Development of HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) Therapy in Inferior Turbinate Hypertrophy

Joon Kon Kim\textsuperscript{1*}, Sung-Woo Cho\textsuperscript{1*}, Hyojin Kim\textsuperscript{3}, Sung Chan Jo\textsuperscript{4}, Hyung Gu Kim\textsuperscript{5}, Tae-Bin Won\textsuperscript{1}, Jeong-Whun Kim\textsuperscript{1}, Jae Hyun Lim\textsuperscript{6}, Chae-Seo Rhee\textsuperscript{1,2}

*These authors contributed equally to this manuscript

\textsuperscript{1}Department of Otorhinolaryngology- Head and Neck Surgery, Seoul National University Bundang Hospital, Seongnam, Korea

\textsuperscript{2}Department of Otorhinolaryngology- Head and Neck Surgery, Seoul National University College of Medicine, Seoul, Korea

\textsuperscript{3}Department of Pathology, Seoul National University Bundang Hospital, Seongnam, Korea

\textsuperscript{4}KORUST Company Limited

\textsuperscript{5}Department of Otorhinolaryngology- Head and Neck Surgery, Hanyang National University Guri Hospital, Guri, Korea

\textsuperscript{6}Department of Otorhinolaryngology-Head and Neck Surgery, National Police Hospital, Seoul, Korea

Running title: HIFU therapy in inferior turbinate hypertrophy

Corresponding author: Chae-Seo Rhee, MD, PhD

Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization: JWK, SWC, and CSR; Data curation: SWC, JKK, and JHL; Formal analysis: JKK; Methodology: CSR, SWC, JKK, HGK, SCJ, HJK and TBW; Writing-original draft: JKK and CSW; Writing-review & editing: SWC, JKK and CSR

ORCID ID:
Joon Kon Kim 0000-0002-6902-476X
Sung-Woo Cho 0000-0003-0827-4471
Hyojin Kim 0000-0001-9201-8328
Sung Chan Jo 0000-0003-2005-9854
Hyung Gu Kim 0000-0002-7847-8843
Tae-Bin Won 0000-0003-2266-3975
Jeong-Whun Kim 0000-0003-4858-3316
Jae Hyun Lim 0000-0003-0699-8687
Chae-Seo Rhee 0000-0002-1361-8585
Highlights

1. HIFU device was made with a thickness of 4 mm and a projection depth of 3 mm.
2. HIFU turbinoplasty resulted in minimal tissue damage with intact epithelial layer.
3. Decreased subepithelial glandular structure and overall increased fibrosis were also observed.
4. Safety and efficacy of HIFU turbinoplasty were observed in animal study. Our results warrant the need for human clinical trials.

Abstract

Objectives

Inferior turbinate (IT) hypertrophy is the main cause of chronic nasal obstruction. We developed a high-intensity focused ultrasound (HIFU) ablation device to treat patients with IT hypertrophy.

Methods

First, computed tomography (CT) images of patients without any evidence of sinonasal disease were evaluated to measure and compared the IT, medial mucosal thickness (MT), and space between the nasal septum and IT according to clinical characteristics such as septal deviation. A HIFU prototype was developed based on human anatomical studies. The experimental study was performed in five pigs; the cross-sectional areas of the nasal cavity
airway and histological changes at 1 and 4 weeks postoperatively were evaluated to compare the efficacy of HIFU turbinoplasty with that of radiofrequency turbinoplasty and control.

Results

The mean medial MT of the anterior, middle, and posterior portions of the IT were 4.66±1.14, 4.23±0.97, and 6.17±1.29 mm, respectively. The mean medial IT spaces was 2.65±0.79 mm. The diameter and focal depth of the prototype were 4 mm and 3 mm. HIFU showed no postoperative complications including bleeding or scar formation. After HIFU treatment, the cross-sectional area of the nasal airway increased by 196.62(7.8%) mm³ and 193.74(8.3%) mm³ at 1 week and 4 weeks, compared with the increase of 87.20(3.1%) mm³ and 213.81(9.0%) mm³, respectively, after radiofrequency therapy. Qualitative histologic analysis after radiofrequency turbinoplasty showed epithelial layer disruption at 1 week and increased fibrosis along with decreased glandular structure at 4 weeks. The HIFU group had an intact epithelial layer at 1 week postoperatively. However, significant differences were observed at 4 weeks, including increased fibrosis, and decreased glandular structure.

