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Endoscopic retrograde cholangiopancreatography in periampullary diverticulum: The challenge of cannulation

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Abstract

Periampullary diverticulum (PAD) is duodenal outpunching defined as herniation of the mucosa or submucosa that occurs *via* a defect in the muscle layer within an area of 2 to 3 cm around the papilla. Although PAD is usually asymptomatic and discovered incidentally during endoscopic retrograde cholangiopancreatography (ERCP), it is associated with different pathological conditions such as common bile duct obstruction, pancreatitis, perforation, bleeding, and rarely carcinoma. ERCP has a low rate of success in patients with PAD, suggesting that this condition may complicate the technical application of the ERCP procedure. Moreover, cannulation of PAD can be challenging, time consuming, and require the higher level of skill of more experienced endoscopists. A large portion of the failures of cannulation in patients with PAD can be attributed to inability of the endoscopist to detect the papilla. In cases where the papilla is identified but does not point in a suitable direction for cannulation, different techniques have been described. Endoscopists must be aware of papilla identification in the presence of PAD and of different cannulation techniques, including their technical feasibility and safety, to allow for an informed decision and ensure the best outcome. Herein, we review the literature on this practical topic and propose an algorithm to increase the success rate of biliary cannulation.

Key words: Periampullary diverticulum; Cannulation techniques; Tips; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography

Core tip: Presence of periampullary diverticulum (PAD) is thought to complicate the application of endoscopic retrograde cholangiopancreatography, which is already a technically difficult procedure. To improve success rates, different techniques have been developed to achieve successful biliary cannulation in patients with PAD. For patients with PAD, endoscopists must be aware of papilla identification and the different available cannulation techniques, as well as the technical feasibility and safety of each.

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INTRODUCTION

Periampullary diverticulum (PAD) is duodenal outpunching defined as herniation of the mucosa or submucosa that occurs *via* a defect in the muscle layer within an area of 2 to 3 cm around the papilla. Prevalence of PAD increases with age, and overall prevalence among the elderly is reportedly 65%[1]. The formation of PAD is related to progression of duodenal motility disorders. Furthermore, increased intraduodenal pressure and progressive weakening of intestinal smooth muscles are known as the main underlying etiologies for this defect[2]. PAD is sub-classified into two categories according to the location of the papilla with respect to the diverticulum. In type Ⅰ, or peri-diverticular papilla, the papilla is located at the edge of the diverticulum or within a radius of 2 cm from the diverticular edge. In type Ⅱ, or intra-diverticular papilla (IDP), the papilla is located inside the diverticulum or lying between two adjacent diverticula[3].

Although PAD is usually asymptomatic and discovered incidentally in patients during endoscopic retrograde cholangiopancreatography (ERCP), it is associated with different pathological conditions such as common bile duct (CBD) obstruction, pancreatitis, perforation, bleeding, and rarely carcinoma[4-7]. Several hypotheses have been put forth to explain the observed higher incidence of biliary stone formation in the presence of PAD. First, it was proposed that dysfunction in the sphincter of Oddi, which in turn causes reflux of pancreatic fluid and intestinal content, can lead to biliary stone formation[8]. Second, it was proposed that diverticula cause spasm of the sphincter, thereby increasing biliary tract pressure that may in turn produce jaundice and cholangitis as well as predispose for choledocholithiasis[9]. Finally, it was proposed that PAD may compress the distal part of the CBD to cause functional biliary stasis, and this hypothesis was supported by the observation of increased incidence of pigment biliary stones[10,11].

Reported success rates of cannulation in patients with PAD have varied from 61% to 95.4%, a range that is significantly lower than that observed in patients without PAD[12]. In recent years, new techniques and new devices for successful biliary cannulation have been developed to improve rates of success in patients with PAD. For patients with PAD, endoscopists must be aware of papilla identification and the different cannulation techniques available, including the technical feasibility and safety of each, in order to make an informed decision and ensure the best outcome. Herein, we review the literature on this practical topic that was obtained through an electronic search of the literature databases of Google Scholar and PubMed using the following terms alone or in combination: ERCP, difficult cannulation, cannulation techniques, and periampullary diverticulum.

TIPS FOR PAPILLARY ORIENTATION AND CANNULATION

The presence of PAD is thought to complicate the application of ERCP, an already technically difficult procedure[2]. Cannulation of IDP can be challenging, time consuming and require the higher level of skill of more experienced endoscopists. A large portion of the failures of cannulation in patients with PAD has been attributed to inability of the endoscopist to detect the papilla[6]. However, in some studies, the finding of PAD during an ERCP was suggested as an indicator of an easier cannulation attempt, with a reported success rate of 94.9% compared to that of 94.8% in non-PAD patients after exclusion of cases with undetectable papillas that were considered to be likely IDPs[7]. In ERCP, identification of the papilla is the first major obstacle, especially in the presence of large diverticula. Thus, it is extremely helpful to know the following tips[13]: (1) in most cases, the papilla is located on the lower edge of the diverticulum or just inside, somewhere between the positions of 4 o'clock and 8 o'clock; (2) large diverticula are usually divided from proximal to distal by a ridge-like septum. This mostly involves the bile duct, with the ridge terminating at the papilla; (3) a catheter can be used to straighten and evert the folds to identify a hidden papilla within the diverticulum; (4) cannulation with the tip of the duodenoscope within the sac is also possible, but care must be taken to avoid perforation; and (5) in contrast to the usual papillary anatomy, the presence of PAD alters the biliary direction. It is often not acutely angulated superiorally, but runs more directly. Thus, acute angulation of the sphincterotome is not necessary.

TECHNIQUES FOR DIFFICULT CANNULATION

To address cases where the papilla is identified but does not point in a suitable direction for cannulation, the below-described techniques are available for consideration (Table 1).

Two-devices in one-channel method

A biopsy forceps is used to pull the duodenal mucosa adjacent to the papilla, bringing the papillary orifice out of the diverticulum. Another instrument, either a cannula or sphincterotome, is then inserted into the working channel of the endoscope together with the biopsy forceps. With coordination of the two instruments, biliary cannulation can be attempted (Figure 1A). A report of this technique applied to two PAD cases showed successful cannulation for both and with no complications in either (success rate

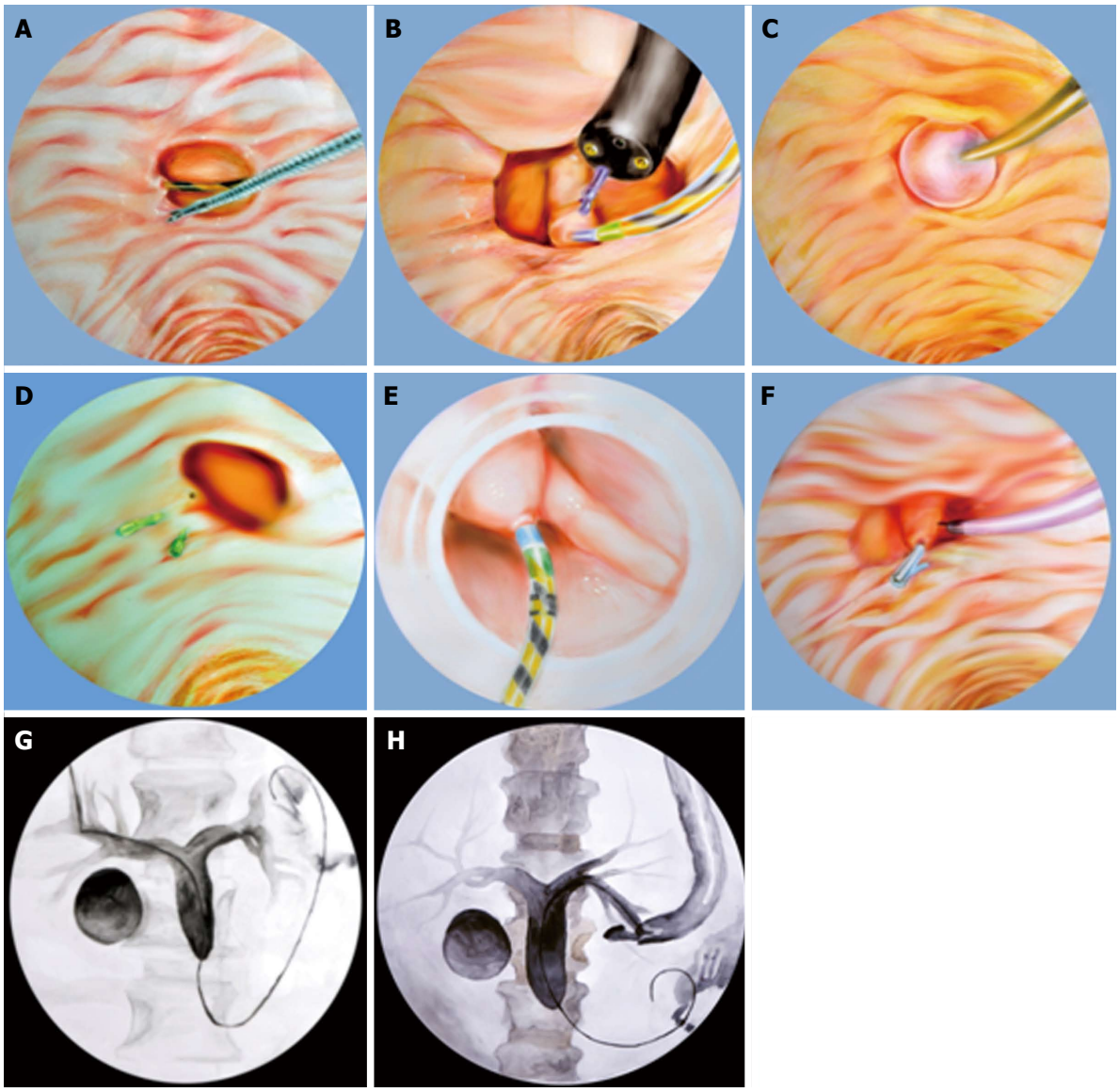

Figure 1 Techniques for difficult cannulation. A: Two-devices in one-channel method; B: Double endoscope method; C: Balloon dilation of the narrow diverticular neck; D: Endoclip-assisted cannulation; E: Cap-assisted cannulation; F: Pancreatic duct stent placement followed by pre-cut biliary sphincterotomy; G: Percutaneous ultrasound-guided rendezvous technique; H: Endoscopic ultrasound-guided rendezvous technique.

Table 1 Techniques for difficult cannulation

Two-devices in one-channel method
Reversed guidewire method
Double endoscope method
Balloon dilation of the narrow diverticular neck
Endoclip-assisted cannulation
Cap-assisted cannulation
Pancreatic duct stent placement followed by pre-cut biliary sphincterotomy
Percutaneous ultrasound-guided rendezvous technique
EUS-guided rendezvous technique

EUS: Endoscopic ultrasound.

100%)[14].

Reversed guidewire method

A second guidewire is advanced in reverse (stiff end forward) through the working channel of the duodenoscope, alongside the sphincterotome. This wire is then used to push the mucosa adjacent to the papilla toward the lumen of the duodenum and to straighten the folds, anchoring the papilla in a better configuration and creating a suitable direction for cannulation. A report of this technique applied to one PAD case showed successful cannulation with no complication (success rate 100%)[15].

Double endoscope method

A forward-viewing gastroscope is inserted inside the diverticulum for better visualization of the papilla. A foreign body forceps is used to grasp the tissue just beside the papilla in order to bring it into a better orientation. The gastroscope holding the papilla is left in place, to avoid backsliding after opening of the forceps. A side-viewing duodenoscope is inserted alongside the gastroscope. With both endoscopes positioned simu-

ltaneously in the duodenum, the CBD can be cannulated (Figure 1B). A report of this technique applied to one PAD case showed successful cannulation with no complication (success rate 100%)[16].

Balloon dilation of the narrow diverticular neck

In narrow-necked papillary diverticula with the papilla located in the fundus of the diverticulum, endoscopic balloon dilation of the narrow diverticular neck, using a 15-mm stone retrieval balloon, can be done safely, bringing the papillary orifice into view. Cannulation of the bile duct can be attempted without any complications (Figure 1C). A report of this technique applied to three PAD cases showed successful cannulation and no complications (success rate 100%)[17].

Endoclip-assisted cannulation

One or more endoclips can be used to rotate the IDP externally and to fix it on the outside rim of the diverticulum. This manipulation can successfully evert and fix the papilla on the diverticular margin in a better position, resulting in successful biliary cannulation (Figure 1D). A report of this technique applied to two PAD cases showed successful cannulation with no complications (success rate 100%)[18].

Cap-assisted cannulation

A transparent cap is attached to the tip of a forward-viewing endoscope. At first, selective biliary cannulation can be attempted through the papillary orifice. If selective biliary cannulation fails, endoscopic fistulotomy can be attempted. Fistulotomy is performed between the lower two-thirds and the upper one-third of the papillary roof. To gain biliary access after the fistulotomy, needle puncture is made and a soft-tipped guidewire is advanced (Figure 1E). A report of this technique applied to twelve PAD cases showed successful cannulation in all cases (success rate 100%) and a minor complication (bleeding at the site of fistulotomy) in two patients (complications rate 16.5%); primary hemostasis was achieved by hemoclipping in one patient and by saline-epinephrine mixture spray in the other[19].

Pancreatic duct stent placement followed by pre-cut biliary sphincterotomy

In the case of pancreatic duct cannulation, placement of a main pancreatic duct stent keeps the papilla out of the diverticulum, thereby facilitating pre-cut needle knife sphincterotomy and selective cannulation of the CBD (Figure 1F). A report of this technique applied to eight cases showed successful cannulation in seven of the patients (success rate 87.5%), with two of those requiring a second ERCP for success. In addition, two patients developed post-ERCP pancreatitis (complication rate 25%)[20].

Percutaneous ultrasound-guided rendezvous technique

After the percutaneous ultrasound-guided transhepatic biliary puncture is performed a sterile guidewire is inserted into the CBD, then into the papilla. A snare or forceps is then used to grasp the guidewire and pull it back through the working channel of the duodenoscope for subsequent over-the-wire cannulation (Figure 1G)[21]. However, it is sometimes difficult to grasp the guidewire, which may be damaged or kinked, during the withdrawal through the working channel of the duodenoscope; thus, passing a catheter over it is difficult or sometimes impossible[22]. A study on the percutaneous-ultrasound guided rendezvous technique applied to a total of fourteen patients showed success in 13 (success rate 93%) with complication (retroperitoneal perforation) experienced in only 1 (complication rate 7%)[21].

Endoscopic ultrasound-guided rendezvous technique

When the echoendoscope is positioned in the stomach or duodenum, and the bile ducts can be visualized by the endoscopic ultrasound (EUS), a 19-gauge or 22-gauge needle are used to puncture the bile ducts. After aspiration of bile, contrast is injected through the EUS needle to facilitate display the intra- and extra-hepatic bile ducts. After confirmation of bile duct puncture, a guidewire is advanced distally through the CBD and across the papilla under fluoroscopic guidance. The endoscope exchange is performed after passage of the guidewire through the papilla into the duodenum. In this process, the echoendoscope is removed, leaving the guidewire in place, after which a duodenoscope is passed up to the papilla alongside the EUS-placed guidewire. Finally, a snare or forceps is used to grasp the guidewire and pull it back out of the working channel of the duodenoscope for subsequent over-the-wire cannulation. After access to the CBD is achieved, a standard ERCP can be performed (Figure 1H). A study on the EUS-guided rendezvous technique applied to a total of 45 patients showed success in 36 (success rate 80%) with complications (bile leakage and pneumoperitoneum) experienced in only 2 (complication rate 4%)[23].

PROPOSED ALGORITHM

We propose an algorithm based on the previous techniques to increase the success rate of cannulation (Figure 2). It is important to note, however, that this algorithm has several limitations. First, it is based on a small number of published cases for most of the techniques. Second, the success rates are comparable in most of the techniques and the choice depends on the endoscopist's preference and experience. Finally, percutaneous ultrasound-guided and EUS-guided rendezvous techniques are not available in all centers.

Feasibility and safety of therapeutic maneuvers

When therapeutic maneuvers are performed in patients with PAD the potential risks of complications are a concern, primarily because of the thin mucosa and the absence of sphincter muscle present in the ampullary area[24]. Currently, endoscopic papillary large balloon dilation (EPLBD) combined with limited endoscopic

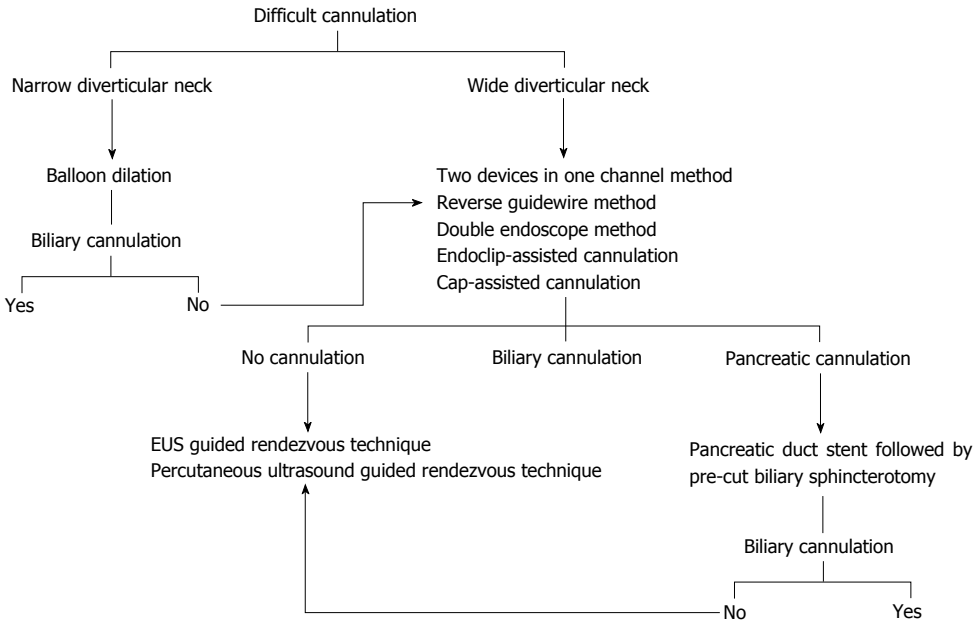

Figure 2 Proposed algorithm to ensure the best outcome. EUS: Endoscopic ultrasound.

sphincterotomy (ES) (EPLBD + ES) is regarded as an effective maneuver for treating difficult CBD stones. It has been reported that perforation and hemorrhage are less frequent in cases treated with EPLBD + ES than in those treated with standard ES alone[25,26]. The tendency toward a shorter ballooning time in patients with PAD can be explained by the lack of sphincter muscle and the ease of ampullary widening facilitated by EPLBD, which suggest that EPLBD is a safe method for retrieval of CBD stones in patients with PAD[24]. Moreover, the complication rates of ERCP are similar in patients with or without PAD and the therapeutic outcome is not affected by the presence of PAD[3,7].

CONCLUSION

PAD represents a technical barrier to the successful application of ERCP. Cannulation of IDP can be challenging, time consuming and require the skill of more experienced endoscopists. In cases where the papilla is identified but does not point in a suitable direction for cannulation, a number of feasible techniques are available for consideration. Moreover, complication rates of ERCP are similar in patients with and without PAD, and therapeutic outcome is not affected by the presence of PAD.

