The Journal of International Advanced Otology

J Int Adv Otol 2023; 19(4): 311–317 • DOI: 10.5152/iao.2023.221009

Original Article

Autologous Fat Injection for the Treatment of Patulous Eustachian Tube

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Cite this article as: Chen J, Xiong H, Chen Y, Yang H. Autologous fat injection for the treatment of patulous eustachian tube. *J Int Adv Otol.* 2023;19(4):311-317.

BACKGROUND: Patulous eustachian tube is a disorder that leads to disturbing symptoms such as autophony, respiratory noise, and aural fullness. There has not been an established treatment found for this disorder. This study aims to assess the efficacy of autologous fat injection for a novel treatment of patients with patulous eustachian tube.

METHODS: Twenty-eight patients with refractory patulous eustachian tube were recruited for the study. Endoscopic autologous fat injection was performed submucosally into the anterior and posterior portion of the pharyngeal orifice of the eustachian tube. The outcomes were quantitatively assessed by comparing the difference between pre- and postoperative scores with the visual analog scale on 4 criteria: aural fullness, respiratory noise, tinnitus, and autophony.

RESULTS: Autologous fat injection was performed successfully in all patients without major complications. According to the combined visual analog scale scores, after the treatments, 20 patients showed significant improvement and 6 showed moderate improvement. The overall success rate of the treatment was 92.9%.

CONCLUSION: Autologous fat injection is an effective and safe procedure for the treatment of patulous eustachian tube.

KEYWORDS: Adipocyte-derived stem cell, autologous fat injection, patulous eustachian tube, reconstructive surgery, visual analog scale

INTRODUCTION

The eustachian tube (ET) connects the middle ear with the nasopharynx to allow for air exchange, middle ear pressure equalization, and drainage, which is thus crucial in maintaining the health of the middle ear.[1,2] The ET is normally closed, with the cartilaginous mucosal surfaces in contact at the ET orifice, and only opens transiently during swallowing, yawning, mouth opening, or blowing the nose for ventilation.[1,3] This could avoid the nasopharyngeal secretions into the tympanic chamber and transmission of physiological noise such as breathing.[1]

A patulous eustachian tube (PET) is defined as pathologic patency of the ET.[4] Primary symptoms of PET mainly include autophony (hearing one's own voice), enhanced respiratory noise, aural fullness, and sometimes tinnitus, hearing loss, and vertigo.[4,5] The symptoms could be temporarily alleviated in a supine position or nasal congestion in an upper respiratory tract infection.[6] The symptoms of PET, particularly the autophony, could pose a great burden to the patients and in severe cases lead to depression or suicide.[4]

The etiology of PET is still a contentious topic. However, it is suspected to be originated from loss of soft tissue in the medial cartilaginous portion of the ET.[4] Patulous eustachian tube could have a hormonal correlate, given its common involvement in rapid weight loss (usually due to malignancy or eating disorders), pregnancy, or hormonal therapy for prostate cancer.[7,8] Observations of hypermobility of the tympanic membrane were also frequently seen in the otoscopy of PET patients, where the membrane freely moves in and out with respiration.[7]

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Received: December 02, 2022 • **Accepted:** March 19, 2023 • **Publication Date:** July 31, 2023
Available online at www.advancedotology.org

Despite the fact that PET is a widely recognized disorder, there has not been a universally accepted treatment. Current interventions include medical treatments and surgical treatments, the efficacy of which remained unsatisfactory. Medical treatments include intranasal, intra tubal/intratympanic administrations of saline,[9] salicylic and boric acid powder,[10] diluted hydrochloric acid, chlorobutanol and benzyl alcohol,[11] and saturated potassium iodide solution.[12] These treatments have shown moderate effects, but they generally require long-term medication.[2] Surgical treatments, on the other hand, mainly include mass loading of the tympanic membrane to reduce tympanic mobility (Boedts, 2014; Si et al., 2016), or introducing materials into the ET orifice to facilitate the occlusion of the ET, such as endoscopic reconstruction of ET, endoscopic endonasal multilayer closure, and ventilation tube placement.[13,14] However, no reliable conclusion can yet be drawn regarding an optimal surgical approach for PET, because of the limited sample sizes and varied outcomes of these studies.[2]