Conclusion

The efficacy and safety of HIFU turbinoplasty had been observed in an animal study. Our results warrant the need for further human clinical trials.

Keywords

High-intensity focused ultrasound ablation; Turbinates; Postoperative complications; Radiofrequency therapy
Introduction

Turbinate hypertrophy is one of the most common causes of chronic nasal obstruction. A recent study showed that 10%–20% of the global population suffers from nasal obstruction of allergic rhinitis, which causes a significant deterioration in the quality of life.(1) The common causes of turbinate hypertrophy include allergic rhinitis, vasomotor rhinitis, and chronic hypertrophic rhinitis. Although transient symptom relief can be achieved through medical treatment with agents such as antihistamines, oral vasoconstrictors, or intranasal corticosteroids, a significant proportion of patients require surgical volume reduction.(2)

Techniques for reducing turbinate hypertrophy include microdebrider-assisted turbinoplasty, radiofrequency turbinoplasty, and turbinate resection. Most of these techniques are effective; however, in terms of minimal invasiveness, the outcomes differ.(3) Turbinoplasty is usually performed as an adjunctive procedure during septoplasty, which is usually performed inside an operation theater. In such situations, techniques providing better outcomes may be preferred, as bleeding can be easily controlled. However, as office-based turbinoplasty is being widely used, there is an unmet need for minimally invasive turbinoplasty.

Recently, high-intensity focused ultrasound (HIFU) has been used for the treatment of benign lesions in obstetrics, gynecology, and urology. HIFU is a non-invasive treatment that effectively coagulates and necrotizes targets tissues (mainly solid tumors) that are located deep within the body without damaging the surrounding tissue.(4) It is applied at a frequency of 0.8–3.0 MHz depending on the type of instrument used.(5) Ultrasonic waves within this
range can reach the tissue and rapidly increase the target focal temperature to 80°C or higher, leading to coagulation and necrosis. Furthermore, the ultrasonic wave also causes vibration of the target tissue, resulting in compression and thinning of the molecular structure. (6) High energy HIFU can be amplified and targeted to a very small focal area without damaging the surrounding tissue. Unlike traditional surgery for tissue removal, HIFU does not physically penetrate the surface tissue. As epithelial injury is unlikely, minimal bleeding and fast wound healing are expected. As the factors influencing hypertrophy include thickened mucosa with enlarged venous sinusoids, (7) we hypothesized that tissue reduction or ablation with HIFU with minimal injury may be a good treatment option for refractory chronic rhinitis. Therefore, the goal of this study was to design and develop an optimal HIFU device for the treatment of turbinate hypertrophy.

This study aimed to confirm an appropriate response to HIFU for the treatment of turbinate hypertrophy causing nasal obstruction in patients with chronic rhinitis. The study describes the development of a HIFU device for turbinoplasty. The diameter and focal depth were determined, followed by an efficacy study in an animal model.

Materials and Methods

Human anatomical analysis

A retrospective review of prospectively collected data was performed. This study was approved by the Institutional Review Board of our hospital (IRB No. B-2012-652-101) and the requirement for informed consent was waived. Patients age >18 years who underwent
non-contrast computed tomography (CT) examination from 2016 to 2017 at our hospital, without any evidence of sinonasal disease, were evaluated. The CT scans were performed with a single-source multi-detector CT system with 256 channels (iCT; Philips, Amsterdam, Netherlands). The scanning parameters were as follows: tube voltage, 120 kVP, tube current, 200 mAs; scan mode, axial scan mode pitch, 0.39; detector collimation, 64 × 0.625 mm; gantry rotation time, 0.5 seconds; and slice thickness, 0.9 mm. The acquired raw data were then reconstructed using images with 2-mm section thickness. The CT images of all patients were reviewed using a picture archiving and communication system (INFINITT PACS®, INFINITT Healthcare, Seoul, Korea). Medial mucosal thickness (MT) of the inferior turbinate (IT) and the space between the nasal septum and the IT (medial space [MS]) were measured in both nasal cavities. (Fig. 1). The MT was measured at three points: anterior–starting point of the IT bone; posterior–ending point of the IT bone; and middle–halfway between the anterior and posterior points. Further analysis was performed according to the presence of septal deviation. Septal deviation was defined as a greater than 5° angle of the nasal septum based on a straight line from the crista galli to the anterior nasal spine. (8) All data were presented as mean ± standard deviation. The analysis of variance test with Tukey test for post-hoc analysis was used to identify potential significance between the values of no septal deviation, narrow side of septal deviation and wide side of septal deviation. Based on the average of the patient’s features, we use an appropriately sized HIFU instrument. The criterion for statistical significance was set at \( P < 0.05 \). The statistical analysis was performed using the SPSS ver. 22.0 (IBM Co., NY, USA).

