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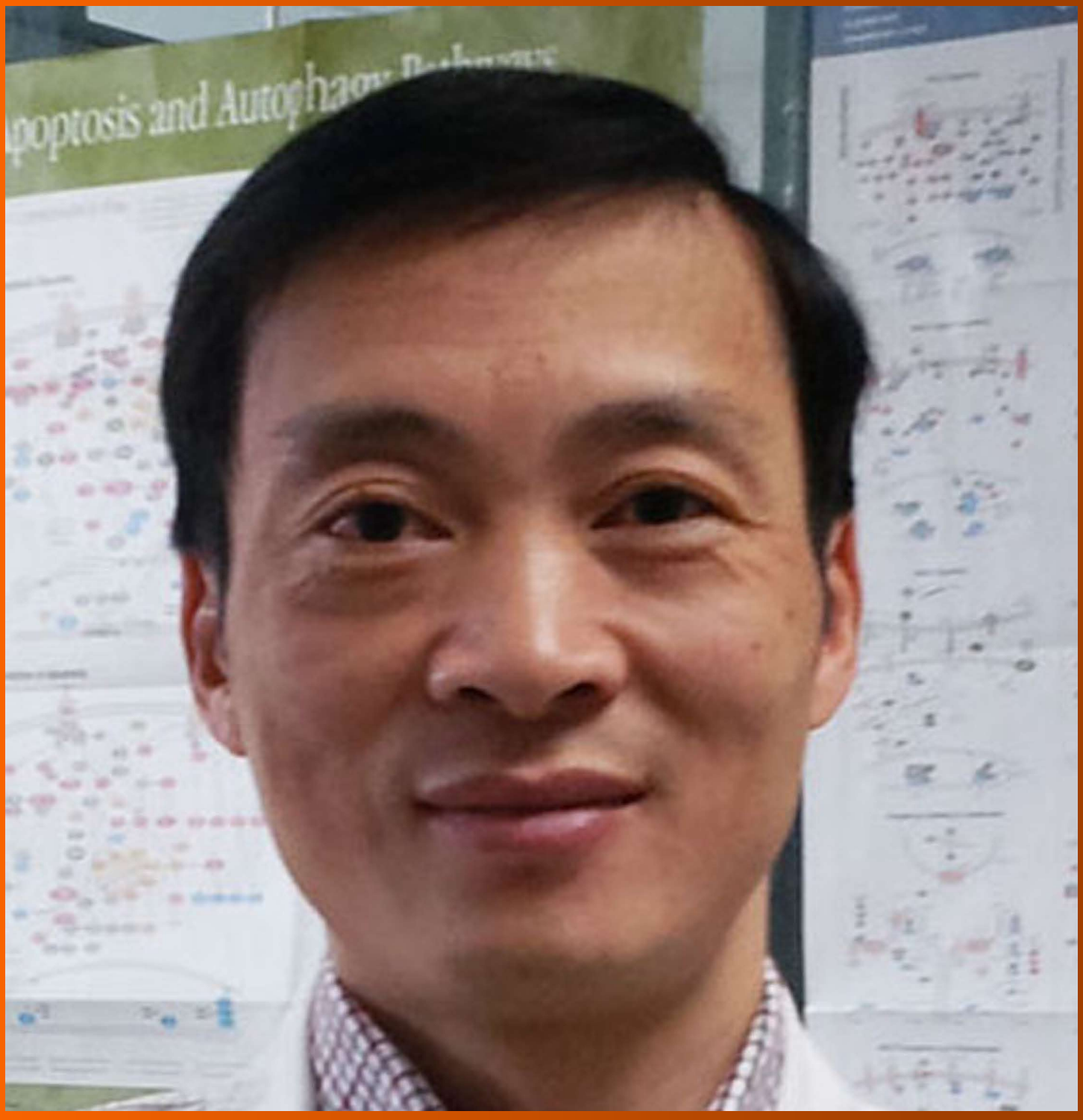

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Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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EDITORIAL

Confocal endomicroscopy: Is it time to move on?

Carlos Robles-Medranda

Carlos Robles-Medranda, Gastroenterology and Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas, University Hospital OMNI, Guayaquil 090505, Ecuador

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Correspondence to: Carlos Robles-Medranda, MD, Head of the Endoscopy Division, Gastroenterology and Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas, University Hospital OMNI, Av. Abel Romeo Castillo y Av. Juan Tanca Marengo, Torre Vitalis, Mezanine 3, Guayaquil 090505, Ecuador. carlosoakm@yahoo.es
Telephone: +593-4-2109180
Fax: +593-4-2109180

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Abstract

Confocal laser endomicroscopy permits *in-vivo* microscopy evaluation during endoscopy procedures. It can be used in all the parts of the gastrointestinal tract and includes: Esophagus, stomach, small bowel, colon, biliary tract through and endoscopic retrograde cholangiopancreatography and pancreas through needles during endoscopic ultrasound procedures. Many researches demonstrated a high correlation of results between confocal laser endomicroscopy and histopathology in the diagnosis of gastrointestinal lesions; with accuracy in about 86% to 96%. Moreover, in spite that histopathology remains the gold-standard technique for final diagnosis of any diseases; a considerable number of misdiagnosis rate could be present due to many factors such as interpretation mistakes, biopsy site inaccuracy, or number of biopsies. Theoretically; with the diagnostic accuracy rates of confocal laser endomicroscopy could help in a daily practice to improve diagnosis and treatment management of the patients. However, it is still not routinely used in the clinical practice due to many factors such as cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist. These limitations are relative, and solutions could be found based on new researches focused to solve these barriers.

Key words: Confocal laser endomicroscopy; *In-vivo* microscopy; Barret esophagus; Gastrointestinal cancer; Confocal laser endomicroscopy probe

Core tip: Confocal laser endomicroscopy (CLE) permits *in-vivo* microscopy evaluation during endoscopy procedures. It can be used in all the parts of the gastrointestinal tract with accuracy in about 86% to 96%. In spite of its high accuracy as well as several clinical applications, CLE is still not used in routine clinical practice. This could be correlated to many factors such as: cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist. However, these limitations are relative, and solutions could be found

based on new research leading to increased consensus overcoming present barriers.

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INTRODUCTION

Confocal laser endomicroscopy (CLE) is an advanced endoscopic imaging modality that provides histology-like images at 1000-fold magnification for *in-vivo* microscopy evaluation[1]. Since the first publication about the use of CLE in the gastrointestinal tract, ten years have passed[2].

The technology was initially developed for an endoscope-integrated CLE system (e-CLE) (EC3870K, Pentax Medical, Japan) with specific applications to upper and lower endoscopy, and a few years later for a probe-based CLE system (p-CLE) (Cellvizio, Mauna Kea Technologies, France)[1,2].

Nowadays only p-CLE is commercially available, with the advantage that it can be used in other parts of gastrointestinal tract as in bilio-pancreatic diseases through endoscopic retrograde cholangiopancreatography and endoscopic ultrasound.

Several studies have demonstrated a high correlation of results between CLE and histopathology in gastrointestinal lesions[1,2]. In fact, CLE has overcome some of the limitations found in endoscopy (macroscopy) and histopathology (microscopy), thus improving patient management.

In spite of its high accuracy and several clinical applications, CLE is still not routinely used in the clinical practice due to many barriers.

CLINICAL EVIDENCE AND APPLICATIONS

It has been demonstrated that white light endoscopy is not accurate for predicting histological inflammation or other alterations such as nonspecific erythema, nodularity, erosions, *etc.*[3].

Moreover, the limits between neoplastic and inflammatory areas are very narrow/unclear due to the coexistance of these processes together.

When using CLE during endoscopy we can clearly understand why the correlation between standard videoendoscopy and histopathology is not higher than 70% in most cases[4].

Many studies evidence an accuracy of 81.5% using p-CLE for the diagnosis of dysplasia in Barret esophagus[5].

In gastric diseases, CLE has had an accuracy of 94%-96% for diagnosis of malignancy when compared directly with histological biopsies[6]; and 88% for premalignant conditions such as intestinal metaplasia[7].

In colon conditions, CLE has had an accuracy of 82% for predicting polyp histology *in-vivo*, increasing to 94% if used in combination with digital chromoendoscopy with narrow band imaging during procedures[8]. Moreover, in inflammatory bowel diseases (IBDs), various studies have examined the role of CLE in surveillance of IBD patients, assessing the extent of disease, targeting biopsies, earlier detection of dysplasia, assessment of mucosal healing, and defining treatment protocols[9,10].

Recently, new applications in the biliary tract and for diagnosing subtypes of pancreatic cysts have been studied showing a mean accuracy of 85% for diagnosis of neoplastic and non-neoplastic lesions[11,12].

IS IT TIME TO MOVE ON?

In spite of its high accuracy as well as several clinical applications, CLE is still not used in routine clinical practice. This could be correlated to many factors such as: cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist.

However, these limitations are relative, and solutions could be found based on new research leading to increased consensus overcoming present barriers. Examples of this could be: cost-effective studies and analysis, meta-analysis, learning curve studies, *etc.*

A recent study performed at our institution demonstrated the benefit of using CLE in cases of "diagnostic doubts", causing changes in diagnostic and therapeutic approach in 40% of cases, in the performance of target biopsies in 100% of cases (17/17) and making other diagnostic or therapeutic methods unnecessary in all cases[13].

In this regard, a patient with Barrett esophagus and dysplasia at histopathology but without dysplasia criteria at high definition with chromoendoscopy could have diagnosis benefits using CLE. Other examples are: patients with biliary tract stenosis of unknown origin where citobrush did not evidence neoplasia, and the difficult management during follow-up repititions. In both cases, need of newer tests and examinations, biopsies, *etc.*, will be unnecessary, reducing the cost management of these patients.

One of the biggest problems when using CLE, is that histopathology remains the gold-standard technique for final diagnosis of diseases. However, histopathology could have a 20% to 30% misdiagnosis rate due to many factors such as interpretation mistakes, biopsy site inaccuracy, or number of biopsies[4].

Another suggestion would be to use CLE in cases where other investigative precedures have shown an absence of malignancy as a method of confirmation of the negative results. This would eliminate many of the medical and cost-related problems mentioned above. The rational for this is based on the fact that 9 out of 10 biopsies are benign and that the accuracy of CLE to confirm non-neoplastic lesions is higher than its

accuracy for confirming positive neo-plastic results.

FUTURE PERSPECTIVES

New studies focused on solving the relative barriers in using CLE are currently necessary. The results obtained during the last ten years validate the use of CLE in clinical practice, and the first step to doing this could be dealing with patients with diagnostic uncertainties. This could improve and solve many unclear diagnoses as well as improve therapeutic decisions and/or follow-up procedures in this kind of patient.

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REVIEW

Bowel cleansing before colonoscopy: Balancing efficacy, safety, cost and patient tolerance

Nicole M Harrison, Michael C Hjelkrem

Nicole M Harrison, Department of Medicine, Fort Belvoir Community Hospital, Fort Belvoir, VA 22060, United States

Michael C Hjelkrem, Department of Gastroenterology, Fort Belvoir Community Hospital, Fort Belvoir, VA 22060, United States

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Correspondence to: Michael C Hjelkrem, MD, Department of Gastroenterology, Fort Belvoir Community Hospital, 9300 DeWitt Loop, Fort Belvoir, VA 22060, United States. mhjelkrem@yahoo.com
Telephone: +1-571-2312014

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Abstract

Effective colorectal cancer screening relies on reliable colonoscopy findings which are themselves dependent on adequate bowel cleansing. Research has consistently demonstrated that inadequate bowel preparation adversely affects the adenoma detection rate and leads gastroenterologists to recommend earlier follow up than is consistent with published guidelines. Poor preparation affects as many as 30% of colonoscopies and contributes to an increased cost of colonoscopies. Patient tolerability is strongly affected by the preparation chosen and manner in which it is administered. Poor tolerability is, in turn, associated with lower quality bowel preparations. Recently, several new developments in both agents being used for bowel preparation and in the timing of administration have brought endoscopists closer to achieving the goal of effective, reliable, safe, and tolerable regimens. Historically, large volume preparations given in a single dose were administered to patients in order to achieve adequate bowel cleansing. These were poorly tolerated, and the unpleasant taste of and significant side effects produced by these large volume regimens contributed significantly to patients' inability to reliably complete the preparation and to a reluctance to repeat the procedure. Smaller volumes, including preparations that are administered as tablets to be consumed with water, given as split doses have significantly improved both the patient experience and efficacy, and an appreciation of the importance of the preparation to colonoscopy interval have produced additional cleansing.

