

Medical treatment for sphincter of oddi dysfunction: Can it replace endoscopic sphincterotomy?

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Received: April 18, 2011 **Revised:** June 16, 2011
Accepted: February 27, 2012
Published online: April 14, 2012

Abstract

AIM: To report the results of a medical management of sphincter of oddi dysfunction (SOD) after an intermediate follow-up period.

METHODS: A total of 59 patients with SOD (2 men and 57 women, mean age 51 years old) were included in this prospective study. After medical treatment for one year, the patients were clinically re-evaluated after an average period of 30 mo.

RESULTS: The distribution of the patients according to the Milwaukee's classification was the following: 11 patients were type 1, 34 were type 2 and 14 were type 3. Fourteen patients underwent an endoscopic sphincterotomy (ES) after one year of medical treatment. The median intermediate follow-up period was 29.8 ± 3 mo (3-72 mo). The initial effectiveness of the medical treatment was complete, partial and poor among 50.8%, 13.5% and 35%, respectively, of the patients.

At the end of the follow-up period, 37 patients (62.7%) showed more than 50% improvement. The rate of improvement in patients who required ES was not significantly different compared with the patients treated conservatively (64.2% vs 62.2%, respectively).

CONCLUSION: Our study confirms that conservative medical treatment could be an alternative to endoscopic sphincterotomy because, after an intermediate follow-up period, the two treatments show the same success rates.

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Key words: Sphincter of oddi dysfunction; Cholecystectomy; Endoscopic sphincterotomy; Biliary scintigraphy

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Vitton V, Ezzedine S, Gonzalez JM, Gasmi M, Grimaud JC, Barthet M. Medical treatment for sphincter of oddi dysfunction: Can it replace endoscopic sphincterotomy? *World J Gastroenterol* 2012; 18(14): 1610-1615 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i14/1610.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i14.1610>

INTRODUCTION

Sphincter of oddi dysfunction (SOD) is a functional gastrointestinal abnormality characterized by pancreatobiliary pain that can be debilitating and may impair the quality of life. The cause of SOD remains speculative, but it could be due to hormonal or neurological disturbances of the sphincter of oddi (SO), leading to its intermittent obstruction despite the absence of organic

abnormalities^[1-4]. The best way to establish diagnosis and manage SOD remains controversial, mainly in SOD type 2 and 3 of the Milwaukee classification^[5,6]. The diagnosis of SOD is usually based on a high index of clinical suspicion. Direct endoscopic manometry of the SO is an invasive procedure that remains the gold standard for the diagnosis of SOD^[7-9]. However, dynamic biliary scintigraphy has been used as a non-invasive tool for evaluation of the SO by providing indirect evidence of increased sphincter resistance. The contribution of the biliary scintigraphy appears to predict, with good effectiveness, the clinical success of biliary endoscopic sphincterotomy in SOD types 1 and 2 of the Milwaukee classification^[10,11]. The management of SOD is also controversial, and it is based on the relaxation of the SO, which should improve the symptoms of SOD. The treatment can be accomplished pharmacologically either by an endoscopic procedure or surgically^[12,13]. The surgical procedure is often replaced by an endoscopic procedure^[14-16]. Several studies have suggested that there is a benefit from endoscopic sphincterotomy (ES) in SOD patients having high SO basal pressures at the time of manometry. However, procedural pancreatitis cannot be completely avoided, and surgical treatment will be necessary in some cases. Morbidity and mortality after ES have been reported to be as high as 9.8% and 2.3%, respectively. Moreover, long-term data regarding the rate of restenosis and complications resulting from repeated therapy are limited. If SO manometry findings are abnormal, the relief of pain after sphincterotomy occurs in 90%-95% of patients with type 1 SOD, 85% of patients with type 2 SOD, and 55%-60% of patients with type 3 SOD. However, almost uniformly and despite ES, some patients continue to have pain that is consistent with nonspecific chronic pain disorders, suggesting a multifactorial cause for SOD^[17-19]. Endoscopic stenting is no longer recommended as a routine method of treatment of SOD because endoscopic stenting is associated with poor symptomatic relief and a high risk of stent-induced pancreatitis^[20]. Many pharmacologic agents that are known to relax the SO have already been used in the management of SOD. However, although medical therapy may be an attractive initial approach in patients with sphincter of Oddi dysfunction, data on intermediate clinical outcomes associated with pharmacological treatment is scant^[21-31]. In a recent study^[32], we showed that a one-year treatment period with trimebutine could significantly reduce pain in patients suffering from SOD, reducing the need for ES. Our aim in the current study was to determine the efficacy of medical therapy in relieving symptoms of SOD compared to ES after a prolonged follow-up period.