Autologous fat grafting has been widely used in cosmetic and reconstructive plastic surgeries.[15,16] It has the benefit of ready availability, easy obtainability, and biocompatibility, and therefore is an ideal filling material for reconstructing deformed body parts.[17,18] It has shown preliminary success in a previous study in treating PET,[19] which adopted a surgical approach involving fat grafting with cauterization and suture ligation, as well as myringotomy tube placement. In the current study, we would further attempt a different approach using autologous fat injection, which is minimally invasive and does not require the placement of a ventilation tube. The objective of this study is to evaluate the efficacy of this approach, that is, the autologous fat injection technique in treating PET.

MATERIAL AND METHODS

Patients

A total of 28 PET patients were included in this study, and their age was between 12 and 68 (39.5 ± 12.12, 12 females). Patients who fit all 3 criteria below were diagnosed as PET:

1. having one or more of the following symptoms: aural fullness, autophony, respiratory noise, and subjective tinnitus;[4]
2. Showing significant improvement of the symptoms after the body is in a forward/supine position or sealing the pharyngeal opening of the eustachian tube;
3. showing positive outcomes in at least one of the following objective checks: tympanic membrane hypermobility with respiration observed with an endoscope; Valsalva examination showing tympanum pressure differential (MED = $P_{max} - P_{min}$) > 100 daPa; and simultaneous changes in tympanum pressure and nasopharyngeal pressure

All of the recruited patients had undergone conservative treatments for at least 1 month without any improvement by the time of the recruitment. No prior surgery on these ears was performed. Symptom duration of PET within the recruited patients ranged from 6 months to 4 years, with a median of 12 months. Two of these patients were in a post-radiotherapy status for nasopharyngeal carcinoma. The postoperative follow-up duration ranged from 12 to 26 months, averaging 14 months.

A written consent form was obtained from each patient, and the study was approved by the Institution Review Board of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval number: SYSKY-2023-852-01, Date: 2023.08.10).

Figure 1 demonstrates a typical PET from one of the patients: The nasopharyngeal orifice of the right ET was significantly enlarged in comparison to the contralateral one, observed under nasopharyngoscopy (Figure 1A). Endoscopy showed abnormal mobility of the tympanic membrane in the right ear that moved outward and inward with respiration (Figure 1B). The whole length of the ET lumen was clearly visualized with computed tomography (Figure 1C) and multiplanar reconstruction under resting condition (Figure 1D).

Given that there is no validated objective assessment of symptom severity for PET, in this study, we adopted a subjective measurement with the visual analog scale (VAS). The VAS is an instrument devised to measure a characteristic or attitude that ranges across a continuum and cannot be directly measured.[20] It has been widely used in clinical research for measurement of symptom severity especially in pain research.[21] The scale includes a 10-cm long line segment, with 0 indicating no symptom at all, 10 indicating severe symptoms, and the middle indicating various degrees of symptoms. In the current study, in order to fully cover the various symptoms pertaining to PET, we performed VAS tests on 4 criteria: aural fullness, respiratory noise, tinnitus, and autophony. Pre- and postoperative (collected at 12 months after the surgery) VAS scores on these 4 criteria were collected and analyzed, based on which a total improvement score (TIS) was calculated as a comprehensive assessment for the effectiveness of the treatment. For details, see the statistical procedures in the "Statistical Analysis" section.

