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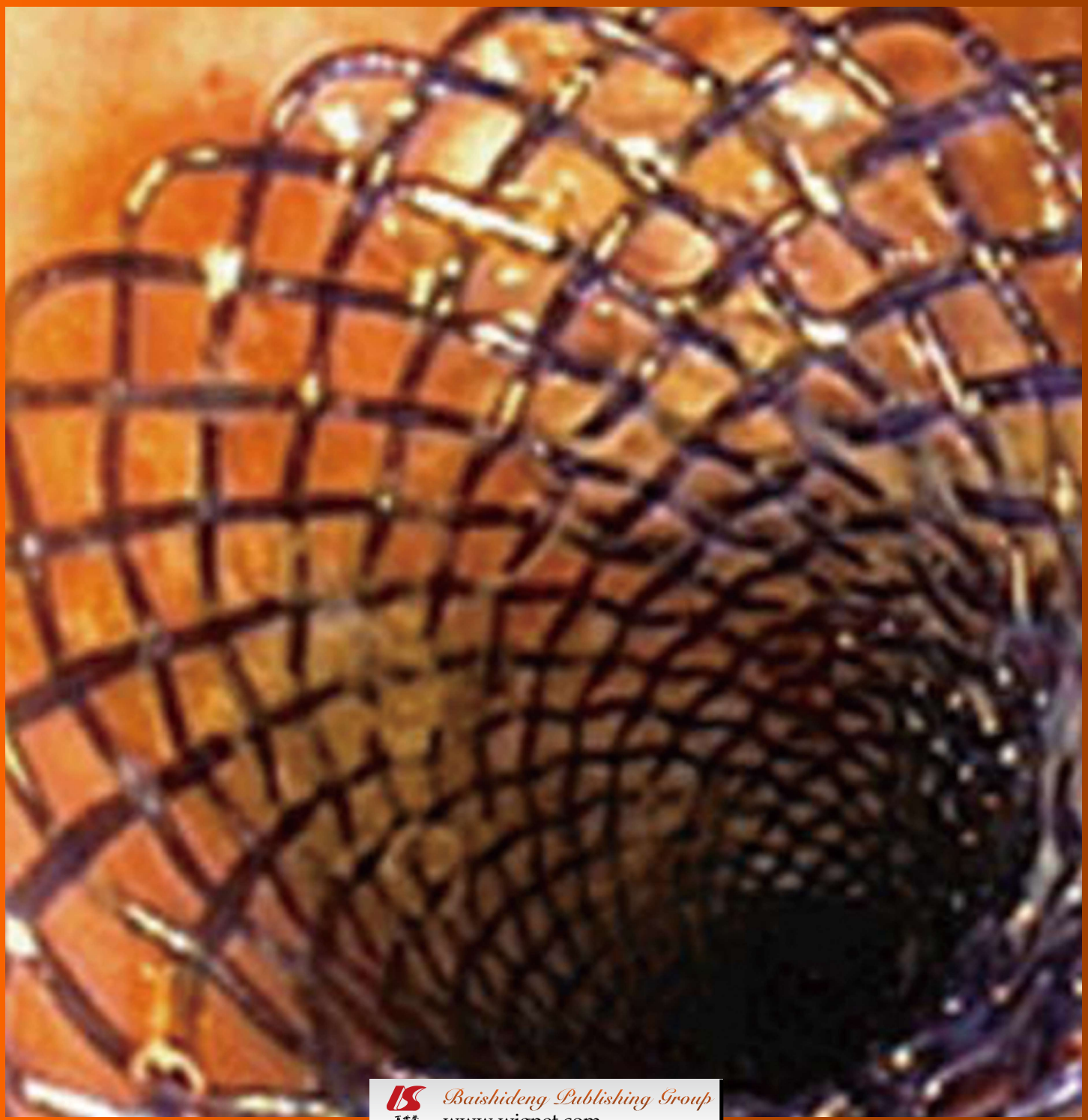

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Single operator choledochoscopy and its role in daily endoscopy routine

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Abstract

Different diagnostic procedures exist for the detection of bile duct lesions in clinical practice. However, neither retrograde contrast imaging of the bile duct endoscopic retrograde cholangiopancreatogram nor other imaging procedures allow a safe diagnosis of the lesions. Therefore choledochoscopy may be a useful diagnostic procedure in macroscopic assessing lesions of the bile duct. Even if the diagnostic sensitivity and specificity is not sufficient, first studies suggest an enhanced diagnostic accuracy for choledochoscopy. Since the progress of choledochoscopy has started in the 1970 different improvements were achieved. Meanwhile, the examination can be performed by an examiner and samples can be taken. Image and Resolution quality has improved over the past years, also. The SpyGlass system is a technically advanced cholangioscopic device to provide endoscopic diagnosis in case of inconclusive bile duct findings. Further more, two more lumina allow specific biopsy forceps and optical fibers for electrohydraulic or laser lithotripsy. The most frequent useful insert of SpyGlass in clinical practice are in complex gallstones and bile duct lesions of unclear dignity.

Key words: Endoscopic retrograde cholangiography; Endoscopic choledochoscopy; SpyGlass Direct Visualization System™; "Mother-baby" endoscope technique; Gallstones; Bile duct lesions

Core tip: To date, technical restrictions of endoscopic retrograde cholangiopan-creatogram may explain the insufficient sensitivity of diagnostics when biliary changes are suspected. Therefore choledochoscopy may be a direct diagnostic procedure to help. SpyGlass™ is a technically advanced cholangioscopy system facilitating diagnostics in the bile duct due to its single-operator feature. Different studies reported a clearly enhance diagnostic accuracy for this technique. However, the visualization of bile duct lesions itself is of great value since it offers precise dignity evaluation based on macroscopic criteria.

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INTRODUCTION

To date, the prediction of dignity for indistinct bile duct lesions in clinical practice are a difficult endeavour and mean a true diagnostic challenge to all disciplines involved. Neither retrograde contrast imaging of the bile duct endoscopic retrograde cholangiopancreatogram (ERCP) nor other imaging procedures allow for a safe diagnosis of the type if biliary duct findings are inconclusive like the ones experienced with strictures or intraluminal defects[1]. Even with steadily improved endosonography and the use of microprobes enhancing bile duct lesion imaging, a number of limitations set by these investigation methods are still to overcome[2]. Choledo-

choscopy may be a direct diagnostic procedure to help in macroscopically assessing inconclusive lesions inside the biliary duct system. However, technical means were limited so far as the "mother-baby" system had to be operated by two interventionalists, while confirming the results of malignity-suspicious findings remained a true histological challenge[3-5]. Technical restrictions of the above mentioned procedures may explain the insufficient sensitivity of diagnostics when it comes to biliary changes[6].

SpyGlass is a technically advanced cholangioscopy system facilitating diagnostics in the bile duct due to its single-operator feature. First studies show that the use of SpyGlass may clearly enhance diagnostic accuracy. First of all, cholangioscopy-guided tissue acquisition in the biliary duct is much easier to perform even though diagnostic sensitivity and specificity require further improvement[7].

PROGRESS IN CHOLEDOCHOSCOPY

Since the 1970s, choledochoscopy is used mainly in centers focussing on hepatobiliary diagnostics to macroscopically diagnose bile duct lesions[8]. This procedure directly investigates the biliary tract endoscopically and benefits from directly assessing the mucous membrane so as to help evaluate the dignity of inconclusive lesions in the bile duct[9]. For the first time, this offered diagnostic options superior to other imaging procedures in this region[8,9].

In choledochoscopy, a general distinction is made between percutaneous transhepatic and retrograde endoscopic access using the so-called "mother-baby" endoscope technique[10,11].

With the frequently used and less invasive "mother-baby" endoscope technique, a thin choledochoscope ("baby scope") is introduced in the bile duct for ERCP *via* instrument channel of a duodenoscope ("mother scope") (Figure 1).

However, a number of limitations using the mother-baby choledochoscopy technique are still to cope with: The first fiber optic choledochoscopies provided a poor image quality with low resolution and poor illumination of the bile duct. The steerability of the microendoscope in only two planes considerably limited the maneuverability in the bile duct. Another clear disadvantage of the mother-baby endoscope technique was the need of two operators required to perform the procedure. However, the greatest detriment of all for a great many years was the fact that tissue acquisition was impossible which limited the use to diagnostic indications.

In the 1980s, a second generation of choledochoscopies was introduced providing a working channel and offering improved maneuverability.

In the late 1990s, first prototypes of video choledochoscopies were tested and first images of staining or virtual chromoendoscopy in the bile duct were presented, yet more to provide evidence of the possible and feasible than to introduce a serious means of routine endoscopy.

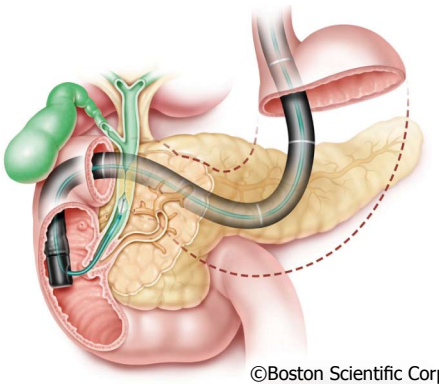

Figure 1 Principle of "Mother-Baby" endoscope technique.

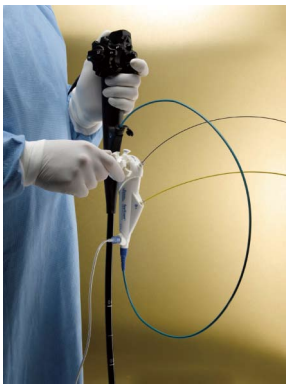

Figure 2 Single-operator choledochoscopy system: "SpyGlass Direct Visualization System®".

To date, all available choledochoscopies on the market are fiber optic systems and all reports of high-resolution video choledochoscopies are based on a few prototype case reports only[12-14].

The first single-operator choledochoscopy system was presented in 2005 by Boston Scientific under the name "SpyGlass Direct Visualization System®". The system is a technically advanced cholangioscopic device to provide endoscopic diagnosis in case of inconclusive bile duct findings[15].

The system does not only without the need of a second operator but also visualizes the bile duct lesions in a way to allow for effective assessment of their dignity (Figure 2). The targeted tissue acquisition performed by the same operator represented another novelty and allowed for further investigation of abnormalities[15].

SPYGLASS DIRECT VISUALIZATION SYSTEM

The SpyGlass system consists of an integrated platform with a light source, camera, and monitor (Figure 3). Proven fiber optic technique is still used to illuminate the bile duct, yet with improved resolution to optimize bile duct visualization. An advanced steering system of the 10 Fr cholangioscopy catheter to be attached to the duodeno-

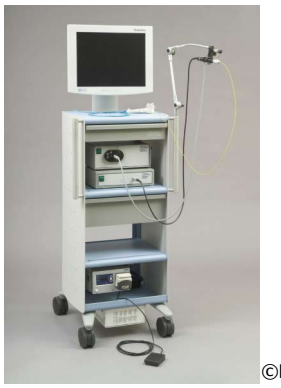

Figure 3 SpyGlass system as integrated platform with light source, camera and monitor.

scope has been re-designed and eliminates the need for a second operator to handle the choledochoscope[15,16]. This steering unit with its two steering wheels provides steering options in four planes, comparable to standard endoscopes (Figure 4).

The steering unit is positioned on top of the so-called 10-Fr guiding catheter or SpyScope equipped with four lumina (Figure 5). One lumen is intended for use of the fiber optic system to be advanced to the SpyScope's end. The fiber optic system consists of a coherent bundle of optical fibers surrounded by light fibers representing the system's most fragile component. Two more lumina are used for irrigation and a fourth one serves as the working channel for the specific biopsy forceps.

The SpyScope itself is advanced into the bile duct similar to the mother-baby technique *via* duodenoscope working channel. Due to the particular stability of the SpyScope offering optimum protection to the optical glass fibers the sometimes unavoidable angulation may be achieved during introduction into the bile duct when fully activating the Albarran lever. When in the bile duct, mucus or tough bile may be removed *via* the SpyScope's two dedicated irrigation channels by foot-activating the irrigation device. The most important access offers a 1.2 mm working channel. A specifically designed biopsy forceps (SpyBite) and also optical fibers for electrohydraulic or laser lithotripsy may thus be introduced into the biliary tract *via* working channel (Figure 6).

SpyGlass technique

First, the steering unit is attached to the duodenoscope handle. Normally, the guidewire already positioned in the bile duct at the distal end of the guiding catheter is now threaded in to the SpyScope *via* working channel to ease bile duct intubation using the guiding catheter (SpyScope) and the guidewire as a guide rail. Before advancing the guiding catheter (SpyScope) *via* duodenoscope working channel to intubate the bile duct the optical fiber should be advanced to the tip with care through a suitable working channel. Self-explanatory symbols pointing to the correct access support the process.

Having reached the papilla the Albarran lever is easily used to achieve the required angulation facilitating intubation of the bile duct. With the SpyScope in the bile duct the optical fiber may be carefully advanced *via* catheter tip to directly inspect the bile duct lumen. Obstructive mucus or tough bile may be removed using the SpyScope's foot-activated dedicated irrigation device.

INDICATIONS

Among the most frequent clinical uses of the SpyGlass choledochoscopy are complex gallstones and bile duct lesions of unclear dignity (Figure 7).

Use of SpyGlass in bile duct lesions

Diseased bile ducts often are a clinical challenge since diagnostics have their limitations; on the other hand, quick and therapeutically relevant decisions for the patient may urgently be required[17,18]. Sound assessment of the dignity is essential for therapy planning, however often difficult. Especially histological confirmation of malignity-suspicious findings is a key issue gastroenterologists have to cope with[19-21]. Cholangiocarcinoma portend a dismal prognosis which makes an early decision for surgery based on timely diagnosis desirable[17]. Limited diagnostic approaches hardly offer any solution, and patients may not be diagnosed properly until symptomatic with the tumor being in an advanced stage beyond any curative therapy[19]. Brush cytology and endosonographically guided fine needle aspiration biopsy may be the preferred investigation methods to date, yet in almost all the studies the low sensitivity of the method is a serious issue[21-26].

Cytology may provide good specificity which is why false positive cases are rarely found in literature but the low sensitivity of about 50% remains a key problem of this method[21-26].

The golden standard when diagnosing bile duct diseases remains to be ERCP[27]. Using ERCP provides good imaging of the bile duct anatomy including any pathological changes such as strictures ad intraluminal filling defects. However, they might be insufficient, especially in early stages, to make definitive therapy decisions.

Special risk populations *e.g.*, patients with a primary sclerosing cholangitis (PSC), have an increased carcinoma risk due to years of chronic bile duct inflammation[28].

Checks on a regular basis are supposed to detect in a timely manner carcinomatous prestages especially in such patient collective with multiple bile duct changes, yet the problem of safe differentiation between inflammatory/benign and dysplastic, potentially malign lesions remains unsolved.

Peroral choledochoscopy as the direct visualization of the bile duct therefore represents an important and interesting enhancement of ERCP[7,29].

Since the introduction of the SpyGlass Direct Visualization System several studies and a number of publications describe a variety of clinical experiences[15] (Table 1). A center point of the publications was the accessibility and macroscopic imaging of suspicious lesions. A cur-

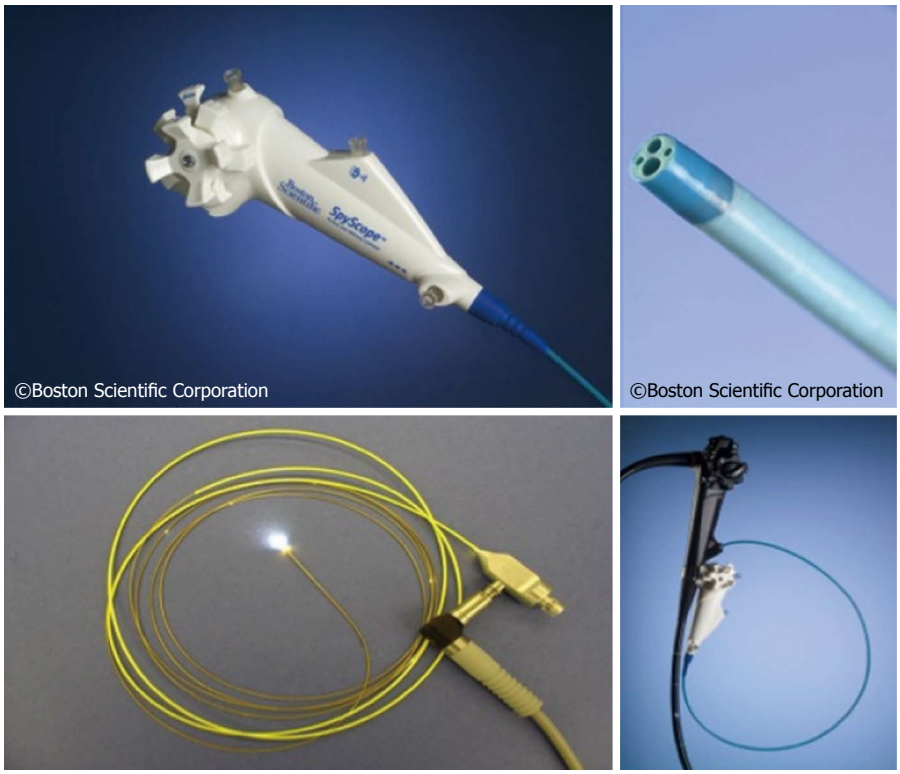

Figure 4 Components of the SpyGlass system.

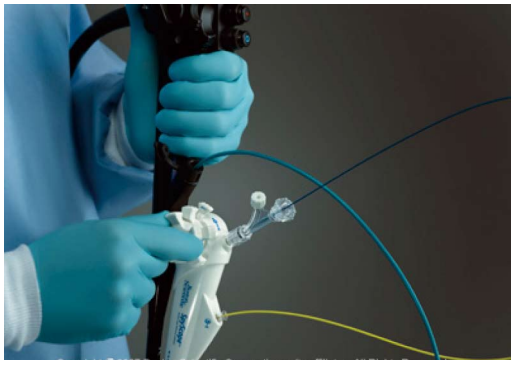

Figure 5 SpyScope.

rent study documents that the sensitivity of macroscopic evaluation using SpyGlass is significantly higher than with ERCP (81% *vs* 53%)[29]. Another multi-center prospective study with nearly 300 enrolled patients investigated as a primary study endpoint whether there was success in reaching the suspicious lesion and acquiring tissue[7].

Secondary study endpoints were the sensitivity and specificity of the cholangioscopically guided biopsies. A total of 96% of the biliary strictures were reached endoscopically using the cholangioscopic catheter and provided sufficient visualization. Additional tissue acquisition was possible in 88% of the cases[7].

In his pilot study, researchers was able to clearly show in 35 patients that SpyGlass not only ensures reaching the lesions but also allows for sufficient macroscopic evaluation of findings with a sensitivity of 100% and specificity of 77%. In an additional SpyGlass-guided biopsy a sensitivity of 71% and specificity of 100% were achieved, both significantly superior to brush cytology results[30].

The most frequently expressed criticism with this method is that sensitivity of the cholangioscopically guided tissue acquisition is low; in some papers it even had to be adjusted downwards. To be stressed are quantity and quality of the acquired tissue frequently considered insufficient by pathologists. Grounds may be the too small a size of the tissue samples acquired using the SpyBite forceps offering no bigger option. To ensure sufficient amount of tissue for pathological investigation multiple tissue acquisitions (3 to 4 biopsies) from the lesion in question are recommended[15,31]. But apart from the already mentioned histological criteria, macroscopic aspects should not be ignored. For effective differentiation of lesions, their macroscopic appearance in the bile duct is of great importance. It is in fact known that almost all malign changes in the hepatobiliary system are characterized by significant vascularization including tortuous and dilated vessels. In addition, exophytic growth, ulcerations, and being raised are considered further aspects of malignity suspicion allowing for correct diagnosis[32].

In a retrospective study including 129 patients, the initial working diagnosis was modified in 68% of the patients with biliary strictures based on the SpyGlass investigation[33]. The significance of this result cannot be overestimated considering that in as many as 45% of the patients an initial tumor suspicion of the lesion was not confirmed when SpyGlass was used for diagnosis meaning for the individual patient a completely different thera-

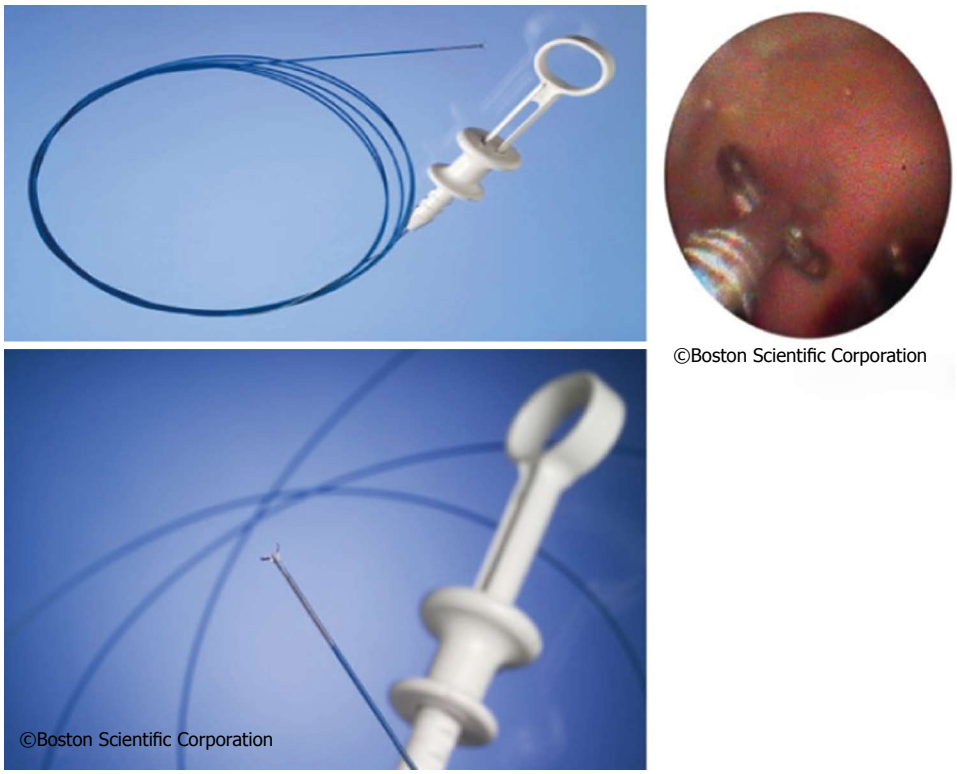

Figure 6 Re-designed biopsy forceps.

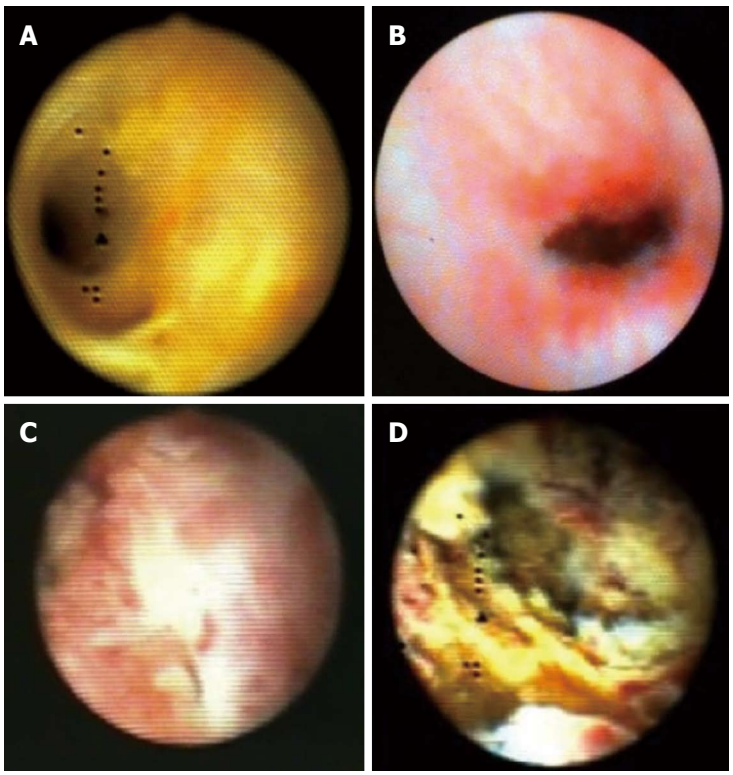

Figure 7 Typical cholangioscopic findings (source: A Hoffman). A: Normale bile duct; B: Inflammation with stricture; C: Cholangiocellular carcinoma with villous like appearance; D: Cholangiocellular carcinoma with ulcers and intraluminal growth.

peutic proceeding.

Use of SpyGlass in the treatment of gallstones

Cholecysto- and choledocholithiasis are an important issues in the Western industrialized countries and a main reason for hospitalization due to gastrointestinal complaints.

An estimated 15%-20% of the Caucasian population is supposed to suffer from some sort of gallbladder disease, 15%-20% of which also have stones in their bili-

Table 1 Overview about the sensitivity and specificity of SpyGlass

First author, publication, year	Study design	Patient (*n*)	Sensitivity for visual diagnosisual diagnosis/ biopsy	Specificity for visual diagnosis/ biopsy	PPV for visual diagnosis/ biopsy	NPV for visual diagnosis/ biopsy	Accuracy for biopsy/visual diagnosis
Chen[15], 2007	Prospective study	35	100%/71%	77%/100%	70%/100%	100%/87%	
Ramchandani *et al*, 2012	Prospective study	36	95%/82%	79%/82%	88%/100%	92%/100%	89%/82%
Hartmann *et al*, 2012	Retrospective analysis	89	/57%	/100%	/100%	/68%	/78%
Chen *et al*, 2011	Prospective study	297	77.8%/48.9%	82%/98%	80%/100%	80%/72%	80%/75%
Kalaitzakis *et al*, 2012	Retrospective analysis	141	72%	97%	93%	86%	88%

PPV: Positive predictive value; NPV: Negative predictive value.

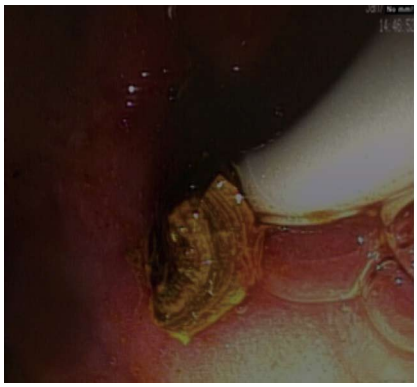

Figure 8 Stone after direct probe-targeted fragmentation *via* short-pulsed laser waves (holmium laser) (Source: A Hoffman).

ary tracts. Normally, ERCP succeeds in removing these stones from the biliary duct system avoiding potential complications such as pancreatitis or cholangitis[34,35]. In some cases, however, stones cannot be removed *via* traditional ERCP due to the large size of the calculi or their specific anatomy. Unfortunately, the success rate of extracorporeal shock wave lithotripsy with subsequent endoscopic extraction is also very low in these special cases[33-35]. Using the SpyGlass system with its option of a full-fledged working channel in addition to dedicated irrigation, a probe may be advanced under direct visual control until it reaches the stone to perform lithotripsy using short-pulsed laser waves (Nd-YAG-2 laser or Holmium laser) or electrohydraulic waves[36-38]. Direct advancement of the probe to the stone reduces the risk of bleeding or perforation of the bile duct and significantly increases the success rate of stone extraction versus extracorporeal shock wave lithotripsy[39,40] (Figure 8).

Another important aspect is stones overlooked during ERCP. In two studies-one particularly with PSC patients, the other after routine ERCPs-an immediately following SpyGlass procedure diagnosed an initially overlooked 29% and 30% of stones[41,42].

COMPLICATIONS

Based on published data for SpyGlass to date, only a few but not severe procedure related complications are to be assumed. But currently published complications do not differ from those of therapeutic ERCP without accompanying cholangioscopy. Apart from the complications associated with ERCP a complication rate of only 0.3% is assumed whereas it is difficult to differentiate whether the complication was caused by ERCP itself or by the cholangioscopy[33].

The most common complication reported is cholangitis (3%). In some reports ascending cholangitis or cholangitis with intrahepatic abscess, especially after taking biopsies are reported. Some cases of ascending cholangitis, which were only marked by jaundice without fever, but white blood cell elevation or positive blood cultures, developed even some days after SpyGlass examination.

Irrigation should not be excessive when proximal of a stenosis especially with already existing cholangitis since it may significantly increase the risk of bacteremia. But all of the published studies are done by experts in ERCP with a low complication rate in all ERCP related therapeutic procedures. There is no published data about the complication rate during the learning curve of choledochoscopy or the complication rate of trainees in ERCP using SpyGlass.

Among other complications are: drop in blood pressure, abdominal pain, pancreatitis, and bile duct perforation caused by the guidewire.

CONCLUSION

The SpyGlass Direct Visualization System introduces a new type of cholangioscope for endoscopic use. Not only can cholangioscopy now be performed by a single operator but the optimized steering unit enables the user to exactly fix the biliary target lesion and acquire tissue providing true diagnostic benefit. The visualization of bile duct lesions itself is of great value since it offers precise dignity evaluation based on macroscopic criteria. Literature includes more and more reports on the safe and efficient use of the unit in clinical practice. Sceptics of the method mostly criticize the low sensitivity of cholangioscopically guided tissue acquisition. Standardization of the number of biopsies and further development of biopsy forceps may result in the desired enhancement of sensitivity.

Even if histological confirmation of the visual findings may remain difficult using SpyGlass-acquired tissue this new investigation method represents a valuable

complement in the diagnostic algorithm of inconclusive bile duct findings in terms of staged diagnostics.

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ORIGINAL ARTICLE

Endoscopic papillary balloon dilation after sphincterotomy for difficult choledocholithiasis: A case-controlled study

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Author contributions: Rosa B carried out the studies and data analyses, and drafted the manuscript; Moutinho Ribeiro P conceived the study, participated in its design and coordination, and helped to draft the manuscript; Rebelo A performed the statistical analysis; Pinto Correia A collaborated in the study conception and design; Cotter J critically revised the manuscript and finally approved the version to be submitted; all authors read and approved the final manuscript.

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Abstract

AIM: To evaluate the efficacy and safety of endoscopic sphincterotomy (EST) + endoscopic papillary large balloon dilation (EPLBD) *vs* isolated EST.