Key words: Bowel preparation; Colonoscopy; Adenoma detection rate; MiraLAX; Polyethylene glycol; Sodium picosulfate; Oral sulfate solution

Core tip: Improvements in efficacy and tolerability of

bowel preparation include new formulations that are more tolerable to patients without sacrificing efficacy or safety, and a better understanding of the ideal timing of bowel preparation administration.

Harrison NM, Hjelkrem MC. Bowel cleansing before colonoscopy: Balancing efficacy, safety, cost and patient tolerance. *World J Gastrointest Endosc* 2016; 8(1): 4-12 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i1/4.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i1.4

INTRODUCTION

Many patients describe the bowel preparation prior to colonoscopy as the most unpleasant part of the whole procedure and the biggest deterrent to repeating it. Unfortunately, in addition to being the most loathed aspect, the bowel preparation is one of the most critical components of effective screening for colon cancer. The ideal bowel preparation, though this has not yet been developed, is one that is safe, highly effective and reliable, convenient, and tolerable enough that patients are not deterred from repeating the procedure.

Inadequate bowel preparations lead to lower adenoma detection rates and more frequent follow up intervals than would otherwise be recommended by guidelines based on colonoscopy findings. The European Panel of Appropriateness of Gastrointestinal Endoscopy found that polyp detection was related to the quality of bowel cleansing[1]. Relative to a low quality preparation, a high quality or intermediate quality preparation produced a 1.46 and 1.73 odds ratio (OR) of polyp detection[1]. Sherer *et al*[2] found a lower detection rate of advanced histology in the setting of poor preparation, though the number of polyps 6-9 mm detected was not different. In studies that have looked at early repeat colonoscopy following a suboptimal preparation, the quality of preparation is strongly associated with incidence of missed polyps and adenomas[3-5]. Lebwohl *et al*[3] found a 42% overall miss rate after inadequate bowel prep with a 47% miss rate for adenomas less than 10 mm and 27% miss rate for adenomas greater or equal to 10 mm. Hong *et al*[4] found that the adenoma detection rate decreased as the quality of bowel prep decreased with a precipitous drop off seen as the quality decreased from fair to poor. Ultimately, the adenoma detection rate was associated with patient tolerability with an OR of 0.39 in the setting of poorly tolerated preparations[6].

The evidence for the benefit of bowel preparation prior to colorectal surgery is less convincing. While it remains the overwhelming practice of surgeons to prescribe a mechanical bowel preparation, studies have not convincingly showed that it reduces the incidence of mortality, skin and soft tissue infections, or peritonitis as compared to no preparation[7]. Recent studies have supported the use of oral and parenteral antibiotics prior to procedure. As with the preparation for endoscopy, there is no clear superiority of one regimen over another.

Poor preparation is not an uncommon occurrence. Rates of inadequate bowel preparation are estimated to be as high as 30.2% with as many as 10% being so poor as to preclude any further evaluation[8]. Due to the increased risk of missed polyps and decreased efficacy of screening in the face of a poor bowel prep, research has found that, in patients with a poor bowel prep, gastroenterologists are less likely to adhere to recommended screening intervals and more frequently recommend closer follow up than would otherwise be appropriate based on intra-procedure findings[9-11]. Shortened follow up intervals translate into increased screening costs, estimated to be as much as a 12% to 22% increase, and greater inconvenience to patients[12].

A 4 L preparation of polyethylene glycol (PEG) has been considered the gold standard in terms of prep efficacy but is reviled by patients due to its poor taste and discomfort associated with the larger volumes. Alternate formulations have been developed, but these have had other drawbacks in terms of safety, tolerability, or efficacy. Recently, new options have received Food and Drug Administration (FDA) approval and these may offer improved tolerability without sacrificing efficacy (Table 1).

POLYETHELENE GLYCOL

Four liters PEG-ELS (electrolyte lavage solution) administered in split doses is considered by most to be the standard against which all other bowel preparations are judged[13]. A systemic review and meta-analysis by Enestvedt *et al*[13] found an OR of 3.46 that a split dose 4 L PEG-ELS preparation would produce a good or excellent bowel preparation compared with other methods. The pooled analysis did not reveal any other significant differences in performance measures such as overall experience or willingness of patients to repeat the procedure, or in side effects such as nausea.

Nonetheless, many studies conclude that patients prefer lower volume preparations to the full 4 L PEG. Often preceded by a stimulant laxative such as bisacodyl or magnesium citrate, 2 L PEG preparations have been found to achieve equivalent levels of bowel cleansing with enhanced patient experience[14-19]. A 1994 study comparing single dose preparations of 4 L PEG-ELS with 2 L PEG-ELS preceded by bisacodyl found comparable cleansing[14]. The subjects in the 2 L PEG-ELS group rated the preparation more tolerable and more patients were able to complete the preparation than in the 4 L group (93% *vs* 66%). Sharma *et al*[15] found similar results in a trial comparing 4 L PEG-ELS with 2 L PEG-ELS with bisacodyl or magnesium citrate. The quality of preparation was rated better with 2 L PEG-ELS with bisacodyl or magnesium citrate than with 4 L PEG-ELS (8.1 *vs* 7.8 *vs* 7.3). This was coupled with lower procedure times and higher patient

Table 1 Relative effectiveness and cost of available bowel preparations

Prep		% Adequate	Lesion detection rate	Cost[1]
4 L PEG	Single	51%-88%[16,64]	PDR 50.5%-51%[26,51]	PEG 3350 with electrolytes 4 L
	Split	71.3%-92.1%[23,51]	ADR 27.8-34.3%[51,70]	$26.59
2 L PEG	Single	83.5%-91%[45,64]	ADR 18.8%[70]	Moviprep 100 g/1 kit
	Split	74.4%-93.5%[45,48]		$91.55
MiraLAX	Single	67.8%-81.8%[29,31]	PDR 47%[26]	MiraLAX 8.3oz/238 g
	Split			$13.99
Sodium Phosphate		84.3%-90%[35,37]	Not Available	OsmoPrep 32 tabs
				$163.05
Sodium Picosulfate	Single	61.5%-82.6%[49,51]	PDR 38.5%-42.9%[51,53]	Prepopik, 2 pkts
	Split	81.6%-87.9%[49,50]	ADR 23.8%-31.3%[51,53]	$121.31
Oral Sulfate Solution	SuPrep	94.7%-98.4%[44,53]	PDR 50.9%[53]	SuPrep 1 kit
				$49.09
	Suclear	93.5%[45]	ADR 26%[53]	Suclear
				$76.38

[1]Prices from RxPriceQuotes.com as listed for CVS w/exception of MiraLAX which was priced at local CVS. PEG: Polyethylene glycol; PDR: Polyp detection rate; ADR: Adenoma detection rate.

satisfaction scores. Of 24 subjects who had a previous bowel prep with 4 L PEG-ELS, 88% of those in the 2 L PEG-ELS plus magnesium citrate and 56% of those in the 2 L PEG-ELS plus bisacodyl preferred the low volume preparation. A follow up study by the same group found small, likely clinically insignificant serum electrolyte changes following low dose PEG-ELS with stimulant laxatives[20]. A low volume PEG plus ascorbic acid in comparison with 4 L PEG-ELS produced an equivalent number of adequate bowel preps (94.6% *vs* 90%), was better tolerated and produced fewer adverse events (80.2% *vs* 89.9%)[21]. Similar results have been obtained in other studies though some have shown that cleansing in the right colon was superior with the 4 L PEG preparation[22,23].

The relative efficacy of the 2 L PEG preparations is undiminished when it is administered as a split dose[24,25]. A 2013 study of of 2 L PEG-citrate plus bisacodyl and simethicone found that successful preps were achieved in 92.8% *vs* 92.1% of patients using the 2 L PEG and 4 L PEG respectively[24]. A higher percentage of excellent right colon preps were observed in the 4 L PEG group. The 2 L PEG prep was better tolerated (31.6% reporting symptoms *vs* 45.2%) and more patients expressed willingness to repeat the same procedure in the future (90.6% *vs* 77%). Similar results were obtained using split dose 2 L PEG-ascorbic acid alone[25]. There was no significant difference in the quality of bowel prep or number of patients achieving an adequate bowel prep in 2 L *vs* 4 L groups (7.0 ± 2.1 *vs* 7.1 ± 2.0 and 73.2% *vs* 76.3%)[25]. The low volume preparation was rated significantly more tolerable with 14.3% of subjects reporting difficulty in taking the preparation *vs* 30.7% with the 4 L PEG preparation[25].

MIRALAX

Though it has not been FDA approved for the purpose, MiraLAX (Bayer Healthcare, Leverkusen, Germany) has come into widespread use as a bowel prep agent in spite of equivocal evidence supporting its efficacy as compared to FDA approved alternatives due to the convenience of using an over the counter product and superior palatability. A recent survey of practicing gastroenterologists found that one third regularly recommend some sort of MiraLAX based bowel prep to their patients with rates as high as 50% in suburban practices and a positive correlation between the number of colonoscopies performed and the likelihood of recommending a MiraLAX based bowel prep[26]. MiraLAX based bowel preps, typically 238 mg of MiraLAX in 64oz of Gatorade, has generally, though not universally, been found to be more tolerable to patients[27-30].

The data regarding the cleansing achieved with MiraLAX is more mixed. McKenna *et al*[30] found that single dose MiraLAX was non-inferior compared to 4 L of PEG-ELS, both taken the night before procedure. Both MiraLAX and PEG-ELS produced equivalent BBPS (7.0 *vs* 7.2) and had similar percentages of patients achieving adequate bowl preps (BBPS $\geqslant$ 6, 81.3% *vs* 84.3%). The authors found no difference in time to cecal intubation or withdrawal time. MiraLAX was preferred by study subjects. Similar results were obtained in a study by Samarasena *et al*[28] comparing split dose MiraLAX with split dose PEG-ELS. Again, no significant difference in BBPS (8.01 *vs* 8.33) was observed and the MiraLAX based prep was given significantly better ratings in terms of taste and tolerability with 96.8% *vs* 75% of subjects willing to repeat the prep in the future. A comparison of MiraLAX in Gatorade plus bisacodyl with 4 L PEG-ELS found superior results overall (93.3% *vs* 89.3% with excellent/good cleansing) and equivalent results when the analysis was limited to only ASA class 1 patients of which there were more in the 4 L PEG-ELS group[31]. The authors noted that the increased rate of adequate preparations derived primarily from more frequent good and less frequent fair preparations.

