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EDITORIAL

High-resolution anoscopy: Unchartered territory for gastroenterologists?

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Abstract

High-resolution anoscopy (HRA) is a procedure where patients with an increased risk of anal cancer, like men who have sex with men, human immunodeficiency virus infected individuals, transplant patients and women with a history of lower genital tract neoplasia, with abnormal anal cytology results, are submitted to anal and perianal visualization under magnification. This will allow for a better detection of anal high-grade lesions that can be treated, in an effort to prevent anal cancer. Anal cancer screening follows the same principles that cervical cancer screening. During this procedure, an anoscope is inserted and a colposcope is used to examine systematically the squamocolumnar junction, the transformation zone and the perianal skin. Initially the observation is done with no staining and then with the application of acetic acid and Lugol's iodine solution, allowing for better lesion identification and characterization. Any suspicious lesion seen should be carefully evaluated and biopsied. Without HRA only a small percentage of suspicious lesions are identified. High-grade lesions that are detected can be ablated under HRA. This is a challenging exam to perform, with a long learning curve and the number of clinicians performing it is limited, although the growing number of patients that need to been screened. Specific equipment is required, with these patients ideally been followed by a multidisciplinary team, in a reference centre. HRA remains unfamiliar for many gastroenterologists.

Key words: High-resolution anoscopy; Anal cytology; High-grade squamous intraepithelial lesions; Low-grade squamous intraepithelial lesions; Anal cancer

Core tip: High-resolution anoscopy is a procedure where high-risk patients are submitted to anal and perianal visualization under magnification, allowing detection of anal high-grade lesions that can be treated. Anal cancer is histologically and biologically very similar to cervical cancer and the screening follows the same principles. The importance, difficulties and the description of the technique will be discussed. This is a difficult exam to perform, with a long learning curve that requires specific equipment and the need for a multidisciplinary team, ideally in a reference centre. It remains unfamiliar for many gastroenterologists.

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DEFINITION AND PRINCIPLES OF HIGH RESOLUTION ANOSCOPY

High-resolution anoscopy (HRA) is a procedure where high-risk patients are submitted to anal and perianal visualization under magnification, allowing detection of anal high-grade lesions that can be treated. HRA can simply be defined as a colposcopy applied to the anal canal and perianal region.

Men who have sex with men (MSM), human immunodeficiency virus (HIV) infected individuals, transplant patients and women with a history of lower genital tract neoplasia have an increased risk of anal cancer. HIV-negative MSM have an estimated incidence rate of 35 per 100000 person-year and anal cancer incidence rates in HIV-positive MSM are two times higher (about 70-100 per 100000 person-year)[1]. Anal cancer has become one of the most common non-AIDS-defining tumors in HIV-infected individuals[2]. Human papillomavirus (HPV) infection is almost always present in HIV-positive MSM, and infections with multiple HPV types are common[3]. Concerning transplantation, most data come from renal transplant recipients, and the relative risk of anal cancer in these patients is 10 fold[4,5].

Anal cancer screening follows the same principles that cervical cancer screening. Both tumors are caused by infection with oncogenic HPV strains, occur at the squamocolumnar transition zone and arise from same precancerous dysplastic lesions, anal intraepithelial neoplasia or cervical intraepithelial neoplasia[6]. Women are screened through cervical cytology and those with abnormal results are then referred for colposcopy. Abnormalities are biopsied, and if high-grade squamous intraepithelial lesions (HSIL) are present, the patient is treated, thereby preventing progression to cervical cancer. Cervical cancer rates have dramatically decreased through cytology screening[7,8], from 40-50 cases per 100000 individuals to about 8-10 cases per 100000 individuals. Anal cancer is likely preceded by HSIL, a colposcope may similarly be used to visualise it and permit biopsy and treatment in an effort to prevent anal cancer.

Progression of biopsy-proven anal HSIL to cancer in a group of 27 HIV-infected MSM has been recently reported[9] and confirmed that individual HSIL lesions can progress to cancer.

High-risk patients like HIV-positive men and women regardless of sexual orientation or HIV-negative MSM submitted to anal cytology as a screening test, that have an abnormal result should be refer to HRA. The prevalence of anal squamous intraepithelial lesions (SIL) has remained high among HIV-positive MSM after the introduction of highly active antiretroviral therapy (HAART); HAART is not associated with a reduced prevalence of anal SIL[10]. Other groups who should be considered for screening include women with cervical cancer, high-grade vulvar disease or cancer, individuals with perianal condyloma acuminata; and transplant recipients[11].

Anal cytology is classified on the basis of the 2001 revised Bethesda System of cervical cytology classification[12]. There is no specific terminology for anal cytology. The specificity and predictive value for anal high-grade lesions on biopsy are highest for HSIL, atypical squamous cells which cannot exclude high-grade squamous intraepithelial lesion(ASC-H), low-grade squamous intraepithelial lesions (LSIL) and atypical squamous cells of undetermined significance (ASC-US).

The severity of cytological findings and infection with high-risk HPV are the most significant predictors of significant preditors for HSIL, underscoring the importance of anal dysplasia screening[13]. A systematic review described that anal cytology has a sensitivity from 69% to 93% and a specificity from 32% to 59%, that is similar to those reported for cervical cancer screening[1]. Abnormal anal cytology seems highly predictive of anal dysplasia on biopsy, in a previous study by Cranston *et al*[14] 2007, the positive predictive value of anal cytological abnormality to predict any degree of anal dysplasia was 95.7%. Both sensitivity and specificity of anal cytology are higher for internal disease as compared to external disease (perianal region)[3].

HIGH RESOLUTION ANOSCOPY TECHNIQUE

Normally, during HRA the patient is in the left lateral position, in the foetal position, with the buttocks at the edge of the table. Bowel preparation is not needed. An anoscope is inserted and a colposcope is used to examine the squamocolumnar junction, the anal canal including the transformation zone and the perianal skin in a systematic manner. The inspection should be performed first with no staining and then with the topical application of acetic acid (3% or 5%), that will allow for better lesion identification and characterization. Most of the anal exam is done under 16 × magnification, once specific areas of interest are visualised, they should be examined under 25 × magnification and the anal verge is viewed with 10 × magnification[15]. After examination with acetic acid, application of Lugol's iodine solution may help to distinguish HSIL from LSIL, to assist the clinician in deciding where to biopsy, as well as to define the margin of the lesion[15].

Lesions seen during HRA should be carefully described concerning localization, contour, margins, acetic acid induced whitening, Lugol's staining, epithelial pattern, vascular pattern (mosaic pattern, punctation, warty vessels, atypical). This will help to distinguish between

low-grade and high-grade lesions. HSIL may be flat or thickened, and often have vascular changes including punctuation or a mosaic pattern, are acetowhite, with a poor uptake of Lugol's solution. In a study by Camus *et al*[16], the positive predictive value for HSIL increased to 68.6% with the following combination of criteria: Acetic acid-induced whitening, no Lugol staining, irregular epithelial pattern, and vascular changes. Many of these anal suspicious lesions have similar aspects to that initially describe in cervical colposcopy[7,8]. Cancers are often friable or ulcerated lesions with atypical vessels. Any suspicious lesion, namely of HSIL or anal cancer should be biopsied.

IMPORTANCE OF HIGH RESOLUTION ANOSCOPY

HRA is fundamental for high-grade lesion detection and subsequently guided treatment. Anal HSIL ablation treatment under HRA may reduce the rate of anal cancer[17].

Previous studies revealed that before HRA is performed, only a small percentage of suspicious lesions are identified. Camus *et al*[16], show that only 38.7% of the lesions were visible with the naked eye before HRA.

Few data are available on the progression of anal SIL to anal squamous-cell carcinoma (ASCC), the true rate of progression from high-grade dysplasia to invasive anal cancer remains unclear[1]. There are clearer data concerning perianal intraepithelial neoplasia or Bowen disease in which approximately 5% of lesions undergo malignant change[18].

Devaraj *et al*[19], published a series of 98 HIV-positive patients, with 40 patients with a follow-up of more than one year, with expectant management of anal squamous dysplasia. In this series, 28 of 40 patients had anal HSIL and three of these patients (11%) developed invasive carcinoma while under surveillance (expectant management). Scholefield *et al*[20] described a series of 35 non-infected HIV patients, all with anal HSIL. In this series, 7 patients where submitted to expectant management due to extensive or multifocal disease and three of these patients (9%) developed invasive ASCC during follow-up, median of 5 years after the initial diagnosis of anal HSIL. In a study by Sobhani *et al*[21], including 199 patients who were successfully treated for anal warts (HIV positive and HIV negative patients included), 38 (19%) later developed anal HSIL, and of these, seven (18%) developed ASCC, 13 to 108 mo after entry in the study.

Wide excision is a morbid procedure that also removes uninvolved healthy tissues to achieve widely clear margins. Nevertheless, there is still a risk of recurrence[22]. HRA guided ablation of anal HSIL has several advantages: It permits a full evaluation of the anorectal anatomy, detection of grossly invisible disease, allowing target therapy with protection of normal tissues, minimal morbidity and reducing the risk of anal stenosis[22]. Cervical HSIL is usually treated with the loop electrosurgical excision procedure, removing the squamocolumnar transformation zone where most dysplasia develops. This is not possible for anal HSIL and treatment most often relies on ablation of individual lesions with laser, electrocautery (ECA), and infrared coagulation (IRC). There is no significant difference in treatment success between IRC and ECA[17]. A recent study by Goldstone *et al*[17] showed that patients undergoing ablation of anal HSIL have high recurrence, but the probability of developing anal cancer is low. The recurrence 1 year after the first ablation for HIV-positive and -negative patients was 53% and 49%, respectively; at 2 and 3 years, the rate of recurrence was 68% and 77% for HIV-positive patients and 57% and 66% for HIV-negative patients. The probability of cancer 3 years post-ablation was 1.97%.

Perianal high-grade dysplasia (Bowen disease) it is traditionally treated with mapping (blind biopsies) and wide excision. A recent study by Johnstone *et al*[23], showed that perianal dysplasia can be successfully treated with HRA-guided targeted ablation (ECA, laser or IRC) with no morbidity, although recurrence remains high. Almost all of these patients have anal canal dysplasia and HIV-positive patients are at the greatest risk for disease and recurrence.

Recommendations on post-treatment follow-up intervals are lacking.

DIFFICULTIES IN PERFORMING HIGH RESOLUTION ANOSCOPY, CAN WE DO IT?

Probably due to the long learning curve, the number of clinicians performing HRA is limited. Although the similarities of HRA and colposcopy, HRA is a more challenging and demanding technique due to the anal anatomy, anal pathology and difficulties in the treatment (excision is not a real option). Previous training in colposcopy is important to understand how to work with the colposcope and detect the aspect of the lesions. To perform this technique, a colposcope is required, and this equipment is not normally available outside a gynaecology clinic. In some cases, patients have not been referred to this technique due to the lack of knowledge of the indications or trained clinicians that can observe these patients. These patients need to be followed by a multidisciplinary team, including the clinicians performing HRA, pathologists, infectiologists, and colon and rectal surgeons.

This is extremely important because there is a growing number of patients, namely, HIV and MSM who need to been screened. It will be a long journey until all of these high-risk patients are referred for screening and more clinicians feel motivated to learn this technique. Recently the results of an internet-based survey on attitudes and practice of Colon and Rectal surgeons (United States members of the American Society of

Colon and Rectal Surgeons) on anal dysplasia revealed that, although most of them treated patients at risk for anal cancer and had read research on HSIL, only one-third had performed HRA and of these less than half (46%) were formally trained. When evaluating patients for HSIL in surgery, only 31% used acetic acid with magnification[24]. Another internet-based survey to members of international surgical and dermatological societies concerning diagnosis, treatment and surveillance of patients with HPV-related anal diseases revealed that to detect dysplastic lesions, 42.0% of surgeons used acetic acid only, 23.2% used this in combination with HRA and 19.5% applied intra-anal cytological smears. Likewise, 64.6% of dermatologists applied acetic acid only, 16.5% combined acetic acid with HRA and 30.2% performed intra-anal cytological smears[25].

It is fundamental to have more and better trained clinicians performing it. This will never be a technique that can be performed by all.

Several clinicians can perform anal cytology, especially those involved with high-risk patients, namely infecciologists, dermatologists, gynaecologists, nephrologists. If an abnormal result is detected, patients should be referred, ideally to a reference centre, to a clinician properly trained in HRA and with a multidisciplinary team. Thus, regarding anal cancer screening, we should inform all clinicians, cytology should be performed by most and HRA by some.

HRA was developed in the 90's, but remains unfamiliar to many, including gastroenterologists, although in some countries gastroenterologists are also proctologists. Much of the gastroenterology daily routine involves diagnostic and interventional therapeutic procedures. These are central concepts of HRA. Basic knowledge regarding the technique and even proper training may well be in the present and future realm of gastroenterologists.

