient is currently systemically or intra-articularly taking steroids and/or has used steroids within the 30 days prior to treatment. • The patient has at the site of surgery an active systemic or local microbial infection, eczematization or inflammable skin alterations (including Protozoonosis: Babesiosis, Trypanosomiasis (e.g. Chagas-Disease), Leishmaniasis, persistent bacterial infections, such as Brucellosis, spotted and typhus fever, other Rickettsiosis, Leprosy, Recurrent Fever, Melioidosis or Tularemia). • Patient has an active cancer. • Patient is currently participating or has participated in any other clinical study within 3 months prior to the screening visit. • Patient has any other condition, which, in the opinion of the investigator, would make the patient unsuitable for the study. • Patient is unable to tolerate local anesthesia. • Intraoperative exclusion criteria: • size of perforation not in the range initially estimated (above 2 cm or below 0.5 cm)

Quality control tests for the release of the grafts included sterility (microbiological monitoring), endotoxin and mycoplasma testing, macroscopic appearance of the graft, cell viability (> 70%) and presence of cartilaginous extracellular matrix (ECM). Viability was estimated on Hematoxylin and Eosin stained tissue section. The content of ECM was assessed by grading Safranin-O stained tissue sections using the Modified Bern Score (MBS), which takes into account the amount of glycosaminoglycans as well as the morphology of the cells and ranges from 0 to 6. The release criterion was fulfilled with a MBS > 3[25].

Table 2

VAS score questionnaire.

How strong have been your problems with the following issues in the last 4 weeks? Please evaluate on a scale from 0 to 10, 0 means no problems, 10 means maximal severe problems. (Total scores range between 0 and 100).

1. Nasal breathing (0–10)
2. Esthetics of the nose (0–10)
3. Pain at the nose/septum (0–10)
4. Crusts in the nose (0–10)
5. Nasal bleeding (0–10)
6. Running nose (0–10)
7. Whistling of the nose (0–10)
8. Obstruction of the nose (0–10)
9. Disability in daily life and in your profession (0–10)
10. Disability in doing sport (0–10).

The second operation was performed by the same two plastic surgeons together with one ENT surgeon with more than 25 years' experience in rhinosurgery. The nasal septal perforation was visualized and the size was measured again by endoscopy during the second operation under general anesthesia. Access to the perforation was achieved either in a closed approach for three patients or in an open approach for two patients[26], depending on the size and location of the perforation. In the closed approach, a Kilian incision was made for submucosal and subperichondrial dissection of the entire cartilaginous septum beyond the septal perforation to the area of the perpendicular plate, keeping the mucoperichondrial flaps intact on both sides. In the open approach, an inverted V-shaped incision was made at the columella and a marginal incision was made in the domal area. Septal skeletonization was performed after flap elevation and midline preparation.

The deep temporal fascia was harvested before implantation. A horizontal incision was made at the mid-temporalis muscle

