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A long-term prospective study of the efficacy and safety of endoscopic septotomy using the LigaSure® system for the treatment of Zenker's diverticulum

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AUTHOR CONTRIBUTIONS

Vicente Pons-Beltrán: research design and performance, literature review and manuscript writing.

Natalia García-Morales: literature review and manuscript writing.

Esteban Sáez-González: literature review and manuscript writing.

Noelia Alonso: statistical analysis.

Marta Ponce: literature review and manuscript writing.

Marco Bustamante: statistical analysis.

Lidia Argüello: manuscript writing.

ABSTRACT

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Background and objectives: endoscopic septotomy of the cricopharyngeal muscle (ESCM) is a technique used for the treatment of Zenker's diverticulum (ZD). The experience with computerized vascular sealing systems (LigaSure® type) is limited. The objective of this study was to evaluate the efficacy and safety of ESCM using LigaSure®.

Methods: this was a long-term prospective study of 18 patients with ZD, who were referred to our hospital due to ESCM between 2010 and 2016. The severity of the symptoms was determined using the Dakkak-Bennett validated scale for dysphagia and the rest with numerical scales. The rates of relapse and retreatment were evaluated.

Results: ESCM with LigaSure® was performed in 17 cases, one case was excluded due to technical difficulties. The median age was 72 years and regurgitation, dysphagia and respiratory symptoms were found in 100%, 89% and 56% of cases, respectively. The median size of the diverticulum was 28 mm (20-60 mm). The median time of the procedure was 35 minutes (25-45 minutes). There were four complications, two hemorrhages and two perforations. The median follow-up was 13 months (range: 12-82 months). Clinical improvements were observed for all symptoms and were maintained 12 months after treatment ($p < 0.05$). There was no relapse during follow-up in 13 patients. A complete section was not achieved and clinical relapse occurred after a median time of seven months that required retreatment in the remaining patients.

Conclusions: ESCM with LigaSure® may be a safe and effective technique in long-term follow-up situations, with low rates of relapse.

Key words: Zenker's diverticulum. Endoscopic surgical procedure. Dysphagia.

INTRODUCTION

Zenker's diverticulum (ZD), also known as cricopharyngeal diverticulum, is the most common diverticulum of the upper digestive tract. It is a protrusion of the pharyngeal mucosa through a relatively weak area of the posterior wall of the pharynx, the so-called *Killian triangle.* The condition was first described in 1769 by Ludlow, although it was Friedrich von Zenker who discovered that it developed secondary to an increase in intrapharyngeal pressure (1). Higher hypopharyngeal pressure during swallowing,

together with a lower resistance in the posterior wall of the hypopharynx, are fundamental factors in the pathogenesis of ZD.

The most common clinical manifestation is dysphagia. This can be caused by a progressive increase in the volume of the diverticulum due to its direct compression on the esophagus (extrinsic dysphagia) or due to a lack of elasticity of the cricopharyngeal muscle (known as intrinsic dysphagia). Other symptoms include regurgitation of food, halitosis and respiratory symptoms due to aspiration of the alimentary content located in the cavity of the diverticulum.

Therapeutic intervention is indicated for all patients with symptoms, regardless of the size of the diverticulum, with the aim of improving and reversing the symptoms of dysphagia and oropharyngeal regurgitation. Furthermore, the technique is used to avoid complications of vital risk such as pneumonia secondary to aspiration and pulmonary abscesses, which can appear in elderly patients (2).

The treatment of ZD can be approached in various ways, via surgery (upper esophageal sphincter myotomy and diverticulectomy or diverticulopexy) or transoral endoscopic surgery using a flexible endoscope or a rigid endoscope. Currently, both surgical and rigid endoscope treatment are being replaced by an endoscopic procedure. Endoscopic septotomy of the cricopharyngeal muscle (ESCM) has become an effective and safe option for the treatment of ZD, reducing the number of complications with respect to classic treatments. The most frequent complication is perforation, which can occur in up to 27% of patients, as described in some published studies (1-3). This procedure has been performed using various devices, such as a stag beetle (SB) knife (1,4-8) or needle knife. However, there is no recommendation with regards to which approach offers the most advantages and the lowest rate of complications. In some centers, computerized vascular cutting and sealing systems (LigaSure® type) have shown promising results in efficacy and safety. However, experience is limited (4-5,9-12).

The objective of our study was to evaluate the efficacy and safety of ESCM with LigaSure® via a prospective long-term follow-up study.