REFERENCES

1 **Shemesh E**, Klein E, Czerniak A, Coret A, Bat L. Endoscopic sphincterotomy in patients with gallbladder in situ: the influence of periampullary duodenal diverticula. *Surgery* 1990; **107**: 163-166 [PMID: 2099745]

2 **Lobo DN**, Balfour TW, Iftikhar SY. Periampullary diverticula: consequences of failed ERCP. *Ann R Coll Surg Engl* 1998; **80**: 326-331 [PMID: 9849331]

3 **Boix J**, Lorenzo-Zúñiga V, Añaños F, Domènech E, Morillas RM, Gassull MA. Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 208-211 [PMID: 16921297 DOI: 10.1097/00129689-200608000-00002]

4 **Oddo F**, Chevallier P, Souci J, Baque J, Buckley MJ, Fabiani P, Diaine B, Coussement A. [Radiologic aspects of the complications of duodenal diverticula]. *J Radiol* 1999; **80**: 134-140 [PMID: 10209709]

5 **Yoneyama F**, Miyata K, Ohta H, Takeuchi E, Yamada T, Kobayashi Y. Excision of a juxtapapillary duodenal diverticulum causing biliary obstruction: report of three cases. *J Hepatobiliary Pancreat Surg* 2004; **11**: 69-72 [PMID: 15754050 DOI: 10.1007/s00534-003-0854-7]

6 **Tyagi P**, Sharma P, Sharma BC, Puri AS. Periampullary diverticula and technical success of endoscopic retrograde cholangiopancreatography. *Surg Endosc* 2009; **23**: 1342-1345 [PMID: 18818967 DOI: 10.1007/s00464-008-0167-7]

7 **Panteris V**, Vezakis A, Filippou G, Filippou D, Karamanolis D, Rizos S. Influence of juxtapapillary diverticula on the success or difficulty of cannulation and complication rate. *Gastrointest Endosc* 2008; **68**: 903-910 [PMID: 18635174 DOI: 10.1016/j.gie.2008.03.1092]

8 **Yildirgan MI**, Başoğlu M, Yilmaz I, Atamanalp SS, Balik AA, Aydinli B, Oztürk G. Periampullary diverticula causing pancreaticobiliary disease. *Dig Dis Sci* 2004; **49**: 1943-1945 [PMID: 15628730 DOI: 10.1007/s10620-004-9597-9]

9 **Hagège H**, Berson A, Pelletier G, Fritsch J, Choury A, Liguory C, Etienne JP. Association of juxtapapillary diverticula with choledocholithiasis but not with cholecystolithiasis. *Endoscopy* 1992; **24**: 248-251 [PMID: 1612038 DOI: 10.1055/s-2007-1010476]

10 **Miyazaki S**, Sakamoto T, Miyata M, Yamasaki Y, Yamasaki H, Kuwata K. Function of the sphincter of Oddi in patients with juxtapapillary duodenal diverticula: evaluation by intraoperative biliary manometry under a duodenal pressure load. *World J Surg* 1995; **19**: 307-312 [PMID: 7754640 DOI: 10.1007/BF00308647]

11 **Shinagawa N**, Fukui T, Mashita K, Kitano Y, Yura J. The relationship between juxtapapillary duodenal diverticula and the presence of bacteria in the bile. *Jpn J Surg* 1991; **21**: 284-291 [PMID: 1906956 DOI: 10.1007/BF02470948]

12 **Zoepf T**, Zoepf DS, Arnold JC, Benz C, Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients.

Gastrointest Endosc 2001; **54**: 56-61 [PMID: 11427842 DOI: 10.1067/mge.2001.115334]

13 **Pohl J**. Periampullary Diverticulum: Cannulation and Sphincterotomy. *Video J Encyclop GI Endosc* 2013; **1**: 516-517 [DOI: 10.1016/S2212-0971(13)70226-7]

14 **Fujita N**, Noda Y, Kobayashi G, Kimura K, Yago A. ERCP for intradiverticular papilla: two-devices-in-one-channel method. Endoscopic Retrograde Cholangiopancreatography. *Gastrointest Endosc* 1998; **48**: 517-520 [PMID: 9831843 DOI: 10.1016/S0016-5107(98)70096-3]

15 **Elmunzer BJ**, Boetticher NC. Reverse guidewire anchoring of the papilla for difficult cannulation due to a periampullary diverticulum. *Gastrointest Endosc* 2015; **82**: 957 [PMID: 26142553 DOI: 10.1016/j.gie.2015.05.054]

16 **Külling D**, Haskell E. Double endoscope method to access intradiverticular papilla. *Gastrointest Endosc* 2005; **62**: 811-812 [PMID: 16246708 DOI: 10.1016/j.gie.2005.06.035]

17 **Tóth E**, Lindström E, Fork FT. An alternative approach to the inaccessible intradiverticular papilla. *Endoscopy* 1999; **31**: 554-556 [PMID: 10533741 DOI: 10.1055/s-1999-59]

18 **Huang CH**, Tsou YK, Lin CH, Tang JH. Endoscopic retrograde cholangiopancreatography (ERCP) for intradiverticular papilla: endoclip-assisted biliary cannulation. *Endoscopy* 2010; **42** Suppl 2: E223-E224 [PMID: 20931451 DOI: 10.1055/s-0029-1215008]

19 **Myung DS**, Park CH, Koh HR, Lim SU, Jun CH, Ki HS, Park SY, Rew JS. Cap-assisted ERCP in patients with difficult cannulation due to periampullary diverticulum. *Endoscopy* 2014; **46**: 352-355 [PMID: 24549783]

20 **Fogel EL**, Sherman S, Lehman GA. Increased selective biliary cannulation rates in the setting of periampullary diverticula: main pancreatic duct stent placement followed by pre-cut biliary sphincterotomy. *Gastrointest Endosc* 1998; **47**: 396-400 [PMID: 9609434 DOI: 10.1016/S0016-5107(98)70226-3]

21 **Calvo MM**, Bujanda L, Heras I, Cabriada JL, Bernal A, Orive V, Miguelez J. The rendezvous technique for the treatment of choledocholithiasis. *Gastrointest Endosc* 2001; **54**: 511-513 [PMID: 11577321 DOI: 10.1067/mge.2001.118441]

22 **Dickey W**. Parallel cannulation technique at ERCP rendezvous. *Gastrointest Endosc* 2006; **63**: 686-687 [PMID: 16564873 DOI: 10.1016/j.gie.2005.10.029]

23 **Tarantino I**, Barresi L, Fabbri C, Traina M. Endoscopic ultrasound guided biliary drainage. *World J Gastrointest Endosc* 2012; **4**: 306-311 [PMID: 22816011 DOI: 10.4253/wjge.v4.i7.306]

24 **Kim HG**, Cheon YK, Cho YD, Moon JH, Park do H, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304 [PMID: 19750573 DOI: 10.3748/wjg.v19.i41.7168]

25 **Kim HG**, Cheon YK, Cho YD, Moon JH, Park DH, Lee TH, Choi HJ, Park SH, Lee JS, Lee MS. Small sphincterotomy combined with endoscopic papillary large balloon dilation versus sphincterotomy. *World J Gastroenterol* 2009; **15**: 4298-4304 [PMID: 19750573 DOI: 10.3748/wjg.15.4298]

26 **Minami A**, Hirose S, Nomoto T, Hayakawa S. Small sphincterotomy combined with papillary dilation with large balloon permits retrieval of large stones without mechanical lithotripsy. *World J Gastroenterol* 2007; **13**: 2179-2182 [PMID: 17465497 DOI: 10.3748/wjg.v13.i15.2179]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Determination of the cut-off score of an endoscopic scoring method to predict whether elderly patients with dysphagia can eat pureed diets

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Abstract

AIM: To identify the cut-off value for predicting the ability of elderly patients with dysphagia to swallow pureed diets using a new endoscopy scoring method.

METHODS: Endoscopic swallowing evaluation of pureed diets were done in patients ⩾ 65 years with dysphagia. The Hyodo-Komagane score for endoscopic swallowing evaluation is expressed as the sum (0-12) of four degrees (0-3) with four parameters: (1) salivary pooling in the vallecula and piriform sinuses; (2) the response of glottal closure reflex induced by touching the epiglottis with the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" following swallowing of test jelly; and (4) pharyngeal clearance after swallowing of test jelly. We used receiver operating characteristic (ROC) curve analysis to retrospectively analyze the association between the total score and successful oral intake of pureed diets.

RESULTS: One hundred and seventy-eight patients were enrolled including 113 men (63%), mean age 83 years (range, 66-98). One hundred and twenty-six patients (71%) were able to eat pureed diets during the observation period (mean ± SD, 19 ± 14 d). In ROC analysis, the cut-off value of the score for eating the pureed diets was 7 (sensitivity = 0.98; specificity = 0.91).

CONCLUSION: The Hyodo-Komagane endoscopic score is useful to predict the ability to eat pureed diets in elderly patients with dysphagia.

Key words: Dysphagia; Endoscopy; Pureed diets; Percutaneous endoscopic gastrostomy

Core tip: Predicting successful oral intake in elderly patients with dysphagia remains a challenge. The scoring method for endoscopic swallowing evaluation was based on final score (from 0 to 12) using four parameters; (1) the salivary pooling in the vallecula and piriform sinuses; (2) the response of glottal closure reflex induced by touching the epiglottis with the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" after the swallowing of test jelly; and (4) the extent of pharyngeal clearance after test jelly is swallowed. A total score of 7 or less during endoscopic swallowing evaluation reliably predicted the ability to eat pureed diets.

Sakamoto T, Horiuchi A, Makino T, Kajiyama M, Tanaka N, Hyodo M. Determination of the cut-off score of an endoscopic scoring method to predict whether elderly patients with dysphagia can eat pureed diets. *World J Gastrointest Endosc* 2016; 8(6): 288-294 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i6/288.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i6.288

INTRODUCTION

With aging of the population, dysphagia is becoming an important medical and social issue[1]. Pneumonia is the fourth most common cause of mortality in the elderly in Japan; the majority of cases in hospital-acquired pneumonia are reported to be related to aspiration[2]. Pureed diets are often used as an initial dysphagia diet for patients with moderate to severe dysphagia because, if the dysphagic patients can fulfill their nutritional requirements by eating pureed diets, they can avoid enteral feeding using a percutaneous endoscopic gastrostomy (PEG) tube. Wilkinson *et al*[3] previously reported PEG should be considered for people unable to tolerate a pureed diet 14 d after their stroke despite the fact that half will recover sufficiently to manage oral intake. They suggested that the texture of the pureed diet is likely to be most useful factor predictive of the need for PEG. No methods for predicting successful oral intake of pureed diets in elderly patients with dysphagia have been established.

Endoscopic and videofluoroscopic examinations are often used to evaluate swallowing and to quantify the risk of aspiration[4-7]. Our facility uses a team approach that includes a gastroenterologist and a speech therapist. Swallowing is evaluated by endoscopy using an endoscope normally used for transnasal esophagogastroduodenoscopy. We previously used this approach to study factors that influenced swallowing of pureed diets[8]. Saliva pooling and pharyngeal residues of pureed foods were shown to predict impaired swallowing of pureed foods. However, endoscopic determination of whether patients could swallow pureed diets was not always reproducible or safe especially for severely dysphagic patients. Irreproducibility was possibly related to variability in the texture and physical characteristics of the pureed diet despite being prepared in the same facility.

We previously developed a scoring system for endoscopic swallowing evaluation using blue-dyed water[9]. We modified the test meal to contain a test jelly instead of blue-dyed water so that elderly patients with severe dysphagia could undergo endoscopic examination of swallowing safely even unable to swallow pureed diets and the data would be reproducible. The aim of this study was to validate the revised scoring system to predict the ability to eat pureed diets in elderly patients with dysphagia.

MATERIALS AND METHODS

Patients

From January 2012 to November 2014, 205 hospitalized patients who underwent endoscopic swallowing evaluation at Showa Inan General Hospital, a municipal local hospital, were consecutively enrolled. We included dysphagia patients able to sit in a chair or up in bed with assistance and whose oral intake had been observed at least for 5 d after endoscopic swallowing evaluation. Subjects were included irrespective of whether oral intake of dysphagic diets was successful or unsuccessful. Exclusion criteria included an age less than 65 years old or the presence of an acute infection.

Study design

Verbal and written informed consent for the endoscopic examination of swallowing was obtained from all patients. Gastroenterologists, who were experienced in transnasal esophagogastroduodenoscopy and PEG, performed the endoscopic swallowing evaluation along with a speech therapist. Results of endoscopic swallowing examination including the new scoring system (Hyodo-Komagane score) were recorded in the endoscopic database. Determination of the validity of the proposed endoscopic swallowing score was based on a retrospective review of the patients' charts with special attention to the Hyodo-Komagane score and the status of oral intake of diets. This retrospective analysis was approved by the ethics committee of Showa Inan General Hospital.

Procedure

Participants underwent the endoscopic swallowing evaluation while sitting in a chair or sitting up in bed. Two minutes prior to inserting the endoscope, 0.2-0.5

Table 1 Hyodo-Komagane score

A: Salivary pooling in vallecula and piriform sinuses	
0	No pooling
1	Pooling at the only vallecula
2	Pooling in vallecula and piriform sinuses and no penetration[1] into larynx
3	Pooling in vallecula and piriform sinuses and penetration into larynx
B: The response of glottal closure reflex induced by touching the epiglottis with the endoscope	
0	Marked reflex by one touching
1	Slow and/or weak reflex by one touching
2	Reflex by two or three touchings
3	No refex despite three touchings
C: The location of the bolus at the time of swallow onset assessed by "white-out"[2] following swallowing of test jelly	
0	Pharyngeal
1	Vallecula
2	Piriform sinuses
3	No swallowing
D: The extent of pharyngeal clearance after swallowing of test jelly	
0	No residues
1	Pharyngeal residues remain, but are absent after swallowing is attempted two or three times
2	Pharyngeal residues remain, but do not penetrate into larynx
3	Pharyngeal residues remain and penetrate into larynx

[1]When saliva or test jelly enters the glottis (opening to the trachea) and moves as far as the vestibule above the true vocal folds, this is termed as "penetration"; [2]"white-out" is defined as the period when the videoendoscopic image is obscured owing to pharyngeal closure. Total score (A + B + C + D) = 0-12.

mL of 4% lidocaine was applied to the nasal cavities of each participant using a nasal splay. An endoscope (GIF-XP260N, Olympus, Tokyo, Japan) was used for endoscopic swallowing evaluations. This is a forward-viewing upper gastrointestinal videoscope with an ultra-miniature, resolution charged-coupled device with a 120 degree field of view. The insertion diameter is 5.5 mm and the videoscope has a tip deflection capability of 210/120 up/down in a single plane. The lubricated endoscope was passed transnasally, typically on the floor of the nose, to obtain a superior view of the hypopharynx. The endoscope was moved throughout the study between swallowing and post-swallow positions to collect the data as described previously[8]. Images of the oropharynx, hypopharynx and larynx were displayed on a monitor and recorded on the digital video recorder (Sony EVO-550H, Tokyo, Japan).

Hyodo-Komagane scoring method

All patients underwent endoscopic swallowing evaluation at least once prior to starting oral intake. First, salivary pooling in the vallecula and piriform sinuses was evaluated. The response of the glottal closure reflex was also evaluated by touching the epiglottis with the tip of endoscope. When glottal closure reflex was not elicited by touching the epiglottis, the result was confirmed by attempting to touch the epiglottis with the endoscope at least three times before absence of glottal closure reflex was declared. The swallowing trial was then performed following ingestion of a 3 mL of test diet contained in a spoon. The interior larynx and airway were examined before and after each swallow for the presence of food within the laryngeal vestibule and/or aspiration of test materials below the true vocal folds. Silent aspiration, defined as lack of cough or gag reflex when the test materials passed into the trachea, was also noted.

This scoring system was based on our previously clinic-based scoring for endoscopic swallowing evaluation using a blue-dyed water test meal[9]. Table 1 shows the modified scoring method that consists of four parameters: (1) salivary pooling in the vallecula and piriform sinuses (Figure 1); (2) the response of glottal closure reflex induced by touching the epiglottis with the tip of the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" following swallowing of test jelly; and (4) the extent of pharyngeal clearance after swallowing of test jelly. The four parameters above are scored using a 4 point scale of 0 to 3 (Table 1). The final Hyodo-Komagane score is expressed as the total score (0 to 12) of the four parameters. All patients for whom the endoscopic swallowing evaluation was performed during the time period of the study had the score recorded in the clinical chart.

Test diets

Test jelly, that is gelatin jelly (Isotonic jelly®, Nutri Co., Ltd., Yokkaichi, Japan) is shown in Figure 2. The characteristics were as follows: Hardness, 5000 N/m^2; cohesiveness, 0.4; adhesiveness, 89 J/m^3. The swallowing of test jelly was attempted for all subjects who underwent endoscopic swallowing evaluation. When the test jelly was absent from pharyngeal cavity after swallowing was attempted two or three times, swallowing of test jelly was regarded as successful. If swallowing of the test jelly was successful, swallowing of a semi-solid diet (Elental® jelly, Ajinomoto Pharmaceutical Co., Tokyo, Japan) and pureed diets was attempted.

The semi-solid diet (Elental® jelly) was made by adding a thickening agent (Jelly mix®, Ajinomoto

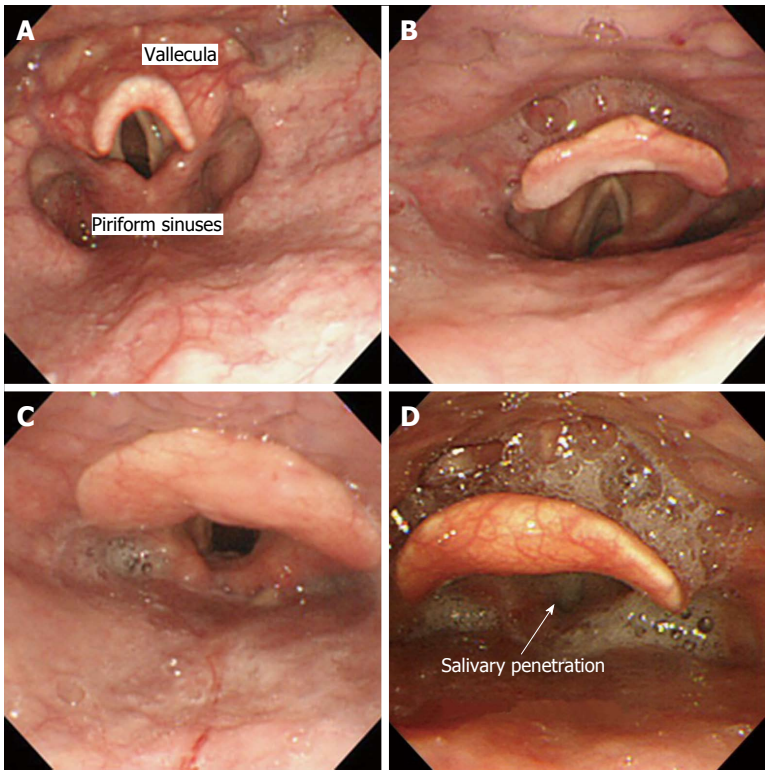

Figure 1 Endoscopic images of Hyodo-Komagane score. Salivary pooling in vallecula and piriform sinuses. A: A-0 no pooling; B: A-1 pooling at the only vallecula; C: A-2 pooling in vallecula and piriform sinuses and no penetration into larynx; D: A-3 pooling in vallecula and piriform sinuses and penetration into larynx.

Figure 2 Test jelly used in this study (Isotonic jelly®, Nutri Co., Ltd., Yokkaichi, Japan).

Pharmaceutical Co.) which contained 11.7% agar, sugar, stabilizer, and other ingredients to an elemental diet, Elental®. The thickening agent (5.8 g) was dissolved with 150 mL of hot water, and 80 g of Elental® was added to the solution which was then cooled to harden. The texture characteristics were: Hardness, 17000 ± 640 N/m^2; cohesiveness, 0.14 ± 0.0066; adhesiveness, 150 ± 49 J/m^3.