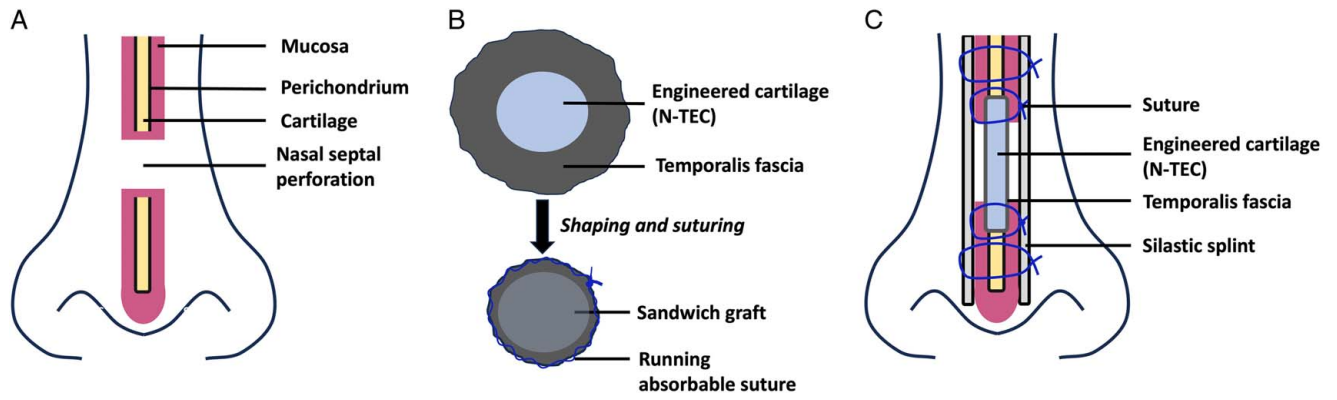

Figure 1. Scheme of the procedure: (A) Showing the nasal septal perforation. (B) Production of sandwich graft (N-TEC enveloped in temporalis fascia). (C) Reconstruction of the perforation with a sandwich graft. Covering of the sandwich graft with silastic splints from both sides over 6 weeks allowing mucosal regrowth.

level. After dissecting the subcutaneous tissue, the deep temporal fascia (DTF) was identified and harvested.

The N-TEC was shaped according to the size required for septal repair visualized by endoscopy (Fig. 1A) and covered from both sides under stretching with the harvested DTF (Fig. 1B). The DTF was sutured to the cartilage graft by using absorbable sutures.

The construct was placed to completely fill the space of the septal perforation, with an overlap of at least 2 mm in each direction (Fig. 1C). Closure of the mucosal defect was not necessary, as it grows from the side over the fascia. The medial crura was reapproximated using suturing. The septal flaps were closed using an absorbable mattress suture to close the potential space and construct the DTF-engineered autologous cartilage tissue in the correct position (Fig. 1C). The incision was closed. Finally, thin silastic splints were placed over the septum to cover the exposed DTF, maintain a constant moisture level, and then secured by suturing (Fig. 1C). The patient received prophylactic oral antibiotic therapy with cefuroxime 500 mg twice a day for 6 weeks, as long as the silastic splints were in place, as in the standard treatment with PDS foil.

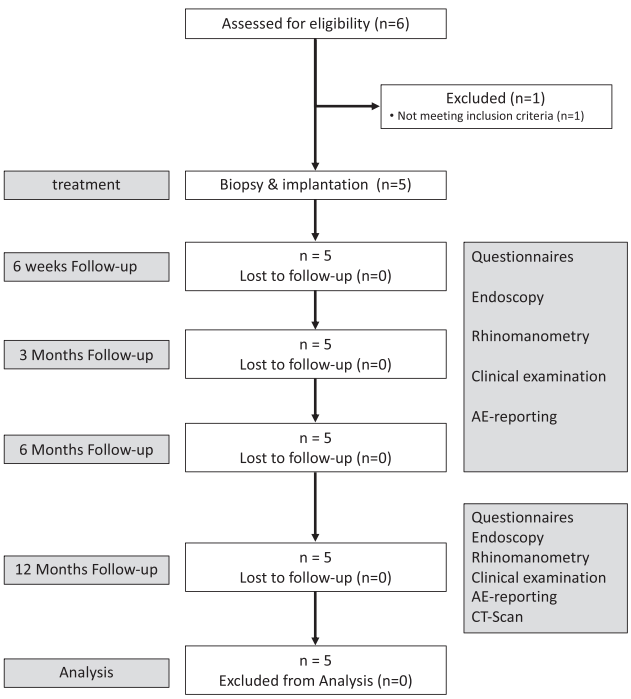

Figure 2. Study flow chart detailing all follow-ups and exclusions.

Outcomes

Primary outcome

The primary outcome of the study was the safety of the procedure until 12 months after the nasal septal reconstruction. Safety was established based on the number of (serious) adverse events ((S)AE), (serious) adverse reactions ((S)AR), and suspected unexpected serious adverse reactions (SUSAR) according to the International Conference on Harmonization (ICH) guidelines. All expected adverse reactions, either local (e.g. pain, swelling, or hematoma) or systemic (e.g. nausea and vomiting), were classified according to the Common Terminology Criteria for Adverse Events (CTCAE)[27].