HRA is fundamental for high-grade anal and perianal lesion detection and subsequently guided treatment in an effort to prevent anal cancer in high-risk patients.

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Upper non-variceal gastrointestinal bleeding - review the effectiveness of endoscopic hemostasis methods

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Abstract

Upper non-variceal gastrointestinal bleeding is a condition that requires immediate medical intervention and has a high associated mortality rate (exceeding 10%). The vast majority of upper gastrointestinal bleeding cases are due to peptic ulcers. *Helicobacter pylori* infection, non-steroidal anti-inflammatory drugs and aspirin are the main risk factors for peptic ulcer disease. Endoscopic therapy has generally been recommended as the first-line treatment for upper gastrointestinal bleeding as it has been shown to reduce recurrent bleeding, the need for surgery and mortality. Early endoscopy (within 24 h of hospital admission) has a greater impact than delayed endoscopy on the length of hospital stay and requirement for blood transfusion. This paper aims to review and compare the efficacy of the types of endoscopic hemostasis most commonly used to control non-variceal gastrointestinal bleeding by pooling data from the literature.

Key words: Upper gastrointestinal bleeding; Non-variceal bleeding; Endoscopic hemostasis; Endoscopic therapy

Core tip: Review and comparison the efficacy of the most commonly used types of endoscopic hemostasis for the control of non-variceal gastrointestinal bleeding in clinical practice by pooling data from the literature.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a common medical entity for which endoscopy has become

the primary diagnostic and therapeutic technique. Endoscopy performed in patients with UGIB corresponds with a reduction in required blood transfusions and length of intensive care unit/total hospital stay[1]. Upper endoscopy is required for most patients with UGIB and should be performed within 24 h of hospital admission after adequate prior fluid resuscitation[2]. The key to improving outcomes is the proper initial management of individuals who present with UGIB. In most clinical conditions, the vast majority (80%-90%) of episodes of acute upper gastrointestinal bleeding are secondary to non-variceal origin. This review addresses different endoscopic techniques of hemostasis that are used to treat acute upper gastrointestinal bleeding of non-variceal origin (NVUGIB) in the world practice.

EPIDEMIOLOGY

UGIB is mostly non-variceal in origin and still remains one of the most common challenges encountered by surgeons, gastroenterologists and endoscopists in a daily clinical setting. The incidence rate of non-variceal UGIB ranges from 50 to 150 per 100000 adults/year[3]. In spite of major advances in the approaches used to manage non-variceal UGIB over the past 2 decades, including the peptic ulcer bleeding prevention, the optimal use of endoscopic therapy, as well as the use of adjuvant high-dose proton pump inhibitors (PPIs) to eradicate *Helicobacter pylori*, it is still associated with considerable morbidity, mortality, and health care costs. The most common non-variceal bleeding etiologies include gastroduodenal peptic ulcer (20%-50%), gastroduodenal erosions (8%-15%), Mallory-Weiss tears (8%-15%), erosive esophagitis (5%-15%), arteriovenous malformations/GAVE (5%); several other conditions [*e.g.*, Dieulafoy's lesion, upper gastrointestinal (GI) tract malignancy] make up the remaining causes[4-7]. Peptic ulcer disease still remains the most common cause of acute NVUGIB and accounts for at least 50% of cases. Ulcers with signs of active spurting (Forrest class ⅠA) or oozing blood (Forrest class ⅠB) and ulcers with a nonbleeding visible vessel (Forrest ⅡA) are at high risk of recurrent bleeding when only medical therapy is used. Thus, endoscopic hemostasis is required for patients with high-risk stigmata [ⅠA, ⅠB] or a visible vessel in an ulcer niche [ⅡA]. Clean-based ulcers (Forrest class Ⅲ) or flat pigmented spots in the ulcer bed (Forrest class ⅡC) are low-risk lesions that only rebleed in 4% to 13% of cases and can therefore be treated with pharmacotherapy alone and considered for outpatient management[8,9]. Ulcers with adherent clots (Forrest class ⅡB) have an intermediate risk of rebleeding (approximately 25%) that depends on the underlying lesion. For that reason, clot removal should be performed with vigorous irrigation and manipulation with an endoscope, forceps, or snare. In patients suffering from peptic ulcer disease, duodenal ulcer bleeding appears more frequently than from gastric ulcers[10]. A Blatchford score or pre-endoscopic Rockall score (based on age, comorbidity, and the presence or absence of hemodynamic instability) should be used to stratify risk and determine which patients require prompt endoscopy or, conversely, to determine suitability for early discharge (Table 1). The Blatchford score, a validated risk-stratification tool based solely on clinical and laboratory variables, is used to predict the need for endoscopic intervention in patients with acute upper GI hemorrhage. A higher score indicates a higher likelihood of needing endoscopic intervention (score ranges from 0 to 23). The clinical Rockall score (*i.e.*, the score obtained before endoscopy is performed) is calculated solely on the basis of clinical variables at the time of patient presentation. The complete Rockall score makes use of both clinical and endoscopic criteria to assess patient risk of re-bleeding and mortality. Rockall score ranges from 0 to 11 points, with higher scores indicating a higher risk for a poor outcome (Table 2)[11,12].

Table 1 Blatchford scoring: Admission risk markers and associated score component values[13]

Admission risk marker	Score component value
Blood urea, mmol/L	
6.5 to ≤ 8	2
8.0 to < 10.0	3
10.0 to < 25	4
≥ 25	6
Hemoglobin for men, g/dL	
12.0-13.0	1
10.0 to < 12.0	3
< 10.0	6
Hemoglobin for women, g/dL	
10.0 to < 12.0	1
10	6
Systolic blood pressure, mmHg	
100-109	1
90-99	2
< 90	3
Other markers	
Pulse ≥ 100/min	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

ENDOSCOPIC MANAGEMENT

The aim of therapeutic endoscopy is to stop any ongoing bleeding and to prevent rebleeding. Cooper *et al*[13] studied the effectiveness of performing an early endoscopy within the first 24 h of an acute UGIB episode and found it to be associated with reductions in the length of hospital stay, the rate of recurrent bleeding, and the need for emergent surgical intervention. According to the 2010 international consensus on non-variceal upper gastrointestinal bleeding, early endoscopy (within 24 h of presentation) is appropriate for most patients with UGIB[2]. In cases of rebleeding, a second attempt at endoscopic therapy is recommended to reduce the need for surgery. In patients who have undergone failed endoscopic therapy, surgery should be considered.

Table 2 Complete rockall risk scoring system for assessment after an episode of acute upper gastrointestinal bleeding[12]

Variables	Score 0	Score 1	Score 2	Score 3
Age	Younger than 60 yr	60-79 yr	80 yr or older	-
Shock symptoms, systolic blood pressure, heart rate	Shock absent, blood pressure 100 mmHg or greater, heart rate 100 bpm or greater	Tachycardia, blood pressure 100 mmHg or greater, heart rate 100 bpm or greater	Hypotension, blood pressure less than 100 mmHg	-
Comorbidities	No major comorbidity	-	Heart failure, coronary artery disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
Endoscopic diagnosis	Mallory-Weiss tear or no lesion identified, and no stigmata of recent hemorrhage	All other diagnoses	Malignancy of upper GI tract	-
Stigmata of recent hemorrhage	Low-risk	-	High-risk	-

Low-risk stigmata of bleeding: Clean base ulcer, pigmented spots; High-risk stigmata of bleeding: Adherent clot, visible or spurting vessel, active bleeding; Bpm: Beats per minute; GI: Gastrointestinal.

Table 3 Recommendations of the american society for gastrointestinal endoscopy concerning upper gastrointestinal bleeding management[38]

We recommend that patients with UGIB be adequately resuscitated before endoscopy
We recommend antisecretory therapy with PPIs for patients with bleeding caused by peptic ulcers or in those with suspected peptic ulcer bleeding awaiting endoscopy
We suggest prokinetic agents in patients with a high probability of having fresh blood or a clot in the stomach when undergoing endoscopy
We recommend endoscopy to diagnose the etiology of acute UGIB. The timing of endoscopy should depend on clinical factors. Urgent endoscopy (within 24 h of presentation) is recommended for patients with a history of malignancy or cirrhosis, presentation with hematemesis, and signs of hypovolemia including hypotension, tachycardia and shock, and a hemoglobin < 8 g/dL
We recommend endoscopic therapy for peptic ulcers with high-risk stigmata (active spurting, visible vessel). The management of PUD with an adherent clot is controversial. Recommended endoscopic treatment modalities include injection (sclerosants, thrombin, fibrin, or cyanoacrylate glue), cautery, and mechanical therapies
We recommend against epinephrine injection alone for peptic ulcer bleeding. If epinephrine injection is performed, it should be combined with a second endoscopic treatment modality (*e.g.*, cautery or clips)
We recommend that patients with low-risk lesions be considered for outpatient management
We recommend against routine second-look endoscopy in patients who have received adequate endoscopic therapy
We recommend repeat endoscopy for patients with evidence of recurrent bleeding

UGIB: Upper gastrointestinal bleeding; PPIs: Proton pump inhibitors; PUD: Peptic ulcer disease.

Despite adequate initial endoscopic therapy, recurrent UGIB can occur in up to 24% of high-risk patients. The use of PPI therapy in addition to endoscopic therapy reduces the rate of recurrent bleeding to approximately 10%. Patients with recurrent bleeding generally respond favorably to repeated endoscopic therapy. Routine second-look endoscopy, defined as a planned endoscopy performed within 24 h of the initial endoscopy, is not recommended. In cases where the initial endoscopy failed to identify the source (*e.g.*, because of a large clot in the stomach) or if there are concerns that inadequate therapy was delivered, second-look endoscopy may be appropriate (Table 3).

Currently, the efficacy and safety of endoscopic hemostasis rely on the identification of lesions that are suitable for endoscopic therapy, the selection of the appropriate hemostatic devices, attention to technique, and prompt recognition and management of procedure-related adverse events. The suitable technique should be chosen based on the appearance of the bleeding focus and the related risk for persistent or recurrent bleeding.

The traditional endoscopic modalities are injection, mechanical therapy, and thermal approaches. Injection agents include saline, dilute epinephrine, sclerosing agents (ethanolamine, polidocanol, absolute alcohol, and sodium tetradecyl sulfate), and tissue adhesives (cyanoacrylate, thrombin, and fibrin glue). Mechanical therapy offers endoscopic clips and band ligation. Thermal devices deliver electrical current (through direct contact or *via* an inert gas plasma) or heat to the target tissue. Moreover, a few new technologies have emerged, such as hemostatic powders.

INJECTION TREATMENT

Injection needles consist of an outer sheath (plastic, Teflon, or stainless steel) and an inner hollow-core needle (19-25 gauge)[14]. Using a handle on the end of the needle sheath, the operator can retract the needle into the sheath for safe passage through the working channel of the endoscope. When the catheter is placed near the target tissue, the needle is extended a preset distance out of the end of the sheath, and a syringe attached to the handle is used to inject liquid agents into the target tissue. Dilute epinephrine in saline (1:10000) is applied with an injection needle in 0.5-1.0 mL boluses to the four quadrants around the high-risk

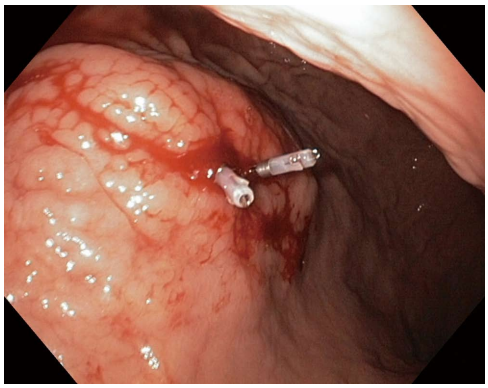

Figure 1 Endoscopic clips.