MATERIALS AND METHODS

As described in our previous study^[32], fifty-nine patients complaining of SOD were included in this prospective monocentric study between 1999 and 2005. The patients

included 57 women and 2 men, with a mean age of 50.5 ± 12.3 years old (range 20-75 years old), which were followed for a mean duration of 29 mo after the end of the endoscopic or medical treatment. The main inclusion criterion was biliary or pancreatic pain after cholecystectomy after ruling out the diagnosis of residual lithiasis or the presence of a tumor. The following data were collected: age, sex, cholecystectomy, the time elapsing since the onset of the symptoms, pain and rate of SOD occurrence. All of the patients underwent biliopancreatic endoscopic ultrasonography in order to rule out the diagnosis of a residual lithiasis or the presence of a tumor (none of the patients underwent secretin-magnetic resonance cholangiopancreatography). The diameters of the main biliary pathway and the canal de Wirsung were systematically measured during these procedures. An initial biological check-up was carried out when the first painful episode occurred after the medical consultation. The biological check-up included the measurement of the following proteins: transaminases (alanine aminotransférase and aspartate aminotransférase), gamma-glutamyl-transferase, alkaline phosphatases, total and conjugate bilirubin, amylase and lipase. PD-SOD was defined as the association between recurrent pancreatic pain with an increased level of serum lipase (> 3N). An initial biliary scintigraphy was carried out systematically on all of the patients. An initial hepatic and pancreatic biological assessment was done at the first event of abdominal pain. In addition, a biliary scintigraphy was performed for all patients in order to determine the isotopic hile to duodenum transit time (HDTT). According to the Milwaukee classification of SOD, the patients were subdivided into three groups. All of the patients were clearly informed about the various therapeutic modalities to manage their disease, the chances of success and the rates of complications of the medical therapy or endoscopic treatment. For each patients, we proposed an initial management of SOD by medical treatment, planned for a one-year duration; it consisted of a combined treatment, an association of trimebutine (200 mg three times per day) and nitrates taken sublingually when needed, mainly at the onset of abdominal pain. In the case of intolerance or counter-indication to the nitrates, a treatment with trimebutine alone was proposed. If previous treatment with trimebutine had been unsuccessful, only the nitrate derivatives were prescribed. If the painful attacks occurred too frequently (> 1 per week), a transdermal nitrate treatment (5 mg/d) was prescribed. The patients attended clinical follow-up consultations every four mo for a period of one year. After one year of medical therapy, an evaluation of painful symptoms was performed for each patient. The efficacy of the treatment was considered complete if there was a complete disappearance of the painful symptoms; the efficacy was considered partial if there was a greater than 50% reduction in the frequency and intensity of the pain and considered poor when the frequency and intensity of the pain decreased by less than 50%. In the cases where the medical treat-