Secondary outcomes

Secondary outcomes addressed feasibility and efficacy of the procedure. Feasibility was defined as successful surgical manipulation of the graft as an interposition graft combined with a temporoparietal fascia graft for the repair of nasal septal perforation. Efficacy was

defined 12 months after reconstruction as an improvement in breathing function and/or in self-assessed symptoms. Breathing function was measured subjectively using the self-assessed Nasal Obstruction Symptom Evaluation score (NOSE score)[22,23] and objectively by rhinomanometry-based quantification of the total respiratory flow rate during inspiration. The normal total air flow during inspiration is over 800 ml/s, 500–800 ml/s is defined as a low obstruction, 300–500 ml/s as moderate obstruction, and <300 ml/s as severe obstruction. Symptoms of NSP were assessed using a self-developed visual analog scale (VAS) score (Table 2), since at the start of the study no validated symptom score for NSP was available. Closure of the perforation was also assessed by endoscopy and CT scans after 12 months.

Table 3

Number of SAE and AR reported during the study.

Classification	Event	Months	# of patients (patient No)	Outcome
SAE	EBV and CMV infection	6	1 (No. 2)	Full recovery
AR	Bleeding after septal cartilage biopsy	0	1 (No. 1)	Full recovery
	Genital infection due to prophylactic antibiotic therapy	1	1 (No. 1)	Full recovery
	Rash in the face and neck due to prophylactic antibiotic therapy	0	1 (No. 5)	Full recovery
	External ear infection	2	1 (No. 1)	Full recovery
	Obstruction of nose	3/3/2	3 (No. 1 No. 2, No. 6)	Full recovery
	Reperforation of the septum	3/12	2 (No. 6, No 1)	1 reoperation

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or manuscript writing. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

We enrolled six women aged 23–54 years (average 39 years) with a medium size nasal septal perforation (min. 0.5 cm, max. 2 cm, average 1.1 cm) (Fig. 2). In one patient the perforation size was later recognized to have a diameter of >2 cm, leading to the exclusion of the patient as screening failure. The etiology was iatrogenic in four patients and in one patient unknown. One patient was a smoker (<10 cigarettes per day).

N-TEC fulfilling the defined release criteria were successfully manufactured for all five treated patients. Cell viability (89% ± 6.5) and cartilage quality (MBS = 4.7 ± 0.7) were all within the specified ranges (Supplementary Fig. 1A, Supplemental Digital Content 1, http://links.lww.com/JS9/D236). Histological analyses of portions of the N-TEC showed the presence of abundant glycosaminoglycan-positive extracellular matrix and round chondrocytes within the grafts (Supplementary Fig. 1B, Supplemental Digital Content 1, http://links.lww.com/JS9/D236).

No severe adverse reactions (SAR) were reported until 12 months postintervention. One serious adverse event (SAE) due to viral infection and three adverse events (AE), including two COVID-19 infections and one sinusitis, were recorded. Nine adverse reactions (AR) were recorded, generally related to concomitant treatment during graft application rather than to the graft itself (Table 3). Therefore, the study reached the primary outcome of safety.

All the generated N-TEC grafts could be intraoperatively enveloped and sutured into the fascia and the resulting sandwich grafts could be stably placed into the defects (Fig. 3B-E). Thus the procedure reached the secondary outcome of feasibility.

The NOSE score improved over time in all patients with the exception of No. 5, who had no preoperative obstruction symptoms (Fig. 4A). The VAS score improved (i.e. decreased) to different degrees in all patients (Fig. 4B), indicating the effectiveness of the treatment.

Respiratory flow rate during inspiration, measured by rhinomanometry, was slightly reduced only in Patient 6 (Fig. 4C). For patient No. 5 no preoperative measurements in rhinomanometry could be performed due to technical issues; postoperative, however, she had a high total airflow during inspiration, indicating a good breathing function.