Animal study
Animals

This study was conducted after receiving approval from the Animal Experimental Ethics Committee of our hospital (No.18-0192-S1A0). Five *Sus scrofa*, weighing approximately 20 kg each and aged 1–2 months were purchased from Cronex (CRONEX Co, Ltd, Hwaseong, Gyeonggi Province, Korea). Pig was selected as an animal model because of the similarities in the similar cylindrical structure of the IT as compared with that in humans. The experimental group was determined, and the experimental schedule was set to conduct the animal experiments.

Procedure

HIFU turbinoplasties were performed and the outcome measures were compared to those of radiofrequency turbinoplasties using a Coblator with a ReFlex Ultra 45 wand (Arthrocare, Austin, TX, USA). HIFU turbinoplasty was performed in the left nostril of all subjects, but in the right nostril of subject 5. Radiofrequency turbinoplasty was performed in the right nostril of subjects 2 and 4. No further treatment was performed in the right nostrils of subjects 1 and 3. Subjects 1 and 2 were sacrificed 1 week after the procedure, whereas subjects 3 to 5 were sacrificed 4 weeks postoperatively (supplementary figure 1).

All turbinoplasty were performed under general anesthesia. Based on the distance from the nostril, the probe was moved back and forth to cover the entire IT. The HIFU procedure was divided into two types (high and low) according to the energy intensity of the HIFU. High and low procedures were performed with 120 shots of total energy irradiation for approximately 5 min (supplementary video 1). The high-HIFU procedure had a 40-ms output time with a heal region size of 1.08 × 1.17 mm, while the low-HIFU procedure used a 24-ms...
output time with a heal region size of $0.5 \times 0.75$ mm. Radiofrequency turbinoplasty was performed with the wand in position for 15 seconds at a power level of 5 mV, with three passes performed submucosally. Care was taken to avoid mucosal penetration posteriorly.

**Outcome evaluation**

Each animal underwent endoscopic and nasal CT scans before and after the surgery. Endoscopy was performed with a 2.7-mm standard rigid endoscope (Olympus Medical Systems Corp., Tokyo, Japan). CT scans were performed before surgery and on the 7th (week 1) and 28th (week 4) day after the surgeries. The volume of the nasal cavity was calculated by summation of the values obtained by multiplying the thickness between the cut and the intranasal cross-sectional area measured at each image cut on the coronal CT image. (supplementary figure 2.) Pre-operative medial MT and MS of our porcine models were measured in the same manner as human to check the feasibility of our device.

The histological evaluation of each group was confirmed by periodic acid-Schiff staining. In the experimental group, the mucous membrane of the IT was collected 1 and 4 weeks after the surgery. A single pathologist who was blinded to the procedure analyzed the pathologic findings. A qualitative assessment of the sections was performed to identify the type of epithelium, presence of inflammation and fibrosis, and estimate the population of the submucosal glands and venous sinusoids.

**Result**

**Human anatomical study**
A total of 117 patients were analyzed. Fifty-seven patients had a straight septum, while the other 60 presented with a deviated nasal septum. Overall, the mean medial MT of the anterior, middle and posterior portion of the IT were 4.66±1.14, 4.23±0.97, and 6.17±1.29 mm, respectively. The mean MS was 2.65±0.79 mm. The mean values of the anterior and posterior medial MT and the mean MS were significantly different among the study groups (P<0.05), with the values of the deviated septum (wide side) being the highest. The results of the subgroup analysis are summarized in Table 1.

