Argon Plasma Coagulation of Cervical Heterotopic Gastric Mucosa as an Alternative Treatment for Globus Sensations

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BACKGROUND & AIMS: Ablation of gastric inlet patches (GIP) in the cervical esophagus by argon plasma coagulation (APC) can alleviate chronic globus sensations in the throat. We investigated the efficacy of this therapy in a randomized, controlled multicenter trial.

METHODS: Patients with chronic globus sensations and GIP were randomly assigned 1:1 to groups that were treated with APC or a sham procedure (controls). Patients and their referring physicians were blinded to therapy. All patients completed a standardized questionnaire about symptoms before and 3 months after the procedure. Thereafter, control patients were eligible for cross-over therapy. Long-term efficacy was assessed in all patients ≥6 months after APC.

RESULTS: Improvement of symptoms was reported in 9 (82%) of 11 patients who received APC, compared with 0 (0%) of 10 patients in the control group (P = .002). Nine (90%) of 10 patients treated with APC had per protocol healing, compared with 0 (0%) of 9 controls (P < .001). Scores for symptom/globus assessment significantly improved in patients in the APC group, whereas patients in the control group did not perceive any symptom relief. Eight of the 10 patients who started in the control group crossed over to the APC group. Long-term efficacy (after a median follow-up of 17 months) was documented in 13 (76%) of 17 treated patients.

CONCLUSIONS: Ablation of gastric inlet patches appears to be an effective therapy for alleviation of associated globus sensations. This new treatment modality might change the paradigm for treatment of these patients.

Globus sensation is defined as a persistent or intermittent nonpainful sensation of a lump or a foreign body in the throat lasting for ≥3 months.1 Globus sensations have an estimated prevalence of approximately 16%-36%.2,3 These symptoms are mostly suspected to have a psychogenic origin.4 In the last decades globus sensations were reported to be an extraesophageal manifestation of gastroesophageal reflux disease. Several studies have shown pathologic pH-metry and multichannel-impedance parameters in these patients as well as a significant symptom relief with acid-suppressive therapy.5,6 Nevertheless, the precise nature of globus sensations in patients unresponsive to antireflux therapy is unclear, and there is no uniform guideline to manage this condition. It has been mentioned that the presence of gastric inlet patches (GIPs) may cause globus sensations.7–9 GIPs comprise an island of heterotopic gastric columnar epithelium in the cervical esophagus. They are often found accidentally at upper endoscopy with a reported prevalence of approximately 1%-2%.10,11 Within the framework of a feasibility study, we have recently treated patients with GIPs in the cervical esophagus complaining about globus sensations by ablation of heterotopic mucosa with argon plasma coagulation (APC).12 Other possible causes of the globus sensations, such as motility disorders or tumors of the pharynx/larynx, were excluded by laryngoscopy and fluoroscopy before therapy. Additional diagnostic tools such as dual-channel pH-metry, phoniatry, esophagus manometry, and endoscopy were applied. Our data showed that patients experienced a significant decrease of their symptoms after complete ablation of the GIPs. Moreover, we highlighted that the benefit achieved from APC treatment was not related to reduced acid regurgitation into the proximal esophagus. We considered a potential placebo effect after interventional therapy as the major drawback of the study. Hence, we aimed to perform a multicenter sham-controlled trial that included a larger patient number to clarify whether APC therapy might indeed be regarded as the treatment of choice for patients with globus sensation and coexisting GIPs.

Materials and Methods

Patients

Between July 2006 and January 2008, patients with globus sensations (lump in the throat) lasting for...
≥3 months and histologic-proven GIPs were identified in 3 outpatient clinics in Germany (Technical University of Munich, Technical University of Dresden, and Dr Horst-Schmidt-Clinic Wiesbaden). Symptoms had to be unresponsive to proton pump inhibitor (PPI) therapy for ≥2 months; the presence of GIPs had to be confirmed by histology. Patients were not eligible for inclusion if they have had a malignant disease, were unwilling to participate, or were unable to provide informed consent. Further exclusion criteria were any condition that contraindicated safe APC therapy, such as coagulation disorders or varices, or GIPs involving >50% of the circumference of the proximal esophagus (to potentially avoid post-interventional strictures).

