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EDITORIAL

Performing colonoscopy in elderly and very elderly patients: Risks, costs and benefits

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Abstract

Many diagnostic and screening colonoscopies are performed on very elderly patients. Although colonoscopic yield increases with age, the potential benefits in such patients decrease because of shorter life expectancy and more frequent comorbidities. Colonoscopy in very elderly patients carries a greater risk of complications and morbidity than in younger patients, and is associated with lower completion rates and higher likelihood of poor bowel preparation. Thus, screening colonoscopy in very elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences. On the other hand, diagnostic and therapeutic colonoscopy are more likely to benefit even very elderly patients, and in most cases should be performed if indicated.

Key words: Colonoscopy; Elderly; Colon polyp; Colon cancer; Screening; Surveillance; Complications; Yield; Bowel preparation

Core tip: Although colonoscopic yield increases with age, the potential benefits in elderly patients decrease because of shorter life expectancy and more frequent comorbidities. Colonoscopy in very elderly patients carries a greater risk of complications and morbidity than in younger patients. Thus, colonoscopy in elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences.

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INTRODUCTION

Colonoscopy is currently the procedure of choice for whole colon evaluation in patients who present with lower gastrointestinal symptoms. In the United States, it is also the most effective and most commonly used modality for colorectal cancer (CRC) screening in asymptomatic individuals (with or without a family history), and for surveillance in patients with a personal history of adenomatous polyps, CRC or inflammatory bowel disease. Finally, in appropriate circumstances it is an important therapeutic procedure, allowing for biopsy of suspicious lesions, treatment of bleeding sources, placement of stents, and, most of all, removal of colorectal adenomatous polyps, thereby preventing the potential occurrence of CRC[1].

COLONOSCOPY IN ELDERLY PATIENTS

Because the incidence of colorectal pathology and symptoms increase with age, a large proportion of diagnostic, screening and surveillance colonoscopies are performed on "elderly" (defined as those > 65 years of age) and "very elderly" patients (> 80 years). In North America, the number of screening procedures in elderly patients has increased dramatically ever since many in-

surance programs, including medicare, began to cover screening colonoscopy in average-risk beneficiaries[2,3]. However, performing colonoscopy in elderly patients poses a unique set of challenges. In the elderly, the risks and benefits of colonoscopy should be carefully assessed in light of lower life expectancy and the frequent presence of co-morbidities, so as to ensure that the potential benefits outweigh the risks and morbidity. This review will discuss issues pertaining to the procedural yield, potential benefits, technical feasibility, complication risks, logistical difficulties and costs associated with performing colonoscopy in elderly and very elderly individuals.

YIELD

The procedural yield is the percentage of patients who are found to have clinically significant findings (especially neoplasia) on colonoscopy. Generally, the yield of colonoscopy increases with age[4]. According to Surveillance Epidemiology End Results (SEER) registry data as of 2007, the incidence of CRC is 120 cases per 100000 in persons aged 50-64 years of age, 186 per 100000 in those 65-74, and 290.1 per 100000 in those ≥ 75[5]. It is well established that elderly patients have a higher prevalence of colorectal neoplasia[6,7], as well as other findings such as diverticulosis and hemorrhoids. As with younger patients, symptomatic elderly patients demonstrate a higher yield than those who are asymptomatic[8].

Numerous studies have confirmed high yields for both screening and diagnostic colonoscopy in elderly patients (Table 1). The reported yield of CRC in symptomatic elderly patients has ranged from 3.7% to 14.2%[9-12]. In a study on 200 symptomatic octogenarians, 80% had colonoscopic findings that explained their symptoms[13]. Controlled studies that compared the yield in patients of different ages have echoed these findings. In one study on 1353 elderly patients, the risk of CRC development was higher in patients > 80 compared to those 70-74 years old[6]. In another study that included 915 symptomatic and screening patients, more advanced adenomas and invasive cancers were identified in 53 patients over the age of 80 than in younger controls[14]. Studies on European patients as well as minority groups in the United States have also reported similar results. A large study on 2000 English patients showed that compared with younger patients, those > 65 years old had higher overall diagnostic yields (65% *vs* 45%) as well as CRC prevalence (7.1% *vs* 1.3%)[15], while another study on 1530 African American and Hispanic patients showed that the CRC yield was significantly higher in those over 65 years of age than in younger counterparts (7.8% *vs* 1.8%)[16].

COMPLICATIONS AND ADVERSE EVENTS

One of the main concerns with performing colonoscopy on elderly patients is the potential for increased risk of complications. Adverse events are typically categorized as those occurring during or immediately after the procedure and those with a delayed presentation. Cardiopulmonary complications are the most common peri-procedural adverse events. The level of sedation, presence of comorbidities and procedure length and complexity all contribute to the risk and should be addressed to the extent known during pre-procedural planning, especially for elective colonoscopies.

Although early, small studies suggested that colonoscopy in elderly patients did not result in more complications[17], more recent, larger and better designed studies have shown convincingly that colonoscopy in the elderly is associated with more risk than in younger patients. As demonstrated by a recent meta-analysis, very elderly patients had a significantly higher rate of overall adverse events, including gastrointestinal bleeding and perforation[18] (Table 2). Studies from Asia have also reported higher risks of cardiovascular complications despite the fact that elderly patients on average received lower doses of sedatives[19].

Nevertheless, when taken in context, the complication rate is still quite low even for patients over 85 years of age, and in most cases colonoscopy can be done safely with appropriate monitoring and precautions[20]. Furthermore, several studies have shown that propofol sedation, despite its propensity to lower blood pressure, can be used safely in elderly patients[21-23]. The overall major

Table 1 Yield of colonoscopy in studies with subgroups of symptomatic and/or screening/surveillance "elderly" patients

Ref.	*n*	Age (yr)	Completion	Cancers	Adenomas/ polyps
Bat *et al*[10], 1992	436	80+	63%	14%	29.80%
Ure *et al*[48], 1995	354	70+	78%	6%	24%
Sardinha *et al*[49], 1999	403	80+	94%	4.50%	-
Clarke *et al*[12], 2001	95	85+	-	12.70%	-
Lagares-Garcia *et al*[50], 2001	103	80+	92.70%	11.60%	19.40%
Arora *et al*[51], 2004	110	80+	97%[1]	20%	-
Syn *et al*[9], 2005	225	80+	56%	11%	25%
Yoong *et al*[52], 2005	316	85+	69%	8.90%	14.20%
Karajeh *et al*[15], 2006	1000	65+	81.80%	7.10%	6%[2]

[1]Adjusted for non-traversable stricture; [2]Large polyps ≥ 1 cm in size.

Table 2 Complication risks based on data from meta-analysis by Day *et al*[18]

Age group (yr)	> 65	> 80
Cumulative adverse events	26.0[1] (25.0-27.0)	34.9[1] (31.9-38.0)
Perforation	1.0% (0.9-1.5)	1.5% (1.1-1.9)
Gastrointestinal bleeding	6.3% (18.0-20.3)	2.4% (1.1-4.6)
Cardiopulmonary complication	19.1% (18.0-20.3)	28.9% (26.2-31.8)
Mortality	1.0% (0.7-2.2)	0.5% (0.006-1.9)

[1]Per 1000 colonoscopies.

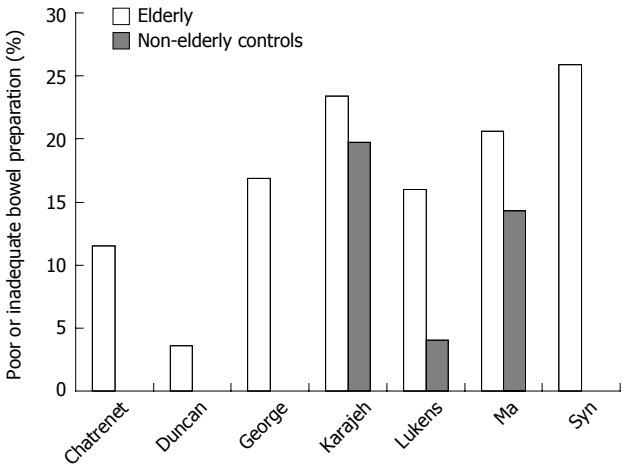

Figure 1 Published studies reporting rates of poor or inadequate bowel preparation for colonoscopy in elderly patients and non-elderly controls: Chatrenet[13], Duncan[11], George[53], Karajeh[15], Lukens[31], Ma[19] and Syn[9].

complication rate in patients over 80 is low, between 0.2% and 0.6%[11,15], although it increased with specific comorbid conditions[24]. A large retrospective study reported an overall perforation rate of 0.082% for adults undergoing colonoscopy, with advanced age as a significant predictor[25]. Studies in minority patients in the United States (African Americans and Hispanics)[16], as well as from Asia[26], have also reported that complication rates are low in elderly patients. When determining procedural risk, physiological age, *i.e.*, presence of comorbidities, is more important than chronological age. Thus, the overall health status of the patient should be considered, instead of relying on rigid age cutoffs.

During colonoscopy, the vital signs, oxygen saturation and cardiac rhythm of all patients should be monitored continuously. Supplemental oxygen is often administered if patients are sedated. Increasingly, capnography is being used to identify early signs of respiratory depression. Conscious sedation is achieved by the use of a short-acting sedative with amnestic properties, such as intravenous midazolam or diazepam, and an opioid analgesic, such as fentanyl or meperidine. The use of deep sedation with propofol, typically administered by an anesthesia provider, is becoming more popular in the United States. However, gastroenterologist-administered propofol has also been shown to be safe in the elderly[22].

Up to one third of patients may have minor side-effects after outpatient colonoscopy, most frequently bloating or abdominal cramps. Depending on their level of independence, elderly patients living alone may require additional post-procedure care. Post-procedure calls within 48 h by medical staff may be helpful.

Many elderly patients have implanted cardiac pacemakers or defibrillators. The use of monopolar electrocautery during snare polypectomy can cause pacemaker inhibition or false detection of cardiac arrhythmias[27]. Thus, these devices are generally inactivated during the colonoscopy.

COLONOSCOPY COMPLETION RATES

Complete colonoscopy requires cecal intubation or, for those who have had an ileocecectomy, reaching the ileocolonic anastomosis. In the United States, studies on patients of all ages undergoing elective screening or surveillance colonoscopy report high completion rates above 95%[28]. Studies on symptomatic patients (including those with non-traversable obstructing lesions) report completion rates of around 83%[29].

Colonoscopy in the elderly is technically more challenging than in younger patients because of various factors, including more extensive diverticulosis, higher incidence of tortuosity or post-surgical adhesions, and higher risk of complications[4]. Elderly patients are also less likely to tolerate large amounts of sedation, and have a higher probability of suffering inadequate bowel preparation[13,30,31], both of which can preclude complete colonoscopy.

A wide range of completion rates in elderly patients have been reported, including 56% (this included 8 obstructing lesions that could not be traversed)[9], 63% (on the first attempt) or 89% (second attempt)[10], 83.5%[13], and as high as 88.1% (for patients > 73 years old)[30]. For patients in their late 60's, the completion rate was quite respectable at 90.3% in one study[16], while a prospective study reported an "endoscopic success rate" of 90% for octogenarians[31]. Overall, a meta-analysis showed that for elderly patients > 65 years of age, the mean completion rate was 84%, while for those > 80, the completion rate was 84.7%[18]. Many of the studies that directly compared completion rates between elderly patients and younger controls showed a significant difference in favor of the younger group[16,31,32].

BOWEL PREPARATION ISSUES

In a previous meta-analysis of 20 studies, suboptimal bowel preparation was documented in 18.8% of patients > 65 years of age, and in 12.1% of those > 80[18]. As summarized in Figure 1, elderly patients have a higher likelihood of poor bowel preparation due to slower colonic transit and higher incidence of obstipation[4,33]. Inadequate bowel preparation was a big factor in many studies that demonstrated lower colonoscopy completion rates in older patients[13,30,31]. The most commonly used bowel preparation regimen, 4 L of pegylated ethylene glycol, represents a substantial ingestion volume for elderly patients, who are also more likely to have renal, cardiac or hepatic conditions that make them ineligible for small volume alternative osmotic laxatives, such as sodium sulfate or sodium picosulfate. Moreover, frequent trips to the commode constitute a fall risk for the frail elderly patient with mobility issues.

DECISION ANALYSES

Several decision analysis studies have addressed the costs,

Table 3 Outcomes for 1244 individuals who underwent screening colonoscopy; classification is according to the most advanced lesion for each patient[41]

Age group (yr)	*n*	Patients with advanced neoplasia	Mean life-expectancy (yr)	Mean polyp lag time[2] (yr)	Mean LE extension (yr)	Adjusted mean LE extension
50-54	1034	33[1] (3.2%)	28.87	5.23	0.85	2.94%
75-79	147	7 (4.7%)	10.37	5.44	0.17	1.64%
80+	63	9[3] (14%)	7.59	3.58	0.13	1.71%

LE $_{extension}$: Extension of life expectancy due to screening colonoscopy. Adjusted LE $_{extension}$ (%) = (LE $_{extension}$/LE) × 100. [1]Includes one patient with high grade dysplasia and two patients with cancers; [2]These values are calculated only for patients with neoplastic findings, not the entire group; [3]Includes two patients with high-grade dysplastic polyps and one with cancer.

risks and benefits of colonoscopy in elderly patients. The potential for screening-related complications was greater than the estimated benefit in some population subgroups aged 70 years and older. At all ages and life expectancies, the potential reduction in mortality from screening outweighed the risk of colonoscopy-related death[34]. In another study, a patient with no familial risk factors with negative colonoscopy at age 50, 60 or 70 is less likely to benefit from additional screening colonoscopy compared to a 75 years old individual with no antecedent screening. Furthermore, an individual in superb health at age 80 may benefit from colonoscopy whereas a patient with prior low risk adenomas but moderate to severe health impairment is unlikely to benefit from colonoscopy even at age < 75. Upfront investment in screening and polypectomy in younger persons may decrease ultimate CRC-related costs, including subsequent screening and surveillance, for older Americans. While these savings could potentially be offset by future health costs for other diseases in the elderly, screening 50 years old persons would still be cost-effective[35].

EQUIPMENT AND LOGISTICAL ISSUES

Colonoscopes and accessories are the same for elderly patients as their younger counterparts, although some endoscopists favor pediatric colonoscopes because the more flexible shaft can facilitate passage in the presence of tortuosity or diverticulosis. All patients undergoing sedation need an adult escort after the procedure, potentially posing a burden on some elderly individuals living in social isolation.

OVERVIEW: SCREENING COLONOSCOPY IN ELDERLY PATIENTS

In the absence of additional risk factors such as family history, the prevailing consensus is to begin screening at age 50 and to continue at intervals determined by the screening modality used, as well as any history of adenomatous polyps or cancer. Currently, all three major United States gastroenterology societies (American Gastroenterological Association, American Society of Gastrointestinal Endoscopy, and American College of Gastroenterology), the American Cancer Society and the United States Preventive Services Task Force (USPSTF) have endorsed screening colonoscopy beginning at age 50 for average risk patients, with subsequent intervals of every 10 years in the absence of any personal history of adenomas or family history of CRC[36-39]. However, the USPSTF is the only body to recommend discontinuation of screening in average-risk individuals at age 75[39]. In a publication on colonoscopy developed by the American Gastroenterological Association for the American College of Physicians "Choosing Wisely" Campaign to control health care costs, it is stated that "routine (colonoscopies) usually aren't needed after age 75."

There is concern that continued screening in very elderly individuals is associated with diminishing utility and increasing costs, morbidity and risks to both individual and society. Life expectancy in light of advanced age and co-morbidities should be considered when considering screening in very elderly persons. Screening may not be warranted in asymptomatic patients for whom detecting and removing precancerous polyps would be unlikely to change their long term survival. Moreover, elderly patients who have been screened often incur frequent early repeat colonoscopies, leading to additional risk, morbidity and cost[40].