Age, mean \pm SD, yr	50.5 \pm 12
Sex, M/F	2/57
Symptoms	
Biliary	47 (79.6)
Pancreatic	9 (15.2)
Biliopancreatic	3 (5)
Occurrence of painful episodes	
Once a week	9 (15.8)
Once a month	20 (35.1)
Every 3 mo	9 (15.8)
Every 6 mo	3 (5.3)
Once a year	7 (12.3)
Dilatation of biliary or pancreatic ducts (bile duct > 12 mm; pancreatic duct > 4 mm)	
Main biliary duct dilatation	29 (49.1)
Main pancreatic duct dilatation	1 (1.7)
Milwaukee classification repartition	
Type 1	11 (18.6)
Type 2	34 (57.6)
Type 3	14 (23.7)
Initial elevation of laboratory data	34 (57.6)
Lengthening of the isotopic transit time	32 (54.2)

ment was only partially successful or poor, endoscopic sphincterotomy was proposed to the patients, but not to the remaining patients. If medical treatment was successful, endoscopic treatment was not proposed. When the indications for endoscopic treatment had been chosen, the patients received clear information concerning the procedure. The endoscopic treatment was performed under general anaesthesia and consisted of an endoscopic retrograde cholangiopancreatography, with realization of a biliary sphincterotomy on patients with isolated biliary symptoms or dual sphincterotomy (biliary and pancreatic) on patients with both biliary and pancreatic symptoms. All of the patients were called by telephone to propose a follow-up examination with a hepatic biological assessment and an abdominal ultrasound in order to measure the diameter of the main biliary and pancreatic ducts; among the patients who refused this assessment, a simple evaluation of the clinical symptoms was proposed. The management was considered successful if there was an improvement greater than 50% compared to the initial symptoms; it was considered a failure if there was an absence of significant improvement by the patient. This study was approved by our local ethics committee.

Statistical analysis

Statistical analysis was carried out on the data with the Statview software program (Abacus concept, Inc., Berkeley, CA, 1992). Quantitative data were expressed as the mean \pm SD. The significance of the differences was tested using the Student's *t* test or paired *t* tests to make comparisons between groups. Nonparametric tests (Mann Whitney tests) were performed when the Student's *t* test was not appropriate. The qualitative variables were compared using the chi-square test with Yate's correction when appropriate and with Fisher's exact test for 2 \times 2 contingency tables. The significance threshold was set at $P < 0.05$.

Global effect		
Complete or partial	38 (64.3)	$P < 0.05$
Poor	21 (35)	
Complete or partial effect according the Milwaukee group		
Type 1	5 (45)	$P = 0.31$
Type 2	23 (67)	
Type 3	10 (71)	
Complete or partial effect according to the increase of HDTT		
With prolongation of HDTT	21 (55.3)	$P = 0.77$
Without prolongation of HDTT	17 (44.7)	

HDTT: Hile to duodenum transit time.

RESULTS

Characteristics of the SOD and treatment

The patients developed the symptoms of SOD after a mean period of 9.3 ± 1.2 years (range, 1-38 years) after the cholecystectomy. The patient's main characteristics are presented in Table 1. According to the three Milwaukee groups, there were no significant differences in age (type 1, 56.2 ± 2.1 years old; type 2, 48.1 ± 2.1 years old; and type 3, 52.1 ± 3.5 years old, $P = 0.22$) or the time elapsing from diagnosis to the cholecystectomy (type 1, 11 ± 3.6 years; type 2, 8.6 ± 1.6 years; and type 3, 10 ± 2.4 years; $P = 0.93$). Five patients were treated with nitrates only (8.4%), 12 were treated with trimebutine only (20.3%), and 42 patients had a combined treatment of nitrates and trimebutine (71.1%). The mean duration of the treatment period was 11.5 ± 0.8 mo. The efficacy of the medical therapy was considered to be complete or partial in 38 patients (64.3%) and poor in 21 patients (35%). Details concerning the success of the medical treatment are presented in Table 2. Among the 21 patients with poor results from the medical management, 14 (23.7%) agreed to undergo ES, including 12 with an isolated biliary sphincterotomy and 2 with an associated pancreatic sphincterotomy (dual sphincterotomy). In patients with a dual sphincterotomy, a pancreatic duct stenting was performed. A lengthening of the isotopic time of transit was present before the ES in 11 patients of the 14 who underwent this intervention (78.5%) and in 21 patients of the 45 without ES (46.6%) ($P = 0.02$). Other characteristics concerning ES are presented in Table 3. The complications of the ES were severe acute pancreatitis in two cases, which had resolved favourably with medical treatment. Among the patients requiring an ES, three patients had mixed biliary and pancreatic symptoms, and 9 patients had an isolated pancreatic pattern; among these patients, only 3 had a lengthening of the HDTT on the biliary scintigraphy corresponding to the 3 patients with isolated pancreatic symptoms as defined in the Materials and Methods section.