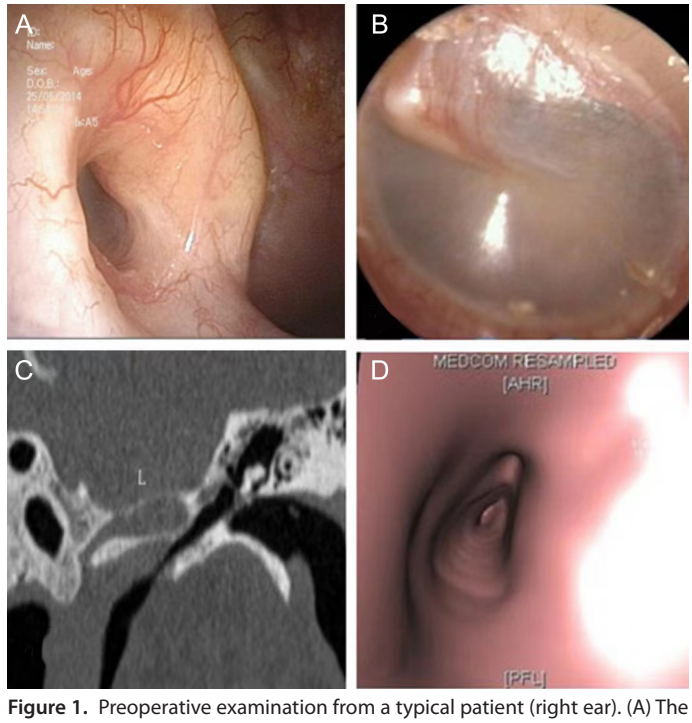

Figure 1. Preoperative examination from a typical patient (right ear). (A) The dilation of eustachian tube was observed under the endoscope. (B) The thin tympanic membrane was observed under the endoscope. (C) The dilation of eustachian tube was viewed by CT. (D) The opening of the tubal valve by 3-dimensional reconstruction. CT, computed tomography.

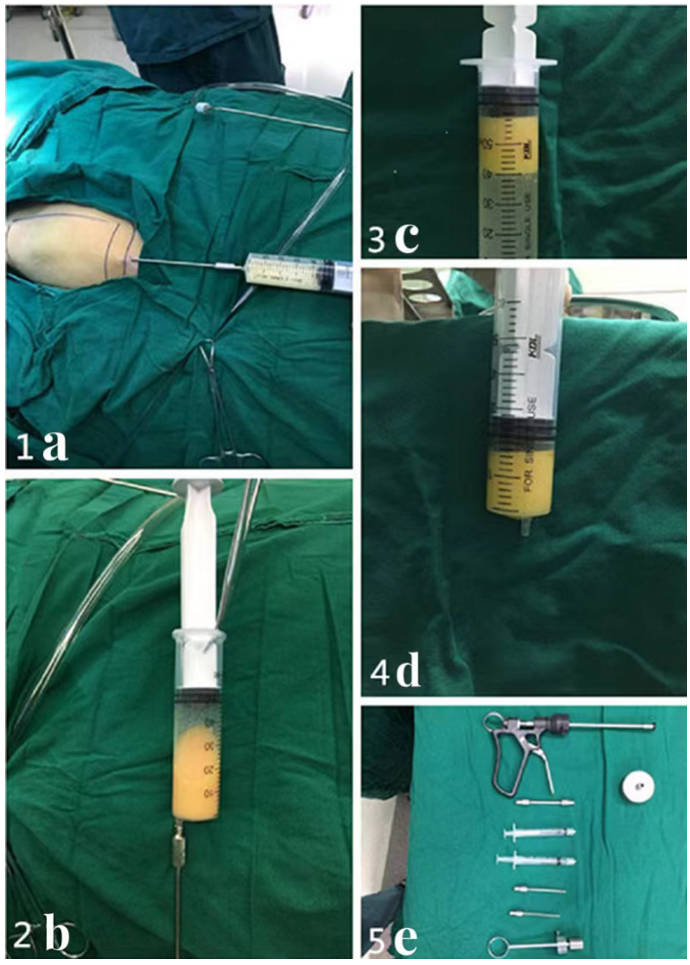

Figure 2. The fat harvesting procedure. (A) Harvesting site. (B) Harvested fat. (C) After sedimentation. (D) After centrifugation. (E) Apparatus for the procedure.

