ORIGINAL ARTICLE
doi: 10.35366/110698

Cirujano General
January-March 2023
Vol. 45, no. 1 / p. 14-20

Type I and II sphincter of Oddi dysfunction: a case-control study

Disfunción del esfínter de Oddi tipo I y II: estudio de casos y controles

Juan de Dios Díaz-Rosales,[*] Sergio Morales-Polanco,[‡]
Dante Deras-Ramos,[§] Goretti Yáñez-Muñoz[¶]

Keywords:
choledocholithiasis, sphincter of Oddi dysfunction, dyskinesia, stenosis.

Palabras clave:
coledocolitiasis, disfunción del esfínter de Oddi, discinesia, estenosis.

ABSTRACT

Introduction: the sphincter of Oddi is a valvular complex that regulates bile flow and pancreatic secretion. The sphincter of Oddi dysfunction is divided into stenosis (type I) or dyskinesia (type II). This study aims to describe this pathology's scenario, compare it with cases of choledocholithiasis, and demonstrate if there are differences or similarities. **Material and methods:** a case-control study was performed where patients sent to gastrointestinal endoscopy with a diagnosis of benign biliary tract obstruction were analyzed between the period from January 2019 to December 2021. **Results:** there was no statistically significant difference between the characteristics of patients with sphincter of Oddi dysfunction and proven choledocholithiasis. Verifying the statistic revealed differences in cannulation strategies or post-endoscopic retrograde cholangiography pancreatitis was also impossible. **Conclusions:** type I and type II sphincter of Oddi dysfunction should be considered as the same entity and treated with the same therapy (endoscopic retrograde cholangiopancreatography with sphincterotomy). Choledocholithiasis and sphincter of Oddi dysfunction behave as similar pathological spectra, since the clinical features involved do not show relevant statistical differences.

RESUMEN

Introducción: *el esfínter de Oddi es un complejo valvular que regulariza el flujo biliar y la secreción pancreática. La disfunción del esfínter de Oddi se divide en estenosis (tipo I) o discinesia (tipo II). El objetivo de este estudio es describir el escenario de esta patología, hacer una comparativa con casos de coledocolitiasis y demostrar si existen diferencias o similitudes.* ***Material y métodos:*** *se realizó un estudio de casos y controles donde se analizaron pacientes enviadas a endoscopia gastrointestinal con diagnóstico de obstrucción benigna de la vía biliar entre el periodo de enero de 2019 a diciembre de 2021.* ***Resultados:*** *entre las características de las pacientes con disfunción del esfínter de Oddi y coledocolitiasis comprobada no hubo diferencia estadísticamente significativa. Tampoco fue posible verificar diferencias estadísticamente reveladoras en las estrategias de canulación ni en la pancreatitis postcolangiografía retrógrada endoscópica.* ***Conclusiones:*** *la disfunción del esfínter de Oddi tipo I y II deberá considerarse como una misma entidad, tratarse con una misma terapéutica (colangiopancreatografía retrógrada endoscópica con esfinterotomía). La coledocolitiasis y la disfunción del esfínter de Oddi se comportan como espectros patológicos similares, ya que las características clínicas implicadas no muestran diferencias estadísticas relevantes.*

[*] General Surgeon and Gastrointestinal Endoscopist. General Hospital of Zone No. 35 of the Mexican Institute of Social Security (IMSS). Mexico.
[‡] Gastroenterologist and Gastrointestinal Endoscopist. Regional General Hospital No. 66 of IMSS. Mexico.
[§] Undergraduate Medical Intern. Institute of Biomedical Sciences, Autonomous University of Ciudad Juarez, Ciudad Juarez, Chihuahua, Mexico.
[¶] Third-year Resident of General Surgery. Regional General Hospital No. 66 of IMSS. Mexico.