Intermediate follow-up period

Five patients refused to participate in the follow-up period. The intermediate follow-up period was 29.8 ± 3 mo (3-72 mo). Thirty-seven patients either did not pres-

Table 3 Results of the endoscopic treatment (n = 14), (%)

Time between the beginning of medical therapy and endoscopic treatment (mo)	12.2 ± 1.5
Patients concerned	
Patients with poor response to medical treatment	12 (57.1)
Patients with a partial response	2 (25)
Indication according to Milwaukee group	
Type 1	4 (36)
Type 2	9 (27)
Type 3	1 (7)
Results according to Milwaukee group	
Type 1	3/4 (75)
Type 2	6/9 (66)
Type 3	0/1 (0)

Table 4 Results after intermediate follow-up (29.8 ± 3 mo) n (%)

Rate of improvement		
Total rate	37 (62.7)	
Without endoscopic sphincterotomy	28 (62)	P = 0.88
With endoscopic sphincterotomy	9 (64.2)	
According to initial lengthening of HDTT		
With lengthening	19 (59.4)	
Without lengthening	18 (66.7)	P = 0.59
According to the Milwaukee group		
Type 1	6/11 (54.5)	
Type 2	23/34 (67.6)	P = 0.75
Type 3	8/14 (57.1)	

HDTT: Hile to duodenum transit time.

ent any additional painful events or improved by more than 50% (62.7%). Twenty-two patients still presented painful episodes (38.6%). The characteristics of the patients following endoscopic treatment are presented in Table 3. An abdominal ultrasound was performed in 45 patients and highlighted a dilation of the main biliary duct in 10 patients (22%). A biological laboratory assessment was also performed in these 45 patients. Among these patients, 6 still presented abnormal liver and pancreatic enzyme serum levels. At the end of the follow-up period, there was no significant difference in the size of the main biliary duct (at the beginning of the study, 49% of patients had dilation, and at the end of the study, 22% still had dilation of the main biliary duct) ($P = 0.49$); these characteristics are presented in Table 4.

DISCUSSION

The present study demonstrates that medical management with trimebutine may improve pain in patients suffering from SOD. Moreover, our study shows that after an intermediate follow-up period, the success of medical treatment (62%) does not differ from that of ES (64%). The medical treatment of SOD is usually disappointing, although nitrates or calcium-channel blockers can decrease basal pressure of the SO^[32-36]. A positive effect of erythromycin on the motility of the SO has been suggested, but its clinical efficacy has not been demonstrated^[29]. Somatostatin also modifies the SO activity but in the direction of an increase in the frequency of the phasic contractions of basal pressure. Therefore, somatostatin would be of little benefit for the indication of SOD and would not be suitable as a preventive measure after endoscopic retrograde cholangiopancreatography. The injection of botulinum toxin within the sphincter was tested in humans and pigs and promoted a significant reduction in the basal pressure in 50% of the cases^[37-41]. On the clinical level, the injection of botulinum toxin was beneficial in 55% of the patients who suffered from biliary pain post-cholecystectomy without disturbance of the hepatic enzymes or dilation of the bile duct. However, 90% of the patients who experienced improvement presented a recurrence of symptoms after 6 mo, making the effect of botulinum toxin inconstant

and transitory^[37-41]. Endoscopic management is mainly based on the ES, requiring SOD diagnosis to be formally established, i.e., based on the description of a basal high pressure of the SO. However, despite its high rate of success (86%-91%), ES is associated with high morbidity (19%-30%). Moreover, the natural course of SOD has not been well documented so far, so that the use of this endoscopic strategy remains highly controversial^[42-49].