Surgical Procedure

Patients agreed to autologous fat injection for their PET treatment after receiving detailed explanations concerning the surgery. All surgeries were performed under general anesthesia. The donor site for fat harvest is the thigh. Two percentage of lidocaine infiltrating fluid (500 mL saline plus 1 mg epinephrine) was injected into the subcutaneous fat layer of the thigh with a syringe.[15] Adipose tissue was harvested with an aspiration cannula attached to a vacuum extractor, and 4-5 mL of tissue was extracted. The extracted tissue was washed with 4° physiological saline. Centrifugation was set at 3000 rpm for 3 minutes.[3,7] The purified tissues were then filled in a syringe. Adrenaline cotton was used to shrink the nasal cavity to help insert the instrument to the nasopharynx.[22] Multisite injections were targeted at 12 o'clock, 3 o'clock, 6 o'clock, and 9 o'clock positions of the pharyngeal orifice submucosa tissue of the ET. To avoid absorption of the autologous fat and ensure effect of the treatment, injections was made into the Ostmann's fat pad, and the volume of the injections large enough (2-3 ml in total) until the sunken mucosa was filled (see Figure 2 for demonstration of the surgical details). Eustachian tube orifice was significantly reduced under a 0° 4-mm nasal endoscopy (usually 0.5-1 mL at each subsite, seen in Figure 3).[13] The patients can be discharged on the second day after the surgery, after being advised to avoid habitual sniffing, as well as to try to properly gain weight so as to ensure optimal condition for fat survival.

Statistical Analysis

Analyses of the outcome measures were performed using Statistical Package for Social Sciences software version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Pre- and postoperative VAS scores on aural fullness, respiratory noise, tinnitus, and autophony were analyzed using the Wilcoxon matched-pairs signed-rank test. The significance level of the result was thresholded at $P < .05$. The results were further corrected for false discoveries from repeated measures using the Bonferroni procedures, in which the original alpha level was adjusted with the number of tests, so that a corrected alpha level of 0.0125 (0.05 divided by 4) was used for the results to be considered significant. After collection and analyses of the individual VAS scores, a further general evaluation of treatment efficacy was performed for each patient, by calculating a TIS. The TIS is calculated by simply adding up the 4 difference scores between pre- and postoperative tests (pre- minus post-), which indicated the extent of overall improvement brought upon by the treatment. Four levels of efficacy were defined based on the TIS: significantly improved if TIS ≥ 12 (indicating an average improvement of at least 3 for each of the 4 tests); improved if 12 > TIS ≥ 6 (indicating an average improvement of at least 1.5 for each test); not improved if 6 > TIS ≥ 0 (indicating a negligible or inconsistent improvement), and worsened if TIS < 0. This general evaluation was a comprehensive reflection of the treatment outcomes and was used for a final assessment of the success rate of the treatment, in which the top 2 levels (significantly improved and improved) were counted as successful.

RESULTS

As shown in Figure 4, the comparisons between pre- and postoperative VAS scores in the 4 criteria were all significant (aural fullness: $Z = -4.637$, $P < .001$; respiratory noise: $Z = -4.316$, $P < .001$; tinnitus: $Z = -4.164$, $P < .001$; autophony: $Z = -4.396$, $P < .001$). For the general evaluation, a total of 20 patients showed significant improvement, 6 showed moderate improvement, and 2 remained the same. No

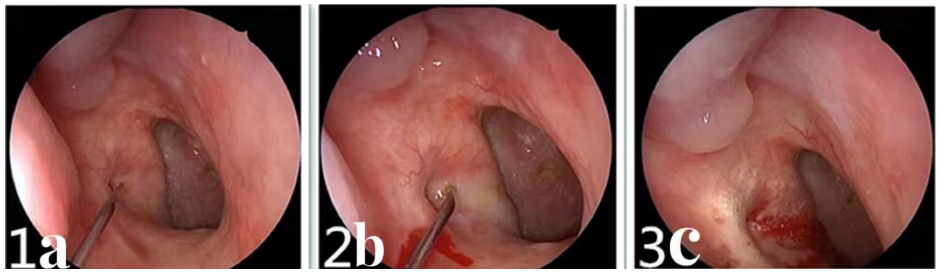

Figure 3. The procedure of intraoperative injection. (A) Initiating the injection. (B) The mucous membrane turned pale when the adipose tissue was being injected. (C) After injection.