Assessment of oral intake of pureed diets

Except for patients in whom pureed diet was noted to penetrate into the larynx after swallowing the pureed diet, feeding of pureed diets was attempted and assessed once each day by a speech therapist throughout the subjects' hospitalization, irrespective of Hyodo-Komagane score. When patients were able to eat sufficient pureed diet to meet their daily nutritional requirements for at least 5 d, they were judged to be able to be managed with pureed diets. Dysphagia diets at next higher level were then attempted at the discretion of the speech therapist. The status of oral intake of dysphagia diets was noted.

Statistical analysis

Sensitivity and specificity of variables were based on receiver operating characteristic (ROC) curve analysis. In a ROC curve the true positive rate (sensitivity) is plotted in function of the false positive rate (100-specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve is a measure of how well a parameter can distinguish between two groups (successful/unsuccessful). Statistical analysis was performed by using JMP® 9.0.2 version software (SAS Institute, Inc., Japan).

RESULTS

One hundred and seventy-eight dysphagic subjects were included in this study. Their demographic and clinical data are shown in Table 2. There were 113 men (63%) with a mean age of 83 years (range: 66-98). Approximately 70% (124 patients) were 80 years and over. Severe comorbid diseases such as cerebrovascular disease (38%), aspiration pneumonia (32%), and

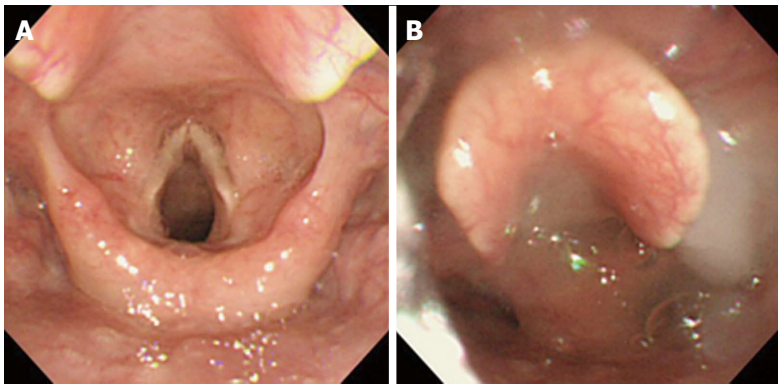

Figure 3 Endoscopic image of Hyodo-Komagane score. A: Before swallowing of test jelly; B: D-3 pharyngeal residues remain and penetrate into larynx after swallowing of test jelly.

Table 2 Demographic and clinical data in 178 patients who underwent endoscopic evaluation of swallowing

	n (%)
Gender male, female	113 (63), 65 (37)
Mean age range (yr)	83 (66-98)
65-69	11 (6)
70-79	43 (24)
80-89	88 (50)
90 and over	36 (20)
Comorbid diseases	
CVD	68 (38)
Aspiration pneumonia	57 (32)
Neuromuscular disease	35 (20)
Others	18 (10)

Values are *n* (%) of patients except for mean age. CVD: Cerebrovascular disease.

neuromuscular disease (20%) were common. Patients who had developed new cerebrovascular disease, myocardial infarction, and aspiration pneumonia within two weeks were not included. Fifty-two patients had remaining pharyngeal residue seen to penetrate into the larynx after swallowing the test jelly (D-3) (Figure 3). In nine of these patients the pureed diet also penetrated into larynx. With these patients feeding trials were not attempted to avoid aspiration pneumonia. In the remaining 169 patients, swallowing trials of the pureed diet were attempted. Overall, 126 (71%) of 178 patients were able to eat pureed diets or a higher level of dysphagia diet that fulfilled their daily nutritional needs [the observation period: Mean ± SD (range), 19 ± 14 d (5-58 d)]. The remaining 43 patients were judged to fail the subsequent pureed food tests because the amount they ate was less than their daily nutritional needs.

Figure 4 shows the distribution of Hyodo-Komgane scores among the 178 patients who underwent endoscopic swallowing evaluation (lower scores are better). Using ROC curve analysis of the Hyodo-Komagane scores, the area under the curve was 98.3% (95%CI: 0.097-0.996) (Figure 5). The optimal cut-off value of successful oral intake of pureed diets was a score of 7 (sensitivity = 0.98; specificity = 0.91). In 115 patients

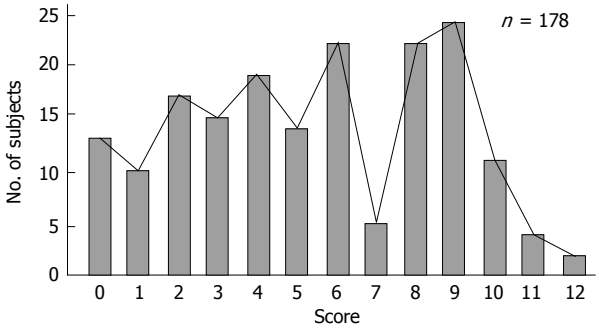

Figure 4 Distribution of a new scoring (Hyodo-Komgane score) in 178 patients undergoing endoscopic evaluation of swallowing.

with Hyodo-Komagane scores of 7 or less only one patient was not able to maintain adequate nutritional status with pureed diets (his Hyodo-Komagane score was 6). Ten (53%) of the 19 patients whose scores were 8 were able to eat pureed diets after a rehabilitation using the semi-solid diet made from an elemental diet. Oral intake of pureed diets was unsuccessful for those with scores of 9 or higher on the Hyodo-Komagane score (Table 3). For patients who could not eat pureed diets, enteral feeding was employed.

Adverse events

No adverse events such as cardiopulmonary events or aspiration pneumonia occurred in included subjects of this study.

DISCUSSION

The aim of this study was to obtain a cut-off value of the Hyodo-Komagane score that reliably predicted the ability to eat pureed diets in elderly patients with dysphagia. The Hyodo-Komagane scoring system differs from the original Hyodo score[9] with regard to the assessment of salivary pooling in that it uses a test jelly instead of blue-dyed water as the test meal. Jelly was used because it is very difficult for severe dysphagic patients to swallow water. In addition, we previously demonstrated a low agreement in judging the presence or absence of glottal closure response as whether the

Table 3 Association between Hyodo-Komagane score and oral intake of pureed diets

Score	Oral intake of pureed diets
0-7	Successful 100%
8[1]	Successful in some cases
9-12	Unsuccessful

[1]Some patients were able to eat pureed diets after a rehabilitation.

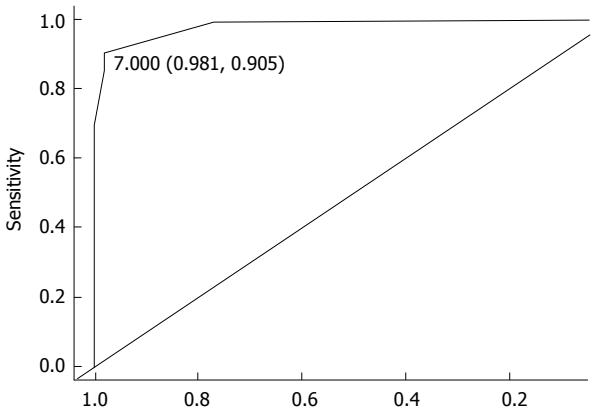

Figure 5 Receiver operating characteristic curve to evaluate the prediction capability of the Hyodo-Komgane score for successful oral intake of pureed diets.

reflex was elicited depended on how and whether the endoscopists actually touched the epiglottis[9]. Because it is difficult to be confident that the tip of the endoscope touches the epiglottis, we attempted to touch the epiglottis with the endoscope at least three times prior to scoring the reflex of glottal closure as absent. We speculate that this increased the reliability of making that determination and thus the Hyodo-Komagane modification of the scoring system improved both the validity and reliability of Hyodo score.

Dysphasia diets vary considerably from facility to facility. Dysphagia diets are designed to adjust food/liquid intake in terms of amount, consistency, and timing of the meal to achieve maximal nutritional intake and minimize swallowing difficulty. Traditional oral dysphagia diets typically involve a stepwise progression of bolus consistencies. A pureed diet is the basic level of swallowing for severe dysphagia patients. When dysphagia patients can swallow pureed diets, they generally do not require enteral nutrition including PEG[3,8]. The aim of this study was to develop methods to prospectively assess whether elderly patients with severe dysphagia could eat pureed diets. ROC analysis of this study suggested that the cut-off value of the Hyodo-Komagane score for eating the pureed diets is 7 (sensitivity = 0.98; specificity = 0.91) for predicting successful oral intake of pureed diets in elderly patients with dysphagia.

In the Hyodo-Komagane score the extent of pharyngeal clearance after swallowing of test jelly was regarded as important. Pharyngeal residue has consistently been identified to be greater using endoscopic evaluation of swallowing than when using videofluoroscopy[10] and penetration/aspiration was also perceived to be more severe with endoscopic evaluation of swallowing compared to videofluoroscopy images[11]. Penetration/aspiration is thought to be a clinically important variable in patients with swallowing dysfunction and is likely to be associated with an increased risk of aspiration/pneumonia. However, the agreement between the gastroenterologists regarding the presence of penetration/aspiration was found to be poor in our previous study[8]. Here, we scored penetration/aspiration only when penetration of saliva or the pharyngeal residues of test jelly into the larynx occurred. These phenomena were adopted as A-3 or D-3 in Hyodo-Komagane score.

In addition, the response of glottal closure reflex induced by touching the epiglottis with the endoscope was examined to assess the relationship between the sensory and motor components of the swallow. The relationship between laryngopharyngeal sensation and motor function has been well documented[12] and patients with impaired pharyngeal squeeze at different levels of sensory deficits are at significantly greater risk for aspiration of pureed foods compared with those with normal squeeze[13]. While the use of 0.5 mL of 4% lidocaine during endoscopic swallowing evaluation has been reported to impair swallowing ability in patients with dysphagia, this result did not achieve statistical significance and was associated with a reduction in subjective pain and discomfort[14]. A recent study confirmed that 0.2 mL of 4% lidocaine improved examination tolerability and did not impair the swallowing activity in dysphagic patients during endoscopic swallowing evaluation[15]. Therefore, we speculated that the amount (0.2-0.5 mL) of lidocaine used in this study had minimal effects on testing the sensory aspects of swallowing.

Our study has some limitations. This study was retrospective and comparative data using established competitive techniques are absent in part because there was no gold standard for detection of failure to swallow. Comparison with the other commonly used method such as with a videofluoroscopic swallowing study may provide useful comparative data in subsequent studies. Finally, all subjects were older than 65 years. It is unknown whether the prediction based on the Hyodo-Komagane endoscopic score are applicable to those less than 65 years old.

In conclusion, the modified scoring method for endoscopic swallowing evaluation was based on final score (from 0 to 12) using four parameters: (1) the salivary pooling in the vallecula and piriform sinuses; (2) the response of glottal closure reflex induced by touching the epiglottis with the endoscope; (3) the location of the bolus at the time of swallow onset assessed by "white-out" after the swallowing of test jelly; and (4) the extent of pharyngeal clearance after test jelly is swallowed. A total score of 7 or less during endoscopic swallowing evaluation reliably predicted the ability to eat pureed

diets. The use of the modified scoring system appears to be a reliable method to decide whether the elderly patients can eat pureed diets or requires enteral feeding.

ACKNOWLEDGMENTS

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COMMENTS

Background

Pureed diets are often used as an initial dysphagia diet for patients with moderate to severe dysphagia because, if the dysphagic patients can fulfill their nutritional requirements by eating pureed diets, they can avoid enteral feeding using a percutaneous endoscopic gastrostomy tube. However, no methods for predicting successful oral intake of pureed diets in elderly patients with dysphagia have been established.

Research frontiers

The authors' group pioneered a scoring system for endoscopic swallowing evaluation in elderly patients with dysphagia; the authors think that the method for predicting successful oral intake of pureed diets in elderly patients with dysphagia should be established and they provide support to their hypothesis with this paper, reporting that the Hyodo-Komagane endoscopic score is useful to predict the ability to eat pureed diets in elderly patients with dysphagia.

Innovations and breakthroughs

Endoscopic and videofluoroscopic examinations have been used to evaluate swallowing and to quantify the risk of aspiration. However, endoscopic determination of whether patients could swallow pureed diets was not always reproducible or safe especially for severely dysphagic patients. Irreproducibility was possibly related to variability in the texture and physical characteristics of the pureed diet despite being prepared in the same facility. This paper shows a new scoring system for endoscopic swallowing evaluation using a test jelly so that elderly patients with severe dysphagia can undergo endoscopic examination of swallowing safely even unable to swallow pureed diets; in addition, the cut-off value of the score for eating the pureed diets was defined as 7 (sensitivity = 0.98; specificity = 0.91).

Applications

Elderly patients with dysphagia will benefit from the use of Hyodo-Komagane endoscopic score which is useful to predict the ability to eat pureed diets. If evaluated with this scoring system, avoiding unfavorable enteral feeding.

Terminology

When saliva or test jelly enters the glottis (opening to the trachea) and moves as far as the vestibule above the true vocal folds, this is termed as penetration; aspiration is defined when the test materials passed into the trachea below the true vocal folds. White-out is defined as the period when the videoendoscopic image is obscured owing to pharyngeal closure.

Peer-review

This is a nice study, well-conceived and written.

REFERENCES

1 Annual Health, Labour and Welfare Report, For the Realization of a Society of Health and Longevity. Ministry of Health, Labour and Welfare, Japan, 2014. Available from: URL: http://www.mhlw.go.jp/english/wp/wp-hw8/dl/summary.pdf

2 **Teramoto S**, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. *J Am Geriatr Soc* 2008; **56**: 577-579 [PMID: 18315680 DOI: 10.1111/j.1532-5415.2008.01597.x]

3 **Wilkinson TJ**, Thomas K, MacGregor S, Tillard G, Wyles C, Sainsbury R. Tolerance of early diet textures as indicators of recovery from dysphagia after stroke. *Dysphagia* 2002; **17**: 227-232 [PMID: 12140651 DOI: 10.1007/s00455-002-0060-9]

4 **Langmore SE**, Schatz K, Olson N. Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. *Ann Otol Rhinol Laryngol* 1991; **100**: 678-681 [PMID: 1872520]

5 **Kidder TM**, Langmore SE, Martin BJ. Indications and techniques of endoscopy in evaluation of cervical dysphagia: comparison with radiographic techniques. *Dysphagia* 1994; **9**: 256-261 [PMID: 7805425]

6 **Wu CH**, Hsiao TY, Chen JC, Chang YC, Lee SY. Evaluation of swallowing safety with fiberoptic endoscope: comparison with videofluoroscopic technique. *Laryngoscope* 1997; **107**: 396-401 [PMID: 9121321]

7 **Leder SB**, Sasaki CT, Burrell MI. Fiberoptic endoscopic evaluation of dysphagia to identify silent aspiration. *Dysphagia* 1998; **13**: 19-21 [PMID: 9391224 DOI: 10.1007/PL00009544]

8 **Sakamoto T**, Horiuchi A, Nakayama Y. Transnasal endoscopic evaluation of swallowing: a bedside technique to evaluate ability to swallow pureed diets in elderly patients with dysphagia. *Can J Gastroenterol* 2013; **27**: 459-462 [PMID: 23936875]

9 **Hyodo M**, Nishikubo K, Hirose K. [New scoring proposed for endoscopic swallowing evaluation and clinical significance]. *Nihon Jibiinkoka Gakkai Kaiho* 2010; **113**: 670-678 [PMID: 20845709 DOI: 10.3950/jibiinkoka.113.670]

10 **Kelly AM**, Leslie P, Beale T, Payten C, Drinnan MJ. Fibreoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? *Clin Otolaryngol* 2006; **31**: 425-432 [PMID: 17014453 DOI: 10.1111/j.1749-4486.2006.01292.x]

11 **Kelly AM**, Drinnan MJ, Leslie P. Assessing penetration and aspiration: how do videofluoroscopy and fiberoptic endoscopic evaluation of swallowing compare? *Laryngoscope* 2007; **117**: 1723-1727 [PMID: 17906496 DOI: 10.1097/MLG.0b013e318123ee6a]

12 **Setzen M**, Cohen MA, Mattucci KF, Perlman PW, Ditkoff MK. Laryngopharyngeal sensory deficits as a predictor of aspiration. *Otolaryngol Head Neck Surg* 2001; **124**: 622-624 [PMID: 11391251 DOI: 10.1067/mhn.2001.116035]

13 **Perlman PW**, Cohen MA, Setzen M, Belafsky PC, Guss J, Mattucci KF, Ditkoff M. The risk of aspiration of pureed food as determined by flexible endoscopic evaluation of swallowing with sensory testing. *Otolaryngol Head Neck Surg* 2004; **130**: 80-83 [PMID: 14726914 DOI: 10.1016/j.otohns.2003.09.026]

14 **Fife TA**, Butler SG, Langmore SE, Lester S, Wright SC, Kemp S, Grace-Martin K, Lintzenich CR. Use of topical nasal anesthesia during flexible endoscopic evaluation of swallowing in dysphagic patients. *Ann Otol Rhinol Laryngol* 2015; **124**: 206-211 [PMID: 25204714 DOI: 10.1177/0003489414550153]

15 **O'Dea MB**, Langmore SE, Krisciunas GP, Walsh M, Zanchetti LL, Scheel R, McNally E, Kaneoka AS, Guarino AJ, Butler SG. Effect of Lidocaine on Swallowing During FEES in Patients With Dysphagia. *Ann Otol Rhinol Laryngol* 2015; **124**: 537-544 [PMID: 25667217 DOI: 10.1177/0003489415570935]

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ORIGINAL ARTICLE

Retrospective Study

Use of automated irrigation pumps improves quality of bowel preparation for colonoscopy

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Author contributions: Ravi S, Sabbagh R and Antaki F designed the study; Ravi S and Sabbagh R collected data; Ravi S and Antaki F performed data analysis and interpretation, drafting of manuscript and draft revision; Ravi S, Sabbagh R and Antaki F approved the final manuscript.

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Institutional review board statement: The study was approved by the Wayne State University Institutional Review Board (IRB# 025911M1E(V)) and the John D. Dingell Veterans Affairs Medical Center Research Committee.

Informed consent statement: A waiver of informed consent was granted by the Wayne State University Institutional Review Board (IRB) as the study satisfied the following criteria: (1) risk is no more than minimal, (2) the waiver does not adversely affect the rights and welfare of research participants and (3) the research could not be practicably carried out without the waiver. All research participants had signed informed consent for the colonoscopy procedure.

Conflict-of-interest statement: None of the authors have any financial conflict of interest in relationship to the submitted manuscript.

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Abstract

AIM: To evaluate the effectiveness of automated irrigation pumps (AIPs) in improving the quality of the bowel preparation and the yield of colonoscopy.

METHODS: A retrospective observational study was conducted at a single medical center. Outpatient colonoscopies performed during a 4-mo time period when AIPs were not in use, were compared to colonoscopies performed during control period. The main outcomes measured were quality of bowel preparation, procedures aborted due to poor preparation, recommendations to repeat at short interval due to suboptimal bowel preparation and adenoma detection rates.

RESULTS: One thousand and thirty-seven colonoscopies were included. A higher proportion of cases did not achieve a satisfactory bowel preparation when AIPs were not used (24.4% *vs* 10.3%, $P < 0.01$). The number of procedures aborted due to inadequate preparation was not significantly different, however a repeat procedure at a short interval was recommended in a higher proportion of cases when AIPs were not used (21.3% *vs* 6.9%, $P < 0.01$). Good or excellent preparation was 2.91 (95%CI: 2.04-4.15) times more likely when AIPs were used. Detection of polyps and adenomas was not significantly different.