In a previous study using Declining Exponential Approximation of Life Expectancy analysis, we found that the prevalence of neoplasia was 13.8% in 50-54 years old patients, 26.5% in the 75 to 79 years old group, and 28.6% in the group aged 80 years or older. Despite higher prevalence of neoplasia in elderly patients, estimated mean extension in life expectancy was much lower in the group aged 80 years or older than in the 50 to 54 years old group (0.13 years *vs* 0.85 years). Even though prevalence of neoplasia increases with age, screening colonoscopy in very elderly persons (aged ≥ 80 years) results in only 15% of the expected gain in life expectancy in younger patients (Table 3)[41]. In a similar study, the survival of elderly patients undergoing colonoscopy was significantly lower than that for younger patients, with important screening implications[42]. Another decision analysis also showed that the benefits of screening were outweighed by screening-related complication risks in subgroups of patients over 75, especially if they were in poor health[34]. Surveys have shown that providers do incorporate age and comorbidity in screening recommendations; however, their recommendations were often inconsistent with guidelines[43]. Other factors come into

play when screening decisions are made; for example, elderly patients of low socioeconomic class were less likely to be screened for CRC regardless of insurance status[44].

OVERVIEW: DIAGNOSTIC COLONOSCOPY IN ELDERLY PATIENTS

Many gastrointestinal conditions, such as constipation, incontinence, diverticulosis and hemorrhoids, are more common with advancing age. CRC is much more common in symptomatic patients over 65 than in younger controls, with a risk ratio as high as 17[45]. In all patients with colorectal symptoms, colonoscopy is usually the preferred diagnostic test for whole colon evaluation and has supplanted barium enemas and sigmoidoscopy. Direct visualization of the colonic mucosa can be extremely useful for the diagnosis of colitis and confirmation of polyps or masses. Of course, colonoscopy also allows for histologic assessment through biopsies. Certainly any elderly patient without prior colonoscopy who presents with significant new colorectal symptoms should be offered diagnostic colonoscopy.

One of the most common colorectal symptoms leading to hospitalization is lower gastrointestinal bleeding. With advancing age there is an increased incidence of bleeding from diverticulosis, arteriovenous malformations, malignancy, ischemic colitis, radiation colitis and ano-rectal lesions. When feasible, colonoscopy is the best diagnostic test and may offer therapeutic options. In elderly hospitalized patients, completing a 4 L polyethylene glycol preparation can be difficult; sometimes placement of a nasogastric tube is required. As an alternative diagnostic modality, the technetium red blood cell scan can localize active bleeding, while angiography is another diagnostic option, and like colonoscopy offers therapeutic possibilities.

OVERVIEW: THERAPEUTIC COLONOSCOPY IN ELDERLY PATIENTS

Colonoscopy offers a variety of therapeutic options to control bleeding, remove polyps and small tumors, and relieve colonic obstruction due to benign or malignant strictures; these maneuvers are especially useful in elderly patients because they may obviate the need for surgery. However, small polyps may not need to be removed because the relative complication risk is high and the benefit is probably low[41].

For bleeding patients, endoscopic hemostasis can be achieved using epinephrine injection, thermal or electrocoagulation, or deployment of clips. Polypectomy is performed in the same manner independent of age, *i.e.*, small polyps are removed with cold snare polypectomy or biopsy forceps, larger polyps are removed with snare polypectomy with monopolar coagulation, and flat or sessile polyps are removed after saline submucosal injection, perhaps supplemented by argon plasma coagulation. With increasing age, large and flat polyps are more common. Benign colonic strictures may be seen in patients with a surgical anastomosis, or in the presence of chronic ischemic colitis, inflammatory bowel disease or diverticulitis. In such patients, endoscopic dilation can be attempted under fluoroscopic observation. Malignant strictures are at greater risk of perforation with dilation. In selected patients with colonic malignancy who are not surgical candidates or who need preoperative decompression, self-expanding stents can be placed across the obstruction. Studies on endoscopic mucosal resection and endoscopic submucosal dissection have included small numbers of elderly and very elderly patients, showing that these procedures are possible even in advanced age, although there are significant complication risks similar to those seen in younger patients[46,47].

CONCLUSION

Colonoscopy in very elderly patients (over 80 years of age) carries a greater risk of complications, adverse events and morbidity than in younger patients, and is associated with lower completion rates and higher chance of poor bowel preparation. Although colonoscopic yield increases with age, several studies have suggested that the potential benefits are significantly decreased because of shorter life expectancy and greater prevalence of comorbidities. Thus, screening colonoscopy in very elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences. Diagnostic and therapeutic colonoscopy are more likely to benefit even very elderly patients, and in most cases should be performed if indicated.

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REVIEW

Colonoscopy, pain and fears: Is it an indissoluble trinomial?

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Abstract

Colonoscopy is the reference method in the secondary prevention, diagnosis and, in some cases, treatment of colorectal cancer. It can often cause pain associated with embarrassment, anxiety, and physical and emotional discomfort. Pain intensity is influenced by a lot of factors, and there is a strict relationship among pain, pain perception, and mind. Several methods can be used to break the trinomial colonoscopy, pain and fear. Sedoanalgesia is recommended by several guidelines. If no sedation is offered, the patient must accept a higher chance of unacceptable discomfort and the endoscopist a lower chance of completing the procedure because of patient discomfort. Other non-pharmacologic methods such as acupuncture, music, and hydrocolonoscopy can be used as alternatives to pharmacologic sedoanalgesia. Furthermore, new endoscopic technologies such as variable-stiffness colonoscopes and ultrathin colonoscopes, or the use of carbon dioxide instead of air for colon insufflation, can reduce the pain caused by colonoscopy. In the future, technical improvements such as wireless capsules or robotic probes, will probably enable to overcome the present concept of colonoscopy, avoiding the use of traditional endoscopes. However, at present the poor attention paid by endoscopists to the pain and discomfort caused by colonoscopy can not be justified. There are several methods to reduce pain and anxiety and to break the trinomial colonoscopy, pain and fear. We must use them.

Key words: Colonoscopy; Pain; Fear; Anxiety; Discomfort; Conscious sedation

Core tip: Colonoscopy can often cause pain associated with embarrassment, anxiety, and physical and emotional discomfort. Control of discomfort and pain during colonoscopy is considered to be a high priority by patients. This review of the literature encompasses the main methods for reducing pain and anxiety, to break the trinomial colonoscopy, pain and fear.

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INTRODUCTION

At present, colonoscopy is the reference method in the secondary prevention, diagnosis and, in some cases, treatment of colorectal cancer[1,2]. For this reason, and as a consequence of the improvement of both imaging techniques (for instance, magnification) and interventional procedures (ESD), and the screening programs for the colon cancer prevention that are ongoing in many countries, the annual number of colonoscopies is strongly increasing. However, colonoscopy is considered highly invasive and is usually assumed to be an uncomfortable and often painful procedure. These concerns can result in anxiety that unfavourably decreases patient cooperation and satisfaction with the procedure[3]. Therefore, analgesia and sedation are frequently used. The decision to use premedication and the kind of premedication are influenced by national and cultural differences among

countries[4,5]. Moreover, there is a wide variation in colonoscopy practice also among centers in the same country[6], probably caused by the poor attention paid to the pain control during invasive procedures[7].

However, the fear of experiencing pain during colonoscopy can cause the patient refusal to undergo the examination, with possible negative implications on both diagnosis and treatment. Several studies showed that fear of being embarrassed or fear of pain during colonoscopy were positively associated with unwillingness to participate in colorectal cancer screening[8,9].

Therefore, it is quite evident that colonoscopy, pain and fear (of being embarrassed during colonoscopy, of experiencing pain, of having cancer, *etc.*) are strictly linked together, and only reducing the procedure-related patient discomfort can break such a trinomial, making colonoscopy more accepted with increase of the diagnostic yield.

In this review, we will discuss the relationship among fear, anxiety, and pain, as well as the ways of breaking the trinomial colonoscopy, pain, and fear.

RELATIONSHIP AMONG PAIN, FEAR, AND ANXIETY

All invasive procedures can cause pain associated with embarrassment, anxiety, and fear. Such a situation was defined by Morrison as "discomfort"[10]. Discomfort can be physical (malaise and trouble due to the duration of the procedure, need to maintain an uncomfortable position, or need to remain motionless for a long time); or emotional (embarrassment of showing the body, anxiety and fear of experiencing pain, anxiety and fear of an unfavorable diagnosis). Pain intensity during an invasive procedure varies according to patient compliance, and is influenced by a lot of factors, such as previous experience, pre-existing pain and/or chronic pain, presence of fear or anxiety, type and duration of the procedure, and related expectation of pain[10,11]. There is a strict relationship among pain, pain perception, and mind, and mind-body medicine can examine interactions as they occur among the brain, mind, body, and behavior[12]. Mind can be defined as "conscious and unconscious thought patterns, including images, perceptions and intentions, generated by a functional network of distributed neural centers in the brain and body, including homeostatic representations that provide the context for human self awareness and emotional experience"[12]. An expanding evidence base reveals that the limbic system (in particular the amygdala) has the capacity to up- or down-regulate pain's emotional response[13].

Fear represents a normal emotional response to a threat that is true, or is recognized as true by the individual (*i.e.*, fear of colonoscopy and related pain). Conversely, anxiety is an irrational state of mind, characterized by a sensation of uncertainty and inadequacy and often associated with neurovegetative symptoms (such as tachycardia, hypertension, tachypnea, shakes, and so on), and can become a pathological and distressing condition[14].

Pain can cause both immediate and long-term harmful effects. The effects of acute procedural pain consist of a variety of physical, emotional, behavioral, cognitive, and psychological manifestations, including fear, anxiety, anger, aggressive behavior, inability to concentrate, embarrassment, refusal to consent to further procedures, and distrust of the health care team, and may effect overall economic, social, and spiritual well-being[15-17]. For these reasons, a recent position statement on the procedural pain management recommends the use of anxiolytic drugs associated with analgesics to manage the pain related to medical procedures. Furthermore, methods of non-pharmacologic management are also recommended during all phases of the procedures[18].

Patient experience is a critical aspect of medical procedures, in particular of endoscopic procedures. Patients with favorable endoscopy experience are more likely to comply with medical advice, adhere to screening and use medical service in the future, whereas patients with poor experience are more likely to leave their care provider and be less compliant[19].

A systematic review of literature showed that the control of discomfort and pain during the colonoscopy was considered to be a high priority by patients[20].

Given the mind's ability to influence the pain perceived during colonoscopy, acting on the pain and/or patient's discomfort is mandatory to break the trinomial "colonoscopy, pain and fears".

SEDOANALGESIA AND OTHER METHODS TO REDUCE PAIN

Sedoanalgesia practices

The use of sedoanalgesia by administering *iv* drugs for lower gastrointestinal endoscopic procedures is strongly recommended by several guidelines. If no sedation is offered, the patient must accept a higher chance of unacceptable discomfort and the endoscopist a lower chance of completing the procedure because of patient discomfort[21]. However, the use of sedation for lower gastrointestinal endoscopic procedures is considerably influenced by the cultural differences among countries and the rules which regulate the drugs use[4,5].

Propofol deep sedation is frequently used in some countries, whereas in other ones conscious sedation induced by means of a combination of a benzodiazepine and an opioid is more frequently used[22-24]. Recently, a new option for sedation has been approved by the Food and Drug Administration. It is a Computer Assisted Personalized Sedation system called the SEDASYS® System (Ethicon Endo-Surgery, Inc., Cincinnati, OH, United States), that is indicated for the intravenous administration of Propofol for the initiation and maintenance of minimal to moderate sedation for ASA I or II patients undergoing endoscopic examination. Although the intention of this approval is to cut the anesthesia related

expenses, at present this system is scarcely used. Consequently, in many countries-such as Italy-moderate sedation using benzodiazepine (like Midazolam) and an opioid (like Pethidine), is the most popular method of sedation, although the use of Propofol is progressively increasing, because the satisfaction of both patients and endoscopists is greater. Moreover, recovery and discharge times are shorter with the use of Propofol[25,26].

Several other drugs can be used for colonoscopy sedation, such as Alfentanyl, Fospropofol, Remifentanil, Remimazolam[5]. However, some of these drugs are still scarcely used, because they have been marketed quite recently, and can be only used by anaesthetists.

The optimal sedative for colonoscopy should be short acting, safe, easy to administer, and with minimal side effects, but this sedative is yet to be found. In this perspective, the use of nitrous oxide gas as an alternative method to *iv* sedoanalgesia for colonoscopy appears quite interesting and promising. Two systematic reviews suggest that nitrous oxide gas provides comparable analgesia with the advantage of a shorter recovery time and greater safety than *iv* analgesia-sedation methods used during colonoscopy[27,28].

However, all sedoanalgesia methods can cause adverse cardio-respiratory events, even though the incidence of serious adverse events is low with all currently available agents[29]. Some other methods that do not require the *iv* administration or the inhalation of drugs are reported in the literature to reduce patient's discomfort and to increase the acceptability of the examination.

Acupuncture

The use of this ancient technique displayed several effects on gastrointestinal tract, and a United States National Institute of Health consensus statement published in 1998 indicated that acupuncture might be useful for the treatment of certain pain conditions[30].

In 2003, Fanti *et al*[31] conducted a randomized placebo-controlled study to evaluate the analgesic effect of electro-acupuncture in a group of patients who were undergoing colonoscopy. They found that patients in the acupuncture group reported not significantly reduced pain during the procedure. Some years later, Ni *et al*[32] reported a randomized study on two groups of 40 patients undergoing colonoscopy. In the first group, acupuncture was performed in the traditional points ST 36, ST 37, SP 9, SP 6, LI 4 from 30 min before colonoscopy to the end of the procedure; in the latter group no treatment was performed. Cecum was reached significantly more frequently, and discomfort resulted less marked, in the patients who underwent acupuncture. The same authors reported similar results in a subsequent study, in which they also observed lower plasma concentrations of beta-endorphin in the patients treated with electro-acupuncture, confirming a meaning attenuation of the patients' stress response during colonoscopy after electro-acupuncture[33].

However, on the basis of these data and some few other studies with conflicting results, currently available data do not support the use of acupuncture as an analgesic adjuvant during colonoscopy[34].

Audio distraction

Listening relaxing music during pain-invoking experience is considered to have a therapeutic effect, as it promotes relaxing responses, triggers positive associations, and diverts attention from anxiety[35]. For this reason, music has been used to decrease anxiety levels in patients in a variety of scenarios, such as digestive and bronchial endoscopy[36,37]. However, the studies published in the literature are very heterogeneous as concerns either the type and design of the study, or the type of music used (classical, easy-listening, relaxing, Turkish classical music, *etc*.). Moreover, also the results are often conflicting.

From 2007 to 2009 three meta-analyses were published on this topic. The first of them included six randomized controlled trials that involved 641 patients undergoing esophagogastroduodenoscopy, flexible sigmoidoscopy or colonoscopy, with or without intervention through music therapy. This meta-analysis yielded significantly lower anxiety levels, reduction in analgesia requirements, reduction in sedation requirements, and procedure times in patients receiving music therapy in comparison with controls[38].

The second meta-analysis dealt with the effect of music on procedure time and sedation during colonoscopy. Eight randomized controlled trials for a total of 722 patients enrolled were included into the meta-analysis, that concluded that music is effective in reducing procedure time and sedative requirement during endoscopic examination[39].

Also the third meta-analysis dealt with the effect of music during colonoscopy[40]. One hundred and seven articles were examined, but just 8 randomized controlled trials for a total of 712 patients enrolled met the inclusion criteria. Music played during colonoscopy was shown to improve patients' overall experience, but it did not alter other parameters, such as sedative pain medication requirements, procedure times, patients' pain, and patients' willingness to repeat the same procedure in the future.

Finally, Lee *et al*[41] designed a prospective randomized controlled trial to test the hypotheses that visual distractions could reduce the requirement for sedatives during colonoscopy, and that the combination of audio and visual distractions could have additive beneficial effects. One hundred and sixty-five patients were randomly allocated into three groups to receive different modes of sedation: visual distraction plus sedation, audio-visual distraction plus sedation, sedation alone. Visual distraction alone did not decrease the dose of sedative medication required for colonoscopy. When audio distraction was added, both the dose of sedative medication required and the pain score decreased significantly.

