ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 June 10; 8(11): 418-438

Published by Baishideng Publishing Group Inc

WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

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2014-2017

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WJGE World Journal of Gastrointestinal Endoscopy

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Biweekly Volume 8 Number 11 June 10, 2016

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ORIGINAL ARTICLE

Retrospective Study

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

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PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
June 10, 2016

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i11.418

World J Gastrointest Endosc 2016 June 10; 8(11): 418-424
ISSN 1948-5190 (online)

MINIREVIEWS

Management of gastric subepithelial tumors: The role of endoscopy

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Author contributions: Kim SY and Kim KO contributed equally to this work.

Conflict-of-interest statement: No author has any personal or financial conflict of interest.

Manuscript source: Invited manuscript

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Received: March 26, 2016
Peer-review started: March 27, 2016
First decision: April 19, 2016
Revised: April 28, 2016
Accepted: May 17, 2016
Article in press: May 27, 2016
Published online: June 10, 2016

Abstract

With the wide use of esophagogastroduodenoscopy, the incidence of gastric subepithelial tumor (SET) diagnosis has increased. While the management of large or symptomatic gastric SETs is obvious, treatment of small (≤ 3 cm) asymptomatic gastric SETs remains inconclusive. Moreover, the presence of gastrointestinal stromal tumors with malignant potential is of concern, and endoscopic treatment of gastric SETs remains a subject of debate. Recently, numerous studies have demonstrated the feasibility of endoscopic treatment of gastric SETs, and have proposed various endoscopic procedures including endoscopic submucosal dissection, endoscopic muscularis dissection, endoscopic enucleation, endoscopic submucosal tunnel dissection, endoscopic full-thickness resection, and a hybrid approach (the combination of endoscopy and laparoscopy). In this review article, we discuss current endoscopic treatments for gastric SETs as well as the advantages and limitations of this type of therapy. Finally, we predict the availability of newly developed endoscopic treatments for gastric SETs.

Key words: Subepithelial tumor; Endoscopy; Stomach; Treatment; Complication

Core tip: Recently, technical advances in endoscopic treatment, including diverse endoscopic procedures, have been performed for the resection of gastric subepithelial tumors (SETs). However, the presence of gastrointestinal stromal tumors with malignant potential is of concern and endoscopic treatment of gastric SETs remains of subject of debate. In this review article, we discuss current endoscopic treatments for gastric SETs as well as the advantages and limitations of this type of therapy. The information presented in this review should be taken into consideration when making decisions concerning endoscopic treatment for gastric SETs.

Kim SY, Kim KO. Management of gastric subepithelial tumors: The role of endoscopy. *World J Gastrointest Endosc* 2016; 8(11): 418-424 Available from: URL: http://www.wjgnet.

com/1948-5190/full/v8/i11/418.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i11.418

INTRODUCTION

The majority of subepithelial tumors (SETs) are considered to be benign in origin; however, some lesions may be malignant, especially if they originate in the muscularis propria (MP) layer[1]. Gastrointestinal stromal tumors (GIST), the most common mesenchymal neoplasms originating in the MP layer of the stomach, are malignant in 10%-30% of cases[2]. According to the National Comprehensive Cancer Network guidelines, all GISTs larger than 2 cm should be resected. For GISTs smaller than 2 cm without high-risk features on endoscopic ultrasonography (EUS), endoscopic follow-up may be recommended[3]. However, endoscopic surveillance has limitations, including delayed diagnosis of malignancy, high cost, hazards associated with repeated endoscopic procedures, patient discomfort related with long-term follow up examinations, and concerns associated with missing the optimum treatment window. Therefore, even for small sized gastric SETs originating in the MP layer, histological confirmation should be obtained if the tumor was not definitely differentiated as benign.

In the past, the standard treatment for gastric SETs was surgical resection, including laparotomy or laparoscopic partial gastrectomy[4], and endoscopy was used for diagnostic purposes, and was rarely used for treatment. However, surgical resection is invasive and associated with possible surgical complications. Recently, numerous reports have proposed that endoscopic resection can be applied to gastric SETs, including GIST[2,5-11]. The purpose of this article was to examine all practical endoscopic methods that should be taken into consideration when deciding whether to perform endoscopic treatment for gastric SETs. Through this process, we provide orientation for endoscopic treatment of gastric SETs.

WHY IS GASTRIC SET DIFFICULT TO TREAT WITH ENDOSCOPY?

Gastric SETs should be treated using endoscopic procedures; however, they remain challenging to treat. Several factors underlie the difficulties associated with endoscopic treatment. First, determining the possibility of malignancy for gastric SETs is difficult before resection. EUS and computed tomography (CT) can aid in but are by no means satisfactory for accurate diagnosis[5,12,13], and are limited in their ability to evaluate tumor size, fibrosis, and MP layer invasion. Thus, establishing a treatment strategy with endoscopy may be difficult. Endoscopic treatments alone do not guarantee complete resection and prevention of cancer recurrence for gastric SETs. Secondly, when endoscopic resection was performed in patients with gastric SETs originating from the MP layer, the complication rate was relatively high, especially for perforation[2,6]. Furthermore, endoscopic resection removes only the tumor without excision of the surrounding normal tissue; therefore, the tumor is likely to be incompletely resected[14-16]. Third, it is difficult to eliminate large or predominantly extraluminal growth of SETs by endoscopy alone[17]. Even the endoscopic full-thickness resection (EFTR) technique that enables treatment of relatively large gastric SETs cannot be used to treat tumors larger than 4 cm with an extraluminal pattern[18,19]. Lastly, the effectiveness of endoscopic treatment is highly affected by the location of the gastric SET. For instance, endoscope retroflexion should be maintained for gastric SETs located on the fundus or cardiac region, which has been shown to be difficult and to have a high perforation risk[20].

CONVENTIONAL AND MODIFIED ENDOSCOPIC SUBMUCOSAL DISSECTION FOR TREATMENT OF GASTRIC SETS

Endoscopic submucosal dissection (ESD) is an effective and safe tissue resection method for the treatment of early gastric cancer (EGC)[7,21]. Although the focus of this technique has been the treatment of EGC, its use has recently been expanded for the treatment of gastric SETs[7,15]. According to a recent study concerning endoscopic resection of SETs using ESD, the overall rate of R0 resection was 81.1% (30/37) and no recurrence was observed in patients with R0 resections during the follow up period[7]. In lesions that were incompletely resected, the tissue acquired was sufficient for all immunohistochemistry studies and, as a result, ESD can aid in confirming SET diagnosis. In a large study published in China, ESD was an effective and feasible treatment option for gastric SETs with diameters no greater than 50 mm originating in the MP layer[6]. The *en bloc* complete resection rate was 92.4% (134/145) and no recurrence was detected during the follow-up period. In our previous study[2], we discovered that tumors $\leqslant$ 2 cm in size or with a positive rolling sign, which indicates that the SET originated from the submucosal layer or has a narrow connection to the MP layer, had high complete resection rates. Moreover, we found that fixed tumor mobility and neurogenic tumors were significantly associated with perforation[2]. We anticipated that lower tumor mobility was associated with broad muscular connections or intramural-type or subserosal-type tumors, for which it is difficult to dissect the SET from adjacent muscle tissue. To treat gastric SETs, conventional ESD is feasible. However, complete resection rates were inconsistent for the MP layer (68.2%-92.4%), and perforation risk was high[2,6,7]. Specifically, endoscopic resection without perforation is challenging in the gastric fundus compared with other locations in the stomach. In a prospective study, conventional ESD using the "Resolution clip" was a feasible and easy method to prevent perforation of gastric fundus SETs[20]. However, this study

Table 1 Publications reporting conventional and modified endoscopic submucosal dissection for upper gastrointestinal subepithelial tumors originating in the muscularis propria

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Lee *et al*[15] (2006)	11	Cardia/body	20.7	60.9	ESD	75.0	0	10.9/N
Jeong *et al*[14] (2011)	64	Cardia/fundus/body/antrum	13.8	34.7	Endoscopic enucleation	92.3	12.3	10.0[1]/N
Liu *et al*[22] (2012)	31	Esophagus/cardia/stomach	22.1	76.8	EMD	96.8	12.9	17.7/N
He *et al*[6] (2013)	144	Cardia/fundus/body/antrum	15.1	63.4	ESD	92.4	14.5[2]/4.8[3]	19.1/N
Chu *et al*[8] (2012)	16	Cardia/fundus/body/antrum	26.1	52.0	Modified ESD with enucleation	93.8	0	14.8/N
Li *et al*[20] (2013)	11	Fundus	18.8	81.0	ESD	90.9	27.2	6.4/N
Chun *et al*[2] (2013)	35	Cardia/fundus/body/antrum	18.0	32.3	ESD	74.3	5.7	6.1/N

[1]Median follow-up period; [2]Perforation; [3]Bleeding. ESD: Endoscopic submucosal dissection; N: None; EMD: Endoscopic muscularis dissection.

in a relatively small number of patients showed a high perforation rate of 30%[20]. Therefore, conventional ESD is limited for removing SETs originating from the MP layer; modified ESD was introduced to solve these problems.