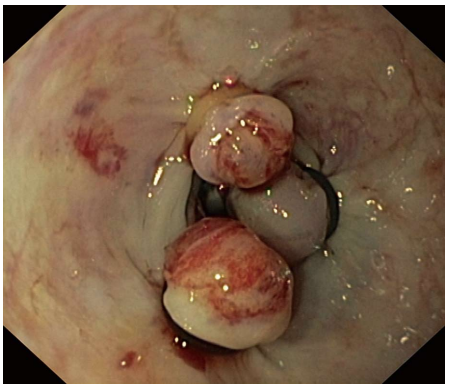

Figure 2 Endoscopic band ligation.

stigmata or to the base of the active bleeding site and then in the middle of it, up to a total of 10 mL[15,16]. Some practitioners prefer to use absolute alcohol in much smaller volumes (1-2 mL in 0.1 mL aliquots) or combinations of epinephrine and alcohol or sclerosants, which are used for the treatment of varices. Epinephrine injection therapy promotes initial hemostasis through a combination of vasoconstriction, compression (local tamponade), and platelet activation, but this effect declines after 20 min. If epinephrine injection is performed, it should usually be combined with a second endoscopic treatment modality (*e.g.*, electrocautery or clips)[17]. If epinephrine is used alone, there is a significant risk of rebleeding. This can be reduced by injecting large volumes, as high as 30 mL, which are associated with no clearly described cardiologic adverse events, and the rebleeding rate decreases linearly with the injected volume[18,19]. Dilute epinephrine injection is inferior at preventing rebleeding and surgery when compared with bipolar electrocoagulation, clips, or fibrin glue[20]. Other injected substances, such as sclerosing agents (*e.g.*, polidocanol, ethanolamine, and ethanol), have similar efficacy but more side effects, including transmural necrosis or perforation[21]. Another class of injectable agents are tissue adhesives, including cyanoacrylate glues, thrombin and fibrin, which are used to create a primary seal at the site of bleeding by inducing thrombosis through direct tissue injury. However, they may also evoke tissue necrosis and, hence, the limit for injected volumes is less than 1 mL. Cyanoacrylate (n-butyl-2-cyanoacrylate, Histoacryl; Braun, Germany) is a liquid tissue adhesive that consists of monomers that rapidly polymerize (creating long and strong chains) in an exothermic reaction after contact with hydroxide ions[22]. Cyanoacrylate is widely used for the management of bleeding esophageal and gastric varices, but it is not recommended for acute non-variceal upper gastrointestinal bleeding. However, in difficult-to-arrest non-variceal bleeding, it could be a useful and safe therapeutic tool.

MECHANICAL THERAPY

Mechanical therapy refers to the use of a device that causes physical tamponade at a bleeding site[15]. It includes endoscopic clips and band ligation (Figures 1 and 2). Metal clips are particularly useful for small bleeding ulcers (*i.e.*, Dieulafoy lesions), for Mallory-Weiss tears, and for large, visible vessels. Endoscopic clips are deployed over a bleeding site (*e.g.*, visible vessel) and typically slough off within days to weeks after placement. Endoscopic clips function by mechanical compression of the bleeding vessel and theoretically cause less tissue injury than cautery methods. Band ligation is widely used in variceal bleeding. However, it has also been found to be effective in treating bleeding Dieulafoy's lesions[23].

The Over-The-Scope Clip (OTSC; Ovesco, Tübingen, Germany) is a modern endoscopic clipping device designed for tissue approximation. It has been used for the closure of fistulas and perforations. OTSC consists of a nitinol clip mounted on an applicator cap that is affixed to the tip of the endoscope. The deployed clip captures and closes tissue suctioned into the applicator cap, thus compressing the lesions until healing. Studies on animal models and limited data from clinical use support the efficacy of OTSC for the treatment of GI bleeding, and a number of small case series have shown effective hemostasis resulting from the use of OTSC in patients for whom epinephrine injection or standard clip placement failed[24]. The OTSC is now available on the market and gives the physician a tool for the immediate management of complications, such as deep-wall lesions, difficult bleeding or perforations.

THERMAL THERAPY

Thermal therapies include electrocautery probes (monopolar, bipolar or multipolar) and heater probes, which are referred to as contact thermal modalities, and argon plasma coagulation (APC) and laser phototherapy, which are known as noncontact techniques. Bipolar and multipolar probes provide constant bipolar electrocoagulation, which is assumed to be safer than monopolar diathermy (which produces an unpredictable depth of damage and a higher risk of perforation). A foot pedal controls the delivery of energy. The power output is in watts (W). Maximum power settings are dependent

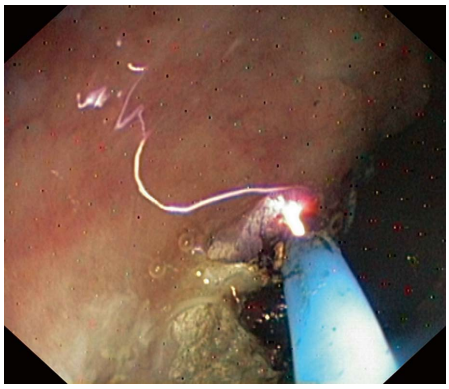

Figure 3 Argon plasma coagulation.

on the generator used but usually do not exceed 50 W. A standard setting is 20 W.

A heater probe provides constant heat at 250 ℃, which is released by a diode in the probe tip and directly transferred to tissue to affect coagulation. Contact treatment devices share some common principles. All can be applied tangentially but are better used face-on, if possible. When the vessel is actively bleeding, direct probe pressure on the vessel or feeding vessel will reduce the flow and increase the effectiveness of treatment. Mechanically pressuring the probe tip directly to the bleeding site, combined with heat or electrical current to coagulate blood vessels, is a process known as "captive coagulation". The bipolar and heater probes incorporate a flushing water jet, which helps to prevent sticking.

Argon plasma coagulation, which is performed without tissue contact, uses the electrical conductivity of argon gas (Figure 3). The argon, passed down an electrode catheter and energized *via* an intelligent-circuitry electrosurgical unit and patient plate, ionizes to produce a local plasma arc. The produced heating effect is inherently superficial (2-3 mm at most, unless the current is applied in the same place for many seconds). Therefore, APC is used to treat superficial mucosal lesions, such as vascular malformations and gastric antral vascular ectasias. The APC probe should be positioned 2-10 mm from the lesion and the argon gas flow should be 1.5-2 L/min at a power of 40-50 W[25,26].

Laser phototherapy uses an Nd:YAG laser to create hemostasis by generating heat to induce direct vessel coagulation. This is a noncontact thermal method. It is not as effective as captive coagulation because it lacks the use of compression to create a tamponade effect[27]. An additional deterrent to its use is expense.

To perform laser coagulation, the area near the vessel is first injected with epinephrine to reduce blood flow (reducing the heat-sink effect). Then, the laser is applied around the vessel, producing a wall of edema. Caution must be taken to avoid drilling into the vessel with the laser, which can cause increased bleeding.

TOPICAL HEMOSTATIC AGENTS

Topical hemostatic agents are new tools used in endoscopic hemostasis. Three different powders are available: Hemospray (Cook Medical, Winston-Salem, NC, United States), Ankaferd BloodStopper, and EndoClot (EndoClot Plus Inc., Santa Clara, CA, United States)[28].

Hemospray (TC-325), a novel proprietary inorganic powder, has recently been approved in Canada for the management of NVUGIB[29]. The powder is administered through a 10- or 7-French catheter *via* a CO_2-pressurised canister. It achieves hemostasis by adhering to the bleeding site, leading to mechanical tamponade and, by concentrating and activating platelets and coagulation factors, promoting thrombus formation. Its ability to cover large areas with multiple bleeding points makes it a suitable choice for hemorrhagic gastritis, gastric antral vascular ectasia, radiation-induced mucosal injury and malignancy-related bleeding[29]. Other advantages include ease of use, the lack of need for precise lesion targeting and access to lesions in difficult locations.

Hemostatic sprays derived from plants have also been invented. Clinical use of these agents for endoscopic hemostasis is currently limited to the off-label use of ankaferd blood stopper (ABS) (Ankaferd Health Products Ltd., Istanbul, Turkey), a mixture of extracts from several plants that is approved in Turkey for the topical treatment of dental and postsurgical external bleeding. ABS is delivered through the working channel of the scope using a spray catheter.

The EndoClot Polysaccharide Hemostatic System (EndoClot Plus Inc., Santa Clara, CA, United States) is the latest available hemostatic powder. It consists of starch, which explains its availability in European countries, Australia, Malaysia, and Turkey, despite a lack of rigorous scientific evidence for its efficacy. The effectiveness of the powder at controlling and preventing bleeding related to endoscopic mucosal resection has been recently described[28].

PRE-ENDOSCOPY PHARMACOLOGIC THERAPY

Prokinetic agents, such as intravenously administered erythromycin or metoclopramide, should be considered for use 30 min prior to endoscopy to improve visibility[30]. Intravenous prokinetic agents, when administered 20 to 120 min before endoscopy in patients with acute UGIB, decrease the need for a repeat endoscopy to determine the site and cause of bleeding. However, their use has not demonstrated any benefit to other clinical parameters, such as transfusion requirement, length of hospital stay, or need for surgery.

Proton pump inhibitor (PPI) therapy is another pharmacologic intervention that should be considered in patients suspected to have UGIB (*e.g.*, pantoprazole 80 mg bolus followed by 8 mg/h continuous drip or 40 mg intravenously every 12 h). The infusion is continued for 48-72 h. The relative efficacy of PPIs may be due to their superior ability to maintain gastric pH at a level above 6.0, thereby protecting ulcer clots

from fibrinolysis. Multiple analyses have shown that applying PPI therapy before a procedure significantly reduced the rate of high-risk stigmata that are identified by endoscopy and the need for endoscopic therapy. Therefore, intravenous PPI therapy is recommended for patients who are suspected of having acute NVUGIB.

EFFICACY AND COMPARATIVE ANALYSIS

Gastroduodenal peptic ulcers are by far the most common etiology of UGIB, accounting for 50% of admissions among patients with upper gastrointestinal hemorrhage[28]. Multiple meta-analyses evaluating endoscopic therapies for bleeding peptic ulcers have demonstrated that thermal devices, injectable agents other than epinephrine (*i.e.*, sclerosants and thrombin/fibrin glue), and clips were all effective methods for achieving hemostasis in PUD, with no single modality being superior to the others. In particular, hemoclip placement, thermocoagulation (*e.g.*, heater probe), and electrocoagulation (*e.g.*, Gold probe, BICAP probe) all seem to be equivalent alternatives[20,31-34]. Dual combination therapy (*i.e.*, epinephrine injection plus other injections or thermal or mechanical methods) was proven to be significantly superior to epinephrine injection alone, but displays no advantage over thermal or mechanical monotherapy. This means that epinephrine should no longer be applied as a monotherapy for treating lesions with high-risk stigmata and should only be used in combination with other methods as these combinations significantly reduce the risk of rebleeding and surgery. Prospective randomized trials have demonstrated that thermal therapy results in significant reductions in bleeding, blood transfusions, length of hospital stays, and the need for urgent surgery in patients with actively bleeding ulcers or nonbleeding ulcers with visible vessels[35]. A meta-analysis of randomized trials that evaluated rebleeding rates following injection, thermal therapy, clips, or combination therapy showed that clips were superior to thermal therapy[33]. The remaining causes of UGIB account for up to 50% of cases. For gastric antral vascular ectasia (GAVE), APC remains the most commonly reported modality that is usually performed over multiple endoscopic sessions. APC is associated with a decrease in transfusion requirements[36]. Mallory-Weiss tear bleeding usually spontaneously stops, with the rates of rebleeding from this etiology reaching up to 10%. Patients with active bleeding or oozing require endoscopic therapy. Bipolar electrocoagulation, epinephrine injection, clips, and band ligation have all been used successfully with no difference in immediate hemostasis or rebleeding. Endoscopic therapy is the first choice in bleeding Dieulafoy's lesions and is usually performed *via* clipping or banding of the lesion[23]. Endoscopic clipping is superior to endoscopic injection and is comparable to thermocoagulation in securing hemostasis in bleeding peptic ulcers and Dieulafoy's lesions[28]. Endoscopic hemostasis of bleeding upper GI tract tumors has proven to be less effective and to have higher rates of rebleeding. Various endoscopic treatment modalities have been described with no clear recommendations. Several studies have reported that cyanoacrylate was used for acute non-variceal gastrointestinal bleeding cessation[21]. Application of cyanoacrylate (by injection and/or spraying) is a safe and effective method for achieving immediate hemostasis when conventional endoscopic treatment has been unsuccessful. This technique is easy to perform and should be considered in cases of patients with difficult-to-arrest acute NVGIB. Recently, promising preliminary data have been reported following the use of the hemostatic powder TC-325 (Hemospray) for bleeding control from upper GI tract tumors[37].

CONCLUSION

Endoscopy is the mainstay for the modern management of NVUGIB. Ideally, endoscopy should be performed within 24 h of presentation, after adequate resuscitation has been performed. Many safe and effective devices are available for endoscopic hemostasis. Combination therapy using the injection of epinephrine plus another hemostatic technique is more effective than epinephrine alone. Hemospray is a new and promising endoscopic therapy. Patients with high-risk stigmata should receive continuous intravenous PPI administration for 72 h after endoscopy. After the acute phase, the underlying cause of the lesion should be verified and treated, when possible. The choice of therapy should remain at the discretion of the physician, based on the nature and position of the lesion, the availability and experience of the endoscopist and the previous endoscopic therapy that the patient has received.

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ORIGINAL ARTICLE

Retrospective Study

Hospitalization for esophageal achalasia in the United States

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Abstract

AIM: To assess the outcome of different treatments in patients admitted for esophageal achalasia in the United States.