METHODS: We conducted a retrospective single center study over two years, from February 2010 to January 2012. Patients with large (≥ 10 mm), single or multiple bile duct stones (BDS), submitted to endoscopic retrograde cholangio-pancreatography (ERCP) were included. Patients in Group A underwent papillary large balloon dilation after limited sphincterotomy (EST+EPLBD), using a through-the-scope balloon catheter gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. Patients in Group B (control group) underwent isolated sphincterotomy. Stones were removed using a retrieval balloon catheter and/or a dormia basket. When necessary, mechanical lithotripsy was performed. Complete clearance of the bile duct was documented with a balloon catheter cholangiogram at the end of the procedure. In case of residual lithiasis, a double pigtail plastic stent was placed and a second ERCP was planned within 4-6 wk. Some patients were sent for extracorporeal lithotripsy prior to subsequent ERCP. Outcomes of EST+EPLBD (Group A) *vs* isolated EST (Group B) were compared regarding efficacy (complete stone clearance, number of therapeutic sessions, mechanical and/or extracorporeal lithotripsy, biliary stent placement) and safety (frequency, type and grade of complications). Statistical analysis was performed using χ^2 or Fisher's exact tests for the analysis of categorical parameters and Student's *t* test for continuous variables. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS: One hundred and eleven patients were included, 68 (61.3%) in Group A and 43 (38.7%) in Group B. The mean diameter of the stones was similar in the two groups (16.8 ± 4.4 and 16.0 ± 6.7 in Groups A and B, respectively). Forty-eight (70.6%) patients in Group A and 21 (48.8%) in Group B had multiple BDS ($P = 0.005$). Overall, balloon dilation was performed up to 12 mm in 10 (14.7%) patients, 13.5 mm in 17 (25.0%), 15 mm in 33 (48.6%), 16.5 mm in 2 (2.9%) and 18 mm in 6 (8.8%) patients, taking into account the diameter of the largest stone and that of the bile duct. Complete stone clearance was achieved in sixty-five (95.6%) patients in Group A *vs* 30 (69.8%) patients in Group B, and was attained within the first therapeutic session in 82.4% of patients in Group A *vs* 44.2% in Group B ($P < 0.001$). Patients submitted to EST+EPLBD underwent fewer therapeutic sessions (1.1 ± 0.3 *vs* 1.8 ± 1.1, $P < 0.001$), and fewer required mechanical (14.7% *vs* 37.2%, $P = 0.007$) or extracorporeal (0 *vs* 18.6%, $P < 0.001$) lithotripsy, as well as biliary stenting (17.6% *vs* 60.5%, $P < 0.001$). The rate of complications was not significantly different between the two groups.

CONCLUSION: EST+EPLBD is a safe and effective technique for treatment of difficult BDS, leading to high

rates of complete stone clearance and reducing the need for lithotripsy and biliary stenting.

Key words: Endoscopic papillary large balloon dilation; Bile duct stones; Endoscopic sphincterotomy; Choledocholithiasis

Core tip: The technique described by Ersoz comprises endoscopic limited sphincterotomy followed by papillary large balloon dilation. In theory, it increases efficacy on the extraction of large bile duct stones, while reducing the risk of bleeding that would occur if a larger sphincterotomy had to be performed, particularly in patients with coagulopathy or surgically modified anatomy, and simultaneously reduces the risk of post endoscopic retrograde cholangio-pancreatography acute pancreatitis that occurs when isolated papillary balloon dilation is performed. In this case-controlled study, the combined technique achieved higher rate of complete stone clearance than isolated endoscopic sphincterotomy, and reduced the need for lithotripsy and biliary stenting, with a similar safety profile.

Rosa B, Moutinho Ribeiro P, Rebelo A, Pinto Correia A, Cotter J. Endoscopic papillary balloon dilation after sphincterotomy for difficult choledocholithiasis: A case-controlled study. *World J Gastrointest Endosc* 2013; 5(5): 211-218 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i5/211.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i5.211

INTRODUCTION

Endoscopic sphincterotomy (EST), first described by Classen *et al*[1] in 1974, remains the standard procedure for the treatment of bile duct lithiasis. Some years later, in 1983, Staritz *et al*[2] described endoscopic papillary balloon dilation (EPBD), which emerged as an alternative to EST, with comparable efficacy in patients with up to 3 bile duct stones (BDS) and ≤ 10 mm of diameter[3]. EPBD is associated with a lower risk of bleeding than EST, although an increased risk of post endoscopic retrograde cholangio-pancreatography (ERCP) acute pancreatitis has been reported[3-10]. When performed to a diameter that does not exceed 10 mm, EPBD may preserve the function of the sphincter of Oddi[11,12], reducing late complications such as recurrence of biliary stones and papillary stenosis[13-15]. However, both techniques have limitations in the setting of large (≥ 10 mm) BDS. Indeed, the completion of a large sphincterotomy may be limited by local anatomy and is associated with a higher risk of bleeding, while performing EPBD above 10 mm is associated with an increased risk of post-procedural acute pancreatitis[3-9]. Because of these considerations, in the setting of large BDS the biliary orifice often cannot be safely opened wide enough to enable their extraction, and additional mechanical lithotripsy is often needed[6,16-19]. To overcome these limitations, in 2003, Ersoz *et al*[20] described the technique of endoscopic papillary large diameter (12-20 mm) balloon dilation after limited sphincterotomy (EST+EPLBD), for the treatment of large BDS. This combines the advantages of EST and EPBD by increasing the efficacy of stone extraction while minimizing complications of both EST and EPBD when used alone[20,21]. This technique introduced a new concept that is different from isolated EPBD, as it actually results in the rupture of the orifice and permanent loss of the sphincter. It is progressively gaining widespread acceptance, with many authors reporting promising results regarding its efficacy and safety over the last few years[10,11,18, 21-29]. In this study, we aimed to evaluate the efficacy and safety of EST+EPLBD in the treatment of difficult BDS, performing a comparative analysis with a control group of patients submitted to isolated EST.

MATERIALS AND METHODS

This was a retrospective single center study, covering a 2-year period, from February 2010 to January 2012. Patients meeting the following inclusion criteria were consecutively included: (1) referral for ERCP because of bile duct lithiasis; (2) 18 years of age or older; (3) informed consent obtained before ERCP; (4) large BDS identified at ERCP (≥ 10 mm in diameter, single or multiple); and (5) deep cannulation of the bile duct achieved without precut. Patients with previous ERCP, ongoing acute pancreatitis or cholecystitis, history of previous gastric or biliary surgery (except for cholecystectomy), severe haemostatic disorders, intrahepatic lithiasis and concomitant pancreatic or biliary malignant disorders were excluded. According to the study design, patients who underwent EST+EPLBD were included in Group A, while patients who were submitted to EST alone were allocated to a control group (Group B). Every ERCP was performed using Olympus® TJF 160 VR or TJF 145 side-viewing endoscopes. Patients were under propofol sedation assisted by an anaesthesiologist. Deep biliary cannulation was generally attained with a triple lumen sphincterotome (Papillotomy knife, wire-guided type, Olympus®). Stone size and number were documented on the initial diagnostic cholangiogram at ERCP. EST was performed over a 0.035 guide wire (Hydra Jagwire® guide wire, Boston Scientific Corp.®). Patients in Group A underwent papillary balloon dilation using a through-the-scope balloon catheter for oesophageal/pyloric dilation (CRE® wire-guided balloon dilatation catheter, Boston Scientific Microvasive®), gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. The biliary sphincter was considered adequately dilated when the waist of the balloon had completely disappeared in the fluoroscopic image. The fully expanded balloon was maintained in position for 60 s and then deflated and removed (Figure 1). Stones were removed using

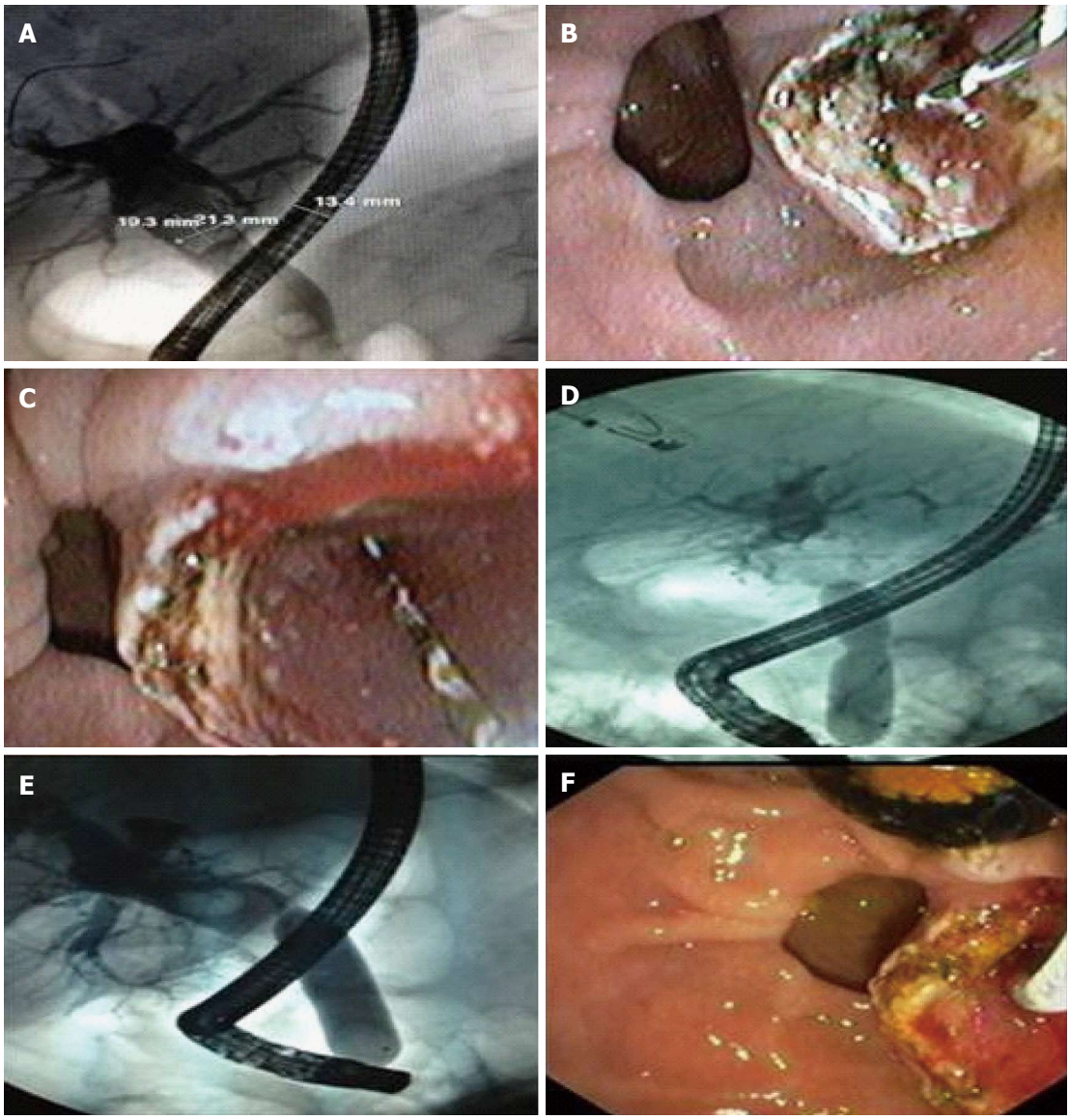

Figure 1 Combined endoscopic technique: Limited endoscopic sphincterotomy followed by endoscopic papillary large balloon dilation.

a retrieval balloon catheter (V-System single-use triple lumen stone extraction balloon, Olympus®) and/or a Dormia basket (Web® extraction basket, Wilson-Cook Medical Inc.®). When necessary, mechanical lithotripsy (BML 4Q, Olympus®; Fusion Lithotripsy Basket, Wilson-Cook Medical®) was performed to fragment the stones prior to removal. Complete clearance of the bile duct was documented with a balloon catheter cholangiogram at the end of the procedure. In the case of residual lithiasis, a biliary 7 Fr double pigtail plastic stent was placed and a second ERCP was planned within 4-6 wk. Some patients were sent for extracorporeal lithotripsy prior to subsequent ERCP. At the end of each ERCP, 100 mg rectal indomethacin was routinely given. Prophylactic antibiotics were not routinely administered. The primary efficacy endpoint was the success rate regarding complete clearance of the bile duct. Secondary endpoints included other efficacy criteria (number of ERCP until achievement of complete stone extraction, use of mechanical or extracorporeal lithotripsy, biliary stenting) and assessment of the safety of the procedure (occurrence of complications such as bleeding, pancreatitis, cholangitis or perforation, which were classified and graded according to the 1991 consensus guidelines)[30]. To assess complications, blood samples for complete blood count, liver function tests and serum levels of amylase, lipase and C-reactive protein were routinely obtained 24 h after the procedure.

Ethical considerations

This was a retrospective case-controlled study. All patients provided written consent to undergo ERCP and were informed of the risks and potential benefits of the procedures.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS® Inc., Chicago, IL, United States). Categorical parameters were analyzed using χ^2 or Fisher's exact tests

Table 1 Population baseline characteristics

Characteristics	EST + EPLBD	EST	*P* value
n	68 (61.3%)	43 (38.7%)	
Age (yr)	70.8 ± 13.4	72.8 ± 12.4	NS
Female gender	45 (66.2%)	28 (65.1%)	NS
Multiple lithiasis	48 (70.6%)	21 (48.8%)	0.005
Largest stone diameter (mm)	16.8 ± 4.4 (12-30)	16.0 ± 6.7 (10-30)	NS
Bile duct diameter (mm)	17.1 ± 3.4 (8-35)	16.4 ± 7.2 (8-30)	NS
Presence of biliary stricture	4 (5.9%)	2 (4.7%)	NS
Balloon dilation diameter (mm)			
12	10 (14.7%)		
13.5	17 (25.0%)		
15	33 (48.6%)		
16.5	2 (2.9%)		
18	6 (8.8%)		

EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; NS: Not significantly.

and continuous variables were analysed by Student's *t* test. Quantitative data were summarized as the mean ± SD. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

From February 2010 to January 2012, 111 patients with large BDS meeting the inclusion criteria were enrolled in the study. Sixty-eight (61.3%) patients underwent EST+EPLBD and were included in Group A. Group B, the control group, included 43 (38.7%) patients who underwent isolated EST, with no subsequent papillary balloon dilation. Forty-eight (70.6%) patients in Group A and 21 (48.8%) in Group B had multiple BDS (P = 0.005). The mean diameter of the stones was 16.8 ± 4.4 and 16.0 ± 6.7 in Groups A and B, respectively (P = Not significant). Overall, balloon dilation was performed up to 12 mm in 10 (14.7%) patients, 13.5 mm in 17 (25.0%), 15 mm in 33 (48.6%), 16.5 mm in 2 (2.9%) and 18 mm in 6 (8.8%) patients, taking into account the diameter of the largest stone and that of the bile duct. Baseline characteristics of patients in both groups are summarized in Table 1.

Complete stone clearance was achieved in sixty-five (95.6%) patients in Group A *vs* 30 (69.8%) patients in Group B, and was attained within the first therapeutic session in 82.4% of patients in Group A *vs* 44.2% in Group B (P < 0.001). The mean number of ERCP sessions until complete clearance of the bile duct was 1.1 ± 0.3 in Group A *vs* 1.8 ± 1.1 (P < 0.001) in Group B. Failure to obtain bile duct clearance occurred in 3 (4.4%) patients in Group A *vs* 13 (30.2%) patients in Group B (P < 0.001). Mechanical lithotripsy was performed with a lithotripsy basket in 10 (14.7%) patients in Group A and in 16 (37.2%) in Group B (P = 0.007). Additionally, 8 (18.6%) patients in Group B were sent to extracorporeal lithotripsy, *vs* none of the patients in Group A (P < 0.001). A plastic biliary stent was placed in 12 (17.6%) patients in Group A, *vs* 26 (60.5%) patients in Group B (P < 0.001), because of persistent BDS in all cases except for two patients in Group B, in whom the stents were placed because of ongoing cholangitis and delayed clearance of the contrast at the end of the procedure. Efficacy outcomes are summarized in Table 2 and Figure 2.

Table 2 Efficacy outcomes

Efficacy outcomes	EST + EPLBD	EST	*P* value
Complete stone removal	65 (95%)	30 (70%)	< 0.001
Complete stone removal in single session	56 (82.4%)	19 (44.2%)	< 0.001
Number of ERCP until complete stone removal	1.1 ± 0.3	1.8 ± 1.1	< 0.001
Mechanical lithotripsy	10 (14.7%)	16 (37.2%)	0.007
Extracorporeal lithotripsy	0	8 (18.6%)	< 0.001
Plastic biliary stenting	12 (17.6%)	26 (60.5%)	< 0.001
Failure	3 (4.4%)	13 (30.2%)	< 0.001

EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; ERCP: Endoscopic retrograde cholangio-pancreatography.

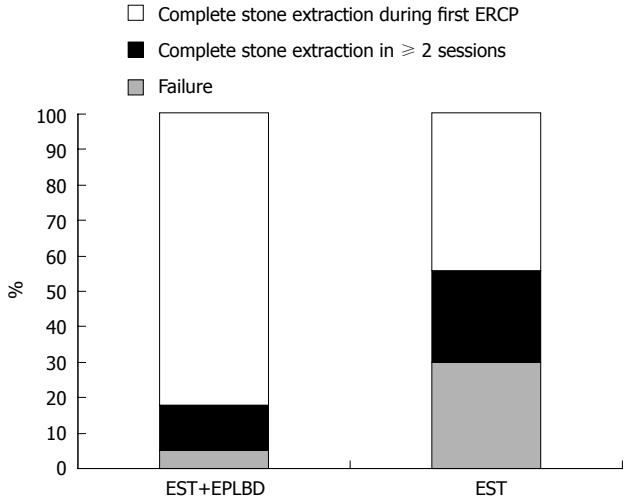

Figure 2 Efficacy of endoscopic sphincterotomy + endoscopic papillary large balloon dilation *vs* isolated endoscopic sphincterotomy for the treatment of difficult bile duct stones. EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; ERCP: Endoscopic retrograde cholangio-pancreatography.

In a subanalysis of efficacy outcomes, taking into consideration the number and size of the stones, patients submitted to EST+EPLBD had a trend towards a higher rate of complete stone extraction at first ERCP session when a single stone was present (95.0% *vs* 77.1%, P = 0.072), and a higher use of plastic stents when multiple stones were present (22.9% *vs* 5.0%, P = 0.072), while none of the efficacy outcomes was influenced by the size of the stones in this group of patients. Conversely, in Group B, the number of stones did not seem to influence any of the efficacy outcomes, while the size of the stones seemed to be the key factor for their successful removal. Indeed, patients with smaller stones had significantly higher rates of complete bile duct clearance at first session (13 ± 4 mm *vs* 18 ± 8 mm, P = 0.029) and lower

rates of biliary stenting (18 ± 8 mm *vs* 13 ± 3 mm, P = 0.042). Moreover, patients with larger stones were more frequently referenced to extracorporeal lithotripsy (20 ± 8 mm *vs* 15 ± 6 mm, P = 0.065).

Regarding procedural-related complications, in our series 9/68 (13.2%) patients in Group A and 2/43 (4.7%) in Group B developed mild to moderate post-ERCP pancreatitis. This resolved with conservative treatment in less than 72 h, apart from two cases in Group A who required up to 10 d of hospitalization. In Group A, 7 (77.8%) patients who developed post-ERCP acute pancreatitis had been dilated up to 15 mm, and in the other 2 patients (22.2%) the papilla had been dilated to 13.5 mm. Significant bleeding did not occur in any of the patients in Group A, but in 2 (4.7%) patients from Group B. One patient in Group A (1.5%) and 1 patient in Group B (2.3%) developed acute cholangitis, both with good clinical evolution and short hospitalizations under conservative management. No cases of perforation or mortality occurred in our series. Overall, in Group A, the size of the stones did not influence the prevalence of complications (15 ± 1 mm in patients with complications *vs* 17 ± 5 mm in patients without complications, P = 0.086), although more complications occurred in the case of multiple BDS (9/48, 18.8% *vs* 1/20, 5.0%, P = 0.138). In patients from Group B, the rate of complications did not seem to be influenced either by the size (16 ± 7 mm in patients with complications *vs* 18 ± 8 mm in patients without complications, P = 0.582) or the number of stones (single stone: 2/24, 8.3% *vs* multiple stones: 3/19, 15.8%, P = 0.019).

DISCUSSION

Over the last few years, the technique of using EPLBD after limited EST has been increasingly recognized as an important therapeutic option for patients with large BDS[10,11,18,21-29]. In our series, this approach proved to be highly effective in patients with large BDS when compared to the performance of EST alone, with no significant increase of complications. Indeed, patients who underwent EST+EPLBD had significantly higher rates of complete stone clearance (95.6% *vs* 69.8%), and this was achieved more often within the first therapeutic session (82.4% *vs* 44.2%). Moreover, the need for mechanical or extracorporeal lithotripsy was significantly lower (14.7% *vs* 37.2% and 0 *vs* 18.6%, respectively), as was the use of plastic biliary stents (17.6% *vs* 60.5%). These outcomes did not seem to be influenced by the size of the stones, but there was a trend towards higher rates of complete stone clearance at first ERCP (95.0% *vs* 77.1%) and reduced biliary stenting (5.0% *vs* 22.9%) in patients with a single bile duct stone. Conversely, in patients submitted to isolated EST, efficacy outcomes were mainly influenced by the size of the stones, rather than by its number. It must be stated, however, that this was a non-randomized retrospective case-controlled study, where the decision to perform isolated EST or EST+EPLBD was made on an individual basis at the time of each examination. Thus, a possible selection bias influencing the results could be considered, particularly concerning the relatively low overall successful clearance rates (69.8%) and stone clearance in the first ERCP session of isolated EST (44.2%). In this group of patients, the size of the largest stone was the key factor influencing incomplete clearance, biliary stenting or referral for extracorporeal lithotripsy. Nonetheless, the mean diameter of the stones was comparable between Group A (16.8 ± 4.4 mm) and Group B (16.0 ± 6.7 mm), and also the prevalence of larger stones, up to 30 mm, was similar in both groups of patients. In our experience, EST+EPLBD was the preferred technique when multiple large BDS were detected in the initial cholangiogram, being chosen as first-line approach in this particular setting significantly more often than EST alone. The presence of bile duct strictures, such as papillary stenosis, has been reported to be manageable by papillary balloon dilation, although the safety of this approach has not been fully elucidated for EPLBD, and may constitute a limiting factor. In our series, 4 patients with biliary strictures were submitted to EPLBD up to 12 mm, allowing for stone removal with no complications. Overall, failure to obtain a complete clearance of the bile duct occurred in only 3 (4.4%) patients in Group A, as compared to nearly one third of patients in Group B (30.2%). Some authors had reported that by reducing the need for mechanical lithotripsy (5.7% *vs* 25.0%, P < 0.01), EST+EPLBD additionally reduced the total procedure time and radiation exposure[11,31], however these outcomes were not evaluated in our study.

Our results challenge the conclusions of a recent meta-analysis of 7 randomized controlled trials that included 790 patients, comparing EST+EPLBD with EST[32]. The authors reported that both techniques resulted in similar outcomes for overall successful clearance rates of BDS (97.4% *vs* 96.4%, P = 0.54) and stone clearance in the first ERCP session (87.9% *vs* 84.2%, P = 0.21), although EST+EPLBD significantly decreased the use of mechanical lithotripsy (OR: 0.51, P = 0.01). Regarding biliary stenting, some authors have reported that the temporary placement of plastic stents may be able to fragment large BDS, and that this could possibly constitute an alternative method for clearing difficult stones not amenable to extraction at the first attempt[33,34]. In our study, 60.5% of patients submitted to EST alone required the placement of at least one plastic biliary stent, while this was the case in just 17.6% of patients who underwent EST+EPLBD.

Beyond improving efficacy outcomes, this combined technique has been shown to potentially reduce the complications typically associated with the performance of EST or EPBD alone. The risk of pancreatitis after EPBD seems to be related to the pressure overload on the orifice of the main pancreatic duct during balloon dilation, particularly when dilations are performed above the diameter of 10 mm or if the balloon is inflated very abruptly[3-10,35,36]. Conversely, the combined EST+EPBD approach does not appear to increase significantly the

risk of post-ERCP pancreatitis. This may be due to the fact that EST guides the orientation of the dilating balloon towards the common bile duct, thus preventing the pressure overload on the main pancreatic duct[20]. The risk of post-EPLBD pancreatitis may, however, be increased in the case of lower bile duct diameter or longer procedure time[29]. In our study, we could not exclude that the comparable rate of post-EPLBD (9/68, 13.2% *vs* 2/43, 4.7%) might be related to the relatively low case number in this series. Patients from Group A had a trend towards increased complications when two or more BDS were present. Although differences were not statistically significant, it should be noted that 9/10 patients who experienced a complication after EST+EPLBD, particularly acute pancreatitis, presented with multiple BDS. Conversely, in patients from Group B, the rate of complications did not seem to be influenced either by the size or the number of the stones. In a recent meta-analysis[32], EST+EPLBD was associated with fewer overall complications than EST (5.8 *vs* 13.1%, $P = 0.0007$). In particular, bleeding occurred less frequently with EST+EPLBD than with EST (OR: 0.15, $P = 0.002$), suggesting that compression by ballooning may be effective for haemostasis. The authors did not find significant differences in post-ERCP pancreatitis, perforation and cholangitis. Based on EST+EPLBD being associated with fewer cases of significant bleeding, it may be reasonable to recommend this technique for the removal of difficult BDS in patients with underlying coagulopathy or need for anticoagulation, as well as for those in whom the local anatomy may increase the risks of a large sphincterotomy, such as patients with periampullary diverticulum[37], Billroth II gastrectomy[38,39] or Roux-en-y anastomosis[40]. The risk of duodenal perforation during EST+EPLBD seems quite low, possibly due to the fact that EST guides the orientation of the dilation and controls the impact of its radial force, which is furthermore monitored in real time by the endoscopist, both endoscopically and fluoroscopically.

Finally, the most frequent long-term complication after bile duct stone extraction is the recurrence of symptomatic BDS[3,41,42]. The recurrence rate seems to be higher in patients who undergo EST (6%-24%)[43,44] than in those submitted to EPBD alone, which may be due to the preservation of the sphincter of Oddi in the latter group, preventing the chronic reflux of duodenal contents and bacteria into the biliary tree. Currently, our patients are enrolled in a controlled prospective study to evaluate the rate of recurrence of BDS after EST+EPLBD. One study evaluated the recurrence rate and the risk factors in 100 patients with BDS after EST+EPLBD, *vs* a control group of 109 patients submitted to EST alone[13], with a mean follow-up of over 30 mo in both groups. The recurrence rate was similar in patients who underwent EST+EPLBD (11.0%) and EST (13.8%). The larger diameter of the bile duct was the only risk factor for stone recurrence in this study[13].

In conclusion, EST+EPLBD should be considered among the first line therapeutic options for the treatment of difficult bile duct lithiasis. The results from our study showed that it is an effective technique for the management of large BDS, being superior to isolated EST in all efficacy outcomes, with no significant increase of complications.

COMMENTS

Background

The combined endoscopic technique of limited sphincterotomy followed by papillary large balloon dilation, described by Ersoz *et al* in 2003, is an attractive approach for the removal of large bile duct stones. In a recent meta-analysis, it was found to achieve high rates of complete bile duct stone clearance while reducing the use of mechanical lithotripsy.

Research frontiers

In this study, the authors aimed to evaluate the efficacy and safety of endoscopic papillary large balloon dilation after sphincterotomy in the treatment of large (≥ 10 mm) bile duct stones, in a comparative analysis with a control group of patients with similarly large bile duct stones that was submitted to isolated sphincterotomy.

Innovations and breakthroughs

In the authors' case-controlled study, the combined technique achieved higher rate of complete stone clearance than isolated endoscopic sphincterotomy (EST), and this was more often achieved within the first therapeutic session, reducing the need for further endoscopic retrograde cholangio-pancreatography. Moreover, it reduced the need for lithotripsy and biliary stenting, with a similar safety profile.

Applications

The results of this study suggest that the use of endoscopic papillary balloon dilation after limited sphincterotomy should be considered among the first line therapeutic options for the treatment of difficult bile duct lithiasis.

Terminology

Endoscopic papillary balloon dilation involves the progressive dilation of the papillary orifice after limited sphincterotomy, using a through-the-scope oesophageal/pyloric balloon catheter, gradually inflated up to the size of the largest stone and/or the maximal diameter of the distal bile duct according to the cholangiogram. Mechanical lithotripsy is performed when there is a need to fragment the stones prior to removal, using a through-the-scope lithotripsy basket under radiologic guidance. Extracorporeal lithotripsy focuses high-pressure shock wave energy to fragment the stones while minimizing energy exposure to adjacent tissues.

Peer review

In this study, the authors concluded that EST followed by papillary large balloon dilation can achieve a higher rate of complete stone clearance and a less need for lithotripsy and biliary stenting, with equivalent safety to isolated sphincterotomy.

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BRIEF ARTICLE

Small bowel polypectomy by double balloon enteroscopy: Correlation with prior capsule endoscopy

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Abstract

AIM: To investigate the feasibility of small bowel polypectomy using double balloon enteroscopy and to evaluate the correlation with capsule endoscopy (CE).

METHODS: This is a retrospective review of a single tertiary hospital. Twenty-five patients treated by enteroscopy for small bowel polyps diagnosed by CE or other imaging techniques were included. The correlation between CE and enteroscopy (correlation coefficient of Kendall for the number of polyps, intra-class coefficient for the size and coefficient of correlation kappa for the location) was evaluated.

RESULTS: There were 31 polypectomies and 12 endoscopic mucosal resections with limited morbidity and no mortality. Histological analysis revealed 27 hamartomas, 6 adenomas and 3 lipomas. Strong agreement between CE and optical enteroscopy was observed for both location (Kappa value: 0.90) and polyp size (Kappa value: 0.76), but only moderate agreement was found for the number of polyps (Kendall value: 0.47).

CONCLUSION: Double balloon enteroscopy is safe for performing polypectomy. Previous CE is useful in selecting the endoscopic approach and to predicting the difficulty of the procedure.

Key words: Small bowel polyps; Double balloon enteroscopy; Capsule endoscopy; Polypectomy; Correlation

Rahmi G, Samaha E, Lorenceau-Savale C, Landi B, Edery J, Manière T, Canard JM, Malamut G, Chatellier G, Cellier C. Small bowel polypectomy by double balloon enteroscopy: Correlation with prior capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(5): 219-225 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i5/219.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i5.219

INTRODUCTION

The main indication for double balloon enteroscopy (DBE) and capsule endoscopy (CE) is the endoscopic exploration of patients with obscure gastrointestinal bleeding[1-5]. Small bowel polyps and tumours are important causes of small bowel pathology, which occur most frequently in familial or non-familial polyposis syndromes[1,6-10]; the most frequent are familial adenomatous

polyposis (FAP) and Peutz-Jeghers syndrome (PJS)[11,12]. The advent of CE and DBE has improved our ability to perform deep exploration of the small bowel. DBE has the additional advantage of permitting the retrieval of tissue and removal of premalignant polyps. The primary aim of the present study was to assess the feasibility of polypectomy by DBE in patients with small bowel polyps diagnosed by CE or other imaging techniques including computer tomography (CT) scan and magnetic resonance imaging (MRI). The secondary aim was to evaluate the correlation between CE and DBE in terms of determining the size, location and number of polyps.