Hydro-colonoscopy and other substances instilled into the colon

Historically, air insufflation was used to advance the

colonoscope through the colon. In 1984, Falchuk and Griffin[42] described a water technique that facilitated colonoscopy in patients with severe diverticular disease. Fifteen years later, a prospective randomized study on 100 unsedated patients undergoing colonoscopy showed that the passage through the left colon was significantly faster with the water intubation method than with the traditional method[43]. Afterwards, several studies investigated the usefulness of this technique, based on the assumption that the instillation of water at 37 ℃ into the colic lumen could minimize colon spasms, reducing pain and maintaining the same efficacy of air in reaching the cecum. The water weight would enable to enlarge the lumen without stretching the colon walls. However, this technique requires a thorough colon cleansing to allow a good visualization of the lumen.

In 2012, a systematic review and meta-analysis of randomized controlled trials on hydro-colonoscopy examined nine studies for a total of 1283 patients enrolled. Warm water infusion resulted less painful than standard air insufflation, reducing the need for sedation/analgesia, and improving patient acceptance of colonoscopy[44].

Some authors proposed also the corn seed oil assistance in colonoscopy. Theoretically, warm water is thought to decrease spasm of the colon and straighten the sigmoid colon due to the gravity of water when the patient is in the left decubitus. On the other hand, oil lubrication decreases the friction between the colonic mucosa and the shaft of the scope, but it is devoid of the aforementioned effects by warm water. Brocchi *et al*[45] performed two prospective, randomized and controlled studies comparing the oil method with a standard technique in one[46] and with a warm water technique in the other. The results of the two studies were similar and consistent with a favorable effect of the oil technique on successful intubation to the cecum, level of patient pain, and degree of difficulty during colonoscopy.

Beside warm water and corn seed oil, other substances have been instilled into the colon to reduce spasms. Peppermint oil has a satisfactory spasmolytic effect on the smooth musculature of colon. Asao *et al*[47] instilled a solution of peppermint oil through the accessory channel of the colonscope in 409 patients undergoing colonoscopy. About twenty seconds later, they documented a relaxation of the musculature that lasted about twenty minutes. Finally, Ai *et al*[48] evaluated the antispasmodic effect of the Chinese herbal medicine Shakuyaku-kanzoto (TJ-68) on the colonic wall by direct spraying during colonoscopy. TJ-68 is an extract powder composed of Shakuyaku (*Paeoniae radix*) and Kanzo (*Glycyrrhizae radix*) combined at a ratio of 1:1, and inhibits acetylcholine-induced contraction and the contractile machinery of the smooth muscle.

The authors conducted a randomized study on 101 patients, and concluded that direct spraying of TJ-68 on the colonic mucosa suppressed colonic spasm. However, the effectiveness use of TJ-68 has been evaluated in just few studies, and there are no systematic reviews and meta-analyses supporting its actual clinical usefulness.

NEW ENDOSCOPIC TECHNOLOGIES FOR COLON EXAMINATION

Fixed, angulated sigmoid colons or long, floppy colons are the main causes of both the difficulty of reaching the cecum and the pain experienced by the patient. Several studies have been designed to evaluate the use of pediatric colonoscope for colonoscopy in adults, based on the assumption that the pediatric colonoscope could provide greater comfort in adult patients, because of its smaller diameter and greater flexibility. The results of these studies showed that the pediatric colonoscope is suitable for colonoscopy in adult, and is also useful in patients in whom colonoscopy with the adult colonoscope is unsuccessful in reaching the cecum[49]. Furthermore, ultrathin colonoscopes (diameter 9.2 mm) are available today, and theoretically they should allow for a further reduction of the pain experienced by the patient. However, at present there is no evidence about such an assumption. Moreover, an initial "learning curve" is needed in using these colonoscopes for endoscopists used to an adult colonoscope, because the ultrathin tool is quite less stiff, and more pull-back maneuvers are required during the examination.

The need of flexibility must often be balanced with the need of stiffness, to avoid the risk of creating loops in the mobile tracts of the colon. In the last years, variable-stiffness colonoscopes have become available in both adult and pediatric classes. These new tools have a stiffness control ring that allows to modify the flexibility during the examination, reducing the risk of creating loops in the left tract of the colon, and allowing for a higher cecal intubation rate with less abdominal pain, according to the conclusion of a meta-analysis of randomized controlled trials published in 2009[50]. However, the results of the comparison between variable-stiffness colonoscope and standard adult colonoscope are conflicting. In another meta-analysis, Xie *et al*[51] concluded that variable-stiffness colonoscope significantly improved the cecal intubation, but cecal intubation time was similar for the two colonoscope types (standard and variable-stiffness colonoscopes). Moreover, the sedation dose used with the two types of instrument resulted similar; and no difference in pain scores for patients could be demonstrated, because of the differences in the scale used in the selected studies.

Insufflation of the bowel is necessary to improve visualization during colonoscopy, but it is one of the main causes of the abdominal pain experienced by the patient. It is common practice to use ambient atmospheric air, also termed "room air", to insufflate the lumen. However, the safety of carbon dioxide (CO_2) insufflation during colonoscopy is well known starting from 1974[52]. CO_2 is more rapidly absorbed from the bowel than room air, allowing for a more rapid intestinal decompression

and potentially decreasing intraprocedural and postprocedural pain. Many studies evaluated the safety and efficacy of CO_2 insufflation for gastrointestinal endoscopy. Two recent systematic reviews and meta-analysis showed that CO_2 insufflation is safe in patients without severe pulmonary disease, and is associated with decreased bowel distension and postprocedural pain[53,54]. Furthermore, one of them showed that insufflation with CO_2 in colonoscopy could also decrease abdominal pain during colonoscopy[54]. For these reasons, the use of carbon dioxide insufflation, instead of air, is currently a quality standard to maximize comfort during colonoscopy[55]. Nevertheless, the use of CO_2 for insufflation has not been widely adopted in practice for various reasons (cultural prejudices, lack of knowledge, costs, *etc*.).

In the last years, the traditional concept of colonoscopy and colon examination is changing, as new tools are going to be available. The wireless capsule colonoscopy, with the second generation of PillCam® Colon, is becoming available in routine clinical practice[56]. Likewise, the Endotics® system, that consists of a robotic probe moving forward with an inchworm locomotion, allows for the painless progression into the colon, because it does not create loops, nor cause stretching of the colon walls[57]. The applicability of the Endotics® system in clinical practice has already been proven[58], and in 2014 its second version will be marketed with an operative channel of 3 mm in diameter, that will enable to take biopsies and will open the way to perform also other operative maneuvers.

CONCLUSION

Fifty years after the introduction of flexible colonoscopy in clinical practice, psychological and religious barriers due to the indignity of the procedure, fear of the procedure related to either the procedure-related pain or possible unfavorable diagnosis, are still working to make colonoscopy, pain, and fear an apparently indissoluble trinomial.

In the future, technical improvements will probably enable to overcome the present concept of colonoscopy, avoiding the use of traditional endoscopes. However, the next availability of such technical improvements can not justify the poor attention paid by endoscopists to the pain and discomfort caused by colonoscopy, as highlighted by the variability in the use of sedoanalgesia, either among countries, or in the same country. There are several valid methods to reduce pain and anxiety and to break the trinomial colonoscopy, pain and fear. We must use them.

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Role of simulation in training the next generation of endoscopists

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Abstract

The use of simulation based training in endoscopy has been increasingly described, simulation has the potential reduce the harm caused to patients by novices performing procedures, increase efficiency by reducing the time needed to train in the clinical environment and increase the opportunity to repeatedly practice rare procedures as well as allowing the assessment of performance. Simulators can consist of mechanical devices, employ cadaveric animal tissue or use virtual reality technology. Simulators have been used to teach upper and lower gastrointestinal endoscopy as well as interventional procedures. This review reviews the currently available endoscopic simulators, and the evidence for their efficacy, demonstrating that the ability of simulators to differentiate between novice and expert endoscopists is well established. There is limited evidence for improved patient outcome as a result of simulation training. We also consider how the environment within which a simulation is placed can be manipulated to alter the learning achieved, broadening the scope of simulation to develop communication as well as technical skills. Finally the implications for future practice are considered; technology is likely improve the fidelity of simulators, increasing the potential for simulation to improve patient outcomes. The impact of the simulation environment, and the correct place of simulation within the training curriculum are both issues which need addressing.

Key words: Gastroenterology; Endoscopy; Simulation; Simulation environment; Interventional endoscopy

Core tip: Evidence is increasing that simulation is an effective means of teaching interventional procedures. We review the current use of simulators and the evidence for their efficacy, before considering the impact of the simulation environment on the learning that can be achieved. We argue that the use of the simulation environment as a tool to broaden the educational scope of simulation to teach skills other than the technical, is important to maximum utilisation of simulation.

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INTRODUCTION

Simulation has been increasingly described in endoscopy since the late 1970s. As a method of teaching it has a number of potential advantages. These include reducing the harm caused to patients by novices performing procedures[1-4], an increase in efficiency by reducing the time needed to train in the clinical environment[5], the opportunity to repeatedly practice rare procedures and assessment of performance. The use of simulation moves

the focus of an encounter firmly onto the learner, so education becomes the sole object of the exercise, which distinguishes it from clinical training, where the interests of the patient must always be placed ahead of education. In simulation, mistakes that would be unacceptable in clinical practice can be allowed to occur, providing opportunities for learning[6]. There has also been increasing interest in the use of simulation for assessment and credentialing purposes[7].

In order to further describe the use of simulation in endoscopy and its potential future role in training endoscopists, some definitions are needed. McGaghie defines simulation as: "a person, device, or set of conditions which attempts to present (education and) problems authentically. The student or trainee is required to respond to the problems as he or she would under natural circumstances[8]".

The importance of this definition is that it sees simulation as a process. A simulator, by contrast, can be seen as the device used to represent the problem itself, performing an endoscopic procedure.

The simulation environment is, importantly, distinct from the simulator. For the purposes of this review we define the simulation environment as "the context in which the simulation is placed". This definition is deliberately rather loose. The majority of the following discussion will focus on the physical space in which the simulator is placed, as well as its contents, but this environment can be seen in broader terms. How a simulation is placed within the broader curriculum of training, for example, may have a profound effect on its usefulness.

This review will discuss the various endoscopic simulators available, before considering the evidence for their efficacy. The role of the simulation environment will then be considered, before we speculate on the role of simulation in training the next generation of endoscopists.

ENDOSCOPIC SIMULATORS

Broadly, simulators currently available are able to simulate upper gastrointestinal (GI) endoscopy, lower GI endoscopy and interventional procedures. The devices available can be divided into mechanical simulators, those involving animal tissue, whether living or cadaveric and virtual reality tools.

Mechanical simulators

Mechanical simulators have been available for some time. The Erlangen plastic mannequin was described in 1974, and allowed upper GI endoscopy to be simulated[9]. These models are typically limited by a lack of fidelity (the subjective sense of how "real" a simulation is) and by a lack of variation, as the simulator is the same for every simulation.

Animal models

The use of animal tissue for endoscopic simulation has the advantage of producing a higher degree of fidelity, as animal tissue behaves more like that of a human than a mechanical model. The use of live animals in simulation has been limited by expense, the need for expensive infrastructure and ethical concerns. The use of live animals for simulating medical procedures is currently banned in the United Kingdom.

Cadaveric animal tissue has been used rather more extensively, particularly in composite simulators, where animal tissue and mechanical models are combined. This is perhaps of most use in simulators seeking to replicate interventional procedures. The Erlangen active simulator for interventional endoscopy (EASIE) (ECE-Training GmbH, Erlangen, Germany), for example, uses specially prepared cadaveric porcine organs with arteries sewn into their linings, and an electric pump to produce spurting blood[10,11]. Similar, more portable composite simulators have subsequently been developed to allow the diagnostic endoscopy, polypectomy, percutaneous endoscopic gastrostomy (PEG) gastrostomy and endoscopic retrograde cholangio-pancreatography (ERCP) to be practiced[12-14]. With the exception of anatomical variation, the placement of the porcine duodenal papilla being more proximal than the human for example, these models offer a high degree of fidelity but at the cost of the time required for preparation, requiring deep frozen animal tissue to be thawed and placed within the simulator on a baseplate[9].

Virtual reality

The introduction of virtual reality (VR) technology to simulators has had a large impact on the possibilities offered. Two commonly used examples are the GI bronch mentor (Sim-bionix, Cleveland, Ohio) and the CAE accutouch (CAE Healthcare, Montreal, Quebec, Canada; previously marketed by Immersion Medical, San Jose, California). Both simulators consist of a plastic mannequin on a trolley and possess both a mouth and an anus, allowing upper and lower GI procedures to be performed. The instruments used are standard endoscopes and the operating end and are attached to the simulator at the other. Sensors in the mannequin deliver haptic feedback to the user as well as guiding the simulation. Haptic feedback produces forces on the endoscopic which resemble those experienced in real endoscopy, thus allowing tactile as well as visual feedback to be gained by the learner. Both simulators have supplemental modules, which allow more complex procedures to be simulated. The GI bronch mentor can simulate haemostasis, flexible sigmoidsoscopy, ECRP and diagnostic EUS. The CAE accutouch has supplemental modules, which allow polypectomy, biopsy and haemostasis to be practiced.

VR simulators have a variety of potential advantages. They require very little set up time and can be used repeatedly by learners for practice. The addition of anatomical variation and varying degrees of difficulty to the simulator means that repeated procedures can be simulated with different pathologies and anatomical variations.

One of the most important features of VR simula-

tors is the ease with which performance feedback can be produced. Both the VR simulators described provide a feedback to the leaner with performance parameters including the total time of the examination, pathological findings recognised, degree of air insufflation, patient degree of discomfort, percentage of mucosa visualized and time spent in "red out" (in contact with the bowel wall)[9].

The provision of performance feedback has been recognised as an important feature of successful simulation based education[15]. The provision of feedback by the simulator itself has the potential to allow sustained practice by trainees without the need for the continuous presence of a trainer.

EVIDENCE FOR EFFICACY

Having described the simulators available, it can be seen that the potential exists to reproduce clinical scenarios outside a clinical environment. The use of simulators in training endoscopists is however, only of use if it translates into a benefit which is observable when procedures are performed on real patients, either in terms of improved performance by the trainee or, ideally, in measurable improvement in patient outcomes. The literature on simulation has, in general adopted two approaches to demonstrating the efficacy of simulators. The first is validation studies, where the end point used is performance on the simulator[16]. The two main means of validation reported are the ability of a simulator to demonstrate difference in performance between novices and experts (construct validity)[17] and the ability for practice on a simulator to produce a measurable improvement in performance[18]. The second approach is to compare the performance of simulation and non simulation trained learners in the clinical environment. As we shall see, few studies have investigated the relationship between patient outcome and simulation training.

The performance metrics produced by VR simulators make construct validity easy to demonstrate, as performance is assessed by the simulator and not by an external observer[19]. Construct validity for upper GI endoscopy was been demonstrated some time ago[20,21]. A series of studies have also demonstrated that VR simulators can distinguish novice from expert endoscopists in lower GI endoscopy (Macdonald)[22-26]. The GI mentor has also been shown to have construct validity when simulating ECRP[27]. A recent systematic review by Ansell *et al* demonstrated that the most valid metrics for training and assessment across VR simulators for colonoscopy are total procedure time, caecal intubation time, efficiency and the percentage of muscosa visualised[28]. This review also highlighted the fact that the majority of validity evidence pertains to the construct validity of VR simulators, with only one study reporting validation of a bovine model[9].

What is more difficult to demonstrate, however, is the ability of simulators to distinguish the intermediate level endoscopist from the expert[17,22,29], leading to the speculation that the role of VR simulators is limited to the teaching of basic navigational skills rather than more complex interventional procedures[5].

There is also increasing evidence from clinical studies. The overall efficacy of skills transfer into the operating room was the subject of a recent systematic review by Dawe *et al*[30], which included 10 studies looking at the effect of simulation based training on clinical performance. This concluded that the current evidence demonstrates that simulation-based training, as part of a training program and incorporating the achievement of reaching predetermined proficiency levels, results in skills that are transferable to the operative setting for laparoscopic cholecystectomy and endoscopy. Di Giulio *et al*[31] demonstrated in 2004 that simulation trained fellows performed more complete procedures and had their performance assessed as "positive" more frequently.