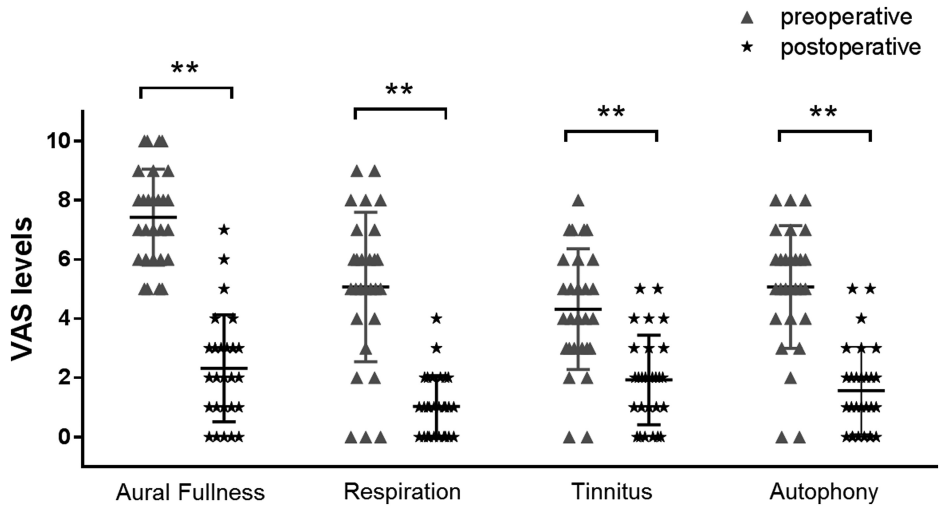

Figure 4. Comparisons of the pre- and postoperative VAS scores in 4 criteria. The analyses were performed using the Wilcoxon matched-pairs signed-rank test. Results shown were corrected for multiple comparisons using the Bonferroni procedure, in which the corrected alpha level was 0.0125 (dividing 0.05 by 4, the number of tests). In this figure, the "**" symbol corresponds to $P < .001$. VAS, visual analog scale.

patients got worse (see Table 1 for details and Table 2 for a summary of the results). The total success rate of the treatment is 92.9%.

All procedures were performed successfully without major complications. One patient was ineffective after the first injection and was reinjected 2 weeks later. Two patients experienced transient otitis media with effusion for 2 weeks. Further endoscopy observation found in all cases a markedly narrow pharyngeal orifice of the ET, as well as no more tympanic membrane hypermobility.

DISCUSSION

In this study, we attempted autologous fat injection as a treatment for PET on 28 patients. Visual analog scale scores showed significant improvements after the treatment in all 4 criteria: aural fullness, respiratory noise, tinnitus, and autophony. General assessment measured a success rate of 92.9%, and no major complications were found during the follow-up period. These results demonstrated that autologous fat injection could be an effective treatment option for PET.

Various previous attempts have been made in search of an optimal intervention approach for the treatment of PET, whereas a satisfactory outcome has yet to be achieved. Medical interventions for PET could usually provide only temporary relief of the symptoms.[23] Current surgical interventions, on the other hand, have not accumulated enough data to support a definitive conclusion. One of the current surgical procedures targets mass loading the tympanic membrane. For instance, 2 recent studies attempted a novel approach of paper patching to the tympanic membrane to alleviate symptoms. Unfortunately, this approach seems to be limited in long-term effects, in which the symptoms tend to recur after a period.[24] Another line of research concentrates on ET occlusion, with ET plugging cautery of the ET orifice, material injection, muscle ligation, etc., from which the collective outcomes were assessed to be 72.4%.[23] For instance, placement of a trans-tympanic catheter was a relatively common procedure, with an 82.9% success rate.[25] However, this approach suffers from the risk of developing long-term otitis media with effusion.[2,25] In the attempt to occlude the ET, various materials have been tried as filler materials, such as polydimethylsiloxane elastomer and hydroxyapatite, were injected into the submucosa ET orifice.[3] However, artificial materials suffer from poor biocompatibility, which in bad cases could cause serious consequences such as arterial thrombosis.[2]