METHODS

Study design

A prospective and descriptive study was performed to evaluate the long-term efficacy and safety of ESCM using the LigaSure® device. A consecutive series of 18 patients with ZD who were referred to a tertiary hospital for ESCM with LigaSure® between 2010 and 2016 were included. Information about symptoms was collected before and after the procedure including dysphagia, regurgitation and respiratory symptoms. The severity of the symptoms was determined using the Dakkak-Bennett validated scale for dysphagia (0: asymptomatic to 4: aphagia) and the remaining of symptoms using analog numerical scales (0: asymptomatic to 4: daily symptoms) (13). The subjective state of health as perceived by the patient was also evaluated (1: very good to 5: very poor) (Table 1). In addition, the rate of relapses and retreatments required during follow-up, as well as any complications that might have occurred, were also analyzed.

A protocol was designed that informed patients about the endoscopic procedure (endoscopic material, personal physician, nursing, medication) and clinical follow-up after the procedure. This was performed in order to standardize all procedures and subsequent follow-up. All the patients were properly informed, both orally and in writing, about the endoscopic procedure and its possible complications. They subsequently signed the informed consent for both the procedure and the follow-up study. The study met the principles of the Declaration of Helsinki and no external funding was received for its implementation.

Endoscopic treatment

All the procedures were performed in an operating room by expert endoscopists, as complications may require immediate surgical intervention. All patients were given one dose of prophylactic antibiotic (ciprofloxacin 400 mg or ampicillin 2 g) before treatment. The patient was placed under deep sedation or general anesthesia, under tracheal intubation, in the left lateral decubitus position. Subsequently, a complete gastroscopy with a conventional endoscope (Olympus GIF-H180/165, 9.9 mm) was performed to evaluate the diverticulum and the septum to be treated and also to exclude any other associated pathology. A metal guide (0.35 Fr) was inserted and the distal part was left in the gastric cavity. The diverticuloscope (Cook) was then positioned. For this purpose, an orifice was made manually with a trocar, at the end of

the longer tongue, through which the metal guide was passed. This facilitated the placement of the diverticuloscope in its correct position.

Then, an ultra-thin endoscope (Olympus GIF-H180/165, 5.9 mm) was inserted until the septum was visualized. The LigaSure® device (LigaSure V LS1500 5 mm, laparoscopic sealer/divisor 37 cm) was inserted parallel to the endoscope, the valves were placed at the midpoint of the septum and the section of the septum was performed. Figure 1 shows how the endoscopic septotomy of the cricopharyngeal muscle (ESCM) with LigaSure® was performed.

Several consecutive sections (1-3) were usually performed to a few millimeters from the bottom of the diverticulum in order to prevent perforation. In addition, if there were any concerns about a possible perforation after the septum section or if a hemorrhage was evident, hemostatic clips were placed. Subsequently, the patients were hospitalized for 24 hours for clinical observation. A six-hour liquid diet was started with intravenous fluid therapy and an intravenous proton pump inhibitor. If there was a suspected perforation, fever or elevation of acute phase reactants in the blood tests, a broad-spectrum antibiotic was administered (amoxicillin-clavulanic acid every eight hours).

After hospital discharge, two visits to the Digestive Endoscopy Unit (at one month and at 12 months) were scheduled to perform a complete clinical evaluation of the patient using various symptom scales. At the one-month post-procedure visit, a radiographic esophagogram with barium was performed to evaluate the size of the remnant of the diverticular septum or to verify the absence of contrast retained (Fig. 2). If there was no persistent and disabling symptomatology 12 months after the procedure, the patient was followed-up once a year. If the patient had ZD-related limiting symptoms (dysphagia, regurgitation, respiratory symptoms) or any complications (digestive bleeding, fever, chest pain) between one month and 12 months after the procedure, the patient was referred to the Digestive Endoscopy Unit for additional assessment.

Statistical analysis

The variables evaluated included the rate of adverse effects, the duration of the procedure, the clinical improvement and the duration of hospital stay. Descriptive

statistics were expressed as the mean, interquartile range and range for continuous variables. The measurement scales used were considered as continuous variables and the differences before and after treatment were analyzed using the Mann-Whitney U test. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Of the 18 patients referred to our center, ESCM using the LigaSure® was performed in 17 cases and one case was excluded due to technical difficulties in placing the diverticuloscope. The median age of the patients was 72 years (range 56-94 years) and 55% were male. With regard to associated comorbidities, 58% of the patients had diabetes mellitus, 26% had hypertension and 42% were dyslipemic. The median body mass index was 25 (range: 21-30).