METHODS: This is a retrospective analysis using the Nationwide Inpatient Sample over an 8-year period (2003-2010). Patients admitted with a primary diagnosis of achalasia were divided into 3 groups based on their treatment: (1) Group 1: patients who underwent Heller myotomy during their hospital stay; (2) Group 2: patients who underwent esophagectomy; and (3) Group 3: patients not undergoing surgical treatment. Primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), discharge destination and total hospital charges.

RESULTS: Among 27141 patients admitted with achalasia, nearly half (48.5%) underwent Heller myotomy, 2.5% underwent esophagectomy and 49.0% had endoscopic or other treatment. Patients in group 1 were younger, healthier, and had the lowest mortality when compared with the other two groups. Group 2 had the highest LOS and hospital charges among all groups. Group 3 had the highest mortality (1.2%, $P < 0.001$) and the lowest home discharge rate (78.8%) when compared to the other groups. The most frequently performed procedures among group 3 were esophageal dilatation (25.9%) and injection (13.3%). Among patients who died in this group the most common associated morbidities included acute respiratory failure, sepsis and aspiration pneumonia.

CONCLUSION: Surgery for achalasia carries exceedingly low mortality in the modern era; however, in complicated patients, even less invasive treatments are burdened by

significant mortality and morbidity.

Key words: Esophageal achalasia; Outcomes; Myotomy

Core tip: We aimed to assess the outcomes of different treatments in patients hospitalized for esophageal achalasia in the United States. We queried the Nationwide Inpatient Sample database from 2003 to 2010. Patients admitted with a primary diagnosis of achalasia were divided into 3 groups, based on treatment, and compared. About half of the patients did not actually undergo a surgical procedure; yet, they had the highest mortality and lowest home discharge rate. Our data suggest that when achalasia has gone too far and previous treatments have been untimely or ineffective, patients may face non-negligible mortality and morbidity even with endoscopic treatment or supportive care.

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INTRODUCTION

Achalasia is a chronic, progressive disease characterized by loss of peristalsis of the distal esophagus, failure of the lower esophageal sphincter to completely relax with deglutition, and elevated baseline intraluminal esophageal pressure[1]. The pathophysiology of the impaired peristalsis is represented by the progressive degeneration and destruction of a subpopulation of inhibitory neuronal ganglion cells of the Auerbach myenteric plexus of the esophagus[2]. The resulting long lasting contraction of the lower esophageal sphincter (LES) causes stasis of food within the esophageal lumen until the rising intraesophageal pressure overcomes the obstacle represented by the cardial spasm and the bolus slowly transits into the stomach. The outflow obstruction inevitably leads, over time, to progressive esophageal dilation and tortuosity, if the condition is left untreated.

The treatment of achalasia is substantially palliative and aims to relieve symptoms and to contrast the natural history of the disease through improvement of passive esophageal transit. The distal esophageal obstacle to food progression can be eliminated with endoscopic pneumatic dilation or surgical myotomy, both with similar short-term success of about 80%-90% and a long-term control of symptoms of approximately 50% with dilation, and 80%-90% with myotomy[3-6].

The therapeutic options for achalasia also include endoscopic botulin toxin injection, especially for the high-risk patients or those patients with contraindications to pneumatic dilation or surgery; this procedure, however, is burdened by high long-term costs, short lasting results and a high recurrence rate[7]. Pharmacological treatment of achalasia, targeted to induce LES relaxation with nitrates and calcium channel blockers, has been shown to yield unsatisfying results with poor control of symptoms[8,9].

We believe that the severity of the disease is often underestimated, especially in more advanced stages, due to its slow progression and to its common classification as a benign condition. We therefore queried the Nationwide Inpatient Sample (NIS), in order to assess the outcome of different treatments in patients admitted for esophageal achalasia in the United States.

MATERIALS AND METHODS

Data source and study population

A retrospective review was performed using the NIS database from 2003-2010. NIS consists of 20% stratified sample of all United States hospitals, and it provides discharge weights to produce a 95% of all discharges in the United States[10]. International Classification of Diseases, ninth revision (ICD-9) coding was used to establish the desired study population. All patients admitted with a primary diagnosis of achalasia (ICD-9 diagnosis code of 530.0) were included in the study. These patients were divided into 3 groups based on their in-hospital treatment: (1) Group 1: Achalasia patients who underwent Heller myotomy during their hospital stay (ICD-9 procedure code of 42.7); (2) Group 2: Achalasia patients who underwent esophagectomy (ICD-9 procedure codes of 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151); and (3) Group 3: Achalasia patients not undergoing surgical treatment. This study was limited to adult patients (> 17 years old) without a diagnosis of esophageal cancer (ICD-9 diagnosis codes of 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151). This study was granted exempt status by the Johns Hopkins Medicine Institutional Review Board.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), discharge destination (home/transfer), total hospital charges (TOTCHG), and complications such as, pneumonia, urinary tract infection (UTI), shock/sepsis, and pulmonary compromise. These complications were obtained by using previously validated ICD-9 diagnosis codes (1-2) (Table 1). Total hospital charges were adjusted for inflation to reflect 2011 United States dollars.

Statistical analysis

All statistical analyses were performed using STATA/MP, version 11.2 (Stata Corp, College Station, Texas). Weighting strategy was applied prior to conducting statistical analysis. Adjusted Wald test and Pearson's χ^2 were used for continuous and categorical variables, respectively. Multivariable logistic regressions were performed to compare odds of each outcome while

Table 1 International Classification of Disease, ninth revision procedure and diagnosis codes used to determine surgical procedure categories and complications

	ICD-9 code
Achalasia	530
Heller[1]	427
Esophagectomy[1]	42.4, 42.41, 42.42, 42.5, 42.51-59, 42.6, 42.61-69
Esophageal cancer	150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 151
Complications	
Pneumonia	481, 482.0-482.4, 482.8-482.9, 483, 484, 485, 486, 507.0, 482.40, 482.41. 482.42, 482.49
Urinary tract infection	997.5, 599.0-599.9
Shock/sepsis	998.0, 995.9, 995.90, 995.91, 995.92, 038
Pulmonary compromise	514, 518.4, 518.5, 518.81, 518.82

[1]Indicates procedure codes. ICD-9: International Classification of Disease, ninth revision.

adjusting for age, gender, and Charlson Index score. Adjusted TOTCHG and LOS were obtained from a multiple regression, while adjusting for age, gender, and Charlson Index score. A level of significance was set at $\alpha = 0.05$.

RESULTS

Baseline demographic and clinical characteristics

A total of 31769 achalasia patients met the study criteria, including, 15567 Heller patients (49.0%), 785 esophagectomy patients (2.5%), and 15417 non-surgical patients (48.5%) (Table 2). The overall mean age was 59 (median 59), with 54.3% females, and 70.8% white patients. Heller group was the youngest (median age of 51) and the healthiest (mean Charlson score of 0.34). While the non-surgical group was the oldest (median age 72) with the highest comorbidity (mean Charlson score of 0.93). Among the most common procedures performed for patients who underwent non-surgical treatment of achalasia (group 3) were: esophagogastroduodenoscopy (65.2%), dilation of esophagus (26.9%), and injection of therapeutic/prophylactic substance-including botulism antitoxin (17.3%) (Table 3).

Unadjusted outcomes

The overall in-hospital mortality was 0.65%, with the highest unadjusted mortality seen in the esophagectomy group (1.96%) (Table 4). There was no significant difference between the in-hospital mortality for the esophagectomy group *vs* non-surgical group. The esophagectomy group stayed in the hospital the longest (median LOS of 13 d) and had highest total hospital charges (median TOTCHG of $134670.40). Achalasia patients undergoing Heller myotomy were the most likely to be discharged home (97.2%) and were less likely to acquire pneumonia, UTI, shock/sepsis, and pulmonary compromise (3.3%, 2.0%, 0.3%, and 1.6%, respectively). Pneumonia, shock/sepsis, and pulmonary compromise were the most common complications in the esophagectomy group. Mean LOS, TOTCHG, and pneumonia were significantly different across all three groups (even when the pairwise comparison was applied).

Adjusted outcomes

Multivariable logistic regression was performed for the two surgical groups *vs* the non-surgical group, while adjusting for age, gender, and Charlson Index score.

Heller vs non-surgical group

The likelihood of in-hospital mortality was more than four times higher in the non-surgical group (OR = 4.73, 95%CI: 1.16-19.31, $P = 0.03$), and the chance to develop pneumonia and UTI was doubled (OR = 1.91, 95%CI: 1.42-2.58, $P < 0.001$; OR = 2.31, 95%CI: 1.67-3.18, $P < 0.001$, respectively) when compared to the Heller group. Moreover, the non-surgical group was significantly more likely to be transferred (OR = 3.76, 95%CI: 2.85-4.97, $P < 0.001$). The non-surgical achalasia patients paid $14594.24 less ($P < 0.001$) in TOTCHG and stayed in the hospital about one day longer ($P < 0.001$) than the Heller patients (Table 5).

Esophagectomy vs non-surgical group

The esophagectomy group was seven times as likely to have an in-hospital mortality (OR = 7.28, 95%CI: 2.06-25.79, $P = 0.002$) and nearly twice as likely to be transferred compared to the non-surgical group (OR = 1.84, 95%CI: 1.16-2.94, $P = 0.01$). Achalasia patients who underwent esophagectomy had also higher complications such as pneumonia, shock/sepsis, and pulmonary compromise (OR = 3.68, 95%CI: 2.40-5.64, $P \leqslant 0.001$; OR = 16.53, 95%CI: 6.36-42.96, $P < 0.001$; OR = 37.97, 95%CI: 22.85-63.07, $P < 0.001$, respectively). Esophagectomy patients stayed in the hospital twelve days longer ($P < 0.001$) and paid $181167.90 more ($P < 0.001$) than the non-surgical patients (Table 6).

DISCUSSION

Our study shows that more than 30000 patients were hospitalized over an 8-year period for the treatment of esophageal achalasia in the United States. It would be intuitive to assume that most patients were admitted to undergo surgery, since endoscopic treatment is commonly performed in the outpatient setting. Only half of them underwent a surgical procedure instead, thus suggesting that the natural history of the disease can potentially lead to complications severe enough to require admission.

As broadly demonstrated in previous studies, we confirmed that patients treated with Heller myotomy benefit from low mortality, morbidity and LOS. The most frequent procedures performed among the non-surgical group were endoscopic pneumatic dilatation (25.9%) and endoscopic drugs injection (13.3%). It is common and widespread practice to elect non-surgical,

Table 2 Baseline demographic and clinical characteristics of patients among the three groups, Nationwide Inpatient Sample, 2003-2010 *n* (%)

	Total 31769	Group 1 Heller 5567 (49.00)	Group 2 Esophagectomy 785 (2.47)	Group 3 Non-surgical 15417 (48.53)	*P*
Age, mean (median)	59 (59)	51.2 (51)	53.8 (54)	67.1 (72)	< 0.001
Age category					< 0.001
18-44	8041 (25.31)	5576 (35.82)	251(31.97)	2214 (14.36)	
45-64	10554 (33.22)	6330 (40.66)	308 (39.24)	3916 (25.40)	
65-74	4746 (14.94)	2254 (14.48)	141 (17.96)	2351 (15.25)	
⩾ 75	8428 (26.53)	1407 (9.04)	85 (10.83)	6936 (44.99)	
Gender[1]					< 0.001
Male	14429 (45.73)	7883 (51.21)	371 (47.41)	6175 (40.17)	
Female	17120 (54.27)	7510 (48.79)	412 (52.59)	9198 (59.83)	
Race[2]					0.002
White	17663 (70.77)	8662 (71.64)	403 (65.96)	8598 (70.15)	
Black	3662 (14.67)	1533 (12.68)	75 (12.27)	2054 (16.76)	
Other	3633 (14.56)	1896 (15.68)	133 (21.77)	1604 (13.09)	
Charlson score	0.63	0.34	0.48	0.93	0.036
0	21147 (64.53)	11681 (75.04)	508 (64.71)	7958 (51.62)	< 0.001
1	7390 (22.55)	3015 (19.37)	206 (26.24)	4169 (27.04)	
⩾ 2	4232 (12.91)	871 (5.59)	71 (9.05)	3290 (21.34)	

[1]Missing data for 220 patients; [2]Missing data for 6811 patients.

Table 3 Most common procedure types for patients who underwent non-surgical treatment of achalasia

ICD-9 code	Procedure type	Group 3 Non-surgical 15417
45.13 and 45.16	Esophagogastroduodenoscopy	65.15%
42.92	Dilation of esophagus	26.94%
99.57 and 99.29	Injection of therapeutic/prophylactic substance-including botulism antitoxin	17.32%
98.02	Removal of intraluminal foreign body from esophagus without incision	6.44%
43.11	Percutaneous endoscopic gastrostomy percutaneous transabdominal gastrostomy	5.73%
29.31	Cricopharyngeal myotomy	2.77%

ICD-9: International Classification of Diseases, ninth revision.