The optimal diameter and projection depth should correspond to the MS (2.65 mm) and the MT (4.23–6.17 mm) respectively. However, to deliver sufficient energy to the target tissue, the diameter had to be increased and was adjusted to 4 mm. Considering the gap between the airway space and the diameter, the projection depth was adjusted to 3 mm (Fig 2).

Treatment outcomes in the animal study

Eschar formation, as well as bleeding and crusting were observed at 1 week after the procedure in the radiofrequency group compared to the control group. (Fig 3A, B, E, F) In the radiofrequency group, bleeding and crusting were no longer visible at 4 weeks postoperatively; however, scar formation was observed (Fig 3C, D, G, H). In contrast, mucosal damage such as eschar formation and bleeding were not observed in the HIFU group (Fig 3I, J, K, L). At 1 week postoperatively, the nasal volume decreased in the control group and the HIFU low group by 132.51(5.5%) and 134.70(4.5%) mm$^3$, respectively, but increased in the radiofrequency and HIFU high groups by 87.20(3.1%) and 196.62(7.8%) mm$^3$, respectively. (Fig 4 A) At 4 weeks postoperatively, the nasal cavity volume decreased in the
control group by 241.08(9.5%) mm$^3$, while in the radiofrequency, HIFU low and HIFU high
groups, the volume increased by 213.81(9.0%), 57.99(2.4%), and 193.74(8.3%) mm$^3$ (range:
135.83-230.26 mm$^3$), respectively. (Fig 4 B) Histological analysis showed marked structural
changes in the radiofrequency and HIFU-treated areas when compared with the control areas
(Fig. 5A). Epithelial layer disruption, increased fibrosis, and decreased glandular structure
were observed in the radiofrequency-treated turbinates at 1 week after turbinoplasty (Fig 5B).
In contrast, an intact epithelial layer without any evidence of tissue disruption was observed
in the HIFU-treated turbinates at 1 week postoperatively (Fig. 5C); however, the HIFU-
treated group showed increased polymorphonuclear cell infiltration. Infiltrated
polymorphonuclear cells tended to be prominent in the turbinate treated with a high-level
HIFU compared that treated with the low-level HIFU. (Fig 5D, E, F). At 4 weeks after the
turbinoplasty, both the radiofrequency and HIFU groups showed increased fibrosis, decreased
glandular structure, and a healed epithelial layer compared to the control areas (Fig 6A, B, C).
Both levels of HIFU turbinoplasty showed similar results. (Fig 6D, E, F)

The pre-operatively measured mean medial MT was 1.55 mm (range 1.1–1.9), 1.42 mm
(range 1.3–1.5) and 1.87 mm (range 1.1–2.1) for the anterior, middle, and posterior points,
respectively. The mean MS was 2.35 mm (range 1.8–3.5) (supplementary table 1). The
medial MT and MS of the porcine model was lower than that of humans, suggesting that the
feasibility of our animal model is limited.

Discussion

Hypertrophy of the IT is an important anatomical factor leading to chronic nasal obstruction
in patients with chronic rhinitis. The underlying factors for hypertrophy include mucosal and bone hypertrophy with enlargement venous sinusoids.(7) These pathophysiological findings can be corrected by total/partial turbinate resection or turbinoplasty, for which various techniques have been developed: the classical technique involves raising a submucosal flap and partially removing the submucosal tissues. Recently, remarkably simple radiofrequency ablation equipment and microdebriders have been developed for turbinoplasty. A recent meta-analysis showed that both radiofrequency and microdebrider-assisted turbinoplasty were equally effective and, achieved significant improvements in cases of nasal obstruction.(10)