Procedure

Symptom assessment. Symptoms were assessed by applying an established and standardized questionnaire before the initial verum/sham procedure and 3 months later, before the follow-up endoscopy. All data assessment was done by a research fellow (V.B.) blinded to the type of therapy at any time point. In short, patients were asked about the following symptoms: feeling of something stuck in the throat, pain in the throat, irritation in the throat, difficulty in swallowing food, throat closing off, swelling in the throat, catarrh down the throat, cannot empty the throat when swallowing, urge to swallow continuously, and food sticking when swallowing. Patients graded the severity of the respective symptoms by marking an analogue scale ranging from 0 for no symptoms to 7 for unbearable symptoms. An additional 2 components determined the issue about how much time the patients spent with thinking about their throats (0 for no time and 7 for all the time) and how annoying they found the current situation (0 for not at all and 7 for extremely). From the initial 10 components and the 2 latter components, we calculated the symptom score. Furthermore, a globus score was calculated by adding the numbers for the most common complaints of globus sensations as described by Deary et al: feeling of something stuck in the throat, discomfort or irritation in the throat, and wanting to swallow all the time. Finally, at follow-up 3 months later, patients were asked about overall symptom improvement (yes or no) after therapy (APC or sham).

Endoscopy. Each patient with globus sensations was scheduled for random assignment after GIP was histologically proven with a biopsy at prior endoscopy. Random assignment into either group (APC therapy or sham procedure) was performed according to a computer-generated list. Patients and their referring physicians were blinded to the respective treatment arm for the whole course of the study, ie, until the last follow-up examination was performed.

Endoscopy was performed after an overnight fast under conscious sedation with midazolam (2.5 mg) in combination with propofol (50–300 mg). Endoscopies were only performed by experienced endoscopists (A.M., F.E., S.M., and O.P.) at 3 different centers. All APC applications were done with the use of the ERBE APC300 (Erbe GmbH, Tübingen, Germany). Power setting was 60 W and argon flow was set to 2 L/min. A mucosectomy cap was fitted at the distal tip of the endoscope to enable a better view and to decrease the risk of damage of surrounding squamous epithelium. The aim of the procedure was to completely ablate the GIPs in a single session as shown in Figure 1A and B. In case of a sham procedure, the preparations were in line with the above-mentioned verum arm: all potentially needed equipment was set up; patients were connected with APC applicator. APC therapy was simulated but not performed because current flow was disconnected as soon as patients were asleep. Patients from both groups were scheduled for follow-up endoscopy 3 months after random assignment. Endoscopy was performed to check for potential side effects (stricture formation) and completeness of APC therapy in the verum group.

Figure 1. Endoscopic images (NBI mode) of a gastric inlet patch with the use of a fixed mucosectomy cap at the distal tip of the endoscope before (A) and after the APC procedure (B).
Cross-over and long-term follow-up. Patients who had received a sham procedure were offered the opportunity to undergo APC therapy for their GIPs after they had been told that only a sham procedure had been performed. Eight of 10 patients in the sham group were willing to be treated beyond the study protocol (cross-over). All patients were asked within a telephone interview performed at 6 months after APC therapy whether initial symptoms improved.

Statistical Analysis

On the basis of the results of our previous feasibility study, successful therapy was expected in 90% of all patients. A placebo effect in the sham group was expected in approximately 50%. Hence, provided an α of 5% and a β of 20%, the study population was estimated to include 40 patients. An interim analysis was intended after inclusion of the first 20 patients (≥10 patients in both arms after having finished the study). Statistical analysis was done by using the chi-square or Fisher’s exact test for evaluation of treatment success of APC therapy versus sham treatment as assessed at the follow-up examination (intention-to-treat and per protocol). The Wilcoxon test was used for pairwise comparison of symptom scores before and after APC therapy or sham procedure. The Mann–Whitney test was applied for further comparison between both groups (anamnestic data, symptoms scores before therapy). A P value less than .05 was regarded as statistically significant. SPSS 16.1. software package (SPSS Inc, Chicago, IL) was used for analysis.