Table 4 Observed unadjusted rates of outcomes across the three patient groups, Nationwide Inpatient Sample, 2003-2010 *n* (%)

	Total 31769	Group 1 Heller 15567 (49.00)	Group 2 Esophagectomy 785 (2.47)	Group 3 Non-surgical 15417 (48.53)	*P*
In-hospital mortality	206 (0.65)	16 (0.1)	15 (1.96)	180 (1.17)	< 0.001
Disposition					
Home[1]	27916 (87.87)	15130 (97.19)	637 (81.15)	12149 (78.80)	< 0.001
Transfer[2]	3504 (11.03)	416 (2.67)	133 (16.89)	2955 (19.17)	< 0.001
Pneumonia	1959 (6.17)	509 (3.27)	150 (19.11)	1300 (8.43)	< 0.001
UTI	1462 (4.60)	311 (2.00)	50 (6.37)	1101 (7.14)	< 0.001
Shock/sepsis	171 (0.54)	50 (0.32)	46 (5.86)	75 (0.49)	< 0.001
Pulmonary compromise	813 (2.56)	241 (1.55)	245 (31.21)	327 (2.12)	< 0.001
Median LOS (d)	3	2	13	4	< 0.001
Median TOTCHG	$26299.41	$30118.12	$134670.40	$21175.23	< 0.001

[1]Home is discharge to home with and without home health care; [2]Transfer is discharge to short term hospital, skilled nursing facility, intermediate care and other type of facilities. LOS: Length of hospital stay; TOTCHG: Total hospital charges; UTI: Urinary tract infection.

thus less invasive, treatment as the best option for high-risk patients. This phenomenon can be indeed observed in demographics of group 3, which included the oldest patients and those with highest comorbidity. Nevertheless, it is interesting to remark that, even after adjusting for age, gender, and Charlson Index score, the non-surgical group was more than four times as likely to have in-hospital mortality, and twice as likely to have pneumonia and UTI compared to the Heller group. This finding, which might appear counterintuitive at first glance, finds a logical explanation when recalling that non-surgical treatment of achalasia is usually administered in the outpatient setting. The youngest and most fit patients undergoing non-surgical treatment were therefore likely not captured by this analysis focusing on hospitalized patients. Conversely, many of

Table 5 Adjusted odds ratios of outcomes and complications for the non-surgical group (in comparison to the Heller group)

	OR	*P*	95%CI
In-hospital mortality	4.73	0.03	1.16-19.31
Disposition			
Home	0.24	< 0.001	0.19-0.31
Transfer	3.76	< 0.001	2.85-4.97
Pneumonia	1.91	< 0.001	1.42-2.58
Urinary tract infection	2.31	< 0.001	1.67-3.18
Shock/sepsis	1.18	0.726	0.47-2.97
Pulmonary compromise	0.83	0.413	0.54-1.29

All the analyses were adjusted for age, gender, and Charlson Index score.

Table 6 Adjusted odds ratios of outcomes and complications for the esophagectomy group (in comparison to the non-surgical group)

	OR	*P*	95%CI
In-hospital mortality	7.28	0.002	2.06-25.79
Disposition			
Home	0.54	0.009	0.35-0.86
Transfer	1.84	0.010	1.16-2.94
Pneumonia	3.68	< 0.001	2.40-5.64
Urinary tract infection	1.28	0.507	0.62-2.67
Shock/sepsis	16.53	0.001	6.36-42.96
Pulmonary compromise	37.97	< 0.001	22.85-63.07

All the analyses were adjusted for age, gender, and Charlson Index score.

the patients of our group 3 were probably complicated patients, such as subjects affected by advanced stage, recurrent or refractory achalasia, or individuals at high risk for surgery. In addition, our analysis is likely to have included in group 3 also those patients who faced serious complications of endoscopic treatments. Pneumatic dilation, although offering fast recovery and low overall complication rate, is burdened by a tangible risk of esophageal full-thickness perforation, especially when the procedure is repeated multiple times to maintain satisfactory results[11,12].

Heller myotomy is usually performed laparoscopically and an antireflux procedure is commonly added; randomized studies have in fact confirmed its efficacy in decreasing postoperative gastroesophageal reflux disease[13,14]. It is reasonable to hypothesize that the ongoing technical advancements in minimally invasive surgery, along with the widespread of advanced laparoscopic skills to an increasing number of surgeons, will strengthen the role of Heller myotomy as the safest and most durable choice for the treatment of achalasia.

The findings of our analysis outline the potential risks resulting from the insidious, slowly progressive nature of achalasia. When the disease has gone too far and previous treatments have been untimely or ineffective, patients may face non-negligible mortality and morbidity even with endoscopic treatment or supportive care. We therefore think that Heller myotomy should be strongly considered early in patients with esophageal achalasia and should be offered to all patients as the first therapeutic option, in absence of absolute contraindications to surgery.

This recommendation might change in the future, once the long term outcomes of patients treated with per-oral endoscopic myotomy (POEM) will become available. POEM, in fact, represents the cutting edge of minimally invasive treatment for achalasia and offers comparable early outcomes to Heller myotomy with the adjunctive benefit of being performed endoscopically[15,16]. Therefore, if randomized studies will demonstrate long-term outcomes similar to those of laparoscopic Heller procedure, POEM might become the new gold standard for the treatment of esophageal achalasia.

Pulmonary symptoms as well as functional abnormalities have been demonstrated to be present in a significant percentage of patients with achalasia and are readily apparent in the poor pulmonary outcomes of our non-surgical group[17]. Respiratory complications represent one of the most frequent causes of morbidity in patients with achalasia, if the natural history of the disease is not radically modified by treatment. In addition, radiological pulmonary abnormalities in the form of consolidation, ground glass opacities, nodular opacities, air trapping, fibrotic changes and bilateral alveolar findings that resemble aspiration pneumonia have been widely described in achalasia patients[18]. Data in the literature support the hypothesis that surgery could not only improve the symptoms, but also lead to regression of the functional and radiological pathologic findings[17,18].

The results of our analysis confirm that esophagectomy, as previously shown, is an operation burdened by significant mortality and morbidity. It has been reported that laparoscopic myotomy may still play a role and improve outcomes in patients with stage IV disease, even when a remarkable esophageal dilation is present; this is particularly true for patients with an enlarged but linear esophagus[19].

However, about 5% of all patients with achalasia will eventually require esophagectomy and it is our belief that this procedure remains a reasonable option and a precious last resort in patients with end stage disease[20-22]. Moreover, we have previously shown that operative outcomes, including mortality, overall morbidity, and LOS are comparable between patients undergoing esophagectomy for achalasia and for esophageal cancer[23].

Our study presents some limitations worth mentioning. First of all, NIS is an administrative database, which is prone to errors due to missing or inaccurately entered ICD-9 codes. This database does not include any outpatient information, therefore patients that may have been treated by pneumatic dilation and sent home the same day are not captured. In addition, ICD-9 coding system is not perfect and specific procedures might be difficult to identify using the current ICD-9 procedure codes. For example, there is no specific

code for pneumatic balloon dilation, but there exists an ICD-9 code (42.92) for dilation of esophagus. There is no way to know if these dilations were merely routine dilations *vs* true pneumatic dilations with a 30 mm balloon. This fact, together with a small number of patients in the endoscopic injection group, did not allow us to meaningfully compare treatment subgroups among the non-surgical patients. No information is given on symptomatic relief and functional outcomes with this database, nor there is trace of postoperative events occurred after patients' discharge. Finally, it is not possible to know the stage of patients' disease at admission or if previous treatments for achalasia had been attempted.

That said, this study provides a useful general overview of the trends and outcomes of achalasia management and, in particular, it sheds light over the less studied populations of non-surgical patients who nonetheless needed hospitalization.

In conclusion, it is important to remark that the common labeling of achalasia as "benign condition" can be misleading and delay referral for definitive treatment. If left untreated or if treated with less than optimal approach, the disease will progress and can lead to complications, which will significantly affect patients' quality of life or potentially become life threatening. Although this database does not allow us to compare outcomes between endoscopic and surgical treatment of achalasia, the analysis of our data suggests that a timely and effective relief of esophageal obstruction may avoid future complications brought by the natural history of the disease.

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COMMENTS

Background

Achalasia is a chronic, progressive disease characterized by loss of peristalsis of the distal esophagus, failure of the lower esophageal sphincter to completely relax with deglutition, and elevated baseline intraluminal esophageal pressure. The treatment of achalasia is substantially palliative and aims to relieve symptoms and improve passive esophageal transit. The authors believe that the severity of the disease is often underestimated, especially in more advanced stages, due to its slow progression and to its common classification as a benign condition. Comparing the outcomes after different treatments in patients hospitalized for achalasia can help provide additional clinical insights for providers who care for these patients.

Research frontiers

Early intervention and modification of the history of achalasia is paramount, since the disease is prone to an insidious and burdensome progression, as evidenced by several studies, including the authors'. Awareness should be raised and efforts focused on early diagnosis and treatments. Surgical treatment remains the gold standard for improving symptoms, however less invasive procedures, like per-oral endoscopic myotomy (POEM), are being frequently used. Studies of POEM's long-term outcomes is a current hotspot in the field.

Innovations and breakthroughs

This study takes an innovative approach, since it focuses on a different population than most other publications. It provides data and analysis of patients that were hospitalized for traditional treatments for achalasic in addition to patients that were admitted for complications of achalasia itself.

Applications

The data raises awareness for the common misconception in considering achalasia a benign condition. It is, in fact, an insidious disease that can lead to non-negligible mortality and morbidity when treated late or not incisively. This becomes apparent when analyzing the outcomes and characteristics in the authors' non-surgical group.

Peer-review

The authors have provided a valuable review on surgical treatment options in achalasia. The study design, discussion and conclusion are fine.

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ORIGINAL ARTICLE

Prospective Study

Triradiate caecal fold: Is it a useful landmark for caecal intubation in colonoscopy?

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Abstract

AIM: To determine the frequency of identification of the triradiate fold during colonoscopy and evaluate its reliability as a marker of caecal intubation.

METHODS: One hundred consecutive patients undergoing colonoscopy in a tertiary hospital colorectal unit from May to September 2013 were studied. Video documentation of the caecum was recorded and shown to consultant colorectal surgeons on the unit. Each reviewer was asked through a series of questions to independently identify the triradiate fold. The main outcome was the frequency of visualisation of the triradiate fold in the caecum.

RESULTS: The triradiate fold was seen on average in 18% of cases, but inter-observer agreement was poor. There were only four patients (4%) in which all reviewers agreed on the presence of a triradiate fold. In patients who had undergone previous appendicectomy, the appendiceal orifice was less frequently seen compared with patients who had not undergone appendicectomy.

CONCLUSION: The triradiate fold is infrequently seen during colonoscopy and is therefore an unreliable landmark of caecal intubation.

Key words: Colonoscopy; Triradiate fold; Appendiceal orifice; Caecal intubation; Prospective study

Core tip: The triradiate fold is often described as a major landmark of caecal intubation in colonoscopy, but its frequency of visualisation has not been previously documented. This study shows that identification of the triradiate fold is infrequent and its presence is subjective. Inclusion in guidelines or colonoscopy software programs as a sole marker of complete colonoscopy is questionable.

Finlayson A, Chandra R, Hastie IA, Jones IT, Shedda S, Hong MK-Y, Yen A, Hayes IP. Triradiate caecal fold: Is it a useful landmark for caecal intubation in colonoscopy? *World J Gastrointest Endosc* 2015; 7(13): 1103-1106 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i13/1103.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i13.1103

INTRODUCTION

Accurate assessment of the extent of colonoscopy relies on the identification and cognitive integration of several caecal landmarks to the trained endoscopist. These landmarks may include the ileocaecal valve, ileal mucosa, appendiceal orifice and caecal folds.

Of these many landmarks, the ileocaecal valve has been shown to be the single most reliable landmark, being viewed 98% of the time when caecal intubation had been confirmed with fluoroscopy[1]. The same study found the appendiceal orifice to be the second most reliable landmark. Others contend that the most accurate method to ensure caecal intubation is to enter the terminal ileum and confirm with a biopsy of ileal mucosa[2].

Various names and descriptions have been given to the folds in the caecum. The converging folds have been named the triradiate fold, Mercedes sign, crows-foot and caecal strap fold[2-5]. The term triradiate fold is used in many computerized colonoscopy databases and also by the Australian National Bowel cancer screening project as a landmark for caecal intubation with colonoscopy[6]. Last's Anatomy textbook describes the three taenia of the colon converging at the base of the appendix[7]. However in practice, a clearly defined triradiate fold is not always seen at colonoscopy. We undertook this study to document how frequently a triradiate fold is seen at the caecal pole during colonoscopy.

MATERIALS AND METHODS

This study was approved by the Melbourne Health Human Research Ethics Committee at the Royal Melbourne Hospital, Parkville, Australia. All consecutive patients undergoing colonoscopy from May to September 2013 either performed or supervised by two colorectal fellows were included in the study. Exclusion criteria were previous caecal resection, inadequate bowel preparation, technical issues with recording equipment and incomplete colonoscopies.