Various modified ESD techniques exist, consisting of a combination of ESD and endoscopic muscularis dissection (EMD). Depending on the degree of connection between the tumor and the muscularis layer, the application ratio of ESD and EMD can be determined. According to Liu *et al*[22], EMD was effective for treatment of gastric SETs originating in the MP layer. In their study, a longitudinal incision was made to cut the overlying mucosa, and electrical or blunt dissection was then used to dissect the SET from the submucosa and MP layers. Finally, the wound was closed with endoscopic clips[22]. Using this method, the complete resection rate was as high as 96.8%, but perforation was also high, at 12.9%. Many trials of SET endoscopic resection using conventional and modified ESD exist (Table 1). In a study published in South Korea, in which the mucosa covering the SETs was eliminated using a coagulation snare to reveal the hidden tumors, the successful complete resection rate by endoscopic enucleation was 92.3% (60/65)[14]; however, the perforation rate was comparatively high (12.3%). The most common location of perforation was the fundus, as it has a thin wall and is difficult to approach endoscopically. Moreover, all perforations occurred in schwannomas and GISTs; these tumors do not have intact tumor capsules and have tight adhesions[14]. Another study demonstrated the feasibility of modified ESD with enucleation for treatment of gastric SETs[8]. Two incisions were performed (longitudinal and transverse), which resulted in more obvious exposure of the tumor and its underlying MP layer, and an easier resection[8]. All tumors were larger than 2 cm, and the complete resection rate was 93.8% (15/16) with no perforation or overt bleeding[8]. This method demonstrates the beneficial results of endoscopic resection compared with surgical resection. Open or laparoscopic surgery can lead to late stenosis and gastroesophageal reflux after surgery, resulting in decreased patient satisfaction. Despite the advantages of endoscopic enucleation, several limitations, including the difficulty of complete removal of tissue with a large enough margin around the tumor[14], are associated with this method. Therefore, if the histologic diagnosis of a SET is highly malignant, clinicians should consider additional treatment. Moreover, in many studies, the follow-up period was short and research was performed at a single center.

ENDOSCOPIC SUBMUCOSAL TUNNEL DISSECTION FOR GASTRIC SETS

Inoue *et al*[23] (2010) investigated peroral endoscopic myotomy (POEM) for endoscopic treatment of achalasia. This method involves creating a submucosal tunnel to create space for endoscopic treatment under the mucosal layer, and can also be used to remove muscle layer lesions. The POEM procedure was applied to SETs originating in the MP layer, and was named endoscopic submucosal tunnel dissection (ESTD), which was introduced in 2012[10,24]. A mucosal incision was made proximal to the lesion, and a submucosal tunnel was created to resect the tumor completely using an electrosurgical knife. After removing the tumor, the mucosal layer was sutured using endoscopic clips. Compared with ESD, this method has several benefits, including fast wound healing and maintaining an intact mucosal layer, thus preventing leakage of bowel contents[10,25]. A Japanese study with a small sample size demonstrated that ESTD resulted in safe resection of SETs without complications[10]. Since then, other studies have shown the efficacy of ESTD for removal of SETs in the esophagus and the cardia, with compete resection rates of 100% (Table 2)[26,27]. According to Liu *et al*[26], esophageal and cardiac SETs originating

Table 2 Publications reporting endoscopic submucosal tunnel dissection for upper gastrointestinal subepithelial tumors originating in the muscularis propria

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Inoue *et al*[10] (2012)	7	Esophagus/cardia	19.0	152	Submucosal endoscopic tumor resection	100	0	5.5/N
Gong *et al*[24] (2012)	12	Esophagus/cardia	19.5	48.3	ESTD	83.3	16.7	NA
Liu *et al*[26] (2013)	12	Esophagus/cardia	18.5	78.3	tEMD	100	66.7	7.1/N
Ye *et al*[25] (2014)	85	Esophagus/cardia/stomach	19.2	57.2	STER	100	9.4	8[1]/N
Zhou *et al*[27] (2015)	21	Esophagogastric junction	23.0	62.9	STER	100	42.9	6[1]/N

[1]Median follow-up period. ESTD: Endoscopic submucosal tunnel dissection; N: None; NA: Not available; tEMD: Tunneling endoscopic muscularis dissection; STER: Submucosal tunneling and endoscopic resection.

in the MP layer were more easily dissected using ESTD than with EMD. Treatment of SET at the esophagogastric junction is difficult due to the interference of esophageal peristalsis and respiration with a detailed endoscopic view and control. ESTD allows for the endoscope to enter into the submucosal tunnel, improving visibility and enabling direct cutting. Moreover, SETs originating from the MP layer can be removed without damage to the mucosa around the lesion, diminishing procedure-related strictures and scars[27]. In another prospective study, ESTD was successful for the treatment of SETs located in the upper gastrointestinal tract, and revealed GIST and lesions in deeper MP layers as risk factors for complications[25]. The ESTD method is relatively safe and results in a high rate of complete resection; however, it is not without limitations. In the majority of studies, ESTD was performed for SETs of the esophagogastric junction, while few studies have been performed to determine the effect of ESTD on SETs of the stomach. Because the stomach mucosa is thick and has greater curvature, submucosal tunneling can be challenging in regions including the gastric fundus and the proximal corpus. Therefore, it is difficult to perform consistent tunneling of the stomach. In addition, large SETs (> 3 cm) are difficult to remove with ESTD because confines of tunneling space may give rise to poor endoscopic visualization and insufficient *en bloc* resection[10,25].

EFTR FOR GASTRIC SETS

Many gastric SETs originate in the deep MP layer. EFTR allows for *en bloc* resection of such SETs, including those tightly connected to the MP layer (Table 3)[18,19,28], which was first reported in 2001 in Japan[29]. In the past, EFTR was only applied to small lesions. The usefulness of EFTR with laparoscopy was reported in animals in a 2006 study; however, it also demonstrated the risk for perforation-induced intraperitoneal infections[30]. In 2011, Zhou *et al*[28] showed the feasibility of EFTR without laparoscopy for gastric SETs originating in the MP layer. This strategy was effective in treating deep gastric SETs with a complete resection rate of 100% (26/26) and no severe complications. These results were mirrored in another study published in China, in which EFTR resulted in successful complete resection (98.0%) without severe complications[18]. However, this study used clip closures and endoloop ligatures as additional closure devices[18], which may have strengthened the suturing technique to avoid gastric perforation. Moreover, endoloop ligatures are simple and do not require specific equipment. Recently, a new technique was introduced using endoscopic suturing devices in EFTR[11]; full-thickness sutures were deployed underneath the subepithelial mass and the SET was removed using an endoscopic electrocautery snare. This technique, explained by Schmidt *et al*[11] as "suture first, cut later", has several advantages including the fact that it is applicable to large tumors (up to 4 cm), it can be applied to tumors at all stomach sites, and it does not require laparoscopic assistance.

While EFTR is effective in treating gastric SETs originating in the MP layer, EFTR without laparoscopy has several limitations, as it is not suitable for the removal of very large tumors, it requires advanced endoscopic skills, and it has a high risk for perforation or peritonitis. Two reports published in Japan investigated the efficacy and feasibility of laparoscopic and endoscopic cooperative surgery (LECS) (Table 3)[31,32]. In this procedure, three-quarters of the tumor submucosal layer was dissected circumferentially using the ESD technique. Then, laparoscopic seromuscular dissection was performed at the three-quarter cut line around the tumor. Finally, the tumor was raised using laparoscopic forceps, and the resection was performed using laparoscopic stapling devices. This method is applicable to gastric SETs irrespective of tumor dimension and site. Additionally, this procedure only requires a minimal area of the stomach to be resected[31,32]. To avoid excessive normal gastric tissue removal, Abe *et al*[33] studied laparoscopy-assisted

Table 3 Publications reporting endoscopic full-thickness resection with or without laparoscopy for gastric subepithelial tumors

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Hiki *et al*[31] (2008)	7	Esophagogastric junction/stomach	46	169	LECS	100	0	NA
Abe *et al*[33] (2009)	4	Body	30	201	LAEFR	100	0	8/N
Tsujimoto *et al*[32] (2012)	20	Esophagogastric junction/body/antrum	37.9	157.5	LECS	100	0	20.7/N
Ye *et al*[18] (2014)	51	Fundus/body/antrum	24	52	EFTR	98	0	22.4[1]/N
Mitsui *et al*[36] (2014)	6	Body	22.7	273.5	NEWS	100	0	8/N
Schmidt *et al*[11] (2015)	31	Carida/fundus/body/antrum	20.5	60	EFTR	90.3	9.6[2]/38.7[3]	7 (roughly)/N

[1]Median follow up period; [2]Perforation; [3]Bleeding. LECS: Laparoscopic and endoscopic cooperative surgery; NA: Not available; LAEFR: Laparoscopy-assisted endoscopic full-thickness resection; N: None; EFTR: Endoscopic full-thickness resection; NEWS: Non-exposed endoscopic wall-inversion surgery.

endoscopic full-thickness resection (LAEFR) (Table 3); this technique is a hybrid of natural orifice transluminal surgery. Using the ESD technique, the tissue surrounding the gastric SET was circumferentially incised and the submucosal layer was dissected, and EFTR including the serosal layer was then performed surrounding approximately two-thirds to three-fourths of the tissue surrounding the SET. A laparoscopic full-thickness incision was made to resect and remove the remaining tumor in the peritoneal cavity. Finally, the stomach wall was sutured using laparoscopic hand-sewn closures without linear staples[33]. Advantages of LAEFR include ease and accuracy, a small resection margin, and it is inexpensive compared to other laparoscopic procedures[33]. In addition, an important advantage of LECS and LAEFR is that these methods are appropriate for the treatment of intraluminal gastric SETs in the MP layer. Another recent study showed that indications for endoscopic assistance during laparoscopic resection included growing type (intraluminal) tumors and a tumor size $\leqslant$ 18 mm[34]. It is difficult to determine the correct location and proper resection margin of these tumors by laparoscopy, which could result in excessive tissue elimination. Indeed, complications such as stenosis or deformity can occur. LECS or LAEFR could prevent these side effects, as the resection margin is determined through endoscopy[17].