Looking at colonoscopy specifically, Cohen *et al*[32] randomised GI fellows to 10 h of unsupervised practice on the GI mentor or no training. Simulator trained fellows had higher competency rates during the 1st 100 cases than non-simulator trained fellows, but this effect was reduced with time. Both groups required 160 cases to achieve 90% competence. The simulation training in this study was distinguished by the absence of feedback from faculty, and by being limited to the early part of training, rather than being sustained throughout it.

The majority of the literature on training in interventional techniques has described the use of composite ex vivo simulators, which, have been shown to improve performance in several randomised trials[33-35]. These studies, however are mostly limited by the fact that assessment of skills was performed on the simulator rather than in the clinical setting, although one also demonstrated that procedure times were reduced in clinical practice in simulation trained residents and that a non significant reduction in complications occurred in their patients[35]. One randomised study has demonstrated that ERCP skills learned by novices can be shown to lead to improved performance when procedures are performed in patients[36].

In the end, one of the ultimate goals of procedural training is improved outcomes for patients. If demonstrable improvements in patient outcome can be delivered by simulation based training, then the case for its use is made. There is some evidence emerging in the laparoscopic and anaesthetic literature that the use of simulation reduces complication rates[37]. Within endoscopy, there is limited evidence. Although reduced complication rates have been hinted at in interventional procedures as described above, and one study has demonstrated improved patient comfort during conscious procedures performed by novices trained using simulation[38].

In summary, the current evidence demonstrates construct validity for VR simulation. There is evidence for improved performance in the clinical environment but this may not be maintained in later endoscopies as competence is not reached any sooner by simulation trained learners[5,39]. There is a little evidence for better patient outcome but this has only been demonstrated by one

study looking at patient comfort[38].

SIMULATION ENVIRONMENT

As we have seen, the majority of the evidence for the use of simulation to teach endoscopy and endoscopic procedures focuses on the efficacy of the use of simulators to teach practical skills. This, of course is an extremely important component of learning to perform endoscopy in the clinical environment. Adverse clinical events, which lead to the potential for harm to patients, however, are more often related to failures of communication, clinical judgement and teamwork than to technical error[40-42].

The role of simulation can be extended to allow the potential for teaching skills beyond the technical if the simulation environment is modified. The simulation environment can place the practice of technical skills in a range of contexts, from the use of portable trainer at home[43] to a completely simulated operating theatre containing a theatre team[44]. What is being taught and assessed during the simulation is, therefore, highly dependent on the simulation environment.

One means of broadening the scope of endoscopic simulation is to place an actor within the simulation environment, producing a "simulated patient". This simulation demands more of the learner than the simple performance of a technical task, as the interaction with the simulated patient must occur alongside the simulated endoscopic procedure[45-47]. Kneebone *et al*[48] describe a course for novice nurse endoscopists in which a component is the use of "hybrid simulation" in which an actor and a VR simulator are combined. These authors achieved this by setting up the room with the actor leaning on their left side next to the simulator, with a blanket covering both, producing the illusion that the procedure was being carried out on a real patient. This course led to an improvement in simulator metrics from the VR simulator, and extremely positive qualitative feedback about the improvement in communication skills facilitated by the use of simulated patients.

Another example of using the simulation environment to broaden the scope of simulation is the placement of a simulator within the normal clinical environment, achieving a degree of fidelity that is not usually achievable, unlocking the potential of simulation to reveal interactions within clinical teams as well as between clinicians and patients.

Finally, the use of a portable space for simulation as a simulation environment has the potential to avoid both the problem of simulation being inaccessible to trainees located away from central clinical skills centres and simulation sessions disturbing the normal function of the clinical environment. This has been described by a group from Imperial College London using an inflatable environment in which a large number of simulations can be produced[49]. This space can then be filled with equipment that allows a clinical area to be simulated with enough realism to produce a high degree of fidelity, whilst being portable enough to be placed in a car.

CONCLUSION

The use of simulation to train the next generation of endoscopists needs to be supported by an increasing amount and quality of evidence, particularly for the clinical transferability of simulation training, but it is arguable that the evidence available already supports the use of simulation to train novice endoscopists.

The technology available for simulators is likely to lead to an increase in fidelity and to an increase in the complexity of metrics available, and validity studies supporting the use of each new generation of simulators is important both to support their use for training and also, in particular, to support their use for assessment.

We would argue that further thought also needs to be given to the simulation environment. Increasing the sophistication of simulation by manipulating the simulation environment, as we have seen, contains the potential to address the teaching of skills beyond the technical.

Further work is needed to place simulation within a broader curriculum of training. The majority of studies looking at simulation in endoscopy have looked at the effect of short periods of simulation training before clinical experience. It may be that integration of simulation alongside developing clinical practice might increase its efficacy and lead to a more sustained benefit than those demonstrated by studies to date.

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ORIGINAL ARTICLE

Monitoring salivary amylase activity is useful for providing timely analgesia under sedation

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Abstract

AIM: To detect the criteria and cause of elevated salivary amylase activity (sAMY) in patients undergoing endoscopic submucosal dissection (ESD) under sedation.

METHODS: A total of 41 patients with early gastric cancer removed *via* ESD under deep sedation (DS) were enrolled. The perioperative sAMY, which was shown as sympathetic excitements (SE), was measured. The time at which a patient exhibited a relatively increased rate of sAMY compared with the preoperative baseline level (IR, %) ⩾ 100% (twice the actual value) was assumed as the moment when the patient received SE. Among the 41 patients, we focused on 14 patients who exhibited an IR ⩾ 100% at any time that was associated with sAMY elevation during ESD (H-group) and examined whether any particular endoscopic procedures can cause SE by simultaneously monitoring the sAMY level. If a patient demonstrated an elevated sAMY level above twice the baseline level, the endoscopic procedure was immediately stopped. In the impossible case of discontinuance, analgesic medicines were administered. This study was performed prospectively.

RESULTS: A total of 26 episodes of sAMY eruption were considered moments of SE in the H-group. The baseline level of sAMY significantly increased in association with an IR of > 100% at 5 min, with a significant difference (IR immediately before elevation/IR at elevation of sAMY = 8.72 ± 173/958 ± 1391%, $P < 0.001$). However, effective intervention decreased the elevated sAMY level immediately within only 5 min, with a significant difference (IR at sAMY elevation/immediately after intervention = 958 ± 1391/476 ± 1031, $P < 0.001$). The bispectral indices, systolic blood pressure and pulse rates, which were measured at the same time, remained stable throughout the ESD. Forceful endoscopic insertion or over insufflation was performed during 22 of the 26 episodes. Release of the gastric wall tension and/or the administration of analgesic medication resulted in the immediate recovery of the elevated sAMY level, independent of body movement.

CONCLUSION: By detecting twice the actual sAMY based on the preoperative level, the release of the gastric wall tension or the administration of analgesic agents should be considered.

Key words: Salivary amylase activity; Endoscopic sub-

mucosal dissection; Analgesia; Anesthesia; Sedation; Sympathetic excitement; Gastric wall tension

Core tip: The analgesia in patients during endoscopic submucosal dissection (ESD) under deep sedation (DS) has not yet been developed. There was no way of measuring the degree of the pain in those patients. This study revealed that the salivary amylase activity (sAMY) shown as sympathetic excitement (SE) sometimes was elevated during ESD without any change in circulatory dynamics or consciousness. We suggest that sAMY is elevated when patients feel pain during ESD under DS. By detecting twice the actual sAMY based on the preoperative level, the release of gastric wall tension or the administration of analgesic agents should be considered.

Uesato M, Nabeya Y, Akai T, Inoue M, Watanabe Y, Horibe D, Kawahira H, Hayashi H, Matsubara H. Monitoring salivary amylase activity is useful for providing timely analgesia under sedation. *World J Gastrointest Endosc* 2014; 6(6): 240-247 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i6/240.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i6.240

INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely used to treat early gastric cancer because the *en bloc* resection of lesions *via* ESD provides a detailed pathological assessment and possible radical cure[1-4]. However, technical difficulties and the expanded eligibility criteria for ESD can also result in a prolonged procedure time[1,5,6], and ESD is generally performed under deep sedation (DS)[7,8]. Accordingly, there is an increased risk of anesthesia-related complications that are associated with higher doses of sedative drugs as more opportunities to perform ESD for gastric tumors arise[9]. The effect of analog-sedation for the patients in the intensive care unit has recently attracted attention. Egerod *et al*[10] recommends an interdisciplinary effort to target patients requiring less because issues of oversedation and inadequate pain management still require additional attention. In addition, the administration of additional analgesics can stabilize the condition of patients under sedation during endoscopic procedures[11]. Consequently, providing timely and adequate analgesia in addition to sedation for the entire duration of ESD is essential. Several methods can be used to determine the state of the consciousness in patients, including the bispectral index monitor designed by Aspect Medical Systems (Norwood, MA, United States) and the Ramsey sedation score. However, a method for measuring analgesic degree has not yet been developed. In practice, endoscopists administer analgesics to patients during ESD without following specific criteria.

The salivary amylase activity (sAMY) is controlled by epinephrine secreted from the adrenal medulla, which is caused by enhanced activity of the sympathetic-nervous-adrenomedullary system[12,13]. Recent studies have demonstrated the efficacy of assessing psychological stress objectively by monitoring sAMY[14,15], and an instrument using this method to assess stress with rapidity and low invasiveness has been marketed for practical use[16,17]. We have already reported that using this instrument, the analgesic level can be monitored easily and accurately according to the sAMY level, which may positively contribute to performing safe and secure ESD under DS[18]. Hence, we first disclosed that monitoring the sAMY level can be used to objectively assess stress in response to pain in patients undergoing ESD[18].

As a next step, two aims of this study are to detect the sAMY level, which can be shown as a significant sympathetic excitement (SE) in patients undergoing ESD for gastric tumors under DS, and to explore which particular endoscopic surgery techniques cause a significant SE.

MATERIALS AND METHODS

This study enrolled 41 consecutive patients with early gastric cancer who were treated at the Department of Frontier Surgery or the Department of Endoscopic Diagnostics and Therapeutics, Chiba University Hospital. The patients underwent ESD under properly maintained DS with midazolam (0.04-0.06 mg/kg *iv*) or propofol (1-2 mg/kg *iv*) and pentazocine (7.5 mg *iv*); neither anticholinergic nor vasopressive agents were used. Carbon dioxide was used in the insufflation of the endoscope.

The sAMY levels were determined as previously reported[18]. Briefly, we measured the sAMY level using enzyme analysis equipment, a sAMY Monitor (NIPRO Co., Osaka, Japan), prior to performing ESD in the morning, immediately following the induction of sedation, and every five minutes after the initiation of ESD. sAMY measurement requires only 1 min after saliva sampling under the tongue. We evaluated the intraoperative sAMY value by calculating the relative rate of increase in the sAMY level compared with the control level (IR, %) as follows: (the elevated sAMY level-the baseline level prior to ESD in the morning)/the baseline level × 100. According to the results of our previous study[18], the median (range) of IR was 105.2% (1.7-3050). Taken together, in this study, we assumed the time when a patient exhibited an IR of $\geqslant$ 100% (twice the actual value) as the moment when the patient received SE. This study was performed prospectively. In addition, we simultaneously monitored the endoscopic procedures and the perturbation of the sAMY level and examined which techniques were associated with SE during ESD. However, completing ESD as soon as possible was more important than exploring the possible causes of SE. Similar to the case in a previous report[18], intense body movement occurred in a patient after a high sAMY level was overlooked. Therefore, if a patient appeared to a high sAMY level during ESD, the operator attempted to remove the source of the SE immediately and not to overlook it.

Fourteen patients who exhibited an IR of $\geqslant$ 100%

Table 1 Patient characteristics

	H-group	M-group	L-group	*P* value
No. of patients	14	8	19	
Gender (male/female)	9/5	6/2	16/3	0.429
Age (yr)	71.5 ± 11.7	71.6 ± 8.9	69.9 ± 7.0	0.569
(range)	(40-84)	(58-86)	(58-81)	
Body weight (kg)	57.3 ± 10.6	62.4 ± 10.0	58.8 ± 8.7	0.443
(range)	(43.1-82)	(49-80.3)	(44-76)	
No. of tumors	14	8	19	
Location U/M/L	1/5/8	0/2/6	3/6/10	0.464
Less, post/great, ant	9/5	3/5	10/9	0.485
Resected tumor size (mm)	29.0 ± 10.0	29.3 ± 12.7	30.2 ± 11.4	0.827
(range)	(15-49)	(17-58)	(12-50)	
Procedure time (min)	78.0 ± 54.1	92.5 ± 55.9	73.7 ± 46.8	0.717
(range)	(35-240)	(35-200)	(20-205)	

The data are presented as the mean ± SD. U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; Less: Lesser curvature; Great: Greater curvature; Ant: Anterior wall; Post: Posterior wall.

at any time associated with sAMY elevation during ESD were categorized into the H-group. Nineteen patients who failed to exhibit an IR of ≥ 100% at any time associated with sAMY elevation during ESD were categorized into the L-group. The remaining eight patients exhibited various IR values and were categorized into the M-group. When a patient demonstrated an elevated sAMY level during ESD, the endoscopic procedure was immediately stopped. In the impossible case of discontinuance, analgesic medicines were administered. Therefore, we calculated the recovery rate of sAMY (%) as follows: (the elevated sAMY level-the decreased sAMY level immediately following intervention)/the elevated sAMY level × 100. We defined a forceful endoscopic insertion when the tip of the endoscope was inserted more than 80 cm from the incisor line to stomach and an over insufflation when the gastric fold completely disappeared.

The patient's blood pressure and pulse rate were also assessed at the time of sAMY measurement. In addition, a bispectral index monitor was used to evaluate the level of consciousness. All patients were interviewed using a questionnaire prior to discharge to determine their subjective consciousness level.

The institutional review board approved the study protocol, and written informed consent was obtained from all patients before enrollment.

Statistical analysis

Continuous data are presented as the mean ± SD. The Mann-Whitney *U* test was used to analyze the differences in continuous or ordinal variables between the groups. Fisher's exact test was used to evaluate the differences in proportions between the groups, and the Kruskal-Wallis test was used in proportion among the three groups. Perioperative changes in the IR values around the moment of sAMY elevation were compared using the Wilcoxon signed rank-sum test. All statistical analyses were conducted using the SPSS 15.0 software package (SPSS Inc., Chicago, IL, United States). *P* values of less than 0.05 were considered to be statistically significant.

Table 2 Body movement during salivary amylase activity elevation

	H-group	M-group	L-group	*P* value
No. of patients	14	8	19	
No. of elevated sAMY (times)	26	30	16	
≥ twice the actual value	26	11	0	
< twice the actual value	0	19	16	
with body movement	17	16	6	0.215 ([1]0.078)
without body movement	9	14	10	

[1]Indicates a comparison between the H- and L-groups. sAMY: Salivary amylase activity.

RESULTS

The patient characteristics are shown in Table 1. No significant differences were observed among the three groups in terms of clinical characteristics, including the procedure time. The H-group demonstrated 26 episodes of sAMY elevation (with an IR of ≥ 100%). The M-group exhibited 30 episodes of sAMY elevation (11 episodes of an IR of ≥ 100% and 19 episodes of an IR of < 100%), and the L-group exhibited 16 episodes of sAMY elevation (with an IR of < 100%). The number of episodes of an elevated sAMY level associated with body movement was higher in the H-group than it was in the L-group ($P = 0.078$) (Table 2). However, even in the H-group, nine (34.6%) of the 26 episodes of an elevated sAMY (with an IR of ≥ 100%) were not accompanied by simultaneous body movement. The method of sedation failed to affect the sAMY level immediately after the induction of sedation (midazolam/propofol = 39.70 ± 49.18/29.26 ± 44.62 KU/L, $P = 0.926$). All 41 patients responded with "I did not wake up at all" on the post-ESD questionnaire.