MATERIALS AND METHODS

This retrospective cohort study included patients treated by DBE for small bowel polyps diagnosed with CE (84%) or other imaging techniques (16% of cases) in our tertiary referral centre between January 2005 and January 2008. Patients were included or excluded based on the following keywords in the CE or radiology reports: (1) Inclusion criteria for CE were "pedunculated or sessile polyps" and for MRI or abdominal CT scan "lesions with polyp aspects"; (2) Exclusion criteria for CE were "the tumour or mass appears as a thickened fold with pathologically abnormal vessels, aspects of stenosis, aspects of diffuse infiltration of the small bowel wall and aspects of submucosal lesions with intact overlying mucosa", and MRI or abdominal CT scan "the tumour or mass appears with tissue density picture and aspects of stenosis".

All patients had previously undergone at least one upper gastrointestinal endoscopy and colonoscopy. The data were obtained from the patient medical records and were entered into a semi-standardised electronic database. If one DBE route did not yield a diagnosis, the opposite route was used for the second investigation. Complete DBE was confirmed by tattooing the small bowel.

The lesions diagnosed by the physician in charge of interpreting CE were classified according to their size, location and imputability according to Saurin *et al*[13], using the following criteria: P3 (presence of blood), P2 (high imputability), P1 (intermediate imputability) and P0 (low imputability). Capsule video endoscopy was performed with the PillCam™ SB (Given Imaging Ltd, Yoqneam, Israel). All patients were prepared with 2 L of polyethylenglycol (PEG) solution the night before examination. The capsule transmitted continuous video images at a rate of 2 frames per second for about 8 h during its passage through the gastrointestinal tract. The route of insertion of the DBE was found by calculating Gay's index; the oral route was chosen if the time to lesion/time to cecum was less than 0.75[14]. The oral and anal routes were not taken during the same procedure because of the long procedure duration. In our series, no patients received total enteroscopy. For 6 patients, DBE from the anal route permitted the resection of polyps. For one patient, CE showed polyps in the jejunum and ileum, and DBE by the oral and anal routes was performed 48 h apart for the resection of these polyps. We failed to perform a complete enteroscopy. For the other 5 patients, CE showed polyps in the ileal position; in these cases, DBE by the anal route was the first choice and permitted the resection of polyps.

The following locations were examined: the proximal jejunum (the first quarter of the small intestine), distal jejunum (the second quarter of the small intestine), proximal ileum (the third quarter of the small intestine) and distal ileum (the fourth quarter of the small intestine). No a posteriori readings of CE or DBE were performed.

All of the DBE procedures were performed by an experienced endoscopists aided by an assistant holding the overtube. The DBEs (Fujinon Inc., EN-450P5 or EN-450T5) had a diameter of 8.5 and 9.3 mm with an operating channel of 2.2 and 2.8 mm, respectively. All of the patients were sedated by propofol with endotracheal intubation. Fluoroscopy was reserved for difficult cases. The depth of insertion into the small bowel was calculated according to the method described by May *et al*[10]; the advancement of the instrument was measured by counting the number of full 40 cm advancement sequences carried out after the reference point established by an initial full-length insertion of the endoscope. The procedure for enteroscopy *via* the anal route was different; in this case, the initial introduction was performed *via* the colon to the ileocecal valve, with or without the balloons. The advancement was measured by counting the number of 40 cm sequences from the ileocecal valve. For the oral route, the endoscopic procedure was performed in the left lateral position, and no bowel preparation was required. For the anal route, four litres of PEG solution was given to the patient the day before the procedure.

Analogous to the Paris classification for gastrointestinal superficial tumours, we treated small bowel lesions according to the endoscopic appearance[15]. A simple snare polypectomy was performed to remove pedunculated polyps, which was the most frequent situation. Endoscopic mucosal resection (EMR) was performed for any superficial polypoid sessile tumours or non-polypoid tumours (slightly elevated, flat, and slightly depressed). After the lesion was lifted by a submucosal saline injection, we used a polypectomy snare. EMR was not attempted in ulcerated or excavated lesions because of the risk of invasion depth.

The polyp number and size in each small bowel segment (proximal and distal jejunum and proximal and distal ileum) were documented. Polyp size was estimated using open biopsy forceps. Depending on the polyp size, a submucosal injection of epinephrine-saline solution (1:10000) was delivered before resection. PJS polyps measuring over 10 mm were resected, and the smaller polyps were left in place. It is consensus not to remove small polyps (less than 10 mm) in PJS because the malignant transformation of small bowel polyps in these patients is a rare event[16,17]. Patients with Lynch syndrome, PJS and FAP syndrome received genetic counselling and, if necessary, genetic testing.

Table 1 Clinical and demographic characteristics of patients with small bowel polyps diagnosed with double balloon enteroscopy *n* (%)

Patient characteristics	
Total	25
Males	18 (72)
Mean age (yr, range)	44 (8-83)
Only 1 DBE	20 (80)
DBE characteristics	
Total	32
Insertion	
Oral route	26 (81)
Anal route	6 (19)
Indications	
Occult bleeding	11 (34)
Overt bleeding	4 (12)
Peutz-Jeghers syndrome	10 (31)
Hereditary non-polyposis colon cancer	3 (9)
Familial adenomatous polyposis	3 (9)
Familial liver adenomatosis	1 (3)
Others (abdominal pain)	3 (9)

DBE: Double balloon enteroscopy.

Statistical analysis

For statistical analysis, categorical variables are presented as number (%), and continuous variables are presented as the mean ± one SD or median (25% percentile - 75% percentile). The correlation between the number of diagnosed polyps by CE and DBE was estimated using the Kendall coefficient of concordance (W); the closer the W is to 1, the higher the correlation. To compare the size of the polyps, we considered the first polyp measured at CE or DBE, and the correlation was calculated by an intra-class correlation coefficient (Fleiss formula: two-way mixed model, with a random effect for the subject and a fixed effect for the method). Finally, the agreement between CE and DBE for polyp location was estimated using a weighted kappa. All calculations were performed with the SAS statistical software (version 9.1). Statistical tests were two-sided with an alpha level of 0.05.

RESULTS

From January 2005 to January 2008, 403 enteroscopies were performed at our centre; thirty-two (8%) were performed for small bowel polyps in 25 patients (Table 1). The indications were occult or overt gastrointestinal bleeding (34% and 12%, respectively); PJS, Lynch syndrome or FAP follow-up (31%, 9% and 9%, respectively); and one case of familial liver adenomatosis. Two patients with polyps suspected on CE had a negative DBE; the first of these patients underwent a second CE that did not show any polyps, and the second patient, who had multiple suspected polyps in the ileum based on CE, was diagnosed with lymphoid hyperplasia without polyps on DBE (anal route).

The results of the CE and DBE are summarised in Table 2. CE showed lesions with P1 (11%), P2 (81%) and P3 (8%) imputability (Figure 1). The median number of polyps diagnosed by CE was 1.5 (range: 1-10), and the median size was 30 mm (range: 5-50 mm). The results of the CE determined the route of DBE insertion; the oral route was designated for 26 procedures (81%) in patients with a Gay's index < 0.75 and anal route was designated for the other patients. No total enteroscopy was possible. The mean total duration of the procedure for the oral and anal routes was 65 min (35-250 min) and 80 min (50-280 min), respectively. The mean polyp size with DBE was 20 mm (8-50 mm) (Figure 2). More than 50% of the polyps were located in the proximal small bowel. Using DBE, we found one small bowel polyp in 22 procedures and more than one in 10 procedures. In total, 31 polypectomies and 12 mucosectomies were performed. Eight polyps were not resected (simple biopsies) because their size was over 5 cm, and two of these polyps appeared as large submucosal lesions.

Immediate bleeding occurred in 6 patients, and there was no delayed bleeding. No patient had anticoagulant or antiplatelet therapy before or during the procedure. In 4 cases, there was a large peduncle and a polyp with a size of 30 to 40 mm, which was treated by polypectomy with a snare; two of them were bilobed and ulcerated on the top. Bleeding was stopped using haemostatic clips and a diluted adrenalin injection. In the other 2 cases, the polyps were sessile, measuring 20 to 30 mm. Haemostatic clips stopped the bleeding and closed the EMR wound. For one patient, acute pancreatitis occurred after a long

Table 2 Results of capsule endoscopy and double balloon endoscopy: polyp number, size and location *n* (%)

	Capsule endoscopy *n* = 27	Double balloon enteroscopy *n* = 32
Median number of polyps	1.5 (1-10)	1 (1-13)
Mean size (mm)	30 (5-50)	20 (8-50)
Location		
Proximal jejunum	17 (63)	20 (63)
Distal jejunum	4 (15)	6 (19)
Proximal ileum	6 (22)	3 (10)
Distal ileum	6 (22)	4 (12)

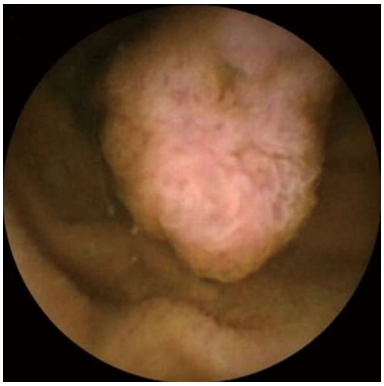

Figure 1 Polyp showed by capsule endoscopy in patient with Peutz-Jeghers syndrome.

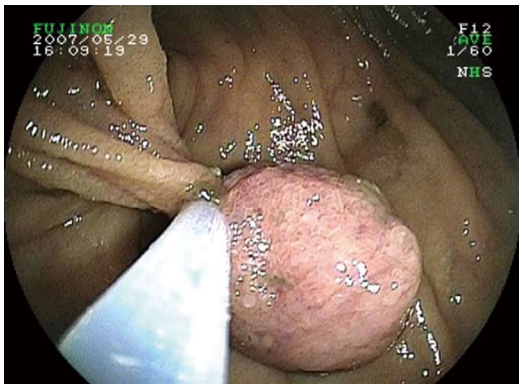

Figure 2 Polypectomy during double balloon enteroscopy for a patient with Peutz-Jeghers syndrome.

and difficult procedure resulting in the large resection of a polyp located in the distal part of the jejunum (grade D of Balthazar's classification); this condition resolved within 2 d after medical treatment. There was no mortality related to DBE.

Histological analysis was available for 36 of the 43 polyps (83%) because of an inability to retrieve all of the polyps after resection, especially in the case of multiple polyps. There were 27 hamartomatous polyps (three with low-grade dysplasia), all of which occurred in patients with PJS; six were adenomatous polyps (five with low-grade and one with high-grade dysplasia), and three were lipomas (all were small, ulcerated and responsible for the gastrointestinal bleeding). All of the adenomas polyps were observed in patients with Lynch syndrome or FAP. All the margins were tumor free.

Polyp resection was impossible in 9 patients who underwent surgical treatment with small bowel resection; among these patients, 2 had an ulcerated lesion mimicking a sessile polyp causing bleeding and had surgery as the bleeding failed to stop despite an argon plasma coagulation and adrenalin solution injection. Histological examination of the polyps from these 2 patients showed gastro-intestinal stromal tumour (GIST). For 6 patients, the polyp was larger than 5 cm with difficult enteroscopic positioning, making resection impossible; post-procedure histological examination showed hamartomas in PJS. The remaining patient had more than 10 large polyps, leading to a decision to perform intraoperative enteroscopy.

The agreement between CE and DBE was good for the location and size of polyps with kappa values of 0.90 (95%CI: 0.73-1) and 0.76 (95%CI: 0.43-0.91), respectively, but moderate for the number of polyps (Kendall coefficient value, 0.47, $P = 0.0076$).

Five treated patients were lost to follow-up. Among the 20 remaining patients, the median follow-up was 14.2 mo (range: 2-36 mo). Another polypectomy was necessary in 4 patients during the follow-up period. Three patients had PJS, and the initial CE showed multiple lesions that could not be removed during one DBE. One patient with PJS had an ileal polypectomy during the first DBE by the anal route. One year later, CE showed a large polyp in the proximal jejunum that was probably not detected on the previous CE. The polyp was resected by DBE using the oral route. For patients with adenoma polyps, one was lost to follow-up; there was no recurrence for the other patients, with a mean follow-up of 26 mo (range: 3-35 mo).

DISCUSSION

We report 25 patients treated for small bowel polyps by DBE. All of the procedures were well tolerated. The agreement between CE and DBE was good for both the location and size of polyps, but was poor for the number of polyps.

Therapeutic DBE is associated with an incidence of complications of approximately 1%-5%, the most frequent of which are perforation, bleeding and pancreatitis[18,19]. In our series, only 1 case of acute pancreatitis out of 403 enteroscopies occurred, which was rapidly resolved with medication. Episodes of bleeding were successfully treated during DBE with an injection of epinephrine-saline solution and clips. In a recent study describing complications after DBE[19], the perforation rate was 1.5% per polyp (2 among 137 polyps removed) and 2.9% per patient (2 among 68 patients). In their series of 79 polyps in 15 patients with PJS, Gao *et al*[20] reported no perforation after polyp removal, and we observed the same results. The majority of the removed polyps in our series were pedunculated, and all sessile polyps had a good elevation after serum sub-mucosa injection. Good exposure of the polyp is very important in the case of large polyp size because of a higher risk of perforation. The change in position of the patient (left lateral or supine position) can reduce this risk during resection. We believe that polyp resection should not be attempt when there is no lifting sign or when the appearance is a submucosal lesion.

In our series, most of the polyps were localised to the proximal region of the jejunum, and some of the polyps were nearly 5 centimetres in size. The polyp location shown on CE was used to indicate whether the DBE route should be oral or anal using Gay's Index. Moreover, when CE showed a large polyp, it was possible to predict the resection difficulty and the duration of the procedure. The moderate correlation between CE and DBE count is probably due to DBE distension of the small bowel by air insufflation in the case of numerous polyps, which provided a more accurate way of counting a larger number of small polyps compared to CE. In studies addressing the same issue, Marmo *et al*[21] showed that CE and DBE show good agreement for vascular and inflammatory lesions, but not for polyps or neoplasia. In this study, in concordance for the polyp size, the number or the location of the polyp was not analysed separately.

In our study, 10 patients had PJS. This high number of PJS can be explained by the presence of a genetics unit in our centre that treats patients with gastrointestinal polyposis. Several studies have shown that polypectomy

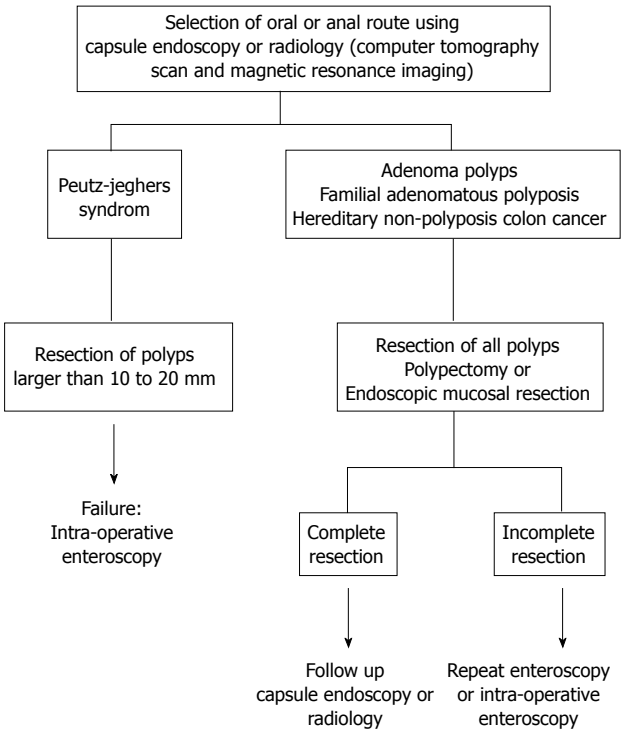

Figure 3 Suggested algorithm for resection of small bowel polyps by double balloon enteroscopy.

during DBE is effective and may decrease the need for urgent laparotomy for occlusion due to a large polyp. Chen *et al*[22] showed that a total of 17 enteroscopies resulted in polypectomy in six patients with PJS without complications. All patients underwent complete small bowel exploration in 1 or 2 steps. Another technique that allows for small bowel polypectomy is intraoperative enteroscopy, but DBE is less invasive and more convenient for the patient[23].

The screening and management of small bowel polyps and tumours is important for patients with familial and non-familial polyposis syndromes. Mönkemüller *et al*[24] studied the usefulness of DBE-assisted chromoendoscopy for the detection and characterisation of small bowel polyps in patients with FAP; jejunal polyps were detected in 67% of the patients, and chromoendoscopy helped detect additional polyps in two patients.

The second most frequent and most important site, after the colon, of adenomas in FAP is the duodenum. The three patients in our study were stage I or II according to the Spigelman score (between 5 and 20 polyps, measuring between 1 and 10 mm, tubular and without high-grade dysplasia).

Our study has the potential limitation of being a single-centre retrospective study in a university setting with an associated recruitment bias. However, to our knowledge, this is one of the largest endoscopic series focusing on the diagnosis and management of small bowel polyps excluding tumours. Another criticism could be that our patient sample has been selected based on a positive CE, which can lead to an optimistic estimation of agreement because these patients are not taken into account for kappa calculation. However, any missed patients probably harbour small lesions, and their absence from our sample probably has no influence on our estimation of the complication rate. Another limitation is the lack of complete small bowel exploration. Sakamoto *et al*[25] showed that several sessions of enteroscopy in PJS patients with resection of polyps more than 20 mm in size was useful for reducing polyp size and number, preventing intussusceptions, and avoiding laparotomy. In our study is the use of the first small-bowel CE device PillCam™ SB (Given imaging, Yoqneam, israel). Actually, improvements have been made as the PillCam™ SB2, and new capsules were developed: EndoCapsule™ (Olympus, Tokyo, Japan), MiroCam™ (introMedic Co., seoul, South Korea) and OMOM capsule endoscope (Jianshan Science and Technology Group Co., Ltd., Chongqing, China)[26-28]. Advantages are deeper field of view (up to 156°), higher frame rate (3 per second for MiroCam™), longer battery life (over 11 h) and the possibility of real-time image acquisition. With the OMOM capsule, the frame rate can be changed during the study. All these improvements allow a better visualization of the intestinal mucosa and may help for polyps' detection. In Figure 3, we have summarized our endoscopic strategy for small bowel polyp resection in PJS patients and in adenoma polyps in patients with Lynch syndrome and FAP. For patients with FAP, the resection of small bowel polyps should be always attempted because of the potential risk of progression to adenocarcinoma. For those suffering from PJS syndrome, we suggest to remove only larger polyps more than 10 mm, since the major risk is bleeding and intussusception. Follow-up by CE or DBE should be recommended after the removal of adenomatous or hamartomatous polyps, but future studies have to determine which interval should be chosen for the follow-up.

In summary, DBE is a safe and effective technique for diagnosing and resecting most polyps in the small bowel with a low complication rate. However, it is a time-consuming procedure that is not always capable of visualising the entire small bowel and should be preceded by CE witch is a less invasive technique. CE allows to show the number, location and size of the polyps and thus, indicate the route (*i.e.*, oral or anal) and predict the difficulty of the polypectomy during optical enteroscopy.

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COMMENTS

Background

Capsule endoscopy (CE), after being ingested by the patient, allows entire small bowel exploration. Double balloon enteroscopy (DBE) is an overtube-assisted endoscopic technique which allows deep exploration of the small bowel and resection of polyps diagnosed by CE. Polyps must be resected because of the risk of malignant transformation and/or the risk of small bowel obstruction.

Research frontiers

Endoscopic techniques, as DBE, allow mini-invasive treatment for small bowel polyps as an alternative to surgery.

Innovations and breakthroughs

DBE is a safe and effective technique for diagnosing and resecting most polyps in the small bowel with a low complication rate. CE allows to show the number, location and size of the polyps and thus, indicate the route (*i.e.*, oral or anal) and predict the difficulty of the polypectomy during optical enteroscopy.

Applications

Any patient with suspected small bowel disease should be eligible to an endoscopic small bowel exploration by DBE and CE.

Terminology

Enteroscopy: endoscopic exploration of small bowel; Polypectomy: polyp's resection.

Peer review

This study demonstrates the utility of C followed by DBE to better care for patients with small bowel polyps.

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BRIEF ARTICLE

Colonoscopy in rats: An endoscopic, histological and tomographic study

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Abstract

AIM: To describe colon anatomy with colonoscopy and computed tomography (CT) to develop a rat model for future studies of therapeutic colonoscopy.

METHODS: Eighteen male Sprague-Dawley rats, on average 400-420 g, underwent total colonoscopy, CT and histological examination. Colonoscopy was performed after bowel preparation with a baby upper gastrointestinal endoscopy with an outer diameter of 6.7 mm. CT obtained a 3D image of total colon after a rectal enema with radiological contrast. Macroscopic and microscopic examinations were examined with a conventional technique (hematoxylin and eosin). Colonic wall thickness, length and diameter measurements were taken from the anus, 3, 7, 14 and 20 cm from the anal margin.

RESULTS: The median colonoscope depth was 24 cm (range 20-28 cm). Endoscopic and tomographic study of colon morphology showed an easy access with tubular morphology in the entire left colon (proximal left colon and rectum). Transverse colon was unapparent on colonoscopy. Right colon, proximal to the splenic flexure, was the largest part of the colon and assumed saccular morphology with tangential trabecula. Radiological measurements of the colonic length and diameter substantiate a subdivision of the right colon into two parts, the cecum and distal right colon. In addition, histological measurement of the colonic wall thickness confirmed a progressive decrease from rectum to cecum. The muscular layer was thinner in the proximal left colon.

CONCLUSION: The combination of colonoscopy, tomography and histology leads to a better characterization of the entire colon. These data are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

Key words: Rat; Colonoscopy; Tomography; Colon anatomy; Histological measurements

Core tip: There is a need for a solid colonoscopy animal model, complemented with digital radiology. Our subdivision of the rat colon constitutes a simplification of subdivisions presented by others who have emphasized the theoretical anatomical data. Our proposed subdivision of the colon is practical and justified by the

importance of endoscopic access and the thickness of various portions of the colon wall. This study identified that the muscular layer was thinner in the proximal left colon. These findings are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

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INTRODUCTION

The rat is widely used as a laboratory animal for medical biological and molecular research. The anatomy and topography of the rat colon have been described on the basis of macroscopic and conventional radiological observations on the whole animal[1]. Radiology is useful for studying normal arterial and mucosal anatomy of the explanted rat colon. In contrast, in clinical practice, endoscopy is one of the keystone diagnostic techniques allowing follow-up and management of gastrointestinal inflammation[2-9]. Interestingly, there are no detailed endoscopic descriptions of the gross anatomy of the colon by total colonoscopy (TC)[10-19]. Significant progress in endoscopic techniques has been made in the last years. There is a need for a solid colonoscopy animal model, complemented with digital radiology. The aim of the present study was to describe the colon anatomy with high-definition colonoscopy and computed tomography (CT) to develop a rat model for future studies of therapeutic colonoscopy.

MATERIALS AND METHODS

Rats

Eighteen male Sprague-Dawley, on average 400-420 g, were used in this study. Rats were acclimatized for a minimum of 7 d preoperatively. Rats were kept at constant room temperature (20-22 ℃) with a relative humidity (27%-31%) with aeration under an alternating 12 h cycle of fluorescent light and darkness. The rats were housed individually in polycarbonate box cages with free access to water and food (Teklad Global 2014, Harlan Laboratories Models SL, Barcelona, Spain). Rats are the smallest and lowest among the species suitable for TC. The rats suffered minimal pain and distress due to the use of anesthesia. The protocol was approved by the Institutional Animal Care and Use Committee of Hospital Universitari Germans Trias i Pujol.

Bowel preparation

The animals had free access to water but food was withdrawn 8 h prior to the initiation of bowel preparation. A rectal enema with saline solution was performed immediately prior to TC[20].

Colonoscopic examination

Colonoscopy was performed with a baby upper gastrointestinal Olympus GIF-XP160 video endoscope with an outer diameter of 6.7 mm and a 2.3 mm working channel (Olympus, Tokyo). After a 24 h fasting period with free access to drinking water, the rats were anesthetised by isofluorane inhalation (1.5% with 98% O_2) and placed in a supine position. Remaining feces were flushed away by injecting water through the anus. A drop of lubricating jelly (Aquagel®, Ecolab, Leeds, England) was applied on the anal sphincter to facilitate insertion of the scope. The endoscope was then gently passed through the anus and under endoscopic vision further introduced. Water was injected through the scope's working channel to visualize the lumen of the colon. Occasionally the colon was inflated with air for better visualisation of the lumen. The tip of the endoscope was introduced to the cecum, about 24 cm proximal from the anus. Pictures were captured in each procedure. Rats were placed under surveillance during recovery and were returned to their cages when regaining consciousness.

CT

In vivo X-ray Microtomograph (SkyScan 2002, Aartselaar, Belgium) was used in order to obtain a 3D image of total colon. Briefly, animals were anesthesized with isofluorane, 20 mL of radiological contrast (Plenigraf®, Juste, Madrid, Spain) was administered through a rectal enema and then the animals were placed in the scanning area. Acquisition images for 3D reconstruction of the whole colon lasted over 40 min with a resolution of 32 μm.

Macroscopic examination

Rats were sacrificed 48 h after colonoscopy by anesthetic overdose (60 mg pentobarbital, *ip*). After sacrifice, the colon was collected and rinsed with ice-cold Krebs solution. The colon was opened longitudinally and pinned out on a Petri dish to examine the colonic mucosa. The mucosal surface of the distal colon was inspected with a binocular microscope (Harvard Apparatus, Panlab, Barcelona, Spain).

Microscopic examination

Full-thickness samples of approximately 1 cm were taken from anus, 3, 7, 14 and 20 cm from the anal margin. Segments were fixed in 4% formaldehyde for 24 h, embedded in paraffin and cross sections of 5 μm were stained with hematoxylin and eosin. Histological sections were examined using a conventional microscope (Olympus, Shinjuku-ku, Tokyo, Japan).

RESULTS

Colonoscopic examination

Bowel preparation resulted in complete evacuation of

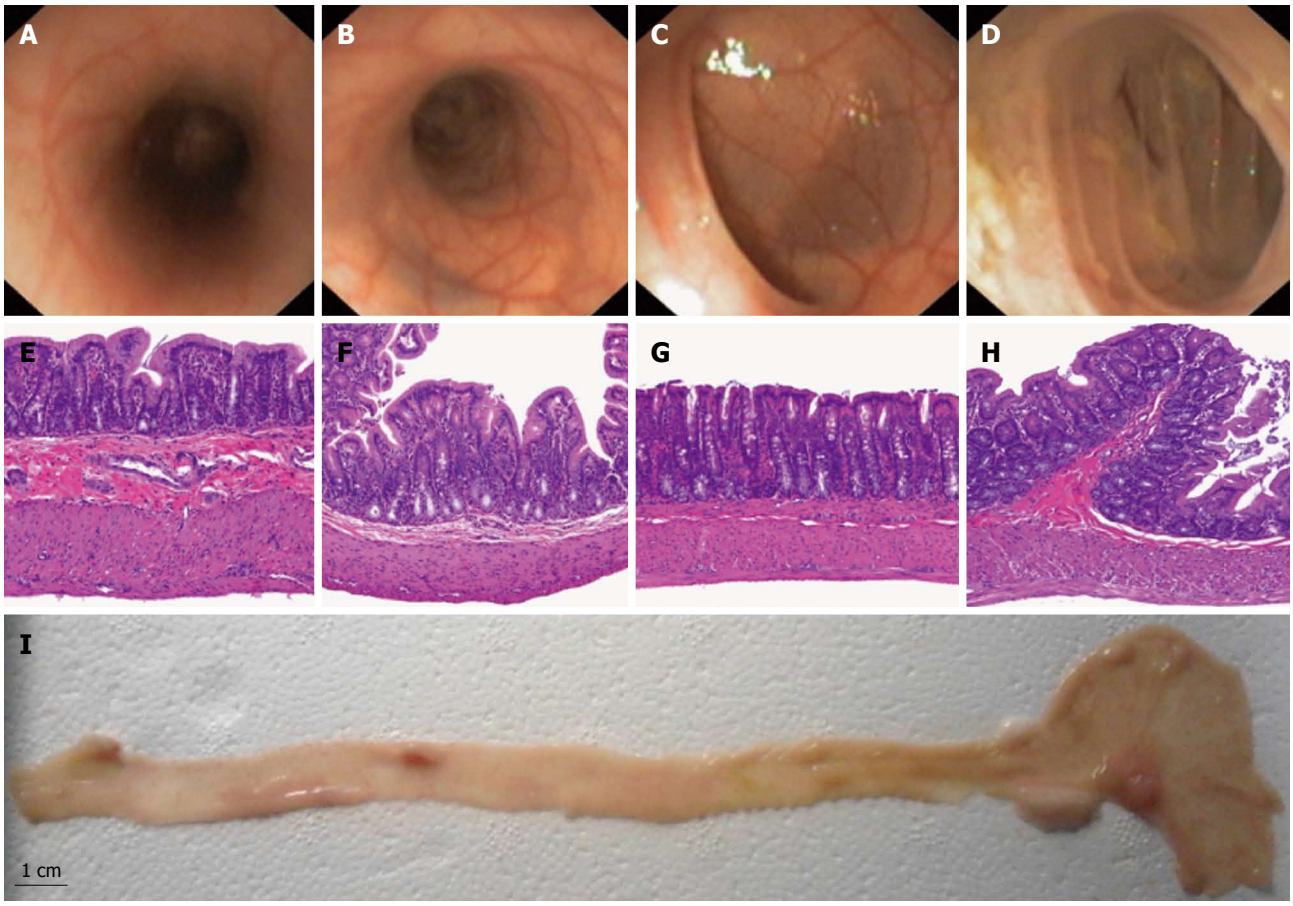

Figure 1 Representative pictures of *in vivo* colonoscopy (A-D), photomicrograph of histological study with hematoxylin and eosin stains of colon sections (E-H) in rats at 3 (A,E), 7 (B,F), 14 (C,G) and 20 cm (D, H) from the anal margin. Macroscopic picture of the entire colon (I).

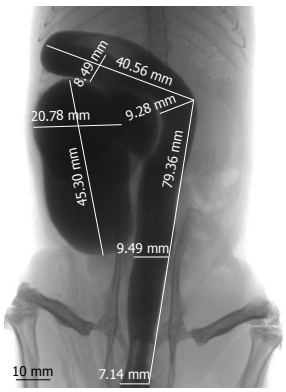

Figure 2 Tomographic picture of rat colon with length and diameter measurements.

stools in the left colon. In the right colon we found one solid stool and liquid feces that were flushed away. The median colonoscope depth was 24 cm (range 20-28 cm). Confirmation of cecal intubation during colonoscopy was achieved by transillumination through the abdominal wall. The appendiceal orifice was not identified in any case**.** The scope reached the splenic flexure easily and the tube went straight up from the anus so that the entire left colon (proximal left colon and rectum) assumed a tubular morphology. The transverse colon was unapparent on colonoscopy. The right colon, proximal to the splenic flexure including the cecum, was the largest part of the colon and assumed saccular morphology with tangential trabecula. Splenic and liver impronta were evident in both flexures. Mucosal and vascular pattern were similar in the left and distal right colon. In the cecum, the mucosal surface of the insufflated colon presents folds (Figure 1).