Some researchers have developed new combinations of endoscopic and laparoscopic treatments for full-thickness resection. A combination of laparoscopic and endoscopic approaches to neoplasia using the non-exposure technique (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS) were developed to avoid malignant tumor dissemination during full-thickness resection[35,36]. The CLEAN-NET procedure involves mucosal marks made during endoscopy and four full-layer stay sutures to fix the mucosal layer to the seromuscular layer. Following submucosal injection of solution, the seromuscular layer is dissected using a laparoscopic electrocautery knife. Then, the full-layer specimen is lifted and dissected using a laparoscopic linear stapler. The CLEAN-NET procedure results in no transluminal communication; therefore, it reduces the risk of potential malignant seeding. However, CLEAN-NET has limitations, such as risk of a mucosal tear, and it is difficult to determine the incision line[35,37-39]. The NEWS procedure is performed as follows. A laparoscopic seromuscular dissection is performed after endoscopic submucosal injection. Then, the seromuscular layer is closed with a laparoscopic suture and the dissected portion is inverted to the luminal side. A circumferential mucosal incision and mucosal layer dissection are made using the ESD technique. The NEWS procedure has various benefits. Similar to CLEAN-NET, the NEWS procedure avoids potential cancer seeding into the peritoneal cavity. Also, it ensures an accurate resection line. The disadvantages of the NEWS procedure are that it is time-consuming and tumor size is limited[5,36,38-40]. The CLEAN-NET and NEWS procedure are effective novel hybrid techniques. However, these methods are rarely applied to treat gastric SETs. Therefore, further studies of these methods are needed for application to gastric SET treatment.

CONCLUSION

To expand the role of endoscopy for the treatment of gastric SETs, several problems must be resolved. First, it is important to determine ways in which to reduce complications associated with endoscopic treatment, focusing specifically on perforation. Carbon dioxide insufflation during endoscopic procedures could be considered as it may reduce the risk of emphysema and pneumoperitoneum[9,27]. Several closing devices for the prevention of procedure-induced perforation have been also described[19,20]. Indeed, methods including OTSC and the "Resolution clip" are efficient in reducing perforation. However, these only apply to a few patients with small perforations and specific lesions sites, and

are not suitable for larger SETs. Thus, the development of new methods to address this limitation is warranted. Secondly, the mean follow-up period of the majority of the studies presented in this review was under 2 years. Although complete resection was preceded by endoscopic treatment, gastric SETs with malignant potential have a risk of recurrence. Therefore, further studies with longer-term follow-up periods and appropriate follow-up duration guidelines after endoscopic SET treatment are required. Next, until now, most studies were performed at a single institute, were retrospective in nature, and only included a small number of participants. Due to the characteristic of SETs, recruitment of a large sample size can be difficult and, thus, may introduce statistical errors including selection bias. Therefore, larger prospective multicenter studies or meta-analyses studying the effects of endoscopic treatment in gastric SETs are warranted. Moreover, the limitations involving large gastric SETs or tumors of the esophagogastric junction or posterior wall must be resolved. As ESTD showed promising results for the treatment of gastric SETs located on the esophagogastric junction, appropriate procedures for other difficult locations should be developed. Finally, a hybrid approach combining endoscopy and laparoscopy should be considered. This method has the advantage of preserving the volume and function of the stomach, and may increase a patient's satisfaction with the procedure. In addition, novel hybrid techniques (CLEAN-NET and NEWS) avoid exposing malignant SETs to the peritoneal cavity. In conclusion, technical modifications and improvements are required to define the role of endoscopy for treating gastric SETs.

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P- Reviewer: Arigami T **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

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DOI: 10.4253/wjge.v8.i11.425

World J Gastrointest Endosc 2016 June 10; 8(11): 425-432
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Endoscopic retrograde cholangiography for pediatric choledocholithiasis: Assessing the need for endoscopic intervention

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Author contributions: Fishman DS designed and performed the research and wrote the manuscript; Chumpitazi BP designed and performed the research, wrote the manuscript and edited and approved the final manuscript; Raijman I designed the research, supervised the report, contributed to the analysis, edited and approved the final manuscript; Smith EO performed the statistical analysis and supervised the report; Tsai CMW and Mazziotti MV contributed to the analysis, edited and approved the final manuscript; Gilger MA designed and performed the research, supervised the report and contributed to the analysis and final editing and approval of the manuscript.

Institutional review board statement: This study was approved by the Baylor College of Medicine Institutional Review Board.

Informed consent statement: A waiver for informed consent was approved by the Baylor College of Medicine Institutional Review Board. Patients were not required to give informed consent to the study because subjects had previously received standard of care; the study could not be completed without the waiver; and all precautions were taken to prevent loss of private health information.

Conflict-of-interest statement: Dr. Douglas Fishman is on an advisory board for Norgine Pharmaceuticals, and has served as a consultant for Cook Medical. Dr. Raijman is a speaker and consultant for Boston Scientific. Dr. Chumpitazi has received research support from QOL Medical, Inc. and is a consultant for Mead Johnson Nutrition.

Data sharing statement: No additional data are available.

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Received: November 13, 2015
Peer-review started: November 16, 2015
First decision: January 4, 2016
Revised: February 16, 2016
Accepted: March 7, 2016
Article in press: March 9, 2016
Published online: June 10, 2016

Abstract

AIM: To assess pediatric patients for choledocholithiasis. We applied current adult guidelines to identify predictive

factors in children.

METHODS: A single-center retrospective analysis was performed at a tertiary children's hospital. We evaluated 44 consecutive pediatric patients who underwent endoscopic retrograde cholangiography (ERCP) for suspected choledocholithiasis. Patients were stratified into those with common bile duct stones (CBDS) at ERCP *vs* those that did not using the American Society of Gastrointestinal Endoscopy (ASGE) guidelines (Very Strong and Strong criteria) for suspected CBDS.

RESULTS: CBDS were identified in 84% at the time of ERCP. Abdominal ultrasound identified CBDS in 36% of patients. Conjugated bilirubin $\geqslant$ 0.5 mg/dL was an independent risk factor for CBDS (P = 0.003). The Very Strong (59.5%) and Strong (48.6%) ASGE criteria identified the majority of patients (P = 0.0001). A modified score using conjugated bilirubin had a higher sensitivity (81.2% *vs* 59.5%) and more likely to identify a stone than the standard criteria, odds ratio of 25.7 compared to 8.8. Alanine aminotransferase and gamma-glutamyl transferase values identified significant differences in a subset of patients with odds ratio of 4.1 and 3.25, respectively.

CONCLUSION: Current adult guidelines identified the majority of pediatric patients with CBDS, but specific pediatric guidelines may improve detection, thus decreasing risks and unnecessary procedures.

Key words: Endoscopic retrograde cholangiography; Pediatric; Endoscopy; Choledocholithiasis; Children; Gallstones; Abdominal ultrasound

Core tip: In pediatric patients with gallstones, biliary obstruction has been reported in up to 30% of patients with limited data to predict need for endoscopic retrograde cholangiography for choledocholithiasis. In this single-center retrospective study we evaluated 44 consecutive pediatric patients and used the American Society of Gastrointestinal Endoscopy guidelines for suspected choledocholithiasis. We found that the Very Strong and Strong criteria identified the majority of patients. Conjugated bilirubin was also identified as an important predictor. Current adult guidelines can be used in the majority of patients, but specific pediatric guidelines may improve detection, thus decreasing risks.

Fishman DS, Chumpitazi BP, Raijman I, Tsai CMW, Smith EO, Mazziotti MV, Gilger MA. Endoscopic retrograde cholangiography for pediatric choledocholithiasis: Assessing the need for endoscopic intervention. *World J Gastrointest Endosc* 2016; 8(11): 425-432 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i11/425.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i11.425

INTRODUCTION

Choledocholithiasis can complicate symptomatic gallstones in up to 10% of adults at cholecystectomy[1]. Children may be at higher risk with recent studies demonstrating up to 30% of patients evaluated for pediatric gallbladder disease having some form of complicated bile duct obstruction as evidenced by jaundice, pancreatitis, or imaging with a visualized stone or dilated bile duct[2-4]. As in adult patients with choledocholithiasis, management options in children include both endoscopic and surgical methods. However, normal laboratory value differences and differences in bile duct size between pediatric and adults patients pose further challenges to appropriate patient selection for the management of pediatric choledocholithiasis.

Multiple studies in adult patients have evaluated specific keys in identifying common bile ducts stones at endoscopic retrograde cholangiography (ERCP)[5-9]. Algorithms and scoring systems have been developed in order to identify patients with a high likelihood of having common bile duct stones (CBDS) that would benefit from treatment with ERCP, or other modalities such as laparoscopic cholecystectomy with intraoperative cholangiogram.

Current American Society of Gastrointestinal Endoscopy (ASGE) guidelines stratify adult patients using several predictors[10]. A probability of stone identification of greater than 50% at ERCP is set as an appropriate level of detection of CBDS. These conditions are met if any of the following were identified: The value of total bilirubin (measured in mg/dL) was greater than 4, a CBDS is visualized by trans-abdominal ultrasound, or the presence of cholangitis. If both the CBD diameter was greater than 6 mm by ultrasound and the total bilirubin was greater than 1.8 mg/dL, ERCP was recommended and considered to meet the 50% threshold. When present these factors were useful for CBDS prediction, while other factors such as age greater than 55 years old, presence of gallstone pancreatitis and abnormal markers of liver and biliary inflammation [*e.g.*, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γGT), and alkaline phosphatase] were less likely to predict CBDS. In contrast, limited data and recommendations are available for the management of suspected CBDS or gallstone pancreatitis in children[11-13]. The aim of our study was to determine the applicability of the current ASGE guidelines in pediatric patients with suspected CBDS and to identify other factors that may be predictive in the pediatric population.