In this study, because we aimed to explore the relationships among the sAMY elevation associated with SE, the patients' condition, and the endoscopic procedure, we focused on the patients in the H-group, who were considered to experience the potential pain at any time of sAMY elevation during ESD compared with the patients in the "painless" L-group. Figure 1 shows the variation in the IR and bispectral index associated with the 26 episodes of sAMY elevation in the H-group. The baseline level of sAMY significantly increased in association with an IR of > 100% at 5 min, with a significant difference (IR immediately before elevation/IR at sAMY elevation = 8.72 ± 173/958 ± 1391%, $P < 0.001$). However, an effective intervention decreased the elevated sAMY level immediately within only 5 min, with a significant difference (IR at sAMY elevation/immediately after intervention = 958 ± 1391/476 ± 1031, $P < 0.001$). The bispectral indices in the patients undergoing ESD proved to be stable throughout the procedures, even when the sAMY

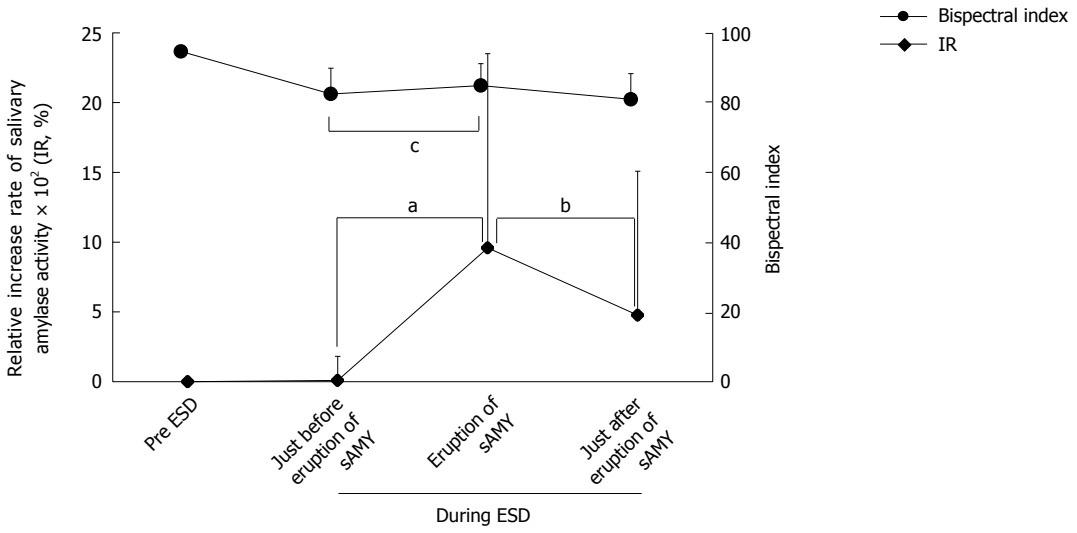

Figure 1 Changes in the relative rate of increase of the salivary amylase activity level compared with the control level, salivary amylase activity (IR, %), and the bispectral index around the 26 episodes of salivary amylase activity elevation in the H-group. The baseline level of sAMY significantly increased in association with an IR of > 100% at only 5 min, with a significant difference (IR immediately before elevation/IR at elevation of sAMY = 8.72 ± 173/958 ± 1391%, [a]*P* < 0.001). However, the release of gastric wall tension and/or pentazocine injection effectively decreased the elevated sAMY level immediately within only 5 min with a significant difference (IR at sAMY elevation/immediately after intervention = 958 ± 1391/476 ± 1031, [b]*P* < 0.001). The bispectral indices in the patients undergoing ESD proved to be stable throughout the procedures ([c]*P* = 0.272), even when the sAMY level was elevated in association with an IR of > 100%, *i.e.*, when the patient received SE. All 14 patients responded with "I did not wake up at all" on the post-ESD questionnaire. The data are presented as the mean ± SD. ESD: Endoscopic submucosal dissection; DS: Deep sedation; sAMY: Salivary amylase activity; SE: Sympathetic excitement; H-sAMY: A high value of salivary amylase activity; L-sAMY: A low value of salivary amylase activity.

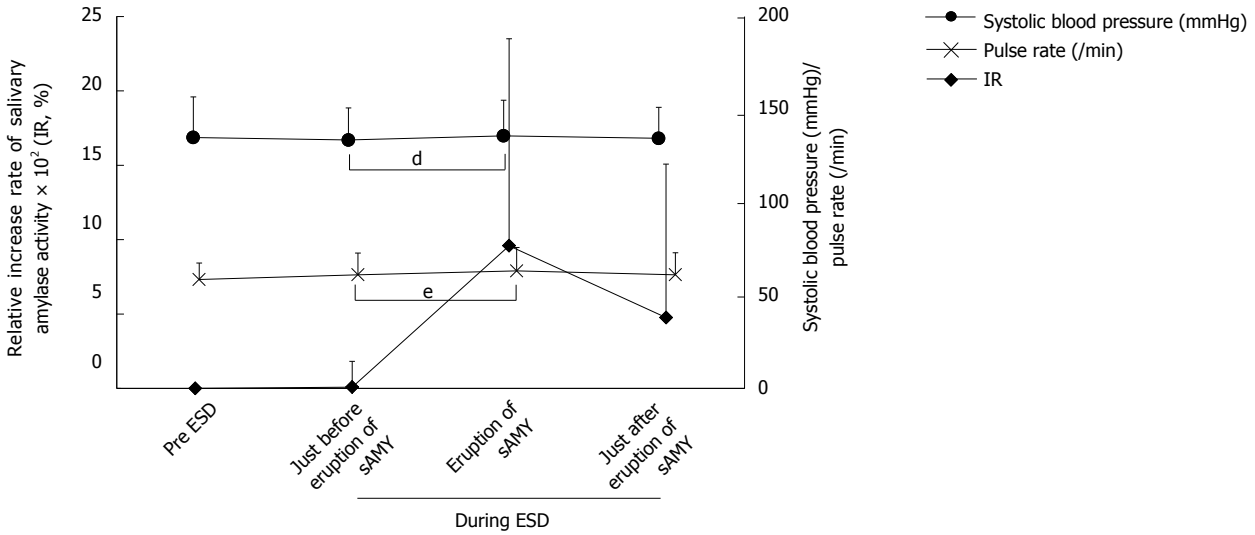

Figure 2 Changes in the relative rate of increase of the salivary amylase activity level compared with the control level, salivary amylase activity (IR, %), the systolic blood pressure (mmHg) and pulse rate (/min) around the 26 episodes of salivary amylase activity elevation in the H-group. The values of systolic blood pressure and pulse rate also remained stable during ESD, regardless of the change in the sAMY ([d]*P* = 0.660 and [e]*P* =0.614, respectively). The data are presented as the mean ± SD. ESD: Endoscopic submucosal dissection; DS: Deep sedation; sAMY: Salivary amylase activity; SE: Sympathetic excitement; H-sAMY: A high value of salivary amylase activity; L-sAMY: A low value of salivary amylase activity.

level was elevated in association with an IR of > 100%, *i.e.*, when the patient received SE (Figure 1). Figure 2 shows the variations in systolic blood pressure and pulse rate that were associated with perturbation in the IR in the H-group. The systolic blood pressure values and pulse rates were also stable throughout ESD. The status of simultaneous body movement did not significantly affect the IR in the H-group, while the IR values that were not associated with body movement (nine episodes) were relatively higher than those associated with body movement (17 episodes) (Figure 3, *P* = 0.236).

The technical status at the moment of sAMY elevation was compared between the H- and L-groups (Table 3). In both groups, the most frequent operative technique was "Dissection" (H-group/L-group; 11/26 = 42.3%/10/16=62.5%), and no significant differ-

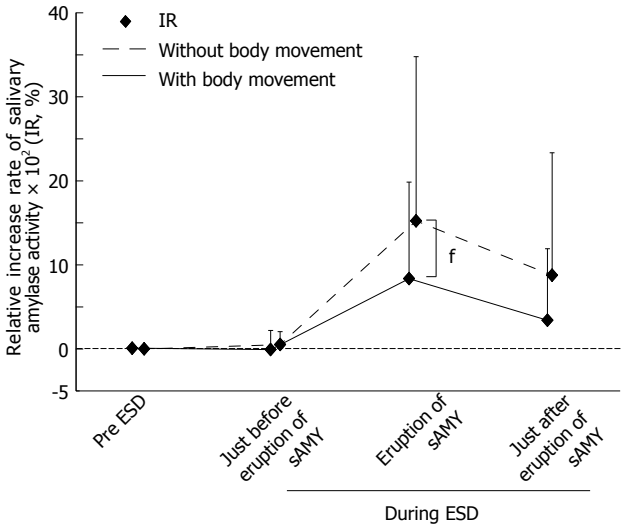

Figure 3 Changes in the relative rate of increase of the salivary amylase activity level compared with the control level, salivary amylase activity (IR, %), with reference to the status of body movement in the H-group. The levels of IR that were not associated with body movement (9 episodes) were relatively higher than those associated with body movement (17 episodes); however, no significant differences were observed ($^{f}P = 0.236$). The patients received SE shown as the elevation of sAMY, even if they were unconscious and exhibited no body movement. The management of the sAMY might prevent the patient's body movement that may occur in the near future. The data are presented as the mean ± SD. ESD: Endoscopic submucosal dissection; DS: Deep sedation; sAMY: Salivary amylase activity; SE: Sympathetic excitement; H-sAMY: A high value of salivary amylase activity; L-sAMY: A low value of salivary amylase activity.

ences were found in the frequency of this technique ($P = 0.430$). "Inversion" was the most frequent direction (H-group/L-group; 14/26 = 53.8%/10/16, 62.5%) in both groups, without significant intergroup differences in the frequency of this direction ($P = 0.582$). Forceful endoscopic insertion or over insufflation were performed during 22 of the 26 episodes (84.6%) of sAMY elevation in the H-group; the frequency of these procedures was significantly higher in the H-group than it was in the L-group (56.3%, $P = 0.042$). The interventions used to treat sAMY elevation, which indicated SE, in the H-group are shown in Table 4. To relieve SE immediately, either release of gastric wall tension or pentazocine injection were performed during the 14 episodes of sAMY elevation associated with body movement. In two cases, both technical and medical interventions (*i.e.*, release of gastric wall tension and medication administration) were concomitantly performed. The recovery rate of a sAMY elevation that was not associated with body movement did not significantly differ from that of a sAMY elevation that was associated with body movement. Midazolam or propofol were administered in only two patients with high bispectral indices and were very effective in both cases.

DISCUSSION

The results of this study first demonstrated that the gastric wall tension caused by forceful endoscopic insertion or over insufflation is a major cause of SE in patients undergoing ESD for gastric tumors under DS. A link between SE and the status of the endoscopic procedure was clearly shown by monitoring the sAMY level, which objectively reflects the analgesic level in unconscious gastric ESD patients. The management of the sAMY might prevent the unanticipated body movement in patients during ESD.

Kiriyama *et al*[19] reported that local lidocaine injections into the submucosal layer are effective for local pain control both immediately after and during ESD, because local pain can be caused by the formation of artificial gastric ulcers. In their study, the level of pain and the effects of lidocaine during surgery were evaluated indirectly based on the reduced total dose of pentazocine[19]. However, our current study demonstrated that an IR of sAMY ⩾ 100%, which indicates intraoperative SE, was not always observed, although every patient suffered from artificial ulcers induced by ESD. Moreover, there were no significant differences between the H- and L-groups in terms of the size of the resected tumors. Therefore, the degree of SE demonstrated by the sAMY level may not necessarily depend on ulcer formation, and the size of an artificial ulcer may not be crucial for SE, at least in patients undergoing gastric ESD. This idea is supported by our experience, as most patients who are conscious do not feel pain when they are treated with gastric

Table 3 Technical status during salivary amylase activity elevation

	H-group	L-group	*P* value
No. of elevated sAMY (times)	26	16	
Operative techniques			
Incision	9	4	0.430
Dissection	11	10	
Hemostasis	6	2	
Endoscopic direction			
Straight	12	6	0.582
Inversion	14	10	
Forceful endoscopic insertion or over insufflation			
Presence	22	9	0.042
Absence	4	7	

sAMY: Salivary amylase activity.

Table 4 Interventions used to treat salivary amylase activity elevation and the improvement in terms of body movement [number of episodes of salivary amylase activity elevation/ recovery rate of salivary amylase activity (%)]

Body movement	Presence	Absence
Number (times)	17	9
Release of gastric wall tension only	2/86.2	5/66.1
Medication (pentazocine injection) only	12/94.7	3/95.9
Release and medication (pentazocine)	2/119.6	0/-
Medication (midazolam or propofol injection) only	1/124.2	1/85.6

Recovery rate of sAMY (%) = (the elevated sAMY level-decreased sAMY level immediately after intervention)/the elevated sAMY level × 100. sAMY: Salivary amylase activity.

or colonic endoscopic mucosal resection. We therefore hypothesized that the operative time or some particular technique of the operative procedure, which varies among individuals, is associated with the development of SE in patients undergoing gastric ESD.

Our data suggest that the development of SE during gastric ESD is not related to a long operative time (Table 1). However, we found that the status of forceful endoscopic insertion or over insufflation significantly differed between the H- and L-groups (Table 3). Regarding the sudden production of sAMY, sympathetic fibers directly trigger the salivary gland, which secretes amylase before the gland responds to norepinephrine from the adrenal medulla[20]. In the current study, the systolic blood pressure values and pulse rates remained stable, even when the sAMY level suddenly changed during gastric ESD. Most likely, an increased sAMY level reflects sympathetic nerve excitement before circulatory dynamics become unstable. If the endoscopic procedures were to be subsequently continued, the sympathetic nerves would be further excited, and the blood pressure and pulse rate would become unstable. In this study, we successfully demonstrated this relationship by monitoring the sAMY level, which reflects the degree of potential pain during gastric ESD under DS and proper interventions.

Sensory receptors (mechanoreceptors) that are present in the mucosa, musculature (bowel wall), serosal surface, and mesentery[21-23] primarily respond to mechanical events, such as distension, torsion, contraction, and compression or stretching of the gut[23]. According to basic science experiments, gastric and/or colorectal distention induces acute visceral pain[24,25]. In particular, colorectal distension in rats stimulates cardiovascular and visceromotor responses[25]. Moreover, both morphine and clonidine produce a dose-dependent inhibition of cardiovascular and visceromotor responses to colorectal distension[25]. Clinically, the degree of discomfort a patient feels during a colonoscopic examination varies considerably and is related to the force imparted on the colon by the colonoscopy instruments, stretching the colonic wall, and mesenteric attachments, causing excessive gaseous insufflation[26,27]. These previously reported findings are consistent with the results of our gastroscopy study. However, there have been no such reports on the link between the objective evaluation of pain, *i.e.*, measurement of the sAMY level, and the technical status during gastric ESD. If ESD is performed under steady pressure automatically controlled endoscopy[28], we might reveal more clinical details of the relationship between the pain and the over insufflation.

While assessing and measuring pain are very important considerations for both patients and physicians, as previously described[19], pain tolerance varies greatly among individuals. Accordingly, the results of our study are significant with respect to the individualized, safe management of patients who undergo ESD for gastric tumors under DS. First, the operator should avoid causing gastric wall tension to relieve intraoperative pain. However, if releasing gastric wall tension cannot be achieved due to necessary technical steps or if it is not effective at reducing the patient's pain, analgesic drugs, such as pentazocine, should be administered immediately. These results support the findings of a previous report showing that morphine produces a dose-dependent inhibition of visceromotor responses to colorectal distension in rats[25]. In addition, in our study, analgesic evasion resulted in a significant decrease in the sAMY level within only 5 min.

Until recently, ESD operators have typically used body movement to indicate the moment that a patient feels pain during ESD performed under DS. However, it is important to note that 34.6% of the patients in the H-group exhibited no body movement in our study. This result suggests that, when sAMY elevation indicating pain is observed, analgesic drugs should be administered immediately to decrease the pain, even in patients without body movement. If the sAMY elevation is overlooked, significant variations in systolic blood pressure, pulse rate, and body movement will occur. Therefore, an elevation of the sAMY level is a timely, practical, and objective indicator of intraoperative pain during gastric ESD, even when the patient fails to move simultaneously. The incidence of complications, such as bleeding or perforation, increases if the patient moves during ESD. It is therefore clinically important to address pain before movement occurs. In this study, we focused on the patients in the H-group, who were considered to experience potential pain at any time of sAMY elevation during ESD, compared with the patients in the "painless" L-group. However, the degree of sAMY elevation varied among the patients. Therefore, to safely complete gastric ESD, continuously monitoring the sAMY level throughout the ESD procedure is advisable to accurately assess the real-time degree of pain in individual patients and to determine when to release endoscopic stretching or appropriately administer analgesics after detecting twice the actual sAMY based on the preoperative value.