As a research project that prospectively assigned human subjects to study the cause-and-effect relation between an interventional endoscopic therapy and a sham procedure, the study was preliminarily announced in www.clinicaltrials.gov (Identifier: NCT00439439) and was also approved by the Ethics Committee of the Technical University of Munich.

Results

The study had to be terminated prematurely after an interim analysis. The reason was a highly significant treatment effect of APC therapy in comparison to the sham procedure. Hence, further randomization was deemed unethical. On an intention-to-treat basis, improvement of symptoms was reported in 9 (82%) of 11 patients after APC therapy in comparison to 0 (0%) of 10 patients after the sham procedure (P = .002, chi-square test). One patient in the verum group insisted to be unblinded 3 days after random assignment; a further patient in the sham group was lost to follow-up. Per-protocol healing rates were therefore 9/10 (90%) compared with 0/9 (0%) (P < .001, chi-square test). For globus score and symptom score (see Materials and Methods) a significant improvement was observed in the verum group, whereas no such differences were seen in the sham group before endoscopy and at follow-up examination. The median (minimum to maximum [range]) scores for the symptom score and the globus score decreased from 44 (range, 29–78) and 11.5 (range, 8–17) before therapy to 9 (range, 0–46) and 2 (range, 0–9) at follow-up examination (P = .006 and P = .001, respectively, Wilcoxon test). No significant differences were observed between the verum and the sham groups for both scores assessed within the initial examination: 44 (range, 29–78) and 39 (range, 14–60) for the symptom score and 11.5 (range, 8–17) and 9 (range, 5–12) for the globus score. Figures 2 and 3 summarize the course of symptom scores from the initial examination to fol-

![Figure 2. Boxplots showing median, lower, and upper quartile and sample minimum and maximum of summed globus score before and after therapy in the respective treatment group (ns, not significant).](image)

![Figure 3. Boxplots showing median, lower, and upper quartile and sample minimum and maximum of summed symptom score before and after therapy in the respective treatment group (ns, not significant).](image)
In light of the results of our consecutive sham-controlled trial, we are now able to show that a placebo effect is rather unlikely and that it is indeed the ablation of the heterotopic mucosa which leads to such a treatment success. Eighty-two percent of all patients experienced an improvement of their symptoms in comparison to no patients randomly assigned to the sham procedure. On the basis of our limited number of patients, this absolute risk reduction of 0.8 results in a number needed-to-treat of 1.2. In addition, scores for overall symptoms and globus decreased significantly if APC therapy was performed, whereas no such effect was found in patients undergoing a sham procedure. Overall, we observed a continuous treatment success of 76% of patients in the verum group and who and crossed over after a median follow-up period of 17 months. In general, the therapy was well tolerated. Transient dysphagia after APC therapy was the only side effect observed in approximately two-thirds of all patients. However, 60% of patients undergoing a sham procedure also reported transient dysphagia. This highlights that such mild side effects were most likely caused by the endoscopy itself (performed with a rigid hood attached at the tip of the endoscope) rather than caused by the APC therapy. Nevertheless, it remains unclear which pathophysiologic factors may be related to the presence of globus sensations associated with GIPs. It is already well known that globus symptoms represent an atypical manifestation of gastroesophageal reflux disease, possibly originating from a severe reflux episode up to the proximal esophagus.\(^5\,6\) Another explanation is that GIPs themselves, which are reported to be capable of producing acid as measured by dual-channel pH-metry,\(^17\) may lead to similar symptoms. In both conditions acid-suppressive therapy with PPIs should lead to symptom relief.\(^18\) However, patients were only included if symptoms persisted despite therapy with PPIs. In our previous pilot trial we were able to show that globus persisted despite suppression of acid as determined by dual-channel pH monitoring.\(^12\) This conforms with other data showing that globus sensations are not necessarily related to the presence of acid.\(^19\,20\) Histological analysis of GIPs confirmed only cardiac mucosa without parietal cells, \(H\, pylori,\) or dysplasia. Hence, the globus sensations might be more related to production of mucus rather than acid.