Closure of the NSP and healing of the mucosa could be observed in 3 out of 5 patients 12 months after reconstruction, as assessed by endoscopy and CT scans. In two of the five patients (patients No. 1 and No. 6) we observed a small reperforation of 1 mm. Patient No. 6 was reoperated at her request because she was suffering of whistling. Representative images of patient No. 5 showing a healed perforation are reported in Figure 5. None of the patients had severe air restrictions during daily activities or sport practice and the pain level consistently decreased 1 year after reconstruction (Supplementary Fig. 2, Supplemental Digital Content 1, http://links.lww.com/JS9/D236). The esthetic evaluation of the nose by each patient did not change after the operation.

Discussion

In this phase I clinical trial, we demonstrated the safety and feasibility of reconstructing NSP of a medium size using autologous nasal chondrocyte tissue-engineered cartilage (N-TEC), with preliminary evidences of efficacy. No SARs or infections in the nose due to implantation of the graft were recorded in any patient. The preparation of a sandwich graft consisting of N-TEC and deep temporalis fascia (DTF), as well as the implantation of the sandwich graft into the defect for septal reconstruction, were possible in all patients without any challenge.

Subjective (NOSE and VAS scores) and objective (total airflow during inspiration) measurements of respiratory function established that the clinical outcomes were overall satisfactory in our small cohort. Improved NOSE and VAS scores did not systematically correlate with airflow values measured using rhinomanometry (for example, in patient No. 2). Although rhinomanometry provides more objective data, patient-reported outcomes are clinically more relevant and should be preferred as the primary outcome in future trials aiming at assessing efficacy. Although the VAS score here introduced has not been validated, the importance of these self-assessed data was confirmed through the validation of the NOSE-Perf scale, similar to our VAS score and published in 2021 while our phase I study was ongoing[28]. Such validated NOSE-Perf questionnaire evaluates the symptoms of NSP and could be used as a patient-reported outcome measure in further studies.

The perforation fully healed in three of the five patients after one year, as assessed by endoscopy and CT. Two patients exhibited a small reperforation, most likely related to an interface problem at the graft border. Indeed, the stiffness of the grafts – even if not objectively measured – was clearly lower than that of the surrounding native septum cartilage and such mechanical discontinuity in conjunction with expected micromovements could have hindered the formation of a stable interfacial tissue. However, reperforations typically occur also with the standard-of-care procedure and anyway