MATERIALS AND METHODS

Retrospective analysis was performed on consecutive ERCPs in children ages 6-18 years of age, performed over 24 mo. Cases were reviewed for patients with suspected common bile duct stones with gallbladder *in situ* evaluated in the hospital or emergency department. Patients were excluded if they were status post-

Table 1 Demographics of patients with suspected choledocholithiasis

Group number		1	2	Total
n		37	7	44
Mean age		14.5 (± 3.8)	14.5 (± 2.0)	14.5 (± 3.5)
Sex	Male	14	0	14
	Female	23	7	30
Ethnicity	White	4	2	6
	African-American	12	0	12
	Latino-Hispanic	20	5	25
	Other	1	0	1
Imaging	CBDS on US	16	0	16
	No CBDS on US	21	7	28
	CBDS on MRCP	6 of 8	3 of 6	9 of 14
Clinical	Gallstone pancreatitis	11	4	15

CBDS: Common bile duct stone; US: Ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

cholecystectomy, had ERCP for another indication, or ultrasound (US) results were not available. Presence of CBDS by US and bile duct diameter (measured in millimeters) were recorded. Bilirubin (unconjugated and conjugated) and other laboratory values were captured pre-procedure (within 24 h). This study approved by the Institutional Review Board at Baylor College of Medicine, Houston, Texas.

For the purposes of this study, total bilirubin was calculated as the sum of unconjugated and conjugated bilirubin levels. Normal values for unconjugated bilirubin at our institution is 0-1.0 mg/dL, and for conjugated bilirubin is 0-0.3 mg/dL. Biliary cannulation and sphincterotomy was performed in all patients at the time of the procedure. Patients were classified into two groups; Group 1, patients with CBDS found at ERCP and Group 2 those without CBDS at ERCP.

ASGE guidelines to predict the likelihood of detecting CBDS at ERCP were used to classify patients[10]. Predictors per ASGE guidelines were: Very Strong (VS) if CBDS was identified on abdominal US or total bilirubin > 4 mg/dL or Strong (S) if both CBD diameter $\geqslant$ 6 mm on US and bilirubin $\geqslant$ 1.8-4 mg/dL.

Patients were assessed on each of the following ASGE factors: (1) Visualized CBDS on ultrasound imaging; (2) CBD diameter > 6 mm on ultrasound imaging; and (3) Total bilirubin level.

For subset analysis, patients were divided into one of two groups: VS: Either CBDS on US or total bilirubin > 4, or those meeting S criteria, with the combination of having both a total bilirubin > 1.8 and a CBD diameter of > 6 mm.

Statistical analysis

SPSS (Statistical Package for the Social Sciences, IBM, Armonk, NY) Version 19.0 was used for statistical calculations. χ^2 with McNemar's test to compare correlated groups was used with interquartile range (IQR) and medians and percentiles calculated for continuous data. Similarly, Mann-Whitney test was used to compare groups with non-parametric data and the Mantel-Haenzsel test was used to calculate a Common Odds Ratio Estimate. A *P*-value of < 0.05 was considered to be statistically significant. Unless otherwise specified, values are presented as median with interquartile range in parentheses. Confidence intervals were calculated using http://vassarstats.net/clin1.html. The statistical methods of this study were reviewed by Dr. Smith, biostatistician, Baylor College of Medicine.

RESULTS

Forty-four consecutive children with gallbladder *in situ* hospitalized for evaluation of suspected CBDS were evaluated. The median age was 15.4 years (ages 6-18 years old) (Table 1). Eight of 44 patients (18.2%) had hemolytic disease. Gallstone pancreatitis was the initial presentation in 15 patients (34%). Forty-three/forty-four patients had general anesthesia, and the remaining patients received deep sedation with intravenous midazolam and propofol. Magnetic resonance cholangiopancreatography (MRCP) was performed in 14/44 patients, and identified choledocholithiasis in 9 of 14. ERCP identified stones in 84% (*n* = 37), referred to as Group 1. In Group 2, (*n* = 7) that did not have CBDS at ERCP, common bile duct dilation > 6 mm was evident in 85.7% (*n* = 6), and all had endoscopic or radiographic findings suspicious for papillary stenosis, suprapapillary stricture from stone passage or recent pancreatitis. All patients had a native papilla, and sphincterotomy was performed at time of the procedure. No patients had a clinical picture of cholangitis. Adverse event rates in both groups were similar, with one case of mild pancreatitis in each group.

Use of abdominal US in diagnosis of CBDS

All patients had abdominal ultrasound performed and a portion of the common bile duct was visualized in all but one patient (43/44). CBDS were identified by US in 36% (*n* = 16), and this differed from the 85% (*n* = 37) found to have CBDS by ERCP (*P* = 0.029). Sensitivity of US for CBDS was poor, 43% (95%CI: 28%-60%), with specificity 100% (95%CI: 56%-100%), positive predictive value (PPV) of 100% (95%CI: 76%-100%) and a negative predictive value (NPV) of 25% (95%CI: 11%-45%).

The median CBD diameter in Group 1 was 9.0 mm (7.0, 11.0) and 8.0 mm (6.1-10.0) in Group 2 (Table 1). A CBD greater than 6 millimeters was demonstrated in 36 (81.8%) patients, 30 in Group 1 and 6 in Group 2 (*P* = NS). The combination of ultrasound findings of CBDS and a dilated bile duct > 6 mm was seen in 15 patients (34.1%). Twenty-two patients had one or the other, 16 in Group 1 and 6 in Group 2. Seven patients had a CBD diameter of less than 6 mm or CBDS by ultrasound, and the majority (84%) were in Group 1. Conversely, all 6 patients in Group 2 had a bile duct diameter > 6 mm.

Table 2 Univariate analysis of clinical parameters with interquartile ranges

	Combined group data median (IQR)	Group 1 median (IQR)	Group 2 median (IQR)
Age (yr)	15.8 (12.5, 17.3)	16.1 (12.2, 17.3)	14.8 (12.5, 15.4)
Time to procedure (d)	2 (1.0, 2.3)	2 (1.0, 2.0)	2 (1.0-3.0)
US CBD diameter (mm)	8.8 (6.8, 10.5)	9 (7.0, 11.0)	8 (6.1-10.0)
ERCP CBD diameter (mm)	11 (9.0, 13.0)	11 (9.3, 13)	9 (7.0, 10.0)
Total bilirubin (mg/dL)	2 (0.8, 3.6)	2.5 (0.9, 3.8)	0.9 (0.6-1.5)
Conjugated bilirubin (mg/dL)	1 (0.0-2.1)	1.3 (0.0, 2.4)	0 (0, 0)
ALT (u/L)	242 (142.5, 386.5)	253 (145.0, 403.0)	166 (122.0-166.0)
AST (u/L)	128 (86.0, 188.0)	129 (89.0, 215.0)	119 (53-150)
γGT (u/L)	259 (177.0, 453.5)	259 (181.0, 521.0)	203 (159.0-333)
Alkaline phosphatase (u/L)	252 (179.0, 349.0)	254 (182.0, 405.0)	208 (107.0-256.0)

Combined group data, Group 1 (patients with CBDS) and Group 2 (patients without CBDS). IQR: Interquartile range; CBD: Common bile duct; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γGT: Gamma-glutamyl transferase; US: Ultrasound; ERCP: Endoscopic retrograde cholangiography.

Although it would be expected that in the presence of a larger bile duct, a greater chance for CBDS would be found but this was not the case emphasizing the importance of using multiple parameters in making the clinical assessment.

Serum bilirubin was measured in all patients (Table 2 and Figure 1). There were significant differences between Group 1 and 2 for mean values of total bilirubin (P = 0.004) and conjugated bilirubin P = 0.02 (0.004 including patients with hemolytic disease). In Group 1, 8 (22%) patients had a total bilirubin greater than 4 mg/dL, while none did in Group 2 (P = 0.0001). Twenty-one (58%) patients in Group 1 and 1 patient in Group 2 had total bilirubin > 1.8 mg/dL (P = 0.0001). In comparison, 25 (68%) patients in Group 1 had a conjugated bilirubin ⩾ 0.5 mg/dL, and none in Group 2 (P = 0.003). Sensitivity was also higher using conjugated bilirubin ⩾ 0.5 mg/dL than cut-offs of total bilirubin of 4 or 1.8 mg/dL (Table 3). Multivariate logistic regression identified conjugated bilirubin ⩾ 0.5 mg/dL as an independent risk factor for detection of CBDS.

Categorization using current ASGE guidelines in management of CBDS

Determinations for each patient were made as to whether patients met the ASGE VS or S criteria (Table 3). As expected, there was a significant difference between patients in Group 1 and 2 using the VS criteria to stratify patients (P = 0.0001). The sensitivity for CBDS at the time of ERCP in our population using VS criteria was 59.5%, compared to 48.6% in the patients meeting S criteria (Table 3). Specificity ranged from 86%-100% for each of the VS and S categories.

Development of "modified" pediatric parameters in management of CBDS

Because conjugated bilirubin levels are a prominent finding in obstruction and a component in the liver panel/biochemistries at many pediatric facilities, conjugated bilirubin was substituted for total bilirubin. Thus, ⩾ 0.5 mg/dL was substituted into both the VS and S categories. A VS "Pediatric Modified" (VS-PM) criteria was defined as either a stone visualized on US or a conjugated bilirubin ⩾ 0.5 mg/dL. To meet the Strong "Pediatric modified" criteria (S-PM), a patient needed to have a bile duct diameter > 6 mm and a conjugated bilirubin ⩾ 0.5 mg/dL. In comparing patients in Group 1 and 2 using the VS-PM there was not a significant difference (P = 0.07) but significant using the S-PM criteria, (P = 0.001). An imputed odds ratio for a child meeting VS-PM criteria was calculated to be 25.7 times more likely to have a stone at ERCP, and 8.8 times more likely in those meeting S-PM criteria. The VS-PM and S-PM criteria also had improved sensitivity when compared to the respective adult criteria, up to 81.2% for identifying a CBDS at time of ERCP. The S-PM performed as well as the adult VS criteria, both with sensitivities of 59.5% (Table 3).