Other researchers have found inferior bowel prep

with MiraLAX based regimens compared with PEG-ELS. Hjelkrem *et al*[27] compared split doses of 4 L PEG-ELS with MiraLAX (alone and with either bisacodyl or lubriprostone) and demonstrated inferior preps with all of the MiraLAX based preps (Ottawa score of 5.1 *vs* 6.9, 6.3, and 6.8). Cleansing was adequate with all preps, but there was a higher incidence of excellent preps in the Golytely arm (49% *vs* 15%, 20%, and 19%). No difference in adenoma detection rates was observed. A lower rate of excellent prep and overall inferior BBPS was also observed by Enesvedt *et al*[29] when comparing MiraLAX with 4 L PEG-ELS. PEG-ELS produced a mean BBPS of 9% and 70% of preps were rated excellent which was superior to a mean BBPS of 8% and 55% of preps rated excellent for MiraLAX. A follow up study by Enestvedt *et al*[32] comparing MiraLAX with PEG-ELS showed that, in addition to less frequently achieving a BBPS greater than or equal to 7, MiraLAX was associated with a lower adenoma detection rate (16.1% *vs* 26.2% with PEG-ELS).

There have been concerns about the safety of MiraLAX for bowel preparation after reports of severe hyponatremia[33]. Unlike the electrolyte solutions used for prescription bowel preps, the sports drink (typically Gatorade) is not osmotically balanced and is relatively hypotonic. Two randomized controlled trials have since demonstrated comparable safety with standard 4 L PEG preparations[28,30]. Neither trial detected a clinically or statistically significant difference in serum electrolytes. Though, the study populations were relatively small and may not detect very infrequent adverse events, it is reassuring that not even a trend toward greater electrolyte abnormalities was observed.

SODIUM PHOSPHATE

Sodium phosphate (NaP) is an osmotic laxative that was initially prescribed as a more tolerable alternative to whole gut lavage with PEG preparations. It was widely used and well tolerated by patients as a much smaller volume of fluid was required for successful prep; however, concerns about safety and confounding mucosal changes have limited the use of this agent more recently. Because of concerns of significant electrolyte disturbances and even acute renal failure, the use of sodium phosphate preps is not recommended in multiple populations including patients over the age of 55, patients taking certain medications such as angiotensin converting enzyme inhibitors (ACEi), and those with pre-existing renal disease, heart failure, and liver disease. Sodium phosphate carries a black box warning regarding the risk of acute phosphate nephropathy.

In comparison to single dose 4 L PEG-ELS, NaP produced equivalent to superior bowel cleansing with improved patient tolerability[34-38]. The greater tolerability of NaP as compared to PEG preparation has been nearly universal[35-38]. Subjects, including 37 who had been prepped with PEG for prior colonoscopy, rated NaP easier to complete and less uncomfortable[35].

Unfortunately, in spite of its superior tolerability, NaP is not without significant adverse side effects[39]. Hyperphosphatemia following NaP has been well documented in patients with both normal and impaired renal function and has been associated with hypocalcemia. Cases of acute phosphate nephropathy have largely occurred in patients with pre-existing renal disease, but have also occurred in setting of dehydration in patients with otherwise normal renal function[40]. NaP is thought to cause renal injury by precipitating nephrocalcinosis[39,40]. The risk of adverse events is increased patients taking ACEi or angiotensin receptor blockers and who are of advanced age[39]. Additional suspected risk factors include existing renal disease, female gender, volume depletion, and abnormal bowel motility[39].

NaP has also been reported to cause mucosal inflammation and ulcerations that give the appearance of inflammatory bowel disease. A randomized control trial compared patients receiving PEG-ELS with NaP and found an association between NaP use and the presence of nonspecific aphthoid like mucosal lesions[41]. Lesions were present in 24.5% of subjects receiving NaP *vs* 2.3% of those receiving PEG. Though pathological evaluation of the lesions was not consistent with IBD, the authors reported that they were endoscopically similar to those seen in Crohn's disease. This association was substantiated in a larger observational trial of 730 patients who were administered a NaP bowel prep and followed for 3 years after the procedure[42]. In this study, only 3.3% of patients exposed to NaP demonstrated mucosal lesions on endoscopy, but these lesions were of the type seen in anti-inflammatory drug induced injury and in IBD. As a result of these observations, NaP is not recommended in patients undergoing colonoscopy to evaluate for suspected IBD[41,42].

ORAL SULFATE SOLUTION

Sulfate is a poorly absorbed anion that does not cause significant fluid or electrolyte shifts[43,44]. In comparison with sodium phosphate, sodium sulfate produced more liquid stool and, unlike phosphate, did not increase the propensity for calcium to precipitate in renal tubules[43]. Oral sulfate solution (OSS) is available in two formulations: SuPrep (two doses of sodium, phosphate, and magnesium sulfate; Braintree Laboratories, Braintree, MA) and Suclear (one dose of sodium, phosphate, and magnesium sulfate followed by a second dose of PEG 3350 in 2 L of water; Braintree Laboratories, Braintree, MA).

A 2009 study by Di Palma *et al*[44] demonstrated equivalent bowel cleansing with OSS and 2 L PEG-ELS given as single and split doses. Split dosing was superior to single dose for both preparations (82.4% and 80.3% *vs* 97.2% and 95.6% for OSS and PEG-ELS respectively). OSS was associated with a higher frequency of excellent preparations in the split dose arm

(63.3% *vs* 52.5%). A subsequent study by this group comparing split dose OSS (SuPrep) with single dose 4 L sulfate free PEG-ELS found a significantly higher rate of adequate and excellent preparations in the OSS group (98.4% *vs* 89.6% and 71.4% *vs* 34.4%)[45]. OSS also resulted in less residual stool in the right colon. There were small changes in serum electrolytes with OSS which the authors reported as clinically insignificant. A third study by this group compared split dose OSS plus PEG-ELS (Suclear) with split dose 2 L PEG-ELS and OSS plus PEG-ELS given the night before procedure with 10 mg bisacodyl followed by 2 L PEG-ELS[46]. The split dose administration produced equivalent rates of successful prep (93.5% in both arms). Single dose OSS with PEG-ELS was non-inferior to PEG-ELS given with bisacodyl (89.8% *vs* 83.5%) and associated with significantly more excellent preparations (47.7% *vs* 35.6%). In both arms of the study, OSS plus PEG-ELS was associated with a higher incidence of side effects (vomiting in the split dose arm and overall discomfort in single dose arm.) The authors looked specifically at the efficacy in the elderly (age $\geqslant$ 65) and found that the split dose OSS with PEG-ELS produced more successful preparations (93% *vs* 86%) in this population. Patients with pre-existing comorbidities (cardiac or renal disease, diabetes, and hypertension) had similar rates of adverse events with both preps.

SODIUM PICOSULFATE

Sodium picosulfate (PMC) is a stimulant laxative given in combination with an osmotic laxative component such as magnesium citrate or magnesium oxide and citric acid which combine to form magnesium citrate. PMC has been used extensively in Canada and Europe for the past 20 years, but was only recently approved for use as a bowel preparative agent in the United States. The formulation available in the United States, Prepopik (Ferring Pharmaceuticals, Parsippany, NJ), is given as a split dose. Like sodium phosphate, this is a hyperosmolar preparation may not be suitable for patients with heart failure, renal insufficiency, end stage liver disease, or baseline electrolyte abnormalities. There have been reports of clinically significant hyponatremia following PMC bowel preparations and a retrospective cohort study by Weir *et al*[47] confirmed that use of PMC in patients older than 65 years was associated with an increased risk of 30 d hospitalization for hyponatremia, but not with increased risk of acute neurological symptoms or mortality.

Katz *et al*[48] compared PMC, given as single and split doses, with single dose 2 L PEG and bisacodyl administered the day before. Single dose PMC compared favorably with single dose PEG producing successful cleansing in 83.0% *vs* 79.7% or patients and comparable cleansing seen throughout all segments of the colon. Adverse events were similar between the two groups, and patient acceptability was significantly greater in the PMC arm. With split dose administration, PMC performed significantly better than single dose 2 L PEG with bisacodyl[49]. Good or excellent Aronchick scores were more frequent in the PMC arm in both the overall colon (84.2% *vs* 74.4%) and in the individual segments. Again, PMC was rated more tolerable than 2 L PEG. Similar results were observed by Kojecky *et al*[50] in a comparison of PMC and 4 L PEG in single and split doses. Split dose regimens were preferable regardless of the agent. Single dose PMC produced a higher percentage of acceptable preps compared to PEG (82.6% *vs* 73%). There was no significant difference in the number of subjects with adequate prep among the remaining study arms; split dose PMC (81.6%), single dose PMC (82.6%), and split dose PEG (87.3%). Both PMC based regimens were rated more tolerable than either PEG based prep. Single dose PEG was most associated with nausea and bloating. Single dose PMC had the least abdominal pain reported, but split dose PMC had the highest association with incontinence. There was a slight preference for the single dose PMC preparation among older subjects and for the split preparation in younger subjects. These findings have been replicated in other studies with PMC achieving similar percentages of adequate bowel cleansing compared with PEG while being significantly preferred by study subjects[51,52]. Another study evaluated PMC alone verse in combination with PEG found little additional benefit with PEG[53]. Only in the right colon was there a significant difference in Ottawa bowel prep scores between the PMC alone and PMC plus 2 L PEG groups (1.34 ± 1.022 *vs* 1.11 ± 0.97). As in other studies, the PMC alone regimen was preferred by patients (89% *vs* 72.3%) and had less associated nausea.

There has been only one study directly comparing PMC with OSS[54]. Rex *et al*[54] found a higher rate of successful and excellent preparations with OSS in comparison with PMC (94.7% *vs* 85.7% and 54% *vs* 26%). Unlike the OSS arm, there were 4 patients in the PMC arm who required additional preparation before the procedure could be attempted and 9 patients in whom the cecum was not reached. There was no significant difference in the polyp detection rate (50.9% *vs* 42.9%), adenoma detection rate (26.0% *vs* 23.8%), or flat lesion detection rate (9.5% *vs* 4.8%), and no difference in the procedure duration (mean 16.5 min *vs* 16.6 min). There was no difference in adverse events in the two arms and, though nausea was generally mild in both arms, subjects taking PMC reported better scores for nausea (Table 2).

TIMING OF PREP

Regardless of the preparation used, the quality of preparation has proven higher with split dose *vs* day before administration. This has been demonstrated most clearly with PEG based preparations. A 2005 study compared 4 L PEG preparations given as a single dose with dietary restrictions on the evening before the procedure or as a split dose without dietary restrictions

Table 2 Advantages and disadvantages of available bowel preparations

Prep	Advantages	Disadvantages
4 L PEG	Effective	Poor taste
	Safe in most populations	Very high volumes
		Poorly tolerated by patients
2 L PEG	Effective	Poor taste
	Safe in most populations	High volumes
		High cost
MiraLAX	Well tolerated by patients	Not as effective as prescription PEG preparations
	Available over the counter	Rare reports of hyponatremia
	Existing studies indicate it is safe	
Sodium phosphate	Available as oral tab	Inappropriate for use in patients with renal disease, volume depletion, heart or liver failure, or who are taking ACEi or NSAIDs
	Well tolerated by patients	Risk of acute phosphate nephropathy and subsequent chronic kidney disease
Sodium picosulfate		Cost
	Well tolerated by patients	Not as effective as PEG or OSS
OSS	Small volumes to be ingested	Inappropriate for patients with heart failure, renal insufficiency, end stage liver disease, or baseline electrolyte abnormalities
	Pleasant taste	High cost
	Well tolerated by patients	High cost
	Highly effective	Not as well studied
	Available as oral tab	

PEG: Preparation of polyethylene glycol; ACEi: Angiotensin converting enzyme inhibitors; NSAIDs: Nonsteroidal anti-inflammatory drugs; OSS: Oral sulfate solution.

and found that, even without dietary restrictions, the split dose preparation produced significantly better preps[55]. A randomized control trial of evening before *vs* split dose PEG preparations that included both high and low volume preparations found that, regardless of the volume of preparation, split dose administration produced significantly more successful preps (75.2% *vs* 43.0%) and a lower rate of aborted procedures (6.9% *vs* 21.2%)[56]. A pre-post study by the Veteran's Health Administration assessed efficacy and acceptance of split dose bowel preps in an elderly populations with multiple co-morbidities and found that the split dose preparations were better tolerated by patients and produced superior results[57]. Both right and left colon preparations were improved with split dose administration (excellent/good preps achieved in 81.4% *vs* 63% and 85.9% *vs* 71.6% respectively)[57].