Received: 11/13/2022
Accepted: 02/22/2023

INTRODUCTION

The sphincter of Oddi is a valvular complex composed of smooth muscle that regulates bile flow and pancreatic secretion into the duodenal lumen. It has a resting pressure of 15 mmHg. It comprises a biliary sphincter and a pancreatic sphincter joined at their distal portion to form the ampullary sphincter at the level of the second duodenal portion.[1]

Sphincter of Oddi dysfunction (SOD) is a diagnosis of exclusion and encompasses a variety of disorders that result in inappropriate function (stenosis or dyskinesia) of this valve.[2] This dysfunction is associated with abdominal pain (although

How to cite: Díaz-Rosales JD, Morales-Polanco S, Deras-Ramos D, Yáñez-Muñoz G. Type I and II sphincter of Oddi dysfunction: a case-control study. Cir Gen. 2023; 45 (1): 14-20. https://dx.doi.org/10.35366/110698

a non-painful variant exists),[3] elevation of liver and pancreatic enzymes, bile duct and pancreatic duct dilatation, and may also be associated with pancreatitis.[4] Although both genders can be affected, it is more common in women aged 20-50 years.[5] The prevalence of this disease in patients with biliary pain after cholecystectomy is 14%.[6]

In both variants of SOD (stenotic and dyskinetic), it is suggested that its etiology is similar, and trauma is necessary (probably from a litho smaller than 5 mm), which, when passing through the sphincter of Oddi, causes inflammation and the consequent formation of a fibrotic ring by scarring (in half of the cases) leading to the SOD syndrome.[4]

This entity has been controversial since its first description, initially stratified according to the Milwaukee classification *(Table 1)* and later modified by Rome IV scale *(Table 2)*. This study aims to describe the scenario in a second-level center facing this pathology, compare it with cases of choledocholithiasis, and demonstrate if there are differences or similarities.

MATERIAL AND METHODS

A case-control study was conducted where female patients referred to the gastrointestinal endoscopy service diagnosed with benign bile duct obstruction (diagnosis of choledocholithiasis referral) were studied from January 2019 to December 2021. Patients were selected for the case group who met the criteria for SOD: biliary pain, altered LFTs (liver function tests) and bile duct dilatation, absence of choledocholithiasis and structural alteration in the bile duct (Rome IV criteria), who had a history of uncomplicated cholecystectomy (open or laparoscopic). As

Table 1: Milwaukee classification for sphincter of Oddi dysfunction.

	Type I	Type II	Type III
Biliary pain	+	+	+
Altered LFTs	+	±*	–
Bile duct dilatation	+	±*	–
Delayed biliary drainage	+	±*	–

LFTs = liver function tests with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) twice the average on two or more occasions.
Bile duct dilatation ≥ 12 mm on ultrasound or > 10 mm on cholangiography.
Delayed biliary drainage = drainage of contrast medium delayed for > 45 minutes after ERCP.
* One or two positive factors.

Tabla 2: Criterios diagnósticos para disfunción de esfínter de Oddi de tipo biliar según Roma IV.

Must include:
1. Biliary-type pain
2. Elevated liver enzymes or dilated bile duct (> 6 mm)
3. Absence of choledocholithiasis or other structural alterations of the biliary tract

Support criteria:
1. Normal amylase/lipase
2. Abnormal sphincter of Oddi manometry
3. Abnormal hepatobiliary scintigraphy

Suspected sphincter of Oddi dysfunction: biliary type pain + at least one associated objective finding.
Episodic functional abdominal pain: biliary-type pain without any other alteration.

support criteria, patients with amylase/lipase within normal parameters at the time of the study were included. For the control group, 60 female patients with endoscopic retrograde cholangiopancreatography (ERCP)-confirmed diagnoses of choledocholithiasis whose resolution occurred at the endoscopic event were selected. In both groups, an inclusion criterion was that they had not undergone previous ERCP.

The following were evaluated: age, weight, height, body mass index (BMI), age over 55 years, previous pancreatitis, bilirubin and their differential, alanine aminotransferase, aspartate aminotransferase, extrahepatic bile duct (EHBD) size, difficult cannulation, cannulation attempts, precutting, and post-ERCP pancreatitis.