The current study described the development of a HIFU prototype for turbinoplasty, which was based on evaluations of the diameter and focal depth of the nasal cavity. HIFU turbinoplasty showed no complications such as bleeding and scar formation and efficiently reduced the turbinate size in a porcine model. Unlike a radiofrequency device, that requires saline injection, pre-treatment manipulation of the turbinate is not needed with our HIFU-assisted technique. Therefore, the device should fit the existing space in the nasal cavity for prompt device manipulation and visualization of the nasal cavity. The HIFU prototype device was designed considering the available range of the nasal cavity airway space. The mucosal depth was also considered to be effective for the treatment with HIFU as a HIFU wave beyond this depth would be transmitted through the bone and may reduce the treatment efficacy; in contrast, a shallower depth could lead to epithelial damage. In this study, the space in the nasal cavity was approximately 2.65 mm. For technical reasons, a diameter of at least 4 mm was needed to deliver sufficient energy, which would lead to compression of the turbinate mucosa with a difference of approximately 1.35 mm from the thickness (4.23–6.17 mm). Therefore, the projection depth was adjusted to 3 mm.
Histological examinations showed an increased submucosal polymorphonuclear cell counts, decreased glandular structure, and increased fibrosis in the HIFU-treated group. Increased fibrosis and the replacement of large venous sinusoids by veins are well-known histological changes observed in radiofrequency turbinoplasty. We also found that histological changes in the IT mucosa were affected by the HIFU intensity, as demonstrated by the higher degree of polymorphonuclear cell infiltration after 1 week of treatment in the HIFU high group than that in the HIFU low group. Polymorphonuclear cell infiltration with maintenance of the tissue architecture is the hallmark of coagulation necrosis, which may be further replaced by tissue fibrosis. A higher degree of submucosal polymorphonuclear cell infiltration appeared to increase the nasal airway space after 1 week in the HIFU high group than that in the HIFU low group. However, the difference was not significant with both HIFU levels after 4 weeks. Our results indicate that both levels of HIFU treatment were effective for IT hypertrophy after 4 weeks of treatment.

In our study, the efficacy of HIFU turbinoplasty was similar to that of radiofrequency turbinoplasty. However, it was more beneficial for treatment of the IT with HIFU turbinoplasty than radiofrequency turbinoplasty. First, on endoscopic and histological examinations, the HIFU group showed minimal epithelial layer damage and no bleeding, while the radiofrequency group showed gross and microscopic tissue surface damage. Second, HIFU was performed in a local area without further preparation such as saline injection. Therefore, the convenience and utility of the HIFU device indicates its potential for use in the outpatient setting.

The depth of our prototype is 3 mm, which is larger than the medial MT in our animal models. However, volume reduction was achieved in all the animal models 4 weeks after
HIFU turbinoplasty. This can be explained by several possible reasons. As the energy transmission seems to be focused on the turbinate bone, which has a high absorption rate, only a small portion of the ultrasound may have been transmitted to the soft tissue. However, thermal energy can be secondarily transmitted to the adjacent periosteum from the bone which may have affected the turbinate mucosa. In addition, an oval shaped heal region (1.08 × 1.17 mm) from the center indicates a partial energy transmission to the turbinate mucosa. The effect of focal depth on efficacy of HIFU turbinoplasty needs to be further evaluated.

Our study has several limitations. First, a quantitative analysis was not performed to compare the histological changes. Second, while the nasal cycle is present in swine, we did not consider these factors when measuring the airway space by CT scan. Changes in the nasal airway space may have been affected by the nasal cycle. Third, the HIFU turbinoplasty demonstrated only short-term efficacy. Therefore, additional studies using swine models may be warranted. However, this is the first study to demonstrate the efficacy of HIFU turbinoplasty in animal models by showing both radiological and histological changes after HIFU treatment. Considering the safety of HIFU turbinoplasty, human clinical studies may be initiated with our device.

In conclusion, in our study, nasal endoscopic findings showed better mucosal preservation in HIFU-treated turbinates than in radiofrequency-treated turbinates. The volume of the nasal cavity calculated by a CT scan was higher in the HIFU-treated turbinates than in non-treated turbinates, which was similar to the effect observed in radiofrequency-treated turbinates. The histopathological findings of HIFU-treated turbinates revealed induction of focal tissue coagulation of the submucosal layer, while preserving the mucosal layer. Therefore,
compared with other treatments, HIFU turbinoplasty is a useful technique that can reduce IT hypertrophy without complications.