These results were validated in 2 meta-analyses[58,59]. Kilgore *et al*[58] included 5 trials in an analysis which found split dose PEG produced an OR of 3.7 of a satisfactory bowel preparation as well as improved patient tolerability. Martel *et al*[59] obtained similar results in an analysis of 47 trials. In this study which included split dose preparations of PEG, NaP, and PMC, the OR of a successful prep with split *vs* evening before preparation was 2.51. Subjects reported greater willingness to repeat the split dose preparation.

Concerns have been raised about the risk of peri-procedural aspiration with split dose regimens. In 2010, Huffman *et al*[60] examined 712 patients with EGD of which 254 had received split dose bowel preps for concurrent colonoscopy. While the residual gastric volume was higher in patients who received the split dose preparation as compared with patients scheduled for EGD only (19.7 mL *vs* 14.6 mL), there was no difference between when compared with patients who received day before preparation (20.2 mL) and the 5 mL difference is unlikely to be clinically significant[60].

Recent studies have shed light on the reason for the improved cleansing seen with split dose preparations and highlighted the importance of a short duration between the completion of a bowel prep and the start of the colonoscopy[61-64]. A prospective analysis of colonoscopy start times and the time of the last dose of bowel prep showed an inverse relationship between the degree of cleansing and the length of this interval[64]. Subsequent studies have reinforced this finding and clarified the ideal time interval between bowel prep and colonoscopy. Eun *et al*[62] compared intervals of more and less than 7 h and of more and less than 4 h and found that, in each case, superior cleansing was seen with the shorter interval. A 3 to 5 h interval produced the best cleansing throughout the colon in a prospective study by Seo *et al*[61], though the association was not as high as with the amount of PEG ingested (OR 1.85 for prep to colonoscopy time *vs* 4.34 for quantity of PEG ingested).

Following from these findings, researchers have looked at the feasibility of preparations completed entirely on the morning of the planned procedure[65-67]. Varughese *et al*[65] compared morning only preparation with preparation completed entirely the evening prior and, consistent with the finding that the interval between preparation and procedure is a determinant of the quality of preparation, found that morning only preparation is superior to evening before preparation. Matro *et al*[66] compared morning only to split dose administration of PEG-ELS and found equivalent cleansing and adenoma detection with improved tolerability in the morning only

group. Similar findings were obtained by Longcroft-Wheaton *et al*[67] in comparing morning only to split dose sodium picosulfate.

CONCLUSION

Effective, safe, and reliable options for bowel preparation are becoming increasingly available though the most tolerable options remain the most costly. Improved efficacy has also been achieved with alterations in the dosing schedule, namely split dose administration and a better understanding of the optimal interval between preparation and the colonoscopy. These adjustments have proven more tolerable as well as more effective. The consensus of the major Gastrointestinal Societies is that the choice of agent should be tailored to the individual patient, but that a split dose regimen can be recommended in all cases[68,69]. Additional research is needed to develop tools to assist providers in choosing an optimal regimen for their patients as factors such as age and comorbid conditions may affect the efficacy and safety of a particular agent. The optimal choice of bowel preparation must be guided by the circumstances of the individual patient undergoing procedure; however, low volume PEG preparations would appear to come closest to being the ideal preparatory agent in that it is effective, generally well tolerated, has an excellent safety record in a population of patients with a range of comorbid conditions, and is relatively inexpensive. Ongoing studies are evaluating the impact of interventions such as improved pre-procedure patient education and smart phone based applications that remind patients of when to take their prep are showing promise with regard to improved patient tolerability and adherence and may offer a path toward both patient and endoscopist satisfaction.

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REVIEW

Role of endoscopic clipping in the treatment of oesophageal perforations

György Lázár, Attila Paszt, Eszter Mán

György Lázár, Attila Paszt, Eszter Mán, Department of Surgery, University of Szeged, Szeged 6720, Hungary

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Correspondence to: György Lázár, MD, PhD, Head, Department of Surgery, University of Szeged, H-6720 Szeged, Szőkefalvi-Nagy Béla u. 6., Szeged 6720, Hungary. gylazar@gmail.com
Telephone: +36-62-545701
Fax: +36-62-545701

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Abstract

With advances in endoscopic technologies, endoscopic clips have been used widely and successfully in the treatment of various types of oesophageal perforations, anastomosis leakages and fistulas. Our aim was to summarize the experience with two types of clips: The through-the-scope (TTS) clip and the over-the-scope clip (OTSC). We summarized the results of oesophageal perforation closure with endoscopic clips. We processed the data from 38 articles and 127 patients using PubMed search. Based on evidence thus far, it can be stated that both clips can be used in the treatment of early (< 24 h), iatrogenic, spontaneous oesophageal perforations in the case of limited injury or contamination. TTS clips are efficacious in the treatment of 10 mm lesions, while bigger (< 20 mm) lesions can be treated successfully with OTSC clips, whose effectiveness is similar to that of surgical treatment. However, the clinical success rate is significantly lower in the case of fistulas and in the treatment of anastomosis insufficiency. Tough prospective randomized multicentre trials, which produce the largest amount of evidence, are still missing. Based on experience so far, endoscopic clips represent a possible therapeutic alternative to surgery in the treatment of oesophageal perforations under well-defined conditions.

Key words: Oesophageal perforation; Endoscopic clipping; Upper gastrointestinal perforation; Endoscopy; Over-the-scope clip

Core tip: With advances in endoscopic technologies, endoscopic clips have been used successfully in the treatment of various types of oesophageal perforations, anastomosis leakages and fistulas. We summarized the results of oesophageal perforation closure with endoscopic clips [the through-the-scope (TTS) clip and the over-the-scope clip (OTSC)]. We processed the data from 38 articles and 127 patients using PubMed search. Based on the evidence, TTS clips are efficacious in the treatment of 10 mm lesions, while bigger (< 20 mm) lesions can be treated successfully with OTSC clips. Based on experience so far, endoscopic clips represent a possible therapeutic alternative to surgery in the treatment of oesophageal

perforations under well-defined conditions.

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INTRODUCTION

Despite remarkable advances in surgery and intensive care, oesophageal perforation is still a life-threatening condition[1,2]. It is iatrogenic (caused by a device) in a majority of cases; perforation caused by a foreign body or trauma and spontaneous perforation are less frequent. Several well-known factors influence its course: location and cause of perforation, time from diagnosis until care, co-morbidities of the oesophagus, general condition of the patient and selected treatment[3,4]. In addition to oesophageal perforation, suture insufficiency of the oesophagus and other oesophageal fistulas also pose serious therapeutic challenges nowadays.

With the development of endoscopic technology during the last two decades, endoscopic clips and self-expanding stents have been used successfully and ever more widely in the treatment of oesophageal perforations/fistulas of various origins[5,6]. Oesophageal injury was first closed endoscopically with the placement of clips in 1995; the injury had occurred as a consequence of pneumatic dilatation in a patient with achalasia[7]. Since then, this method has been used for oesophageal perforations of various aetiologies, including Boerhaave syndrome[8-11]. To date, the method has been successful, especially in the treatment of small (< 2 cm) injuries. The following review article describes indications of endoscopy and endoscopic clips in the treatment of oesophageal perforation.

DISCUSSION

Aetiology of oesophageal perforation

Various causes of perforation or rupture of the oesophagus are well-known: iatrogenic, foreign body, postemetic (spontaneous, Boerhaave syndrome) trauma, tumour and surrounding inflammation. Iatrogenic injuries are still the most common cause; the second most common is spontaneous oesophageal rupture. These two types represent more than two-thirds of the perforations based on a number of publications from different countries[12,13]. Suture insufficiency in the oesophagus (oesophageal/gastric resections and other sutures) and fistulas of various aetiologies fall into a separate group. In recent decades, the appearance and more widespread use of new therapeutic endoscopic methods have significantly increased the incidence of iatrogenic oesophageal perforations. It can be well determined which endoscopic interventions confer increased risk of perforation: (1) dilatation of the oesophagus (balloon/bougie); (2) endoscopic resections [endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)]; and (3) removal of a foreign body. Dilatation of the oesophagus is almost as old as endoscopy; however, this method is still not without risks. The risk of perforation is greatest in the case of balloon dilatation (especially due to achalasia), with an approximate 2% overall cumulative rate, which can be reduced if endoscopic guidance is provided and if a balloon with a small (30 mm) diameter is used at the beginning of the intervention[14-16]. The risk of perforation in the dilatation treatment of peptic and other benign strictures is significantly lower with the use of a guide wire and a bougie (0.18%); however, in the case of malignant strictures, the risk of injury is increased again (0.48%)[17]. In the case of endoscopic resections (EMR and ESD), the risk of perforation is similar to that of balloon dilatation (2%-3%)[10,18].

Diagnosis of oesophageal perforation

A bidirectional chest X-ray is usually taken in addition to an oesophagogram with water-soluble contrast material to confirm perforation. The oesophagogram is the most common test procedure, but there are a number of false negative results (10%)[19]. Nowadays, abdominal and thoracic CT examinations are also routine[20]. The sensitivity of the CT examination is especially important in detecting a small amount of mediastinal/pleural air and/or fluid[21,22]. If the examination is combined with an oesophagogram, the exact location of extravasation can be determined more precisely. An endoscopic examination[23] may likewise be helpful in the diagnosis. Endoscopy is not only important in setting up the diagnosis, but also in confirming previously unknown accompanying co-morbidities of the oesophagus (such as tumour and stricture), which may significantly modify the treatment strategy. Endoscopy also offers an immediate treatment option (if the conditions are suitable), and it may also be helpful intraoperatively during surgical intervention (in checking whether the sutures are intact, in inserting a nasogastric/jejunal probe, *etc.*)[23]. The diagnosis of a perforation is especially important in the case of an endoscopic intervention (EMS, ESD, balloon dilatation, *etc.*), which also determines therapy and prognosis[24].

TREATMENT OF OESOPHAGEAL PERFORATION: GENERAL CONSIDERATIONS

Essential elements in the treatment of oesophageal perforation include resolving the source of the infection, operative or non-operative closure of the defect, and thoracic and mediastinal debridement. Important parts of therapy are controlling sepsis, intensive monitoring, targeted antibiotic/antimycotic treatment, fluid therapy

and strengthening the immune system of the body with enteral nutrition.

Several obvious factors determine treatment strategy and prognosis: (1) time of the diagnosis (delay); (2) localization of the perforation; (3) severity and size of the perforation; (4) presence of septic complications, physiologic reserves of the patient and existing co-morbidity of the oesophagus; and (5) the experience of the professionals providing care.

Primary closure of the oesophagus is successful in more than 90% of cases if the defect is closed within 24 h and there were no co-morbidities in the oesophagus (tumour, stricture, *etc.*)[25,26]. In this phase, tissues are not oedematic and are easy to suture/close; in addition, there is no active bacterial infection in the thoracic cavity and/or mediastinum. If the perforation occurred more than 24 h beforehand, the prognosis is significantly reduced due to rapidly developing septic complications and less successful surgical/conservative treatment[12,27].

It is well-known that thoracic transmural injuries of the oesophagus have the worst prognosis due to rapidly developing mediastinitis and sepsis, followed by injury of the abdominal segment, while perforation in the cervical segment has the best prognosis.