CONCLUSION: AIP use during colonoscopy results in a higher proportion of colonic preparation rated as satisfactory, although polyp detection rate is not significantly affected. Recommendations for repeat colonoscopy at shorter interval significantly decrease with the use of AIPs. This study supports the use of the irrigation pumps in endoscopy units to improve the quality of colonoscopy.

Key words: Automated irrigation pumps; Adenoma; Quality; Polyps; Bowel preparation; Surveillance interval; Colonoscopy

Core tip: The use of automated irrigation pumps during colonoscopy results in higher quality of preparation and decreases recommendations for repeating colonoscopy at short interval.

Ravi S, Sabbagh R, Antaki F. Use of automated irrigation pumps improves quality of bowel preparation for colonoscopy. *World J Gastrointest Endosc* 2016; 8(6): 295-300 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i6/295.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i6.295

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer deaths in the United States[1,2]. Colonoscopy is used for screening to detect early cancer, and may also prevent CRC by detection and removal of the CRC neoplastic precursor, the adenomatous polyp[3-5]. Improving the yield of colonoscopy has attracted much attention in recent years[6]. In the past, manual irrigation using water-filled syringes, was used to clean any retained fecal matter or colonic contents, in order to allow for a detailed examination of the colonic mucosa and therefore to improve the yield of colonoscopy[7,8]. Automated irrigation pumps (AIPs), which are operated by a foot pedal and connect to the auxiliary channel of newer generation endoscopes have largely replaced the manual irrigation method, as they are much more efficient and convenient. It is, however, not known whether the AIPs increase the detection of polyps during colonoscopy when compared to the manual method. Moreover, the efficacy of these AIPs in decreasing the rate of procedures prematurely repeated due to inadequate bowel preparation has also never been studied. The aim of this study is to evaluate the effectiveness of AIPs in improving the quality of the bowel preparation, improving the yield of colonoscopy and decreasing the rate of repeat colonoscopy for inadequate bowel preparation.

MATERIALS AND METHODS

Study design

The study was conducted at the John D. Dingell Veterans Affairs Medical Center (JDDVAMC) in Detroit, Michigan. It was approved by the Wayne State University Institutional Review Board and the JDDVAMC Research Committee.

A retrospective chart review was performed for colonoscopies completed during the study periods. The use of AIPs was suspended at the endoscopy unit of the JDDVAMC for a period of 4 mo in 2009 for administrative reasons; therefore patients who underwent colonoscopy during this period constituted the main study group. For these procedures, manual irrigation was performed at the request of endoscopist, when retained fecal or bilious material was encountered. It was done by a technician using syringes filled with 60 mL of sterile water through the suction channel of the endoscope. Patients who underwent colonoscopy in an eight-month period in 2008 and 2009 constituted the control groups. They were selected to match the level of training of the gastroenterology fellows involved and the calendar year of the study group. Standard bowel preparation for both groups consisted of conventional dosing of a 4-L polyethylene glycol solution and 15 mg of Bisacodyl the evening prior to endoscopy. Colonoscopies that were aborted due to reasons other than poor colonic preparations, procedures repeated at a short interval (such as for follow-up after piecemeal polypectomy), colonoscopies performed on hospitalized patients, and those performed by non-gastroenterologists were excluded from the study.

Information was collected by review of the medical records about each patient's demographics, indication for the procedure, history of prior adenomatous polyps or cancer, involvement of a gastroenterology fellow, use of the AIPs, quality of the colonic preparation, detection of polyps and adenomas, with all associated details, and if the procedure was aborted due to sub-optimal preparation or if it was advised to repeat the procedure sooner than recommended by guidelines due to the quality of the preparation.

Colonoscopy was performed using Olympus Q160 and Q180 endoscopes (Olympus America Inc., Center Valley, PA). Some procedures were performed by an

Table 1 Baseline characters of the study population

	Manual flushes	Automated irrigation pumps	*P* value
n	328	709	
Age, yr (mean, 95%CI)	60.0 (59.0-61.1)	60.3 (59.6-61.1)	0.70
Gender, *n* (%)			0.34
Female	18 (5.5)	49 (6.9)	
Male	310 (94.5)	660 (93.1)	
Race, *n* (%)			0.47
African-American	176 (53.7)	359 (50.6)	
Caucasian	146 (44.5)	341 (48.1)	
Others	6 (1.8)	9 (1.3)	
Performed by: *n* (%)			0.42
Attending physician alone	65 (19.8)	156 (22.0)	
GI fellow with attending physician	263 (80.2)	553 (78.0)	
Indications, *n* (%)			0.09
Screening	191 (58.2)	373 (52.6)	
Diagnostic	137 (41.8)	336 (47.4)	
History of CRC/polyps, *n* (%)			0.55
No	238 (72.6)	527 (74.3)	
Yes	90 (27.4)	182 (25.7)	

GI: Gastroenterology; CRC: Colorectal cancer.

attending physician alone (board-certified in Gastroenterology), while, in other cases, the attending physician directly supervised a gastroenterology fellow. Attending physicians involved in the procedures were the same during the different study periods. AIPs (OFP, Olympus America Inc., Center Valley, PA) were available in every procedure room and routinely connected to the endoscope during the control period. Indications for colonoscopy were classified into either screening or diagnosis. The bowel preparation was determined by the attending physician for every case and reported in the endoscopy report using the Aronchick scale[9], as excellent, good, fair or poor. For our study, we considered the bowel preparation to be satisfactory if the procedure report described it as either good or excellent, no retained fecal material was mentioned in the findings and no recommendation for repeat at short interval for sub-optimal bowel preparation was made.

The primary outcomes were quality of the bowel preparation and the number of procedures aborted or repeated early due to sub-optimal preparation. The secondary outcomes evaluated were detection rates for polyps and adenomas.

Statistical analysis

SAS version 9.3 (SAS Institute, Cary, NC) was used for statistical analyses. For the preliminary descriptive analyses, χ^2 test was used for the description of categorical variables and a two-sided *t*-test was used for continuous variables for the comparison of means. Multivariable logistic regression model was used to compare the outcomes between the groups. Odds ratio was considered to be statistically significant if the *P* value was less than 0.05.

RESULTS

Information was collected for a total of 1037 colonoscopies. AIPs were used for 709 procedures. Mean age of the group was 60.23 years. Majority was male (93.5%). The study group included 535 (51.6%) African-Americans and 487 (47%) Caucasians. Five hundred and sixty-four colonoscopies were performed for screening or surveillance (54.4%), while 473 (45.6%) were performed for diagnostic purposes. Two hundred and seventy-two (26.2%) of the patients had a prior history of polyps/CRC. The two groups were not significantly different in the demographic factors, endoscopist, indication for the procedure or history of polyps or CRC (Table 1).

A significantly higher proportion of cases did not achieve a satisfactory bowel preparation when manual flushes were used as compared to when AIPs were used (24.4% *vs* 10.3%, $P < 0.01$) (Table 2). Although the number of procedures aborted due to poor preparation was slightly higher in the group with manual flushes, this was not statistically different ($P = 0.10$). However a repeat procedure at a short interval was recommended in a significantly higher proportion of cases when manual flushes were used (21.3% *vs* 6.9%, $P < 0.01$). On multivariate logistic regression analysis, after adjusting for indication, history of polyps or CRC, sex, age and race, odds of calling bowel preparation satisfactory was 2.91 (95%CI: 2.04-4.15) times more likely when AIPs were used in comparison to manual flushes. When adjusted for the same variables, the detection of polyps and adenomas was not significantly different between the two groups.

DISCUSSION

Colonoscopy is a cost-effective (USD 11900 per year of life gained)[10] tool for screening and prevention of CRC through the detection and removal of pre-cancerous, adenomatous polyps. However sub-optimal bowel preparation limits the effectiveness of colonoscopy as it

Table 2 Colonoscopy results stratified by the use of the automated irrigation pumps

	Manual flushes	Automated irrigation pumps	Odds ratio (95%CI) *P* value
n	328	709	
Prep quality, *n* (%)			2.91 (2.04-4.15) $P < 0.01$
Sub-optimal prep	80 (24.4)	73 (10.3)	
Satisfactory prep	248 (75.6)	636 (89.7)	
Procedure aborted due to poor prep, *n* (%)			2.45 (0.92-6.50) $P = 0.10$
No	323 (98.5)	684 (96.5)	
Yes	5 (1.5)	25 (3.5)	
Recommendation to repeat early due to prep quality, *n* (%)			0.27 (0.18-0.40) $P < 0.01$
No	258 (78.7)	660 (93.1)	
Yes	70 (21.3)	49 (6.9)	
Polyp detection, *n* (%)			0.85 (0.64-1.12) $P = 0.60$
Yes	194 (59.2)	407 (57.4)	
No	134 (40.8)	302 (42.6)	
Adenoma detection, *n* (%)			0.99 (0.75-1.31) $P = 0.65$
Yes	133 (40.6)	298 (42.0)	
No	195 (59.4)	411 (58.0)	

can result in a higher than usual rate of missed polyps, which can lead to interval cancers[11]. Studies have shown than endoscopists do not always follow guidelines and frequently recommend repeat colonoscopy at a shorter interval than suggested by those guidelines[12,13]. This makes colonoscopy less cost-effective as a CRC screening modality. The reasons for such recommendations are not well known[12], however the fear of missed lesions when bowel preparation is sub-optimal is probably a major factor[14].

For all these reasons, a lot of attention has been paid in recent years towards improving the quality of bowel preparation, such as multiple studies comparing different types and brands of laxatives used for bowel preparation, as well as the recommended changes in the timing of those laxatives to "split dose"[15].

However, there has not been much research to evaluate the effectiveness of AIPs in enhancing the adenoma detection rate, improving the quality of bowel preparation or decreasing the rate of procedures prematurely aborted and repeated due to inadequate bowel preparation. Our study supports the hypothesis that the use of AIPs during colonoscopy results in a significantly higher proportion of colonic preparation being rated as satisfactory with a corresponding decline in the odds of recommending a repeat procedure at a shorter than usual interval.

Our study results are in concurrence with other studies evaluating the relationship between quality of the bowel prep and the recommendation from the endoscopist about the timing of the repeat procedure[16-18]. As colonoscopy is usually aborted when the bowel preparation is very poor and unlikely to be improved with any type of irrigation, manual or automated, there was no difference in the rate of procedures aborted for poor preparation in our study.

Although studies have shown an increase in adenoma and polyp detection rate with improvement in the quality of bowel prep[16,19-21], we did not find an increased rate of adenoma or polyp detection with the use of AIPs, despite the improvement in the quality of the bowel preparation. We believe this could possibly be from the heightened vigilance of the endoscopist when the use of AIPs was suspended for a limited period of time in our unit, and the results might have been different if the AIPs were introduced for the first time during the study.

The study has a few limitations. The retrospective design has some inherent limitations. The determination of the quality of preparation was based on each individual endoscopist's interpretation on the Aronchick scale. Withdrawal time was not routinely recorded in our endoscopy unit at the time of the study. The influence of cleaning using manual flushes or AIPs on total procedure as well as on withdrawal times, which might be different depending on the quality of the bowel preparation, could not be determined. The total volume of water used in either group was not recorded. Although the devices were routinely connected to the endoscope for every single case in the AIPs group, while they were not available in the other group, we could not determine if irrigation by either method was indeed used in every case. Some of the information that could influence adenoma detection rate such as lifestyle and dietary habits could not be evaluated. The sample in itself included both diagnostic and screening colonoscopies. We attempted to alleviate the bias by adjusting for indication of colonoscopy. In addition, our study population was from a Veterans Affairs medical center with a majority of African-American males. This

might limit the generalizability of the results of the study. The suspension of the use of AIPs for a period of time might by itself have led to results that could be different if AIPs were being introduced to an endoscopy unit for the first time. As we used the conventional bowel preparation regimen in our endoscopy unit at the time of the study, we could not evaluate the usefulness of AIPs with split dose bowel regimen.

In conclusion, our study provides evidence that AIPs improve the endoscopist assessment of the quality of the bowel preparation and reduce the number of repeat procedures due to sub-optimal preparation. This supports the widespread use of these devices in endoscopy units to improve the quality of colonoscopy.

COMMENTS

Background

Colonoscopy is used for screening to detect early cancer, and may also prevent colorectal cancer (CRC) by detection and removal of the CRC neoplastic precursor, the adenomatous polyp. Automated irrigation pumps (AIPs), which are operated by a foot pedal and connect to the auxiliary channel of newer generation endoscopes have largely replaced the manual irrigation method, as they are much more efficient and convenient. It is, however, not known whether the AIPs increase the detection of polyps during colonoscopy when compared to the manual method. Moreover, the efficacy of these AIPs in decreasing the rate of procedures prematurely repeated due to inadequate bowel preparation has also never been studied.

Research frontiers

AIPs, which are operated by a foot pedal and connect to the auxiliary channel of newer generation endoscopes have largely replaced the manual irrigation method, as they are much more efficient and convenient.

Innovations and breakthroughs

The aim of this study is to evaluate the effectiveness of AIPs in improving the quality of the bowel preparation, improving the yield of colonoscopy and decreasing the rate of repeat colonoscopy for inadequate bowel preparation.

Applications

This study provides evidence that AIPs improve the endoscopist assessment of the quality of the bowel preparation and reduce the number of repeat procedures due to sub-optimal preparation. This supports the widespread use of these devices in endoscopy units to improve the quality of colonoscopy.

Peer-review

This manuscript by Ravi *et al* describes a retrospective evaluation of patients receiving colonoscopy performed with manual irrigation or an automatic irrigation device. The manuscript is certainly relevant to modern endoscopic practices.

REFERENCES

1 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71-96 [PMID: 18287387 DOI: 10.3322/CA.2007.0010]

2 **American Cancer Society**. Cancer Facts & Figures 2014. Atlanta: American Cancer Society, 2014

3 **Zauber AG**, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]

4 **Bokemeyer B,** Bock H, Huppe D, Düffelmeyer M, Rambow A, Tacke W, Koop H. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. *Eur J Gastroenterol Hepatol* 2009; **21:** 650-655 [DOI: 10.1097/MEG.0b013e32830b8acf]

5 **Lieberman DA**, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; **343**: 162-168 [PMID: 10900274]

6 **Imperiale TF**, Glowinski EA, Juliar BE, Azzouz F, Ransohoff DF. Variation in polyp detection rates at screening colonoscopy. *Gastrointest Endosc* 2009; **69**: 1288-1295 [PMID: 19481649 DOI: 10.1016/j.gie.2007.11.043]

7 **Froehlich F**, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005; **61**: 378-384 [PMID: 15758907]

8 **Harewood GC**, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003; **58**: 76-79 [PMID: 12838225]

9 **Aronchick CLW**, Wright S, DuFrayne F, Bergman G. Validation of an instrument to assess colon cleansing. *AM J Gastroenterol* 1999; **94**: 2667

10 **Maciosek MV**, Solberg LI, Coffield AB, Edwards NM, Goodman MJ. Colorectal cancer screening: health impact and cost effectiveness. *Am J Prev Med* 2006; **31**: 80-89 [PMID: 16777546]

11 **Baxter NN**, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; **150**: 1-8 [PMID: 19075198]

12 **Saini SD**, Nayak RS, Kuhn L, Schoenfeld P. Why don't gastroenterologists follow colon polyp surveillance guidelines?: results of a national survey. *J Clin Gastroenterol* 2009; **43**: 554-558 [PMID: 19542818 DOI: 10.1097/MCG.0b013e31818242ad]

13 **Mysliwiec PA**, Brown ML, Klabunde CN, Ransohoff DF. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. *Ann Intern Med* 2004; **141**: 264-271 [PMID: 15313742]

14 **Menees SB**, Kim HM, Elliott EE, Mickevicius JL, Graustein BB, Schoenfeld PS. The impact of fair colonoscopy preparation on colonoscopy use and adenoma miss rates in patients undergoing outpatient colonoscopy. *Gastrointest Endosc* 2013; **78**: 510-516 [PMID: 23642491 DOI: 10.1016/j.gie.2013.03.1334]

15 **Cohen B**, Tang RS, Groessl E, Herrin A, Ho SB. Effectiveness of a simplified "patient friendly" split dose polyethylene glycol colonoscopy prep in Veterans Health Administration patients. *J Interv Gastroenterol* 2012; **2**: 177-182 [PMID: 23687605]

16 **Lebwohl B**, Kastrinos F, Glick M, Rosenbaum AJ, Wang T, Neugut AI. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest Endosc* 2011; **73**: 1207-1214 [PMID: 21481857 DOI: 10.1016/j.gie.2011.01.051]

17 **Ben-Horin S**, Bar-Meir S, Avidan B. The impact of colon cleanliness assessment on endoscopists' recommendations for follow-up colonoscopy. *Am J Gastroenterol* 2007; **102**: 2680-2685 [PMID: 17714555]

18 **Menees SB**, Elliott E, Govani S, Anastassiades C, Judd S, Urganus A, Boyce S, Schoenfeld P. The impact of bowel cleansing on follow-up recommendations in average-risk patients with a normal colonoscopy. *Am J Gastroenterol* 2014; **109**: 148-154 [PMID: 24496417 DOI: 10.1038/ajg.2013.243]

19 **Adler A**, Wegscheider K, Lieberman D, Aminalai A, Aschenbeck J, Drossel R, Mayr M, Mroß M, Scheel M, Schröder A, Gerber K, Stange G, Roll S, Gauger U, Wiedenmann B, Altenhofen L, Rosch T. Factors determining the quality of screening colonoscopy: a prospective study on adenoma detection rates, from 12,134 examinations (Berlin colonoscopy project 3, BECOP-3). *Gut* 2013; **62**: 236-241 [PMID: 22442161 DOI: 10.1136/gutjnl-2011-300167]

20 **Chokshi RV**, Hovis CE, Hollander T, Early DS, Wang JS. Prevalence of missed adenomas in patients with inadequate bowel

preparation on screening colonoscopy. *Gastrointest Endosc* 2012; **75**: 1197-1203 [PMID: 22381531 DOI: 10.1016/j.gie.2012.01.005]
21 **Sherer EA**, Imler TD, Imperiale TF. The effect of colonoscopy preparation quality on adenoma detection rates. *Gastrointest Endosc* 2012; **75**: 545-553 [PMID: 22138085 DOI: 10.1016/j.gie.2011.09.022]

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Retrospective Study

Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis

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Abstract

AIM: To identify characteristic endoscopic findings and risk factors for cytomegalovirus (CMV)-associated colitis in patients with active ulcerative colitis (UC).

METHODS: A total of 149 UC patients admitted to the Department of Gastroenterology, Nagoya University Hospital, from January 2004 to December 2013 with exacerbation of UC symptoms were enrolled in this retrospective study. All medical records, including colonoscopy results, were reviewed. CMV infection was determined by the presence of CMV antigen, CMV inclusion bodies in biopsy specimens, or positive specific immunohistochemical staining for CMV. Multivariate analysis was used to identify independent risk factors for CMV colitis.

RESULTS: Multivariate analysis indicated independent associations with the extent of disease (pancolitis) and

use of > 400 mg corticosteroids for the previous 4 wk. In contrast, no association was seen with sex, age at UC diagnosis, immunomodulator use, or infliximab use. Punched-out ulceration was also significantly associated with CMV infection in patients with active UC (odds ratio = 12.672, 95%CI: 4.210-38.143).

CONCLUSION: Identification of a total corticosteroid dose > 400 mg for 4 wk, extensive colitis and a specific endoscopic finding of punched-out ulcer might facilitate the more rapid diagnosis and timely initiation of anti-viral therapy for CMV-associated colitis in patients with active UC.

Key words: Colonoscopy; Risk factor; Ulcerative colitis; Antigenemia; Cytomegalovirus

Core tip: It has been reported that cytomegalovirus (CMV) infection can be associated with steroid resistance and be an exacerbating factor in ulcerative colitis (UC). This paper provides important information regarding characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC. A total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis. In addition, punched-out ulceration appears predictive of CMV-associated colitis in active UC.