The most frequent referred symptom was regurgitation in all cases. Another 89% of patients had dysphagia and 56% had respiratory symptoms, with a high score in the evaluated scales (3, 2 and 1, respectively). The median score of the subjective health status score perceived by the patient before treatment was 4 (range 2-5). The demographic and clinical characteristics of the patients evaluated are presented in table 2.

An esophagogram was performed on all the patients before the procedure. The median size of the diverticulum was 28 mm (range: 20-60 mm) and the ZD was larger than 40 mm in 22% of patients. This was considered as large according to the Morton and Bartley classification (14). The median time of the procedure was 35 minutes (range: 25-45 minutes). Four peri-procedure complications were recorded, two mild hemorrhages that were resolved during the same procedure with the placement of hemostatic clips and two micro-perforations. One was treated conservatively and the other required surgical treatment in the same operating room. None of the complications had significant consequences for the patient. All the patients stayed in hospital for 24 hours after the procedure, except for the patient who required surgery, who stayed for seven days for typical postsurgical care.

The median follow-up was 13 months (range: 12-82 months) and the clinical efficacy of the procedure was evaluated in the first month and 12 months after treatment using

the following scores: dysphagia score, regurgitation score, respiratory symptoms score and the patients' overall subjective state score. After 30 days, there was a significant clinical improvement in the dysphagia score, regurgitation score, respiratory symptoms and the subjective assessed health status score (Table 3).

This improvement was significantly maintained after 12 months. A complete section of the septum was performed in 13 patients (78%) who remained asymptomatic for a median of seven months (range: 2-10). The entire section of the septum was not possible and required surgical (two) or endoscopic (two) retreatment in the other four patients (22%), who are currently asymptomatic. One of the patients had a clinical recurrence after 12 months with mild symptomatic relapse and, therefore, rejected the retreatment option. Figure 3 shows a flowchart of the follow-up of the patients included in the study.

DISCUSSION

The treatment of ZD has changed in recent years. Historically, there were two different treatment techniques, open surgery (upper esophageal sphincter myotomy and diverticulectomy or diverticulopexy) or transoral endoscopic surgery with a flexible endoscope or rigid endoscope. At present, both the surgical and rigid endoscope treatments have been relegated. Currently, the less invasive technique with apparently better results is the flexible endoscopic ESCM (3,7,10-12,15-18).

Compared with surgery, endoscopic treatments have a shorter intervention time and hospital stay and a lower rate of complications, a faster recovery and a lower economic cost (7,10-16,19). However, the available scientific evidence is not of good quality. It is important to develop and evaluate new techniques and devices that reduce complications and procedural time and maintain a good long-term clinical response. The most common reasons for switching from endoscopy to open surgery are difficulties in extending the neck or opening the mouth in order to accommodate the diverticuloscope, or when a tear of the mucosa causes a perforation.

The development of endoscopic cutting systems is continuously evolving. Along these lines, computerized vascular cutting and sealing systems (LigaSure® type) that are characteristic of laparoscopic surgery have shown promising results in terms of efficacy

and safety. Although they have only been evaluated in a few centers, with small patient cohorts and with short- to medium-term follow-up. A total or partial remission of symptoms has been reported very early after the intervention in 78-96% of cases, although late relapses occur in 10-20% of cases (4-5,9,11,12).

All of our patients experienced a total remission of symptoms in the first month after treatment and four patients (23%) had a late relapse after a minimum follow-up of 12 months. Our study is the first to analyze the efficacy and safety of ESCM using LigaSure® in a large sample of patients with long-term follow-up of at least 12 months. The LigaSure® device simultaneously uses computerized vascular cutting and sealing systems, achieving the fusion of vessels up to 7 mm in diameter. It offers some advantages in relation to other devices that have been used, such as a greater precision in sections, cuts of up to 10 mm in length, a small diameter (5 mm) and the possibility of electrocoagulation (LigaSure Impact®) (5). The mean hospital stay and procedure time, associated complications and the medium-term clinical response were similar to other devices previously evaluated (1,6,8,16,20).

In 2015, Giorgio Battaglia et al. reported a study of 31 patients who underwent ESCM using the SB knife. They initially obtained a good response in 83.9% of the cases, but two patients suffered a clinical recurrence at four and nine months. However, they did not require treatment and there was a median follow-up of seven months (1). Subsequently in 2016, S.K. Goelder published another study of 52 patients treated with the SB knife. In this study, 90.4% of the patients required a single treatment session with a good response and 9.6% relapsed in a median time of seven months that required a new intervention. The median follow-up was 16 months (6). In both cases, the rates of complications and relapse were low, with results similar to those presented in our series with LigaSure®.