Two groups were pooled, the group with SOD versus choledocholithiasis, and the established variables were analyzed. Values were expressed as absolute values and percentages for categorical variables. They were compared with the χ^2 test or Fisher's exact test. In contrast, quantitative variables are expressed as averages, ± standard deviation, and were compared with Student's t-test (for variables of normal behavior) or Mann-Whitney U test (for non-normal behavior variables). A value of less than 0.05 was considered statistically significant. The analyses were performed with SPSS Statistics, Version 25.0 (Armonk, NY: IBM Corp).

RESULTS

Twenty-two cases with a diagnosis of SOD were studied, and 60 control patients with choledocholithiasis were included. Patients who met the criteria for suspected DEO were referred with a diagnosis of suspected choledocholithiasis. Four patients (18.2%) had a previous diagnosis of pancreatitis. The papilla of native characteristics was found in all 22 patients. Cholangiography evidenced increased caliber without filling defects in all patients; a pencil-point termination and adequate drainage of contrast medium were observed after sphincterotomy. Ten patients (45.4%) were cannulated with difficulty criteria with an average of 3.8 attempts. Precut papillotomy was used to cannulate in four patients (18.2%), and in all 22 patients (100%), cholangiography and sphincterotomy were performed as treatment of the presumed diagnosis of SOD. Extrahepatic bile duct sweeping was performed in 17 patients (77.3%) as part of bile duct securing. Three patients (13.6%) had post-ERCP pancreatitis as a complication (in one of these patients was severe), but there was no mortality.

In the characteristics of patients with SOD and proven choledocholithiasis, there was no statistically significant difference in any of the morphological or laboratory variables *(Table 3)*.

Nor could it prove statistically significant differences in cannulation strategies or post-ERCP pancreatitis *(Table 4)*.

DISCUSSION

SOD is a broad functional disorder involving a valve with inappropriate spasm or relaxation and stenosis. It has an estimated prevalence of 1.5% in the general population; however, it appears underestimated due to the lack of biochemical markers for its identification. Manometric studies reveal that up to 10% of biliary tract interventions involve the papilla, even with no lithosclerosis lesions.[7] In a study carried out in the *Hospital Juárez de México*, a prevalence (probable diagnosis) of DEO of 16.5% was observed,[8] while in the *Hospital Central Militar*, the prevalence was 18.9% (52 cases in 269 CPREs),[9] while in another study published by our group a prevalence of 20% was reported.[10] In patients with chronic or idiopathic pancreatitis, the prevalence of SOD can reach 59 and 72%, respectively.

In our study, the mean age of patients with SOD was lower than in another study performed in Japan (50.5 versus 62 years); however, our study was performed only in women, whereas in the study mentioned above, women accounted for 69.4% of the participants.[11] In that same study, previous pancreatitis was observed in 22%, whereas in our analysis, the history of previous pancreatitis was 18.2%. Regarding the caliber of the SBV, in the Japanese study, it was 12.2 mm, while in our study, it was 9 mm.

The Milwaukee classification was first used in SOD; however, this classification could lead to confusion, so the Rome IV criteria (which avoid using manometry) are now used to diagnose.[12] According to Rome IV, type I SOD no longer exists and should be classified as benign papillary stenosis (mechanical obstruction), not a functional disorder. In contrast, type III SOD is considered a functional entity that appears to be unrelated to the sphincter of Oddi per se.[3] Thus, type II SOD (according to Rome IV) is currently classified as the true SOD.[13] It will take some time to separate benign papillary stenosis from functional disorders (Rome IV). This diagnosis will be permanently linked to SOD and will probably continue to be referred to as type I SOD (even if manometry is not used to make the diagnosis).

Table 3: Patient features.