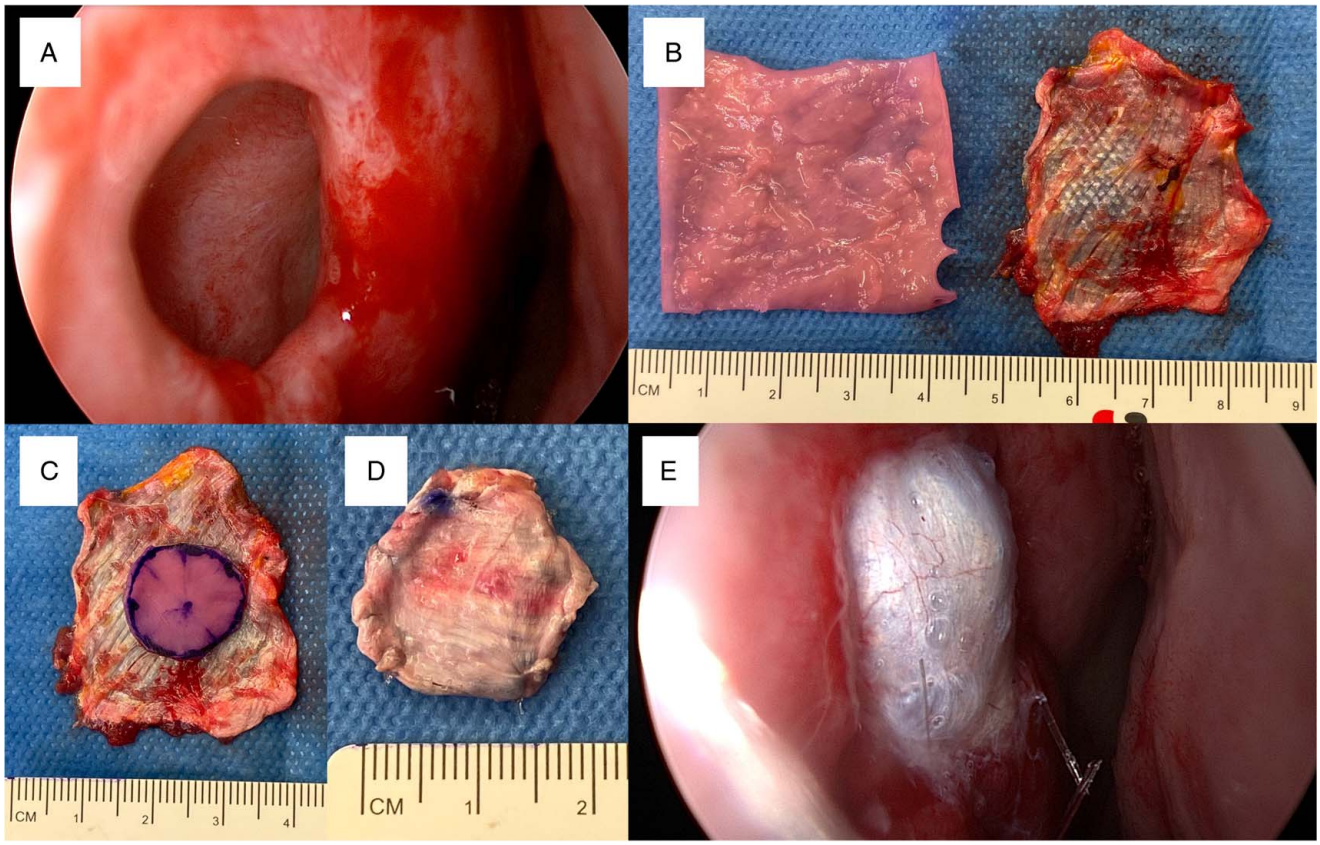

Figure 3. Feasibility: Intraoperative shaping and fixation of the sandwich graft in the defect: (A) Nasal septal perforation with a diameter of 0.7 cm. (B) Tissue engineered cartilage (N-TEC) (left side) and deep temporalis fascia (DTF) (right side). (C) Shaped N-TEC and (D) envelopment into the DTF to create the sandwich graft. (E) Final fixation of the sandwich graft into the defect shown as endoscopic picture of the left side of the septum.

did not prevent improvements in NOSE and VAS scores in the two patients (Patients 1 and 6) and increase in flow inspiration in one of them (Patient 1).

In this study, we decided to target medium-sized nasal septal perforations (NSP) for several reasons. First, this allowed to harmonize the patient population (i.e. an important requisite considering the small patient cohort). Second, medium-sized NSP are more common than larger perforations and their healing with standard procedure is often not optimal (thus more patients could benefit from our approach); smaller NSP perforations would, instead, not represent a proper indication, considering that their closure can be frequently achieved by the sole grafting of local mucosa flaps.

Obviously, assessment of efficacy beyond anecdotal experience requires a larger patient cohort, the introduction of additional indicators in imaging studies to assess cartilage changes (i.e. MRI), and precise definition of minimal clinically relevant improvements in patient-reported outcomes.