In our study, the initial clinical response rate was 78%, which was maintained during 12 months of treatment. There were four complications; three were minor and treated conservatively or in the same endoscopic session. The other complication did not increase the patient morbidity and mortality during the 12-month follow-up. In our opinion, although the device has the ability to seal small vessels, it is safer not to perform a complete section of the septum and avoid the most proximal millimeters of

the septum, even if another session or a subsequent retreatment is necessary in order to reduce the rate of perforations or hemorrhages. Currently, it is recommended to apply hemostatic clips after the section of the septum in order to prevent this complication and to treat perforations endoscopically if this was the case. In addition, symptomatic relapse can be minor and does not lead to a poorer quality of life, thus a new procedure would not be necessary.

The main limitation of our study was the small sample size, although it was considerable for a pathology with a low prevalence. In addition, as in previously published studies that evaluated this technique, it is not directly compared with another device such as the SB knife. The follow-up time for our study was considered to be adequate, as there was a low rate of relapse (5.6%) at 12 months and it was not clinically relevant for the patient.

In conclusion, flexible endoscopic ESCM using the LigaSure® system might be a safe and effective long-term technique. Given the results of our study and based on the literature reviewed, the clearest indication of endoscopic ESCM would be a medium-sized diverticulum. In this case, the cut system could be accommodated to achieve an adequate myotomy of the cricopharyngeal muscle, whereas small diverticula should be treated by surgery, as open myotomy alone is probably the most effective and safe procedure. The endoscopic approach may be preferable for elderly patients with a medium-sized diverticulum, as it is a safe and effective technique with a high percentage of symptom relief. However, it is necessary to perform studies with a larger sample size, long-term follow-up and comparative tests that evaluate various endoscopic devices and open surgical techniques. This will aid to establish a recommendation with regard to the safest and most effective technique for the patients with ZD.

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Table 1. Clinical scales

Dysphagia (Dakkak and Bennett)	
Asymptomatic	0
Dysphagia with solids	1
Dysphagia with semisolids	2
Dysphagia with liquids	3
Aphagia	4
Subjective state of health	
Very good	1
Good	2
Regular	3
Bad	4
Very bad	5
Regurgitation and respiratory symptoms	
Asymptomatic	0
< 1 time per week	1
> 1 time per week, < 1 time per day	2
1 time day	3
Daily symptoms	4

Table 2. Demographic and clinical characteristics of the population studied

Patients	
Total	18
Male (%)	10 (55)
Women (%)	8 (45)
Age, median (IQR, range), years	72 (17, 56-94)
Clinical characteristics	
Size of the diverticulum, median (IQR, range), mm	27.50 (21, 20-60)
Body mass index, median (IQR, range)	25 (4, 21-30)
Patients with dysphagia (%)	16 (88.9)
Score dysphagia, median (IQR, range)	2 (2, 0-3)
Patients with regurgitation (%)	18 (100)
Score regurgitation, median (IQR, range)	3 (1.25, 1-4)
Patients with respiratory symptoms (%)	10 (55.6)
Score respiratory symptoms, median (IQR, range)	1 (2.25, 0-3)
Score subjective health state, median (IQR, range)	4 (0, 2-5)

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Table 3. Results after treatment in 12 months

	Before	1 month	p	12 months	P
Dysphagia, median (range)	2 (0-3)	0 (0-1)	0.001	0 (0 - 1)	0.001
Regurgitation, median (range)	3 (1-4)	0 (0-1)	< 0.05	0 (0 - 1)	< 0.001
Respiratory symptoms, median (range)	1 (0-3)	0 (0-1)	0.007	0 (0 - 1)	0.007
Subjective health state, median (range)	4 (2-5)	1 (1-2)	< 0.05	1 (1-2)	0.001

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Fig. 1. Endoscopic septotomy of the cricopharyngeal muscle (ESCM) with LigaSure®. From left to right: the LigaSure® device; initial exposure of the septum after the correct placement of the diverticuloscope; section of the septum with no immediate complications.

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Fig. 2. Pre- and post-treatment radiology images. A. Esophagogram pre-septotomy: Zenker's diverticulum with retained contrast inside. B. Sequence of videodeglution images after treatment; there is an absence of retained contrast in the remnant.

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Fig. 3. Flowchart of the study.