Use of aminotransferases and γGT in diagnosis of CBDS

Both ALT and AST levels were collected (Table 2 and Figure 1). The mean ALT and AST were not significantly different between Group 1 *vs* Group 2 (P = 0.127 and 0.149, respectively). When an arbitrary cut-off for ALT of 350 u/L was used, the differences between the two groups was significant (P = 0.0001), but not at 300 u/L (P = 0.052). Given that aminotransferases are elevated in hemolysis, when patients with hemolytic disease (n = 7) were excluded there was still a significant difference between means in Group 1 and 2 (P = 0.027).

Additionally, γGT is known to be elevated during biliary obstruction as a surrogate marker of biliary obstruction. The median γGT in patients with CBDS was 259 u/L (181-521) compared to 203 u/L (159-333) in those without CBDS at ERCP (P = 0.268). When a γGT cut-off level of 400 u/L was used, a high sensitivity and positive predictive value were seen (P = 0.0001). These findings suggest that aminotransferases and γGT may be of value in the prediction of CBDS in children.

DISCUSSION

While several groups have reported their experience using ERCP in pediatric patients, to our knowledge

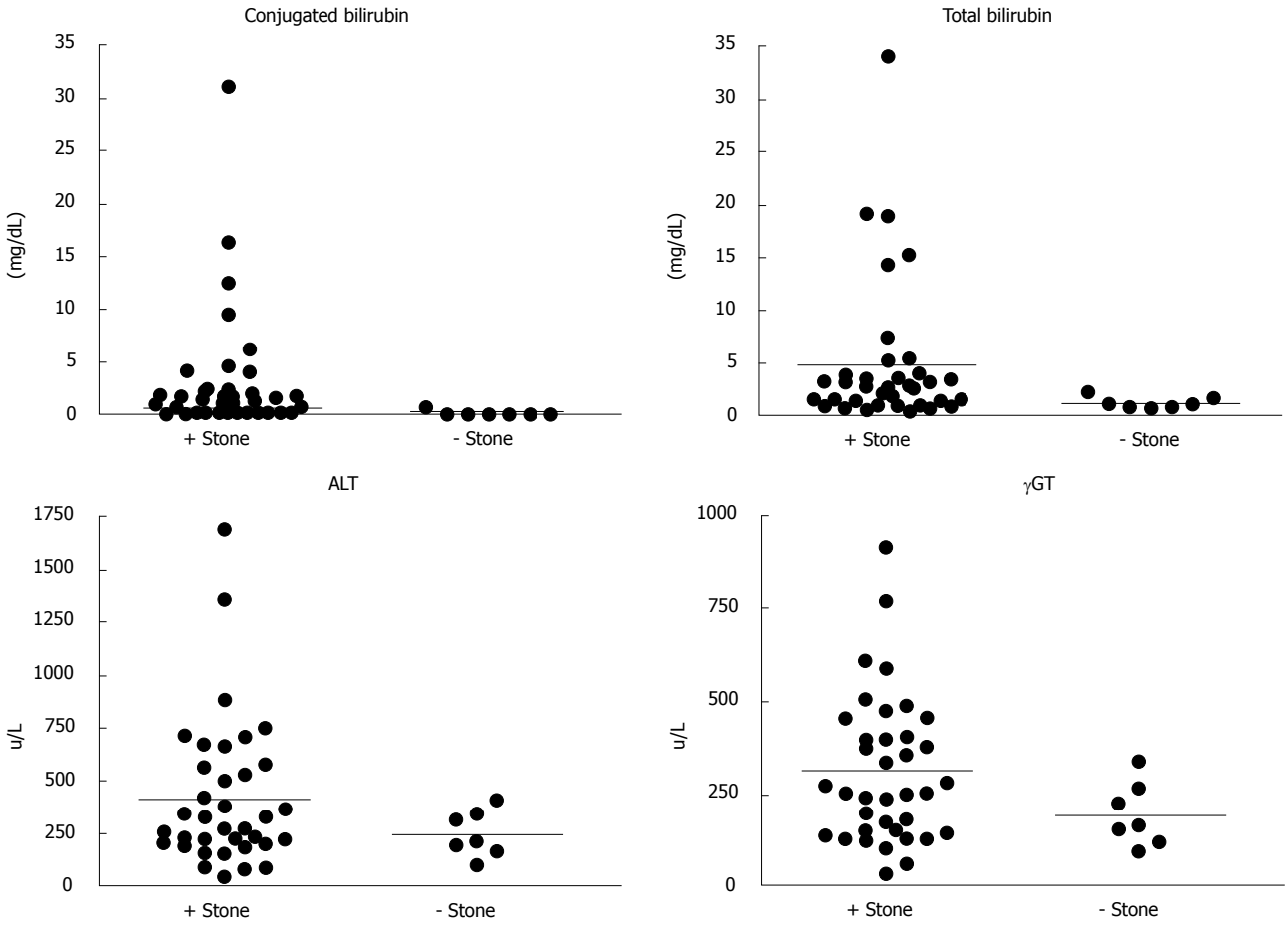

Figure 1 Laboratory comparison of patients with common bile duct stones at endoscopic retrograde cholangiography. Laboratory parameters (conjugated bilirubin, total bilirubin, alanine aminotransferase, and gamma-glutamyl transferase) in patients with and without stones. ERCP: Endoscopic retrograde cholangiography; ALT: Alanine aminotransferase; γGT: Gamma-glutamyl transferase.

this is the first series to evaluate the management of choledocholithiasis using current clinical practice guidelines[13-15]. The ASGE guidelines published in 2010 utilize ultrasound findings of CBD stones or common bile duct diameter, total bilirubin, age, and presence of cholangitis to identify patients at highest risk for CBDS[10]. We classified a series of pediatric patients with suspected choledocholithiasis that underwent ERCP using these criteria at an acceptable sensitivity of 59.5 (VS) and 48.6% (S). However, we found that using conjugated bilirubin instead of total bilirubin improved the sensitivity for CBDS identification to 81%. However in practice, deciding on ERCP in those without a visualized stone on initial imaging and mild elevations or normal bilirubin is quite challenging. In this setting both the standard and modified pediatric strong criteria are important. In our subset of patients, the S-PM had a higher sensitivity than the standard criteria, and the same specificity. These criteria are dependent on both abnormal bilirubin and ductal dilatation, but in both criteria the major driver is the bilirubin level as even in children ductal dilatation is quite common in stone related disease.

The majority of published series and accepted guidelines in adults use identification of CBDS and bile duct diameter by trans-abdominal ultrasound as critical determinants[5-10]. The sensitivity of ultrasound for CBDS is reported up to 55% in adults, whereas in our series only 43% of patients had CBDS identified by ultrasound[16]. Additionally, the sensitivity of the modified VS criteria exceeded the lower limit of sensitivity for CBDS detection by ultrasound. Normal common bile duct diameters in adults are reported to be 4-6 mm, with small increases with advancing age[17]. A common bile duct diameter greater than 6 mm suggests obstruction and is used in the current ASGE guidelines. Early studies of pediatric common bile duct diameter using intravenous cholangiography, demonstrated an upper limit of 6 to 7 mm in children and that they were more distensible than adult bile ducts[18,19]. By ultrasound, the common bile duct in early adolescence should not exceed 2.5-3.0 mm, although values for teenagers are largely based on adult normative values[14,16,18-20]. In our series, patients in Group 2, had a median common bile duct diameter of 8 mm, suggesting some discrepancy in what should be considered abnormal or inflammatory change from a recently passed stone. For this reason and in keeping with current guidelines, a 6 mm cut-off was used for data

Table 3 Univariate characteristics in the evaluation of choledocholithiasis

Criteria	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Odds ratio (95%CI)	*P*-value
VS-PM	81.2 (64-91)	85.7 (42-99)	96.8 (81-100)	46.2 (20-74)	25.7 (2.65-249)	0.07
S-PM	59.5 (42-75)	85.7 (42-99)	95.7 (76-100)	28.6 (12-52)	8.8 (0.96-80.7)	0.001
VS-Adult	59.5 (42-75)	100 (56-100)	100 (81-100)	31.8 (15-55)	[1]8.8 (0.96-80.7)	0.0001
S-Adult	48.6 (32-65)	85.7 (42-99)	94.7 (72-100)	24 (10-45)	5.68 (0.62-51.97)	0.0001
CBDS by US	43.2 (28-60)	100 (56-100)	100 (76-100)	25 (11-45)	[1]4.57 (0.50-41.9)	0.0001
CBD > 6 mm	81.1 (64-91)	14.3 (1-58)	83.3 (67-93)	12.5 (1-33)	0.714 (0.074-6.92)	1
CBD > 8 mm	91.7 (76-98)	28.6 (5-70)	86.8 (71-95)	40 (7-83)	4.4 (0.58-33.2)	0.727
TB > 4.0	21.6 (10-39)	100 (56-100)	100 (60-100)	19.4 (8-37)	11.66 (0.17-15.82)	0.0001
TB ≥ 1.8	56.8 (41-71)	85.7 (49-97)	95.5 (75-100)	27.3 (12-50)	7.88 (0.86-72.12)	0.0001
CB ≥ 0.5	67.6 (50-81)	85.7 (42-99)	96.2 (78-100)	33.3 (14-59)	12.5 (1-115)	0.003
ALT > 300	56.8 (40-72)	14.3 (1-58)	77.8 (57-91)	5.9 (0-31)	0.219 (0.024-2.00)	0.052
ALT > 350	40.5 (26-57)	100 (56-100)	100 (80-100)	24.1 (11-42)	[1]4.1 (0.45-37.5)	0.0001
AST > 155	43.2 (28-60)	85.7 (42-99)	94 (69-100)	22.2 (9-43)	4.57 (0.499-41.9)	0.0001
γGT > 400	35.1 (21-53)	100 (56-100)	100 (72-100)	22.6 (10-42)	[1]3.25 (0.352-30.0)	0.0001