Intramural injuries usually respond well to conservative treatment. Transmural and transpleural injuries represent the worst defects. Treatment strategy is also essentially influenced by the size of the defect. These factors are especially important in using the endoscopic technique (see below).

General stress tolerance of the patient, existing co-morbidities and severe septic condition are known to worsen the prognosis[12,27]. Existing co-morbidities of the oesophagus are especially important in selecting a treatment option, but may also influence the prognosis significantly (such as tumorous perforation).

Today, it is only possible to manage oesophageal perforations with multidisciplinary co-operation. The role of a surgeon experienced in the treatment of perforations and that of a gastroenterologist familiar with new innovative endoscopic techniques are decisive. Treatment has to be administered individually with an understanding of the general principles involved.

TREATMENT OPTIONS FOR OESOPHAGEAL PERFORATION

Endoscopic procedures representing a minimal or significantly lower burden are more widely used not only in the diagnosis of oesophageal perforation, but also in its treatment. A number of publications, especially case histories, demonstrate the successful use of endoscopic clips and self-expanding stents in the treatment of oesophageal injuries[5,28]. The applicability of endoscopic methods has also been confirmed in experimental animal models (endoscopic clipping *vs* suturing *vs* thoracoscopic repair)[29]. Endoscopic clipping basically results in the immediate resolution of the oesophageal defect, while various types of stents aid in resolving extravasation from the oesophagus (diversion of enteral contents) and provide further slow healing of the injury. Stent implantation is mainly used in the treatment of large (> 2.5-3 cm) injuries of the middle and lower third segments of the oesophagus, and is especially suitable for the treatment of tumorous perforations where dysphagia is also resolved. Several types of stents are known, such as self-expanding plastic stents and fully and partially covered, self-expanding metal stents. In the case of injuries of the gastro-oesophageal junction, a partially covered stent is recommended with the smallest migration tendency if there is no oesophageal stricture[30]. The success of the procedure also depends on early application. Any delay in endoscopic treatment significantly reduces the chances of healing of the oesophageal perforation, as is the case with other treatment options[5]. According to the latest systematic review, the overall technical and clinical success rates of oesophageal stent placement in patient groups were 91% and 81%, respectively, and mortality was also acceptably low at 13%[31]. One of the most common complications of stent implantation is stent migration, which occurs in 20.8% of cases; this percentage is lower (11%) in the case of metal stents and higher for plastic stents (27%)[31]. However, stent migration may be reduced significantly with clips (proximal clip fixation[32]).

Vacuum-assisted technology

A method providing permanent continuous suction/drainage, is used in a number of areas with high efficacy, such as in the treatment of open abdomen, chronic wounds and suture insufficiency (rectum and oesophagus)[33]. The procedure is suitable for the treatment of chronic fistulas, particularly well-defined peri-oesophageal abscesses. It can also be used for intrathoracic oesophagus anastomosis insufficiency. It may be used to stimulate the formation of granulation tissue; therefore, the duration of prolonged secondary wound healing is decreased significantly[34-36]. Due to excessive granulation tissue formation, oesophageal stenosis can occur later within a 6%-40% range, but with an incidence of 15% in most cases[37]. Due to severe mediastinal/intrathoracic infection, the mortality rate is also naturally high (0%-20%) with this method[37].

ENDOSCOPIC CLIPS

Endoscopic clips have been used in the treatment of oesophageal perforation for 20 years; however, the number of publications on their use has only increased during the last few years. Generally, experience is available with two types of clip: the through-the-scope (TTS) clip and the over-the-scope clip (OTSC). TTS clips were developed for haemostasis and the treatment of mucosal ruptures. However, they may only be used in treating small (< 10 mm) injuries due to their limited (< 11 mm) wingspan.

The wingspan of the OTSC (OVESCO Endoscopy,

Tübingen, Germany) is not significantly larger (11-14 mm), but the system also features a special applicator cap[38]. The entire thickness of the tissue may be pulled into the cap by suction and/or with graspers, and the tissue may be united with special clamps (a bear claw). Experience shows that this innovative clipping device made of biocompatible nitinol also provides stronger closure of large (1-2 cm) defects[39]. Nowadays, several types of clips are available (blunt/atraumatic and pointed-teeth/traumatic). There is also a special "anchor" which aids in the closure of fibrotic fistulas. It only takes an experienced endoscopic professional a few minutes to close a defect[40]. One iatrogenic oesophageal injury has been reported with the use of this device when an endoscopic OTSC was inserted[40]; the injury may have been caused by the 2 mm rim of the plastic cap. However, experience shows that the device can be used safely, and the complication rate is around 1%[40,41].

CLOSURE OF OESOPHAGEAL PERFORATION WITH ENDOSCOPIC CLIPS

Tables 1 and 2 summarize the results of the PubMed (Medline) search.

We used the following key words: Oesophageal perforation, gastrointestinal perforation, endoscopic clip (ping) and OTSC (latest search date: 15 March 2015). We processed the data from 38 articles and 127 patients. We placed causes of perforation into three categories in the table: Perforation was defined as an acute iatrogenic or spontaneous defect, leak as an insufficiency/disruption of a surgical anastomosis, and fistula as a chronic residual inflammatory communication between the oesophagus, with a mediastinal or pleural space or tracheobronchial tract under the skin.

Statistical analysis: Categorical data were analyzed using χ^2 and Fisher's exact test [SPSS version 15.0 (© 2007 SPSS Inc.)].

Most publications are case reports or retrospective analyses with heterogeneous indications. The number of publications significantly increased after the first clinical use of the OTSC clip in 2007, first in Europe and then in the United States and other countries as well. Neither randomized nor comparative (TTS *vs* OTSC) studies have been conducted with the use of clips. One prospective European multicentre study and two retrospective North American multicentre studies have been published on the use of OTSC clips in the treatment of GI perforations[40-42]. Unfortunately, salient information is missing from numerous articles, and generally there are no reports on the follow-up period at all.

Based on the results, it can be concluded that both clips are suitable for the treatment and early management (< 24 h) of iatrogenic, spontaneous oesophageal perforation in the case of limited injury and contamination. TTS clips are successfully used for injuries of an average of 10 mm, while OTSC clips may also be successful in the treatment of larger injuries. More clips may also be used to close a defect, and various clips may be combined[40,43]; in addition, closure with a clip may be repeated[44]. In accordance with the latest recommendations from the European Society of Gastrointestinal Endoscopy[30], clips may only be used in the treatment of an injury in the case of safe care, in stable patients, with a clear oesophagus, limited mediastinal contamination and limited injury (intramural/transmural). Certain immediately diagnosed iatrogenic perforations meet this criterion system in particular. If the amount of mediastinal and/or pleural fluid is more significant, mediastinal and/or pleural space drainage/VATS treatment usually cannot be avoided. The treatment algorithm is summarized in Figure 1.

PERFORATIONS

Based on our analysis (Tables 1 and 2), clips were used early (immediate diagnosis, < 24 h), especially in the case of minimally contaminated iatrogenic injuries or spontaneous ruptures, and the success of healing was similar to that of surgical treatment [TTS 88.8% (24/27); OTSC 92.86% (26/28)]. Although TTS and OTSC clips were used for injuries of varying sizes, their success rates did not diverge significantly (88.8% *vs* 92.85%, $P > 0.12$). Of further interest, clips were used with a similar success rate for the far smaller number of perforations of > 24 h which are only associated with a well-defined mediastinal inflammation/abscess [TTS 100% (8/8) *vs* OTSC 83.3% (5/6)]. Transoesophageal lavage of the process or even vacuum therapy may be of great aid in resolving the abscessing mediastinal process[45].

In selected cases of Boerhaave syndrome, closing the oesophageal injury with endoscopic clips might also be successful. TTS clips were used in two cases. In one patient, a minimal transmural oesophageal injury was diagnosed (a little air in the mediastinum), only the mucosal injury was partially closed with endoscopy, and conservative treatment was administered[46]. In another patient, a 5-7 mm transpleural injury was closed with 3 TTS clips, and additional thoracic drainage and enteral nutrition were administered[47]. In three additional cases, OTSC clips were used successfully to close a spontaneous transmural injury[43,48,49]. In the two matured (> 24 h) perforations, additional VATS therapy was necessary. Similarly, only limited cases have been reported on the treatment of injuries caused by foreign bodies[50,51].

Broad-spectrum antibiotic therapy and suspension of oral nutrition are required in addition to successful early endoscopic care. In the majority of cases, complication-free healing can be expected with careful indication. However, close monitoring of the patient and additional therapy such as mediastinal/pleural drainage or even

Table 1 Published literature reporting endoscopic through-the-scope clip closure for oesophageal perforations

Ref.	Cause	Size/mm	Time to treatment	Im/Tm/Tp	Method	Nr	Clinical success	Additional treatment	Hospital stay /d	Follow-up
Wewalka *et al*[7]	Perforation (1)	< 10	< 24	Tm	Endoclip		1/1 (100%)	None	ND	ND
Rodella *et al*[44]	Leak (7)	10-20	> 24	ND	Endoclip	ND	2/7 (14%)	Yes	ND	9.6 mo avg.
van Bodegraven *et al*[57]	Fistula (1)	12	> 24	ND	Endoclip + argon beam electrocoagulation	ND	1/1 (100%)	Yes	ND	7 mo
Cipolletta *et al*[8]	Perforation (2)	7-8	< 24	Im/Tm	Endoclip	1	1/1 (100%)	No	5	9 mo
		10	< 24	Im/Tm	Endoclip	2	1/1 (100%)	No	6	14 mo
Shimamoto *et al*[50]	Perforation (1)	20	< 24	Tm	Endoclip	3	1/1 (100%)	No	37	ND
Abe *et al*[58]	Perforation (1)	5	> 24	Tm	Endoclip	ND	1/1 (100%)	Yes	36	ND
Mizobuchi *et al*[59]	Fistula (1)	ND	> 24	Tm	Endoclip	1	1/1 (100%)	Yes	> 31	ND
Raymer *et al*[9]	Fistula (3)	≤ 25	> 24	Tm/Tp	Endoclip	ND	3/3 (100%)	Yes	ND	ND
			> 24	Tm/Tp	Endoclip +	ND		Yes	ND	ND
			> 24	Tm/Tp	surgery	ND		Yes	ND	ND
Shimizu *et al*[10]	Perforation (3)	8/10/2008	< 24	Tm	Endoclip	ND	3/3 (100%)	Yes	14	ND
Schubert *et al*[60]	Leak (1)	ND	> 24	Tm	Stent + endoclip	ND	1/1 (100%)	ND	ND	1 mo
Wehrmann *et al*[45]	Perforation (4)	ND	> 24	Tm	Endoclip	ND	4/4 (100%)	Yes	9-22	12 mo
	Leak (3)	ND	> 24	Tm	Endoscopic lavage + endoclip	ND	3/3 (100%)	Yes		
Matsuda *et al*[46]	Perforation (1)	25	< 24	Im	Endoclip	ND	1/1 (100%)	No	ND	ND
Sriram *et al*[11]	Perforation (1)	10	> 24	Tm	Endoclip	ND	1/1 (100%)	Yes	ND	ND
Fischer *et al*[61]	Perforation (4)	20-40	< 24	Tm	Endoclip	2-6	4/4 (100%)	No	7-18	No
			< 24	Tm	Endoclip			No		No
			< 24	Tm	Endoclip			No		No
			< 24	Tm	Endoclip			No		No
Gerke *et al*[62]	Perforation (1)	15	< 24	Tm	Endoclip	3 + 1	1/1 (100%)	No	7	6 mo
Qadeer *et al*[28]	Fistula (1)	3	> 24	Tm	Endoclip + stent	4	1/1 (100%)	Yes	65	17 mo
Luigiano *et al*[56]	Fistula (1)	25	> 24	Tm	Endoclip	5	1/1 (100%)	ND	ND	1 mo
					Endoloop	1				
Ivekovic *et al*[55]	Perforation (1)	15 × 10	≤ 24	Im/Tm	Endoloop	1	1/1 (100%)	ND	ND	4 wk
					Endoclip	4				
Jung *et al*[63]	Perforation (1)	25	> 24	Im/Tm	Endoclip	12	1/1 (100%)	Yes	ND	2 mo
					Endoloop	1				
Rokszin *et al*[47]	Perforation (1)	5-7	< 24	Tp	Endoclip	3	1/1 (100%)	Yes	14	6 mo
Coda *et al*[64]	Perforation (1)	20 (distal)	< 24	Tm	Endoclip	6	1/1 (100%)	Yes	15	6 mo
Sato *et al*[24]	Perforation (1)	ND	< 24	Im/Tm	Endoclip	ND	1/1 (100%)	No	ND	ND
Biancari *et al*[65]	Perforation (4)	8 (median)	< 24	Tm	Endoclip	ND	3/4 (75%)	Yes	32 (median)	No
Huang *et al*[66]	Perforation (4)	ND	< 24	ND	Endoclip	2	4/4 (100%)	ND	ND	ND

Im: Intramural; Tm: Transmural; Tp: Transpeural; ND: Non determined; VATS: Video assisted thoracoscopy.

surgical treatment, if necessary, are also essential.