Hirayama Y, Ando T, Hirooka Y, Watanabe O, Miyahara R, Nakamura M, Yamamura T, Goto H. Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis. *World J Gastrointest Endosc* 2016; 8(6): 301-309 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i6/301.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i6.301

INTRODUCTION

Cytomegalovirus (CMV), a member of the double-stranded DNA human herpes virus family, is reported to infect between 40% and 100% of the general population[1]. Primary CMV infection is asymptomatic or minimally symptomatic, and is followed by a latent state, similar to other herpes virus infections[2,3]. Most cases of symptomatic CMV infection are therefore caused by reactivation of latent virus[1-3].

Although active CMV infection can occur in immunocompetent individuals, it occurs most frequently in immunocompromised patients, such as those with acquired immunodeficiency syndrome, leukemia patients during chemotherapy, and patients on high-dose immunosuppressants (*e.g.*, recipients of solid organ or bone marrow transplants)[1,4-7].

Powell *et al*[8] reported that CMV infection in patients with ulcerative colitis (UC) was associated with exacerbation of symptoms, while one early retrospective study reported the presence of CMV in surgical specimens of patients who underwent colectomy for the treatment of toxic megacolon or steroid-resistant UC[9]. However, the significance of CMV infection in inflammatory bowel disease (IBD) is still controversial, and the pathogenic role of CMV infection in IBD is debated: Some authors believe that CMV is only an "innocent bystander" and does not significantly impact outcome, whereas many other studies have reported a significant association between CMV infection and IBD[10-13].

Active CMV infection has been observed in UC patients receiving high-dose corticosteroid therapy[13-17]. From 27% to 100% of patients with steroid-refractory UC have been found to harbor CMV, and steroid resistance is one of the central characteristics of CMV infection in UC patients[9,16,18-21]. Moreover, multiple studies have concluded that CMV infection can be an exacerbating factor in UC patients and that UC prognosis is generally poor in patients with CMV if anti-viral therapy is not started at an early stage[2,3,13-15,21-23].

Thus, CMV infection may exacerbate UC and may even cause death if appropriate treatment is not given. Although the development of ganciclovir (GCV) antiviral therapy has improved outcomes of CMV-associated colitis[5,17,20], CMV infection must still be diagnosed early in corticosteroid-resistant UC patients so that antiviral therapy can be initiated as soon as possible. However, it is difficult to distinguish exacerbation of UC by CMV infection from exacerbation not associated with CMV on the basis of symptoms and signs alone. In such cases, UC symptoms, signs, and severity in patients at risk of CMV-associated colitis are routinely evaluated by endoscopy. While a few such studies have reported the absence of any characteristic endoscopic findings in patients with UC complicated by CMV infection[24], others have reported characteristic endoscopic features, including the absence of large single ulcers and the presence of longitudinal ulcers, microerosions, deep ulcers, pseudotumors, punched-out ulcers, mucosal defects, geographic ulcers, and irregular ulcers[1,25-30]. These studies have methodological differences, however, and no consensus on unique endoscopic features that can be used to facilitate early diagnosis of CMV-associated colitis in UC has yet been obtained.

Against this background, we conducted a retrospective review of all clinical and endoscopic findings in a large cohort of patients with moderate to severe UC with symptom exacerbation to identify risk factors and characteristic endoscopic findings of CMV-associated colitis.

MATERIALS AND METHODS

Patients

This study was a retrospective analysis of medical charts and endoscopic images obtained from patients diagnosed with moderate to severe (active) UC. From

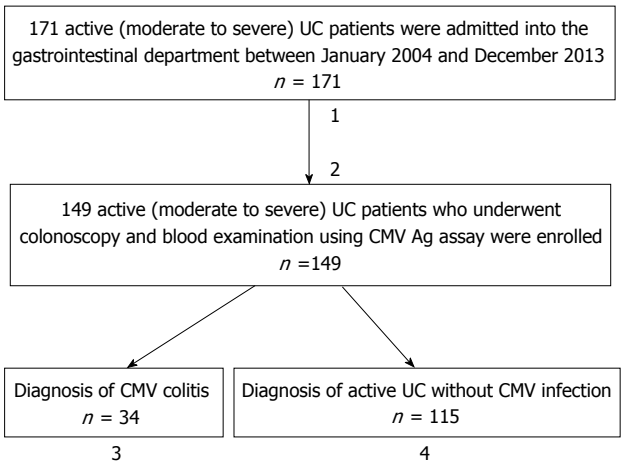


Figure 1 Clinical course of cytomegalovirus-associated colitis in patients with moderate to severe ulcerative colitis. Flow chart of the 171 patients admitted to our department with active UC. [1]Seven patients with a history of CMV-associated colitis or anti-CMV treatment were excluded; [2]Fifteen patients who had not undergone colonoscopy and examination using the CMV antigenemia assay were also excluded; [3]Out of 34 UC patients with CMV-associated colitis, 26 received GCV antiviral therapy. After GCV therapy, 13 patients achieved remission, but 13 required colectomy. Eight patients did not receive GCV antiviral therapy, 4 of whom underwent colectomy; [4]The remaining 115 UC patients not diagnosed with CMV-associated colitis received treatment for active UC, of which 81 achieved remission. Of the remaining patients, some improved but did not fulfill remission criteria, while others required a second treatment, hospitalization, or colectomy. CMV: Cytomegalovirus; UC: Ulcerative colitis; Ag: Antigenemia; GCV: Ganciclovir.

January 2004 to December 2013, a total of 171 UC patients were admitted to the Department of Gastroenterology, Nagoya University Hospital, with exacerbation of UC symptoms (Figure 1). The diagnosis of UC was based on clinical, endoscopic, radiological, and pathological criteria, and the severity of UC was assessed according to Stange *et al*[31], Truelove *et al*[32] and Dignass *et al*[33]. We routinely examine CMV antigenemia in such patients, and almost all undergo colonoscopy or sigmoidoscopy at admission[34-36]. Of the present 171 patients, we excluded 7 patients with a previous history of CMV-associated colitis or anti-CMV treatment, as well as 15 patients who had not undergone colonoscopy or examination using the antigenemia assay. Finally, 149 patients who received both a blood test for CMV antigenemia and endoscopic examination at admission were included in the analysis.

The following demographic and clinical data were obtained at the time of admission and classified according to the Montreal Classification[31,33]: Age at admission, age at diagnosis, sex, familial or spontaneous disease (familial disease was considered when at least one first- or second-degree relative was diagnosed with IBD), and disease localization (proctitis, left sided colitis, or pancolitis) as revealed by colonoscopy.

Endoscopic findings

Disease severity was assessed by colonoscopy. If ulcers were present, the shape and depth were described, and biopsies were obtained at the margin and base for histologic investigation. If no ulcers were detected, biopsies were obtained in the areas with the most severe inflammation. Colonic biopsy specimens were fixed, paraffinized, and stained with hematoxylin and eosin (HE) and specific immunohistochemical (IHC) staining with monoclonal antibody against CMV immediate early antigen[6,37]. Specimens were also evaluated for the presence of characteristic CMV inclusion bodies by experienced pathologists.

Diagnosis of CMV infection/CMV-associated colitis

CMV infection was defined by a positive CMV antigenemia assay, the presence of inclusion bodies in HE stained sections, or positive specific IHC staining for CMV. Diagnosis of CMV-associated colitis in patients with active UC was determined by active UC complicated by CMV infection.

Ethical considerations

The study protocol was approved by the institutional review board of Nagoya University Graduate School of Medicine.

Statistical analysis

Data are presented as mean ± SD or number (%) as appropriate. Categorical data were compared between groups using the χ^2 or Fisher's exact test. Continuous variables were compared using the Mann-Whitney *U* test. To identify candidate risk factors and characteristic endoscopic features for CMV-associated colitis, univariate analyses were conducted using Fisher's exact test. All factors which were significant on univariate analysis were entered into multivariate logistic regression models constructed to identify significant independent risk factors and characteristic endoscopic features of CMV-associated colitis. For continuous variables, we found the best cut-off value with plotting the area under the receiver operating characteristic curve. The results are expressed as odds ratios (ORs) with 95%CIs. *P*-values less than 0.05 were considered statistically significant for all tests. All statistical analyses were performed using SPSS Statistics 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

A total of 149 UC patients presenting with UC symptom exacerbation between January 2004 and December 2013 were included in the study. Of these, 34 (22.8%) tested positive on CMV antigenemia assay or had biopsy specimens with indicative of CMV infection. The clinical and demographical parameters of CMV-positive and CMV-negative patients are presented in Table 1. Univariate analysis revealed statistically significant group differences in age at UC diagnosis, age at admission, extent of disease (pancolitis), serum albumin level, systemic steroid dose on the day of admission, total systemic steroid dose for the week before admission, and total systemic steroid dose for 4 wk before admi-

Table 1 Clinical and demographic characteristics of patients with active ulcerative colitis (n = 149)

	CMV (+) n = 34	CMV (-) n = 115	P value
Sex (male/female)	19/15	64/51	0.981
Age at UC diagnosis (yr)	42.3 ± 14.4	29.0 ± 14.4	< 0.001
Age at admission (yr)	46.9 ± 18.1	35.0 ± 15.6	< 0.001
Disease duration (yr)	4.6 ± 4.9	6.0 ± 7.4	0.294
Clinical course			
Relapse	23 (67.6%)	79 (68.7%)	0.908
Chronic active	4 (11.8%)	11 (9.6%)	0.708
First attack	7 (20.6%)	25 (21.7%)	0.886
Disease extent			
Extensive UC (pancolitis)	28 (82%)	52 (45%)	< 0.001
Left-sided UC/proctitis	6 (18%)	63 (55%)	-
BMI at admission	19.5 ± 3.2	18.9 ± 3.1	0.384
Severity			
Severe	11 (32%)	27 (23%)	0.297
Moderate	23 (68%)	88 (77%)	-
Laboratory data at admission			
CRP (mg/dL)	3.4 ± 4.1	3.8 ± 5.4	0.685
WBC (× 10^3/μL)	8.7 ± 3.7	9.9 ± 4.2	0.132
Hemoglobin (g/dL)	11.4 ± 1.8	11.7 ± 1.2	0.387
Platelet (× 10^3/μL)	321.0 ± 118.9	349.9 ± 120.2	0.219
Total cholesterol (mg/dL)	155.3 ± 39.7	155.1 ± 44.3	0.979
Albumin (g/dL)	3.0 ± 0.54	3.4 ± 0.68	0.002
Medication			
Total lifetime systemic steroid dose before admission (g)	4.69 ± 5.80	4.86 ± 8.45	0.892
Total systemic steroid dose for 4 wk before admission (mg)	1083.4 ± 1113.5	245.5 ± 328.4	< 0.001
Total systemic steroid dose for 1 wk before admission (mg)	260.7 ± 103.9	92.3 ± 117.0	< 0.001
Systemic steroid dose on the day at admission (mg)	37.5 ± 15.0	13.9 ± 17.6	< 0.001
5-ASA	29 (85.3%)	82 (71.3%)	0.100
SASP	1 (2.9%)	10 (8.7%)	0.260
Cytapheresis	5 (15%)	11 (9.6%)	0.395
Immunomodulator use	8 (24%)	20 (17%)	0.421
AZA	4 (12%)	16 (14%)	0.747
6-MP	2 (5.9%)	2 (1.7%)	0.177
Tacrolimus	2 (5.9%)	2 (1.7%)	0.177
Infliximab use	5 (15%)	7 (6.1%)	0.105
Family history of IBD	1 (2.9%)	1 (0.87%)	0.356
PSC	0	2 (1.7%)	-
Outcome			
Ganciclovir use	26 (76%)	0	-
Colectomy	17 (50%)	37 (32%)	0.058
Colectomy for cancer or dysplasia	0	4 (3.5%)	-

Values presented as mean ± SD or number (%) as appropriate. CMV: Cytomegalovirus; CRP: C-reactive protein; WBC: White blood count; BMI: Body mass index; 5-ASA: 5-aminosalicylate acid; SASP: Salicylazosulfapyridine; AZA: Azathioprine; 6-MP: 6-mercaptopurine; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis.

Table 2 Risk factors for cytomegalovirus-associated colitis among the 149 patients with active ulcerative colitis (multivariate analysis)

	Odds ratio	95%CI	P value
Age at UC diagnosis > 30 yr	2.764	0.581-13.152	0.202
Age at admission > 35 yr	1.433	0.295-6.951	0.655
Pancolitis	3.419	1.077-10.856	0.037
Albumin < 3.0 g/dL	1.402	0.480-4.098	0.537
Total systemic steroid dose for 4 wk before admission > 400 mg	26.697	5.848-121.868	< 0.001

UC: Ulcerative colitis; CMV: Cytomegalovirus.

ssion. There were no significant group differences in sex ratio, disease duration, clinical course, total lifetime systemic steroid dose, immunomodulator use, infliximab use, or laboratory data at admission other than serum albumin level.

For multivariate analysis, we selected a total systemic steroid dose for 4 wk before admission as the most important factor among factors regarding steroid dose. This multivariate analysis using a logistic regression model identified pancolitis and a total systemic steroid dose > 400 mg for 4 wk before admission as significant independent risk factors for CMV infection (Table 2). Patients treated with more than 400 mg corticosteroid for UC exacerbation over the 4 wk prior to admission had a 27-fold greater risk of CMV-associated colitis and patients with extensive UC (pancolitis) had about a 3-fold greater risk. The other factors tested (age at UC diagnosis, age at admission, and serum albumin) were not significant risk factors by multivariate analysis.

Table 3 Endoscopic findings in patients with active ulcerative colitis (n = 149)

	CMV (+) n = 34	CMV (-) n = 115	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
Deep ulcer	17 (50.0%)	14 (12.2%)	79.2	50.0	87.8	54.8	85.6	< 0.001
Punched-out ulcer	20 (58.8%)	8 (7.0%)	85.2	58.8	93.0	71.4	88.4	< 0.001
Geographical ulcer	14 (41.2%)	25 (21.7%)	76.5	41.2	78.2	35.9	81.8	0.024
Longitudinal ulcer	11 (32.4%)	24 (20.9%)	68.5	32.4	79.1	31.4	79.8	0.165
Mucosal defect	6 (17.6%)	10 (8.7%)	74.5	17.6	91.3	37.5	78.9	0.139
Mucopurulent exudate	24 (70.6%)	66 (57.4%)	49.0	70.6	42.6	26.7	83.1	0.167
Spontaneous bleeding	14 (41.2%)	19 (16.5%)	73.8	41.2	83.5	42.4	82.8	0.002
Cobblestone-like appearance	5 (14.7%)	7 (6.1%)	75.8	14.7	93.9	41.7	78.8	0.105
Post inflammatory polyp	9 (26.5%)	21 (18.3%)	75.8	26.5	81.7	30.0	79.0	0.294

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

Table 4 Characteristic endoscopic findings for cytomegalovirus-associated colitis in patients with active ulcerative colitis (multivariate analysis)

	Odds ratio	95%CI	P value
Deep ulcer	2.128	0.678-6.680	0.196
Punched-out ulcer	12.672	4.210-38.143	< 0.001
Geographical ulcer	1.919	0.664-5.542	0.229
Spontaneous bleeding	2.106	0.735-6.036	0.166

Endoscopic findings

To identify endoscopic findings characteristic of CMV-associated colitis in patients with active UC, we analyzed ulcerative features (*e.g.*, deep ulcer, punched-out ulcer, geographical ulcer, longitudinal ulcer, and mucosal defect) and mucosal features (*e.g.*, mucopurulent exudate, spontaneous bleeding, cobblestone-like appearance, and post inflammatory polyp). Characteristic colonoscopic features of CMV-associated colitis included deep ulcer, punched-out ulcer, geographical ulcer, longitudinal ulcer, and mucosal defect (Figure 2). We defined endoscopic findings according to published reports[28,38]. Deep ulcer was defined as deep excavated ulceration near or beyond muscularis propria with or without slightly raised edges. Punched-out ulcer was defined as ulceration with an almost round shape and clear demarcation. Geographical ulcer was defined as ulceration with an irregular pattern and a branched shape. Longitudinal ulcer was defined as ulceration with a longitudinal spread along the lumen of the colon. Mucosal defect was defined as a wide area of defect with a longitudinal and/or transverse spread, indicating that more than one-fourth of the mucosa in the endoscopic field was defective. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for each of these features were determined. Univariate analysis revealed that deep ulcer, punched-out ulcer, geographical ulcer, and spontaneous bleeding were more frequent in CMV-positive patients than in CMV-negative patients (Table 3).

Multivariate analysis showed that only punched-out ulcer was a significant independent predictor of CMV colitis (OR = 12.672, 95%CI: 4.210-38.143) (Table 4).

Patient outcomes

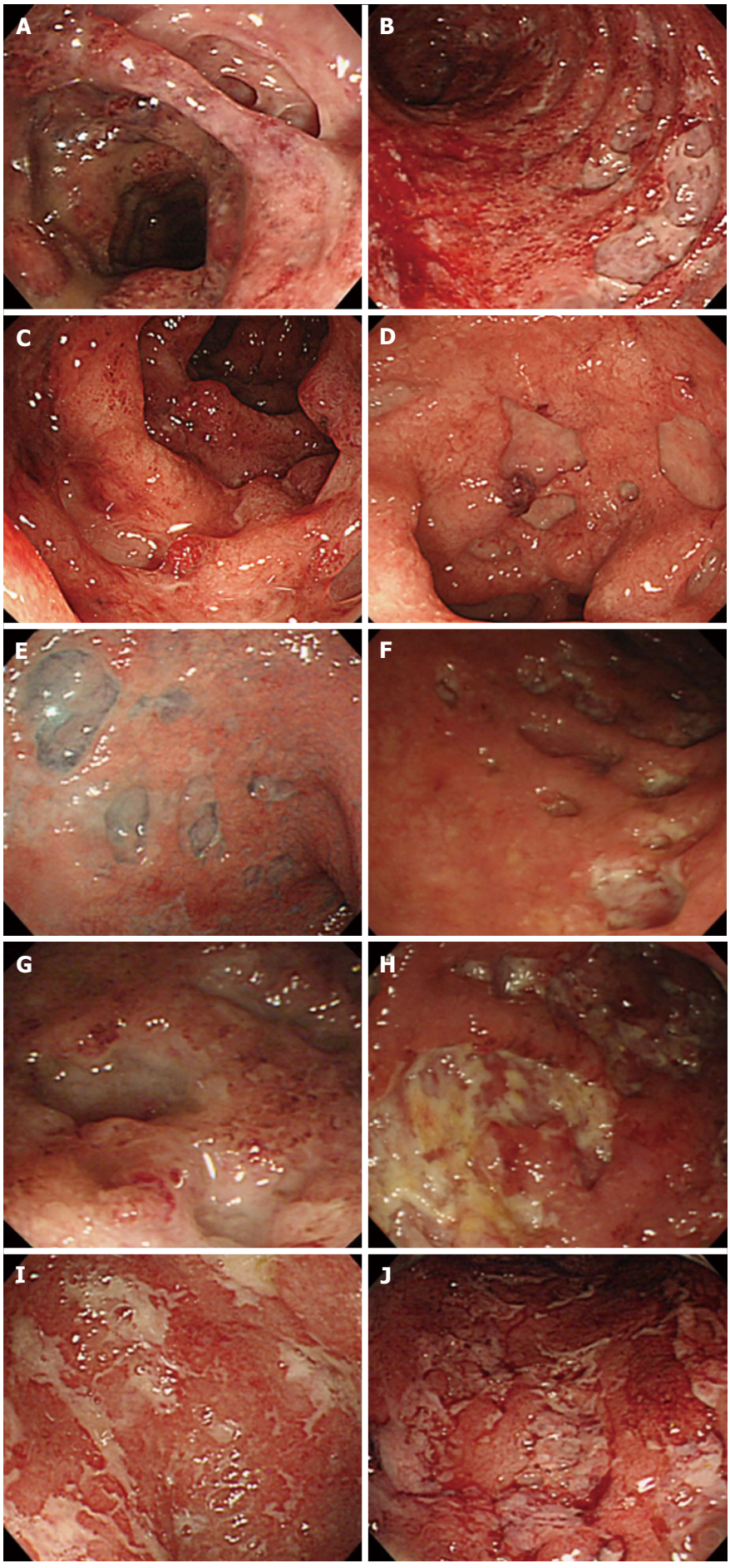
In the CMV-positive (CMV-associated colitis) group, 26 of the 34 patients (76.5%) received antiviral therapy with GCV. After GCV therapy, 13 of these patients achieved remission, while 13 required colectomy because of severe and refractory UC. Of the remaining 8 patients who did not receive GCV antiviral therapy, 4 underwent colectomy because of severe UC.