In this study, even when an elevated sAMY level was observed in the patients undergoing ESD, the average bispectral index was stable (Figure 1). Furthermore, all patients responded with "I did not wake up at all" on the post-ESD questionnaire. Midazolam and/or propofol injection was effective in two patients with both high bispectral indices and high sAMY elevation levels (one case without body movement) in the H-group. High levels of both the bispectral index and sAMY suggest that a patient may be in a waking state. Accordingly, monitoring the sAMY level simultaneously with the bispectral index enables physicians to differentially understand the levels of pain and consciousness in patients undergoing gastric ESD under DS and is of great clinical significance.

In conclusion, pain, as represented by twice the actual sAMY based on the preoperative level, in unconscious patients undergoing ESD under DS for gastric tumors may be caused by the gastric wall tension, which can elevate the sAMY level quickly, even without body move-

ment, before a change in cardiovascular response. Therefore, continuously monitoring the changes in the sAMY level and either modifying the endoscopic technique or administering analgesics can be used to treat pain in a timely manner, and patients undergoing ESD for gastric tumors under DS can be managed more securely.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) is widely used to treat early gastric cancer under deep sedation (DS) and analgesia. Accordingly, there is an increased risk of anesthesia-related complications associated with higher doses of sedative and analgesic drugs as the opportunities to perform ESD for gastric tumors arise. There are several methods to know the state of the consciousness in patients. However, a method to measure analgesic degree has not yet been established.

Research frontiers

Recent studies have demonstrated the efficacy of assessing psychological stress objectively by monitoring salivary amylase activity (sAMY), and an instrument using this method to assess stress with rapidity and low invasiveness has been marketed for practical use.

Innovations and breakthroughs

Until recently, ESD operators have usually judged body movement to indicate the moment that a patient feels discomfort during ESD performed under DS and given the analgesics to patients without criteria. The authors aimed to detect the criteria of sAMY level shown as a significant sympathetic excitement in patients undergoing ESD of gastric tumors under DS and to explore which particular techniques of endoscopic surgery cause the sAMY elevation.

Applications

The study results suggest that by detecting twice the actual sAMY based on the preoperative level, the release of gastric wall tension or the administration of analgesic agents should be considered.

Terminology

sAMY: salivary amylase activity is controlled by epinephrine secreted from the adrenal medulla, caused by enhanced activity of the sympathetic nervous-adrenomedullary system.

Peer review

In this manuscript, Uesato *et al* provided a novel way to measure the depth of analgesia by a quantitative marker. This manuscript is interesting.

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RETROSPECTIVE STUDY

Predictors of double balloon endoscopy outcomes in the evaluation of gastrointestinal bleeding

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Abstract

AIM: To identify patients' characteristics associated with double balloon endoscopy (DBE) outcomes in investigation of obscure gastrointestinal bleeding (OGIB).

METHODS: Retrospective study performed at an academic tertiary referral center. Evaluated endpoints were clinical factors associated with no diagnostic yield or non-therapeutic intervention of DBE performed for OGIB evaluation.

RESULTS: We included fifty-five DBE between August 2010 and April 2012. The mean age of the sample was 67 with 32 males (58.2%). Twenty-four DBE had no diagnostic yield and 30 DBE did not require therapy. Non-diagnostic yield was associated with performing two or more DBE studies in one day [odds ratio (OR): 13.72, P = 0.008], absence of blood transfusions within a year of the DBE (OR: 7.16, P = 0.03) and absence of ulcers or arteriovenous malformations (AVMs) on prior esophagogastroduodenoscopy (EGD) or colonoscopy (OR: 19.30, P = 0.033). Non-therapeutic DBE was associated with performing two or more DBE per day (OR: 18.579, P = 0.007), gastrointestinal bleeding episode within a week of the DBE (OR: 11.48, P = 0.003), fewer blood transfusion requirements prior to DBE (OR: 4.55, P = 0.036) and absence of ulcers or AVMs on prior EGD or colonoscopy (OR: 8.47, P = 0.027).

CONCLUSION: Predictors of DBE yield and therapeutic intervention on DBE include blood transfusion requirements, previous endoscopic findings and possibly endoscopist fatigue.

Key words: Double balloon endoscopy; Enteroscopy; Obscure gastrointestinal bleeding; Small bowel; Anemia; Arteriovenous malformations; Arteriovenous malformations

Core tip: Double balloon endoscopy (DBE) is an excellent tool to visualize the small bowel and provide treatment. However, it may be unable to identify a source for bleeding in 20% to 40% of obscure gastrointestinal bleeding (OGIB) cases. This small retrospective case-control study showed that factors such as fewer blood transfusion requirements, absence of arteriovenous malformations or ulcers on prior endoscopies and possibly endoscopist fatigue may predict a negative diagnostic and therapeutic yield of DBE. This may help manage patients with OGIB and multiple comorbidities and potentially reduce health care costs by classifying patients who are most likely to

benefit from this time intensive procedure.

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent gastrointestinal hemorrhage for which no definite source has been identified by esophagogastroduodenoscopy (EGD) or ileocolonoscopy. It accounts for approximately 5% of all cases of gastrointestinal bleeding[1]. It can present as overt bleeding, or without visible blood but signs of iron deficiency anemia suggestive of a gastrointestinal source.

OGIB is a dilemma for gastroenterologists. It often requires multiple endoscopies[2]. Push enteroscopy, small bowel follow-through, radionuclide scanning, and angiography have had variable success in this setting[3,4]. Traditionally, intraoperative enteroscopy has been the only method available for complete small bowel evaluation. However, because of its increased morbidity and mortality compared to wireless capsule endoscopy and device assisted small bowel enteroscopy, it has decreased in popularity[5].

Video capsule endoscopy (VCE) is safe, simple and has a high sensitivity in evaluation of small bowel lesions. It is however limited in its ability to obtain tissue for histology and to provide endoscopic therapy[5]. Double-balloon endoscopy (DBE) was first introduced by Yamamoto *et al*[6] in 2001. In contrast to push enteroscopy and wireless capsule endoscopy, DBE can potentially visualize the entire small bowel and offers therapeutic potential[7-9]. Wireless capsule endoscopy and double balloon endoscopy provide similar diagnostic yield and have satisfactory concordance rate in the evaluation of OGIB[10,11].

DBE is associated with a relatively low complication rate profile of 1.2%[12]. Suspected small bowel bleeding is the main indication for DBE[7]. However, DBE may be unable to identify a source for bleeding in 20% to 40% of OGIB cases[13-16]. DBE is also time-consuming and labor-intensive, with an average examination time of approximately 60 to 90 min[8,13]. Identifying patients with a higher probability of successful detection and therapy of bleeding sources with DBE is important for resource utilization. Our study investigates factors that may predict negative findings on double balloon endoscopy based on clinical, laboratory and endoscopic findings.

MATERIALS AND METHODS

Study patients

We retrospectively reviewed patients referred to Saint Louis University Hospital for double balloon endoscopy between August 1, 2010 and April 6, 2012. Inclusion criteria included 18-80 years old patients who underwent double balloon endoscopy for OGIB.

Review of medical records

The medical records of all patients who met inclusion criteria were reviewed. Data collected included demographics, clinical, laboratory and endoscopic data. This study was approved by the institutional review board at Saint Louis University.

Endoscopists

Two experienced endoscopists performed all the DBE procedures. The endoscopists received dedicated training in balloon endoscopy through an ASGE course and initial case monitoring by an expert in the field.

DBE procedure

Informed consent was obtained prior to all DBE procedures. The DBE system (Fujinon, Inc., Saitama, Japan) was utilized. Initial approach with anterograde double balloon endoscopy was performed if capsule findings were within the proximal two third of small bowel, rectal approach if findings were more distal in the small intestine. We used the standard DBE method for insertion, withdrawal and observation, as described previously[17]. For anterograde DBE, patients were kept nothing by mouth (NPO) at least 8 h prior to procedure and no particular bowel preparation was given. For retrograde DBE, bowel preparation with 4 L polyethylene glycol was used. Monitored anesthesia care with intravenous propofol, administered by staff anesthesiologists was used for most cases. Midazolam and narcotics were added occasionally to optimize sedation at the discretion of the anesthesiologist. Spot ink tattoo was placed to mark the maximum insertion depth reached. The small bowel segment suspected to have pathology on VCE was carefully inspected. The opposite route was used if pathology was not reached with the initial insertion route as deemed clinically appropriate.

Classification

Active gastrointestinal (GI) bleeding at the time of DBE was defined as overt bleeding within one week from DBE while non-active GI bleeding was defined as overt bleeding beyond one week from DBE. Acute GI bleeding was defined as GI bleeding within one month from VCE or DBE. Positive diagnostic yield on DBE was defined as cases with significant endoscopic findings [ulcers, arteriovenous malformations (AVMs), ulcerated masses or polyps] consistent with patients' clinical presentation and/or VCE findings. Therapeutic yield on DBE was defined as cases in which endoscopic intervention was performed. Positive findings on capsule endoscopy were defined as either the visualization of a lesion (AVMs, ulcerated polyps, mass, ulceration, multiple erosions) or the presence of blood and/or blood clots in the lumen of the small bowel. Negative or nonspecific capsule findings were assigned when an investigation showed no ab-

Table 1 Double balloon endoscopy findings

Findings	*n* (%)
AVM	20 (36.4)
Ulcer	3 (5.5)
Ulcerated polyp	3 (5.5)
Ulcerated mass	1 (1.8)
Multiple erosions	2 (3.6)
Portal HTN enteropathy	1 (1.8)
Vascular polyp	1 (1.8)
Negative findings	24 (43.6)

AVM: Arteriovenous malformation.

Table 2 Bivariate analysis of negative diagnostic double balloon endoscopy

Variables	Negative diagnostic yield	No therapeutic intervention
Pre-DBE ASA score ≤ 2	0.611	0.044
GI bleed within 1 wk prior to DBE	0.179	0.010
Blood transfusions ≤ 4 units 10 yr prior to DBE	0.149	0.027
> 1 DBE in one day by single endoscopist	0.016	0.024
Hgb > 9 mg/dL in the week prior to DBE	0.010	0.035
No blood transfusions in the year prior to DBE	0.019	0.044
Prior EGD with no ulcers or AVMs	0.031	0.004
Prior EGD or colonoscopy with no ulcers or AVMs	0.001	0.001
Prior enteroscopy with no AVMs	0.013	0.009

DBE: Double balloon endoscopy; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

normalities or showed nonspecific findings (isolated red spots or single erosion). Endoscopic hemostasis by argon plasma coagulation, electrocoagulation, or clipping was used for vascular lesions. Ulcers were treated if they were actively bleeding or had visible bleeding vessels. Small polyps were removed and tumors were generally tattooed and biopsied for histopathology.

Statistical analysis

SPSS software (Version 20 SPSS Inc., Chicago) was used to collect and analyze the data. Descriptive statistics, chi square, Fisher's exact test and logistic regression were conducted to analyze and identify variables associated with negative findings or no therapy during DBE. A P value < 0.05 was considered to be statistically significant.

RESULTS

A total of 55 DBE cases were reviewed. The mean age of the sample was 67.4 ± 11.2 years old with 32 men (58.2%). The majority of patients with overt GI bleeding presented with melena (30 cases, 54.5%), whereas 9 (16.4%) presented with hematochezia. An additional 5 cases presented with both (9%). The majority of patients had chronic GI bleeding of more than 1 mo duration (75.5%). The mean lowest hemoglobin was 7.42 ± 2.16 mg/dL in the 5 years prior to DBE.

A total of 13 cases were missing prior EGD or colonoscopy official reports. Push enteroscopy was performed on 23 cases prior to DBE and most procedures had preceding VCE (96.4%). 83.6% of cases had positive findings on VCE. However only 54.3% of positive VCE led to significant DBE findings. Presence of AVMs or active bleeding on VCE were noted on DBE in 65% of cases. Ulcers on VCE were only found in half of the follow up DBE cases. Polyps on VCE led to the lowest DBE yield (22%). Also, 5 cases had positive DBE findings that were not seen on VCE. The missed lesions were AVMs, ulcers, an ulcerated hamartoma and carcinoid tumor that led to surgery.

The mean duration of the DBE procedures was 109.8 ± 26.4 min. Fifty DBE cases (90.9%) were performed via the anterograde route. All of the anterograde DBE procedures reached the mid-distal jejunum and 35 (70%) reached the ileum. One patient had a total enteroscopy through the anterograde approach and one patient had a total enteroscopy using both oral and rectal approach.

AVMs accounted for most of our DBE findings (36.4%), as shown in Table 1. In total, 24 DBEs (43.6%) had negative diagnostic findings and 30 DBEs (54.5%) did not require endoscopic therapy. Based on our classification: 20 cases (36.4%) had active bleeding at the time of DBE, 23 (41.8%) were not active and 11 (20%) had occult GI bleeding. Positive diagnostic yield was seen in 10 (50%) active GI bleeding cases, 16 (69.5%) non-active and 4 (36.3%) occult GI bleeding cases. Five of 11 cases (45.5%) with acute GI bleeding at the time of DBE had positive diagnostic yield on DBE as opposed to 12 out 13 cases (92.3%) with acute GI bleed at the time of VCE. 4 patients required repeat DBE during our study period due to recurrent GI bleeding. Lower ASA score, negative findings on previous push enteroscopy and hgb of more than 9 prior to DBE were associated with negative diagnostic and therapeutic yield on bivariate analysis (Table 2). DBE diagnostic or therapeutic yield was not associated with age, gender, use of antiplatelets or anticoagulation medications, occult or overt bleeding, DBE procedure time, platelets, INR or albumin on bivariate analysis. Table 3 illustrates the relationship between diagnostic and therapeutic outcomes and time between GI bleed, VCE and DBE. In multivariate analysis, smaller blood transfusion requirements, absence of findings on EGD and colonoscopy and performance of more than one DBE per day per endoscopist were associated with negative diagnostic and negative therapeutic yield (Tables 4 and 5).

DISCUSSION

DBE was first described by Yamamoto *et al*[6] in 2001. Due to its potential insertion depth and total enteroscopy success, it has been an effective tool in obscure GI bleeding evaluation and management[18,19]. Previous reports indicate a 60%-80% diagnostic yield of DBE[13-16]. However, past studies have not focused on factors that may

Table 3 Time between gastrointestinal bleed, video capsule endoscopy and double balloon endoscopy in relation to outcomes *n* (%)

Variables		Less than 1 wk	1 wk to 1 mo	1 mo to 1 yr	More than 1 yr
Time from onset of GI bleed to VCE	VCE with positive findings/total No. of VCE	10/10 (100)	2/3 (66.7)	11/14 (78.6)	15/18 (83.3)
Time from onset of GI bleed to DBE	DBE with positive findings/total No. of DBE	2/8 (25)	3/3 (100)	9/14 (64.3)	17/27 (63)
	DBE leading to therapy/total No. of DBE	1/8 (12.5)	3/3 (100)	7/14 (50)	14/27 (51.9)
Time from VCE to the DBE procedure	DBEs with positive diagnostic yield/total No. of DBEs	8/15 (53.3)	3/6 (50)	15/25 (60)	3/6 (50)
	DBEs that led to therapy/total No. of DBEs	7/15 (46.7)	2/6 (33.3)	13/25 (52.0)	2/6 (33.3)

VCE: Video capsule endoscopy; DBE: Double balloon endoscopy; GI: Gastrointestinal.