	SOD (N = 22)	Choledocholithiasis (N = 60)	p
Age [years]*	50.5 ± 16.4	46.6 ± 16.2	0.3‡
Weight [kg]*	76.2 ± 17.4	76.7 ± 15.9	0.9‡
Height [m]*	1.58 ± 0.8	1.62 ± 0.8	0.08§
BMI [kg/m²]*	29.9 ± 5.05	28.9 ± 5.7	0.5‡
> 55 years, n (%)	9 (40.9)	11 (27.5)	0.3¶
Pancreatitis prior to ERCP, n (%)	4 (18.2)	5 (12.5)	0.7¶
TB [mg/dl]	3.5 ± 1.9	3.6 ± 2.5	0.8‡
DB [mg/dl]	2.2 ± 1.2	2.1 ± 1.6	0.9‡
IB [mg/dl]	1.3 ± 0.7	1.5 ± 1.01	0.4‡
ALT	264 ± 215.5	250.8 ± 192.6	0.8§
AST	228 ± 271	204.1 ± 192.6	0.8§
EBD size [mm]	9 ± 3.7	11.2 ± 5.2	0.6§

SOD = sphincter of Oddi dysfunction. BMI = body mass index. ERCP = endoscopic retrograde cholangiopancreatography. TB = total bilirubin. DB = direct bilirubin. IB = indirect bilirubin. ALT = alanine aminotransferase. AST = aspartate aminotransferase. EBD = extrahepatic bile duct.
* Data are mean ± standard deviation. ‡ Student's t-test. § Mann-Whitney U. ¶ Pearson's χ^2.
Source: IMSS electronic file HGZ No. 35.

Table 4: Sphincter of Oddi cannulation.

Variable	SOD (N = 22) n (%)	Choledocholithiasis (N = 40) n (%)	p
Cannulation (difficult)	10 (45.5)	14 (35)	0.4‡
Cannulation attempts*	3.8 ± 2.5	2.9 ± 2.01	0.18§
Precut	4 (18.2)	12 (30)	0.35¶
Post-ERCP pancreatitis	3 (13.6)	5 (12.5)	0.6¶

* Data are mean ± standard deviation. ‡ Pearson's χ^2. § Mann-Whitney U test. ¶ Fisher's exact test.
SOD = sphincter of Oddi dysfunction.
Source: IMSS electronic file HGZ No. 35.

It is questionable whether SOD is a primary pathologic process or a consequence of a traumatic alteration of the sphincter of Oddi. The surgical history suggests that it is the second option, so a patient with recurrent symptoms after cholecystectomy (due to cholelithiasis) may be a case of secondary benign papillary stenosis or type I SOD. Differentiating the purely dysfunctional process (dyskinesia) from the stenotic process is very complex. Since the treatment is similar, it can be stated that patients with a history of cholecystectomy could suffer from stenosis-type dysfunction. In contrast, those without a history of cholecystectomy and evidence of gallbladder or common bile duct lithiasis could be considered fully functional (dyskinesia).

Diagnosis is complex, and overlooking it leads to complications such as recurrent biliary symptoms, elevated liver enzymes, and even pancreatitis.[14] There will be controversy regarding the pain of SOD because the characteristic is biliary type, which is related to food (there are authors who refer that pain in SOD is not related to food), usually lasting from 30 minutes to a few hours and resolves spontaneously. The diagnostic suspicion starts with the pain clinic and laboratories, including bilirubin, liver enzymes, amylase, and lipase. Alkaline phosphatase may provide a clue for diagnosis without increased bilirubin or pancreatic enzymes.[7] It is imperative to rule out the presence of choledocholithiasis or other biliopancreatic or ampulla of Vater alterations, which could condition the picture.[6]

Differentiating it from choledocholithiasis was not possible in this study; there were no characteristics with statistically significant differences, so in our environment, ERCP has a current role in the diagnosis and treatment of this entity, even without a previous diagnostic suspicion.