Among the CMV-negative group, 81 patients (70.4%) achieved remission with anti-inflammatory therapy (including relapse cases), while 37 (32.2%) eventually underwent colectomy during the course of follow-up. Among these 37 patients, 4 underwent colectomy for cancer or dysplasia.

DISCUSSION

In this retrospective study of 149 UC patients presenting with exacerbation of symptoms, we identified extensive UC (pancolitis) and 4 wk of high-dose steroid treatment as independent risk factors for CMV-associated colitis in active UC. The only endoscopic finding indicative of CMV-associated colitis by multivariate analysis was punched-out ulcer. To our knowledge, this is the first study to identify both risk factors and characteristic endoscopic findings for CMV-associated colitis in patients with moderate to severe UC. These factors may help facilitate both the timely diagnosis and treatment of UC complicated by CMV infection.

We evaluated total systemic steroid dose over the patient's lifetime, as well as dose over the 4 wk before admission, over the previous week before admission, and on the day of admission. Between CMV-positive and CMV-negative patients, total systemic steroid dose over the 4 wk prior to admission (total dose > 400 mg) was an independent risk factor for CMV-associated colitis in active UC patients. Furthermore, neither immunomodulator nor infliximab use was associated with CMV-associated colitis. However, this study included only a few cases treated by immunomodulators or infliximab, and additional studies are required to confirm these results. Nonetheless, the finding that immunomodulator and infliximab use did not alter the risk of CMV-associated colitis is important, because it suggests an alternative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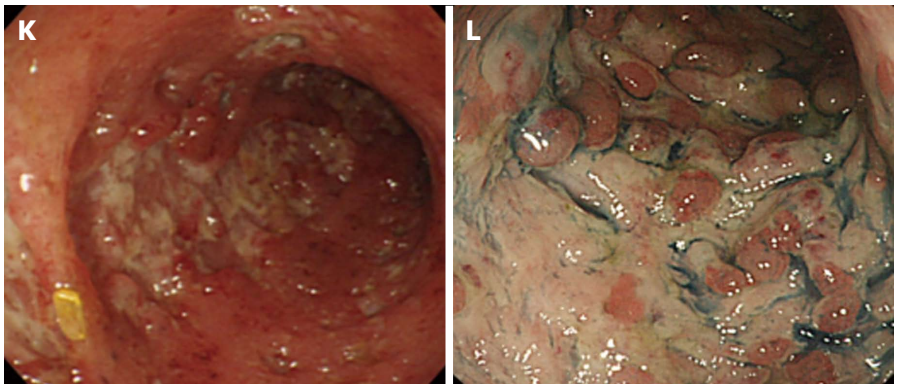

Figure 2 Endoscopic images of cytomegalovirus-associated colitis in patients with active ulcerative colitis. A-C: Deep ulcer; D-G: Punched-out ulcer; H-J: Geographical ulcer; K: Longitudinal ulcer; L: Mucosal defect.

treatment regimen for patients with moderate to severe UC rather than using high-dose corticosteroids for corticosteroid-refractory cases or corticosteroid-resistant cases. Given that tumor necrosis factor (TNF)-α from monocytes and dendritic cells plays an important role in the reactivation of CMV and that infliximab is a potent blocker of TNF-α, we consider that this combination therapy may be particularly effective[7,39]. However, the efficacy of infliximab for UC patients with concomitant CMV infection remains controversial, as there have been few case reports and no controlled clinical trials.

Pancolitis was significantly associated with CMV infection in active UC, consistent with the theory that CMV is prone to proliferate in granulation tissue[9]. Some studies reported that CMV was readily found in granulation tissue and tissue from deep ulcers, suggesting that CMV can penetrate inflamed mucosa *via* mononuclear cells and then proliferate in the mucosa[2,9,40,41]. It is thus possible that a more extensive UC lesion may lead to wider CMV infection.

In general, there is no clear consensus on the diagnostic criteria for CMV infection in active UC. There are several methods of detecting CMV infection, including histology with IHC, serology, CMV culture, polymerase chain reaction (PCR) detection of the CMV genome, and CMV antigenemia[6,34-37,42]. Each method offers advantages and disadvantages in the precise diagnosis of CMV infection. For example, histological examination is a relatively easy method, but its sensitivity is lower (10%-87%) than PCR. In contrast, PCR for CMV genes is highly sensitive, but the method is time-consuming and its selectivity is low given the ubiquity of CMV infection. CMV culture is too slow. In contrast, CMV antigenemia is relatively sensitive (60%-100%) and easy to measure within a short period, and has also been used to monitor CMV infection in heart transplant recipients and for the early diagnosis of CMV infection in renal transplant recipients[43]. Moreover, results of CMV antigenemia are good indication for antiviral therapy[44,45].

Accordingly, we adopted CMV antigenemia and histology, including IHC for CMV, to detect CMV infection in our analysis. Results showed that 33 of the 34 CMV-associated colitis patients (97.1%) were positive for CMV antigenemia. Histology including IHC is considered the objective standard for the diagnosis of CMV infection. In our study, however, among the 34 patients with CMV-associated colitis whose biopsy specimens were stained with HE and a CMV antibody, only 8 patients were positive by histology. Only 7 were positive by both CMV antigenemia and hitology. We therefore suggest that our combination of CMV antigenemia and histology including IHC for CMV is an appropriate strategy for diagnosis of CMV infection/CMV-associated colitis in active UC patients.

Colonoscopy is usually performed in patients with exacerbation of UC symptoms because direct observation of the colonic mucosa provides detailed information on disease status and is useful for judging disease severity and treatment efficacy. The rapid and accurate diagnosis of CMV-associated colitis in UC patients is critical, because its treatment strategy differs markedly from that for UC exacerbation not associated with CMV infection. A few reports have documented the endoscopic findings of CMV-associated colitis, but several failed to find features able to rapidly distinguish CMV-associated colitis from unrelated active UC. Endoscopic findings of UC concomitant with CMV infection can range from normal appearing mucosa to mucosal erosion or ulceration, which can be difficult to distinguish from active UC unrelated to CMV infection. In our study, punched-out ulceration was significantly more frequent in UC patients with CMV infection, consistent with reports that CMV tends to localize to the colon mucosa and granulation tissue in deep ulcers[2,9,40,41]. Regardless of etiology, we suggest that a finding of punched-out ulceration may facilitate the rapid and accurate diagnosis of CMV-associated colitis in UC patients.

The limitations of this study include its retrospective nature and evaluation of patients at a single institution. This study also involved a relatively small number of patients, which limits its statistical power.

In conclusion, this study suggests that a total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis in patients with moderate to severe UC. In addition, punched-out ulceration appears predictive of

CMV-associated colitis associated with UC. These clinical predictors and specific endoscopic findings may facilitate rapid diagnosis and antiviral treatment.

COMMENTS

Background

Although it has been reported that cytomegalovirus (CMV) infection can be associated with steroid resistance and be an exacerbating factor in ulcerative colitis (UC), the relationship between CMV and UC is not well studied.

Research frontiers

The aim of this study was to identify characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC.

Innovations and breakthroughs

This is one of a few retrospective studies focused on important information regarding characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC.

Applications

This study suggests that a total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis in patients with moderate to severe UC. In addition, punched-out ulceration appears predictive of CMV-associated colitis associated with UC. These clinical predictors and specific endoscopic findings may facilitate rapid diagnosis and antiviral treatment.

Peer-review

An interesting article dealing with clinically relevant subject of risk factors in ulcerative colitis. There is a solid number of patients and good experimental and clinical design. Data are good and discussion is a good representation of the problem.

REFERENCES

1 **Goodgame RW**. Gastrointestinal cytomegalovirus disease. *Ann Intern Med* 1993; **119**: 924-935 [PMID: 8215005 DOI: 10.7326/0003-4819-119-9-199311010-00010]

2 **Hommes DW**, Sterringa G, van Deventer SJ, Tytgat GN, Weel J. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. *Inflamm Bowel Dis* 2004; **10**: 245-250 [PMID: 15290919 DOI: 10.1097/00054725-200405000-00011]

3 **Surawicz CM**, Myerson D. Self-limited cytomegalovirus colitis in immunocompetent individuals. *Gastroenterology* 1988; **94**: 194-199 [PMID: 2826283]

4 **Dieterich DT**, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr* 1991; **4** Suppl 1: S29-S35 [PMID: 1848619]

5 **Papadakis KA**, Tung JK, Binder SW, Kam LY, Abreu MT, Targan SR, Vasiliauskas EA. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 2137-2142 [PMID: 11467645 DOI: 10.1111/j.1572-0241.2001.03949.x]

6 **de la Hoz RE**, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. *J Clin Virol* 2002; **25** Suppl 2: S1-12 [PMID: 12361752 DOI: 10.1016/S1386-6532(02)00091-4]

7 **Pereyra F**, Rubin RH. Prevention and treatment of cytomegalovirus infection in solid organ transplant recipients. *Curr Opin Infect Dis* 2004; **17**: 357-361 [PMID: 15241082 DOI: 10.1097/01.qco.0000136933.67920.dd]

8 **Powell RD**, Warner NE, Levine RS, Kirsner JB. Cytomegalic inclusion disease and ulcerative colitis; report of a case in a young adult. *Am J Med* 1961; **30**: 334-340 [PMID: 13737621 DOI: 10.1016/0002-9343(61)90105-X]

9 **Cooper HS**, Raffensperger EC, Jonas L, Fitts WT. Cytomegalovirus inclusions in patients with ulcerative colitis and toxic dilation requiring colonic resection. *Gastroenterology* 1977; **72**: 1253-1256 [PMID: 192627]

10 **Orvar K**, Murray J, Carmen G, Conklin J. Cytomegalovirus infection associated with onset of inflammatory bowel disease. *Dig Dis Sci* 1993; **38**: 2307-2310 [PMID: 8261839 DOI: 10.1007/BF01299914]

11 **Matsuoka K**, Iwao Y, Mori T, Sakuraba A, Yajima T, Hisamatsu T, Okamoto S, Morohoshi Y, Izumiya M, Ichikawa H, Sato T, Inoue N, Ogata H, Hibi T. Cytomegalovirus is frequently reactivated and disappears without antiviral agents in ulcerative colitis patients. *Am J Gastroenterol* 2007; **102**: 331-337 [PMID: 17156136 DOI: 10.1111/j.1572-0241.2006.00989.x]

12 **Lawlor G**, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis* 2010; **16**: 1620-1627 [PMID: 20232408 DOI: 10.1002/ibd.21275]

13 **Cottone M**, Pietrosi G, Martorana G, Casà A, Pecoraro G, Oliva L, Orlando A, Rosselli M, Rizzo A, Pagliaro L. Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis. *Am J Gastroenterol* 2001; **96**: 773-775 [PMID: 11280549 DOI: 10.1111/j.1572-0241.2001.03620.x]

14 **Kaufman HS**, Kahn AC, Iacobuzio-Donahue C, Talamini MA, Lillemoe KD, Hamilton SR. Cytomegaloviral enterocolitis: clinical associations and outcome. *Dis Colon Rectum* 1999; **42**: 24-30 [PMID: 10211516 DOI: 10.1007/BF02235178]

15 **Berk T**, Gordon SJ, Choi HY, Cooper HS. Cytomegalovirus infection of the colon: a possible role in exacerbations of inflammatory bowel disease. *Am J Gastroenterol* 1985; **80**: 355-360 [PMID: 2859801]

16 **Wada Y**, Matsui T, Matake H, Sakurai T, Yamamoto J, Kikuchi Y, Yorioka M, Tsuda S, Yao T, Yao S, Haraoka S, Iwashita A. Intractable ulcerative colitis caused by cytomegalovirus infection: a prospective study on prevalence, diagnosis, and treatment. *Dis Colon Rectum* 2003; **46**: S59-S65 [PMID: 14530660]

17 **Kambham N**, Vij R, Cartwright CA, Longacre T. Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. *Am J Surg Pathol* 2004; **28**: 365-373 [PMID: 15104299 DOI: 10.1097/00000478-200403000-00009]

18 **Kuwabara A**, Okamoto H, Suda T, Ajioka Y, Hatakeyama K. Clinicopathologic characteristics of clinically relevant cytomegalovirus infection in inflammatory bowel disease. *J Gastroenterol* 2007; **42**: 823-829 [PMID: 17940835 DOI: 10.1007/s00535-007-2103-3]

19 **Domènech E**, Vega R, Ojanguren I, Hernández A, Garcia-Planella E, Bernal I, Rosinach M, Boix J, Cabré E, Gassull MA. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. *Inflamm Bowel Dis* 2008; **14**: 1373-1379 [PMID: 18452205 DOI: 10.1002/ibd.20498]

20 **Roblin X**, Pillet S, Oussalah A, Berthelot P, Del Tedesco E, Phelip JM, Chambonnière ML, Garraud O, Peyrin-Biroulet L, Pozzetto B. Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. *Am J Gastroenterol* 2011; **106**: 2001-2008 [PMID: 21788989 DOI: 10.1038/ajg.2011.202]

21 **Kojima T**, Watanabe T, Hata K, Shinozaki M, Yokoyama T, Nagawa H. Cytomegalovirus infection in ulcerative colitis. *Scand J Gastroenterol* 2006; **41**: 706-711 [PMID: 16716970 DOI: 10.1080/00365520500408584]

22 **Nakase H**, Matsumura K, Yoshino T, Chiba T. Systematic review: cytomegalovirus infection in inflammatory bowel disease. *J Gastroenterol* 2008; **43**: 735-740 [PMID: 18958541 DOI: 10.1007/s00535-008-2246-x]

23 **Nakase H**, Yoshino T, Ueno S, Uza N, Mikami S, Matsuura M, Chiba T. Importance of early detection of cytomegalovirus infection in refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 364 [PMID: 17206718 DOI: 10.1002/ibd.20033]

24 **Franzin G**, Muolo A, Griminelli T. Cytomegalovirus inclusions in

the gastroduodenal mucosa of patients after renal transplantation. *Gut* 1981; **22**: 698-701 [PMID: 6271652 DOI: 10.1136/gut.22.9.698]
25 **Battaglino MP**, Rockey DC. Cytomegalovirus colitis presenting with the endoscopic appearance of pseudomembranous colitis. *Gastrointest Endosc* 1999; **50**: 697-700 [PMID: 10536332 DOI: 10.1016/S0016-5107(99)80025-X]
26 **Nishimoto Y**, Matsumoto T, Suekane H, Shimizu M, Mikami Y, Iida M. Cytomegalovirus infection in a patient with ulcerative colitis: colonoscopic findings. *Gastrointest Endosc* 2001; **53**: 816-818 [PMID: 11375602 DOI: 10.1067/mge.2001.114955]
27 **Falagas ME**, Griffiths J, Prekezes J, Worthington M. Cytomegalovirus colitis mimicking colon carcinoma in an HIV-negative patient with chronic renal failure. *Am J Gastroenterol* 1996; **91**: 168-169 [PMID: 8561127]
28 **Suzuki H**, Kato J, Kuriyama M, Hiraoka S, Kuwaki K, Yamamoto K. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection. *World J Gastroenterol* 2010; **16**: 1245-1251 [PMID: 20222169 DOI: 10.3748/wjg.v16.i10.1245]
29 **Omiya M**, Matsushita M, Tanaka T, Kawamata S, Okazaki K. The absence of large ulcer predicts latent cytomegalovirus infection in ulcerative colitis with positive mucosal viral assay. *Intern Med* 2010; **49**: 2277-2282 [PMID: 21048360 DOI: 10.2169/internalmedicine.49.3657]
30 **Iida T**, Ikeya K, Watanabe F, Abe J, Maruyama Y, Ohata A, Teruyuki S, Sugimoto K, Hanai H. Looking for endoscopic features of cytomegalovirus colitis: a study of 187 patients with active ulcerative colitis, positive and negative for cytomegalovirus. *Inflamm Bowel Dis* 2013; **19**: 1156-1163 [PMID: 23619714 DOI: 10.1097/MIB.0b013e31828075ce]
31 **Stange EF**, Travis SP, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, Feakins R, Fléjou JF, Herfarth H, Hommes DW, Kupcinskas L, Lakatos PL, Mantzaris GJ, Schreiber S, Villanacci V, Warren BF. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. *J Crohns Colitis* 2008; **2**: 1-23 [PMID: 21172194 DOI: 10.1016/j.crohns.2007.11.001]
32 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: 13260656 DOI: 10.1136/bmj.2.4947.1041]
33 **Dignass A**, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012; **6**: 965-990 [PMID: 23040452 DOI: 10.1016/j.crohns.2012.09.003]
34 **Mazzulli T**, Drew LW, Yen-Lieberman B, Jekic-McMullen D, Kohn DJ, Isada C, Moussa G, Chua R, Walmsley S. Multicenter comparison of the digene hybrid capture CMV DNA assay (version 2.0), the pp65 antigenemia assay, and cell culture for detection of cytomegalovirus viremia. *J Clin Microbiol* 1999; **37**: 958-963 [PMID: 10074509]
35 **Mori T**, Mori S, Kanda Y, Yakushiji K, Mineishi S, Takaue Y, Gondo H, Harada M, Sakamaki H, Yajima T, Iwao Y, Hibi T, Okamoto S. Clinical significance of cytomegalovirus (CMV) antigenemia in the prediction and diagnosis of CMV gastrointestinal disease after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004; **33**: 431-434 [PMID: 14676775 DOI: 10.1038/sj.bmt.1704369]
36 **Nagata N**, Kobayakawa M, Shimbo T, Hoshimoto K, Yada T, Gotoda T, Akiyama J, Oka S, Uemura N. Diagnostic value of antigenemia assay for cytomegalovirus gastrointestinal disease in immunocompromised patients. *World J Gastroenterol* 2011; **17**: 1185-1191 [PMID: 21448424 DOI: 10.3748/wjg.v17.i9.1185]
37 **Beaugerie L**, Cywiner-Golenzer C, Monfort L, Girard PM, Carbonnel F, Ngô Y, Cosnes J, Rozenbaum W, Nicolas JC, Châtelet FP, Gendre JP. Definition and diagnosis of cytomegalovirus colitis in patients infected by human immunodeficiency virus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **14**: 423-429 [PMID: 9170416 DOI: 10.1097/00042560-199704150-00005]
38 **Annese V**, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kießlich R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R; European Crohn's and Colitis Organisation. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: 982-1018 [PMID: 24184171 DOI: 10.1016/j.crohns.2013.09.016]
39 **Nakase H**, Chiba T. TNF-alpha is an important pathogenic factor contributing to reactivation of cytomegalovirus in inflamed mucosa of colon in patients with ulcerative colitis: lesson from clinical experience. *Inflamm Bowel Dis* 2010; **16**: 550-551 [PMID: 19637380 DOI: 10.1002/ibd.210]
40 **Yoshino T**, Nakase H, Ueno S, Uza N, Inoue S, Mikami S, Matsuura M, Ohmori K, Sakurai T, Nagayama S, Hasegawa S, Sakai Y, Chiba T. Usefulness of quantitative real-time PCR assay for early detection of cytomegalovirus infection in patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm Bowel Dis* 2007; **13**: 1516-1521 [PMID: 17828781 DOI: 10.1002/ibd.20253]
41 **Pfau P**, Kochman ML, Furth EE, Lichtenstein GR. Cytomegalovirus colitis complicating ulcerative colitis in the steroid-naive patient. *Am J Gastroenterol* 2001; **96**: 895-899 [PMID: 11280572 DOI: 10.1111/j.1572-0241.2001.03672.x]
42 **Kishore J**, Ghoshal U, Ghoshal UC, Krishnani N, Kumar S, Singh M, Ayyagari A. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. *J Med Microbiol* 2004; **53**: 1155-1160 [PMID: 15496396 DOI: 10.1099/jmm.0.45629-0]
43 **Bernabeu-Wittel M**, Pachón-Ibáñez J, Cisneros JM, Cañas E, Sánchez M, Gómez MA, Gentil MA, Pachón J. Quantitative pp65 antigenemia in the diagnosis of cytomegalovirus disease: prospective assessment in a cohort of solid organ transplant recipients. *J Infect* 2005; **51**: 188-194 [PMID: 16230214 DOI: 10.1016/j.jinf.2004.10.014]
44 **Manteiga R**, Martino R, Sureda A, Labeaga R, Brunet S, Sierra J, Rabella N. Cytomegalovirus pp65 antigenemia-guided pre-emptive treatment with ganciclovir after allogeneic stem transplantation: a single-center experience. *Bone Marrow Transplant* 1998; **22**: 899-904 [PMID: 9827819 DOI: 10.1038/sj.bmt.1701439]
45 **Boeckh M**, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. *Blood* 1996; **88**: 4063-4071 [PMID: 8916975]

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Systematic review comparing endoscopic, percutaneous and surgical pancreatic pseudocyst drainage

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at anthonyteoh@surgery.cuhk.edu.hk. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To perform a systematic review comparing the outcomes of endoscopic, percutaneous and surgical pancreatic pseudocyst drainage.