**Table 1.** Anamnestic Data and Size of Gastric Inlet Patches (GIPs)

<table>
<thead>
<tr>
<th></th>
<th>Sham procedure (N = 10)</th>
<th>APC procedure (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female), n</td>
<td>6/4</td>
<td>7/4</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>52.5 (33–74)</td>
<td>40 (30–71)</td>
</tr>
<tr>
<td>Size of GIPs, median (range), mm</td>
<td>7.5 (2–30)</td>
<td>8 (3–30)</td>
</tr>
<tr>
<td>Number of GIPs, median (range)</td>
<td>2 (1–3)</td>
<td>2 (1–6)</td>
</tr>
</tbody>
</table>

**Note.** No significant differences were observed between the 2 groups (\(P > .1\), chi-square test and Mann–Whitney test).

Discussion

APC has been reported to be an effective treatment of rare neoplasia arising from heterotopic gastric mucosa in the cervical esophagus.\(^14\,15\) Because globus sensations as well as other laryngeal and pharyngeal disorders have been linked to the presence of GIPs in the cervical esophagus,\(^7\,16\) we recently presumed that patients with globus sensations and GIPs in the cervical esophagus experienced a significant decrease of their symptoms after complete ablation.\(^12\) Nevertheless, a placebo effect could not be excluded which made a sham-controlled trial necessary to be performed subsequently.

low-up in both groups. Table 1 shows anamnestic data (sex, age, size of GIPs) of patients from both groups. No significant differences could be observed. Side effects after endoscopy were transient dysphagia lasting <3 days in 7 (64%) of 11 patients in the verum group and in 6 (60%) of 10 patients in the sham group (\(P = NS;\) chi-square test). Stricture formation, bleeding episodes, or perforations did not occur. The histopathologic finding of all GIPs did not show any parietal cells within the GIPs, solely cardiac mucosa was detected. \(Helicobacter pylori\) or dysplasia was not present.

Cross-over of sham-treated patients was accomplished in 8 of 10 patients (1 patient refused to undergo further therapy; another was lost to follow-up as mentioned before). Hence, a total of 18 patients received APC therapy of their GIPs. Total eradication of the GIPs was documented in all these cases.

All patients were asked within a telephone interview performed ≥6 months after APC therapy whether initial symptoms improved. Median follow-up period was 17 months (range, 7–30 months), and 1 patient (verum group) could not be contacted and was therefore lost to follow-up. Symptom relief was indicated by 13 (76%) of 17 patients overall. Four of 17 patients did not notice any symptom relief. However, 2 patients felt an improvement 3 months after the procedure, but with long-term follow-up complaints returned despite therapy to the intensity that was initially perceived. However, recurrent GIPs were excluded by re-endoscopy in these 2 cases.

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So far, treatment of patients with globus sensations not responding to PPIs was limited to behavioral or psychotropic drug therapy.\(^21\) However, to the best of our knowledge there are no data on the outcome of such measures, and cost effectiveness is unproven. In contrast, we speculate that our new treatment modality is fairly cheap and can be considered highly effective. One might argue that the number of patients included was too low and the time period of follow-up was too short. However,
the treatment success was highly pronounced already after the first interim analysis. Hence, further randomization was deemed unethical.

In conclusion, on the basis of data as shown we propose to perform an upper endoscopy in all patients with globus sensations despite therapy with PPIs. The endoscopist should pay special attention to the presence of GIPs in the cervical esophagus and, if present, ablate such heterotopic gastric mucosa. Our previous feasibility trial and the present sham-controlled study have impressively shown a continuous clinical benefit for patients with globus with coexisting GIPs. Albeit, further long-term follow-up data are currently not available, in our opinion, this new alternative treatment modality has the potential to change our paradigm in treating at least some of the many patients with globus sensations.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2009.04.053.

References


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Author contributions were as follows: M.B. recruited patients and wrote and approved the manuscript. V.B. collected and analyzed data. F.E. performed examinations and approved the manuscript. A.M. performed examinations, wrote and approved the manuscript. O.P. recruited patients, collected data, and performed examinations. C.P. wrote and approved the manuscript. R.M.S. approved the manuscript. A.M. performed examinations, wrote and approved the manuscript, and was guarantor of the paper. The paper was presented in part at the UEGW 2008 meeting and the annual meeting of the German Society for Metabolic Disorders and Digestive Diseases (DGVS) in 2008.

Conflicts of interest

The authors disclose no conflicts.