References


**Figure Legends**
Fig 1. Anatomical evaluation of the nasal cavity by computed tomography (CT). MS, medial space; MT, mucosal thickness. The unit for MT and MS is millimeter (mm).

Fig. 2. Specifications of the HIFU prototype design and energy. X: width of heal region; Z: length of the heal region. HIFU, high-intensity focused ultrasound.

Fig. 3. Nasal endoscopic findings in the control, radiofrequency, and HIFU groups. (A) and (B) represent the preoperative and postoperative findings in the control group (week 1). (C) and (D) represent the preoperative and postoperative findings in the control group (week 4). (E) and (F) represent the preoperative and postoperative findings in the radiofrequency group (week 1). (G) and (H) represent the preoperative and postoperative findings in the radiofrequency group (week 4). The red circle in (F) indicates eschar formation, bleeding, and crust formation, while the red circle in (H) indicates scar formation. (I) and (J) represent preoperative and postoperative findings in the HIFU group (week 1). (K) and (L) represent preoperative and postoperative findings in the HIFU group (week 4).

Fig. 4. Computed tomography (CT) evaluation of the control, radiofrequency, and HIFU groups at 1 week (A) and 4 weeks (B) after the turbinoplasty. The numerical values imply the 3-dimensional volume of the nasal cavity (mm$^3$) measured pre- and post-operatively. NC: nasal cavity.

Fig. 5. Pathologic evaluation of the control, radiofrequency and the HIFU high and low groups at postoperative week 1. (A, B, C Slide magnification: × 100; D, E, F Slide magnification: × 400) (A) control; (B) radiofrequency group, and asterisk shows epithelial disruption; (C) HIFU group, and the sign represents intact epithelium; (D) control; (E) HIFU high group; (F) HIFU low group; Star symbol in (E) and asterisk in (F) represent similar findings of infiltrated polymorphonuclear cells. The infiltrated polymorphonuclear cells...
appears prominently in the HIFU-treated turbinate with high level compared to low level.

**Fig. 6.** Pathologic evaluation of the control, radiofrequency and HIFU groups at postoperative week 4. (A, B, C Slide magnification: × 100; D, E, F Slide magnification: × 400). (A) control; (B) radiofrequency group; (C) HIFU group; asterisk symbol in (B) and star in (C) represents similar findings of increased fibrosis/decreased glandular structure. (D) control; (E) HIFU high group; (F) HIFU low group. Similar findings of increased fibrosis/decreased glandular structure are confirmed in both the HIFU high and low groups.
## Table 1. Characteristics of inferior turbinate hypertrophy using computed tomography

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
<th>Medial MT (mm)</th>
<th>MS (mm)</th>
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<tr>
<td></td>
<td></td>
<td>Anterior</td>
<td>Middle</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>117</td>
<td>4.66±1.14</td>
<td>4.23±0.97</td>
</tr>
<tr>
<td><strong>Straight septum</strong></td>
<td>57</td>
<td>4.56±1.18</td>
<td>4.20±1.00</td>
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<td><strong>Deviated septum (narrow)</strong></td>
<td>60</td>
<td>4.15±1.12</td>
<td>4.11±1.21</td>
</tr>
<tr>
<td><strong>Deviated septum (wide)</strong></td>
<td>60</td>
<td>5.37±1.59</td>
<td>4.41±1.11</td>
</tr>
</tbody>
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| **P-value**     | <0.001**          | 0.191         | 0.044*   | 0.014**   |

MT, mucosal thickness; MS, medial space.

*P<0.05 compared to straight septum, **P<0.05 compared to deviated septum (narrow)
Fig 2.

<table>
<thead>
<tr>
<th>Energy Level</th>
<th>Focal Region Size (X-axis, Z-axis)</th>
<th>Frequency</th>
<th>Focal Depth</th>
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<tr>
<td>5 (HIGH)</td>
<td>1.08 mm x 1.17 mm</td>
<td>7.0 MHz</td>
<td>3.0 mm</td>
</tr>
<tr>
<td>3 (LOW)</td>
<td>0.5 mm x 0.75 mm</td>
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Fig 3.
Fig 4.
Fig 5.
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