METHODS: Comparative studies published between January 1980 and May 2014 were identified on PubMed, Embase and the Cochrane controlled trials register and assessed for suitability of inclusion. The primary outcome was the treatment success rate. Secondary outcomes included were the recurrence rates, re-interventions, length of hospital stay, adverse events and mortalities.

RESULTS: Ten comparative studies were identified and 3 were randomized controlled trials. Four studies reported on the outcomes of percutaneous and surgical drainage. Based on a large-scale national study, surgical drainage appeared to reduce mortality and adverse events rate as compared to the percutaneous approach. Three studies reported on the outcomes of endoscopic ultrasound (EUS) and surgical drainage. Clinical success and adverse events rates appeared to be comparable but the EUS approach reduced hospital stay, cost and improved quality of life. Three other studies compared

EUS and esophagogastroduodenoscopy-guided drainage. Both approaches were feasible for pseudocyst drainage but the success rate of the EUS approach was better for non-bulging cyst and the approach conferred additional safety benefits.

CONCLUSION: EUS-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystojejunostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

Key words: Interventional endosonography; Endoscopic ultrasound; Pancreatic pseudocyst; Cystogastrostomy; Cystojejunostomy; Pseudocyst drainage

Core tip: Pancreatic pseudocysts are traditionally managed by open surgical internal drainage. With continued improvements in medical technology, the uses of percutaneous, endoscopic and laparoscopic drainage were increasingly reported. Nevertheless, trials comparing these different approaches are lacking. In this systematic review, endoscopic ultrasound-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystojejunostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

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INTRODUCTION

Pancreatic pseudocysts are amylase rich fluid collections in the peri-pancreatic tissues surrounded by a well-defined wall[1]. There should be absence of necrosis or solid component in the collections. The relative proportion of acute and chronic pseudocyst varies between reports and depends on how the pseudocysts are being defined[2]. The incidence is higher in patients suffering from chronic pancreatitis. Pancreatic pseudocysts are traditionally managed by open surgical internal drainage. With continued improvements in medical technology, less invasive options including percutaneous, endoscopic and laparoscopic drainage were increasingly reported. Nevertheless, trials comparing these different approaches are lacking and there is an absence in consensus on the best approach for management of this condition. Thus, the aim of the current systematic review was to evaluate the outcomes of comparatives studies on endoscopic, percutaneous and surgical pancreatic pseudocyst drainage and to summarize the findings of available data.

MATERIALS AND METHODS

Inclusion criteria

Eligible studies were comparative studies on endoscopic, percutaneous or surgical methods of pancreatic pseudocyst drainage. The definition of pseudocyst was according to the revised Atlanta's classification[1] (Table 1). In brief, pseudocyst referred to a fluid collection in the peri-pancreatic tissues persisting for more than 4 wk on computed tomography, surrounded by a well-defined wall and contained no solid material. Studies describing the results of pancreatic necrosis or abscesses were excluded. The indications for treatment of pancreatic pseudocyst was if they persisted for more than 4 to 6 wk and are $\geqslant$ 6 cm in size, causing symptoms or complications[3,4].

Search strategy and trial identification

A computerized systematic literature review from January 1980 to May 2014 on PubMed, Embase and the Cochrane controlled trials register was performed. Articles were selected using MeSH headings and text words related to pancreatic pseudocyst, pseudocyst drainage, cystogastrostomy, cystojejunostomy, transmural pseudocyst drainage, transpapillary pseudocyst drainage and percutaneous pseudocyst drainage. Only English comparative studies involving the concerned treatment approaches were included. Reference lists from eligible trials were checked to locate missing publications. The titles of the articles and abstracts located were evaluated (Anthony Yuen Bun, TEOH1 and Vinay DHIR2). Where the article fulfilled the selection criterion, a copy of the full manuscript was obtained. Full manuscripts were then reviewed and a final decision was made about the inclusion. Studies published only in abstract form, conference abstracts, symposium proceedings and case reports were not eligible for inclusion. Any disagreements were resolved by consensus.

Data extraction and outcomes

Data were extracted using a standard extraction form. Parameters included were study methodology (including randomization and blinding), inclusion criteria, demographics, the indications of treatment and types of pancreatic fluid collection. Procedural data including the technical approaches, methods of anastomosis, catheters and stents used were also recorded. The primary outcome was the treatment success rate. Secondary outcomes included were the recurrence rates, re-interventions, lengths of hospital stay, adverse events and mortalities. Treatment success was defined

Table 1 Definition of peri-pancreatic fluid collections according to the revised Atlanta's classification

Name of the collection	Definition
Onset < 4 wk after initial attack	
Acute peripancreatic fluid collection	Fluid collections that develop in the early phase of pancreatitis. They do not have a well-defined wall, are homogeneous, are confined by normal fascial planes in the retroperitoneum
Acute necrotic collection	A collection containing variable amounts of fluid and necrotic tissue without a well-defined wall
Onset ⩾ 4 wk after initial attack	
Pancreatic pseudocyst	A collection of fluid in the peripancreatic tissues surrounded by a well-defined wall and contains no solid material
Walled-of pancreatic necrosis	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis and has a well-defined inflammatory
Any time after initial attack	
Infected necrosis	Presence of superimposed infection of the necrotic pancreas. May be indicated by presence of gas in the collection

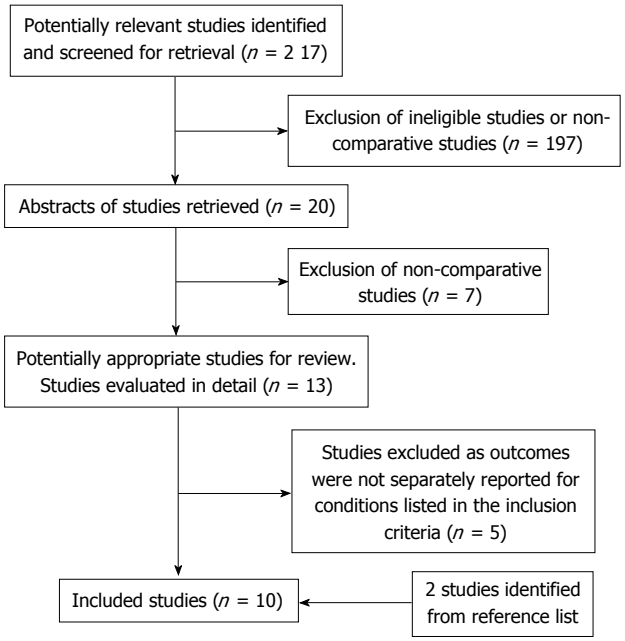

Figure 1 Flow chart showing selection of included studies.

as radiographic cyst resolution after the index intervention. Re-intervention was defined as the need for repeat interventions owing to persistent symptoms in association with a residual pseudocyst. Adverse events were defined according the individual study criteria.

Assessment of methodological quality and risk of bias of the included studies. Assessment of risk of bias were performed by AT and VD according to principles of the Cochrane Handbook for systemic reviews of interventions version 5.1[5]. For randomized trials, the assessment focused on sequence generation, allocation concealment, blinding, incomplete outcome data, follow-up losses, intention to treat method of analysis and selective reporting. For non-randomized comparative trials, quality assessments were according to the Newcastle-Ottawa scale and the studies were scored on 3 domains including: Case selection, comparability of cases and controls and outcome assessments[6]. The results of this study were reported according to the PRISMA guidelines[7].

RESULTS

The search identified 217 potentially relevant publications and 20 articles were selected for reviewing of the abstracts. Seven studies were rejected as they were not comparative studies and the full manuscripts of the remaining 13 publications were reviewed. Two studies were further excluded as the outcomes for pseudocyst drainage were not separately reported and in 3 studies the outcomes of the different techniques were not reported individually. Two further articles were identified from the reference list of the included studies (Figure 1)[8-17]. Since there was significant heterogeneity amongst the study interventions, recruitment and outcome measurements, statistical pooling of the results was not performed.

Description of the techniques

Surgical drainage procedures: Cystogastrostomy, cystoduodenostomy and cystojejunostomy: Surgical drainage of pseudocysts is traditionally performed by the open approach[18,19]. However in recent years, laparoscopic pseudocyst drainage is increasingly reported[9,20]. For the open approach, midline or bilateral subcostal incisions were employed. The type of surgical drainage depended on the location of the cysts and whether it was adherent to the stomach or duodenum. When adhered to the posterior wall of the stomach, a cystogastrostomy were performed. If the cyst were not adhered to the stomach or duodenum, then a Roux-en Y cystojejunostomy would be fashioned. It is acknowledged that resectional procedures are sometimes required for patients with concomitant pancreatic ductal pathologies or complicated pseudocyst. However, resectional procedures do not have comparable endoscopic counterparts and these are not considered in this review.

In laparoscopic drainage procedures, various techniques have been described to replicate their open equivalents[9,20]. These include intragastric, transgastric or exogastric approaches and they differ in the method of accessing the posterior wall of the stomach to create a cystogastrostomy. The anastomosis is usually created with a laparoscopic stapler and the enterostomy closed

by laparoscopic suturing. Laparsocopic cystojejunostomy is also possible for pseudocysts that protrude into the infracolic compartment and this is usually drained by a Roux-en Y jejunal loop.

Percutaneous drainage

Percutaneous drainage can be performed by ultrasound or computed tomography (CT) guidance and this can be achieved by the retroperitoneal route or transperitoneally[15-17]. The appropriate drainage site is first identified, followed by progressive track dilation and insertion of a 7 to 12 Fr drainage catheter into the pseudocyst. In patients that received transperitoneal drainage, a transgastric needle puncture can be performed and the passage through the stomach could allow subsequent exchange of a double pigtail stent and internalization into the stomach. In patients with retroperitoneal drainage, the pigtail stents would be connected to an external bag for free drainage.

Endoscopic drainage

Endoscopic drainage can be performed transpapillary or transmurally[21]. Transpapillary drainage can be performed if the pseudocyst communicates with the pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP) and a transpapillary stent is passed through the pancreatic duct into the pseudocyst. In patients with pancreatic ductal leak or ductal stricture, the stent may also serve to bridge the leak or stricture site[22].

Endoscopic transmural drainage can be performed with or without endoscopic ultrasound (EUS) guidance[11-13]. A prerequisite is that the pseudocyst is in direct apposition with the gastric or duodenal wall. When performed under esophagogastroduodenoscopy (EGD) guidance, the location of the pseudocyst is usually identified by the presence of bulging on the stomach wall. This is then confirmed by needle puncture, aspiration of the fluid and injection of contrast. A catheter and guidewire is then passed into the pseudocyst. The fistula track is dilated with a balloon catheter and 1 or 2 plastic stents would be inserted. When performed under EUS guidance, the puncture site of the pseudocyst is chosen away from intervening vessels or structures. The pseudocyst is then punctured with a 19-gauge needle and a guidewire passed to form 2 or more loops. The needle tract is dilated and plastic stents would be inserted. Recently, the use of metallic stents for draining pseudocyst has also been described but results from comparative studies are lacking[23,24]. All the studies included in the current review used plastic stents.

Description of the studies

The identified studies covered a heterogeneous group of patients and mostly included small numbers from a single center (Table 2). In only one study, the outcomes of percutaneous drainage were compared to surgical drainage on a national level. Amongst the 10 included studies, 3 were randomized controlled trials[8,10,12]. One compared EUS drainage with open cystogastrostomy and 2 compared EGD *vs* EUS guided-drainage. The remaining seven studies were non-randomized trials, 1 compared laparoscopic, endoscopic and open cystogastrotomies[9], 1 study compared EUS drainage with open cystogastrostomy[10], 1 study compared EGD and EUS-guided drainage and 4 studies compared percutaneous and open surgical drainage[13-17]. The definition of pseudocyst was clearly stated in all the randomized studies and in 6 out of 7 non-randomized studies. The indications for intervention were defined in all the randomized studies and 2 non-randomized studies.

Assessment of risk of bias of the included studies

The risks of bias in the randomized trials were assessed according to the principles of the Cochrane Handbook for systemic reviews of interventions (Table 3). None of the studies blinded the assessor of the outcomes. In one study comparing EGD *vs* EUS drainage[11], the patients randomized to the EGD arm also received EUS when the pseudocyst could not be located. This resulted in a hybrid technique and may contaminate the data in the EGD arm resulting in contamination bias. The risks of bias in non-randomized trials were assessed using the Newcastle-Ottawa scale (Table 4). Most studies were of moderate quality and scored between 4 to 7 stars out of 10.

Assessment of outcomes by the different approaches of pseudocyst drainage

Percutaneous *vs* surgical drainage: Four retrospective studies were included (Table 5). The largest United States study included more than 14000 patients (Percutaneous: 8121 and surgical: 6409) that were identified using a US national database[14]. Significant differences in background demographics between the groups were noted, including the cause of pseudocyst, the percentage of patients that received CT or ERCP and the proportion of patients that were treated in a teaching hospital. After adjusting for these confounding variables, a reduction in mortality was still observed in the surgical drainage arm (OR = 1.37, 95%CI: 1.12-1.68). Both emergency admission and acute pancreatitis increased the odds of in-patient mortality (OR = 2.45, 95%CI: 1.87-2.30 and OR = 2.36, 95%CI: 1.89-2.96, respectively) and the use of ERCP yielded a protective effect (OR = 0.68, 95%CI: 0.51-0.9). This study was the largest and most statistically robust amongst all the included studies. Yet, there is also a risk of selection biases, as the patients who were poor candidates for surgery tended to receive percutaneous drainage.

Heider *et al*[15] compared the results of expectant treatment with percutaneous and open surgical drainage. No statistical analysis of the results was performed (no *P*-values given). The patients that were treated by percutaneous drainage had a re-intervention rate of

Table 2 Characteristics of the included studies

Ref.	Design	Study duration	Follow-up duration[1]	Interventions	Sample size	Pseudocyst defined	Inclusion criteria or indications for intervention
Varadarajulu *et al*[8] (United States)	Single center RCT	Jan 2009-Dec 2009	24	EUS *vs* open cystogastrostomy	20:20	Yes	Pseudocyst > 6 cm and adjacent to stomach History of acute or chronic pancreatitis Persistent pain Complications of pseudocyst
Melman *et al*[9] (United States)	Single center retrospective	Mar 1999-Aug 2007	9.5	EUS *vs* laparoscopic *vs* open cystogastrostomy	45:16:22	Yes	Symptomatic pseudocyst
Varadarajulu *et al*[10] (United States)	Single center retrospective	Jul 2005-Jun 2007	24	EUS *vs* Open cystogastrostomy	20:10	Yes	NA
Park *et al*[11] (South Korea)	Single center RCT	Jan 2004-Dec 2007	25 - 27	EGD ± R-EUS *vs* EUS	29:31	Yes	Symptomatic pseudocyst > 4 wk
Varadarajulu *et al*[12] (United States)	Single center RCT	May 2007-Oct 2007	NA	EGD *vs* EUS	15:15	Yes	Symptomatic pseudocyst > 4 wk
Kahaleh *et al*[13] (United States)	Single center retrospective	2000-2005	11	EGD *vs* EUS	53:46	Yes	NA
Morton *et al*[14] (United States)	National multicenter retrospective	Jan 1997-Dec 2001	NA	Percutaneous *vs* Surgical drainage	8121:6409	Yes	NA
Heider *et al*[15] (United States)	Single center retrospective	1984-1995	NA	Percutaneous *vs* Surgical drainage	66:66	Yes	NA
Adams *et al*[16] (United States)	Single center retrospective	1965-1991	NA	Percutaneous *vs* Surgical drainage	52:42	No	Percutaneous drainage: Symptomatic pseudocyst > 5 cm without PD dilation
Lang *et al*[17] (United States)	Single center retrospective	Jan 1978-Jun 1988	NA	Percutaneous *vs* Surgical drainage	12:14	Yes	Wall thickness < 3 mm

[1]Mean duration of follow-up shown in months. RCT: Randomized controlled trial; NA: Not available; R-EUS: Radial echoendoscope; PD: Pancreatic duct; EGD: Esophagogastroduodenoscopy.

Table 3 Methodological summary of the risk of bias of the included randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Other bias
Varadarajulu *et al*[8]	Low risk	Low risk	High risk	Low risk	Unclear risk
Park *et al*[11]	Low risk	Unclear risk	High risk	Low risk	High risk
Varadarajulu *et al*[12]	Low risk	Unclear risk	High risk	Low risk	Low risk

Assessment of the risk of bias was according to principles of the Cochrane Handbook for systemic reviews of interventions version 5.1.

Table 4 Methodological summary of the risk of bias of the included non-randomized comparative studies

	Selection (++++)	Comparability (++)	Outcomes (++++)
Melman *et al*[9]	++		++
Varadarajulu *et al*[12]	++	+	+++
Kahaleh *et al*[13]	++		+++
Morton *et al*[14]	++	++	+++
Heider *et al*[15]	++	+	++
Adams *et al*[16]	++		++
Lang *et al*[17]	++		++

Quality assessment was according to the Newcastle-Ottawa scale for non-randomized trials. +: Higher quality of the studies.

50%, adverse events rate of 67% and mortality rate of 9.1% and the results were worse than surgery. On the contrary, two smaller studies favored the percutaneous approach. Adams noted higher risk of mortalities, morbidities and re-interventions in patients that were treated with surgical drainage[16]. Whilst in another study, similar risks of mortalities and adverse events were observed in both groups but the patients that underwent surgery required more subsequent re-interventions[17].