[1]A zero denominator was substituted with a unit of one for odds ratio only. Includes sensitivity, specificity, positive predictive value, and odds ratio. *P*-values were calculated for each category for differences between patients with and without stones using McNemar's test. PPV: Positive predictive value; NPV: Negative predictive value; VS-PM: Very Strong Pediatric "Modified"; S-PM: Strong Pediatric "Modified"; VS-Adult: Very Strong Adult; S-Adult: Strong Adult; CBDS: Common bile duct stone; CB: Conjugated bilirubin; TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γGT: Gamma-glutamyl transferase; CBD: Common bile duct.

analysis. Using a CBD diameter of 6 mm in the scoring is reasonable for older pediatric patients and likely to improve sensitivity of CBDS detection children compared to adults. However, an 8 mm cut-off compared to 6 mm for CBD diameter had improved sensitivity, with modest increase in PPV, NPV and specificity.

Both MRCP and endoscopic ultrasound (EUS) are commonly used in the pre-procedure management of choledocholithiasis[21]. MRCP use in pediatrics is common[22,23]. However, some patients require sedation or anesthesia, and access is sometimes limited. There is an expanding experience and accessibility of EUS in pediatric patients[24-27]. In a recent study by Adams *et al*[28], EUS and MRCP were used along with ERCP to identify the likelihood of CBDS in patients. Specific utilization of EUS and MRCP was not reported, however, using these modalities in addition to available guidelines and laboratory investigations, overall sensitivity and specificity were improved[28]. Despite the limited use of MRCP and no cases of EUS, in our population, CBDS at the time of ERCP were identified in 84% of patients.

One limitation of our study was the variation in timing of patient presentation to abdominal ultrasound to ERCP from 1 to 6 d. However, the majority of procedures occurred less than 48 h of presentation with a mean of 1.9 (± 1.3) d. Approximately one-fourth of patients had MRCP prior to ERCP, frequently extending time to definitive procedure by 12-24 h. In the patients with a positive MRCP, but negative CBDS, that variability was accentuated and likely contributed to the passage of stones during the interim period. Timing of MRCP and its relationship to ERCP should be considered when planning procedures. Due to restrictions or delays in either of these modalities, it can be expected to have some stone passage, but these should be mitigated by process improvement actions. Based on patient selection completed during routine clinical practice, and low rate of negative ERCP, our data is likely to represent a reasonable population in which to make predictions. Given the reported rates of stone migration (21% to 80%), we anticipate that data used within 24 h of ERCP, is applicable to optimize patient selection[14,29]. Another limitation of this study is the limited sample of patients that had ERCP in which CBDS were not identified. Although there was a clinical suspicion for a stone in those cases for which ERCP was considered (*e.g.*, known gallstone disease), a passed stone, suprapapillary stricture or papillary stenosis from a stone was suspected. In the absence of stone this information was identified in the post-procedure note, but based on a normal appearing ampulla or post-sphincterotomy where the dilated bile duct is traced to a stenotic area above the ampulla (suprapapillary stricture) or tactile perception or visibly stenosed ampullary os (papillary stenosis).

Since the primary endpoint was the presence of a stone, this resulted in wide confidence intervals and did not allow for appropriate ROC curve representation. Similarly, due to the zero denominator in several calculations, imputed odds ratios were calculated for the following categories: Total Bilirubin > 4 mg/dL, VS-Adult criteria, and CBDS by US, but likely underestimating these factors.

There are also major differences in normal laboratory values and testing, such as alkaline phosphatase, typically several fold higher in pediatric patients compared to adults[30]. Similarly, conjugated bilirubin is more often utilized rather than total bilirubin in pediatric laboratory investigations of hepatobiliary inflammation and obstruction. Conjugated bilirubin is a thus a more sensitive marker of significant biliary obstruction, even when patients with hemolytic disease were separated from the analysis ($P < 0.004$ *vs* 0.02 respectively). Cholesterol stone disease is now more common in

pediatric patients compared to pigmented stones from hemolytic disease, but the laboratory examinations in patients with hemolytic disease typically often have marked elevations in both total and conjugated bilirubin.

Our data is probably most applicable when the ASGE criteria are applied to adolescents, as they are more similar in mechanisms of disease and anatomy[2]. However, when consideration for bile duct size is taken into account, and with increases for advancing age, the use of imaging criteria (*e.g.*, CBD diameter) may require a higher threshold for use in children and adolescents[18,31,32]. Management algorithms are highly dependent on patient population (*e.g.*, rate of hemolytic disease or obesity), local expertise and availability of ERCP, surgical techniques, and different radiographic modalities. Although the current guidelines for adults use an accepted likelihood of stone identification of greater than fifty percent, a higher cut-off may be more appropriate for children[10,21,28]. It is our hope that the findings may serve as a clinical framework to pursue multi-center studies to identify optimal lab and imaging criteria in children in the management of CBDS prospectively.

Due to the relative variability in each of the available tests as well as the reported rates of both missed stones at ERCP and rates of stone passage, clinical experience should complement these tools and should take into consideration the inherent risks of the procedure with the risks of a retained stone (*e.g.*, cholangitis, pancreatitis). It is also important to consider the possibility of an alternative diagnosis contributing to intraductal stones such as familial intrahepatic cholestasis or sclerosing cholangitis, both carrying malignancy risks. Intrahepatic stone disease has also been linked to cholangiocarcinoma[33].

Using ASGE guidelines in a series of pediatric patients with suspected CBDS, stones were appropriately identified in the majority of cases, while US was poorly predictive of a sensitivity of 42%. Modified criteria using conjugated bilirubin $\geqslant$ 0.5 mg/dL instead of total bilirubin performed better at identification of CBDS. Conjugated bilirubin, γGT, ALT and AST may improve specificity in identification of CBDS. Future studies are needed to assess pediatric specific criteria in children including both imaging (US, MRCP and EUS) and laboratory data. In the future, pediatric specific guidelines should be developed to optimize ERCP management in children with suspected CBDS.

COMMENTS

Background

Gallstones are an increasingly reported problem in children and reported rates of choledocholithiasis may be higher in pediatric patients than adults. In patients with suspected choledocholithiais, criteria have been proposed for adults to help predict the likelihood of identifying and ultimately removing a stone at endoscopic retrograde cholangiography (ERCP). Limited data is available specific to children to guide management for this problem.

Research frontiers

There is great interest in the study of choledocholithiasis and its related management. It offers opportunity to improve patient care by decreasing risks of a given procedure or related sedation. There is also great variability in the management in these patients despite guidelines due to numerous factors, which may impact both patients and endoscopists.

Innovations and breakthroughs

Using both a standard "adult" scoring system as well as a modified scoring system in a series of pediatric patients, the majority of patients could be identified. Specific laboratory tests such as bilirubin or findings on abdominal ultrasounds can assist in directing care for a pediatric patient with choledocholithiasis.

Applications

Using a combination of labs and imaging as well as clinical experience can help in identifying appropriate patients for ERCP. Utilization of newer applications such as endoscopic ultrasound or magnetic resonance cholangiopancreatography may improve our patient selection for ERCP. Multicenter studies may help to corroborate this data or identify other factors so that pediatric specific guidelines can be created.

Terminology

ERCP: Endoscopic retrograde cholangiography, an endoscopic procedure used with X-ray to evaluate the biliary and pancreatic systems.

Peer-review

This manuscript applied the current adult guidelines from the American Society of Gastrointestinal Endoscopy in pediatric patients with suspected common bile duct stones to identify factors that may be predictive in the pediatric population. It is well designed and performed.

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P- Reviewer: Chen CH, Lai KH, Sergi CM, Sun LM
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World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v8.i11.433

World J Gastrointest Endosc 2016 June 10; 8(11): 433-438
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate, and clear liquid diet alone prior to small bowel capsule endoscopy

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Author contributions: Chatur N and Donnellan F contributed to study concepts, design and interpretation; Donnellan F contributed to study analysis, editing the manuscript and final approval; Rayner-Hartley E and Cramer P contributed to data acquisition and analysis; Rayner-Hartley E and Alsahafi M contributed to interpretation of results and writing the manuscript.

Institutional review board statement: This was a retrospective study, and institution review board was not required.

Informed consent statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

Conflict-of-interest statement: No conflict of interest for all authors.

Data sharing statement: No additional data are available.

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Received: November 5, 2015
Peer-review started: November 7, 2015
First decision: December 10, 2015
Revised: February 10, 2016
Accepted: February 23, 2016
Article in press: February 24, 2016
Published online: June 10, 2016

Abstract

AIM: To compare low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate and clear liquid diet alone as bowel preparation prior to small bowel capsule endoscopy (CE).