CT

Radiological measurements of the colonic length and diameter substantiate a subdivision of the right colon into two parts, the cecum and distal right colon (Figure 2). The cecum of the rat is 54.6 ± 22.1 mm long, is the most prominent part of the colon and assumes a sack form with a major diameter measurement of 20.78 ± 1.88 mm. The cecum does not have a vermiform appendix. Straight down from the cecum, the colon has a tubular morphology, curved in the distal right colon and linear in the left colon. The distal right colon is 89.3 ± 17.6 mm long with a diameter of 8.49 ± 0.29 mm. The left colon in the rat is 95.4 ± 13.5 mm long, with a diameter of 9.28 ± 0.37 mm in the proximal part and 8.05 ± 0.39 mm in the distal part (Table 1).

Histological examination

Histological measurement of the colonic wall thickness

Table 1 Histological and radiological features of the rat colons

Measurements	Left colon (distal to splenic flexure)		Right colon	
	Rectum	Proximal left colon	Distal right colon	Cecum
Distance to anal margin (mm)	0-45.6 ± 8.4	45.6 ± 8.4 - 95.4 ± 13.5	95.4 ± 13.5 - 184.7 ± 20.1	184.7 ± 20.1-244.3 ± 25.8
Length (mm)	45.6 ± 8.4	49.8 ± 10.5	89.3 ± 17.6	54.6 ± 22.1
Macroscopic diameter (mm)	7.79 ± 0.46	8.18 ± 0.28	8.01 ± 0.32	20.11 ± 2.31
Radiological diameter (mm)	8.05 ± 0.39	9.28 ± 0.37	8.49 ± 0.29	20.78 ± 1.88
Full-thickness samples to anal margin (cm)	3	7	14	20
Wall thickness (μm)	658.3 ± 50.7	600.0 ± 58.6	562.5 ± 21.6	550.0 ± 49.2
Muscular thickness (μm)	229 ± 42.9	118.8 ± 11.3	170.0 ± 33.6	140.0 ± 24.3
Mucosal thickness (μm)	283.0 ± 25.6	289.0 ± 23.4	256.3 ± 16.0	260.0 ± 22.8

and description of the mucosal pattern substantiates a subdivision of the colon into 4 parts (cecum, distal right colon, proximal left colon and rectum). The wall thickness progressively decreases from the rectum to cecum, whereas the muscular layer was thinner in the proximal left colon (Table 1 and Figure 1).

DISCUSSION

The present study successfully described the rat colon anatomy to develop a rat model for future studies of therapeutic colonoscopy. Endoscopic and tomographic study of colon morphology showed an easy access with tubular morphology in the entire left colon. The right colon does not assume a linear morphology, the cecum being the most prominent part. In addition, histological measurement of the colonic wall thickness confirmed a progressive decrease from rectum to cecum. The muscular layer was thinner in the proximal left colon. These findings are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments because of the effects of thermal injury and coagulation necrosis of the muscularis propria and serosa. Colonoscopic perforation is a potentially life-threatening complication with an incidence rate ranging from 0.07% to 0.1% in diagnostic and therapeutic colonoscopies, respectively[21,22].

Our anatomical description differs from that of others[23] because in colonoscopy the colonic inflexions are much less evident. Currently available animal models in rats for endoscopy research contain inherent flaws, fail to meet the criteria for extrapolation to humans, and therefore are unlikely to be valid. The description of the normal anatomy is an indispensable premise in experimental therapeutic endoscopy. Proposals have been made to distinguish subdivisions of the rat colon resembling those used for human anatomy with conventional radiology[1,24]. A solution was presented 15 years ago when Hull *et al*[10] showed that it was feasible to perform bowel preparation and TC on rats. The authors successfully performed TC with a pediatric bronchoscope. Colonoscopy limited to the splenic flexure in rats has been previously reported[10]. Confirmation that the cecum was reached was done by visualizing liquid stool which was present only in the cecum in all rats[25,26].

Our subdivision of the rat colon constitutes a simplification of subdivisions presented by others[11] who have emphasized the theoretical anatomical data. Our proposed subdivision of the colon is practical and justified by the importance of endoscopic access and the thickness of various portions of the colon wall.

In conclusion, a reproducible rat model has been achieved. These data are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

COMMENTS

Background

Significant progress in endoscopic techniques has been made in the last years. There is a need for a solid colonoscopy animal model, complemented with digital radiology.

Research frontiers

The present study successfully described the rat colon anatomy to develop a rat model for future studies of therapeutic colonoscopy.

Innovations and breakthroughs

The subdivision of the rat colon constitutes a simplification of subdivisions presented by others who have emphasized the theoretical anatomical data. The proposed subdivision of the colon is practical and justified by the importance of endoscopic access and the thickness of various portions of the colon wall. This study identified that the muscular layer was thinner in the proximal left colon.

Applications

These findings are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

Terminology

Colonoscopy is an invasive technique that permits a direct visualization of the colon mucosa. Computed tomography is a radiology technique that allows obtaining 3D images.

Peer review

The authors described the rat colon anatomy to develop a rat model for future studies of therapeutic colonoscopy. Endoscopic and tomographic study of colon morphology showed an easy access with tubular morphology in the complete left colon. Otherwise, the results identified that the muscular layer was thinner in the proximal left colon.

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BRIEF ARTICLE

Usefulness of applying lidocaine in esophagogastroduodenoscopy performed under sedation with propofol

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Abstract

AIM: To determine whether topical lidocaine benefits esophagogastroduoduenoscopy (EGD) by decreasing propofol dose necessary for sedation or procedure-related complications.

METHODS: The study was designed as a prospective, single centre, double blind, randomised clinical trial and was conducted in 2012 between January and May (NCT01489891). Consecutive patients undergoing EGD were randomly assigned to receive supplemental topical lidocaine (L; 50 mg in an excipient solution which was applied as a spray to the oropharynx) or placebo (P; taste excipients solution without active substance, similarly delivered) prior to the standard propofol sedation procedure. The propofol was administered as a bolus intravenous (*iv*) dose, with patients in the L and P groups receiving initial doses based on the patient's American Society of Anaesthesiologists (ASA) classification (ASA Ⅰ-Ⅱ: 0.50-0.60 mg/kg; ASA Ⅲ-Ⅳ: 0.25-0.35 mg/kg), followed by 10-20 mg *iv* dose every 30-60 s at the anaesthetist's discretion. Vital signs, anthropometric measurements, amount of propofol administered, sedation level reached, examination time, and the subjective assessments of the endoscopist's and anaesthetist's satisfaction (based upon a four point Likert scale) were recorded. All statistical tests were performed by the Stata statistical software suite (Release 11, 2009; StataCorp, LP, College Station, TX, United States).

RESULTS: No significant differences were found between the groups treated with lidocaine or placebo in terms of total propofol dose (310.7 ± 139.2 mg/kg per minute *vs* 280.1 ± 87.7 mg/kg per minute, $P = 0.15$) or intraprocedural propofol dose (135.3 ± 151.7 mg/kg per minute *vs* 122.7 ± 96.5 mg/kg per minute, $P = 0.58$). Only when the L and P groups were analysed with the particular subgroups of female, < 65-year-old, and lower anaesthetic risk level (ASA Ⅰ-Ⅱ) was a statistically significant difference found (L: 336.5 ± 141.2 mg/kg per minute *vs* P: 284.6 ± 91.2 mg/kg per minute, $P = 0.03$) for greater total propofol requirements). The total incidence of complications was also similar between the two groups, with the L group showing a complication rate of 32.2% (95%CI: 21.6-45.0) and the P group showing a complication rate of 26.7% (95%CI: 17.0-39.0). In addition, the use of lidocaine had no ef-

fect on the anaesthetist's or endoscopist's satisfaction with the procedure. Thus, the endoscopist's satisfaction Likert assessments were equally distributed among the L and P groups: unsatisfactory, [L: 6.8% (95%CI: 2.2-15.5) *vs* P: 0% (95%CI: 0-4.8); neutral, L: 10.1% (95%CI: 4.2-19.9) *vs* P: 15% (95%CI: 7.6-25.7)]; satisfactory, [L: 25.4% (95%CI: 10-29.6) *vs* P: 18.3% (95%CI: 15.5-37.6); and very satisfactory, L: 57.6% (95%CI: 54-77.7) *vs* P: 66.6% (95%CI: 44.8-69.7)]. Likewise, the anaesthetist's satisfaction Likert assessments regarding the ease of maintaining a patient at an optimum sedation level without agitation or modification of the projected sedation protocol were not affected by the application of lidocaine, as evidenced by the lack of significant differences between the scores for the placebo group: unsatisfactory, L: 5.8% (95%CI: 1.3-13.2) *vs* P: 0% (95%CI: 0-4.8); neutral, L: 16.9% (95%CI: 8.9-28.4) *vs* P: 16.7% (95%CI: 8.8-27.7); satisfactory, L: 15.2% (95%CI: 7.7-26.1) *vs* P: 20.3% (95%CI: 11.3-31.6); and very satisfactory, L: 62.7% (95%CI: 49.9-74.3) *vs* P: 63.3% (95%CI: 50.6-74.7).

CONCLUSION: Topical pharyngeal anaesthesia is safe in EGD but does not reduce the necessary dose of propofol or improve the anaesthetist's or endoscopist's satisfaction with the procedure.

Key words: Lidocaine; Propofol; Esophagogastroduodenoscopy; Sedation; Adverse effects

Core tip: We are pleased to report the second study in the literature about the possible efficacy of using an adjuvant topical anaesthesia, in this case lidocaine applied as a spray to the oropharynx, during esophagogastroduodenoscopy performed under sedation with propofol. This study is unique, however, in that it is the first randomized controlled trial demonstrating that this routine application has no beneficial effect on reduction of propofol dose or procedure-related complications, or on improved satisfaction of the endoscopist or anaesthetist. These findings may help to improve and streamline the current procedures used for endoscopy sedation, saving resources such as time during surgery and monetary costs for the topical agent.

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INTRODUCTION

Sedation in gastrointestinal endoscopy was traditionally performed with benzodiazepines in isolation or in combination with opioids. However, since the introduction of propofol nearly two decades ago, this very powerful ultrashort action hypnotic agent has emerged as the primary method for sedation in digestive endoscopy[1-4]. Nevertheless, its use is not without risk[5], such as serious cardiorespiratory consequences[6], and the ability to resolve cases of over-sedation is hindered by the lack of antagonists.

Previous studies of non-sedated esophagogastroduodenoscopy (EGD) have shown that the use of topical pharyngeal anaesthesia improves the patients' perceived satisfaction with the procedure[7,8]. Another study of patients undergoing EGD with sedation *via* the traditional drugs indicated that administration of topical anaesthesia facilitated the endoscopic examination and increased patients' tolerance[9]. However, this beneficial effect has not been sufficiently researched in patients sedated *via* propofol[10]. Therefore, the purpose of this study was to establish whether application of topical pharyngeal anaesthesia benefits patients undergoing EGD by reducing total propofol dosage required for sedation or affecting the rate of procedure-related adverse effects. In addition, this study assessed whether the use of topical lidocaine impacts the quality of the endoscopic examination as perceived by the endoscopist/anaesthetist.

MATERIALS AND METHODS

Patients

Consecutive patients over 18-year-old referred to the Endoscopy Unit of the Infanta Cristina Hospital for diagnostic or therapeutic EGD with sedation were recruited for the study. Patients were excluded from enrolment according to the following criteria: undergoing urgent endoscopy; presence of encephalopathy; refusal of cooperation for the treatment or study procedures; refusal to provide informed consent; not having fasted; having a history of or predisposition to methemoglobinemia (NADH reductase, pyruvate kinase, or glucose-6-phosphate dehydrogenase deficiency); women who were pregnant or lactating; or presence of known allergies to propofol and/or lidocaine (or the amide group of local anaesthetics). All enrolled study participants provided informed consent prior to the treatment procedure. The study was approved by the Clinical Trials and Research Committee, the Spanish lidocaine drug manufacturer (Inibsa, Spain), and the Spanish Medical Products Agency (AEMPS 2012-01-02).

Study design

Designed as a double blind, randomised, prospective trial, this study was conducted with patients from a single centre (Infanta Cristina Hospital Endoscopy Unit in Parla, Madrid, Spain) treated between January 2012 and May 2012. The 120 enrolled patients were randomised by computer-generated numerical codes that were marked on spray devices containing lidocaine (L) or placebo (P) and enclosed in opaque envelopes that were unsealed for use during the surgical procedure. Thus, the patient, endoscopist, and anaesthetist were all "blinded" to the

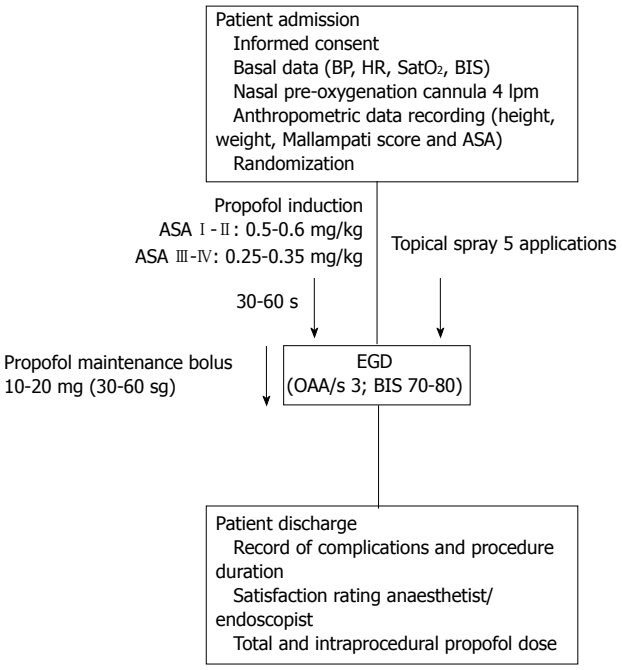

Figure 1 The sedation protocol used in this trial. BP: Blood pressure; HR: Heart rate; BIS: Bispectral index; EGD: Esophagogastroduodenoscopy; ASA: American Society of Anaesthesiologists.

group assignment. The spray application and subsequent sedation procedure are illustrated in Figure 1 and described in the proceeding section.

To guarantee the integrity of the treating physicians being blinded to the group assignment during the physical application of the spray, eight pressurized phials with controlled dosage release mechanisms were used, four of them contained 10% lidocaine (10 mg = 1 puff; Xilonibsa, Inibsa, Spain) mixed with excipients (menthol, saccharine, banana aroma, macrogol 600, and ethanol) and the other four contained the excipient solution without lidocaine (for use as placebo, so that the patient could not distinguish the two by taste). In the event of an adverse reaction and the need to unmask, only the number of the phial concerned would be identified, so that the study could continue.

A single endoscopist and anaesthetist, both experts in their fields, performed the respective procedures on all study participants. All endoscopies were performed with a EG-2990K video-esophagogastroduodenscope equipped with a 9 mm diameter insertion tube (Pentax Corporation, Tokyo, Japan).

Anaesthesia and sedation protocols

The topical pharyngeal anaesthesia or placebo was administered 180 s prior to endoscope insertion. The various spray dispensers administered a controlled volume of 10 mg per spray. A total 50 mg of lidocaine or placebo was administered to each patient by five sequential spray applications. Gentle tongue traction was used to expose the targeted spray area: the posterior wall of the oropharynx, tonsillar pillars, soft palate and base of tongue. Between each spray, patients were asked to swallow in order to maximize the anaesthetic effect on the hypopharynx. The spray procedure was performed in a room adjoining the endoscopy unit and by trained nurses who were not involved in the subsequent endoscopy and sedation procedures, thereby further ensuring masking.

Sedation was administered by bolus intravenous (*iv*) injection of 1% propofol at various dosages adjusted by patient weight and corresponding to the patient's physical status classification according to the American Society of Anaesthesiologists (ASA) guidelines[11]. ASA Ⅰ-Ⅱ patients received an initial dose of 0.5-0.6 mg/kg, followed by sequential 10-20 mg maintenance doses every 30-60 s given at the anaesthetist's discretion. ASA Ⅲ-Ⅳ patients received an initial dose of 0.25-0.35 mg/kg, followed by the same maintenance protocol. This regimen aimed to achieve and maintain an optimum level of moderate sedation for the EGD procedure, which was defined as a score of 3 on the observer alertness assessment scale (OAA/S3) and estimated values of 70-80 for the bispectral range (BIS) measured by four frontal electrodes and the BIS View monitoring system (Aspect Medical System Inc., Norwood, MA, United States). Once the desired sedation level was reached, the endoscopic examination began. Regulation of maintenance propofol doses and administration frequency fluctuated according to three factors: patient's tolerance as perceived by the anaesthetist (indicated by movement, coughing, nausea, agitation), sedation level (to maintain OAA/S3), and pre-determined physical characteristics and individual factors of each patient (including age, weight, and toxic habits).

All patients were fitted with a nasal cannula prior to the procedure to deliver oxygen at 4 lpm, which was initiated at least 180 s prior to the endoscopy procedure and continuing until completion. Pulsoxymetry, electrocardiography and blood pressure measurements were taken and recorded every 120 s.

Occurrence of the following adverse effects was recorded: hypoxemia ($SatO_2 < 90\%$, or a > 4% drop relative to the baseline value if it was ≤ 93%), bradycardia (< 60 bpm, or a > 10% drop in relation to the baseline value), hypotension (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg), anaphylactic reaction, bronchoaspiration (clinical diagnosis based on coughing, fever and/or lung infiltrations up to 48 h after the endoscopic examination), or methemoglobinemia. Suspicion of methemoglobinemia secondary to lidocaine or cyanosis with normal oxygen saturation was addressed by sampling the arterial blood for assessment by CO-oxymetry to determine the necessary treatment.

This protocol is registered at ClinicalTrials.gov under identifier number NCT01489891.

Data recorded for statistical analyses

The following data were recorded for each patient: age, sex, weight (kg), height (m), ASA classification, medical recommendation, Mallampati score, prior history of EGD under sedation, history of or on-going alcohol/

Table 1 Comparison of basal characteristics of patients randomly assigned to the lidocaine and placebo treatment groups

	Lidocaine	Placebo	Diff[1]	*P*[2]
n	59	60		
Age, yr	49.7 ± 15.81	51.7 ± 14.9	-2.0 (-7.6, 3.5)	0.47
Male sex	51.10%	48.60%	1.10%	0.85
	(37.0-65.0)	(37.6-51.8)	(0.5-2.3)	
Weight, kg	70.8 ± 14.0	76.6 ± 17.0	-5.8 (-0.1, -11.4)	0.04
Height, cm	162.1 ± 9.0	162.2 ± 11.0	0.10 (-3.6, 3.7)	0.50
ASA Ⅰ-Ⅱ	50.4 (40.5-60.5)	46.1 (28.7-64.5)	1.10 (0.7-1.7)	0.60
Mallampati Ⅰ-Ⅱ	51 (41.2-60.7)	48.9 (24.4-66.5)	0.84 (0.5-1.4)	0.49
Drug abuse	50 (26.3-76.3)	49.5 (40.3-58.7)	1.00 (0.5-1.9)	1.00
Previous sedated EGD	47.6 (28.3-67.6)	50 (40.2-59.7)	0.95 (0.6-1.5)	0.80

[1]Differences are expressed as RR with their respective CIs or absolute values; [2]Values in bold are statistically significant. Quantitative and qualitative variables are expressed as average ± SD and as percentage with 95%CI, respectively. EGD: Esophagogastroduodenoscop.

drug abuse, total propofol dose administered (mg), initial and maintenance propofol doses administered (mg), total and partial examination time (defined as the period from endoscope insertion to removal, in s), average BIS level reached, complete or incomplete examination, and complications. In addition, the endoscopist recorded a global satisfaction rating for the ease of performing each examination and the anaesthetist recorded a rating on the ease of reaching and maintaining the desired sedation level; these subjective ratings were based on a Likert-type 4-element scale of very satisfactory, satisfactory, neutral, and unsatisfactory.

Study objectives

The primary study objective was to determine whether use of lidocaine reduced the subsequent need for total propofol without increasing adverse effects or incomplete endoscopies, or causing significant variations in the subjective rating scales of the endoscopist and the anaesthetist. The secondary objectives were to determine the precise differences in adverse effect incidence between the lidocaine and placebo groups, and to establish the existing differences between the procedure-related satisfaction ratings awarded by the endoscopist and the anaesthetist.

Statistical analysis

Continuous variables are expressed as average ± SD and were compared between groups using the Student's *t*-test. Categorical variables are expressed as percentage and were compared between groups using the Pearson's χ^2 test. The threshold of statistical significance was set at 0.05. Stratification analysis was carried out to control for effects by potentially confounding variables. All statistical tests were performed by the Stata statistical software suite (Release 11, 2009; StataCorp, LP, College Station, TX, United States).

Sample size was calculated based on achieving a reduction of the total average propofol dose by at least 30 mg to reach and maintain the same level of objective sedation in the lidocaine group as in the placebo group. It was estimated that at least 59 patients were required for each study section (L and P) to detect statistically significant differences, admitting a risk α of 0.05 and a statistical power of 90%.

Table 2 Influence of lidocaine on propofol dose

	Lidocaine	Placebo	Diff[1]	*P*
Average BIS	68.1 ± 7.5	68.8 ± 7.6	0.76 (-2.0, 3.5)	0.58
Total examination values				
Total examination time, s	405.0 ± 134.8	387.0 ± 127.6	18.6 (-29.0, 66.2)	0.44
Total propofol dose, mg	134.9 ± 42.5	129.2 ± 40.4	5.6 (-9.4, 20.7)	0.45
Total propofol dose adjusted weight and time, mg/kg per minute	310.7 ± 139.2	280.1 ± 87.7	30.6 (-11.5, 72.7)	0.15
Intraprocedural examination values[2]				
Partial examination time, s	281.8 ± 137.3	265.5 ± 122.3	16.3 (-30.8, 63.5)	0.49
Partial propofol dose, mg	40.9 ± 33.7	38.9 ± 31.4	2 (-9.7, 13.8)	0.73
Partial propofol dose adjusted weight and time, mg/kg per minute	135.3 ± 151.7	122.7 ± 96.5	12.6 (-33.5, 58.7)	0.58

[1]Differences are expressed as RR with their respective absolute values; [2]Measurements recorded from the time of endoscope insertion into the oral cavity up to the time of withdrawal, excluding the time of anaesthetic induction. Quantitative and qualitative variables are expressed as average ± standard deviation and as percentage with 95%CI, respectively. BIS: Bispectral index.

RESULTS

Patient characteristics

A total of 127 patients were prospectively recruited between January and May 2012. After applying the exclusion criteria, three patients were denied enrolment: two for age < 18 years and one for history of sensitivity to amide group anaesthetics. Four additional patients refused to participate in the study. Thus, 120 patients were initially enrolled. One enrolled patient from the lidocaine group was subsequently excluded from analysis due to a technical problem that occurred in the endoscopy room during the examination procedure.

The randomization process assigned 59 patients to the L group and 60 patients to the P group. Comparison of the two groups showed no statistically significant differences in anaesthetic risk, age, sex, Mallampati scale, drug abuse, and prior experience regarding endoscopies under sedation. However, the average weight of individuals in the placebo group was significantly higher: 5.8 kg [95%CI: (-0.1)-(-11.4)] higher than those in the lidocaine

Table 3 Influence of potentially confounding factors on the propofol dose (mg/kg per minute, adjusted for patient weight and examination time)

			Diff[1]	*P*[2]
Age, yr				
	< 65	> 65		
Total propofol dose	315.3 ± 118.9	223.9 ± 73.7	91.4 (49.3, 133.5)	< 0.001
Partial[3] propofol dose	138.2 ± 135.5	96.0 ± 81.4	42.2 (-5.6, 90.0)	0.08
Sex				
	Male	Female		
Total propofol dose	263.7 ± 87.9	314.6 ± 127.9	-59.9 (-93.8, -8.0)	0.02
Partial propofol dose	111.5 ± 101.9	139.6 ± 139	-28.1 (-75.4, 19.2)	0.20
ASA classification				
	I - II	III-IV		
Total propofol dose	310.8 ± 121.3	239.8 ± 77.7	71.0 (21.2, 120.8)	< 0.001
Partial propofol dose	135.9 ± 136.3	104.1 ± 80.1	31.9 (-23.6, 87.4)	0.20
Mallampati classification				
	I - II	III-IV		
Total propofol dose	302.4 ± 119.5	262.4 ± 98.6	40.0 (-15.3, 95.3)	0.10
Partial propofol dose	127.1 ± 133.9	137.7 ± 85.9	-10.6 (-71.5, 49.9)	0.70
Drug abuse				
	Yes	No		
Total propofol dose	320.5 ± 92.1	293.0 ± 118.7	27.5 (-48.9, 103.9)	0.40
Partial propofol dose	120.3 ± 87.1	129.8 ± 129	-9.5 (-92.6, 73.6)	0.80
Previous sedated EGD				
	Yes	No		
Total propofol dose	260.2 ± 102.7	302.8 ± 118.6	-42.6 (-97.4, 12.2)	0.10
Partial propofol dose	128.9 ± 108.4	129.0 ± 130.6	-0.1 (-60.1, 59.9)	0.90

Quantitative and qualitative variables are expressed as average ± SD and as percentage with 95%CI, respectively. [1]Differences are expressed as RR with their respective absolute values; [2]Values in bold are statistically significant; [3]Measurements recorded from the time of endoscope insertion into the oral cavity up to the time of withdrawal, excluding the time of anaesthetic induction. ASA: American Society of Anaesthesiologists; EGD: Esophagogastroduodenoscopy.

group. The results are summarized in Table 1.

Propofol dose (primary objective)

As shown in Table 2, no statistically significant differences were found between the L and P groups in total or partial propofol doses, sedation level reached by BIS, or average total or partial examination time. However, there was a trend towards longer examination time for the L group. Stratification analysis of the increased examination time (using patient weight) indicated that the differences for total values (mg/kg per minute) and for time from endoscope insertion to removal were not significant.

Table 3 summarizes the results of stratification analyses to assess the influences of potentially cofounding factors on the propofol dose. Statistically significant differences were found between the L and P groups for greater total propofol requirements among patients who were female, < 65-years old, and with lower anaesthetic risk level (ASA Ⅰ-Ⅱ). The latter two factors were found to be related, with the low ASA groups having a significantly greater proportion of young patients [relative risk (RR) = 3.2 (95%CI: 1.75-6.01)]. The significance of these differences was lost, however, when only the patients receiving partial doses were considered in each of these categories.

Table 4 summarizes the results of stratification analyses to assess the influence of lidocaine on the propofol dose variations according to the potential confounding factors. Lidocaine only produced a significant modifying effect on the amount of total or partial propofol administered in any the ASA Ⅰ-Ⅱ patients, for whom lidocaine administration prior to endoscopy appeared to have a pernicious effect, with greater total doses of propofol required as compared to the corresponding patients in the P group. However, there were no significant differences between the ASA Ⅰ-Ⅱ patients in the L and P groups in terms of age (45.3 ± 13.5 years *vs* 48.7 ± 14.8 years), female sex [66.6% *vs* 67.4%; RR = 0.98 (95%CI: 0.74-1.31)], and BIS level (67.4 ± 7.5 *vs* 69.6 ± 7.6), and the underlying influential factor remains unknown. Nevertheless, the significance of the pernicious effect in the ASA Ⅰ-Ⅱ group was lost when only the patients receiving partial propofol doses were considered for each category.

Adverse events and endoscopist/anaesthetist satisfaction (secondary objectives)

Minor complications occurred in 29.4% of the endoscopic examinations, none of which necessitated suspension of the procedure. None of the patients showed signs of methemoglobinemia. There were no significant differences between the L and P groups for total complication rates or incidence rates of the various types of adverse events (Table 5). Furthermore, stratification analysis of the complication incidences and the various risk factors (*i.e.*, advanced age, ASA level, female sex, Mallampati score, previous drug abuse, previous endoscopy, total propofol dose administered, and BIS depth) revealed no significant differences between the groups (Table 6).

Finally, the systematic use of lidocaine in EGDs under propofol sedation did not significantly affect the endoscopist's or anaesthetist's perception of satisfaction with the procedure (Figure 2, respectively).

DISCUSSION

This study shows the ineffectiveness of lidocaine as a standard sedation coadjuvant to propofol in EGDs; specifically, the systematic use of lidocaine did not reduce total or partial doses of propofol, lower incidence of adverse effects, nor increase the treating physician's satisfaction with the performance of endoscopic or anaesthetic procedures. Our data generally coincided with those of the only other study reported to date on clinical application and utility of lidocaine with propofol[12]. In addition

Table 4 Influence of lidocaine treatment on propofol dose (mg/kg per minute, adjusted for patient weight and examination time) in relation to patients' individual characteristics

	Lidocaine	Placebo	Diff[1]	P^2
Age, yr				
< 65				
Total propofol dose	338.1 ± 138.7	292.0 ± 90.3	46.1 (-2.2, 94.4)	0.06
Partial[3] propofol dose	147.2 ± 165.6	128.9 ± 96.5	18.3 (-37.7, 74.3)	0.51
> 65				
Total propofol dose	203.6 ± 77.8	241.1 ± 68.0	-37.5 (-96.5, 21.5)	0.20
Partial propofol dose	88.7 ± 61.6	102.3 ± 97.1	-13.6 (-80.8, 53.6)	0.67
Sex				
Male				
Total propofol dose	280.0 ± 101.3	246.7 ± 69.6	33.3 (-19.2, 85.8)	0.20
Partial propofol dose	97.3 ± 95.5	125.0 ± 108.0	-27.7 (-33.7, 89.1)	0.36
Female				
Total propofol dose	330.4 ± 157.0	299.6 ± 92.1	30.8 (-28.5, 90.0)	0.30
Partial propofol dose	141.9 ± 175.2	137.5 ± 95.2	4.4 (-60.5, 69.3)	0.89
ASA classification				
Ⅰ-Ⅱ				
Total propofol dose	336.5 ± 141.2	284.6 ± 91.2	51.9 (2.8, 100.9)	0.03
Partial propofol dose	149.6 ± 164.5	122.1 ± 99.6	27.5 (-28.6, 83.6)	0.16
Ⅲ-Ⅳ				
Total propofol dose	209.7 ± 70.0	265.7 ± 76.7	56.0 (-3.8, 115.8)	0.06
Partial propofol dose	79.4 ± 63.3	125.0 ± 88.9	-45.6 (-19.3, 110.5)	0.16
Mallampati classification				
Ⅰ-Ⅱ				
Total propofol dose	319.6 ± 140.0	284.3 ± 91.4	35.4 (-12.2, 83.0)	0.14
Partial propofol dose	136.1 ± 159.2	117.7 ± 102.1	18.4 (-35.4, 72.2)	0.49
Ⅲ-Ⅳ				
Total propofol dose	260.8 ± 130.7	263.6 ± 72.3	-2.8 (-96.0, 90.5)	0.95
Partial propofol dose	130.8 ± 108.0	142.8 ± 69.9	-12.0 (-93.2, 69.2)	0.76
Drug abuse				
Yes				
Total propofol dose	313.5 ± 115.2	327.6 ± 75.4	-14.1 (-156.1, 127.9)	0.82
Partial propofol dose	96.1 ± 100.8	144.4 ± 73.8	-48.3 (-177.1, 80.5)	0.41
No				
Total propofol dose	310.5 ± 142.2	275.9 ± 88.2	34.6 (-10.2, 79.4)	0.12
Partial propofol dose	138.9 ± 155.1	120.8 ± 98.6	18.1 (-31.1, 67.3)	0.46
Previous sedated EGD				
Yes				
Total propofol dose	297.6 ± 116.3	226.1 ± 79.1	71.6 (-18.4, 161.7)	0.11
Partial propofol dose	124.4 ± 129.5	132.9 ± 91.5	-8.5 (-110.1, 93.1)	0.86
No				
Total propofol dose	313.4 ± 144.4	292.3 ± 85.7	21.1 (-26.9, 69.1)	0.38
Partial propofol dose	137.5 ± 157.0	120.4 ± 98.4	17.1 (-35.8, 70.0)	0.52

Quantitative and qualitative variables are expressed as average ± SD and as percentage with 95%CI, respectively. [1]Differences are expressed as RR with their respective absolute values; [2]Values in bold are statistically significant; [3]Measurements recorded from the time of endoscope insertion into the oral cavity up to the time of withdrawal, excluding the time of anaesthetic induction. ASA: American Society of Anaesthesiologists; EGD: Esophagogastroduodenoscopy.

to the main conclusions stated above, the previous study also showed that the application of lidocaine may help to reduce the gag reflex. Some important differences that exist between their study design and our own may explain their unique result. First, the previous study used a lower dose of lidocaine (40 mg *vs* 50 mg in our current study). Second, the previous study did not consider dosage as an objective, and did not monitor sedation levels using objective methods. These differences may affect the comparative interpretation of the previous and current studies' results.