An ideal filler material for deformity reconstruction should be readily available, easily obtainable, with low donor-site morbidity; reusable; inexpensive; versatile; and biocompatible.[17] Autologous cartilage has some of the above qualities and is a viable candidate for this line of clinical applications. One research has attempted tragal cartilage insertion into the concavity of the ET valve and received a 64.3% satisfactory improvement rate[13]; another study attempted using autologous cartilage injection[26] and achieved a success rate of 69.7%. Unfortunately, these moderate outcomes, as well as the limited sample sizes, are insufficient to draw any conclusions.

Autologous fat has been proposed to be an ideal filler material.[18] Autologous fat transplantation has become popular since the first half of the 20th century and has gained a wide range of clinical applications especially in plastic surgeries.[17] However, it gained a bad reputation in the 1950s, given primarily for its absorption rate, which could range between 25% and 75%.[27] This renders unpredictable outcomes for treatments and thus discouraged surgeons.[17] After that, a different perspective was brought upon by a series of studies done by Coleman[28] with modifications to the methods in treating the adipose tissue, and it was demonstrated that survival of the fat graft depends critically on the procedure of the harvesting, processing, and application of the tissue, in which vital adipocytes and the proportion of the adipose-derived stem cells and preadipocytes would determine the regeneration speed of the graft.[29,30] In addition, the transplant could stimulate the paracrine effect, in which revascularization starting from the periphery of the graft would take place and facilitate tissue growth and development.[31,32]

Two previous studies have also used autologous fat in treating PET.[7,19] Although Doherty's research has too limited sample sizes (2 cases) for any meaningful conclusions to be drawn, Rotenberg et al's[19] research did show promise for this method (85.7% for 14 ears). They used

Table 1. Detailed Scores from All the Subjects in the Pre- and Postoperative VAS Tests

No.	AF_pre	AF_post	RN_pre	RN_post	Tinn_pre	Tinn_post	Auto_pre	Auto_post	TIS	Effect
1	8	3	6	1	4	3	6	0	17	S
2	9	0	6	1	5	2	5	3	19	S
3	8	2	4	1	4	4	5	1	13	S
4	7	3	0	0	0	0	4	2	6	I
5	6	1	3	1	2	1	6	4	10	I
6	8	7	0	0	3	2	0	0	2	N
7	5	3	5	1	6	5	5	5	7	I
8	7	1	2	4	2	1	4	2	7	I
9	6	5	0	0	3	2	0	0	2	N
10	8	0	5	0	5	5	6	3	16	S
11	9	6	6	2	3	4	7	2	11	I
12	10	3	8	1	0	0	5	1	18	S
13	8	3	7	2	4	2	8	5	15	S
14	6	2	5	3	3	2	3	1	9	I
15	7	1	5	0	4	3	6	2	16	S
16	5	3	9	2	5	4	3	1	12	S
17	6	0	5	0	3	0	5	2	17	S
18	5	1	6	2	6	3	6	3	14	S
19	7	3	6	1	7	2	6	0	18	S
20	6	2	8	2	5	1	5	2	17	S
21	10	0	5	0	7	0	8	0	30	S
22	10	2	7	1	4	2	6	1	21	S
23	8	4	8	1	6	0	7	0	24	S
24	9	4	9	0	5	1	8	1	25	S
25	10	3	6	0	7	0	5	0	25	S
26	7	1	2	0	7	1	4	2	16	S
27	8	2	4	2	8	2	7	1	20	S
28	5	0	5	1	3	2	2	0	12	S

AF, RN, Tinn, Auto represents aural fullness, respiratory noise, subjective tinnitus and autophony. S, I, and N represents Significantly improved, Improved and Unchanged. TIS, total improvement score; VAS, visual analog scale.

autologous fat grafts in combination with endoluminal cauterization, suture ligation, and placement of a ventilation tube. Unfortunately, the size of their sample and the length of their follow-up period (6 months) were too limited for a decisive conclusion. In our study, we adopted a (slightly) larger sample size, a prolonged follow-up, and more importantly, a simpler surgical procedure with a possibly better approach in handling the graft material. The sedimentation and centrifugation procedures in our method have been proposed to be able to optimize the separation of debris and superfluous tumescent fluid, so as to preserve the vital contents in the adipose tissue such as stem cells and the angiogenic growth factors.[28,33] In our study, no obvious absorption was observed after the transplant during the follow-up period.