FISTULAS/CHRONIC INJURIES

Fistulizing chronic injuries and treating anastomosis insufficiencies represent a separate group. Experience shows that OTSC clips have provided relatively secure closure so far, but the success rate in acute cases [OTSC 57.7% (15/26) *vs* TTS 100% (4/4) ($P < 0.05$) for fistulas; OTSC 77.7% (12/18) *vs* TTS 54.5% (6/11) ($P < 0.05$) for leaks] differed significantly in the groups.

Closure is technically often unfeasible, especially in the case of fibrotizing, scarred fistulas and a severely inflamed environment[52]. Most problems stem from insufficiency of the oesophageal anastomosis diagnosed in the early postoperative state. These cases are usually subacute, the tissues are extremely fragile, often ischaemic, and therefore the tendency to heal is already decreased[53]. The success rate for the closure of chronic fistulas is also reduced by previous radiation therapy. If a TTS clip is used, argon plasma coagulation and other mechanical freshening up (with a cytology brush) may aid in stabilizing the clip. These extra manoeuvres may only increase tissue oedema and the success of clip deployment when OTSC clips are used[41,52]. There are only a few case reports on successful closure of a chronic spontaneous oesophageal rupture and a consequently developed fistula with endoscopic clips[9,11].

Endoscopic vacuum therapy may be helpful in reducing the inflammatory cavity and closing the remaining fistula with good localization in the case of chronic injuries and mediastinal/pleural inflammation[37,45]. Following initial stent placement and removal in the treatment of an early, well-defined injury, a cavity marked by chronic inflammation may remain, one which may not be resolved with primary clipping alone. In these cases, EVT and/or surgical treatment (VATS) represent the primary therapeutic procedure[34-36,45].

Table 2 Published literature reporting over-the-scope clip closure of oesophageal perforations

Ref.	Cause	Size/mm	Time to treatment (< 24 h <)	Im/Tm/Tp	Method	Nr	Clinical success	Additional treatment	Hospital stay /d	Follow-up
Pohl *et al*[67]	Leak (1)	< 0	> 24	Tp	OTSC	1	1/1(100%)	No	30	ND
	Perforation (1)	ND	> 24	Tp	Surgery + stent + OTSC		0/1(0%)	Yes	Died	ND
von Renteln *et al*[68]	Fistula (2)	ND	> 24	Tm	OTSC	1	0/2(0%)	ND	ND	ND
		ND	> 24	Tm	OTSC	1		Yes	ND	ND
Traina *et al*[69]	Fistula (1)	ND	> 24	Tm	OTSC	1	1/1(100%)	ND	ND	4 wk
Albert *et al*[70]	Fistula (1)	ND	> 24	Tm	OTSC	1	1/1(100%)	ND	ND	46 wk
	Leak (1)	ND	> 24	Tm	OTSC	1	0/1(0%)	Stent	ND	4 wk
	Leak (1)	ND	> 24	Tm	OTSC	1	1/1(100%)	ND	ND	63 wk
Kirschniak *et al*[71]	Leak (1)	ND	> 24	ND	OTSC	ND	1/1(100%)	ND	10	ND
Manta *et al*[72]	Fistula (1)	8 × 4	> 24	Tm	OTSC + standard clips	1+3	1/1(100%)	No	0	ND
Surace *et al*[73]	Leak (1)	ND	> 24	ND	OTSC	ND	1/1(100%)	ND	ND	ND
Baron *et al*[41]	Leak (3)	ND	> 24	Tm	OTSC	4	1/3(33%)	ND	ND	77 avg. (30-330 d)
	Perforation (1)	ND	< 24	Tm			1/1(100%)	ND	ND	
Hadj Amor *et al*[74]	Perforation (1)	20	< 24	Tp	OTSC + stent	1	1/1(100%)	VATS	ND	ND
Hagel *et al*[53]	Leak (2)	28 × 13	> 24	Tm/Tp	OTSC	3	1/2(50%)	Surgery	Died	30 d
		8 × 4						No	12.3 ± 11	30 d
	Perforation (2)	8 × 3	> 24	Tm/Tp	OTSC	1	0/2(0%)	Surgery		30 d
		14 × 3	> 24					Surgery		30 d
Jacobsen *et al*[75]	Perforation (3)	9	> 24	ND	OTSC	2	3/3(100%)	No	ND	ND
		10 (distal)	> 24	ND		1		No	ND	ND
		10	> 24	ND		2		No	ND	ND
Markar *et al*[76]	Leak (1)	ND	> 24	Tm	OTSC	2	1/1(100%)	Yes	ND	3 mo
Voermans *et al*[40]	Perforation (5)	< 30	< 24	ND	OTSC	ND	5/5(100%)	No	ND	6 mo
Zolotarevsky *et al*[77]	Fistula (1)	5	> 24	ND	OTSC	ND	1/1(100%)	ND	7	3 mo
Braun *et al*[43]	Perforation (6)	10-40	< 24	Tm/Tp	OTSC	1-4	6/6(100%)	VATS	9-19	6-12 wk
Ferreira *et al*[51]	Perforation (1)	10 (distal)	> 24	Tm	OTSC	1	1/1(100%)	No	21	3 mo
Noronha Ferreira *et al*[78]	Leak (1)	10 × 6	> 24	Tm	OTSC	1	1/1(100%)	No	14	ND
Nishiyama *et al*[79]	Perforation (1)	20	> 24	ND	OTSC	ND	1/1(100%)	ND	ND	56 d
Ramhamadany *et al*[49]	Perforation (1)	ND	> 24	ND	OTSC	ND	1/1(100%)	Yes	ND	6 mo
Bona *et al*[48]	Perforation (1)	10	> 24	Tm/Tp	OTSC	1	1/1(100%)	No	28	No
Haito-Chavez *et al*[42]	Perforation (10)	ND	< 24	Tm/Tp	OTSC		10/10(100%)	ND	ND	Median follow-up: 121-207 d
	Leaks (5)	ND	> 24	Tm/Tp			4/5(80%)	ND	ND	
	Fistula (16)	ND	> 24	Tm/Tp			9/16(57%)	ND	ND	
Mönkemüller *et al*[52]	Fistula (4)	10-15	> 24	ND	OTSC	1-2	2/4(50%)	No	ND	10 mo (1-10)
	Leak (1)	10-12	> 24	ND	OTSC		0/1(0%)	No	ND	

Im: Intramural; Tm: Transmural; Tp: Transpeural; ND: Non determined; VATS: Video assisted thoracoscopy.

Very few articles report long-term follow-up data. The biggest and most detailed report is a North American study which evaluated gastrointestinal defects in 188 patients treated with OTSC. Success was achieved in 60.2% of the patients in a median follow-up of 146 d. The long-term rate for clinically successful closure of perforations (90%) and leaks (73.3%) was significantly higher than that of fistulas (42.9%). The study also showed significantly greater long-term success when OTSCs were used in primary therapy.

On the whole, it is clear that closure with clips shows the best results in the treatment of early injuries, and the success rate for clinical recovery approaches the result for surgical treatment.

Other uses of clips

Endoscopic clips may also be used with endoloop. The method was first used for endoscopic mucosal resection to resolve large defects[54]. Later, it was successful in the treatment of Mallory-Weis syndrome[55] and in closing oesophageal fistulas[56]. Due to the limited number of these articles, no conclusions can be drawn about their efficacy.

CONCLUSION

A number of case reports and case series reports have been published on the successful outcome of clip closure of endoscopic perforations, but high-evidence, case-controlled, multicentre studies are still missing. This method can only be used under very strict conditions (Figure 1). The introduction of OTSC clips significantly increases the size of treatable lesions (from 1 to 2-3 cm). However, this technique is only used in a limited

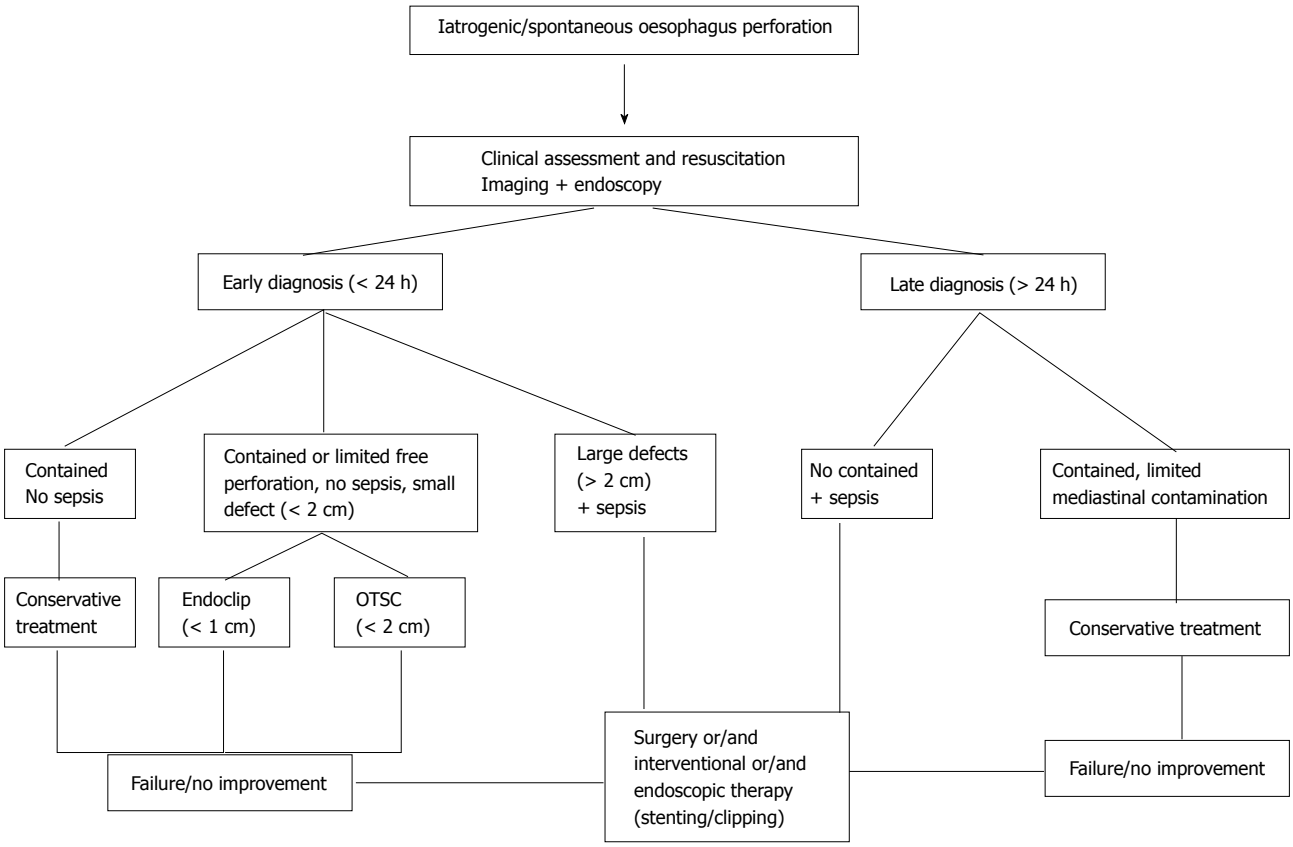

Figure 1 Algorithm for the management of oesophageal perforations.

number of centres. It is important to point out that both conventional TTS and the new OTSC methods are both safe. But a learning curve period and experience will both be necessary in their usage, including the selection of patients suitable for clip treatment. Multidisciplinary teams (surgeon, endoscopy specialist and intensive care therapist) are further important conditions in the successful treatment of oesophageal perforations. Surgical treatment still constitutes the primary therapy in oesophageal perforation. Based on the results so far, we can state that endoscopic closure of early, well-defined oesophageal perforations represents a therapeutic alternative to surgical treatment.