It is worthwhile to note that the definition of pseudocyst in some of the older studies may not be according to the Atlanta's classification and thus, the study population could include some patients with pancreatic necrosis and the results of these may need to be interpreted with caution. Based on the results of the national study, surgical drainage appeared to reduce mortality and adverse events risk as compared to the percutaneous approach. The lack of an external catheter also reduced risk developing pancreatic fistula and wound site infection. However, the validity of these results in the current era needs to be confirmed by a

Table 5 Percutaneous *vs* surgical drainage of pancreatic pseudocysts

Ref.	Sample size	Size (cm)[1]	Clinical success	Hospital stay (d)[1]	Reintervention	Mortalities	Adverse events	Bleeding	Intra-abdominal infection
Morton *et al*[14]	Perc: 8121	-	-	21 (22)[2]		5.9%[2]	-	9.64%[2]	6.8%[2]
	Surg: 6409	-	-	15 (15)		2.8%	-	8.96%	4.54%
Heider *et al*[15]	Perc: 66	8.2 (1.1)	42%	45 (5)	50%	9.1%	64%[2]	9.1%	45.5%
	Surg: 66	7.4 (1.3)	88%	18 (2)	12%	0	27%	4.5%	15.2%
Adams *et al*[16]	Perc: 52	-	-	36.7	9.5%	2	7.7%	1.9%	1.9%
	Surg: 42	-	-	39.8	19.2%	7.1%	16.7%	4.8%	4.8%
Lang *et al*[17]	Perc: 26	-	76.9%	-	11.5%	3.8%	3.8%	3.8%	0
	Surg: 26	-	73.1%	-	23.1%	3.8%	0	0	0

[1]Values in mean ± SD except otherwise indicated; [2]Indicates significant differences between the 2 groups. Perc: Percutaneous drainage; Surg: Surgical drainage.

Table 6 Endoscopic ultrasound *vs* surgical drainage of pancreatic pseudocysts

Ref.	Sample size	Size (cm)	Clinical success	Hospital stay (d)	Reintervention	Mortalities	Adverse events	Bleeding	Intra-abdominal infection
Varadarajulu *et al*[8]	EUS: 20	10.5 (9-14.9)[1]	95%	2 (1-4)[1,3]	5%	0	0	0	0
	Open: 20	11 (8.4-14.5)[1]	100%	6 (5-9)[1]	5%	0	2%	1	0
Melman *et al*[9]	EUS: 45	9.1 (0.4)	51.1%[2]	3.9 (0-25)[2]	-	0	15.6%	2.2%	0
	Lap: 16	10.4 (0.5)	87.5%	6.9 (3-23)[2]	-	0	25%	12.5%	0
	Open: 22	9.5 (0.8)	81.2%	10.8 (4-82)[2]	-	0	22.7%	0	0
Varadarajulu *et al*[10]	EUS: 20	9.8	95%	2.6 (1-11)[2,3]	0	0	0	0	0
	Open: 10	8.9	100%	6.5 (4-20)[2]	10%	0	0	0	0

[1]Values in mean ± interquartile range; [2]Values in mean (range) except otherwise indicated; [3]Indicates significant differences between the 2 groups. EUS: Endoscopic ultrasound drainage; Lap: Laparoscopic drainage; Open: Open drainage.

modernized randomized trial with updated definitions.

EUS *vs* surgical drainage: One randomized trial and two retrospective studies were included (Table 6). Varadarajulu *et al*[10] first published a retrospective case-matched study comparing EUS and open cystogastrostomy. No differences in treatment success, adverse events or re-interventions were noted between the groups. The same author then followed-up with the first randomized study, comparing 20 patients that received EUS drainage with an equal number receiving open cystogastrostomy[8]. The time to pseudocyst recurrence was used as the main outcome measurement. However, none of the patients in the EUS group developed recurrence, thus raising the issue of an underpowered study. Nevertheless, similar rates of clinical success, mortalities and morbidities were observed between the two groups. In addition, the EUS group was associated with significantly lower hospital costs (mean difference of -$8040 USD) and better quality of life scores (physical component scores and mental component scores). Hence, favoring the EUS approach over open cystogastrostomy.

In another study comparing EUS, laparoscopic and open cystogastrostomy, a significantly higher rate of clinical success was observed in the surgery arm. However, the rate of clinical success in the EUS group was unusually low at 51.1% and grade 2 or above complications occurred in up to 15.6% of the patients. Three patients required urgent laparotomy and 2 experienced a gastric perforation. These results reflect that the endoscopist performing the procedures may still be overcoming their learning curves and the difference in outcomes may not be truly representative of the techniques. Nevertheless, this study was the only comparative study that incorporated the results of laparoscopic cystogastrostomy.

EUS *vs* EGD drainage: Two randomized trials and 1 retrospective comparison were included (Table 7)[11-13]. Kahaleh performed a retrospective comparison of patients that underwent EUS or EGD drainage[13]. Those with bulging pseudocyst underwent EGD drainage whilst patients with non-bulging cyst or those at risk of bleeding underwent EUS drainage. No difference in clinical success and adverse event rates were observed between the two groups. In a Korean randomized study, EUS was compared to a modified EGD approach[11]. In patients with bulging cyst, a blind EGD puncture was performed. Whilst in patients with the absence of bulging, radial EUS was employed to mark the site of puncture. This resulted in hybrid EUS-EGD approach in some of the patients. The trial found a significant difference in technical success rates in favor of the EUS approach (94% *vs* 72%, $P = 0.039$). The patients with failed EGD approach then crossed over to EUS drainage and this was successful in all patients. No differences in adverse events were observed in both arms. The third study was also a randomized study comparing EUS with pure EGD drainage of pseudocyst[12]. The EUS approach was shown to have significantly higher success rate as compared to the pure EGD technique (100% *vs* 33.3%,

Table 7 Endoscopic ultrasound *vs* esophagogastroduodenoscopy drainage of pancreatic pseudocysts

Ref.	Sample size	Size (cm)[1]	Clinical success	Hospital stay (d)	Reintervention	Mortalities	Adverse events	Bleeding	Intra-abdominal infection
Park *et al*[11]	EUS: 31	8.2 (3.8)	89%	-	6.5%	0	7%	3.2%	-
	EGD: 29	7.4 (4)	86%	-	6.5%	0	10%	6.9%	-
Varadarajulu *et al*[12]	EUS: 15	6.5 (5-12)[2]	100%[5]	2 (1-9)[2]	-	0	0	0	-
	EGD: 15	7 (4.2-13)[2]	33%[4]	1 (1-8)[2]	-	6.7%	13.3%	13.3%	-
Kahaleh *et al*[13]	EUS: 46	8.6 (4-20)[3]	84%	-	10.9%	0	19.6%	4.3%	8.7%
	EGD: 53	9.5 (3-20)[3]	91%	-	9.4%	0	18.9%	1.9%	7.5%

[1]Values in mean ± SD; [2]Values in mean (interquartile range); [3]Values in mean (range); [4]Values in median (range) except otherwise indicated; [5]Indicates significant differences between the 2 groups. EUS: Endoscopic ultrasound drainage; EGD: Esophagogastroduodenoscopy drainage.

$P < 0.001$) and all patients with failed EGD drainage were successfully drained with the EUS technique. However, of more concern was that 2 patients in the EGD arm suffered from severe bleeding after drainage. One patient died within 4 h after the procedure due to massive bleeding into the cyst and another required endoscopic hemostasis and blood transfusion.

Hence, the results of these studies suggest that although a blind EGD pseudocyst drainage is technically feasible, it may result in life-threatening adverse events. The success rate of the EUS approach was better for non-bulging cyst and the approach conferred additional safety benefits by allowing visualization of extraluminal structures.

DISCUSSION

Although the current review has established a strict criterion for inclusion, the included studies incorporated a heterogeneous group of patients that were treated with a number of different approaches. Thus, the results were not directly comparable and statistical analysis in a form of meta-analysis was inappropriate. Nevertheless, a number of conclusions could still be made. EUS-guided drainage has similar efficacy to surgery but the EUS approach may reduce hospital stay, costs of the procedure and improve quality of life. EGD and EUS-guided drainages are both feasible but the success rate of the EUS approach is better for non-bulging cyst and it may offer additional safety benefit. Whether surgical internal drainage of pancreatic pseudocyst is preferred over percutaneous drainage needs to be validated, as no results from a modern study are available. However, surgical cystogastrostomy may still be preferred it avoids the need of an external catheter and reduces the risk developing an external pancreatic fistula. Consequently, the EUS approach is preferred when anatomy of the pseudocyst allows for direct drainage into the stomach or duodenum. However, if the pseudocyst is located away from the stomach or duodenum, surgical cystojejunostomy or percutaneous drainage could be considered. In addition, it is acknowledged that laparoscopic drainage is the modern minimally invasive approach for surgical drainage. However, results from comparative studies were lacking and the long-term outcomes of the treatment approaches could not be made.

The current study is the only systematic review comparing percutaneous, endoscopic and surgical drainage of pseudocyst. A prior systematic review compared endoscopic and laparoscopic internal drainage by summarizing the results from cohort studies without direct statistical comparison[20]. No randomized or comparative studies were available. The review concluded that both approaches were safe and the laparoscopic approach appeared to have a higher success rate, lower morbidity and recurrence. In a meta-analysis comparing EGD and EUS-guided drainage, 2 randomized studies and 2 prospective studies were included[25]. Technical success was higher for EUS drainage (RR = 12.38, 95%CI: 1.39-110.22) and adverse events were similar between the two techniques. The review concluded that for bulging pseudocysts, both approaches could be selected whereas for non-bulging pseudocyst, portal hypertension or coagulopathy, EUS drainage is the preferred modality.

There were some limitations to the current study. Firstly, the numbers of high quality comparative studies assessing the 3 approaches were lacking. Hence, the robustness of the results generated in this review is limited by the quality of the original studies. Furthermore, with regards to the available randomized trials, all were single center studies with small sample sizes and they were not designed to detect differences in recurrence rates or adverse event rates between the modalities. Thus, the results were prone to type Ⅱ error. In addition, the literature search failed to identify any comparative studies involving endoscopic transpapillary drainage and laparoscopic internal drainage. Therefore, conclusions regarding these approaches could not be made. Furthermore, it was observed that many of the studies did not report on the follow-up time or only reported a very short follow-up period. This may not be adequate to detect longer-term recurrence. Lastly, the definitions of pseudocyst has changed over time and may be different for each study, thus of the patients included in the current review may not be suffering from the modern definition of pseudocyst and the outcomes of treatment may be affected by the definition.

Currently, there is a lack of consensus in the best practice for pseudocyst drainage. A number of professional bodies have attempted to establish guidelines regarding the management of complications of acute pancreatitis including infected pseudocyst and pancreatic

necrosis[26]. However, none of these guidelines have received widespread acceptance. In a systemic review of 16 guidelines published by profession bodies, it was observed that the guidelines lacked consensus and few were graded according to the strength of evidence. In addition, there were wide variations in the recommendations regarding the role of percutaneous and endoscopic drainage of pancreatic fluid collections. For infected pseudocyst, percutaneous drainage was recommended by 6 guidelines, 1 did not recommend its use and for endoscopic drainage, the approach was recommended by 7 guidelines. A recent guideline published by the International Association of Pancreatology and the American Association of Pancreateology, represented the best evidenced-based recommendations concerning key aspects the management of acute pancreatitis[27]. However, the optimal management of pseudocysts were not discussed and there is still a pressing need for more randomized studies to establish the best approach for management of this condition.

In conclusion, significant heterogeneity was present in the included studies and a clear conclusion could not be made. However, EUS-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystogastrostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

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COMMENTS

Background

Pancreatic pseudocysts are traditionally managed by open surgical internal drainage. With continued improvements in medical technology, the uses of percutaneous, endoscopic and laparoscopic drainage were increasingly reported. Nevertheless, trials comparing these different approaches are lacking. Thus, the aim of this study is to perform a systematic review comparing the outcomes of endoscopic, percutaneous and surgical pancreatic pseudocyst drainage.

Research frontiers

Currently, there is a lack of consensus in the best practice for pseudocyst drainage. A number of professional bodies have attempted to establish guidelines regarding the management of complications of acute pancreatitis including infected pseudocyst and pancreatic necrosis. However, the guidelines lacked consensus and few were graded according to the strength of evidence.

Innovations and breakthroughs

Endoscopic ultrasound (EUS)-guided pseudocyst drainage is an endoscopic approach for establishing internal transmural drainage of a pseudocyst. The approach allows visualization of extra-mural structures to allow precise placement of internal stents.

Applications

In the current study, the authors conclude that EUS-guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum. In patients with unfavorable anatomy, surgical cystojejunostomy or percutaneous drainage could be considered. Large randomized studies with current definitions of pseudocysts and longer-term follow-up are needed to assess the efficacy of the various modalities.

Terminology

Pseudocyst are fluid collections in the peri-pancreatic tissues persisting for more than 4 wk on computed tomography, surrounded by a well-defined wall and contained no solid material after an attack of pancreatitis.

Peer-review

The manuscript gives an overview of publications on outcome of endoscopic drainage of pancreatic pseudocysts, compared with percutaneous and/or surgical drainage.

REFERENCES

1 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]

2 **Aghdassi AA**, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM. Pancreatic pseudocysts--when and how to treat? *HPB* (Oxford) 2006; **8**: 432-441 [PMID: 18333098 DOI: 10.1080/13651820600748012]

3 **Yeo CJ**, Bastidas JA, Lynch-Nyhan A, Fishman EK, Zinner MJ, Cameron JL. The natural history of pancreatic pseudocysts documented by computed tomography. *Surg Gynecol Obstet* 1990; **170**: 411-417 [PMID: 2326721]

4 **Bradley EL**, Clements JL, Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. *Am J Surg* 1979; **137**: 135-141 [PMID: 758840 DOI: 10.1016/0002-9610(79)90024-2]

5 **Higgins JPT**, Green S. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. The Cochrane Collaboration, 2011 [DOI: 10.1002/9780470712184]

6 **Wells GA**, Shea B, O'Connell D, Peterson J, Welch WV, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Accessed 2014 May]. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

7 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]

8 **Varadarajulu S**, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583-90.e1 [PMID: 23732774 DOI: 10.1053/j.gastro.2013.05.046]

9 **Melman L**, Azar R, Beddow K, Brunt LM, Halpin VJ, Eagon JC, Frisella MM, Edmundowicz S, Jonnalagadda S, Matthews BD. Primary and overall success rates for clinical outcomes after laparoscopic, endoscopic, and open pancreatic cystgastrostomy for pancreatic pseudocysts. *Surg Endosc* 2009; **23**: 267-271 [PMID: 19037696 DOI: 10.1007/s00464-008-0196-2]

10 **Varadarajulu S**, Lopes TL, Wilcox CM, Drelichman ER, Kilgore ML, Christein JD. EUS versus surgical cyst-gastrostomy for management of pancreatic pseudocysts. *Gastrointest Endosc* 2008; **68**: 649-655 [PMID: 18547566 DOI: 10.1016/j.gie.2008.02.057]

11 **Park DH**, Lee SS, Moon SH, Choi SY, Jung SW, Seo DW, Lee SK, Kim MH. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. *Endoscopy* 2009; **41**: 842-848 [PMID: 19798610 DOI: 10.1055/s-0029-1215133]

12 **Varadarajulu S**, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111 [PMID: 18640677 DOI: 10.1016/j.gie.2008.04.028]

13 **Kahaleh M**, Shami VM, Conaway MR, Tokar J, Rockoff T, De La Rue SA, de Lange E, Bassignani M, Gay S, Adams RB, Yeaton P. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. *Endoscopy* 2006; **38**: 355-359 [PMID: 16680634 DOI: 10.1055/s-2006-925249]

14 **Morton JM**, Brown A, Galanko JA, Norton JA, Grimm IS, Behrns KE. A national comparison of surgical versus percutaneous drainage of pancreatic pseudocysts: 1997-2001. *J Gastrointest Surg* 2005; **9**: 15-20; discussion 20-21 [PMID: 15623440 DOI: 10.1016/j.gassur.2004.10.005]

15 **Heider R**, Meyer AA, Galanko JA, Behrns KE. Percutaneous drainage of pancreatic pseudocysts is associated with a higher failure rate than surgical treatment in unselected patients. *Ann Surg* 1999; **229**: 781-787; discussion 787-789 [PMID: 10363891 DOI: 10.1097/00000658-199906000-00004]

16 **Adams DB**, Anderson MC. Percutaneous catheter drainage compared with internal drainage in the management of pancreatic pseudocyst. *Ann Surg* 1992; **215**: 571-576; discussion 576-578 [PMID: 1632678 DOI: 10.1097/00000658-199206000-00003]

17 **Lang EK**, Paolini RM, Pottmeyer A. The efficacy of palliative and definitive percutaneous versus surgical drainage of pancreatic abscesses and pseudocysts: a prospective study of 85 patients. *South Med J* 1991; **84**: 55-64 [PMID: 1702557 DOI: 10.1097/00007611-199101000-00014]

18 **Frey CF**. Pancreatic pseudocyst--operative strategy. *Ann Surg* 1978; **188**: 652-662 [PMID: 309751 DOI: 10.1097/00000658-197811000-00012]

19 **Aranha GV**, Prinz RA, Freeark RJ, Kruss DM, Greenlee HB. Evaluation of therapeutic options for pancreatic pseudocysts. *Arch Surg* 1982; **117**: 717-721 [PMID: 7073495 DOI: 10.1001/archsurg.1982.01380290163029]

20 **Aljarabah M**, Ammori BJ. Laparoscopic and endoscopic approaches for drainage of pancreatic pseudocysts: a systematic review of published series. *Surg Endosc* 2007; **21**: 1936-1944 [PMID: 17717626 DOI: 10.1007/s00464-007-9515-2]

21 **Binmoeller KF**, Seifert H, Walter A, Soehendra N. Transpapillary and transmural drainage of pancreatic pseudocysts. *Gastrointest Endosc* 1995; **42**: 219-224 [PMID: 7498686 DOI: 10.1016/S0016-5107(95)70095-1]

22 **Varadarajulu S**, Noone TC, Tutuian R, Hawes RH, Cotton PB. Predictors of outcome in pancreatic duct disruption managed by endoscopic transpapillary stent placement. *Gastrointest Endosc* 2005; **61**: 568-575 [PMID: 15812410 DOI: 10.1016/S0016-5107(04)02832-9]

23 **Weilert F**, Binmoeller KF, Shah JN, Bhat YM, Kane S. Endoscopic ultrasound-guided drainage of pancreatic fluid collections with indeterminate adherence using temporary covered metal stents. *Endoscopy* 2012; **44**: 780-783 [PMID: 22791588 DOI: 10.1055/s-0032-1309839]

24 **Itoi T**, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). *Gastrointest Endosc* 2012; **75**: 870-876 [PMID: 22301347 DOI: 10.1016/j.gie.2011.10.020]

25 **Panamonta N**, Ngamruengphong S, Kijsirichareanchai K, Nugent K, Rakvit A. Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. *Eur J Gastroenterol Hepatol* 2012; **24**: 1355-1362 [PMID: 23114741 DOI: 10.1097/MEG.0b013e32835871eb]

26 **Loveday BP**, Mittal A, Phillips A, Windsor JA. Minimally invasive management of pancreatic abscess, pseudocyst, and necrosis: a systematic review of current guidelines. *World J Surg* 2008; **32**: 2383-2394 [PMID: 18670801 DOI: 10.1007/s00268-008-9701-y]

27 **Working Group IAP/APA Acute Pancreatitis Guidelines**. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**: e1-15 [PMID: 24054878 DOI: 10.1016/j.pan.2013.07.063]

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