In the current study, univariate stratified analysis indicated that advanced age, male sex, and elevated anaesthetic risk were independent factors related to reduced total propofol, but not partial, dose required during an EDG examination. In concordance with these results, both advanced age and male sex are factors that have been previously demonstrated as related to need for a lower dose of sedatives during endoscopy[13]. It is important to note here that the patients in our study with a higher ASA classification were administered lower total propofol doses for the sedation induction. Neither the patient's Mallampati score, drug abuse history, nor previous endoscopy under sedation affected the propofol dose. In relation to the Mallampati score, two previous studies have shown modifications in the tolerance perceived by patients from the subgroup with less retropharyngeal space (Mallampati Ⅲ-Ⅳ). It has been suggested that occlusive morphology of the oropharynx may be related to greater endoscope friction on the posterior wall and tonsillar pillars, possibly

Table 5 Distribution of complications between groups

	Lidocaine	Placebo	Diff[1]	*P*
Complications	32.2 (21.6-45.0)	26.7 (17.0-39.0)	1.2 (0.7-2.1)	0.50
Desaturation	57.1 (25.0-84.2)	54.5 (38.0-70.1)	1.0 (0.5-2.1)	0.90
Hypotension	63.6 (42.9-80.3)	66.6 (43.6-84.0)	0.95 (0.6-1.5)	0.80
Bradycardia	13.6 (3.9-34.2)	25.0 (6.3-55.9)	0.5 (0.1-2.7)	0.46
Aspiration	0 (0-17.4)	5.5 (0-27.6)	-	0.26
Bronchospasm	9.0 (1.3-29.0)	0 (0-20.7)	-	0.19

[1]Differences are expressed as RR with their respective CIs. Variables are expressed as percentage with 95%CI. The complication subcategories report incidence in relation to total complications.

Table 6 Distribution of complications according to individual risk factors of patients in endoscopy sedation

			Diff[1]	*P*
Age, yr				
	< 65	> 65		
	22.8 (11.8-39.2)	17.6 (10.8-27.2)	1.3 (0.6-2.7)	0.25
Sex				
	Male	Female		
	31.4 (18.4-48.1)	41.2 (31.3-51.8)	0.7 (0.4-1.3)	0.15
ASA classification				
	Ⅰ-Ⅱ	Ⅲ-Ⅳ		
	22.8 (11.8-39.2)	21.2 (13.7-31.1)	1.1 (0.5-2.2)	0.41
Mallampati classification				
	Ⅰ-Ⅱ	Ⅲ-Ⅳ		
	17.1 (7.7-33.0)	17.6 (10.9-27.2)	0.9 (0.4-2.3)	0.47
Drug abuse				
	Yes	No		
	2.8 (0-15.8)	10.6 (5.4-19.1)	0.2 (0.01-2.0)	0.08
Propofol dose[2]				
	> 277	< 277		
	30.5 (20.2-43.2)	26.7 (17.0-39.1)	1.1 (0.6-2.0)	0.32
Average BIS				
	< 70	> 70		
	33.3 (24.0-44.2)	21.0 (10.8-36.6)	1.6 (0.8-3.1)	0.08
Previous sedated EGD				
	Yes	No		
	17.1 (7.7-33.0)	20.0 (12.4-30.5)	0.8 (0.3-2.0)	0.36

[1]Differences are expressed as RR with their respective CIs; [2]The propofol dose is reported as the cut-off point calculated as the mean of the total propofol dose administered to the patients in the trial: 277 mg/kg per minute. Variables are expressed as percentage with 95%CI. BIS: Bispectral index; ASA: American Society of Anaesthesiologists; EGD: Esophagogastroduodenoscopy.

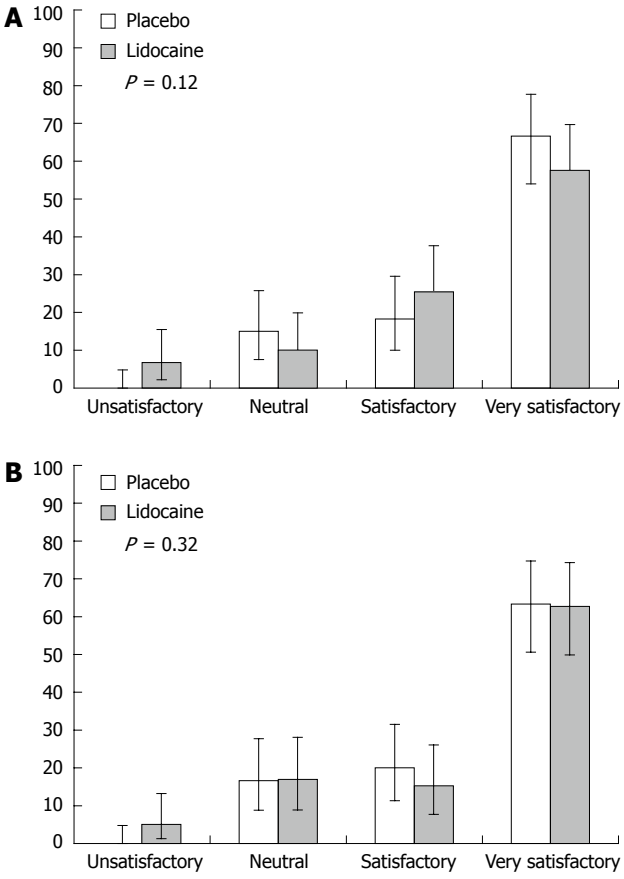

Figure 2 Endoscopist satisfaction index and anaesthetist satisfaction index. A: Endoscopist satisfaction index; B: Anaesthetist satisfaction index. Each category is expressed as a percentage value, with confidence interval adjusted for a significance of 95%.

explaining the lower tolerance of non-sedated EGD observed in this subgroup of patients[14]. Indeed, lidocaine has been shown to have a beneficial effect in Mallampati Ⅲ-Ⅳ patients undergoing non-sedated EGD[7]. Likewise, factors such as not having undergone a previous endoscopy with sedation or drug abuse have been previously identified as factors predisposing to poorer patient tolerance of the EGD procedure[15,16]; the fact that these patients in our study cohort did not require greater propofol doses may suggest a marginal influence of these factors.

The significant difference found in greater total propofol dose requirements for patients with ASA Ⅰ-Ⅱ who received lidocaine were did not exist when intraprocedural doses were considered for the analysis. Therefore, the essential difference between these groups lies in the different induction doses that were used to reach an OAA/S3 sedation level prior to the start of the endoscopic examination. Subordinate analysis of the potential factors that may have explained this different response in ASA Ⅰ-Ⅱ patients (such as the Mallampati score, drug abuse, age, sex, or average BIS level) did not identify any as significantly associated. Only the variation between individuals in relation to the necessary propofol doses and uncontrollable randomization of the study groups for the above-mentioned patient factors might explain the differences found.

Although not statistically significant, the differences observed regarding the increase in the necessary dose (both partial and total) in the lidocaine group as compared to the placebo group may be explained by several factors. First, we propose that the greater average weight of patients in the placebo group, and uncontrollable effect of the randomization process, may have contributed to the results. The patient's individual weights affected the propofol dose administered in the initial bolus as per the protocol used (such that an obese patient received an initially higher dose which may have caused a quicker and more effected sedation level than in the non-obese

or thin patients). These individual responses to propofol doses and dosage administration might paradoxically explain the greater induction phase dose requirement in the lidocaine group (characterized as thinner) as compared to the placebo group (characterized as heavier). Thus, while the placebo group received a bolus with a higher initial dose, the lidocaine group received a lower overall dose.

One of the most important advantages of our study design is the quality control of sedation levels during endoscopic procedures. The optimum sedation level for upper digestive endoscopy has been defined by consensus as moderate in ASA Ⅲ-Ⅳ patients and moderate-deep in ASA Ⅰ-Ⅱ patients[17]. This sedation level is roughly equivalent to level 3 on the OAA/S alert-sedation scale[18]. We believe that the use of a single anaesthetist, who specialises in endoscopic sedation, for all of the examinations performed in this study cohort benefitted the quality of this study by helping to achieve a possibly homogenous sedation level across the patient population. In addition, however, we made objective measurements of the sedation levels reached and performed analysis with the average BIS index of the groups and subgroups. It is known that moderate sedation in correlation with the Ramsay scale at levels 3-4 encompasses BIS values 70-80[19], which was found in 65 of our patients.

Our study showed a greater overall incidence of side effects arising from sedation with propofol as compared to previous reports, but with no significant differences between the lidocaine and placebo groups[20,21]. The most frequent adverse effects observed were hypotension and desaturation, both of which occurred in minor ranges. No serious adverse reactions occurred in any of the 119 participants. In our study, only 5.8% of cases experienced a hypoventilation incident (as defined in endoscopic procedures under sedation with propofol at 50%-84%, with repercussions in mild transitory hypoxemia between 4%-7%[2,20,21]), none of which required ventilation with a mask bag (data not shown). Hypotension occurred in 21.8% of patients, but there was no difference between the incidence in the lidocaine and placebo groups. The incidence of this complication in our study cohort was greater than previously reported in the literature, which ranges between 3%-7%[21]. The possibility of incidentally recording blood pressure figures very close to the initial induction bolus may explain our results, as the method of bolus administration has known risk for causing hypotension, as compared to the continual infusion methods[22,23].

Regarding procedural satisfaction perceived by the treating physician, a Likert scale of four elements was designed for use by the anaesthetist and the endoscopist immediately after the procedure completion to assess the ease of attaining and maintaining an appropriate sedation level for the former and the ease of achieving examination objectives for the latter. Such results may overlap with those recently obtained by Heuss *et al*[12], who also demonstrated the inefficacy of lidocaine to improve the satisfaction of endoscopists.

Our study has three relevant limitations that must be considered when interpreting our findings. The first is the absence of a patient satisfaction assessment. In our opinion, the greater depth of sedation reached with propofol might affect these results and their comparability with results from the older protocols with lower doses. The second limitation is the sedation level achieved, which, while sufficient and subjectively monitored by an expert anaesthetist, had recorded BIS levels at the lower limit of the interpolation validated as OAA/S3. This raises the question as to whether possible over-sedation in some patients might interfere with the conclusions of our study, and whether different results might have been obtained with more superficial sedation. Lastly, the use of patients from a single centre, treated by a single endoscopist, a single anaesthetist and a single nursing team, may have caused some bias.

In conclusion, the use of topical pharyngeal anaesthesia does not reduce the propofol dose required to maintain optimum sedation levels in EGD. While its use does not increase the incidence or type of adverse effects, it also does not improve the treating physician's satisfaction with the procedure itself. This lack of benefit suggests that topical lidocaine application may be removed from the EDG procedure carried out with propofol sedation, and further studies should consider this option.

COMMENTS

Background

Application of topical pharyngeal anaesthesia has been shown to improve patient tolerance of and satisfaction with both non-sedated and traditional sedated endoscopy procedures. However, this effect has not yet been demonstrated specifically with propofol sedation protocols.

Research frontiers

Lidocaine is a common topical aesthetic applied routinely and frequently as coadjuvant with sedation agents in endoscopy procedures, such as esophagogastroduodenoscopies (EGDs), performed without sedation. However, no systematic investigations have yet reported on its utility in propofol-based sedation protocols in terms of reduction of doses or of side effects. This study demonstrates that the systematic use of lidocaine in esophagogastroduodenoscopy with propofol sedation is ineffective for reducing the doses required for or side effects related to propofol sedation.

Innovations and breakthroughs

Potential pitfalls of using a procedure or coadjuvant agent - such topical lidocaine application with propofol-sedated endoscopy - without evidence of actual clinical utility or benefit include unnecessary increases in monetary costs and risk and discomfort to the patient. This is the first study to report that application of topical lidocaine does not decrease the dose of propofol necessary to reach and maintain an optimal level of sedation during an esophagogastroduodenoscopic procedure. Furthermore, the results suggest that its use may increase the propofol dosage required in certain patients.

Applications

Topical pharyngeal anaesthesia neither reduces the necessary doses of propofol nor improves the endoscopist's or anaesthetist's satisfaction with the procedure's performance. However, its use does not increase the incidence or type of adverse effects related to the propofol-sedated esophagogastroduodenoscopy. Therefore, the authors suggest that the routine use of lidocaine in all EGDs performed with propofol sedation be reconsidered.

Terminology

The bispectral index was introduced by Aspect Medical Systems, Inc. in 1994 as a novel measure of the level of a consciousness while under general anaesthesia by using algorithmic analysis of a patient's electroencephalogram. This measurement is used in conjunction with other physiologic monitoring

procedures, such as electromyography, to estimate the dose and administration of anaesthesia in order to minimize the possibility of intraoperative awareness. Meanwhile, the observer's assessment of alertness/sedation scale was developed to measure the level of alertness in subjects who are sedated.

Peer review

In this randomized controlled trial, de la Morena *et al* compare the potential benefit of topical lidocaine as a coadjuvant to propofol sedation during esophagogastroduodenoscopy. In particular, they investigate whether the lidocaine application may reduce the dose and/or side effects of propofol. The study is designed as a single centre, double blinded, prospective trial, in which 119 patients received propofol-sedated EGDs with or without lidocaine. Comparative analysis of quantitative and qualitative variables revealed that the lidocaine application may be safe but unnecessary, providing neither increased risk of complications nor clinical benefit to the patient or the treating physicians.

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BRIEF ARTICLE

Risk of colorectal polyps in patients with sporadic gastric polyps: A case-control study

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Abstract

AIM: To assess the risk of colonic polyps, adenomas and advanced neoplastic lesions (ANL) in patients with sporadic gastric polyps, especially those with fundic gland polyps (FGP).

METHODS: Clinical records of patients who had performed an upper and a lower digestive endoscopy between September 2007 and August 2008 were retrospectively analyzed. A case-control study was carried out, calling patients with gastric polyps as "cases" and patients without gastric polyps as "controls". The risk of colonic polyps, adenomas and ANL (villous component ⩾ 25%, size ⩾ 10 mm, or high grade dysplasia) was assessed [odds ratio (OR) and its corresponding 95%CI].

RESULTS: Two hundred and forty seven patients were analyzed: 78 with gastric polyps (cases) and 169 without gastric polyps (controls). Among the cases, the majority of gastric polyps were FGP (80%, CI: 69-88) and hyperplastic (20%, CI: 12-31); 25% had colonic polyps (25% hyperplastic and 68% adenomas, from which 45% were ANL). Among the controls, 20% had colonic polyps (31% hyperplastic and 63% adenomas, from which 41% were ANL). The patients with sporadic FGP had an OR of 1.56 (CI: 0.80-3.04) for colonic polyps, an OR of 1.78 (CI: 0.82-3.84) for colonic adenomas, and an OR of 0.80 (CI: 0.21-2.98) for ANL. Similar results were found in patients with gastric polyps in general.

CONCLUSION: The results of this study did not show more risk of colorectal adenomas or ANL neither in patients with sporadic gastric polyps nor in those with FGP.

Key words: Colorectal polyps; Advanced neoplastic lesions; Gastric polyps; Fundic gland polyps gastric polyps; Case-control study

Core tip: The risk of colonic adenomas in patients who have sporadic gastric polyps, especially those of fundic gland polyps (FGP), is still to be definitely determined. The purpose of our study was to assess the risk of colonic polyps, adenomas and advanced neoplastic lesions in patients who have sporadic gastric polyps, especially of FGP, due to the fact that these are the most common gastric polyps in our population.

Cimmino DG, Mella JM, Luna P, González R, Pereyra L, Fischer C, Mohaidle A, Vizcaino B, Medrano MA, Hadad A, Pedreira S, Boerr L. Risk of colorectal polyps in patients with sporadic gastric polyps: A case-control study. *World J Gastrointest En-*

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INTRODUCTION

The occurrence of gastric and duodenal polyps is higher in several colonic polyposis syndromes[1,2]. However, the risk of colonic polyps and adenomas in patients who have sporadic gastric polyps, especially the fundic gland polyps (FGP), remains controversial.

Several authors have studied the relationship between the presence of different types of gastric polyps and the risk of colonic polyps and adenomas[3]. Yang *et al*[4] reported that the patients who have gastric adenomas could be more prone to present colorectal adenomas, and suggested that in the case of gastric adenomas the patient should be prescribed a screening colonoscopy.

However, the risk of colonic adenomas in patients who have sporadic gastric polyps, especially those of FGP, is still to be definitely determined.

It has been reported that patients suffering from familial adenomatous polyposis (FAP) show an increased incidence of gastric fundic gland polyps; there are series[5] showing that up to 88% of these patients have FGP. The presence of this type of gastric polyps is supposed to be a marker of colonic neoplasia among the general population. In a retrospective study, Teichmann *et al*[6] showed that patients who had gastric fundic gland polyps were more prone to suffer from colorectal neoplasias. Nevertheless, Dickey *et al*[7] could not confirm Teichmann's findings in a prospective study.

The purpose of our study was to assess the risk of colonic polyps, adenomas and advanced neoplastic lesions (ANL) in patients who have sporadic gastric polyps, especially of FGP, due to the fact that these are the most common gastric polyps in our population.

MATERIALS AND METHODS

A case-control study was carried out. Patients with gastric polyps were regarded as "cases" and those without them as "controls". The clinical records of patients who had undergone an upper and a lower digestive endoscopy between September 2007 and August 2008 were retrospectively analysed. Those patients with previous digestive endoscopies, an inadequate colonic cleansing, an incomplete colonoscopy, gastric or colonic surgeries, and intestinal inflammatory disease were excluded.

Those patients with gastric polyps were identified by an electronic search in the Endoscopy database. The final diagnosis of the different types of gastric polyps was histopathologically assessed. The presence of fundic gland polyps was suspected by the finding of sessile polyps at the body or fundus of the stomach, with their typical appearance (Figure 1). The diagnosis was confirmed by the histological analysis of polyps resections (polypectomies with forceps or snares). The fundic gland polyps diagnosis was based on the finding of enlarged glands in a cystic shape, covered with fundic epithelium (parietal cells and chief cells) mixed with normal glands, generally without inflammation or evidence of dysplasia. Besides, the grade of inflammation of the gastric mucosa was mostly determined by antral and gastric body biopsies. Gastritis were arbitrary classified in two types. Firstly, "active or severe gastritis" were analysed together and they were diagnosed when the gastric mucosa showed acute inflammatory infiltrate. Secondly, "mild or inactive gastritis" were also analysed together and they were diagnosed by the presence of minor inflammatory lymphoplasmacytic infiltrates. Normal gastric biopsies (which is unusual in our medical field) were also analysed together with those that showed "mild-minor or inactive" inflammation. Infection with *Helicobacter pylori* (*H. pylori*) was histopathologically determined due to the presence of curved bacilli typical of *H. pylori* by using Giemsa's stain. The diagnosis of the different types of colonic polyps was histopathologically determined.

The risk of colonic polyps, adenomas and ANL (defined as villous component $\geqslant$ 25%, size $\geqslant$ 10 mm or high grade dysplasia) was assessed in patients with gastric polyps in general, and in particular, in those with FGP.

Statistical analysis

For constant variables, the media with its corresponding SD was calculated. The nominal variables were expressed in percentages with their corresponding 95%CI. The risk of colonic polyps, adenomas and ANL was calculated, measured in odds ratio (OR) with its corresponding 95%CI, using the Fischer's test. Results were considered significant when the OR's with their CI did not include the 1. In order to assess the influence on the main outcomes of the variables that were significantly different between the cases and controls (Table 1), a binary logistic regression model was carried out by introducing these variables, in order to prove if these variables were independent predictor of the outcomes. The relationship between the presence of FGP and the *H. pylori* infection was also analysed. The SPSS 17.1 software for Windows was used.

RESULTS

We analyzed 247 patients (Table 1). Seventy-eight had gastric polyps, from which 62 were of FGP. Table 1 shows the characteristics of patients with and the without gastric polyps.

Among the cases the media age was 62 $\pm$ 11 years old, and 71% (CI: 59%-81%) of the patients were women. Most of gastric polyps were FGP (80%, CI: 69%-88%) and hyperplastic (20%, CI: 12%-31%); no gastric adenomas were found. Seventy six percent (76%, CI: 65%-85%) of the patients had inactive or minor gastritis in the gastric mucosa biopsies, and 24% (CI: 15%-35%) had active or severe gastritis. *H. pylori* infection detected

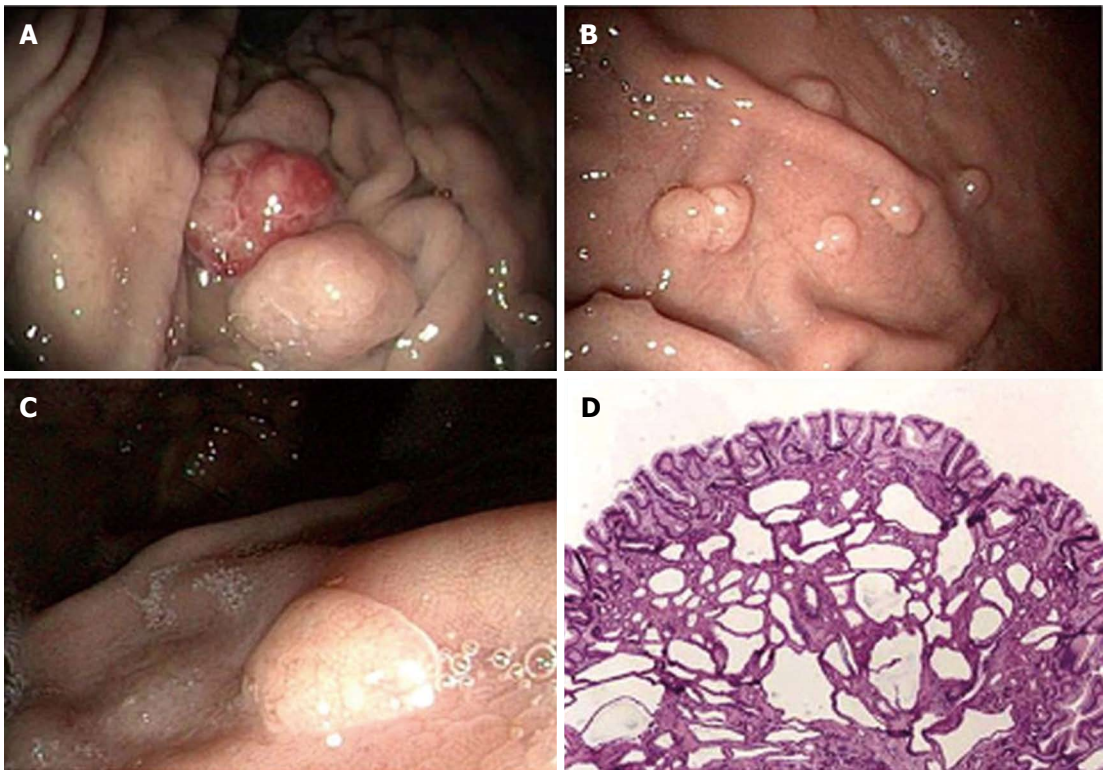

Figure 1 Fundic gland polyps: Sessile polyps at the body or fundus of the stomach, with their typical appearance. The fundic gland polyps diagnosis is based on the finding of enlarged glands in a cystic shape, covered with fundic epithelium mixed with normal glands, generally without inflammation or evidence of dysplasia.

Table 1 Characteristics of the patients (cases and controls)

Characteristics of patients	With gastric polyps (n = 78)	Without gastric polyps (n = 169)	P value
Age years old (average ± SD)	62 ± 11	61 ± 14	0.51
Sex (%women, CI)	71% (59-81)	61% (53-68)	0.11
Gastric polyps (%patients, CI)			
Fundic gland polyps	80% (69-88)	Did not have gastric polyps	
Hyperplastic	20% (12-31)		
Indications of the UGIEs (%patients, CI)			
Epigastralgia	38% (29-50)	46% (39-54)	0.14
Gastroesophageal reflux	22% (13-32)	9% (5-15)	< 0.01
Anemia	10% (4-19)	8% (4-13)	0.32
Abdominal pain	8% (3-16)	10% (6-16)	0.31
Digestive bleeding	4% (1-10)	6 % (3-11)	0.30
Screening	6 % (2-14)	9% (5-14)	0.35
Other	12% (4-19)	12% (4-13)	0.32
Gastric mucosa histology (%patients, CI)			
Minor gastritis	76% (65-85)	68% (60-76)	0.15
Severe gastritis	24% (15-35)	32% (24-39)	0.15
Helicobacter pylori infection (%positives, CI)	20% (11-31)	29% (22-38)	0.07
Indications of the colonoscopies (%patients, CI)			
Screening	37% (26-49)	43% (35-50)	0.25
Abdominal pain	17% (9-27)	23% (17-30)	0.16
Constipation	18% (10-28)	7% (3-11)	< 0.01
Anemia	13% (6-22)	9% (5-14)	0.23
Digestive bleeding	4% (1-11)	7% (3-12)	0.24
Other	11% (5-21)	11% (6-15)	0.12
Colonic polyps (%patients, CI)	25% (16-37)	20% (14-26)	0.17
Type of colonic polyps (%colonic polyps, CI)			
Hyperplastic	25% (7-52)	31% (16-49)	0.95
Adenomas	68% (41-89)	63% (45-78)	0.63
ANL	45% (16-76) of the adenomas	41% (21-63) of the adenomas	0.82

UGIEs: Upper gastrointestinal endoscopies; ANL: Advanced neoplastic lesions.

Table 2 Risk of developing colorectal polyps, adenomas and advanced neoplastic lesions

	Colonic polyps (OR, 95%CI)	Colonic adenomas (OR, 95%CI)	ANL (OR, 95%CI)
Presence of gastric polyps	1.41 (0.75-2.68)	1.63 (0.77-3.42)	1.67 (0.56-5.01)
Presence of gastric fundic gland polyps	1.56 (0.80-3.04)	1.78 (0.82-3.84)	0.8 (0.21-2.98)

ANL: Advanced neoplastic lesions; OR: Odds ratio.

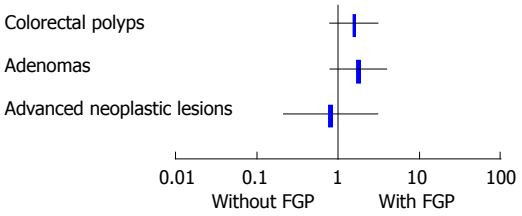

Figure 2 Risk of presenting colonic lesions in patients with fundic gland polyps (odds ratio, 95%CI). FGP: Fundic gland polyps.

by gastric biopsies was found in 20% (CI: 11%-31%) of patients. The most common indications for the upper gastrointestinal endoscopies (UGIEs) were: epigastralgia (38%) and typical gastroesophageal reflux disease (GERD) symptoms (22%). Twenty five percent (25%, CI: 16%-37%) of the cases had colonic polyps from which 25% were hyperplastic and 68% were adenomas (45% of the adenomas were ANL). The most common indications for colonoscopies were: colorectal cancer screening (37%) and constipation (18%).

Among the controls, the media age was 61 ± 14 years old, and 61% (CI: 53%-68%) of the patients were women. Sixty eight percent (68%, CI: 60%-76%) of the controls had inactive or minor gastritis in the gastric biopsies and 32% (CI: 24%-39%) had active or severe gastritis. The gastric biopsies showed that 29% (CI: 22%-38%) of the patients had *H.pylori* infection. The most common indications for the UGIEs were: epigastralgia (46%) and typical GERD symptoms (9%). Twenty percent (20%, CI: 14%-26%) of patients had colonic polyps, from which 31% were hyperplastic and 63% were adenomas (41% of these adenomas were ANL). The most common indications for the colonoscopies were: colorectal cancer screening (43%) and abdominal pain (23%).

Within the patients who had colonic polyps, none of them had colonic polyposis at the moment of the colonic examination. The average number of colonic polyps in each patient who had colonic polyps was 1.46 ± 1 polyp, and the range was from 1 to 6 polyps (in only one patient we found 6 polyps in the colon, from which 3 were hyperplastic and 3 adenomas).

The prevalence of gastric infection due to *H. pylori* was lower among the patients who had gastric polyps in comparison with the ones without them (29% *vs* 20%, $P = 0.07$). This difference was significantly bigger when the group of patients with and without FGP were analyzed (31% *vs* 14%, $P = 0.01$); the relative chances of having the *H. pylori* infection were 63% less (OR: 0.37, CI: 0.16-0.86) in the patients who had FGP.

Table 3 Logistic regression

	P value		
	Colonic polyps	Colonic adenomas	ANL
Female sex	0.488	0.121	0.369
GERD	0.457	0.969	0.525
Constipation	0.083	0.865	0.613
Helicobacter pylori infection	0.557	0.292	0.772

Influences of the analysed variables in the main outcomes. GERD: Gastroesophageal reflux disease; ANL: Advanced neoplastic lesions.

Table 2 shows the main outcomes. Patients with gastric polyps had an OR of 1.41 (CI: 0.75-2.68) for having colonic polyps, an OR of 1.63 (CI: 0.77-3.42) for having adenomas, and an OR of 1.67 (CI: 0.56-5.01) for ANL. Patients with FGP (Figure 2) had an OR of 1.56 (CI: 0.80-3.04) for having colonic polyps, an OR of 1.78 (CI: 0.82-3.84) for having colonic adenomas, and an OR of 0.80 (CI: 0.21-2.98) for ANL. When using a binary logistic regression model for detecting influences on the risk of colonic polyps, adenomas and ANL between cases and controls (Table 3), we observed that the indications of the endoscopies (especially typical GERD symptoms and constipation) and the *H. pylori* infection were not determinants of our main outcomes.