Our research group previously described the effects of trimebutine on Oddi motility in a prospective study on patients with post-cholecystectomy pain^[29]. We also reported in another study^[32] that a one-year medical management could avoid the need for ES and had a success rate of 64%. Kovács *et al.*^[21] previously suggested that, depending on the Milwaukee classification, medical treatment should be first attempted and its efficacy subsequently reassessed; if this treatment fails or is poorly tolerated, ES can then be proposed, especially for type 1 or 2 SOD patients, based on the presence of a lengthening of the HDTT. The lengthening of the HDTT as a factor for predicting a favourable response to ES decreases with the Milwaukee types, as mentioned by Cicala *et al.*^[17]. In our study, 100% of the type 1 patients, 78% of the type 2 patients and none of the type 3 patients showed a lengthening of the HDTT and underwent ES successfully, whereas the immediate efficacy of ES was only 86%. This ES success rate is quite similar to the success rate reported in the literature, which ranged between 86% and 91%^[18,50-52]. Few studies have addressed the intermediate natural history of SOD. The available data suggest that the clinical course is variable depending, in part, on the initial biliary classification. In a one-year follow-up study, seven SOD type 2 patients with abnormal SO pressure treated by a sham procedure continued to have symptoms, which ended only after subsequent ES. All patients continued to do well four years later. Five other SOD type 2 patients with abnormal SO pressure refused ES; after four years, three were unimproved while two had “fair” improvement. The clinical course was unpredictable after a sham or ES treatment in patients with SOD type 3 biliary pain. In another report, 11 such patients were followed for two years after ES. Four improved symptomatically, while

seven had no change in their symptoms. Eleven other patients had a sham procedure, five of which improved, while six had no change in their symptoms during a two-year follow-up period^[53]. In our study, the monitoring of the response rate to ES after an average period of 29 mo showed a loss of efficacy of the ES in 3 patients. Therefore, the rate of patient improvement did not differ significantly in the presence or absence of a previous ES according to the performance or not of an ES.

In conclusion, our study confirms that a conservative medical treatment could be an alternative to ES because, after an intermediate follow-up period, the two treatments show the same success rates.

COMMENTS

Background

Sphincter of oddi dysfunction (SOD) is a symptom characterized by recurrent abdominal pain. It has been showed that endoscopic treatment called endoscopic sphincterotomy (ES) can improve symptoms but with a high level of complications. Pharmacologic agents have been tested in this pathology but are still disappointing.

Research frontiers

Many ways of treatment (medical, endoscopic) are still studied because none of them offer a satisfying and safe rate of prolonged improvement.

Innovations and breakthroughs

The authors here demonstrate that, after a long follow-up (29 mo), a medical treatment with trimebutine can have the same success rate than ES.

Applications

The demonstration of a long-term efficacy of a medical conservative treatment is important because it can avoid the need for ES which is associated with morbidity and mortality after ES of 9.8% and 2.3% respectively. This study demonstrates that a medical conservative treatment with trimebutine may be an effective alternative to the endoscopic sphincterotomy since, after an intermediate follow-up, the two treatments show the same success rate.

Terminology

The sphincter of oddi is a muscular valve that controls the flow of digestive juices (bile and pancreatic juice) through the ampulla of Vater into the second part of the duodenum. ES is an endoscopic technique developed to examine and treat abnormalities of the bile ducts, pancreas and gallbladder. The procedure was developed as an extension to the diagnostic examination, endoscopic retrograde cholangio pancreatography; with the addition of "sphincterotomy", abnormalities found during the study could be treated at the same time without the need for invasive surgery.

Peer review

This study is about the results of a medical management of SOD after an intermediate follow-up. It is well-written.

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