All colonoscopies were performed with an Olympus colonoscope. Once caecal intubation was reached, a short video was recorded on the Olympus Endobase® program. The caecal pole was thoroughly irrigated to adequately display the caecum. Caecal intubation was confirmed on collective visualisation of the ileocaecal valve, blind-ending caecal pole and appendiceal orifice when present. It was not routine in our institution to perform ileal intubation as a marker of complete colonoscopy unless clinically indicated. The videos were recorded in a standard fashion to give a panorama of the caecal pole including established landmarks of the appendiceal orifice and ileocaecal valve, and then zoomed in on the appendiceal orifice and surrounding folds.

All 100 videos were then edited using Corel Video Studio Pro® to delete unnecessary footage. The videos submitted for analysis included continuous footage so that each caecum was easily identifiable. The final length of edited videos ranged from 3 to 26 s. The shortest videos were those where all features of the caecum were very easily seen.

Each video was then shown to six consultant surgeons on the unit who then individually evaluated them. Prior to evaluation, a photograph of what we considered to be a triradiate fold was shown to all surgeons (Figure 1). A photograph showing an appendiceal orifice with no triradiate fold was also shown (Figure 2). For each video the following questions were asked:

Are you satisfied that this is a video of the caecum?

Can you identify the appendiceal orifice?

Is there a triradiate fold at the appendix orifice?

If the reviewer was not satisfied that the caecum was represented in the video, the remaining two questions were obsolete and not answered. Similarly if the appendiceal orifice could not be identified, no judgment could be made on the presence of a triradiate fold.

Statistical analysis

Statistical analysis was performed using Microsoft Excel®. Positive responses from the six reviewers were tallied for each of the 100 videos analysed and for each of the three questions asked. Individual and overall proportions of positive responses were calculated. Inter-rater reliability was measured using Conger's kappa coefficient for multiple raters. The relationship between previous appendicectomy and visualisation of the appendiceal orifice was analysed using Fisher's exact test on a 2 × 2 contingency table. Differences were considered significant when the probability was less than 0.05.

RESULTS

One hundred and thirty-four consecutive colonoscopies were either performed or supervised by two fellows. Of these 134 patients, 34 were excluded, leaving 100 colonoscopies for analysis. Of the patients excluded, 11 had a previous caecal resection, 14 had inadequate bowel preparation, 6 were incomplete colonoscopies and

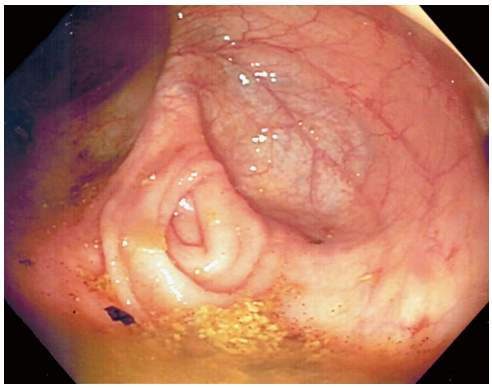

Figure 1 Photograph of a triradiate fold converging on the appendiceal orifice.

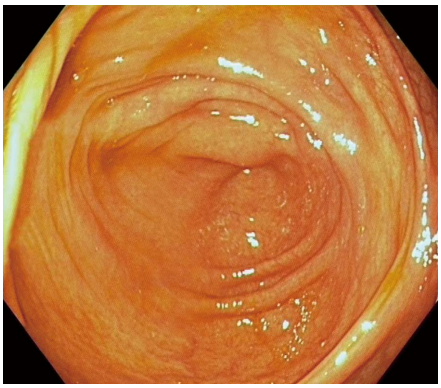

Figure 2 Photograph of an appendiceal orifice with no converging triradiate fold.

Table 1 Indications for colonoscopies

Indication	Number
Per rectal bleeding	26
Polyp follow up	17
Cancer follow up	14
Diverticulitis	9
Altered bowel habit	9
Abnormal imaging	8
Faecal occult blood test positive	6
Fistula investigation	3
Family history	2
Anaemia	2
Iron deficiency	2
Volvulus	1
Rectal prolapse	1

Table 2 Number and percentage of "Yes" answers for each question from each reviewer

Reviewer	Caecum	Appendiceal orifice		Triradiate fold	
1	99	76	77%	13	17%
2	95	79	83%	17	22%
3	96	76	79%	13	17%
4	93	89	96%	18	20%
5	100	89	89%	11	12%
6	97	73	75%	13	18%
Average	97	80	83%	14	18%

Percentages are calculated with denominator being number of "Yes" answers from previous question.

3 had technical problems with the recording equipment. Of the 100 included patients, there were 43 males and 57 females with a mean age of 61 ± 15.8 years. The indications for their colonoscopies are given in Table 1.

A Conger's Kappa coefficient for multiple raters was calculated to assess agreement between the answers to each of the three questions. This showed a strong agreement for each of the three questions, with coefficients of 0.93 for identification of the caecum, 0.79 for identification of the appendix and 0.81 for identification of the triradiate fold.

On average, the reviewers were satisfied the video depicted the caecum in 97% of cases. In those cases where the caecum was identified, the appendiceal orifice could be seen in 83%. In those cases where the appendix orifice was identified, a triradiate fold was seen in 18% (Table 2).

The Kappa coefficient for the triradiate fold was high due to strong agreement among observers about the non-visualization of the triradiate fold. In the smaller percentage of cases where the triradiate fold was identified, there was poor agreement among reviewers. There were only four patients in which all reviewers agreed on the presence of a triradiate fold. The appendiceal orifice was seen in 38 of 54 videos (70.4%) where the patient had undergone previous appendicectomy. When the patient had not undergone an appendicectomy the appendiceal orifice was seen in 444 of 527 videos (84.3%, $P = 0.014$).

DISCUSSION

Accurate identification of the caecum at colonoscopy relies heavily on visualising certain landmarks. The caecal folds have been previously suggested to be an unreliable landmark[8]. In this study we have demonstrated that a triradiate caecal fold is only seen 18% of the time when averaged across all observers. In cases where it was identified, there was poor inter-observer agreement.

Anatomically, the triradiate fold must be centred on the appendiceal orifice. Our study showed that the appendiceal orifice was less frequently seen in patients who had undergone previous appendicectomy. Elsewhere in the colon the intersection of haustral folds and a taenia coli may create a triradiate appearance that could be confused with the triradiate fold of the caecum.

This study is limited by its subjective design. The six consultants who analysed each video were aware of the study hypothesis, which may have influenced their response to the questions. However, they were not aware that all videos were of the caecum. Variables that may influence the identification of the caecal folds include the amount of insufflation. A large amount of inflation of the caecum may flatten the caecal folds,

and thus a triradiate fold that may have been seen in a less distended caecum may have "disappeared" with inflation. Although this theory was not directly tested, we did not observe that inflation had any bearing on the visualization of a triradiate caecal fold through the process of recording, reviewing and editing the videos.

Photo documentation of caecal intubation has been recommended as routine practice although some studies have shown that still photography has poor reliability[9]. Video documentation has previously been shown to be superior to still photography in identifying the caecum to independent observers[3]. Our initial proposal was to use photo rather than video documentation. On review of the first still photographs taken it was our belief that a photograph alone was not sufficient to identify the caecum with certainty. The video however, gave greater detail and provided an accurate depiction of the caecum as demonstrated by the 97% agreement among reviewers. If caecal intubation documentation is to become a marker of quality and successful completion, video documentation appears to be a more reliable method.

This is the first study to look specifically at the triradiate caecal fold as a landmark during colonoscopy. The triradiate fold is an infrequently seen feature of the caecum and as such should not be relied upon to confirm caecal intubation.

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We would like to thank the staff of the endoscopy suite at the Royal Melbourne Hospital for their assistance in the technical aspects of video recording.

COMMENTS

Background

Caecal landmarks are important for accurate assessment of the extent of colonoscopy. The triradiate fold in the caecum is referenced as a major landmark in some guidelines and endoscopy programs. This study was conducted to determine the frequency of identification of the triradiate fold.

Research frontiers

Colonoscopy is a common investigation modality. Quality assurance has become a global focus. One quality measure in colonoscopy is completion rate. This study explores the role of visualisation of the triradiate fold as a marker of colonoscopy completion.

Innovations and breakthroughs

This is the first study that quantifies the rate of visualisation of the triradiate fold, and shows that it is infrequently seen.

Applications

The inclusion of the triradiate fold as a marker of colonoscopy completion in guidelines and endoscopy programs is questionable.

Terminology

Triradiate fold is the appearance of three caecal folds converging upon the appendiceal orifice as seen at colonoscopy.

Peer-review

This is a very interesting, concise and "clever" paper. It is also written in excellent English, fluent and easy to read.

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CASE REPORT

Endoscopic ultrasound guided thrombin injection of angiographically occult pancreatitis associated visceral artery pseudoaneurysms: Case series

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Abstract

Pseudoaneurysm is a known complication of pancreatitis associated with significant mortality and morbidity. Imaging plays an important role in the diagnosis and management. Computed tomography (CT) helps localize the lesion and the severity of the background pancreatitis but digital subtraction angiography with coil embolization is recommended to avoid bleeding and inadvertent surgery. However, in cases where angiographic coil embolization is not feasible due to technical reasons, thrombin injection *via* CT or ultrasound guidance remains a viable option and often described in literature. In this series, effort has been made to highlight the role of endoscopic ultrasound guided thrombin instillation especially in patients with poorly visualized pseudoaneurysm on ultrasound thereby avoiding surgery and the associated mortality and morbidity.

Key words: Pseudoaneurysm; Angiography; Endoscopic ultrasound; Thrombin; Pancreatitis

Core tip: In cases where angiographic coil embolization is not feasible due to technical reasons, thrombin injection *via* computed tomography or ultrasound guidance remains a viable option. Endoscopic ultrasound guided thrombin injection is a new development in this realm especially in those patients where the visualization of the pseudoaneurysm is difficult on transabdominal ultrasound thereby avoiding the need of surgery and the associated morbidity.

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INTRODUCTION

Pancreatitis is associated with high morbidity and mortality. Pseudoaneurysm is a commonly seen fatal complication of pancreatitis, noted in 10% of patients with chronic pancreatitis with the risk of rupture as high as 50% and the mortality after rupture as high as 15%-40%[1,2]. Hence, prompt diagnosis and treatment of pseudoaneurysm is recommended. Diagnostic modality like computed tomography (CT) angiography helps in picking up the lesion and delineating the vessel of origin however, digital subtraction angiography (DSA) and subsequent coil embolization is necessary to occlude the pseudoaneurysm to eliminate the risk of rupture and uncontrolled bleeding. Occasionally, coil embolization is not possible due to varied reasons like inaccessible vascular territory due to small caliber vessel or short neck of pseudoaneurysm. Some pseudoaneurysms may be angiographically occult and seen on ultrasound or CT only. In such cases ultrasound or CT guided percutaneous thrombin injection can be performed. Endoscopic ultrasound (EUS) guided thrombin injection is a new development in this realm especially in those patients where the visualization of the lesion is difficult on transabdominal ultrasound thereby avoiding the need of surgery and the associated morbidity. However, it requires a great deal of expertise. We review a few cases where pseudoaneurysms were occluded using endoscopic guided thrombin injection in our hospital.

CASE REPORT

We encountered three cases of pancreatitis related pseudoaneurysms, which were technically difficult to manage by endovascular route either because of previous surgical clipping of gastroduodenal artery by a laparoscopic surgeon (Figure 1) or that were angiographically occult.

In our center, in hemodynamically stable patients, the usual approach to manage the pancreatitis related pseudoaneurysm is to perform CT angiography for localization of pseudoaneurysm and also to provide road map for endovascular/surgical approach. Subsequently DSA is performed, depending upon the location of pseudoaneurysm on CT angiography; selective cannulation of the culprit vessel is done. If we are able to reach the pseudoaneurysm, coil embolisation is done by occluding the back door, neck and front door of the pseudoaneurysm, so that there is no collateral refilling of pseudoaneurysm. In our present series, we could not reach the pseudoaneurysm by endovascular route due to the reasons mentioned in Table 1. In all three cases, we attempted endoscopic ultrasound guided thrombin injection to treat these technically difficult pseudoaneurysms, after discussing with gastroenterologist experienced in EUS guided procedures. All these three pseudoaneurysms were easily visible on endoscopic ultrasound (Figure 2), which was performed prior to the thrombin injection for technical feasibility.