Table 4 Multivariate logistic regression of factors associated with negative diagnostic yield of double balloon endoscopy

Variables	OR (95%CI)	*P* value
> 1 DBE in one day by single endoscopist	16.63 (2.04-135.45)	0.009
No blood transfusions within year prior to DBE	13.04 (1.53-111.04)	0.019
Prior EGD or colonoscopy with no ulcers or AVMs	19.30 (1.26-295.18)	0.033

DBE: Double balloon endoscopy; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

Table 5 Multivariate logistic regression of factors associated with non-therapeutic double balloon endoscopy

	OR (95%CI)	*P* value
> 1 DBE in one day by single endoscopist	18.28 (2.24 -148.86)	0.007
GI bleed within 1 wk prior to DBE	10.77 (2.18–53.14)	0.004
Blood transfusions ≤ 4 units in the year prior to DBE	4.27 (1.03-17.71)	0.045
Prior EGD or colonoscopy with no ulcers or AVMs	8.47 (1.28-55.87)	0.027

DBE: Double balloon endoscopy; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

help to predict outcomes of DBE.

To our knowledge, this is the first study to look at factors associated with both negative diagnostic and therapeutic yield of DBE. In the management of OGIB, patients often undergo multiple endoscopic procedures prior to DBE. The absence of findings on prior endoscopies may predict a negative diagnostic and therapeutic yield of DBE. In addition, patients with lower blood transfusion requirements were more likely to have a negative diagnostic and therapeutic yield. This is in line with what one would expect clinically and may have implications for risk stratification, utility, and timing of the procedure. Active GI bleeding in the week prior to DBE was not associated with positive DBE findings and led to less therapeutic interventions. This may be due to missed pathology on upper or lower endoscopy or due to poor visualization within the small bowel with active GI bleeding. However, most of the DBE reports did not indicate active bleeding suggesting that perhaps it is not an issue with missed pathology but a source that is no longer bleeding. This may be related to medications that are stopped while awaiting definitive therapeutic management such as anticoagulants or antithrombotics. One previous study demonstrated increased detection rates of bleeding sources on DBE for patients with two or more recurrent bleeding episodes. This was not looked at in our study[20].

Our study involved an older population undergoing DBE for obscure GI bleeding, mainly presenting with overt and chronic GI bleeding. Most of our DBE procedures were through the oral route. Small bowel AVMs were the most common findings in our study. This is consistent with previous studies where vascular lesions accounted for nearly two-thirds (65.9%) of positive findings in the western population[21]. VCE preceded DBE in 96.4% of cases. This helped guide the route and insertion depth of DBE. There was a high rate of positive VCE findings that led to non-diagnostic DBE in our study. These lesions could be classified as falsely positive VCE findings and were mainly polyps (88%), followed by ulcers (50%) and AVMs (35%). This is consistent with a previous multicenter prospective study showing acceptable concordance between DBE and VCE for AVMs and inflammatory lesions, but not for polyps or masses[11]. Protruding or bulging lesions would be falsely seen as polyps or masses on capsule endoscopy but then flattened by air insufflation when endoscopically visualized. This can explain the high rate of false positive findings for polyps. We still recommend further evaluation of polyps seen on VCE with imaging studies or endoscopy.

There are several possible reasons for negative findings on DBE. First, inability to perform complete enteroscopy in most DBE cases may limit findings. Several studies have reported widely variable rates of complete enteroscopy with DBE, ranging from 0% to 86%[7,9,13,14]. Similar to previous study designs, we relied on VCE findings to guide insertion depth and DBE insertion route. The absence of bleeding source beyond our insertion depth could not be confirmed; however our DBE cases evaluated the majority of the small intestine and reached suspected areas where positive lesions were seen on

VCE. An interesting study by Bollinger *et al*[22] using VCE to map the distribution of AVM in the western population identified the jejunum as the most common location for AVMs (80%). The ileum had the lowest distribution of AVM (5.7%)[22]. Thus, it is reasonable that the distance reached in our DBE would capture most AVMs.

Another reason for negative findings may be that lesions found on VCE may heal with time. The same number of cases had acute GI bleed at the time of VCE and DBE based on our classification of acute GI bleed, however more findings were seen with acute GI bleed at the time of VCE. This could be due to increased detection rate on VCE related to shortened time interval to onset of GI bleed. No association was found between DBE outcomes and time between VCE and DBE or time between onset of GI bleed and DBE; this could be due to a limited sample size. Third, lesions may have been missed on prior endoscopies. Fry *et al*[23] reported that a definite source of bleeding was detected in 24.3% of patients outside the small bowel and suggested that repeat upper and lower endoscopy should be considered prior to DBE. Our study only included 7 cases with repeat EGD and colonoscopy prior to DBE. Repeating endoscopy in our study did not alter findings or the need for DBE. Furthermore, an evaluation of the upper GI tract at the time of oral route DBE did not reveal any additional findings.

It is possible that negative diagnostic yield is related to missed lesions on DBE. It was hard to evaluate rebleeding rates post DBE in our study since most patients were seen at the time of DBE for the first time. However as this institution is only one of 2 referral centers in the state to perform DBE (located approximately 250 miles apart). One would assume that repeat DBE requests would again come to our institution for continued bleeding to attempt total enteroscopy through a combined approach. Thus, the low repeat DBE rate may indicate that patients did not have significant recurrent bleeding. Byeon *et al*[24] studied the diagnostic value of repeat DBE. Of 32 patients who underwent repeat DBE, all patients with negative initial DBE had a negative repeat DBE suggesting the reproducibility of the findings. On the other hand, seventeen of 21 patients with positive initial DBE again showed a probable bleeding source on repeat DBE[24]. Additionally, among the patients with normal findings at the first DBE procedure, 62.5% had no recurrent bleeding during the follow-up period of 40.4 ± 16.2 mo[25]. Negative DBE may portend a different clinical picture and a low likelihood of a small bowel source of bleeding.

DBE procedures are labor intensive, and can be tiring. The average examination time is approximately 60 to 90 min[9]. Our cases took longer than average to perform; however length of the procedure was not associated with diagnostic yield. It is known that colonoscopies have lower completion rates and adenoma detection rates in procedures performed in the afternoon compared with the morning, thought to be related to endoscopist fatigue. However, a study by Sanaka *et al*[26] evaluating DBE performance did not show a difference between morning or afternoon procedures. In our study we compared the cumulative effect of doing 2 or more procedures as opposed to one DBE a day. We found that there is an association with negative findings with more procedures in a day, which may indicate fatigue related factors affecting diagnostic and therapeutic yield. Thus, it may not be the timing of the procedure that matters but in fact the number of procedures one does given the long duration of DBE procedures.

There were several limitations to our study. First the small sample size and the retrospective design resulted in a wide confidence interval and less precise findings. Second of all, we were unable to accurately determine insertion depth and could not completely exclude the absence of findings in the unexamined small intestine as very few patients had complete enteroscopy.

In conclusion, this study may help stratify patients into high likelihood or low likelihood of negative diagnostic yield or therapy in DBE for gastrointestinal bleeding. This may help manage patients with multiple comorbidities and reduce health care costs by identifying those who are most likely to benefit from this time intensive procedure.

COMMENTS

Background

Double balloon endoscopy (DBE) is valuable in the setting of obscure gastrointestinal bleeding (OGIB). However, it is invasive, time-consuming and may be unable to identify a source for bleeding in 20% to 40% of OGIB cases.

Research frontiers

To identify patients' characteristics associated with DBE outcomes in investigation of OGIB.

Innovations and breakthroughs

To our knowledge, this is the first study to look at factors associated with both negative diagnostic and therapeutic yield of DBE. Fewer blood transfusion requirements, absence of arteriovenous malformations or ulcers on prior endoscopies and possibly endoscopist fatigue may predict a negative diagnostic and therapeutic yield of DBE.

Applications

This study may help stratify patients into high likelihood or low likelihood of negative diagnostic yield or therapy in DBE for gastrointestinal bleeding. This may help manage patients with multiple comorbidities and reduce health care costs by identifying those who are most likely to benefit from this time intensive procedure.

Peer review

This is a descriptive retrospective study into DBE. The results are therefore to be viewed with some caution and this in mind. Otherwise this study is worthy of publication.

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PROSPECTIVE STUDY

Efficacy and safety of endoscopic prophylactic treatment with undiluted cyanoacrylate for gastric varices

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Abstract

AIM: To evaluate the efficacy and safety of undiluted N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) as a prophylactic treatment for gastric varices (GV) bleeding.

METHODS: This prospective study was conducted at a single tertiary-care teaching hospital between October 2009 and March 2013. Patients with portal hypertension (PH) and GV, with no active gastrointestinal bleeding, were enrolled in primary prophylactic treatment with NBCM injection without lipiodol dilution. Initial diagnosis of GV was based on endoscopy and confirmed with endosonography (EUS); the same procedure was used after treatment to confirm eradication of GV. After puncturing the GV with a regular injection needle, 1 mL of undiluted NBCM was injected intranasally into GV. The injection was repeated as necessary to achieve eradication or until a maximum total volume of 3 mL of NBCM had been injected. Patients were followed clinically and evaluated with endoscopy at 3, 6 and 12 mo. Later follow-ups were performed yearly. The main outcome measures were efficacy (GV eradication), safety (adverse events related to cyanoacrylate injection), recurrence, bleeding from GV and mortality related to GV treatment.

RESULTS: A total of 20 patients (15 male) with PH and GV were enrolled in the study and treated with undiluted NBCM injection. Only 2 (10%) patients had no esophageal varices (EV); 18 (90%) patients were treated with endoscopic band ligation to eradicate EV before inclusion in the study. The patients were followed clinically and endoscopically for a median of 31 mo (range: 6-40 mo). Eradication of GV was observed in all patients (13 patients were treated with 1 session and 7 patients with 2 sessions), with a maximum injected volume of 2 mL NBCM. One patient had GV recurrence, confirmed by EUS, at 6-mo follow-up, and another had late recurrence with GV bleeding after 35 mo of follow-up; overall, GV recurrence was observed in 2 patients (10%), after 6 and 35 mo of follow-up, and GV bleeding rate was 5% (1 patient). Mild epigastric pain was reported by 3 patients (15%). No mortality or major complications, including embolism, or damage to equipment were observed.

CONCLUSION: Endoscopic injection with NBCM, without lipiodol, may be a safe and effective treatment for primary prophylaxis of gastric variceal bleeding.

Key words: Gastric varices; Primary prevention; Endos-

copy; Gastrointestinal; Cyanoacrylates; Gastrointestinal hemorrhage

Core tip: In this prospective study, a total of 20 patients with portal hypertension and gastric varices (GV) were referred for primary prophylaxis of GV bleeding with endoscopic injection of N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) without lipiodol dilution. Eradication of GV was observed in all patients. Overall, GV recurrence confirmed by endosonography was observed in 2 patients (10%), after 6 and 35 mo of follow-up. The prevalence of GV bleeding was 5% (1/20 patients). No major complications, such as embolism occurrence or death, were observed. Undiluted NBCM may be a safe and effective prophylactic against GV bleeding.

Franco MC, Gomes GF, Nakao FS, de Paulo GA, Ferrari Jr AP, Libera Jr ED. Efficacy and safety of endoscopic prophylactic treatment with undiluted cyanoacrylate for gastric varices. *World J Gastrointest Endosc* 2014; 6(6): 254-259 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i6/254.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i6.254

INTRODUCTION

Gastric varices (GV) are less common than esophageal varices (EV) and are estimated to be present in approximately 20% of patients with portal hypertension (PH). Risk of rupture is lower for GV than EV, however GV rupture can be extremely severe and difficult to control, and is associated with higher mortality than EV bleeding (25%-45%)[1].

Endoscopic ultrasound (EUS) is a very sensitive tool for GV detection[2]. It is also very useful for the assessment of GV obliteration with tissue adhesive injection and predicting recurrence of varices[3,4].

Since its introduction in the 1980s, endoscopic therapy with cyanoacrylate (CYA) improved the treatment of GV bleeding, achieving hemostasis rates of 89% to 100%, and reducing the rate of recurrent bleeding to below 30%[5,6]. Treatment of GV using glue injection is a well-established procedure. The most commonly used preparation of CYA is N-butyl-2 cyanoacrylate (Histoacryl®; B. Braun, Germany) diluted with lipiodol (Lipiodol Ultra Fluid®; Guerbert Roissy, France). The adverse events associated with CYA injection are usually minor (fever and mild abdominal pain); however, treatment can be associated with major and potentially life-threatening adverse events, usually related to peripheral embolization of polymerized glue, such as pulmonary embolism, splenic vein and portal vein thrombosis, splenic infarction and recurrent sepsis[7].

Glubran 2® (GEM; Viareggio, Italy) is a preparation of N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM). NBCM has a longer polymerization time than pure N-butyl-2 cyanoacrylate and does not usually require dilution with lipiodol[8]. NBCM seems to be as safe and effective as the combination of N-butyl-2 cyanoacrylate and lipiodol for GV obliteration[9].

Our study was conducted to evaluate the efficacy and safety of endoscopic injection of NBCM without lipiodol as a prophylactic treatment for GV bleeding.

MATERIALS AND METHODS

This prospective study was conducted between October 2009 and March 2013 at São Paulo Hospital, Federal University of São Paulo, Brazil, a tertiary-care teaching hospital. All patients gave written informed consent before enrollment. The study was approved by the Ethics Committee of our institution and was conducted in accordance with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

The following outcomes were analyzed: efficacy (GV eradication); safety (adverse events related to cyanoacrylate injection); GV recurrence; GV bleeding and mortality related to GV treatment.

Patients

Patients with PH and large GV (> 10 mm) and no previous GV bleeding were eligible. Patients were followed clinically and endoscopically. Patient age varied from 18 to 75 years. Exclusion criteria were prior endoscopic treatment for GV, history of hepatocellular carcinoma, pregnancy.

Diagnosis of PH and liver disease was based on physical examination, biochemical tests, imaging studies including Doppler evaluation of the splenoportal axis and histological evidence. Patients were classified according to the Child-Pugh classification as having class A, B, or C liver disease.

Endoscopic diagnosis and interventions

All endoscopic procedures were performed under conscious sedation using the standard technique. Patients with esophageal varices who were high risk for bleeding underwent esophageal variceal eradication with endoscopic band ligation (EBL) prior to GV treatment. Sarin's classification[1] was used to classify GV as type 1 gastroesophageal varices (GOV-1), type 2 gastroesophageal varices (GOV-2), type 1 isolated gastric varices (IGV-1) or type 2 isolated gastric varices (IGV-2); Hashizume's schema[10] was used to classify the form of GV as tortuous (F1), nodular (F2) or tumorous (F3) and the presence of red color signs was recorded. Presence and severity of portal hypertensive gastropathy[11] were also documented. An EUS examination was performed to confirm the presence of GV.

GV puncture, preferentially at the center of the varix, was performed using a regular injection catheter (19 gauge needle), filled with distilled water. Once the intravariceal position of the needle was confirmed, 1 mL of undiluted NBCM was injected followed by enough

Table 1 Demographic characteristics of patients *n* (%)

Characteristics	Patients (*n* = 20)
Mean age in years	47.35 ± 11.37
Male	15 (75)
Etiology	
Viral	9 (45)
Alcohol	5 (25)
Schistosomiasis	2 (10)
Other	4 (20)
Child-Pugh class	
A	13 (65)
B	7 (35)
Prior history of UGB	10 (50)
Eradication of EV	18 (90)
Propranolol use	12 (60)

UGB: Upper gastrointestinal bleeding; EV: Esophageal varices.

Table 2 Endoscopic characteristics of patients *n* (%)

Characteristics	Patients (*n* = 20)
GV Classification	
GOV1	13 (65)
GOV2	3 (15)
IGV1	4 (20)
Form of GV	
F1	7 (35)
F2 or F3	13 (65)
PHG	
Mild	16 (80)
Severe	4 (20)
RCS	4 (20)

GV: Gastric varices; GOV1: Type 1 gastroesophageal varices; GOV2: Type 2 gastroesophageal varices; IGV1: Type 1 isolated gastric varices; PHG: Portal hypertensive gastropathy; RCS: Red color signs.

distilled water to flush all the glue into the GV. The needle was then removed. If necessary, glue injection was repeated at a subsequent session (at 3 mo), up to a maximum injected volume of 2 mL of NBCM.