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Role of self-expanding metal stents in the management of variceal haemorrhage: Hype or hope?

Brian J Hogan, James P O'Beirne

Brian J Hogan, James P O'Beirne, Institute for Liver and Digestive Health, UCL, Royal Free Hospital, London NW3 2QG, United Kingdom

James P O'Beirne, the Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust, Royal Free Hospital, London NW3 2QG, United Kingdom

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Correspondence to: Dr. James P O'Beirne, Consultant Hepatologist, the Shelia Sherlock Liver Centre, Royal Free London NHS Foundation Trust, Royal Free Hospital, Pond Street, London NW3 2QG, United Kingdom. james.o'beirne@nhs.net
Telephone: +44-20-77940500-33998
Fax: +44-20-74726226

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Abstract

Despite the advances of medical, endoscopic and radiological therapy over recent years the mortality rates of acute variceal haemorrhage are still 16%-20% and the medium term outcome has not improved in the last 25 years. Early transjugular intrahepatic portosystemic shunt has proved to be an effective therapy for selected groups of patients with a high risk of re-bleeding and moderate liver disease. However, there is an unmet need for a therapy that can be applied in patients with a high risk of re-bleeding and advanced liver disease either as definitive therapy or as a bridge to permanent therapy. Self-expanding metal stents can be placed without the need for endoscopic or fluoroscopic control and, once in place, will provide effective haemostasis and allow a route for oral fluids and nutrition. They can remain in place whilst liver function recovers and secondary prophylaxis is initiated. We review the results of 6 case series including a total of 83 patients and the first randomised controlled trial of self-expanding metal stents *vs* balloon tamponade (BT) in the management of refractory variceal haemorrhage. We report that self-expanding metal stents provide effective haemostasis and perform better than BT in refractory bleeding, where they are associated with fewer complications. Whilst the most effective place for self-expanding metal stents in the management algorithm needs to be determined by further randomised controlled trials, currently they provide an effective alternative to BT in selected patients.

Key words: Esophageal and gastric varices; Stents; Liver cirrhosis; Gastrointestinal haemorrhage; Portal hypertension

Core tip: Failure to control bleeding in high-risk patients with variceal haemorrhage is still common, and not all patients are suitable for transjugular intrahepatic portosystemic shunts. Self-expanding metal stents can be placed without the need for endoscopic or fluoroscopic control and, once in place, provide effective haemostasis and allow a route for oral fluids and nutrition. They

can remain in place whilst liver function recovers and secondary prophylaxis is initiated or whilst definitive therapy is provided. Self-expanding metal stents provide effective haemostasis and perform better than balloon tamponade in refractory bleeding, where they are associated with fewer complications.

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INTRODUCTION

Acute variceal bleeding represents a devastating decompensating episode and occurs at a rate of 4% per year in patients with cirrhosis, increasing to 15% per year in those with medium or large varices[1].

Outcomes from a single episode of variceal bleeding have improved significantly in recent years. Better endoscopic therapy exists in the form of endoscopic variceal ligation and tissue adhesive glue[2,3] and more effective pharmacotherapy including potent vasoactive drugs[4,5] and prophylactic antibiotics[6]. However, the mortality rates of 16%-20% are still significant and medium term outcome has not improved in the last 25 years[7-10].

Failure to control bleeding, as defined by the Baveno Ⅴ criteria, is estimated at approximately 17% in the modern era[11]. Traditional factors associated with failure to control bleeding at 5 d and mortality at one month were active bleeding at endoscopy, severity of liver disease and an hepatic venous pressure gradient of > 20 mmHg[12,13]. More recently the model for end-stage liver disease (MELD) score has been shown to be useful in predicting outcome, with a MELD score < 11 being associated with < 5% mortality and a MELD score > 19 with > 20% mortality[14].

CURRENT OPTIONS FOR FAILURE OF STANDARD THERAPY

Failure to control bleeding requires salvage therapy such as balloon tamponade (BT) or insertion of transjugular intrahepatic portosystemic shunts (TIPS). These methods are effective at control of bleeding, but have important limitations. BT is a temporary therapy which most experts suggest can be used for a maximum duration of 24 h as a bridge to more definitive therapy[15]. The success of BT in controlling haemorrhage is reported to be between 88%-91% in the first 24 h[16]. BT is associated with the risks of oesophageal tear, mucosal ischaemia and aspiration pneumonia. TIPS carries a risk of worsening liver function and encephalopathy and is associated with a 30 d mortality of 30% when used as a rescue therapy[17]. In addition TIPS is not readily available in many centres that manage upper gastrointestinal haemorrhage.

The importance of early haemostasis was demonstrated in a randomised controlled trial of early TIPS insertion. Participants were randomised to either TIPS insertion within 72 h or standard medical therapy, which could include rescue TIPS. It demonstrated a reduction in uncontrolled bleeding or re-bleeding in the early TIPS group (3% *vs* 45%), a reduction in average intensive care unit stay (3.6 d *vs* 8.6 d) and a significant reduction in 1 year mortality (14% *vs* 39%, $P = 0.001$)[18]. Patients over 75 years of age, those with a Child Pugh score > 13 and those with advanced hepatocellular carcinoma were excluded from this study. Similar results have been shown using early TIPS in high-risk patients selected for a hepatic venous pressure gradient > 20 mmHg[19].

Attempts to replicate these results outside of clinical trials have been encouraging, but show that patient selection is vital and TIPS can be associated with significant complications. A United Kingdom centre began implementing an early TIPS protocol in 2010 for high-risk patients with acute variceal haemorrhage (Childs Pugh C or Childs Pugh B with active bleeding at endoscopy). The median time to TIPS was 12 h and the same exclusion criteria as reported in the above early TIPS study applied. Overall 30-d mortality was 8.6% and at 6 mo it was 14.7%. The re-bleeding rate was 11.4% and all re-bleeding occurred within the first 7 d[20]. A series from France proved similar efficacy with regards to haemostasis, with failure to control bleeding in 1/23 (4%). However, in this series there was a significant deterioration in liver function in 10/23 with 5 patients dying and 5 requiring transplantation. In addition 5/23 patients developed acute heart failure and 3 of these required mechanical ventilation[21].

Based on this data it would seem reasonable to promote TIPS as an initial treatment for high-risk patients with portal hypertensive bleeding. However, TIPS requires specialist equipment and expertise, and the logistics of providing this to all high-risk patients would be difficult for many healthcare systems internationally. There is, therefore, a need for a treatment which can be applied easily and effectively to patients at high risk of re-bleeding that could reduce early re-bleeding and promote a bridge to effective secondary prophylaxis or TIPS.

SELF-EXPANDING MESH-METAL STENT FOR VARICEAL HAEMORRHAGE

The SX-ELLA Danis stent (Ella CS, Hradec Kralove, Czech Republic) is a removable, covered, self-expanding mesh-metal stent (SEMS) that was designed for the emergency treatment of oesophageal variceal bleeding. It is 135 mm long and 25 mm in diameter giving it the ability to tamponade bleeding varices in the distal oesophagus. It is supplied with a unique insertion

system, where by a gastric balloon is inflated to anchor the distal end of the stent at the gastro-oesophageal junction when traction is applied. The Danis stent can be deployed without direct endoscopic or fluoroscopic guidance, and its' position should be confirmed by chest radiograph after insertion. Stents can be left in place for up to 14 d and can be removed endoscopically using the accompanying stent removal device. The stent provides immediate haemostasis and prevents re-bleeding for the time it is *in situ*. This allows recovery of liver function, consideration of definitive therapy and institution of secondary prophylaxis in addition to maintaining an oral route for fluids and nutrition. SEMS have also be useful in the management of BT related oesophageal rupture and for broncho-oesophageal fistula.

CURRENT EVIDENCE FOR SEMS

To date there have been 4 large case series, with ⩾ 10 patients, a number of smaller case series and reports and one randomised controlled trial assessing the safety and efficacy of SEMS in the control of variceal haemorrhage[22-24].

The first series was reported by Hubmann *et al*[25] in 20 patients with Child-Pugh B or C cirrhosis and massive ongoing bleeding. Two patients received Choo stents (140 mm × 18 mm) and three patients received a Boubela-Danis stent (95 mm × 20 mm). The next 15 patients received the purpose designed SX-ELLA Danis stent as described above. The first five were placed *via* an endoscopic guide wire and fluoroscopic control, the remainder were placed using the insertion device without a guide-wire or fluoroscopy. The stents were able to successfully control haemorrhage in all cases with no reported re-bleeding during 30 d of follow-up. In one case there was mild ulceration in the distal oesophagus after removal, no other complications were reported. Following stent extraction at a median of 5 d (1-14 d), 18 patients went on to have a definitive procedure to prevent re-bleeding (TIPS, azygoportal disconnection, liver transplant, radiological embolization or endoscopic intervention (variceal ligation or sclerotherapy). Mortality was 10% within 30 d (one at day three from hepatic failure and one at day five from multi-organ failure) and 20% at 60 d (Figure 1).

The same group of investigators published a further series of the SX-ELLA Danis stent including 15 patients previously described, with an additional 19 patients all of whom had failure to control bleeding following standard endoscopic techniques[26]. Haemostasis was achieved in all 34 cases using the SX-ELLA Danis stent without complications. All stents were deployed successfully, for a mean of 6 d (range 1-14 d). There were a total of 7 instances of stent migration, which was attributed to low stent position at insertion. Mortality was 26.5% at 30 d and 29.4% at 60 d and there was no re-bleeding reported during follow-up.

A tertiary United Kingdom centre reported SEMS use in 10 patients with on-going variceal bleeding despite standard endoscopic therapy[27]. Two patients had the added complication of BT induced oesophageal rupture. Stents were successfully deployed in 9 cases, in once case the gastric balloon failed to inflate and the procedure was abandoned. Nine/ten patients had active bleeding at the time of endoscopy and haemostasis was achieved in 7/9 (78%). The patients with continued haemorrhage were subsequently shown to be bleeding from gastric varices. The mortality rate at 6 wk was 50%.