DISCUSSION

The aim of this study was to establish the risk of colonic polyps and adenomas in patients with gastric polyps, especially those of FGP. We did not find any relationship between the presence of FGP and colorectal polyps (OR: 1.56, CI: 0.80-3.04). In addition, we could not prove that the presence of this kind of gastric polyps predisposed patients to ANL (which might be considered as a surrogate outcome of colorectal cancer; OR: 0.80, CI: 0.21-2.98). It is very important to point out that in our study there were no patients with colonic polyposis syndromes, and therefore, among the patients who had gastric polyps, their origin could be labelled as "sporadic". Our results are important because they are different from other author's.

In 2002, in a prospective study, Jung *et al*[8] concluded that patients who had FGP (Elster's cysts) could have a higher incidence of colorectal tumours and should undergo a diagnostic colonoscopy. These authors found a highly remarkable preponderance of colon adenocarcinoma (12.5%) among the 65 patients analysed who had FGP. In our study none of the 62 patients who had FGP presented colorectal cancer.

In 2005, Declich *et al*[9] suggested that patients who had sporadic FGP should undergo a colonoscopy since they could be more prone to have colonic adenomas. However, in their study, such conclusion is not clearly justified or stated.

In 2008, in a retrospective study, Teichmann *et al*[6] showed that patients who had gastric fundic gland polyps were more prone to suffer from colorectal neoplasias (15.5% in patients with FGP *vs* 9.2% in controls, $P < 0.05$), although they could not prove a higher occurrence of colonic polyps. In their study, the FGPs were diagnosed in patients undergoing endoscopies because of gastrointestinal bleeding, which in term could have originated a selection bias. According to this, the positive relationship between gastric fundic gland polyps and colorectal cancer could be influenced by bias in the process of selection of the patients included in the study. In our study, the gastrointestinal bleeding accounted for less than 10% of the endoscopy indications. We also carried out a logistic regression to determine the influence of the endoscopy indications on the main outcomes.

In 2009, Genta *et al*[10] published the biggest cohort, so far, of patients who had FGP. They assessed the risk of presenting colorectal neoplasias in patients with FGP. The authors analysed 6081 patients who had FGP and showed that the risk of presenting colorectal adenomas was higher among the women who had FGP (OR: 1.43, 95%CI: 1.26-1.63) and would not be increased among the men. They also showed that patients without FGP could be 29 times more prone to be infected with the *H. pylori* bacteria as compared to the patients who had FGP (OR: 29, 95%CI: 20-41). In our study, gastric infection with the bacteria *H. pylori* was almost 3 times more frequent in patients without FGP than in patients with them (OR: 2.65, CI: 1.15-6.27). The presence of FGP was related to a relative reduction of 63% in the risk of *H. pylori* infection. We couldn´t infer that female sex could be a conclusive element in the presence of colonic lesions in patients with FGP as we found that sex had not influence in our main outcomes (Table 3).

Advantages: (1) strict exclusion criteria based on the factors which could increase the power of the bias and modify the analysed groups; (2) thorough description of the characteristics of the patients analysed in both groups; (3) none of the patients included was given a colonic polyposis diagnosis; and (4) correct statistical analysis. Limits: it is a retrospective study.

In the daily practice it is very common to attend patients with "sporadic" FGP which are nowadays the most usual type of gastric polyps in our medical field. The results of this study did not show an increase in the risk of colorectal adenomas or ANL neither in patients with sporadic polyps of FGP, nor in patients with gastric polyps in general. It is very important to point out that we didn´t find gastric adenomas in the patients included, because it is well known that the presence of gastric adenomas have already been shown to be a risk for colorectal adenomas[4]. In our population, the prevalence of gastric adenomas is extremely low. It might be because Argentina has a population with low basal risk for gastric cancer, and also because of the low prevalence of *H. pylori* infection (close to 15%-30%) in our patients."

These results are important because they mark a distinguishing difference between patients with "sporadic" gastric fundic gland polyps and patients who present colonic polyposis hereditary syndromes and who have gastric fundic gland polyps.

In accordance with the findings of other authors, the patients with FGP would be more prone to have "normal" stomachs ("normal, mild or minor" gastritis) and would have less chances of having the *H. pylori* infection. Unfortunately, as our study was retrospective, we could not analyze any connection between proton pump inhibitors (PPI) intake and the presence of FGP, because we could not get secure data about how many patients were on long PPI treatment at the moment of their endoscopies.

COMMENTS

Background

Nowadays, it is common to find incidental gastric polyps in upper gastrointestinal endoscopies. It is well known that the incidence of gastric and duodenal polyps is higher in several colonic polyposis syndromes. However, the risk of finding colonic polyps and adenomas in patients with sporadic gastric polyps, especially the fundic gland polyps (FGP), is not well established. The aim of this study was to assess the risk of presenting colonic polyps, adenomas and advanced neoplastic lesions (ANL) in patients with sporadic gastric polyps, especially those with sporadic FGP.

Innovations and breakthroughs

These results are important because they are different from other author's. The authors did not find any relationship between the presence of FGP and colorectal polyps [odds ratio (OR) 1.56, CI: 0.80-3.04]. In addition, the authors could not prove that the presence of this kind of gastric polyps predisposed patients to ANL (which might be considered as a surrogate outcome of colorectal cancer; OR: 0.80, CI: 0.21-2.98). It is very important to point out that in this study there were no patients with colonic polyposis syndromes, and therefore, among the patients who had gastric polyps, their origin could be labelled as "sporadic".

Applications

In the daily practice it is very common to attend patients with "sporadic" FGP which are nowadays the most usual type of gastric polyps in this medical field. The results of this study suggest that patients with FGP gastric polyps do not have an increase in the risk of colorectal adenomas or ANL.

Peer review

The study by Dr. Cimmino *et al* is interesting and important from clinical point of view. During advanced upper gastrointestinal (GI) endoscopy and colonoscopy person see more and more polyps either in the upper GI tract or in the large bowel. The authors analyzed 78 gastric polyp cases and 169 controls without gastric polyps. Colonoscopy was performed in all cases and the authors studied whether the presence of gastric polyps increases the risk of colorectal polyps. They detected that neither sporadic gastric polyps nor FGP are risks for colorectal adenomas and polyps.

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BRIEF ARTICLE

Endocoil placement after endoscopic ultrasound-guided biliary drainage may prevent a bile leak

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Abstract

AIM: To further reduce the risk of bleeding or bile leakage.

METHODS: We performed endoscopic ultrasound guided biliary drainage in 6 patients in whom endoscopic retrograde cholangiopancreatography (ERCP) had failed. Biliary access of a dilated segment 2 or 3 duct was achieved from the stomach using a 19G needle. After radiologically confirming access a guide wire was placed, a transhepatic tract created using a 6 Fr cystotome followed by balloon dilation of the stricture and antegrade metallic stent placement across the malignant obstruction. This was followed by placement of an endocoil in the transhepatic tract.

RESULTS: Dilated segmental ducts were observed in all patients with the linear endoscopic ultrasound scope from the proximal stomach. Transgastric biliary access was obtained using a 19G needle in all patients. Biliary drainage was achieved in all patients. Placement of an endocoil was possible in 5/6 patients. All patients responded to biliary drainage and no complications occurred.

CONCLUSION: We show that placing endocoils at the time of endoscopic ultrasound guided biliary stenting is feasible and may reduce the risk of bleeding or bile leakage.

Key words: Endoscopic ultrasound; Biliary drainage; Transhepatic; Endocoil

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INTRODUCTION

Advanced biliary tract malignancy complicated by obstructive jaundice has traditionally been managed by palliative stent placement during endoscopic retrograde cholangiopancreatography (ERCP). In 3%-12% of patients with advanced disease tumour involvement of the small bowel or peri-ampullary region may preclude the use of ERCP, necessitating percutaneous transhepatic biliary drainage (PTBD) or surgery[1]. However, surgery has been associated with high complication rates and morbidity[2,3]. In recent years various groups have described endoscopic ultrasound guided access of the left system, allowing placement of metal or plastic stents either across the distal stricture or in the stomach (hepatico-gastrostomy), with high technical success[4,5]. Since the initial case series which described the feasibility of endoscopic ultrasound

guided biliary drainage, various groups mainly from tertiary care academic expert centres have reported similar success rates in small case series[6-8]. However, various obstacles still exist to extending the general applicability of this technique outside expert centres. Firstly, no randomized control trials exist comparing the safety and efficacy of endoscopic ultrasound (EUS) biliary access to percutaneous transhepatic cholangiography (PTC). Secondly, current endoscopic techniques utilize standard endoscopic accessories not specifically developed for use within the biliary system when advanced through the gastric wall. Thirdly, specific EUS strategies are needed to prevent or reduce complications associated with percutaneous approaches. We used an endocoil in the transhepatic tract following biliary access and stent placement to further reduce the risk of bleeding or bile leakage.

MATERIALS AND METHODS

All procedures were performed in an expert referral centre for biliary interventional endoscopy where patients undergoing ERCP for drainage of malignant biliary tract disease are routinely asked to consent to possible EUS-guided biliary drainage in the event of ERCP failure to obtain access. Consensus was always reached between the hepatobiliary surgeon (JO), the interventional radiologist (CS) and the hepatobiliary endoscopist (SvdM) regarding the optimal management of the patient. All EUS-guided biliary access procedures were prospectively entered into a database. All except one patient received general anaesthesia, and were intubated and mechanically ventilated in the supine position for the duration of the procedures (Table 1).

Case 1

A 67-year-old female presented with obstructive jaundice. Spiral computed tomography (CT) of the abdomen showed unresectable locally-advanced pancreatic carcinoma. At ERCP the ampulla could not be identified due to extensive tumour infiltration of the duodenal wall.

Case 2

A 50-year-old female patient was referred with metastatic pancreatic carcinoma with duodenal infiltration and liver metastasis. She also suffered from type II diabetes and systolic arterial hypertension. At ERCP the ampulla could not be identified in the tumour mass.

Case 3

A 46-year-old-female patient was diagnosed with unresectable locally advanced gallbladder carcinoma invading the common bile duct. The patient was managed by percutaneous drainage of both the left and right systems after ERCP failed. However, the stricture could not be transversed and external drainage catheters were placed during interventional radiology. The patient developed cholangitis. EUS-guided biliary access was requested to internalize biliary drainage. After EUS biliary access was achieved, a guidewire could be placed across a long stricture into the duodenum.

Case 4

An 80-year-old male presented with obstructive jaundice. Spiral CT of the abdomen showed dilated intra- and extrahepatic bile ducts with the common bile duct (CBD) dilated up to the level of the ampulla where a mass lesion was seen. He was also known to have alcoholic liver disease. Spiral CT also showed evidence of liver cirrhosis and ascites in the upper abdomen. The patient had severe obstructive airway disease with type I respiratory failure and was oxygen dependent. A large peri-ampullary mass was confirmed by ERCP but the ampulla could not be identified. Due to the presence of ascites between the liver and the lateral abdominal wall, a PTC could not be considered. Endoscopic ultrasound showed no fluid between the stomach and the liver capsule and EUS guided biliary drainage was performed under light conscious sedation.

Case 5

A 44-year-old female patient diagnosed with stage Ⅳ metastatic ovarian cancer with liver metastasis and lymph node masses in the porta hepatis, presented with obstructive jaundice and ascites. Because of her age, third line chemotherapy was considered, but toxicity concerns because of severe cholestasis necessitated biliary drainage before chemotherapy could commence. Magnetic resonance cholangiopancreatography showed a mid-CBD stricture, a common bile duct severely displaced by the tumour and dilated intrahepatic ducts. Biliary cannulation was achieved during ERCP but the guidewire could not be advanced past the stricture into the proximal biliary tract. Ascites precluded the use of PTC. After successful EUS access was achieved, a guidewire could be passed into the duodenum.

Case 6

A 77-year-old female patient was diagnosed with locally advanced pancreatic carcinoma with duodenal infiltration and hypertensive cardiomyopathy. ERCP failed to identify the ampulla due to duodenal infiltration. She was not considered for surgery due to underlying co-morbidity and was referred for EUS-guided biliary drainage.

Endoscopic technique

Linear array endoscopic ultrasound (Pentax Hitachi 7500; Pentax Hitachi, Montvale, NJ) was used to identify the dilated left system. The Doppler mode was used to differentiate intrahepatic bile ducts from portal and hepatic vein branches. A 19G needle (Cook Medical, Limerick, Ireland) was used to puncture a peripherally located dilated segment 2 or 3 duct under EUS guidance. Under fluoroscopic control a cholangiogram was obtained and a standard 0.035 guidewire was advanced into the biliary system. Next, a 6Fr cystotome (Endoflex, Voerde, Germany) was used to create a transgastric tract through the liver parenchyma into the biliary system. A 0.038 catheter was advanced over the wire into the biliary system and

Table 1 Clinical characteristics of the patients

Age (yr)	Cancer diagnosis	Procedures performed	SEMS (cm × cm)	Technical success	Clinical success	Complications
67	Locally advanced Pancreatic	ERCP EUS-BD + coil	8 × 10 uncovered	Yes	Yes	None
50	Metastatic pancreatic	ERCP EUS-BD + coil Duodenal wall stent	8 × 10 uncovered	Yes	Yes	None
46	Infiltrating gallbladder	ERCP EUS-BD + coil	8 × 10 uncovered	Yes	Yes	None
80	Ampullary	ERCP EUS-BD + coil Duodenal wall stent	8 × 10 uncovered	Yes	Yes	None
44	Metastatic Ovarian	ERCP EUS-BD + coil	8 × 10 uncovered	Yes	Yes	None
77	Pancreatic	ERCP EUS-BD EUS-choledochoenterostomy	6 × 10 covered	Failed EUS-BD, Successful EUS-choledochoenterostomy	Yes	None

SEMS: Self-expandable metal stent; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; BD: Biliary drainage.

advanced to the bifurcation. The guidewire was then manipulated across the stricture and into the duodenal lumen (Figure 1). A Hurricane biliary dilation balloon 4 cm × 4 mm (Boston Scientific, Natick, MA Boston Scientific) was advanced through the tract and used to dilate the common bile duct stricture without balloon dilation at the level of the gastric wall liver interface. A 10 mm × 80 mm uncovered metal stent (Boston) was advanced and deployed under fluoroscopy across the papilla and past the duodenal obstruction, when present. To reduce the risk of a bile leak the catheter was withdrawn using contrast injection to verify anatomy, and carefully positioned in the track between the liver capsule and dilated system with the guidewire still in place in the biliary system. The guide wire was then removed and an endocoil (0.035" Fibered Platinum Coils, 6 mm, Boston Scientific, Natick, MA Boston Scientific) loaded into the lumen of a 0.038 prototype catheter before advancing it using a 0.035 guidewire (Boston Scientific, Natick, MA Boston Scientific) under EUS and fluoroscopy guidance (Figure 1).

RESULTS

Transgastric EUS-guided biliary access was successful in 5 of 6 patients. In one patient (patient 6) transgastric biliary access was initially possible and a cholangiogram obtained but guidewire cannulation could not be achieved. The patient was rescued by EUS-guided retrograde placement of a transduodenal covered stent (choledochoenterostomy) above the malignant stricture. In all cases no immediate procedure-related complications were observed. Two cases necessitated further duodenal stent placement during the same session. The mean procedure time (including anaesthesia) was 91 min (49-133). Levofloxacine (500 mg) was administered at the time of the procedure and continued for 5 d. Mild abdominal pain, not accompanied by peritoneal guarding and responding to Tramadol was experienced by two patients and resolved within 4 h. At 30 d all patients had responded with normalization of cholestasis and no late complications, including infections, were observed.

DISCUSSION

In patients with advanced biliary tract malignancy extensive peri-ampullary and duodenal infiltration may occur that may prevent the use of ERCP for palliative stent placement. Under these circumstances percutaneous transhepatic biliary drainage is often utilized. PTBD necessitates transversing of the parietal and visceral peritoneum, potentially causing bile leakage and bleeding into the peritoneal cavity. This procedure is also associated with significant pain, lengthy hospital stays and an overall reduction in quality of life[9]. Severe complications following PTBD including peritonitis, sepsis, bleeding requiring re-intervention, and even procedure-related mortality have been well described[9,10]. Indeed, The Society of Interventional Radiology (SIR) quality improvement guidelines established the procedural risk of severe major complications at 2.5%[11].

Embolization of biliary tracts using different materials including gel foam, fibrin glue, n-butyl cyanoacrylate and endocoils are routinely used in clinical practice at the time when biliary catheters are removed, in order to reduce the risk of bile leakage or bleeding. A recent randomized trial showed that transhepatic biliary tract embolization with n-butyl cyanoacrylate decreased both pain perception as assessed by a visual analog score and the need for analgesia, when compared to the non-embolization group[12]. Endocoil placement is a well-established intervention radiology technique where coils placed in blood vessels (endovascular coils) obliterate flow and induce coagulation, thrombosis and the formation of neo-intimal proliferation[13]. Coils have also been used outside the vascular setting, such as in coil embolization of needle tracks following PTC[14]. In theory, such coils will obstruct the flow of bile, prevent leaking and induce a local tissue response, in the same way gel foam.

Recent advances in endoscopic ultrasound have allowed access to a dilated biliary system through either ret-

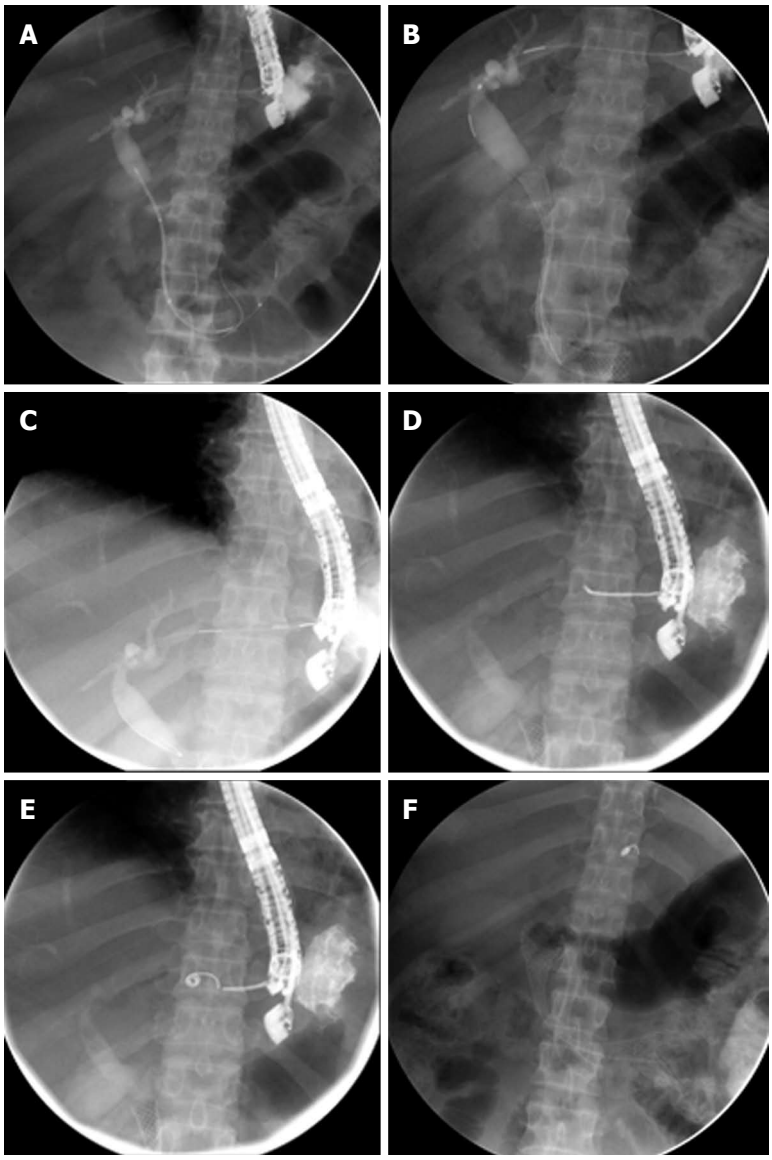

Figure 1 Endoscopic ultrasound-guided biliary drainage followed by endocoil placement. A,B: After successful endoscopic ultrasound cannulation of segment 3 duct a guide wire is passed into the duodenum, the stricture dilated and a 10 mm × 80 mm uncovered biliary stent deployed; C: Next the catheter is withdrawn with the guide wire still in place; D, E: Finally the guide wire is removed with the catheter in position in the track between the dilated segment and the liver capsule an endocoil is advanced and deployed using a standard 0.035 guide wire; F: The final result is shown after stenting of the stricture in the duodenum, showing the biliary stent, duodenal stent and endocoil.

rograde or anterograde approaches. Retrograde cannulation, normally performed from the duodenal bulb, allows access to the biliary tract above a malignant stricture with the intent either to pass a guide wire through the papilla and then perform a rendezvous procedure, or to place a covered metal stent in the stomach[15]. Cannulation of a dilated segment 2 or 3 sectoral duct is also possible from the proximal stomach where the endoscopist performs all procedures in an antegrade fashion[8]. Currently these procedures are selectively performed in specialist centres by expert endoscopists. Overall, EUS biliary drainage is technically successful in 75%-92% of cases, although there have been reports of bile leakage and peritonitis[8]. Endoscopic ultrasound utilizes standard endoscopic accessories and there is a need to create a transhepatic tract, using a 6Fr cystotome, to allow passage of stents from the stomach across biliary strictures. These accessories were not developed for use in EUS settings and are more difficult to use when advanced through the gastric wall. Valid concerns therefore still exist regarding the overall risk of bile leaks, peritonitis, and safety in EUS-guided biliary drainage. Ways should be developed by which these procedures may be improved and the risk of complications decreased. EUS guided biliary drainage theoretically exposes a tract between the dilated left system and the peritoneum.

Here we report the placement of an endocoil through a 0.038 catheter after completion of EUS-guided transgastric stent placement. The catheter was slowly withdrawn and positioned between the dilated sectoral duct and the liver capsule and a standard 0.035 guidewire was used to advance the coil into the tract created by the 6Fr cystotome. We could demonstrate that the placement of an endocoil is safe in all patients and does not add to the

overall complexity of the procedure. Endocoil placement is however not possible through a standard ERCP catheter with internal lumen diameters of 0.035, probably because of the angulation as it passes through the gastric wall and liver parenchyma. Catheters with larger internal lumen, at least 0.038 in diameter, are therefore needed. Currently such catheters do not exist, underscoring the need to develop catheters specific for EUS-guided biliary access. It remains to be seen whether coil placement will improve the overall safety of EUS transgastric procedures in the future. Randomized pilot studies will be needed to determine the usefulness this technique may offer over PTC in the prevention of bile leaks when accessing the biliary tract by EUS.

COMMENTS

Background

Advanced biliary tract malignancy, complicated by obstructive jaundice is managed by endoscopic retrograde cholangiopancreatography (ERCP) and stent placement. In some patients ERCP is not possible due to duodenal or periampullary infiltration, necessitating percutaneous transhepatic cholangiography.

Research frontiers

In recent years developments in endoscopic ultrasound have made it possible to gain access to a dilated left biliary system from the stomach. However only case series from expert medical centres have been reported. It therefore remains important to develop safer endoscopic techniques that can be used more widely and to compare endoscopic ultrasound guided biliary drainage with percutaneous transhepatic biliary drainage in randomized controlled trials.

Innovations and breakthroughs

Here the authors describe placement of an endocoil in the transhepatic tract following endoscopic ultrasound (EUS) guided biliary drainage. The authors propose that placement of an endocoil may prevent leakage of bile to the peritoneum and may thus improve the safety of EUS guided transgastric biliary drainage.

Applications

In remains imperative that further development in the field of interventional endoscopic ultrasound should be undertaken and that accessories specific for endoscopic ultrasound applications should be developed. This will improve efficacy and safety.

Terminology

Endoscopic ultrasound guided biliary drainage refers to the use of EUS in visualizing a dilated left biliary system. This is followed by gaining access to a dilated sectoral duct segment 2, 3 using a 19G endoscopic ultrasound needle. When this is established a guide wire can be passed into the biliary system and advanced past a malignant stricture so that a stent can be placed. This technology has theoretical benefits over percutaneous biliary drainage.

Peer review

Biliary leakage is very rare after balloon dilataion of biliary stenosis followed by self-expandable metallic stent. This manuscript could be accepted after revision.

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BRIEF ARTICLE

Endoscopic ultrasonography in patients with elevated carbohydrate antigen 19-9 of obscure origin

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Abstract

AIM: To evaluate the efficacy of endoscopic ultrasonography (EUS) in patients with elevated carbohydrate antigen (CA) 19-9 levels of obscure origin.

METHODS: Patients who had visited Pusan National University Hospital because of elevated serum CA 19-9 levels, between January 2007 and December 2009, were retrospectively enrolled. EUS had been performed on all subjects, in addition to routine blood tests, endoscopy, abdominal computed tomography (CT) and other clinical exams, which had not revealed any abnormal findings suggestive of the origin of the elevated CA 19-9 levels.

RESULTS: Of the 17 patients, gallbladder sludge was detected in 16 patients (94.1%) and common bile duct sludge was observed in 3 patients (17.6%). After the administration of ursodeoxycholic acid to 12 of the patients with gallbladder sludge, CA 19-9 levels normalized in 6 of the patients after a median of 4.5 mo.

CONCLUSION: EUS is a useful diagnostic method for patients with elevated CA 19-9 levels of obscure origin, even if the reason for abnormal levels of this serum marker cannot be determined through prior examinations, including abdominal CT.

Key words: Carbohydrate antigen 19-9; Endoscopic ultrasonography; Gallbladder; Ursodeoxycholic acid

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INTRODUCTION

Serum carbohydrate antigen (CA) 19-9 is considered to be the best screening marker for pancreatic cancer because of its relatively high sensitivity (70%-90%) and specificity (70%-98%)[1,2]. However, CA 19-9 is also elevated in many other digestive cancers, as well as in a number of benign diseases[3,4]. Although the usefulness of CA 19-9 as a screening marker for the detection of malignancies has not yet been validated, it is not uncommon to measure serum CA 19-9 levels in asymptomatic individuals during routine health examinations.

Pancreaticobiliary disease is one of the most common

causes of benign abnormal serum CA 19-9 levels. Herein, we report 17 cases of patients with elevated serum CA 19-9 levels without any obvious pancreaticobiliary system abnormalities, as revealed on abdominal computed tomography (CT); endoscopic ultrasonography (EUS) was performed as an additional part of their diagnostic examination and was useful in these cases.

MATERIALS AND METHODS

All patients with elevated serum CA 19-9 levels of indeterminate cause who underwent EUS in our institution between January 2007 and December 2009 were retrospectively assessed. Elevated serum CA 19-9 levels had been detected during routine cancer screenings and none of the patients had a history of cancers, surgeries or acute infections. To identify the causes of the elevated serum CA 19-9 levels, the patients, prior to the EUS examination, had provided a medical history regarding their smoking and alcohol consumption habits and had undergone a physical examination, routine blood tests (including liver and thyroid function tests), esophagogastroduodenoscopy, colonoscopy, abdominal ultrasonography, abdominal/pelvic CT and for female patients, mammography and breast ultrasonography.

EUS examinations were performed using a radial echoendoscope (GF-UM2000; Olympus, Tokyo, Japan) at either 5 or 7.5 MHz, by one experienced endoscopist. This study was reviewed and approved by the Institutional Review Board at Pusan National University Hospital. Written informed consent was obtained from all patients.

RESULTS

Of the 17 patients, 13 (76.5%) were female and the median age of the patients was 51 years (range 28-85 years). Two of the patients consumed more than 20 g of alcohol daily. The median serum CA 19-9 level during the screening visit was 64.1 U/mL (range 40.0-381.0 IU/mL). Serum total bilirubin levels were normal in all but 1 patient. This patient had an initial value of 1.6 mg/mL (reference range was < 1.3 mg/mL), which subsequently decreased to within the normal range (1.2 mg/mL) (Table 1).

EUS revealed gallbladder (GB) sludge in 16 of the patients (94.1%) and common bile duct (CBD) sludge in 3 patients (17.6%). Mild CBD dilatation (8 mm) was noted in 1 patient, tiny GB polyps (2-3 mm in size) in 3 patients, and a pancreatic cyst (9 mm in size) was detected in 1 patient.

The median follow-up duration was 12 mo (range 3-51 mo). Of the 16 patients with GB sludge, 12 received ursodeoxycholic acid (UDCA; 600 mg/d) for 3-18 mo (median 6 mo). The median number of CA 19-9 measurements was 3, although subsequent measurements of CA 19-9 were not performed for 2 patients. Six of 11 patients who received UDCA achieved normal CA 19-9 levels after a median of 4.5 mo (range 3-8 mo) (in 1 patient, the subsequent CA 19-9 value was not assessed); 1 of the 4 patients who did not initially receive UDCA did so 5 mo after the initial testing. Serum CA 19-9 levels remained within the normal range during the follow-up period in all patients who attained levels within the normal range as a result of UDCA therapy.

DISCUSSION

Biliary sludge, either GB or CBD sludge, is defined as a suspension of crystals (usually cholesterol monohydrate), mucin, glycoproteins, cellular debris, and/or proteinaceous material within the bile[5-7]. Many studies have suggested that biliary sludge may be a precursor to stone formation[8,9] and a source of potential complications[10-13]. The exact mechanism underlying the elevation of serum CA 19-9 levels, associated with GB sludge, remains unclear. However, the mechanism underlying the elevation in CA 19-9 levels in patients with bile duct obstruction is assumed to be as follows. Increased biliary pressure induces bile duct cells to produce CA 19-9[14], which accumulate in the lumen due to biliary obstruction. An increased permeability between the bile duct and the vasculature is believed to result in CA 19-9 reflux into the circulation[15]. Increased biliary pressure is suspected to be the main outcome of clinically insignificant biliary obstruction, such as is caused by biliary sludge. Furthermore, we hypothesize that sludge may flow down to the CBD during GB contractions, causing transient obstructions of the CBD outlet and increasing bile duct pressure. In this study, CBD sludge was identified by EUS in 3 of 16 patients with GB sludge, which may support our hypothesis.

Sludge may be visualized by abdominal US or EUS. The accuracy of US in detecting cholelithiasis is high, with a reported sensitivity of 92%-96%[16-19]. Nevertheless, when stones are less than 3 mm in diameter or located in the GB infundibulum, the sensitivity of US is only 65%[20]. By contrast, the sensitivity of EUS is approximately 96%[21,22]. Therefore, it is clear that EUS is the most sensitive imaging method for detecting GB sludge.