Technique of EUS guided thrombin injection

Gastroenterologist, who has got experience in EUS guided procedures, in collaboration with interventional radiologist performed this procedure. The procedure was performed without any anaesthesia. Initially EUS was performed using curved linear array transducer (Olympus-GF-UCT180) in conjunction with EVIS EXERA Ⅱ CLV-180 light source (Olympus Medical system Corp, Tokyo, Japan) was performed, pseudoaneurysm was localized and shortest path was chosen to target the pseudoaneurysm. We used the thrombin component of a Tisseel® kit (Baxter AG; Vienna, Austria), containing thrombin 500 IU/mL. Prior to targeting the pseudoaneurysm, thrombin component of Tisseel kit was reconstituted with 1 mL of calcium chloride and the reconstituted 1 mL thrombin was further diluted with normal saline to a total of 5 mL, so that each milliliter of reconstituted solution contains 100 IU of thrombin. Now, each milliliter of reconstituted thrombin was transferred to 1 mL insulin syringe and five such thrombin-loaded syringes were kept ready. Using 22G Echo Tip Ultra endoscopic ultrasound needle (Cook Medical Endoscopy, IN, United States), pseudoaneurysm was punctured under endoscopic ultrasound guidance, and then thrombin was injected in aliquots of 100 IU till the pseudoaneurysm become echogenic resulting in thrombosis. Under color Doppler, success of thrombosis was confirmed and the needle was removed when no color filling was seen inside the pseudoaneurysm sac. The entire procedure from start of localization of pseudoaneurysm to complete thrombosis of pseudoaneurysm lasted for about 15-20 min. After the procedure, patients were monitored closely for signs of internal bleeding. None of our patients developed any

Table 1 Demographic profile, clinical detail, angiographic and procedure details

Cases	Age/sex	Clinical presentation	Etiology of pancreatitis	Artery involved	Reason for angiographic failure	Amount of thrombin used	Follow up imaging	Figure No.
1	56/M	Pancreatitis with UGI bleed	Chronic alcoholic	Gastroduodenal artery	Previous surgical clipping	500 IU	Thrombosed	Figures 1-3
2	45/M	Pancreatitis with UGI bleed	Gall stone disease	Splenic artery	Not seen on DSA	300 IU	Thrombosed	Figures 4 and 5
3	30/M	Pancreatitis with UGI bleed	Gall stone disease	Splenic artery	Not seen on DSA	400 IU	Thrombosed	Figure 6

UGI: Upper gastrointestinal bleed; DSA: Digital substraction angiography; M: Male.

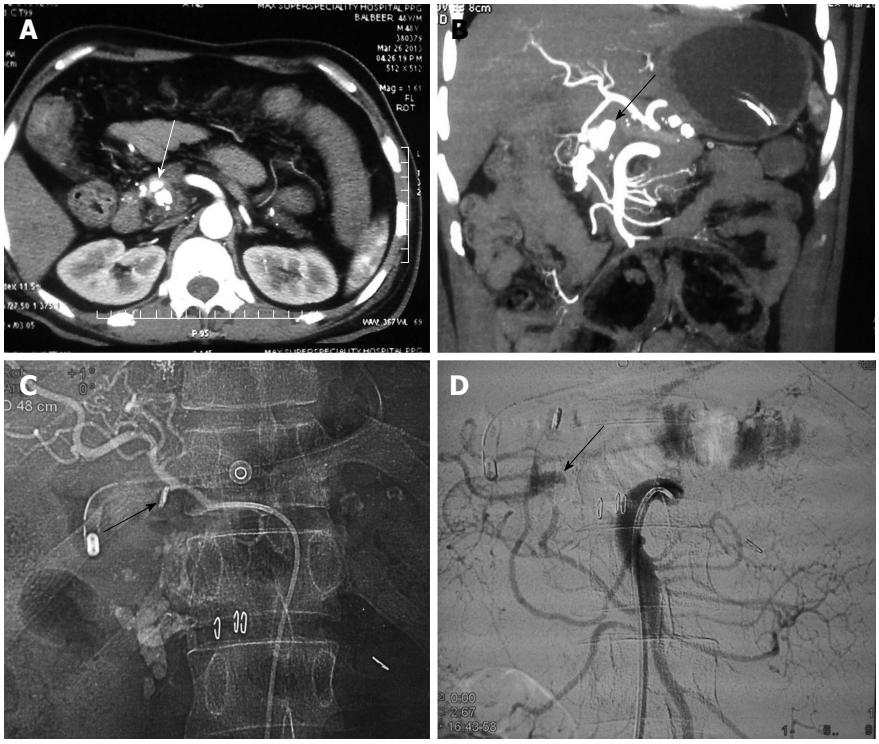

Figure 1 Chronic calcific pancreatitis with pseudoaneurysm of gastroduodenal artery (case 1). A: Axial Contrast enhanced; B: Coronal MIP (3-D reformatted) CT images; C: Angiographic spot image; D: Superior mesenteric DSA image. There is a pseudoaneurysm (arrow, A and B) arising from the gastroduodenal artery, which is filling from pancreatic arcade (Inferior pancreatic branches from SMA, D), because of metallic clip placed surgically at the origin of gastroduodenal artery origin (arrow, C). CT: Computed tomography; MIP: Maximum intensity projection; DSA: Digital substraction angiography; SMA: Superior mesenteric artery.

immediate or late complications. The next day, repeat EUS was done to reconfirm the success of the procedure. In one case we performed, CT angiography to confirmed the success of procedure (Figure 3). All three patients showed complete thrombosis of pseudoaneurysm on next day EUS. Clinical follow up was done after a month and none of these patients had recurrence of symptoms of bleeding.

DISCUSSION

Pseudoaneurysm formation is a known vascular complication of acute pancreatitis due to vessel injury as a result of proteolytic and lipolytic enzymes released due to severe inflammation and pancreatic necrosis[3].

The management of psuedoaneurysm in the setting of pancreatitis is challenging in view of the associated risk of rupture and haemodynamic compromise besides the background association of increased morbidity in pancreatitis itself. A diagnostic modality like CT angiography remains a preliminary imaging modality in acute pancreatitis. This provides a vascular road-map to the vessel of origin of the aneurysm besides adding vital information on the background pancreatitis.

DSA with coil embolization is the gold standard treatment. This offers the advantage of avoiding the associated surgical risks. Besides, it ensures adequate thrombosis of the pseudoaneurysm in most cases.

In situations where the access to the pseudoaneurysm is not possible due to previous clipping/tortuous anatomy (case 1) or not visible on DSA due to slow filling and narrow neck (Figure 4), angiographic coil embolization may not be feasible. Some pseudoaneurysms are occult and detected only with other imaging modality such as CT or endoscopic ultrasound, as seen in one of our case (Figure 5). If left alone, these pseudoaneurysms can rupture or rebleed. The risk of rupture in pancreatic pseudoaneurysms has been as high as 15%-40%[1].

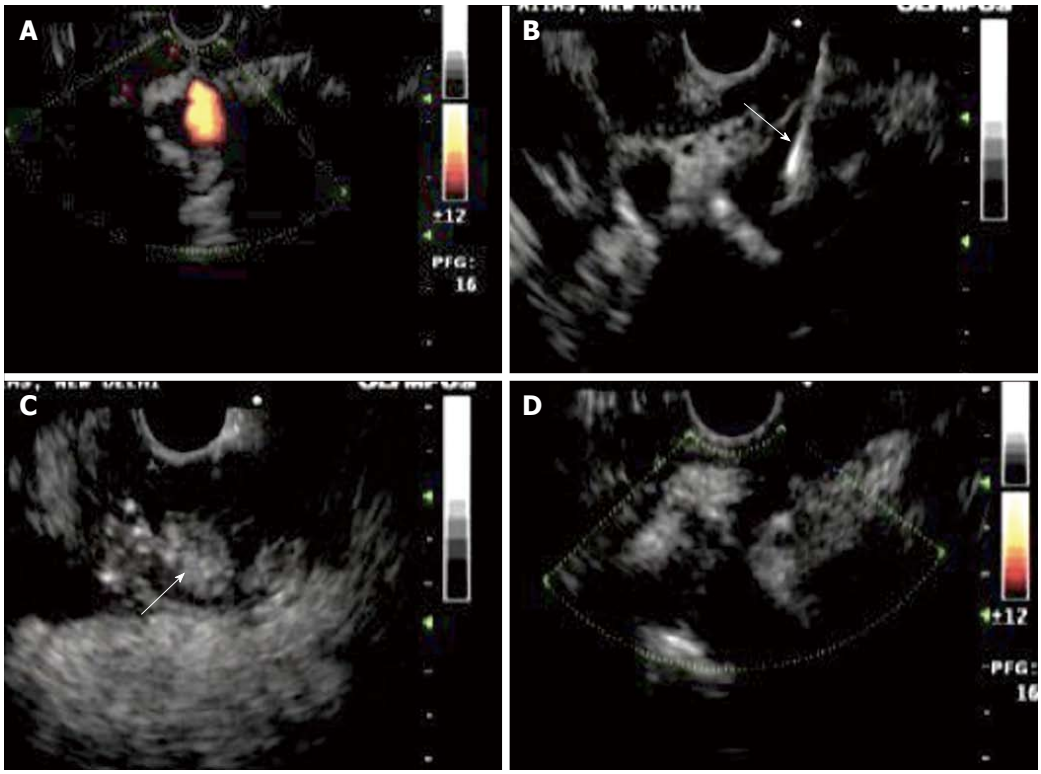

Figure 2 Endoscopic ultrasound guided thrombin instillation procedure (case 1). A-D: Endoscopic ultrasound images. There is a pseudoaneurysm sac (A) filling from pancreatic arcade (shown in Figure 1) with EUS needle (arrow, B) in the center of pseudoaneurysm sac with formation of echogenic thrombus (arrow, C) within the pseudoaneurysm sac following thrombin injection; D: No flow is seen within the pseudoaneurysm sac suggesting successful obliteration of pseudoaneurysm sac. EUS: Endoscopic ultrasound.

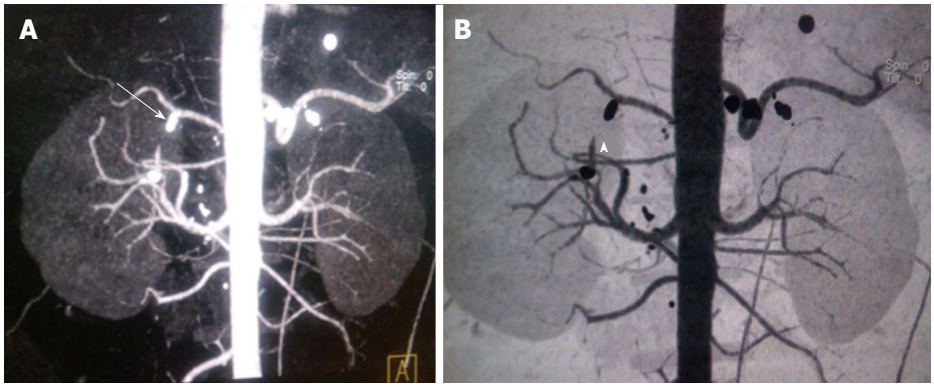

Figure 3 Follow up scan following thrombin injection procedure (case 1). A and B: Coronal MIP (3-D reformatted) CT images. There is non-visualization of the pseudoaneurysm sac (arrowhead, B) with metallic clip (arrow, A) seen at the gastroduodenal artery stump due to previous laparoscopic surgical clipping. CT: Computed tomography; MIP: Maximum intensity projection.

So, embolization is necessary to avoid rupture and rebleeding. Thrombin remains an alternative to coils. It can be instilled directly at the bleeding site and the flow cessation can be assessed. Thombin is a good alternative in those cases not feasible by endovascular route. The success of thrombin for embolization of peripheral pseudoaneurysms[4-6] as well as those of pancreas[7-10] have been described in literature.

Thrombin can be given through transcutaneous route through ultrasound or CT guidance. However, in our patients transabdominal ultrasound could not delineate the lesion clearly posing great challenge for thrombin instillation. EUS was the next step as most of these pseudoaneurysms were in the vascular territory in the vicinity of the peripancreatic region. The advantage of EUS lies in clearly delineating the extent and size of the pseudoaneurysm. Instillation of thrombin under EUS guidance requires a great deal of expertise. Thrombin could ensure immediate occlusion of pseudoaneurysms in all cases (Figure 6). Response assessment can also be done easily. The hallmark finding is the complete thrombosis of the pseudoaneurysm. No associated complications were noted. Follow up scans did not reveal rebleeding or rupture in our cases.