Fierz *et al*[28] described a combined case series of 9 patients from Swiss Hospitals. They reported a total of 9 bleeding episodes in 7 cirrhotic patients (two patients had two separate bleeds). In three cases SEMS was used as first line endoscopic therapy, and in the remaining 6 cases there had been inadequate control of haemorrhage with band ligation or sclerotherapy. The majority of patients were Child-Pugh class C and the mean MELD score was 34. All stents were placed with endoscopic assistance and two cases of distal stent migration were noticed, no other complications were reported. Control of haemorrhage was achieved in all cases, except one where the stent was not deployed correctly. The reported 6 wk mortality rate of 78% is high and reflects the severity of underlying liver disease in this cohort[28].

Zakaria *et al*[29] have reported a series of 16 patients where SEMS was used for the primary therapy of variceal haemorrhage. Patients with hepatitis C related cirrhosis and evidence of on-going bleeding from varices, cherry red spots, or fresh blood in the oesophagus or stomach received a stent for between 2 and 4 d. Successful control of haemorrhage with the SEMS was reported in 14/16 patients. Of the two treatment failures one was caused by the rupture of the gastric balloon and sclerotherapy was applied to the varix and in the second the SEMS failed to control bleeding from a GOV-1 vairx which required cyanoacrylate glue.

The results of the first randomised controlled trial comparing SEMS to BT were published in abstract form in 2013[30]. This was a multicentre trial of 8 hospitals in Spain.

The study included consenting adult patients with cirrhosis and acute variceal bleeding (as defined by the Baveno Ⅱ consensus) who met either of the following inclusion criteria: (1) Failure to control bleeding (as defined by Baveno Ⅳ criteria) despite pharmacological (somatostatin 3 or 6 mg/12 h *iv* or terlipressin, 2 mg/4 h *iv*) AND endoscopic therapy (oesophageal banding ligation preferably or sclerotherapy); and (2) Massive bleeding, uncontrolled despite pharmacological therapy started at any moment, with no need of previous endoscopic therapy. Uncontrolled bleeding was defined as an upper digestive bleeding in which no hemodynamic stability (systolic arterial pressure > 70 mmHg and heart rate < 100 bpm) could be achieved.

The exclusion criteria were oesophageal rupture; oesophageal, gastric or upper respiratory tract tumor; oesophageal stenosis; recent oesophageal surgery;

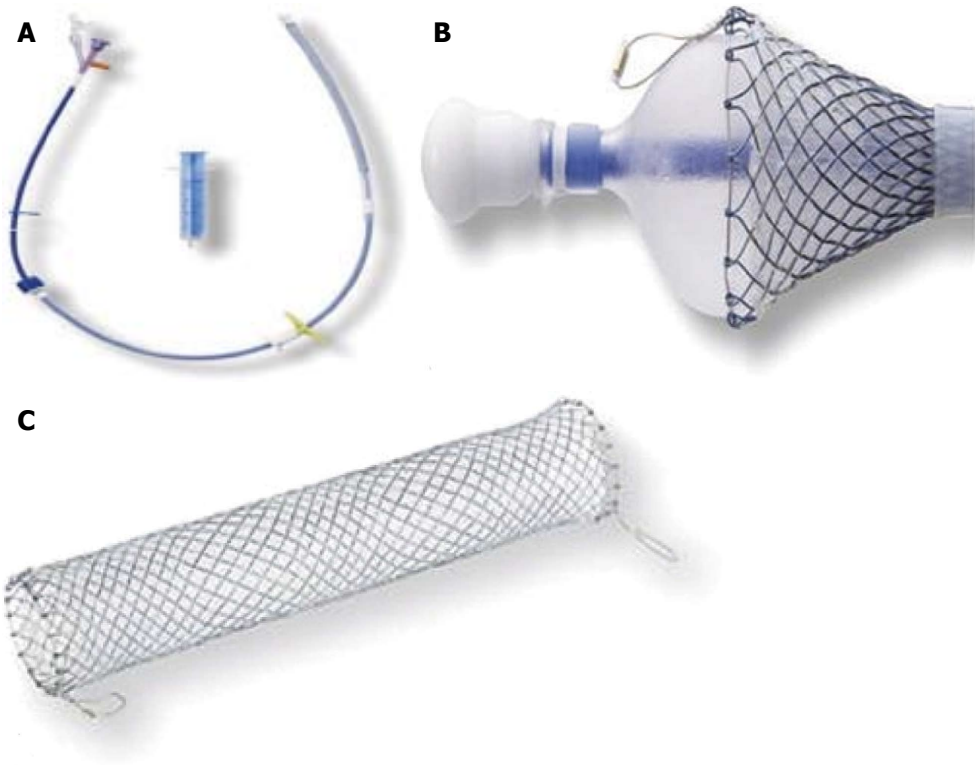

Figure 1 The Danis Stent with delivery system. A: The SX-ELLA Danis stent is supplied preloaded in an insertion device that has a 26F diameter and is 60 cm long; B: A balloon at the distal end of the insertion device (shown partially inflated) allows anchoring of the distal end of the stent at the cardia during deployment; C: The fully deployed stent is 135 mm long and 25 mm wide.

previous oesophageal tamponade to treat the index bleed; a big hiatal hernia precluding the correct placement of the oesophageal device; known hepatocellular carcinoma surpassing Milan criteria and terminal disease.

Twenty-eight patients were randomized to BT (n = 15) or SEMS (SX-Ella Danis; n = 13).

Both groups were matched for the aetiology and severity of liver disease, presence of active bleeding at endoscopy and for the initial therapy received. SEMS were placed without endoscopic or fluoroscopic guidance, but under sedation, and their position confirmed by chest radiograph. Stents remained *in situ* for a maximum of 7 d and during that time patients could undergo a TIPS. The median time to TIPS was reported as 3.5 (0-7) d in the SEMS group and 0.8 (0-1) d in the BT group. The number of patients who underwent successful TIPS placement was not reported. Unfortunately, due to difficulties with participant recruitment the study was under powered. The initial power calculation suggested that 23 patients would be required in each group (Table 1).

One patient in the SEMS group received a BT due to technical difficulties deploying the stent, however the analysis was performed using an intention to treat basis. Haemostasis was achieved in 77% of the SEMS group and 43% of the BT group (P = 0.1). The incidence of serious adverse events was lower in the SEMS group, particularly the incidence of aspiration pneumonia 2/13 *vs* 8/15 in the BT group. Survival at 15 d was 61% and 47% in the SEMS and BT groups respectively (P = 0.4).

LIMITATIONS OF SEMS IN VARICEAL HAEMORRHAGE

There have been reports of minor oesophageal ulceration several case series describing SEMS placement. However, this resolved spontaneously on removal of the stent and neither mortality nor oesophageal perforation have been observed.

Stent migration is the main issue encountered after deployment and, if occurs, impedes effective haemostasis. If adequate traction is not applied to the delivery device at the time of stent deployment, migration is more likely to occur.

There have been a number of reports of failed deployment due to balloon rupture. The insertion device is designed with a safety feature where by the balloon will rupture if more than 100 mL of air is insufflated. This is designed to prevent the complication of an over distended balloon causing an oesophageal tear, should it have been misplaced in the oesophagus (rather than the stomach) prior to inflation. Rupture of the balloon can be avoided if only 100 mL of air is insufflated.

In one case report a patient developed respiratory failure 6 d following successful control of bleeding using an SX-ELLA Danis stent[22]. Bronchoscopy revealed narrowing of the bronchus due to external compression from the proximal portion of the stent. The stent was

Table 1 Summary of case series reporting self-expanding mesh-metal stent use in the control of oesophageal variceal haemorrhage

Ref.	Stent used	*n*	Indications/severity of liver disease	Length of Insertion (d)	Initial Haemostasis with SEMS	Mortality (d)	Complications/notes
Hubmann *et al*[25], 2006	Choo in 2 Elle-Boubela in 3 SX-ELLA Danis in 15	20	FTCB in 19 FTCB and Oesophageal perforation in 1 CP A 0%/B 40%/C 60%	6 (2-14)	100%	10% 30 d 20% 60 d	Minor ulceration in 1 patient Migration in 2 patients
[1]Zehetner *et al*[26], 2008	SX-ELLA Danis	34	FTCB CP A 0%/B 38%/C 62%	5 (1-14)	97%	26.5% 30 d 29.4% 60 d	1 patient continued to bleed from a gastric ulcer Migration in 7 patients
Dechene *et al*[22], 2009	SX-ELLA Danis	1	FTCB	6	100%		Stent extracted at day 6 due to tracheal compression patient died on day 13 of hepatic failure
Mishin *et al*[24], 2010	SX-ELLA Danis	1	FTCB (EBL ulcer)	8	100%	0% 10 d	Outcomes after 10 d not reported
Wright *et al*[27], 2010	SX-ELLA Danis	10	FTCB in 8 BT induced oesophageal tear in 2 Median MELD 26 (14-39)	6 (6-14)	70%	50% 42 d	Uncontrolled bleeding from gastric varices after insertion in 2 patients Failure to place stent in 1 patient
[2]Dechêne *et al*[23], 2012	SX-ELLA Danis	9	FTCB Median MELD 32 (16-40)	11 (7-14)	100%	56% 30 d 67% 60 d	1 patient died within 5 d from liver failure (technically FTCB)
Fierz *et al*[28], 2013	SX-ELLA Danis	9	FTCB Median MELD 27 (11-37)	0.5-5	89%	78% 42 d	1 failure due to incorrect deployment
Holster *et al*[32], 2013	SX-ELLA Danis	5	FTCB Median MELD 21 (11-28)	6-214	100%	Not reported	1 re-bleed at 7 d from the GOJ
Zakaria *et al*[29], 2013	SX-ELLA Danis	16	Primary therapy in acute variceal bleed CP A 13%/B 50%/C 37%	2-4	94%	25%	Uncontrolled bleeding from GOV-1 varix after insertion in 1 patient Failure to place stent in 1 patients

[1]20 patients included in this trial were also included in the first trial by Hubmann *et al*[25]; [2]Dechene *et al*[22] previously reported 1 patient from this series in 2009. FTCB: Failure to control bleeding; BT: Balloon tamponade; EBL: Endoscopic band ligation; CP: Child-Pugh score; MELD: Model for end-stage liver disease score; GOV-1: Gastro-oesophageal varices type 1.

removed and bronchial obstruction resolved. In this case varices were secondary to hilar cholangiocarcinoma and the patient died from liver failure 7 d after the stent was removed.

CONCLUSION

Despite the recent advances in treatment of variceal bleeding there are still significant rates of treatment failure and mortality and there is still considerable variation in patient outcomes.

Current guidelines for the management of variceal haemorrhage suggest that a TIPS should be considered for high risk cases and in patients with bleeding refractory to standard medical and endoscopic therapies[15,31]. However, TIPS is not suitable for all patients and the complications of liver failure and hepatic encephalopathy limit the use of TIPS in some patients. There is, therefore, an unmet need where standard endoscopic therapy is ineffective and TIPS is not a suitable treatment.

SEMS are very effective in the control of oesophageal variceal haemorrhage, and in all of the series reported to date the only "stent failures" have either been where the stent was not deployed correctly or where the bleeding was from concomitant gastric varices. The mortality rates reported in the case series are very variable, and the main determinant is whether they are used as definitive therapy, or as a bridge to another therapy, mortality being improved with the latter.

It is not yet clear whether SEMS have a defined place in the algorithm for the management of variceal haemorrhage. The data from Escorsell *et al*[30] has not confirmed that SEMS perform better than BT in refractory bleeding, but there was a trend towards fewer complications and more effective haemostasis. This has led to a recommendation from the BAVENO Ⅵ committee for SEMS to be considered as an alternative to BT in their most recent concensus report[15]. Further data from randomised controlled trials are required to guide clinicians in their use of these devices, however they are an attractive alternative to BT and may be an effective bridge to definitive therapy.

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