In patients in whom GB sludge has been detected in the absence of biliary symptoms, the natural history of sludge warrants appropriate management of the sludge. In patients with GB sludge and elevated serum CA 19-9 levels, GB sludge is likely to be responsible for the elevation in CA 19-9 levels. The elevated CA 19-9 levels may result in anxiety for patients regarding a potential malignancy; therefore, empirical treatment with UDCA may also represent a practical management option in such patients. The major role of UDCA is limited to the prevention of sludge formation in patients with predisposing conditions, such as weight reduction or total parenteral nutrition[23-25]. Theoretically, however, GB sludge may be more responsive to UDCA treatment than gallstones due to its higher surface-to-volume ratio. Indeed, a prospective, multicenter study showed that UDCA was associated with a 100% dissolution rate for persistent biliary sludge[26]. In the current study, 6 of 11 patients (54.5%) with GB sludge showed normalization of CA 19-9 levels after UDCA treatment, compared with 1 of 4 patients

Table 1 Summary of demographic and laboratory data and endoscopic ultrasonography findings in 17 patients with elevated serum carbohydrate antigen 19-9 values

Case	Gender	Age, yr	EUS findings				CA 19-9 level, IU/mL		Time to CA 19-9 normalization, mo	UDCA administration	Duration of UDCA administration, mo	Other findings	Follow-up duration, mo
			CBD size, mm	PD size, mm	GB sludge	CBD sludge	First visit	Last visit					
1	F	28	3	1	Yes	Yes	78.3	20.7	3	Yes	3		6
2	F	51	2	1	Yes	Yes	187.9	25.6	4	Yes	6		17
3	F	51	3	1	Yes	Yes	63.6	30.2	4	Yes	6	GB polyp	8
4	F	36	5	0.5	Yes	No	46.1	21.3	5	Yes	3		36
5	M	68	3	1	Yes	No	73.3	20.6	7	Yes	3		7
6	M	38	2	0.5	Yes	No	165.3	16	8	Yes	6		16
7	F	63	8	1	Yes	No	48.2	61.1		Yes	3		51
8	F	59	4	1	Yes	No	46.2	40.4		Yes	18		20
9	F	71	5	2	Yes	No	43.9	57.3		Yes	10		10
10	M	43	2	1	Yes	No	162.7	123.9		Yes	15		17
11	F	64	5	1	Yes	No	141.8	122.2		Yes	12	GB polyp	14
12	F	36	4	1	Yes	No	87.6	-		Yes	3		3
13	M	46	3	2	Yes	No	381	19.4	5	No			5
14	F	30	4	2	Yes	No	64.1	50.4		No			3
15	F	55	3	1	Yes	No	51.4	54.1		No			29
16	F	40	4	1	Yes	No	40	43.9		No			12
17	F	85	6	1	No	No	40.3	-		No		GB polyp, Pancreatic cyst	3

CBD: Common bile duct; PD: Pancreatic duct; GB: Gallbladder; UDCA: Ursodeoxycholic acid.

(25%) who did not receive UDCA. This finding appears to support the proposed relationship between GB sludge and elevated CA 19-9 levels.

Additionally, in this study, the median duration of UDCA administration was 4.5 mo in the 6 patients whose CA 19-9 levels normalized, compared with 12 mo for the patients who did not achieve CA 19-9 level normalization. Therefore, although UDCA treatment appears to be effective for normalizing CA 19-9 levels, it should be discontinued if CA 19-9 levels are not decreased after 6 mo of therapy.

To our knowledge, the utility of EUS in determining the potential cause of CA 19-9 level elevation in patients has not been previously described. This study demonstrated that EUS is a useful diagnostic method in patients with elevated CA 19-9 levels of obscure origin, despite inconclusive results from prior examinations, including endoscopy and abdominal/pelvic CT. In addition, the current findings indicate that UDCA therapy may be effective for normalizing CA 19-9 levels in patients with GB sludge. Additional large, prospective studies may clarify the association between CA 19-9 levels, the present of GB sludge, and UDCA treatment.

COMMENTS

Background

Serum carbohydrate antigen (CA) 19-9 levels are commonly examined as part of cancer screening among asymptomatic individuals. However, it can also be elevated by conditions other than pancreatic cancer, as well as in the absence of any specific diseases. When physicians encounter a patient with an elevated CA 19-9 level, they search for possible hidden malignancies. In many cases, although several tests are performed, the putative cause remains unknown.

Research frontiers

Endoscopic ultrasonography (EUS) can detect small lesions in the pancreaticobiliary system that conventional ultrasound (US) or computed tomography (CT) cannot. Therefore, in this study, the authors examined the efficacy of EUS in patients with elevated CA 19-9 levels of obscure origin.

Innovations and breakthroughs

Using EUS, the authors identified gallbladder and bile duct sludge as possible causes of elevated CA 19-9 levels. The presence of this gallbladder sludge had not been detected by transabdominal US and abdominal CT.

Applications

EUS can be used to identify causes of elevated CA 19-9 levels in patients when other examinations show non-specific results.

Peer review

Although this paper is a single center study with a small number of subjects, the novel application of EUS for patients with elevated levels of this tumor marker is an attractive and potentially promising modality for investigating the pancreaticobiliary system.

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CASE REPORT

Miniprobe EUS in management of pancreatic pseudocyst

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Abstract

Pancreatic pseudocysts (PP) arise from trauma and pancreatitis; endoscopic gastro-cyst drainage (EGCD) under endoscopic ultrasonography (EUS) in symptomatic PP is the treatment of choice. Miniprobe EUS (MEUS) allows EGCD in children. We report our experience on MEUS-EGCD in PP, reviewing 13 patients (12 children; male:female = 9:3; mean age: 10 years, 4 mo; one 27 years, malnourished male Belardinelli-syndrome; PP: 10 post-pancreatitis, 3 post-traumatic). All patients underwent ultrasonography, computed tomography and magnetic resonance imaging. Conservative treatment was the first option. MEUS EGCD was indicated for retrogastric cysts larger than 5 cm, diameter increase, symptoms or infection. EGCD (stent and/or nasogastrocystic tube) was performed after MEUS (20-MHz-miniprobe) identification of place for diathermy puncture and wire insertion. In 8 cases (61.5%), there was PP disappearance; one, surgical duodenotomy and marsupialization of retro-duodenal PP. In 4 cases (31%), there was successful MEUS-EGCD; stent removal after 3 mo. No complications and no PP relapse in 4 years of mean follow-up. MEUS EGCD represents an option for PP, allowing a safe and effective procedure.

Key words: Endoscopic ultrasonography; Miniprobe; Pancreatic pseudocyst; Children; Endoscopic gastrocyst drainage

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INTRODUCTION

Pancreatic pseudocysts (PP) in children arise from pancreatic trauma and acute pancreatitis with a blunt duct caused by several pancreatic diseases (*i.e.*, Crohn's disease, cystic fibrosis, pancreas divisum, *etc.*).

Diagnosis is performed by complete radiological evaluation that includes ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI); serum amylase and imaging such as US are considered useful in monitoring the evolution, the occurrence of spontaneous resolution or the need for surgical intervention[1]. Herman *et al*[2] in a pediatric study in 2011 confirmed that maximal amylase (> 1100 U/L) is highly predictive of the risk of developing a pseudocyst.

Differential diagnosis is mandatory with neoplastic

diseases like mucinous cystic neoplasia and acinar cell cyst adenoma, and also of other malformations such as gastric duplication[3-5].

Generally, conservative treatment is resolutive in most cases. According to D'Edigio *et al*[6], in 30%-50% of cases after a period of 6 wk, PP can resolve spontaneously.

Several operative therapies are described for PP: open surgery was the traditional treatment for symptomatic pseudo cysts and abscess, but morbidity and mortality were too high; laparoscopic cyst gastrostomy has also been described in children as a safe and effective technique which gives good results and a good rate of resolution[7].

Endoscopic transmural drainage, first introduced in the mid 1980s, has already been considered a minimally invasive, effective and safe approach in a series of adults affected by PP and abscesses, with success rates exceeding 90% among adults[8,9] and also among children, despite complications such as bleeding and technical difficulties[10-12].

During the last decade, in symptomatic long standing PP with a great increase in volume, endoscopic gastrocyst drainage (EGCD) under endoscopic ultrasonography (EUS) has become the chosen treatment; the endoscopic approach consists of the placement of a drainage catheter into the cysts under direct EUS guidance in order to identify the optimal site for puncture and stent placement, which guarantees greater safety and efficacy in both adults and children[12-14]. Barthet *et al*[15] proposed an algorithm for PP, including EUS-assisted drainage, transpapillary drainage and conventional endoscopic drainage, demonstrating that EUS is required for treatment in half of the cases. In children, few studies have been published on endoscopic marsupialization of PP with the addition of EUS; recent interesting data on ten children come from Jazrawi *et al*[9] with dedicated echo endoscopes[9].

The application of miniprobe endoscopic ultrasonography (MEUS) is not widespread. However, its use in pancreatobiliary disease allows the performance of complex procedures, especially in children and patients who have complications due to severe diseases[16]. The application of MEUS was never prescribed in the management of PP.

CASE REPORT

In this study, we report our experience of EGCD under MEUS guidance in PP. Between 2005-2010, 4 patients with PP were treated with EGCD under MEUS guidance; they were enrolled between 13 consecutive patients with PP followed in our unit. Conservative treatment was always the first option for all the patients.

MEUS EGCD was indicated in retro gastric cysts, with close contact between the cyst and the gastric wall, with cysts larger than 5 cm or that had increased in diameter, or in persistence of symptoms or infection.

The steps of EUS guided drainage were the following: (1) endoscopy (GIF Q165-Q160 Olympus America Corp. Melville, NY) and EUS (20 MHz radial miniprobes Olympus UM-BS 20-26R, balloon sheath Olympus MAJ-643-R inserted through the 2.8 mm biopsy channel of an Olympus GIF Q165-Q160) confirmation of the best contact between the pseudocyst and the gastric wall and identification of the correct place for diathermy needle puncture; (2) according to the patient's age and weight, exchange of the endoscope with a side view duodenoscope was opted for (Olympus TJF 160 VR), diathermy needle puncture (Cook Zimmon needle knife papillotome PTW-1 Wilson Cook Medical Ireland 5 Fr) of the gastric wall in the previously identified correct place, up to entering the cyst; (3) guide wire (0.035 IN) placement under X-ray control; (4) extraction of the needle with the guide in place and opacification of the cystic cavity; (5) hydrostatic balloon dilation of the cystic opening, if necessary; (6) washing of the cyst and the removal of necrotic tissue; and (7) insertion of a biliary drainage pigtail stent (Boston Scientific S.A. France) 7 or a 10 Fr stent gastro-cystic and/or nasal-gastro-cystic 7 Fr drainage. Nasal-gastro-cystic drainage was in place for one week; the stent was planned for three months.

ERCP (TJF 160 VR; Olympus America Corp. Melville, NY) and double sphincterotomy with stent placement and nasopancreatic tube were performed in communicating PP with the main pancreatic duct.

These procedures were always performed under general anesthesia with orotracheal intubation and in the supine position. During all the procedures X-ray was used. Antibiotic prophylaxis with cefazolin administered intravenously was given to all patients prior to endoscopy.

Surgery was preferred when the endoscopic approach was not suitable because there was no evidence of safe contact between the gastric or duodenal posterior wall and the PP, after evaluation by either endoscopy or MEUS.

Informed consent from patients and parents was asked for to enable us to collect and analyze data retrospectively in a confidential manner.

The ethics board of Bambino Gesù Children's Hospital approved our study. Our series consisted of 12 children (male:female = 9:3) with a mean age of 124 mo (range 30 mo-16 years) and one adult (27 years old, male, Belardinelli syndrome, severe esophageal stricture and malnutrition, body mass index: 14 kg/m^2) with PP (all chronic abdominal pain, 5 also had fever, one had enzyme elevation) due to pancreatitis (n = 10: biliary pancreatitis 1, idiopathic pancreatitis 6, mild cystic fibrosis 2, pancreas divisum 1) and trauma (n = 3).

All patients underwent pancreatobiliary examinations, ultrasound, CT and cholangio-pancreatic MRI. The outcome of patients is reported in Figure 1.

In 8 cases (61.5%), we observed a progressive PP disappearance; one patient (7.5%) with pancreas divisum and relapsed acute pancreatitis required surgical duodenotomy and marsupialization of retro-duodenal PP due to incomplete MEUS contact between the PP and the duodenal wall.

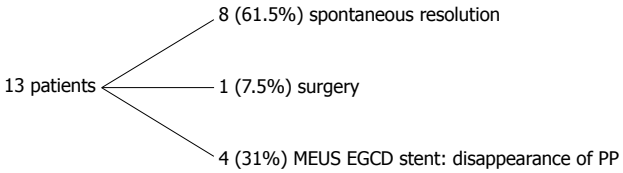

Figure 1 Outcome for patients. PP: Pancreatic pseudocysts; MEUS: Miniprobe endoscopic ultrasonography; EGCD: Endoscopic gastro-cyst drainage.

In Table 1, results of MEUS EGCD were resumed; in 4 patients, 31% (males, 7, 10, 11 and 27 years; one trauma, 3 pancreatitis), successful MEUS EGCD (Figure 2) was performed with stent placement (in all the patients, one 7 Fr stent, in one patient also a 10 Fr stent). In all these patients, we observed a bulge of the gastric wall corresponding to the pseudocyst below.

The patient with post traumatic PP was treated with naso-Wirsung drainage and a gastro-cystic pig tail stent (Figure 3), while those patients affected by cystic fibrosis and chronic pancreatitis even underwent sphincterotomy. Stent removal was performed after 3 mo in all patients. No immediate or late complications occurred and no relapse of PP in 4 years of mean follow up (range: 6 mo-6 years).

DISCUSSION

PP could be suspected in abdominal epigastric pain with an increase in pancreatic enzymes or biliary tree compression, after an acute pancreatitis or trauma (3-4 wk later). Non invasive radiological methods such as CT and MRI help to classify pancreatic trauma, contributing to planning the best and most adequate treatment. It is important to make a correct differential diagnosis for PP, even in pediatric cases.

Transient or persistent pancreatic duct disruption is the most common cause, but pancreatitis represents a spread factor on the basis of PP.

Pseudocysts frequently resolve spontaneously and so conservative treatment is the best option in children with PP. If the cyst is large with a persistency that goes beyond 6 wk, symptomatic and complicated by infection, it is correct to indicate the most appropriate treatment. Delgado Alvira *et al*[17], an interesting study on the best management strategies in PP, reported two children with post-traumatic PP and a large series reviewed by literature between 1990 and 2007. They underlined that asymptomatic PP in children does not require any specific intervention other than expectant management, while children with persistent clinical symptoms or those who develop complications may need further interventions such as external percutaneous drainage, cystogastrostomy, cystojejunostomy or pancreaticojejunostomy, endoscopic drainage or distal pancreatectomy[17].

Surgical treatment has been proposed by several authors: Briem-Richter *et al*[18] reported a rare case of pediatric Crohn's disease with the development of huge pseudo cysts that required surgery; Yoder *et al*[7] described laparoscopic treatment that realized cystogastrostomy in 13 children, with a high rate of complete resolution with minimal morbidity and rapid recovery.

During the last decade, it was gradually recognized that endoscopic treatment could be the preferred approach to manage PP[15]. In 2004, Al-Shanafey *et al*[19] had successfully treated two children with transpapillary drainage and one child with an endoscopic cystoduodenostomy.

The endoscopic therapeutic approach consists of transduct (transpapillar in recent Wirsung disruption) or transmural passage of a guide wire with stent placement to the drainage of the pseudo cyst content[20], under EUS evaluation or through linear echo-endoscope (duodenal-cyst drainage or gastro-cyst drainage), almost 6 wk from evidence of a pseudo cyst[21]. A 15% recurrence rate has been reported. If pseudo cysts persist lifelong, surgery is recommended.

Major ductal injuries caused by blunt abdominal trauma are rare and treated by surgery. ERCP with stent placement is useful to manage post-traumatic pseudo cysts, with rapid clinical improvement and complete resolution of clinical and biochemical pancreatitis.

Barthert *et al*[15] in 2008 in a prospective study based on a systematic treatment algorithm concluded that endoscopic drainage is the first-line method of managing PP and EUS is required in half of the cases to obtain a definitive therapy.

EUS is already widespread in pediatric cases, but experience in pancreatobiliary disease is poor[11]; pediatric experiences of EUS guided endoscopic treatment are very much limited due to several technical difficulties, few experienced centers and few case studies.

According to a study by Varadarajulu *et al*[13] in 2005, EUS could give a diagnostic contribution to chronic pancreatitis, in pancreatic pseudo-cysts, in coledocho-litiasis, in pancreas divisum and in duodenal duplications, because EUS can also be successfully performed in children aged 5 years and over using an adult echo endoscope. Cohen *et al*[22] in 2008 verified the diagnostic impact of EUS, with a demonstration of a radical change of diagnostic and therapeutic strategies when this procedure was used.

In pediatric cases, EUS improved diagnostic and the therapeutic possibility of ERCP in chronic and recurrent pancreatitis, in treatment of pancreatic pseudocysts (gastrocystostomy EUS guided) and duodenal duplication (endoscopic therapy).

Even if endoscopic drainage of PP is successfully reported in children, EUS could add safety to the procedure. In 2010, Theodoros *et al*[23] published the case of a child with post-traumatic PP who was successfully treated with a guided EUS transgastric approach. Jazrawi *et al*[9] reported the largest series of pediatric patients with symptomatic PP due to pancreatitis and trauma; in all ten cases, successful EUS guided transgastric endoscopic drainage was achieved, with placement of double pig tail stents in eight patients and complete cyst aspiration and

Table 1 Results of patients treated by miniprobe endoscopic ultrasonography endoscopic gastro-cyst drainage

Sex	Age Body weight	Associated disease	Etiology	PP size (cm)	PP site	EUS common wall thickness (mm)	Endoscopic treatment	FU yr
M	7 yr 7 m 20 kg	Filippi's syndrome	Pancreatitis	8 × 7	Retrogastric	4.5	GIF Q165 pre-cut needle 7Fr stent	0.5
M	27 yr 43 kg	Belardinelli's syndrome-SEIP	Iatrogenic Biliary pancreatitis	8 × 6 × 5	Retrogastric	3.5	GIFQ165 pre-cut needle, hydrostatic dilation 7 and 10 Fr stent	3
M	11 yr 31 kg	No	Trauma	7 × 5 × 9 10 × 5 × 11	Retrogastric and retroduodenal Pancreatic body and tail	3.5	Transduodenal drainage (TJF) GIFQ165, precut needle 7Fr and nasopancreatic tube	6
M	10 yr 5 m 25 kg	Cystic fibrosis	Pancreatitis	8 × 5 × 9 9 × 6 × 10	Retrogastric Pancreatic body and tail	3.8	TJF double sphincterotomy GIFQ165 precut needle 7Fr stent and naso-pancreatic tube	6

M: Male; F: Female; PP: Pancreatic pseudocysts; EUS: Endoscopic ultrasonography.

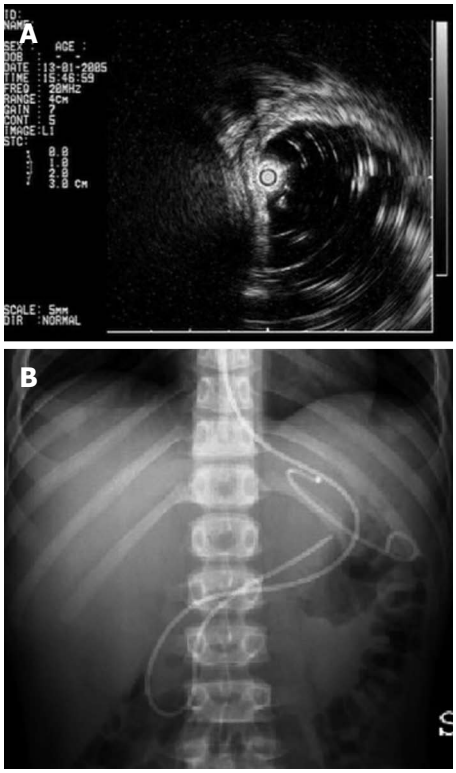

Figure 2 Miniprobe endoscopic ultrasonography endoscopic gastro-cyst drainage. A: Miniprobe endoscopic ultrasonography of pancreatic pseudocyst: the common wall between stomach and pseudocyst. B: Endoscopic view: gastrocystic stent.

collapse by EUS fine-needle aspiration in two cases.

Miniprobe was never described in PP management; this technique is useful in small children and in particular situations such as esophageal stricture that does not allow a dedicated echo endoscope passage. This technique is safe and simple, even with a common endoscope.

The advantages of miniprobe EUS are numerous. We have the possibility of performing therapeutic procedures even when dedicated radial and linear echo endoscopes are not available; the MEUS equipment is less expensive

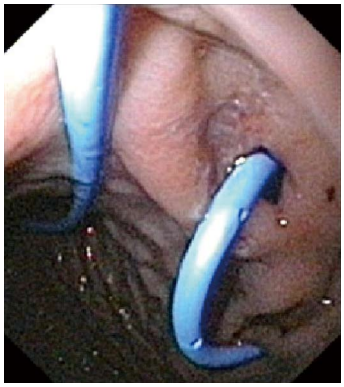

Figure 3 X ray: The naso-pancreatic drainage and the stent in the correct position.

than instruments and the ultrasound generator for linear EUS. MEUS also represents a useful instrument in pediatric surgery and pediatric endoscopy for many other different clinical situations, such as duodenal duplications[16], esophageal congenital strictures[24] and duodenal diaphragms[25]. Generally, we perform EUS with standard front view endoscope to avoid miniprobe damage by the cannula elevator of side view duodenoscope; besides, we can use a small caliber endoscope (operative channel of 2.2 to allow miniprobe passage) with a "frontal vision" commonly used in the clinical practice, to complete the endoscopic therapy.

Miniprobe EUS has an indication in malnourished, small weight patients, syndromic or sick patients in a general bad condition (*i.e.*, cystic fibrosis) and in esophageal stenosis with consequent difficulty of the passage of the echo endoscope. The limitations of this procedure are the lack of a Doppler and difficulty to rule out with certainty the presence of vessels in the common wall with confirmation of blood flow; daily experience allows ascertaining suspected vascular structures inside the wall.

In our small series of four patients, we have applied this innovative technique in special patients, two syndromic cases (one with neurological retardation, Filippi's syndrome

and the other with an esophageal stricture and Belardinelli's syndrome), one cystic fibrosis child and a complex post-traumatic patient. Their clinical conditions and associated diseases contributed to determine a complex approach. Our experience with EUS miniprobe commonly used in our tertiary center for other diseases (*i.e.*, congenital esophageal stenosis, duodenal duplications, duodenal diaphragms, *etc.*) and with pediatric operative endoscopy allowed us to choose this original procedure in our cases and in one case in particular. The daily availability of digestive surgery gives us the possibility to choose the best treatment depending on specific situations, achieving an outcome for patients similar to the literature. While the unavailability of echo endoscope limits our decision making, on the other hand, we need a simple, rapid, safe technique, easy to reproduce, that could be taught during training.

Small series size does not allow a deep analysis that larger cases need to be able to confirm our preliminary data. The choice of the typology of endoscope to perform the puncture of the cyst depends on the availability of a side view adult duodenoscope, the age and weight of the patient, and the possible presence of esophageal stricture. We prefer to use the duodenoscope because it provides the best position in front of the gastric wall and the opportunity to insert large diameter stents.

The choice of the best treatment for PP depends on the medical-surgical team's experience and the management of the endoscopic technique, as well as the availability of interventionist radiology and dedicated pediatric accessories[17]. Despite several techniques, PP therapy remains a challenge for both pediatric surgeons and pediatric endoscopists[23]. A novel hybrid natural orifice transluminal endoscopic surgery has already been reported by Rossini *et al*[26]; probably, in the future, the model of a transgastric approach used to treat PP could be applied in several diseases, even in pediatric cases.

We can conclude that when conservative therapy is ineffective, EGCD represents a viable option to resolve PP permanently. MEUS provides a valuable contribution to help endoscopic cystogastrostomy in children and also in difficult situations, allowing a safe and effective endoscopic procedure.

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CASE REPORT

Serrated adenoma of the stomach: Case report and literature review

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Abstract

Gastric serrated adenomas are histologically characterized by protruding glands with lateral saw tooth-like indentations lined with stratified dysplastic cells containing abundant eosinophilic cytoplasm. Since the first case of gastric serrated adenoma found in 2001, 18 additional cases have been reported. Gastric serrated adenomas have a particular proclivity to progress to invasive carcinoma; 75% or 15 of the 20 cases now in record - including the present one - exhibited invasive carcinoma. The 20th case of gastric serrated adenoma reported here differs from the preceding ones in as much as it evolved in a patient with Lynch syndrome, implying that this adenoma phenotype may develop not only sporadically but also in patients with hereditary traits.

Key words: Gastric; Serrated; Neoplasia; Lynch syndrome

Core tip: Gastric serrated adenomas have a particular proclivity to progress to invasive carcinoma; 75% or 15% of the 20 cases that are now in record - including the present one - exhibited invasive carcinoma.

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INTRODUCTION

Ninety years ago Konjetzny[1] described mucosal polyps in gastric specimens. Six years later Stewart[2] found among 11000 necropsies, 47 gastric polypoid lesions with mucosal aberrations that he called adenomas. Since then, much attention has been centred on gastric adenomas due to their propensity to evolve into invasive carcinoma[3-11].

Throughout the years several classifications of gastric polyps have been proposed[12-15]. Based on the endoscopic appearance, endoscopists have classified gastric polyps (adenomas being a histologic diagnosis) as flat[16] (also called non-polypoid or non-protruding) and polypoid[11] (also called protruding). Non-protruding polyps that appear thinner than the surrounding mucosa are called, depressed lesions[17]. This endoscopic classification was subsequently confirmed at the histological level[18]. Based on the gross appearance, Goldstein *et al*[19] classified gastric polyps into flat topped, villiform, and pedunculated and Ming *et al*[12] into flat and papillary. Based on their histological configuration, gastric polyps were classified by Elster[14] into focal foveolar hyperplasia, hyperplasiogenic polyps, tubular and villous adenomas, and by Appelman[20] into non-neoplastic (focal foveolar hyperplasia and hyperplastic polyps), non-neoplastic possibly

hamartomatous (Peutz-Jehgers-type polyps), and neoplastic adenomas (with or without invasive carcinoma). Nakamura[7] grouped gastric polyps into types I and II (hyperplastic polyps), and types III and IV (adenomas), and Kozuka[10] grouped them into common type (hyperplastic, adenomatous, and carcinomatous polyps), special-type hamartoma (Peutz-Jehgers polyps, juvenile polyps, polyps in Cronkhite-Canada syndrome, and fundic gland cyst polyps), polypoid lesions (inflammatory polyps and polypoid carcinoma), and polyps resulting from a submucosal mass.

In 2001 we reported a novel histologic phenotype of gastric adenoma characterized by protruding glands with lateral saw tooth-like notches due to scalloped epithelial indentations[21]. The serrated elongations were lined with stratified dysplastic cells containing abundant eosinophilic cytoplasm; it was called gastric serrated adenoma since it mimicked other serrated adenomas evolving in the colon[22] the appendix[23], the duodenum[24], the pancreatic duct[25] and the Barretts's esophagus[26]. Remarkably, this adenoma phenotype was not included in any of the aforementioned classifications of gastric polyps[11,18,20-22]. One possible explanation could be that gastric serrated adenomas were classified together with gastric villous adenomas. Another possible explanation could be that this type of lesion is very rare in the stomach. In this context, it should be mentioned that no case of serrated adenoma was recorded in a survey of 67 consecutive gastric adenomas[18], nor in larger series of gastric adenomas in the literature[5,6,10-14].

Subsequently, we reported six additional cases of gastric serrated adenoma[27,28]. More recently, cases with gastric serrated adenomas were reported from such disparate countries as Tunisia[29], Japan[30], Turkey[31] and South Korea[32].

The purpose of the present communication is to report another case of gastric serrated adenoma, this time occurring in a patient with Lynch syndrome, an autosomal dominant genetic condition with an increased risk to develop cancer in various organs, including the stomach.

CASE REPORT

The patient is a 57-year-old male with confirmed *MSH2* mutation Lynch syndrome. His mother was treated for endometrial cancer and an uncle for colorectal cancer. In 1995 the patient was operated for cancer in the right colon. In 2007, a second colon cancer was found at surveillance colonoscopy, this time in the transverse colon. A total colectomy with ileo-rectal anastomosis was performed. In 2009 he was operated for a metastasis in the small bowel. Histology revealed a metastasis from colon cancer.

A gastro-esophagoscopy was done in October 2012, because of protracted gastro-esophageal reflux. Histology showed short Barrett´s esophagus with low-grade dysplasia. During the same séance, a 10 mm in diameter polypoid lesion was detected in the stomach (Figure 1).

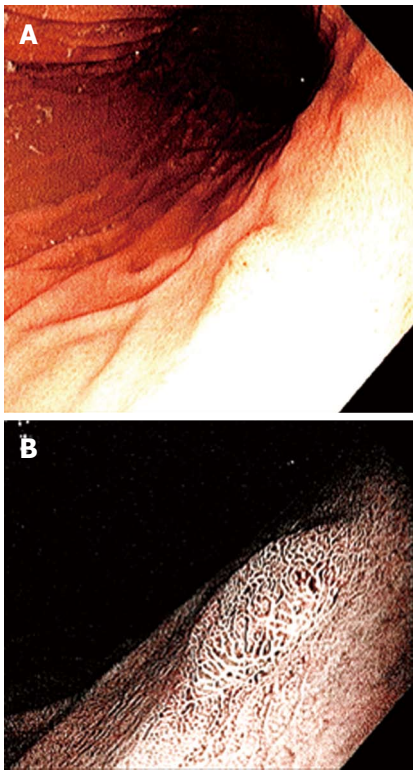

Figure 1 Endoscopic view. A: Gastric polyp; B: Gastric polyp after indigocarmine staining.

The polyp was endoscopically excised. No complications occurred during or after the procedure. The histological examination of the gastric polypoid lesion revealed a serrated adenoma showing protruding glands with lateral saw tooth-like notches due to scalloped epithelial indentations with high-grade dysplasia (Figure 2). In addition, an adenocarcinoma invading the submucosal tissues was demonstrated (Figure 3). The invasive carcinoma component retained the serrated configuration and the cytological features of the adenoma (Figure 4).

DISCUSSION

Despite decreasing incidence, gastric carcinoma continues to be one of the most common cancers world wide[33]. It is generally assumed that the histogenesis of gastric carcinoma of intestinal type follows the atrophic gastritis-intestinal metaplasia-dysplasia-pathway[34]. On the other hand, the histogenesis of gastric carcinomas of diffuse type remains elusive. Thus, the histogenesis in the majority of the gastric carcinomas has not yet being disclosed.

It is known that gastric tubular or villous adenomas may progress to gastric carcinoma of intestinal type[9,10,12,35]. The same fate seems to apply to gastric serrated adenomas, since of the 20 gastric serrated adenomas now in record (including the one reported here), 75% had evolved into invasive carcinoma (Table 1).