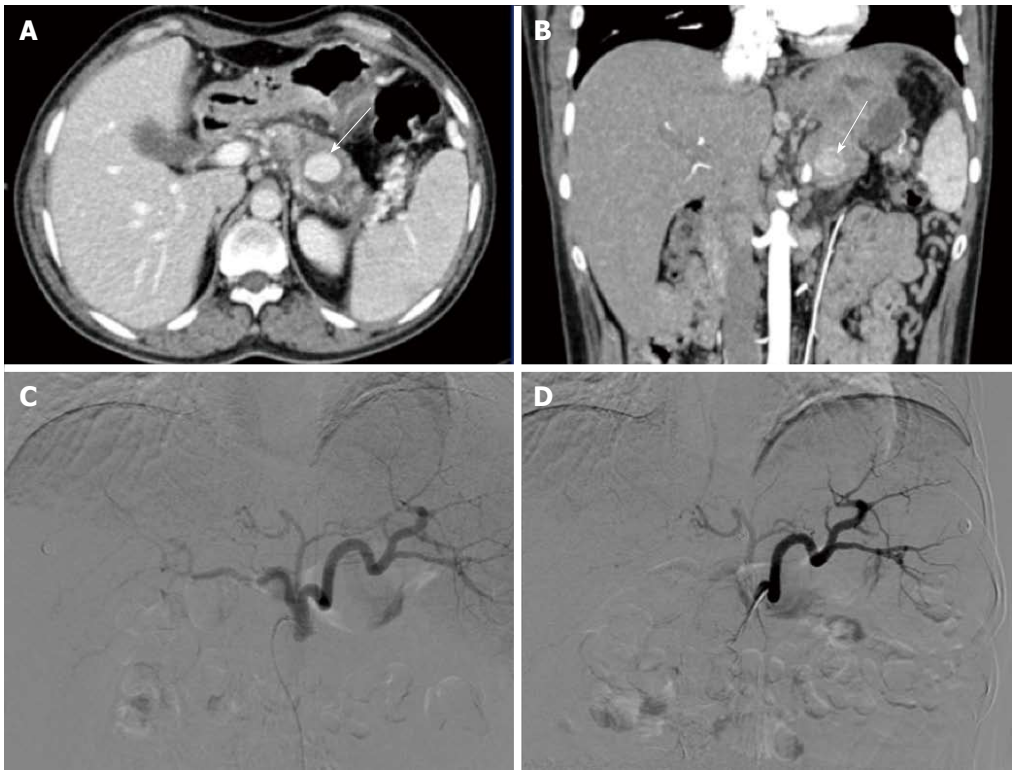

Figure 4 Pancreatitis related pseudoaneurysm (case 2). A: Axial contrast enhanced CT; B: Coronal maximum intensity projection CT images; C and D: Digital substraction Images. In the background of pancreatitis there is a pseudoaneurysm in the distal body of the pancreas (arrow, A and B) which was not revealed on either left gastric artery (C) or splenic artery (D) angiograms. CT: Computed tomography.

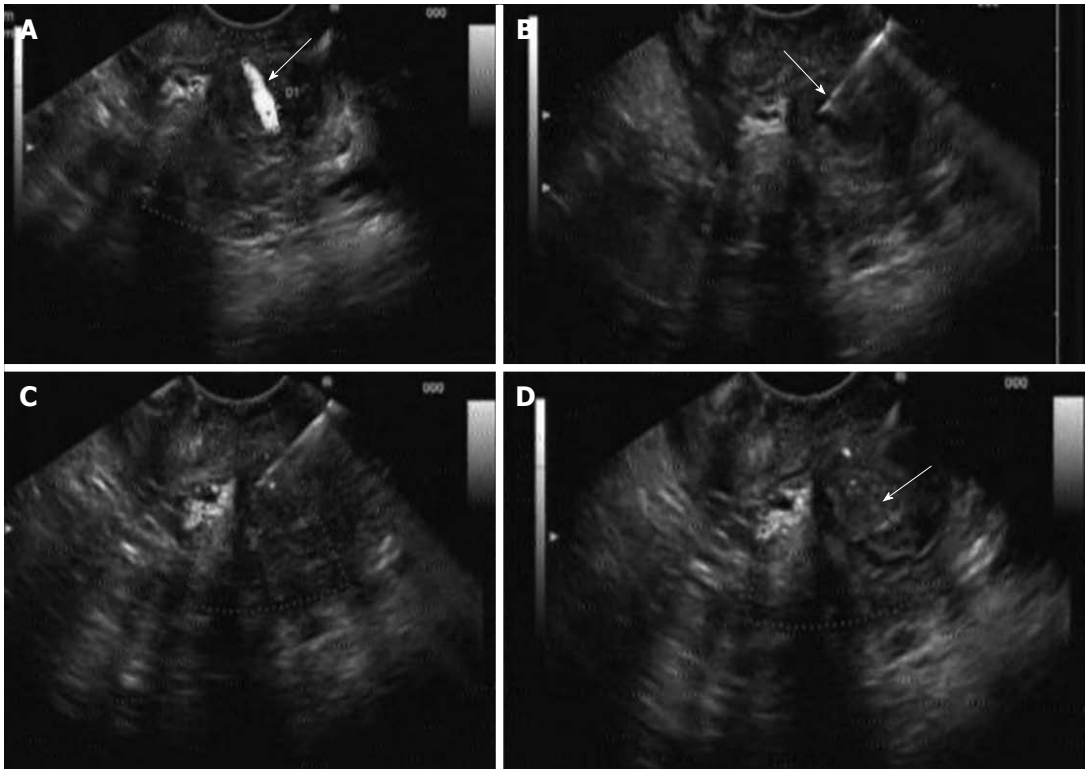

Figure 5 Endoscopic ultrasound guided thrombin instillation procedure (case 2). A-D: Endoscopic ultrasound images. There is a pseudoaneurysm sac (arrow, A) within pancreatic body region (A) with endoscopic ultrasound needle (arrow, B) inside the pseudoaneurysm sac, which was managed by instillation of thrombin (C) with subsequent thrombosis of the pseudoaneurysm sac as shown by echogenic pseudoaneurysm sac (arrow, D).

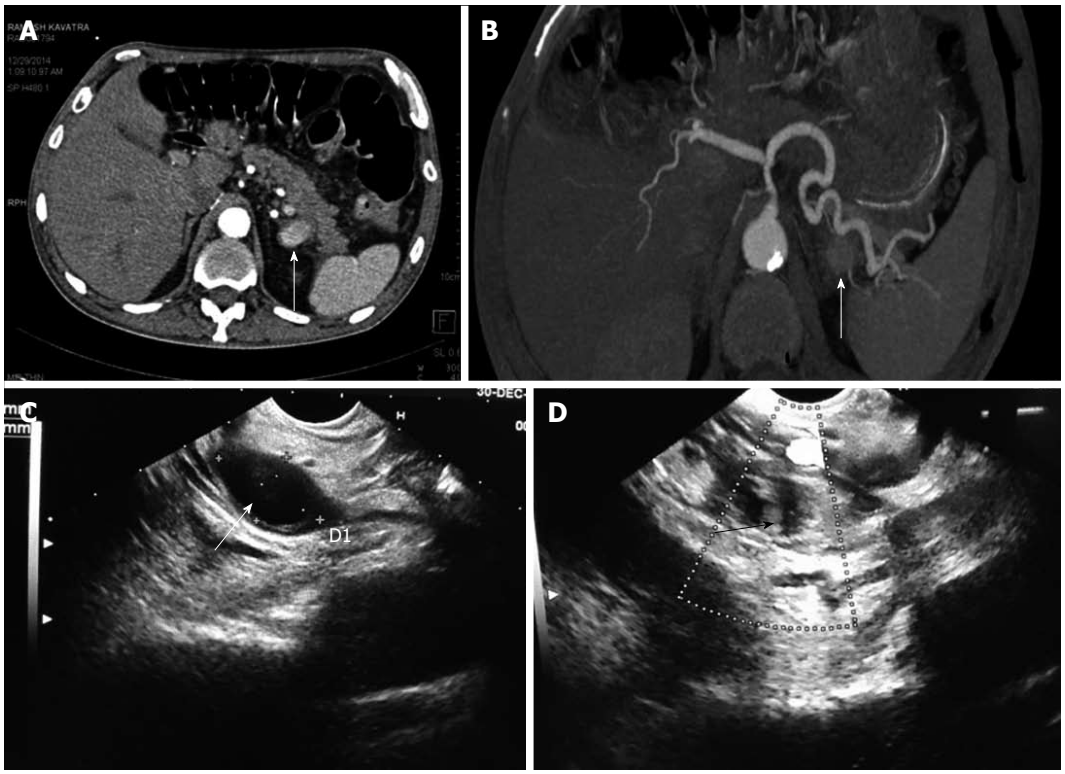

Figure 6 Chronic calcific pancreatitis with upper gastrointestinal bleed. A: Axial contrast enhanced; B: Axial MIP (3-D reformatted) CT images; C and D: Endoscopic ultrasound images. There is a pseudoaneurysm sac (arrow, A) in relation to distal body of the pancreas, in close relation to the splenic artery (arrow, B) and confirmed by endoscopic ultrasound (arrow, C) and subsequently managed by instillation of thrombin under EUS guidance with complete thrombosis of the pseudoaneurysm was achieved as revealed by the transformation of the previously anechoic lesion to an echogenic sac (arrow, D). CT: Computed tomography; MIP: Maximum intensity projection; EUS: Endoscopic ultrasound.

There are very few literature describing the use of EUS guided thrombin instillation of pancreatic pseudoaneurysm. In one of the earliest description Roach *et al*[11] described the EUS guided thrombin occlusion of a pseudoaneurysm arising from a branch of the superior mesenteric artery in a patient presenting with upper gastrointestinal bleed. This was done following failure to embolise angiographically as the feeding artery could not be catheterized.

Use of thrombin is recommended in cases of haemodynamically stable patients with small pseudoaneurysm[12]. Also it can be used in large lesions as an adjunct to coil embolization.

In haemodynamically unstable patients and those with large pseudoaneurysms or those with failure after repeated embolization, surgery remains the only option. But in the setting of pancreatitis, surgery is associated with a grim outcome. Non-invasive imaging modalities like ultrasound and CT have provided good alternatives as means of thrombin instillation. The advent of thrombin instillation through EUS guidance has opened an altogether new arena for managing the difficult pseudoaneurysms and thereby avoiding the surgical risks. Though one cannot undermine the expertise needed in EUS guidance, it offers a new hope to this special group of patients.

Some limitations of thrombin instillation, though rare, include risk of distal thrombosis though thrombin is rapidly diluted and inactivated by fast flowing blood stream[10]. Immunological reactions like sensitivities and cross-reactions are also known[10]. Recanalization after initial successful thrombosis of pseudoaneurysm is another complication. Lastly, the duration of follow-up required after treatment of pseudoaneurysms is not known.

The use of EUS guided thrombin instillation provides a new option for management of pseudoaneurysms caused by pancreatitis specially for those cohort of patients inaccessible angiographically or through transabdominal ultrasound. The avoidance of high risk surgeries, prompt occlusion of the pseudoaneurysm and ease of monitoring and follow-up are the hallmark features of this method though studies are needed to provide data as to efficacy of this method.

COMMENTS

Case characteristics

The three middle-aged male patients presented with similar symptom of upper gastrointestinal bleeding. One patient had surgical clipping of gastroduodenal artery.

Clinical diagnosis

Upon physical examination, all three patients were haemodynamically stable except for tachycardia. Pulse rates were in range of 110-120/min. No other

significant physical findings noted.

Differential diagnosis

Pancreatitis related bleeding pseudoaneurysm, variceal bleeding, peptic ulcer disease.

Laboratory diagnosis

All the patients had low hemoglobin level (range of 4-7 gm/dL). Upper gastrointestinal endoscopy showed blood clots within the stomach and duodenum. No active bleeding site could be seen on endoscopy.

Imaging diagnosis

All three patients had contrast enhanced computed tomography showed pseudoaneurysm arising from gastroduodenal artery (patient 1) and splenic artery (patients 2 and 3). There was evidence of surgical clip at the gastroduodenal (GDA) origin and chronic calcific pancreatitis in first patient.

Treatment

All the patients underwent digital substraction angiography. In first patient pseudoaneurysm could not be reached due to previous surgical clipping of GDA and tortuous collaterals feeding the pseudoaneurysm. In rest two patients, pseudoaneurysms were occult on angiography. All three patients were successfully managed by endoscopic ultrasound (EUS) guided thrombin injection in to the pseudoaneurysm.

Related reports

Thrombin injection into the iatrogenic related peripheral pseudoaneurysm is well known. Very few cases describing the use of EUS guided thrombin instillation of pancreatic pseudoaneurysm have been reported in literature. The advent of thrombin instillation through EUS guidance has opened an altogether new arena for managing the difficult pseudoaneurysms and thereby avoiding the surgical risks.

Term explanation

Thrombin (bovine/human), is available as powder form and is reconstituted with calcium chloride solution, injected into the pseudo aneurysm after direct puncture percutaneously under image guidance. Thrombin converts fibrinogen into fibrin resulting in formation of clots.

Experiences and lessons

This case series represents a new option of EUS guided thrombin instillation for management of pseudoaneurysms caused by pancreatitis especially for that cohort of patients where pseudoaneurysm is inaccessible angiographically.

Peer-review

This is an interesting paper highlighting a method of occluding pseudoaneurysms, which are otherwise difficult to reach.

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