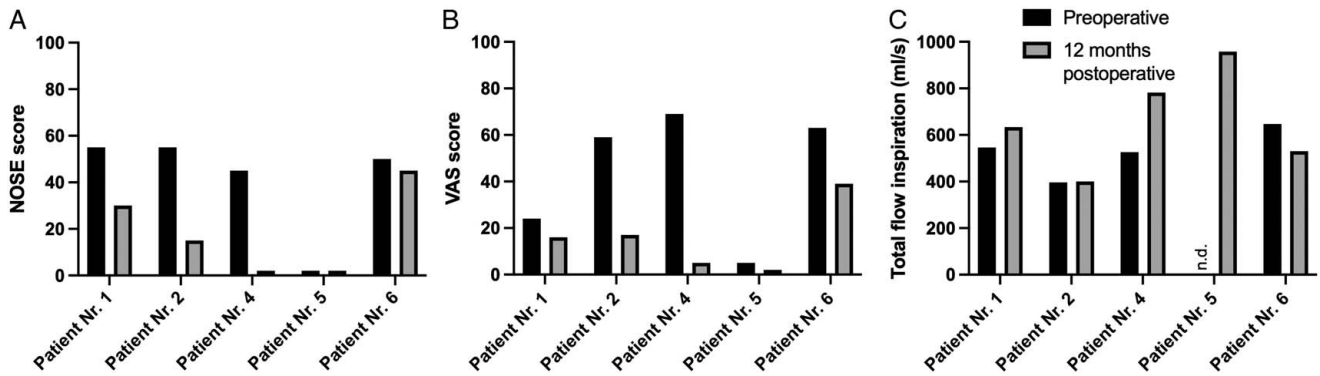

Figure 4. (A) NOSE score (0–100, 0: no symptoms, 100: severe obstruction), (B) VAS score (0–100, 0: no symptoms, 100: severe symptoms), (C) total flow inspiration (ml/s) are shown for all patients preoperative and 12 months postoperative (> 800 ml/s: normal, 500–800 ml/s: low obstruction, 300–500 ml/s: moderate obstruction, <300 ml/s: severe obstruction).