METHODS: We retrospectively collected all CE studies done from December 2011 to July 2013 at a single institution. CE studies were reviewed only if low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate or clear liquid diet alone used as the bowel preparation. The studies were then reviewed by the CE readers who were blinded to the preparation type. Cleanliness and bubble burden were graded independently within the proximal, middle and distal small bowel using a four-point scale according to the percentage of small bowel mucosa free of debris/bubbles: grade 1 = over 90%, grade 2 = between 90%-75%, grade 3 = between 50%-75%, grade 4 = less than 50%. Data are expressed as mean ± SEM. ANOVA and Fishers exact test were used where appropriate. *P* values < 0.05 were considered statistically significant.

RESULTS: A of total of 123 CE studies were reviewed. Twenty-six studies were excluded from analysis because of incomplete small bowel examination. In the remaining

studies, 48 patients took low volume polyethylene glycol with ascorbic acid, 31 took sodium picosulfate-magnesium citrate and 27 took a clear liquid diet alone after lunch on the day before CE, followed by overnight fasting in all groups. There was no significant difference in small bowel cleanliness (1.98 ± 0.09 *vs* 1.84 ± 0.08 *vs* 1.76 ± 0.08) or small bowel transit time (213 ± 13 *vs* 248 ± 14 ± 225 ± 19 min) for clear liquid diet alone, MoviPrep and Pico-Salax respectively. The bubble burden in the mid small bowel was significantly higher in the MoviPrep group (1.6 ± 0.1 *vs* 1.9 ± 0.1 *vs* 1.6 ± 0.1, $P < 0.05$). However this did not result in a significant difference in diagnosis of pathology.

CONCLUSION: There was no significant difference in small bowel cleanliness or diagnostic yield of small bowel CE between the three preparations regimens used in this study.

Key words: Capsule endoscopy; Small bowel; Bowel preparation; Polyethylene glycol; Sodium picosulfate

Core tip: Adequate small bowel preparation is essential for diagnosing small bowel pathology on video capsule endoscopy, but the optimal small bowel preparation method remains unclear. Due the small volume and safety, low volume polyethylene glycol (PEG) based regimens become attractive. However no previous studies have compared low volume PEG with ascorbic acid to sodium picosulfate-magnesium citrate or clear liquid diet alone. In this retrospective study we performed a direct comparison between these three regimens. The bubble burden was significantly higher in the low PEG group but no differences in small bowel cleanliness or diagnostic yield were found between the three regimens.

Rayner-Hartley E, Alsahafi M, Cramer P, Chatur N, Donnellan F. Low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate, and clear liquid diet alone prior to small bowel capsule endoscopy. *World J Gastrointest Endosc* 2016; 8(11): 433-438 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i11/433.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i11.433

INTRODUCTION

Capsule endoscopy (CE) has revolutionized the management of small bowel diseases including obscure GI bleeding, Crohn's disease, polyposis syndromes and advanced celiac disease[1-4]. The diagnostic yield (DY) is affected by a number of factors including intraluminal material, bubbles, and both gastric and small bowel transit times[5].

Adequate small bowel preparation is important to increase the DY. Multiple studies have been done comparing various bowel preparation regimens, including just an overnight fast. Despite numerous studies, controversy exists regarding the optimal bowel preparation prior to CE[6-22]. Previous studies have examined the use of laxatives, prokinetics as well as surfactant agents. The bowel preparation regimen may also have an impact on the gastric and small bowel transit times. Recent consensus guidelines recommend polyethylene glycol (PEG) based laxatives as first line agents[23].

The primary aim of this study was to evaluate the DY, small bowel cleanliness, bubble burden and both gastric and small bowel transit times following three different preparation regimens. To our knowledge, no previous studies compared a low volume PEG based agent to a sodium picosulfate - magnesium citrate based agent and clear liquid diet alone.

MATERIALS AND METHODS

The charts for all patients referred for outpatient CE between December 2011 and July 2013 were reviewed. Patients were included only if they were given one of the following three bowel preparation regimens: Low volume PEG based agent (MoviPrep, Norgine), sodium picosulfate and magnesium citrate based agent (Pico-Salax, Ferring) and a clear liquid diet alone. In this study, the patients in the groups of MoviPrep and Pico-Salax were instructed to take the first sachet at 14h00 and the second at 17h00. All patients ingested the capsule at approximately 8 am of the study day. All CE examinations were performed using the Olympus Endocapsule.

Two experienced reviewers who were blinded to preparation method (FD and NC) reviewed all CE studies for diagnostic evaluation, and both gastric and small bowel transit time. Clinical disagreement was solved by joint review and discussion. One CE reader who was blinded to preparation (ERH) reviewed all CE studies for mucosal visibility grading related to cleanliness and bubble burden. Once the CE studies have been reviewed, patients were assigned into one of the three different groups based on the bowel preparation regimen given according to chart review.

Only CE studies with complete small bowel examinations, determined by identification of the cecum were included for analysis. The primary outcome measures included the DY, intraluminal small bowel cleanliness and bubble burden. Small bowel cleanliness and bubble burden were graded independently within the proximal, mid and distal small bowel using a four-point scale according to the percentage of small bowel mucosa free of debris/bubbles: Grade 1 = over 90%, grade 2 = between 90%-75%, grade 3 = between 50%-75%, grade 4 = less than 50% (Figure 1). This grading system was developed by the authors based on the commonly used grading criteria as there is no validated scoring system available. The anatomic divisions were determined by dividing the small bowel into three segments based on the small bowel transit time.

According to CE protocol in our center, patients are

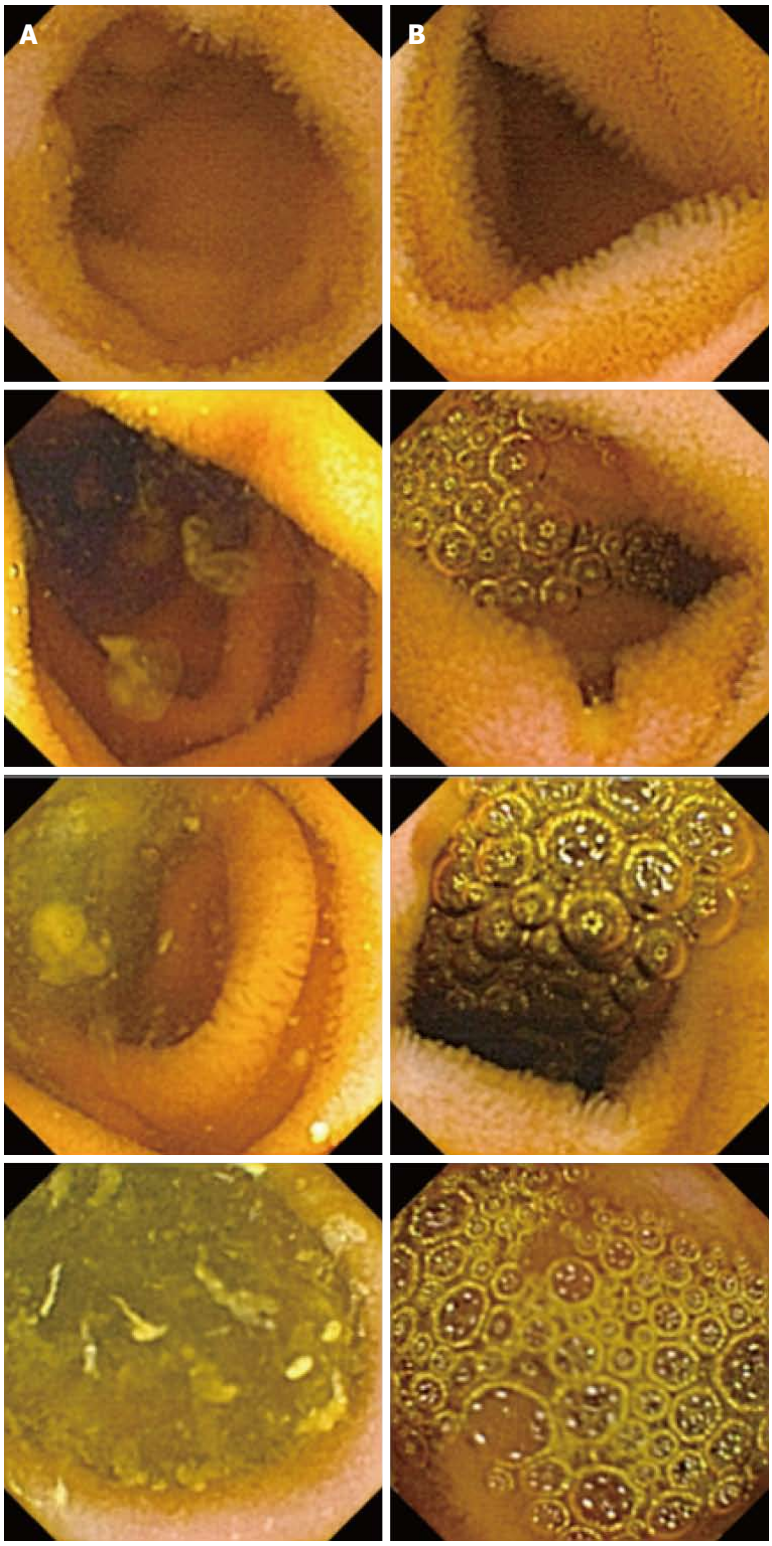

Figure 1 Grading scales of (A) cleanliness and (B) bubble burden. The bowel preparation was graded independently in the proximal, mid and distal third of the small bowel using a 4-grade scale according to the percentage of small bowel mucosa free of debris/bubbles: Grade 1 = over 90%, grade 2 = between 90%-75%, grade 3 = between 50%-75%, grade 4 = less than 50%.

instructed to follow a clear liquid diet after lunch the day prior to CE, followed by an overnight fast as of 21h00. They are permitted to resume a clear fluid diet 2 h after recording begin and a light meal 4 h later. Patients return 8 h after ingestion of the capsule to disconnect the recorder. An abdominal X-ray is obtained at one week following ingestion to determine if the capsule is retained if it did not reach the cecum or the patient did not report its passage.