Table 2. Treatment Outcomes for the Autologous Fat Injection

Outcome Grade	n	%
Significantly improved	20	71.4
Improved	6	21.4
Unchanged	2	7.1
Worsened	0	0
Total (significantly improved + improved)	26	92.9

Several issues concerning this study should be noted. First, although comparable to other recently published literatures, the sample size of this current study is still not ideal. In addition, the subjective nature of the outcome assessment, as well as the arbitrary choice of the cut-off points in evaluating the success rate, is susceptible to biases. Unfortunately, according to a review on treatment efficacies of PET, there has not been an ideal solution to these problems in so far, given that a vast majority of studies use subjective symptom reports from the patients as criteria for efficacy evaluation.[2] A few of these studies adopted endoscopy or tympanometry as objective measures, in addition to symptom reports, to evaluate the treatment outcome.[22] However, these objective measures have a poor correlation with the symptom severity of PET and were thus not reliable as evaluation tools.[2] In order to address this problem, in our study, we utilized

a combination of subjective scales on 4 major symptoms of PET for assessing the outcomes, aural fullness, respiratory noise, tinnitus, and autophony. We believe by doing this, the assessment could be more comprehensive. However, compared to other studies with outcome assessments using a single criterion, pooling results from different criteria could also pose a potential risk of exaggerating the positive outcome. Furthermore, absorption of the injected fat over time is a major issue in fat autotransplantation, which was proposed to vary from 25% to 70%.[17] The 1-year follow-up period of this study might not be long enough to ensure fat survival and success of the treatment after that. Taken it all together, the results of the current study should be interpreted with caution. Second, the various situations of the individual outcomes suggested the need for further investigation into a more refined way for the decision of the volume of injected materials. For instance, the need for a secondary intervention in 1 patient could be the result of insufficient amount of adipose tissue injected for the first time (after the second injection, the patient had a full recovery), and the 2 patients who experienced transient otitis media with effusion, could, in turn, be the result of an excessive amount of injected fat, which could have led to temporary obstruction of ET. The volume of the injection was crucial for the success of the surgery. In current procedures, we generally added one-third to the expected volume for the injections to compensate for the possible absorption. A more refined and accurate method for volume decision calls for further explorations. Lastly, there were 2 patients with no improvement, although their pharyngeal ET orifice was found to be much narrower as compared with that before the operation. Given the subjectivity in our outcome measurements, the correlation between the degree of ET patency and severity of symptoms is not always straightforward. There could be other factors contributing to the symptoms. Further research should be conducted to address these issues.

In search of a minimally invasive, safe, and simple procedure for reconstructing the ET for PET patients, autologous fat injection could be a feasible option. Based on the current study, it is successful in improving symptoms of aural fullness, respiratory noise, tinnitus, and autophony, with a high success rate and no long-term complications. With further validation from more studies with larger sample sizes, it could have the potential to be widely used in a clinical setting.

Ethics Committee Approval: This study was approved by Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval number: SYSKY-2023-852-01, Date: 2023.08.10).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.Y., H.X.; Design – H.Y., H.X.; Supervision – H.X., Y.C.; Resources – H.Y., H.X.; Materials – H.Y., H.X.; Data Collection and/or Processing – J.C., Y.C.; Analysis and/or Interpretation – J.C., Y.C.; Literature Search – J.C., Y.C.; Writing – J.C., H.X.; Critical Review – H.Y., H.X.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study was funded by Guangdong Basic and Applied Basic Research Foundation (grant number 2021A1515010301 to H. Yang) and Guangzhou Science and Technology Foundation (grant number 202102010265 to H. Yang).

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