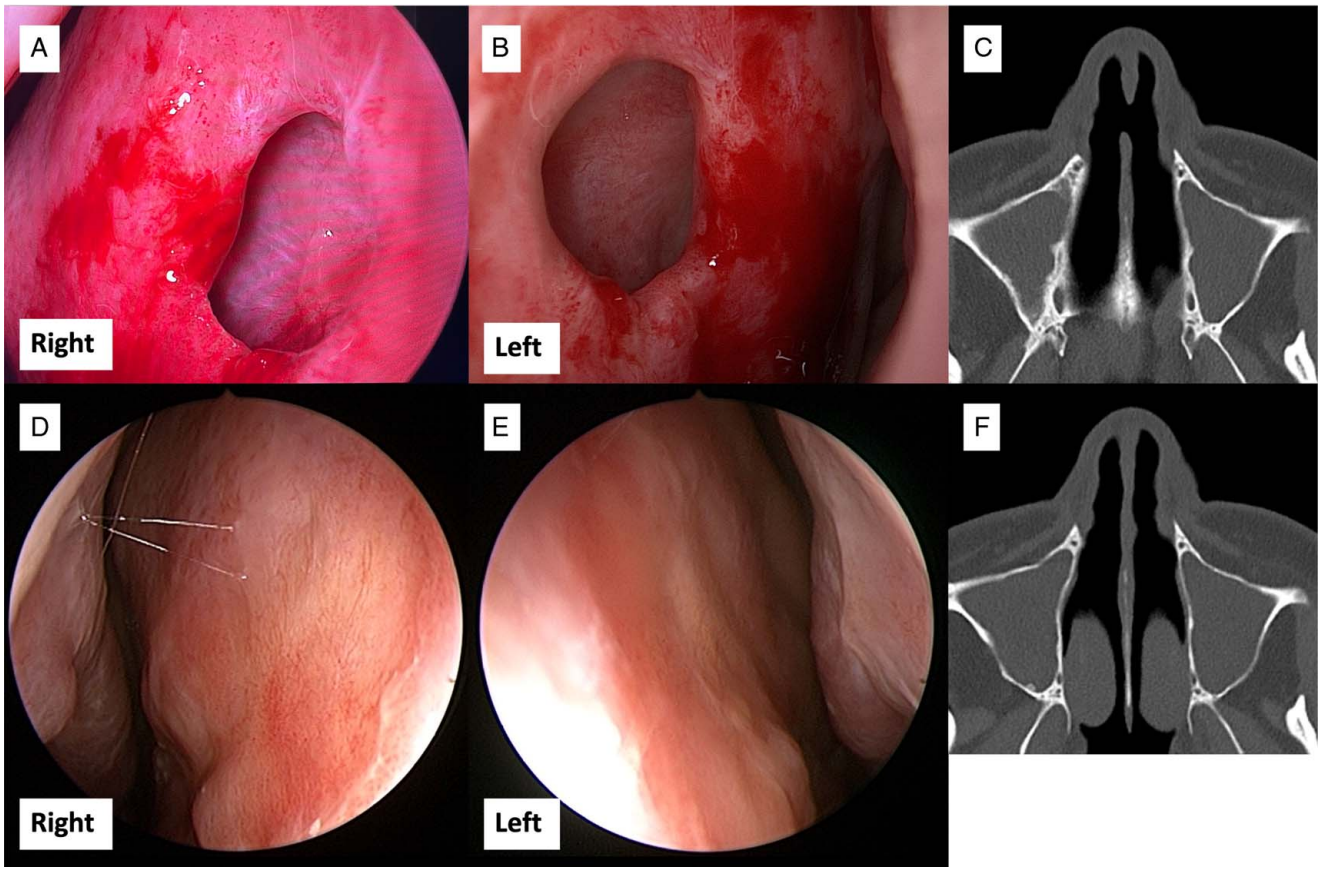

Figure 5. Endoscopy and CT scan of patient No. 5 (preoperative and postoperative): (A, B) Preoperative endoscopy shows on the right and left side the nasal septal perforation of around 7 mm, (C) the axial CT scan shows also the nasal septal perforation. (D, E) Postoperative endoscopy of the septum on the left and right side one year after the operation with a healed perforation. (F) The axial CT scan of the septum one year postoperative also shows a closure of the original perforation.

One important question that needs to be addressed in future studies is also the cost-effectiveness of N-TEC treatment when compared with the PDS-foil. Engineering of autologous cartilage tissues is demanding and costly, but it could be justified as second in line treatment or through a healthy economy analysis together with assessment of benefits in a comparative trial. In the future, the production of the tissue engineered cartilage grafts in a bioreactor system could lower costs and make the clinical application more interesting also from an economic perspective.

Future phase 2 clinical studies will be required to assess the effectiveness of our proposed strategy and to demonstrate whether it could be used for the treatment of larger NSP or for more challenging cases such as L-Strut reconstruction for the nasal framework in general, especially for saddle nose deformities. In the latter cases, however, the engineered cartilage should have higher mechanical properties, which would require longer graft cultivation times or use of two superimposed grafts. The use of N-TEC could also open new therapeutic options for more challenging facial reconstructions and unmet clinical needs such as treatment of empty nose syndrome and microtia.

Conclusions

We report for the first time that N-TEC can be safely used for the repair of NSP, with first evidences of efficacy based on patient-reported outcomes. Our study warrants a controlled trial in which the long-term outcome of the procedure is prospectively compared with PDS foil with DTF as the most accepted therapy.

Ethical approval

This study conformed to the Declaration of Helsinki and was approved by the ethical committee (Ethikkommission Nord-West und Zentralschweiz (EKNZ) BASEC-ID:2020-02431) and by the Swiss Agency for Therapeutic Products (Swissmedic, 701074 (previously 2020TpP1016).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Source of funding

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Author contribution

B.D.: conception and design, acquisition of data, analysis and interpretation of data, and writing original draft; S.M., A.W., O.P., M.E., I.F., and J.V.: analysis and interpretation of data, review of the article, and editing; D.J.S., I.M., A.B., I.M., and M.D.H.: conception and design, interpretation of data, review of the article, and editing. All authors give final approval of the version to be published.

Conflicts of interest disclosure

The authors have declared that no competing interests exist. The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Research registration unique identifying number (UIN)

This study conformed to the Declaration of Helsinki and was approved by the ethical committee. This study is registered with clinicaltrials.gov and the unique identifying number is NCT04633928.

Guarantor

Martin Haug.

Data availability statement

The authors declare that the main data supporting the findings of this study are available within the paper and its Supplementary Information. All data generated for this study are available from the corresponding author upon reasonable request.

Provenance and peer review

No invited.

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