The gold standard for diagnosis is the sphincter of Oddi manometry, whose pressure > 40 mmHg (three standard deviations above average) makes the diagnosis. Patients with benign papillary stenosis (SOD type I) may have normal manometry up to 15-35%,[15] while patients with dyskinesia dysfunction (SOD type II) may have normal manometry up to 45%.[15] This suggests that the pure increase in the sphincter of Oddi pressure is insufficient to cause the disease's symptoms.[15]

ERCP with sphincterotomy is the management in patients with type I (stricture) and type II (dyskinesia) SOD with a short-term success rate greater than 90%;[11] while other series report a success rate of 60 to 94% in patients whose diagnosis was not based on manometry.[16] The recurrence rate after sphincterotomy treatment is 32% within six months; however, this recurrence is related to the presence and development of functional dyspepsia.[11]

The rates of post-ERCP pancreatitis in SOD range from 0 to 30% (if ERCP is accompanied by manometry), so performing manometry seems to be a risk factor for this complication.[2] In this study, the rate of post-ERCP pancreatitis was 13.6% lower compared to a Japanese study, where the rate of post-ERCP pancreatitis was 36%;[11] this is a very high rate even for those patients undergoing sphincterotomy. Mortality from adverse events after ERCP is 0.08%.[17] In our study, all cases underwent sphincterotomy as treatment with a rate of post-ERCP pancreatitis acceptably like controls with choledocholithiasis (13.6 versus 12.5%, p = 0.6). ERCP with sphincterotomy is indicated in patients with SOD who meet the criteria of biliary-type pain, altered liver function tests, and bile duct dilatation[4] with a greater than 90% success rate in patients.[18]

It is recommended that during ERCP for type I and type II SOD, indomethacin 100 mg or diclofenac 75 mg rectally before or after the procedure are administered,[19] and place a pancreatic stent 5 Fr and 4 cm in case of unintentional cannulation of the pancreatic duct,[16] and that epinephrine be sprayed on the papilla after the procedure.[17]

In our region (Ciudad Juarez), there is no access to the sphincter of Oddi manometry studies, and this scenario is constant in most of the country. Moreover, this procedure is less and less used due to the added risk of pancreatitis that it entails. Other study methods include scintigraphy with a lower sensitivity than manometry (which shows

delayed emptying).[20] In public and second-level medical centers, there is also no access to imaging studies of the biliary tract, such as magnetic resonance cholangiography, so ERCP is still valid as a diagnostic study? The diagnosis of SOD in most hospitals is based on the Rome IV criteria or post-ERCP findings (in post cholecystectomy patients). It is stated that 10% of patients may have a complete diagnostic workup, and this percentage needs to be revised.[19] In these cases, how prudent is treating them even without complementary studies? In all the cases in this study, the diagnosis was made post-ERCP, and to make this diagnosis, the presence of choledocholithiasis or an ampullary tumor had to be excluded.[4]

This study has weaknesses: it is a retrospective study in a single hospital center, the lack of follow-up of patients to observe the resolution of their symptoms, and the long-term response rate after sphincterotomy.

CONCLUSIONS

Both type I (stenosis) and type II (dyskinesia) SOD should be considered as the same entity that is treated with the same therapy (ERCP with sphincterotomy). Type III SOD will be reassigned to a functional entity in its entirety, the treatment of which will be purely medical. Ideal medicine is far from our reality, and international guidelines only sometimes fit the national scenario. Considering and treating type I and type II dysfunction with the only thing we have (sphincterotomy) may be risky, but it is still justified. Choledocholithiasis and SOD show that their clinical characteristics involved do not present relevant statistical differences.

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Ethical considerations and responsibility: data privacy. According to the protocols established in our work center, we declare that we have followed the protocols on patient data privacy and preserved their anonymity.

Funding: no financial support was received for the preparation of this work.
Disclosure: none of the authors have a conflict of interest in the conduct of this study.

Correspondence:
Juan de Dios Díaz-Rosales, MD
E-mail: jdedios.diaz@uacj.mx