Recently, Kwon *et al*[32] reported 9 cases of gastric serrated adenomas. These authors found that MUC5AC expression was present in 66.7% (6/9) of the gastric

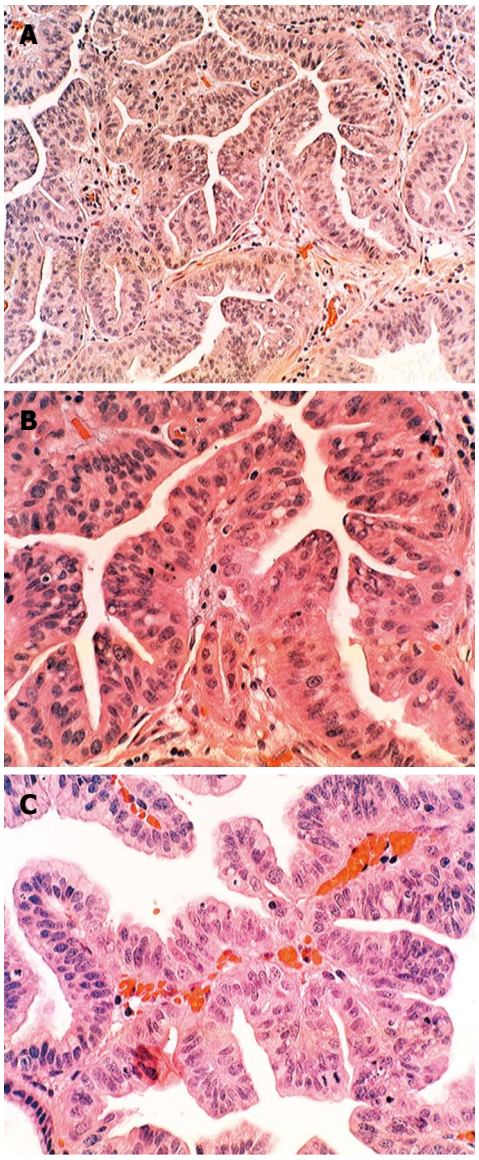

Figure 2 The histological examination of the gastric polypoid lesion revealed a serrated adenoma showing protruding glands with lateral saw tooth-like notches due to scalloped epithelial indentations with high-grade dysplasia. A: Adenoma showing serrated glands lined with high-grade dysplasia [hematoxylin and eosin (HE) × 10]; B: High power view of the adenomatous component showing serrated glands with indentations lined with high-grade dysplasia (HE × 20); C: View of a single elongated gland with saw-tooth-like configuration lined with high-grade dysplasia (HE × 20).

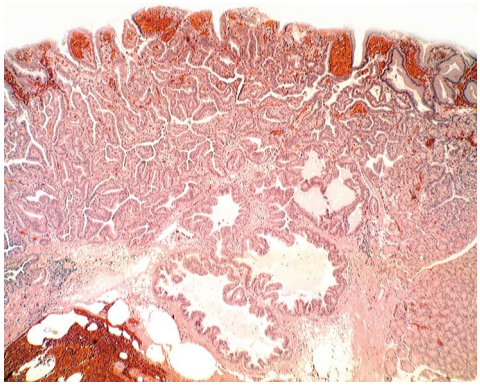

Figure 3 Low-power view of serrated adenoma with invasive carcinoma (hematoxylin and eosin × 10).

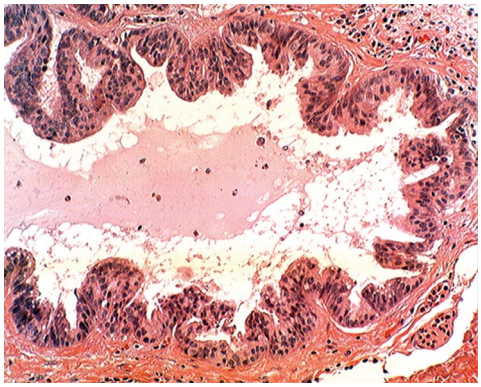

Figure 4 High power view of the invasive component with retained serrated configuration (hematoxylin and eosin × 10).

Table 1 Gastric serrated adenomas case reports

Ref.	Year of publication	No. of cases	No. cases with invasive carcinoma
Rubio *et al*[21]	2001	1	1
Rubio *et al*[27]	2004	5	4
Rubio *et al*[28]	2007	1	1
M'sakni *et al*[29]	2007	1	0
Hasuo *et al*[30]	2009	1	1
Köklü *et al*[31]	2010	1	0
Kwon *et al*[32]	2013	9	7
Rubio *et al*[1]	2013	1	1

[1]Present communication.

serrated adenomas, in 71.4% (5/7) of the serrated adenocarcinomas, and *KRAS* mutations in 33.3% (3/9) of the cases. Kwon *et al*[32] concluded that the high frequencies of malignant transformation and *KRAS* mutations suggested that gastric serrated adenomas might be precursors of gastric mucin-phenotype adenocarcinoma.

Here, we report the first case of serrated adenoma of the stomach in a patient with Lynch syndrome. Lynch syndrome is an autosomal dominant genetic condition which has a high risk of colon cancer as well as other cancers including endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. The occurrence of this case of gastric serrated adenoma in a patient with Lynch syndrome implies that this adenoma phenotype may develop not only sporadically but also in patients with hereditary traits.

Paradoxically, eight out of 20 cases of serrated adenoma of the stomach now in record (including present case) have been reported from a single Institution[21,27,28]. The increased awareness of the existence of these gastric aggressive adenomas may result in more cases being re-

ported from other Institutions in the future.

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CASE REPORT

Biodegradable stent for the treatment of a colonic stricture in Crohn's disease

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Author contributions: Rodrigues C, Pires E and Deus J were attending doctors for the patient; Rodrigues C, Santos L and Pires E performed the endoscopic examinations and stent placement; Rodrigues C and Oliveira A organized the report; and Rodrigues C wrote the paper; all authors read and approved the final manuscript.

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Key words: Crohn's disease; Fibrosis; Intestinal obstruction; Stents; Polydioxanone

Core tip: Strictures in Crohn's disease (CD) are challenging. Until the development of medical therapy that can prevent or reverse intestinal fibrosis, endoscopic management is recommended to avoid surgery. Biodegradable polydioxanone stents originally developed to treat refractory esophageal benign strictures are a promising alternative to balloon dilation with the advantage over metallic stents that they do not need to be removed. However, data on their use in the bowel is limited to a few series, mostly in patients with postsurgical colorectal strictures. We report the case of a CD patient presenting with a symptomatic colonic fibrotic stricture that was successfully treated with a biodegradable stent.

Abstract

Biodegradable polydioxanone stents were developed for the treatment of refractory benign esophageal strictures but have been suggested as a new therapeutic option for intestinal strictures. The primary advantage of biodegradable stents over self-expandable metallic stents is that removal is not required. There are, however, few data available on their use in the small or large bowel. We herein describe the case of a 33-year-old patient with long-standing Crohn's disease (CD) who developed a fibrotic stricture of the sigmoid too long to be amenable to balloon dilation. The use of a biodegradable polydioxanone stent was chosen to avoid surgery. Combined endoscopic and fluoroscopic placement of the stent was technically simple, safe and clinically successful, and no recurrence of obstructive symptoms occurred during a 16-mo follow-up. Further studies are needed to evaluate the long-term efficacy and safety of biodegradable stents in the treatment of intestinal strictures, particularly in the context of CD.

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INTRODUCTION

Strictures are a common complication of Crohn's disease (CD), occurring in 1/3 of patients after 10 years of disease. They occur most frequently in the ileocecal region and rectum and at anastomotic sites where the disease is likely to recur[1]. Medical therapy has not been shown to be effective in the treatment of fibrotic strictures, and its role in preventing stricture formation has been disappointing[2]. As disease recurrence is common, endoscopic methods, such as balloon dilation or stenting for refractory strictures, have been advocated to decrease surgery.

Biodegradable stents were originally developed to treat refractory benign esophageal strictures but are a

promising therapeutic option for intestinal strictures because they do not require removal and may be able to overcome some of the drawbacks of self-expandable metallic stents (SEMS). We report our experience with the off-label use of a biodegradable esophageal polydioxanone stent in the management of a colonic stricture complicating CD.

CASE REPORT

A 33-year-old female with a history of CD was admitted to the hospital in February 2011 with abdominal cramps, constipation and air-fluid levels in the small and large bowel on X-ray. The CD diagnosis had been established at age 16 years. The disease involved the terminal ileum, colon and perianal region and presented with an inflammatory behavior (A1L3B1p according to the Montreal classification)[3,4]. She was initially treated with oral corticosteroids and started on azathioprine, but in 2001 infliximab was added for persistent symptoms. The patient experienced some flares over the years until 2009, when she achieved sustained clinical and endoscopic remission while on azathioprine at 3 mg/kg per day and infliximab at 5 mg/kg every 4 wk.

The laboratory results were unremarkable with no signs of systemic inflammation. A computed tomography scan revealed concentric wall thickening over 6 cm lengths in the sigmoid colon with narrowing of the lumen and prestenotic dilation but no regional lymphadenopathy. The bowel obstruction resolved with nasogastric tube suction and intravenous fluids. Colonoscopy confirmed the existence of a distal sigmoid stricture that precluded the passage of the conventional colonoscope (CF-Q160AL, Olympus Optical Co., Tokyo, Japan). A slim colonoscope (PCF-Q180AL Olympus Optical Co., Tokyo, Japan) was used to reach the terminal ileum. There were no endoscopic signs of inflammation. The colon was shortened and showed extensive scarring and some inflammatory polyps; the ileal mucosa appeared to be normal. Dysplasia and malignancy were excluded by several biopsies of the entire length of the stricture.

A short cycle of oral corticosteroids was completed, but the stricture was refractory to medical therapy, and the patient complained of abdominal pain and experienced a new episode of bowel obstruction in September 2011. After having discussed the therapeutic options in a gastrointestinal multidisciplinary team meeting, we decided to place a SX-ELLA BD biodegradable esophageal stent (ELLA-CS, Hradec Kralove, Czech Republic; Figure 1) with a trunk diameter of 20 mm flaring to 25 mm at both ends and a length of 100 mm. The local ethics committee approved the procedure, and informed consent was obtained from the patient.

The procedure was performed under conscious sedation (intravenous midazolam) *via* an anal approach with the patient lying on her left side. Both margins of the stricture were marked by using intramucosal lipiodol injection. The stent was loaded into its dedicated 28 French delivery system and implanted under endoscopic and fluoroscopic guidance over a stiff 0.035-inch guidewire with a soft tip (Jagwire, Boston Scientific, Natick, United States) that was previously introduced through the stricture. Pre-dilation was not performed. An adequate expansion of the stent occurred immediately after its insertion (Figures 2 and 3). Significant stent shortening occurred upon deployment, and a water-soluble contrast (Xenetix 350, Guerbet Laboratories, Roissy, France) was injected at the end of the procedure to confirm proper stent position and luminal patency. There were no immediate or delayed procedure-related complications, namely perforation, pain, hemorrhage or stent migration. The stent insertion provided rapid clinical improvement and symptom relief, and the patient was discharged within 24 h.

Figure 1 SX-ELLA biodegradable biodegradable esophageal stent. The stent is flared at both ends to reduce the risk of migration and is fitted with radiopaque markers at the midpoint and at the ends to enable precise stent positioning under fluoroscopic control. Because of reduced long-term elasticity, the stent is supplied separate from the delivery system and needs to be manually loaded just before the implantation procedure (see manufacturer's "Instructions for Use").

A clinical and radiographic follow-up was performed one week after the stent insertion and again one month later, with no evidence of stent migration. At that time, an endoscopy follow-up was also performed to monitor the stent patency and degradation. There was no significant mucosal hyperplasic reaction and no resistance to the progression of the conventional scope through the stent (Figure 2). Complete stent degradation was confirmed on a plain abdominal X-ray 4 mo after the insertion (Figure 3). There was no recurrence of the obstructive symptoms during a 16-mo follow-up.

DISCUSSION

We report a case of a patient with a long-standing CD who developed a symptomatic fibrotic stricture of the colon despite optimized medical treatment with infliximab and azathioprine. Fibrotic strictures in CD patients have been traditionally treated with intestinal resection, which is often extensive and associated with high morbidity rates[5]. Furthermore, disease recurrence is common. Within 4 years, approximately 40% of the patients will need another resection[6,7]. Concerns over short-bowel

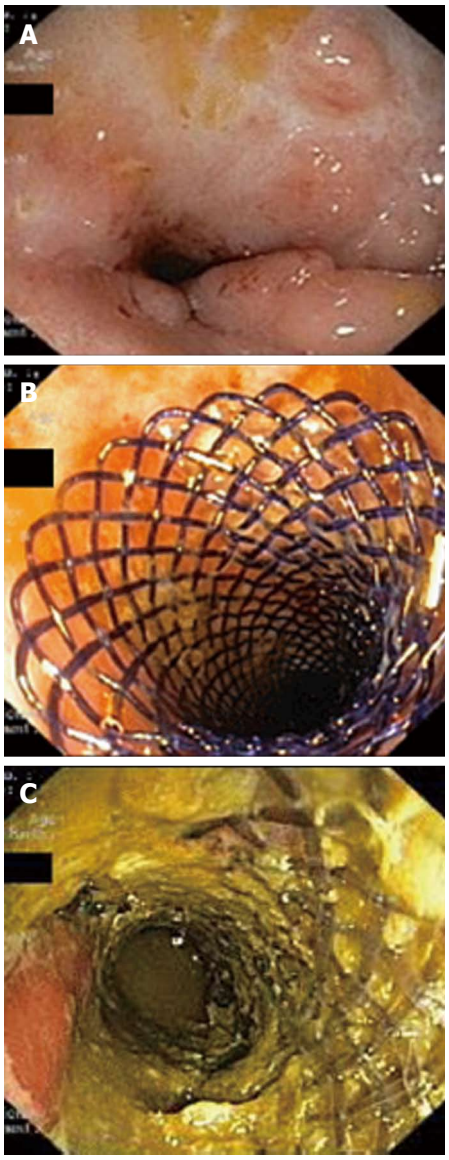

Figure 2 Endoscopic images. A: Stricture of the distal sigmoid colon before stent insertion. The surrounding mucosa show no signs of active inflammation and few inflammatory polyps; B: Biodegradable stent deployed in the stricture at the end of the procedure; C: Endoscopic view 1 mo after the stent placement. The stent fibers present a translucent appearance and partial fragmentation.

syndrome caused by multiple resections and large segment resections led to the development of bowel-sparing surgical techniques or strictureplasty, however, within 10 years, up to 50% of these patients will require repeated surgery because of obstruction recurrence[8]. Facing the problems related to repeated surgery, endoscopic methods have been advocated for managing CD strictures. Balloon dilation (with or without steroid injection) is currently the endoscopic treatment of choice. Several uncontrolled observational studies have shown that balloon dilation is a safe and effective alternative to surgery in selected patients. It has and has a technical success rate that ranges from 71% to 90% and a major complications rate of 2% to 3%[9-11]. However, it is generally accepted that strictures greater than 4 cm are not amenable to balloon dilation, and the recurrence rate of obstructive symptoms is as high as 42% with the need for repeated dilations and their associated perforation risk.

Our patient was not a candidate for balloon dilation because of the extent of the stricture, and surgical resection would likely have been extensive because of the scarring colon. Stent placement was thus considered. Compared with balloon dilation, stents determine slower and more sustained stricture dilation, resulting in reduced trauma and subsequent fibrosis. Furthermore, the radial force is maintained for several weeks, allowing remodeling of the stricture and increased long-term luminal patency with a reduced need for repeated dilations. However, data regarding the efficacy and safety of extractable SEMS in the treatment of symptomatic intestinal strictures in CD are limited and conflicting[12-16]. In general, the use of fully covered SEMS in this setting appears to be effective but has been associated with several drawbacks and complications, such as a high rate of spontaneous migrations and the need for removal, and remains controversial. The recently developed biodegradable stents are a promising option because of their longer patency and no need for removal, although radial force is lower compared with nitinol stents.

Biodegradable stents are manufactured from different synthetic polymers that have other well-established biomedical applications, particularly in the fields of sutures, tissue engineering and controlled drug delivery. The polymers are degraded by random hydrolysis of their molecules' ester bounds, and the degradation products are metabolized *via* normal metabolic pathways. This process compromises the structure and integrity of the stent filaments and leads to the loss of radial force, fracture of the stent skeleton and disintegration. The radial force of polydioxanone stents is maintained for approximately 6-8 wk following implantation and drops to 50% by week 9. Disintegration usually occurs within 11-12 wk, although the degradation rate is dependent on the size, structure, temperature, pH and type of body tissue in which the stent is implanted[17].

Biodegradable polydioxanone stents were developed and licensed for the treatment of refractory benign esophageal strictures[18-22]. The experience with their use in intestinal strictures is encouraging but still in its early stages. Published information regarding intestinal biodegradable stenting is limited to a few small case series that are both prospective and retrospective and focus on patients with refractory anastomotic colorectal strictures following resection for rectosigmoid carcinoma[23-25]. Rejchrt *et al*[26,27] reported the placement of biodegradable stents in patients with stricturing CD. This was the sole report of such a use in the small bowel and proximal large bowel. Proximal stent insertion was accomplished by use of a custom made introducer inserted into an overtube after endoscope removal. The standard delivery system for esophageal implantation has an active length of 75 cm and can only be used for intestinal strictures up to the distal descending colon.

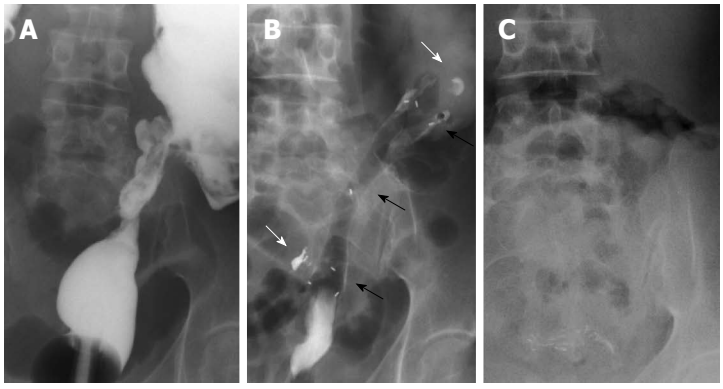

Figure 3 Radiographic images. A: Stricture of the distal sigmoid colon outlined by luminal filling with barium using a rectal catheter (supine position); B: Biodegradable stent *in situ* immediately after insertion (supine position). The stent is radiolucent, but the radiopaque markers at the midpoint and at the ends are visible (black arrows). The margins of the stricture are marked with lipiodol (white arrows); C: Disappearance of radiopaque markers at 4 mo confirming complete stent degradation (erect position).

Intestinal insertion of biodegradable polydioxanone stents is technically possible and relatively simple. However, it has been associated with a significant rate of early stent migration. This issue may be solved by improvements in stent design and appropriate strategies such as clip placement in the upper flare of the stents. It is necessary to clarify whether pre-dilation of the stricture should be performed (unless there is an inability to pass the delivery system through the stricture) because the radial force of biodegradable stents appears to be sufficient to ensure adequate stent expansion. Severe mucosal hyperplastic reaction resulting in obstruction after biodegradable stenting has been documented in esophageal strictures[28,29] but not in intestinal strictures thus far. Most of these cases were treated successfully with single balloon dilation and resolved completely after stent degradation. Neither of these complications was observed in our patient.

In conclusion, early experience suggests that biodegradable polydioxanone stents may represent a new therapeutic option for CD patients with refractory bowel strictures or strictures in which balloon dilation is unsuitable. Further studies are necessary to fully assess their long-term efficacy and safety in this clinical setting.

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CASE REPORT

Boerhaave's syndrome during bowel preparation with polyethylene glycol in a patient with postpolypectomy bleeding

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Abstract

Boerhaave's syndrome is spontaneous rupture of the esophagus, a rare condition with high mortality that occurs most often after forceful vomiting. Polyethylene glycol (PEG) solution is the most common preparation used for colonoscopy. Since large volumes have to be ingested, PEG may induce severe vomiting or retching. However, Boerhaave's syndrome has rarely been reported as a potential problem related to PEG solution. We report a case of spontaneous esophageal rupture due to violent vomiting during bowel preparation with PEG solution in a patient with postpolypectomy bleeding.

Key words: Esophageal perforation; Colonoscopy; Polyethylene glycols

Core tip: A bowel preparation with polyethylene glycol electrolyte solution should be used with care in patients with postpolypectomy bleeding.

Yu JY, Kim SK, Jang EC, Yeom JO, Kim SY, Cho YS. Boerhaave's syndrome during bowel preparation with polyethylene glycol in a patient with postpolypectomy bleeding. *World J Gastrointest Endosc* 2013; 5(5): 270-272 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i5/270.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i5.270

INTRODUCTION

Boerhaave's syndrome is a form of barogenic rupture caused by a sudden post-emetic rise in the intraluminal pressure in the distal esophagus[1]. Esophageal perforation has high mortality, which increases to 40%-60% when treatment is delayed beyond 48 h, leading to mediastinal sepsis and multisystem organ failure[2].

Electrolyte solution with sodium sulfate as the predominant salt and polyethylene glycol (PEG) was developed as an additional osmotic agent in 1980[3]. Since PEG-electrolyte lavage solutions were shown to be safe, well-tolerated, and highly effective in patients with renal failure or congestive heart disease, this became the most common method of preparation for colonoscopy[4]. The main disadvantage of PEG electrolyte solution is that large volumes have to be ingested. In addition, PEG electrolyte solution is poorly tolerated by some patients and may induce severe vomiting or retching[5]. Some cases of Mallory-Weiss syndrome have been reported following the ingestion of PEG-electrolyte solutions[6], but only a few cases of colonoscopy-related esophageal perforation[7-11].

CASE REPORT

A 61-year-old man underwent a screening colonoscopy.

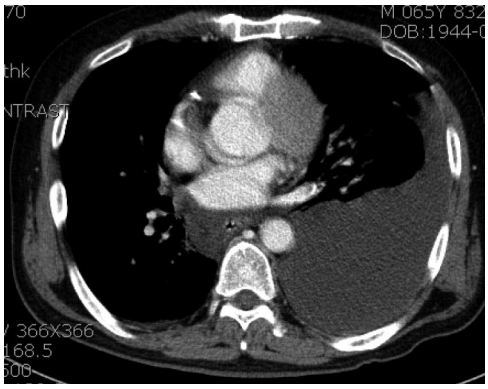

Figure 1 Chest computed tomography shows a left pleural effusion and peri-esophageal fluid collection.

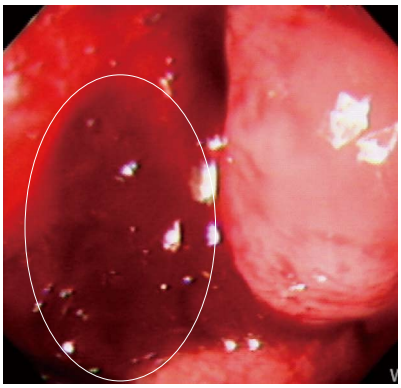

Figure 2 Upper endoscopy shows a 15 mm × 12 mm perforation with stigmata of recent bleeding distal to the Z-line on the left side of the esophagus.

He had been healthy without specific complaints and no significant past medical or family history. The colonoscopy revealed nine small (< 10 mm) sessile polyps from the ascending colon to the descending colon and a 16-mm lateral spreading tumor (LST) in the sigmoid colon. The polyps were resected by hot biopsy for the smaller polyps (< 5 mm), conventional snare polypectomy, or endoscopic mucosal resection for the LST. Hemoclips were applied to the postpolypectomy wound to prevent bleeding, except for the smaller polyps. There were no apparent complications after the colonoscopic polypectomy. Twenty-four hours later, the patient presented to the emergency room with hematochezia. After drinking 2 L of PEG electrolyte solution over a 2-h period for an urgent colonoscopy, the patient had several sudden attacks of vomiting associated with severe chest pain and dyspnea. A chest examination revealed decreased air entry in the lower left lung; there was no subcutaneous emphysema. Abdominal examination revealed tenderness in the epigastric region and right upper quadrant, but no guarding or rigidity. A chest X-ray showed a layered fluid collection in the left chest. Emergency computed tomography (CT) showed a left pleural effusion and peri-esophageal fluid collection (Figure 1), but the esophagus was not clearly identified and no free air or fluid was seen in the abdomen. A left chest drain was inserted and 800 mL of blood tinged fluid were drained. An emergent upper endoscopy revealed a 15 mm × 12 mm perforation with stigmata of recent bleeding distal to the Z-line on the left side of the esophagus, but the perforation could not be clearly demarcated due to blood (Figure 2). Therefore, we diagnosed the patient with Boerhaave's syndrome that developed during bowel preparation using PEG electrolyte solution. The patient took immediate surgical intervention where the primary repair of a ruptured esophagus was reinforced with a pedicled flap of the eighth intercostal muscle. Further evaluation for hematochezia was not performed because it was stopped spontaneously. The patient made an uneventful recovery following surgical management and was discharged soon after without complications, having made a complete recovery.

DISCUSSION

Esophageal perforation is uncommon condition with a high mortality rate. The causes include endoscopic instrumentation, trauma, swallowed foreign bodies, and Boerhaave's syndrome, which is the most serious form of esophageal perforation[2]. Boerhaave's syndrome is often misdiagnosed as acute pancreatitis, myocardial infarction, and peptic ulcer because of its rarity and nonspecific symptoms[1]. A delay in diagnosis leads to more extensive contamination and inflammation of the mediastinum and results in a poor outcome. The rupture in Boerhaave's syndrome is usually in the left lateral wall of the esophagus, just superior to the diaphragm[12]. This might be due to an anatomic weakness at that point. Distal esophageal perforations, most prevalent in Boerhaave's syndrome, commonly show a left-sided pleural effusion and pneumomediastinum on the chest X-ray[13]. The presence and magnitude of these findings are usually related to the length of time since the perforation. The diagnosis can be made earlier and more accurately with additional radiological examinations, such as CT. Since our patient had severe chest pain immediately after violent vomiting in the emergency room, we had a heightened index of suspicion for esophageal perforation and made the diagnosis without delay. The management is still controversial because the treatment modalities range from conservative measures to extensive surgery[12]. If the perforation is detected in less than 24 h, primary repair and wide irrigation of the mediastinum are usually possible[14]. However, when the treatment is delayed beyond 48 h, the treatment is not clear. Recently, endoscopic treatment with stenting allows for non-operative management in selected patients, even if data on endoscopic management of perforations in benign disease are limited[15]. The vacuum endo-sponge therapy, that is a kind of interventional therapy successfully for the treatment of anastomotic insufficiencies in upper gastrointestinal surgery, can be used for small perforation[11]. After the prompt diagnosis in our case, operative management was chosen because endoscopy showed a relatively large perforation. Moreover, the patient had

intractable chest pain and hypotension despite the chest tube drainage.

Nausea is a common adverse effect of the use of PEG electrolyte solution and vomiting is sometimes seen because of the large volume needed to clean the colon. Other adverse effects include urticarial reaction, anaphylaxis, hypothermia, obstruction-perforation, and cardiac arrhythmia[5]. Some cases of Mallory-Weiss syndrome after vomiting due to bowel preparation have been reported[6]. However, only five cases of esophageal perforation related to the use of the PEG electrolyte solutions have been described in the English literature[7-11]. Among these cases, the only reported death was of a patient who had been managed conservatively. This complication could have been avoided if the PEG-electrolyte solution had been given *via* a nasogastric tube before the colonoscopy. However, when administering the solution *via* a nasogastric tube, life-threatening complications such as aspiration and pulmonary edema after vomiting have been described[16]. In addition, anti-emetic medication during the preparation process can prevent this complication in patients who have a tendency to nausea and vomiting[11].

Urgent colonoscopy for acute lower gastrointestinal bleeding usually requires a PEG electrolyte solution purge, either orally or by nasogastric tube to rid the colon of clots, stool, and blood[17]. However, a recent study showed that a bowel preparation for an urgent colonoscopy is not always needed in postpolypectomy patients[18]. Therefore, a bowel preparation with PEG electrolyte solution should be used with care in patients with postpolypectomy bleeding.

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Is idiopathic recurrent pancreatitis attributed to small stones?

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Abstract

Idiopathic recurrent pancreatitis remains a clinical challenge. Intraductal ultrasonography in the management of idiopathic recurrent pancreatitis may be a new strategy for undetermined causes after initial diagnostic approaches, including endoscopic retrograde cholangio-pancreatography (ERCP). However, no definite cause after ERCP should be defined under optimal settings and with experienced technique.

Key words: Endoscopic retrograde cholangio-pancreatography; Idiopathic recurrent pancreatitis; Biliary stone

Core tip: The diagnosis of patients with idiopathic recurrent pancreatitis was revised after intraductal US used the criterion of 0.2-0.3 cm for common biliary duct stones. This implied that endoscopic retrograde cholangio-pancreatography (ERCP) could not be effective for identification of small biliary stones. For a more perfect ERCP study, an ERCP endoscopist should be aware that ERCP is a dynamic study, rather than image reading alone, and it should be possible to select an appropriate concentration of contrast medium for different conditions. Thus, even small stones could be detected without a second diagnostic tool.

Chow WK, Peng YC. Is idiopathic recurrent pancreatitis attributed to small stones? *World J Gastrointest Endosc* 2013; 5(5): 273-274 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i5/273.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i5.273

TO THE EDITOR

We read with interest the paper by Kim *et al*[1] entitled "The role of intraductal US in the management of idiopathic recurrent pancreatitis without a definite cause on endoscopic retrograde cholangio-pancreatography (ERCP)". It is difficult to identify possible causes and make a definite diagnosis in cases of idiopathic recurrent pancreatitis[2]. The authors provided some ideas about the diagnostic process of idiopathic recurrent pancreatitis with intraductal US. However, they did not find biliary stones initially by an ERCP study in cases that were defined as idiopathic recurrent pancreatitis. Their revised diagnosis after intraductal US used the criterion of 0.2-0.3 cm for common biliary stones. This implied that ERCP could not be effective without identification of small biliary stones. We strongly disagree with this implication. In our opinion, ERCP depends on the endoscopist's experience and technique.

Therefore, several points need to be clarified. Firstly, and most importantly, every ERCP endoscopist should be aware that ERCP is a dynamic study, rather than an image reading alone. Once contrast medium is injected into the biliary tract, fluoroscopy should be performed.

Any filling defect, contrast medium flow direction and pressure resistance should be monitored by the endoscopist. It is difficult to clearly define the injection pressure, which may be applied according to individual perception. However, any suspicious lesion should be reviewed immediately on X-ray film because X-ray film is better than fluoroscopy for identifying lesions.

Secondly, an experienced ERCP endoscopist should be able to select an appropriate concentration of contrast medium for different conditions. The radiation quantities depend on concentration of contrast medium, fluoroscopy time and total radiation[3]. Clinical experience suggests that small gallstones within large ducts may be better imaged with dilute contrast, whereas strictures and pancreatic duct anatomy are better imaged with full-strength contrast[4]. A concentration of about 50%-100% (150-300 mg iodine/mL) is usually used to identify opacified stricture lesions and a 25%-30% concentration is used to identify small filling defects in the common bile duct. With a higher concentration of contrast medium, small lesions may be omitted.

Thirdly, ERCP is highly technical and depends on the endoscopist's experience[3]. An experienced endoscopist should have clear concepts, skillful technique and the ability to identify most lesions in an ERCP study. A second diagnostic tool should not be a routine procedure for ERCP.

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Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5190/g_info_20100107135346.htm.

Abbreviations
Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing
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