Statistical analysis

Data are expressed as mean ± SEM. ANOVA and Fishers exact test were used where appropriate. *P* value < 0.05 were considered statistically significant. Statistical analysis was performed by Fergal Donnellan (University of British Columbia).

Table 1 Patient characteristics *n* (%)

Variable	No prep *n* = 38	MoviPrep *n* = 48	Pico-Salax *n* = 37
Male	11 (28.9)	22 (45.8)	18 (48.6)
Mean age (yr)	52.7	54.1	53.2
Indication			
Obscure bleeding	17 (44.7)	27 (56.3)	19 (51.4)
Abnormal imaging	3 (7.9)	4 (8.3)	5 (15.3)
Suspected IBD	11 (28.9)	11 (22.9)	10 (27)
Other	7 (18.4)	6 (12.5)	3 (8.1)
Completion rate	27 (71)	39 (81.3)	31 (83.8)

IBD: Inflammatory bowel disease.

Table 2 Results of small bowel cleanliness, bubble burden and transit time according to the bowel preparation regimen

Result	No prep *n* = 27	MoviPrep *n* = 39	Pico-Salax *n* = 31	*P* value
Cleanliness				
Proximal	1.4 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	0.1
Mid	1.8 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	0.7
Distal	2.1 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	0.6
Bubble burden				
Proximal	1.5 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	0.1
Mid	1.6 ± 0.1	1.9 ± 0.1	1.6 ± 0.1	< 0.05
Distal	1.6 ± 0.1	1.8 ± 0.2	1.5 ± 0.1	0.09
Gastric transit time (min)	26 ± 5	25 ± 6	47 ± 9	< 0.05
Small bowel transit time (min)	213 ± 13	248 ± 14	225 ± 19	0.3

RESULTS

One hundred and twenty-three patients were included, 48 patients took MoviPrep, 37 took Pico-Salax and 38 took a clear liquid diet alone. Table 1 depicts the patients' characteristics. There was no statistically significant different between the three groups in regard to gender, age or complete small bowel examination. Ninty-seven (78.9%) patients had a complete small bowel examination and thus included in the final analysis. This included 39 (81%) patients in the MoviPrep group, 31 (84%) patients in the Pico-Salax group and 27 (71%) patients in the clear liquid group (Figure 2).

Table 2 depicts the results for small bowel cleanliness, bubble burden and both gastric and small bowel transit times. There was a significant increase in the bubble burden in the mid small bowel in the MoviPrep group ($P < 0.05$). Otherwise there was no difference between the three groups in terms of cleanliness or bubble burden. Similarly there was no difference in the small bowel transit time. The gastric transit time, however, was significantly longer in the Pico-Salax group only ($P < 0.05$).

Table 3 depicts the results for DY and abnormal findings. Overall there was no difference in detection of pathology between the three groups ($P = 0.6$). However, there was a trend towards increased detection of vascular lesions in the MoviPrep group and ulceration in the clear liquid diet group, however these findings were not statistically significant ($P = 0.06$ and 0.07 respectively).

Table 3 Diagnostic Yield according to the bowel preparation *n* (%)

Finding	No prep *n* = 27	MoviPrep *n* = 39	Pico-Salax *n* = 31
Abnormal study	13 (48.1)	19 (48.7)	13 (41.9)
Gastric	2 (7.4)	1 (2.6)	0 (0.0)
Small bowel			
Vascular	1 (3.7)	10 (25.6)	5 (16.1)
Ulcer/erosion	7 (25.9)	3 (7.7)	3 (9.7)
Polyp/mass	0 (0.0)	1 (2.6)	3 (9.7)
Blood	0 (0.0)	1 (2.6)	1 (3.2)
Abnormal mucosa	2 (7.4)	3 (7.7)	1 (3.2)
other	1 (3.7)	0 (0.0)	0 (0.0)

DISCUSSION

Since its introduction in 2000, CE is now recognized as a widely applicable, non-invasive tool with a high DY[24]. Unlike conventional endoscopy, which has the advantage of washing and suctioning to improve mucosal visibility, CE relies on the state of the small bowel at time of exam. No universally accepted bowel preparation regimen exists amongst clinicians[6-22].

The most studied agents in small bowel CE preparation are PEG, sodium phosphate and sodium picosulphate. Recent meta-analyses found that the DY and small bowel visualization quality were superior with PEG or sodium phosphate in comparison to clear fluid diet[5,6]. None of these studies included sodium picosulphate. Lower volume PEG (2L) has been shown as effective as 4L, which is preferable for patient tolerance[7,8]. Magnesium citrate is another agent that is less well studied. One retrospective analysis showed significant improvement in clarification of intestinal juices with magnesium citrate as compared to simethicone[10]. Subsequent studies however, have not reported significant differences in cleansing efficacy[9-11].

In our study, we did not find a significant difference in cleanliness, bubble burden or transit time in the three groups studied. Only the bubble burden in the mid small bowel in the MoviPrep group and the gastric transit time in the Pico-Salax group were significantly different. When considering that no difference in pathology detection was noted between the groups, our results concur with previously published studies that CE DY may be preserved with the simplicity of a clear liquid diet. The small bowel is primarily a site of nutrient absorption and not stool formation. Thus, unlike colonoscopy preparation, it is logical that a preparation method without purgative agents could be adequate. We did note a non-significant trend towards increased detection of vascular lesions only in the MoviPrep group and ulceration in the clear liquid diet alone group. It is difficult to conclude that this is due to the regimen, but more likely due to small sample size.

Recent consensus guidelines along with European

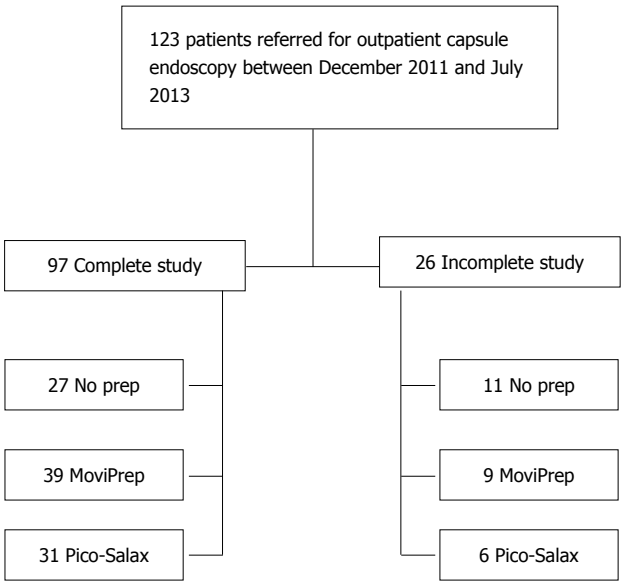

Figure 2 Study diagram.

Society of Gastrointestinal Endoscopy recommendations support the use of PEG based purgative agents prior to CE[23,25,26]. Our findings suggest that a clear liquid diet the day prior to CE followed by an overnight fast is as effective for detection of pathology on CE. We included preparation agents that have not been previously directly compared.

Our study has several limitations. This was a retrospective study with a relatively small sample size. However we reviewed all the CE examinations blindly for the purpose of this study. The compliance with bowel preparation used could not be verified given the retrospective design. The anatomical sections of the small bowel were arbitrarily determined by dividing the total small bowel transit time into three periods, while the CE speed might be variable.

In conclusion, our study demonstrates no clinically significant difference in small bowel cleanliness or DY between three preparations regimens used in this study. Only the bubble burden in the mid small bowel in the MoviPrep group and the gastric transit time in the Pico-Salax group were significantly different. Our study suggests that it is reasonable to consider eliminating the use of bowel preparation prior to outpatient CE.

COMMENTS

Background

Capsule endoscopy (CE) has revolutionized the management of small bowel diseases including obscure GI bleeding, Crohn's disease, polyposis syndromes and advanced celiac disease. Adequate small bowel preparation is required to increase the diagnostic yield (DY). The DY is affected by a number of factors including intraluminal material, bubbles, and both gastric and small bowel transit times. Multiple studies have been done comparing various bowel preparation regimens, including just an overnight fast. Previous studies have also examined the use of laxatives, prokinetics as well as surfactant agents. Despite numerous studies, controversy exists regarding the optimal bowel preparation prior to CE.

Research frontiers

To the authors' knowledge, no previous studies compared a low volume polyethylene glycol (PEG) based agent to a sodium picosulfate and magnesium citrate based agent and clear liquid diet alone.

Innovations and breakthroughs

In this study, the authors compared low volume PEG with ascorbic acid (MoviPrep), sodium picosulfate-magnesium citrate (Pico-Salax) and clear liquid diet alone as bowel preparation prior to small bowel CE. Only the bubble burden in the mid small bowel in the MoviPrep group and the gastric transit time in the Pico-Salax group were significantly different. However the authors did not find a significant difference in the small bowel cleanliness or the DY.

Applications

When considering that no difference in the DY was noted between the three groups, the results concur with previously published studies that CE DY may be preserved with the simplicity of a clear liquid diet alone.

Terminology

Small bowel CE: A pill sized video camera ingested by the patient which allows examination of small bowel.

Peer-review

This is a retrospective study which compared low volume polyethylene glycol with ascorbic acid, sodium picosulfate-magnesium citrate and clear liquid diet alone as bowel preparation prior to small bowel CE.

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P- Reviewer: Chen JQ, Mentes O **S- Editor**: Qi Y
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