GV eradication was assessed by endoscopically detectable features, no varices, residual scar or residual hard varices - assessed by touching with closed forceps - and EUS was used to confirm that there was no blood flow into residual varices. A linear array echoendoscope (EG-530 UT; Fujinon, Saitama, Japan) with VP4400 processor (Fujinon; Saitama, Japan) or SU-7000 ultrasonic processor (Fujinon; Saitama, Japan) was used to perform EUS. Endoscopic follow-up was performed at 3-mo intervals until GV eradication was observed; subsequent reevaluations were made at 3, 6 and 12 mo. Later follow-ups were performed yearly. Any clinical suspicion of gastrointestinal bleeding prompted an endoscopic examination.

Statistical analysis

Quantitative variables were expressed as means ± SD or medians (ranges). Qualitative variables were expressed as frequencies and percentages. Statistical analysis was performed using SPSS 13.0 for Windows.

RESULTS

A total of 20 patients with PH and large GV were included in this study. Demographic characteristics of patients are listed in Table 1. According to the Child-Pugh classification 13 (65%) patients had class A disease, and 7 (35%) class B. We attributed the higher than normal proportion of patients with Child-Pugh A to the design of the study, which selected patients for primary prophylaxis of GV bleeding. Ten patients had a history of upper gastrointestinal bleeding (UGB), due to EV bleeding. Eighteen (90%) patients underwent endoscopic treatment with EBL to eradicate EV before the beginning of the study; the remaining patients had no EV. Twelve patients were taking Propranolol. Most patients presented with GV type GOV1. The endoscopic characteristics of patients are listed in Table 2.

Table 3 Overall results of gastric varices treatment with cyanoacrylate injection *n* (%)

Characteristics	Patients (*n* = 20)
GV eradication	20 (100)
Number of sessions	
1	13 (65)
2	7 (35)
Mean volume NBCM injected in mL	1.37 ± 0.48
Recurrence rate	
3 mo	0
6 mo	1 (5)
> 2 yr	1 (5)
Total	2 (10)
Median follow-up in months (range)	31 (6-40)
Late bleeding rate	1 (5)
Minor adverse events[1]	3 (15)
Major adverse events	0
Overall mortality rate	0

[1]Epigastric pain. GV: Gastric varices; NBCM: N-butyl-2 cyanoacrylate plus methacryloxysulfolane.

After treatment with undiluted NBCM GV eradication was observed in all patients (Table 3). GV obliteration was achieved in 1 session in 13 (65%) patients and in 2 sessions in 7 (35%) patients, with a mean NBCM volume of 1.37 mL (SD = ± 0.48) (Figure 1). Eighteen patients underwent EUS before CYA injection and GV was confirmed in all patients; 12 (66%) had perigastric collaterals, 9 (50%) had paragastric collaterals and 5 (28%) had perforating veins. Eradication of GV after treatment was confirmed in 18 patients using EUS. In two patients GV eradication was based on endoscopic criteria, without EUS evaluation. Only 1 (5%) patient experienced GV recurrence, confirmed by EUS, at 6-mo follow-up. He had hepatitis C infection (Child-Pugh A), and large (F2) type 2 gastroesophageal varices with red spots.

A late endoscopic follow-up, at least 2 years after eradication, was performed in 16 (80%) patients. Late recurrence of GV, confirmed by EUS, was observed in one patient at a 35-mo follow-up. This patient had alcohol-

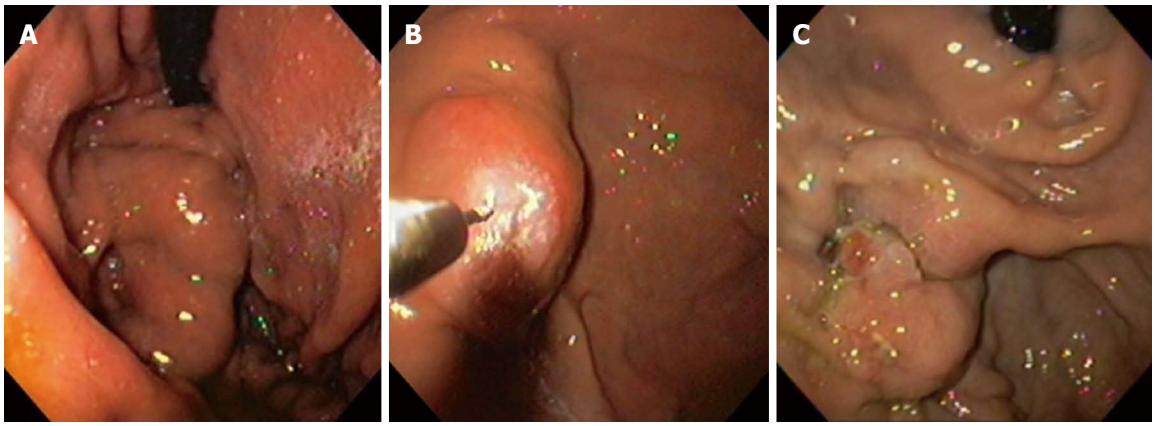

Figure 1 Endoscopic view of cyanoacrylate injection therapy. A: Initial view before injection; B: Aspect immediately after glue injection; C: Six months after injection.

related liver disease (Child-Pugh B), large (F2) type 1 gastroesophageal varices at the first endoscopic evaluation. He presented with upper gastrointestinal bleeding with no significant clinical consequences, and was treated with a second CYA injection and suffered no adverse events. Four patients were lost during follow-up, although none were readmitted to our hospital with GV bleeding. Overall, the GV recurrence rate was 10% and the GV bleeding rate was 5%, over a median of 31 mo (range: 6-40 mo).

No mortality was observed during our study. Mild epigastric pain was reported by 3 patients (15%). No major adverse events (systemic embolism, sepsis or gastrointestinal bleeding due CYA injection) or damage to equipment were observed (Table 3).

DISCUSSION

Endoscopic therapies for esophageal varices, such as band ligation and injection of sclerosant agents, have also been used to treat GV bleeding. However the results in terms of hemostasis, rebleeding and GV obliteration are poor compared with CYA injection[5,12], so endoscopic CYA injection has been recommended as an initial treatment for acute GV bleeding in recent consensus and guidelines[13-15]. Treatment of GV bleeding using transjugular intrahepatic portosystemic shunt (TIPS) has also been studied; although TIPS is as safe and clinically effective as CYA injection, TIPS placement is associated with higher long-term morbidity, due to increased incidence of encephalopathy, and it is also more expensive[16].

There have been recent reports of increased survival with primary and secondary prophylaxis of GV bleeding with CYA injection[17,18], but only a few studies have evaluated the safety and long-term efficacy of prophylactic CYA injection[19,20]. In this study, prophylactic GV eradication was achieved in all patients with NBCM injection. The GV recurrence rate was 10% (2/20) and the prevalence of late GV bleeding was 5% (1/20). There were no reported deaths related to GV bleeding during follow-up. These results are similar to previously published reports on prophylactic treatment of GV with Histoacryl® plus lipiodol over follow-up periods of up to 2 years. Previous studies reported eradication rates ranging from 95% to 100%; GV recurrence rates ranging from 4.3% to 14.0%; GV rebleeding rates from 4.3% to 8.0% and GV-associated mortality rates up to 4.3%[19,20].

Greater dilution of CYA with lipiodol seems to increase the risk of embolization[21]. Most reported major adverse events after CYA injection, such as distal embolization and death, occurred in patients in whom this combination was used[7,21,22].

Dhiman *et al*[23] reported no embolic events after switching from CYA diluted with lipiodol (1:1) to undiluted CYA injection as a treatment for GV bleeding. Similarly Kumar *et al*[24] reported no clinically significant embolization in 87 patients treated for GV bleeding using 261 injections of undiluted CYA.

NBCM (Glubran 2®) does not require dilution with lipiodol because it polymerizes a little more slowly than pure N-butyl-2 cyanoacrylate (Histoacryl®)[8]. One may hypothesize that after injection into the varix NBCM in contact with blood polymerizes faster than N-butyl-2 cyanoacrylate diluted with lipiodol. Such fast local intravasal polymerization of undiluted NBCM might be associated with reduced incidence of embolic events. Further research is required to investigate this hypothesis as there is currently no published empirical evidence.

In our study there were no major adverse events over 27 injections of undiluted NBCM in 20 patients for GV prophylactic eradication. Saracco *et al*[25] reported a single fatal systemic embolism after treatment of GV bleeding with undiluted NBCM using 2 mL of NBCM in one session, in a patient with idiopathic PH. It is recommended that CYA be used as 1 mL injections per session, because larger injected volumes are associated with a higher risk of peripheral embolization[26].

We used EUS to assess GV obliteration and recurrence after treatment with NBCM injections. Flow in residual GV, which would indicate that further CYA injection were required[27], can be detected using EUS. EUS has also been used to support GV eradication by CYA injection into gastric perforating veins, a method which

appears to be safe and effective, with a low recurrent bleeding rate[28].

This study is significant because there are only few reports on the efficacy and long-term safety of prophylactic CYA injection for GV[19,20]. Furthermore, this study is the first to have evaluated the feasibility, efficacy and long-term safety of NBCM as a prophylactic treatment for GV bleeding in adults.

In conclusion, although our findings are subject to some limitations (small series, patients with good liver function, one arm design in a single institution, and loss to follow up of some patients), our results suggest that endoscopic injection with NBCM, without lipiodol, may be a safe and effective primary prophylactic for gastric variceal bleeding.

COMMENTS

Background

Endoscopic cyanoacrylate (CYA) injection has been recommended as initial treatment for gastric varices (GV) acute bleeding. Band ligation and injection of sclerosant agents produce worse outcomes in terms of GV hemostasis and rebleeding than CYA injection. TIPS is associated with increased incidence of encephalopathy.

Research frontiers

Although a recent publication of Mishra *et al* has reported reduced risk of first bleeding and lower mortality with CYN injection, compared with beta-blockers, for prophylactic treatment of large GV, only a few studies have evaluated the safety and long-term efficacy of prophylactic CYA injection.

Innovations and breakthroughs

N-butyl-2 cyanoacrylate diluted with lipiodol is the most commonly used CYA preparation used for endoscopic injection into GV, however it is associated with a risk of peripheral embolization of polymerized glue. N-butyl-2 cyanoacrylate plus methacryloxysulfolane (NBCM) does not usually require dilution with lipiodol for GV injection, and may be associated with a lower incidence of adverse events. This is the first study to have evaluated the feasibility, efficacy and long-term safety of NBCM as a prophylactic treatment for GV bleeding in adults.

Applications

Endoscopic treatment with CYN injection is low cost, widely available, and not hard to do.

Terminology

NBCM is a preparation of N-butyl-2 cyanoacrylate with methacryloxysulfolane. NBCM has a longer polymerization time than pure N-butyl-2 cyanoacrylate.

Peer review

It is interesting that this study was the first to determine the efficacy and safety of prophylactic treatment by undiluted N-butyl-2 Cyanoacrylate plus Methacryloxysulfolane (NBCM) for gastric varices. And the authors concluded endoscopic injection with NBCM, without lipiodol, may be a safe and effective treatment for primary prophylaxis of gastric varices bleeding.

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CASE REPORT

Endoscopic treatment of duodenal fistula after incomplete closure of ERCP-related duodenal perforation

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Author contributions: Yu DW and Hong MY treated the patient and collected the patient's clinical data; Hong SG supervised the two doctors, designed and wrote the case report.

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an important diagnostic and therapeutic modality for various pancreatic and biliary diseases. The most common ERCP-induced complication is pancreatitis, whereas hemorrhage, cholangitis, and perforation occur less frequently. Early recognition and prompt treatment of these complications may minimize the morbidity and mortality. One of the most serious complications is perforation. Although the incidence of duodenal perforation after ERCP has decreased to < 1.0%, severe cases still require prolonged hospitalization and urgent surgical intervention, potentially leading to permanent disability or mortality. Surgery remains the mainstay treatment for perforations of the luminal organs of the gastrointestinal tract. However, evidence from case reports and case series support a beneficial role of endoscopic clipping in the closure of these defects. Duodenal fistulas are usually a result of sphincterotomies, perforated duodenal ulcers, or gastrectomy. Other causative factors include Crohn's disease, trauma, pancreatitis, and cancer. The majority of duodenal fistulas heal with nonoperative management. Those that fail to heal are best treated with gastrojejunostomy. Recently proposed endoscopic approaches for managing gastrointestinal leaks caused by fistulas include fibrin glue injection and positioning of endoclips. Our patient developed a secondary persistent duodenal fistula as a result of previous incomplete closure of duodenal perforation with hemoclips and an endoloop. The fistula was successfully repaired by additional clipping and fibrin glue injection.

Key words: Perforation; Duodenal; Endoscopic retrograde cholangiopancreatography; Fistula; Glue

Core tip: In this report, a patient developed a secondary persistent duodenal fistula following an incomplete endoscopic closure of endoscopic retrograde cholangiopancreatography-related duodenal perforation with hemoclips and an endoloop. The fistula was successfully managed by further endoscopic treatment with additional clipping and fibrin glue injection. This case emphasizes that endoscopists should remain aware of the possibility for a secondary persistent fistula formation due to incomplete closure when long-standing fluctuating free air is detected after endoscopic treatment of bowel perforation.

Yu DW, Hong MY, Hong SG. Endoscopic treatment of duodenal fistula after incomplete closure of ERCP-related duodenal perforation. *World J Gastrointest Endosc* 2014; 6(6): 260-265 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i6/260.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i6.260

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP), an important technique used for diagnosis and therapeutic modality of various pancreatic and biliary diseases, is plagued by serious complications that can

lead to significant morbidity. Overall, complications occur in 5%-10% of cases following ERCP with or without sphincterotomy[1]. The incidences of post-ERCP pancreatitis, hemorrhage, cholangitis, and perforation are 3.5%-3.8%, 0.9%-1.3%, 1.0%-5.0%, and 0.1%-1.1%, respectively. The overall mortality rate after ERCP is 0.3%[2,3]. Early recognition and prompt treatment of these complications may minimize the morbidity and mortality. One of the most feared complications is perforation. Perforation management depends on the location, radiologic imaging findings, and severity of the injury. The majority of duodenal fistulas are surgical complications caused by inadequate closure or devascularization of the duodenum. Other causative factors include Crohn's disease, trauma, peptic ulcer disease, pancreatitis, and cancer[4]. The treatment of choice for patients with duodenal perforation is primary surgical closure. There have been reported cases of endoscopic closures of ERCP-related duodenal perforations using hemoclips[5]. Despite various strategies, from a minimally invasive approach with nutritional support to a more risky open surgery, duodenal fistulas remain difficult to treat[6].

To the best of our knowledge, there has been only one previously published report on a secondary duodenal fistula after ERCP-related duodenal perforation[7]. Recently, a patient in our care experienced a case of duodenal perforation following ERCP. Despite immediate application of multiple hemoclips and an endoloop to close the defect, a secondary persistent duodenal fistula, communicating with the peritoneal cavity, developed due to incomplete primary endoscopic closure. The fistula was successfully treated by further endoscopic treatment with additional clipping and fibrin glue injection.

CASE REPORT

A 66-year-old woman was admitted to our emergency department complaining of upper abdominal pain and vomiting, which occurred 3 h prior to her admission. On physical examination, her blood pressure was 130/75 mmHg, heart rate was 93 beats/min, and body temperature was 36.8 ℃. Palpation revealed tenderness in the right upper quadrant of the abdomen. Laboratory test results were as follows: hemoglobin concentration, 11.5 g/dL; white blood cell count, 6800 cells/μL; aspartate aminotransferase, 222 IU/L; alanine aminotransferase, 86 IU/L; total bilirubin, 0.6 mg/dL; alkaline phosphatase, 49 IU/L; and gamma-glutamyl transpeptidase, 52 IU/L.

On the initial abdominal computed tomography (CT), a small (approximately 4 mm) distal common bile duct (CBD) stone was suspected. ERCP was performed on the day of admission (Figure 1A). While placing the scope in a short scope position, the scope was rapidly withdrawn into the pylorus and an approximately 10 mm linear perforation occurred in the lateral wall of the duodenal bulb. Multiple hemoclips (Olympus Corp., Tokyo, Japan) with a detachable plastic snare (Endoloop; Olympus Corp.) were immediately applied to close the perforation (Figure 1B-D). The patient developed chills and diffuse abdominal pain; the chest X-ray showed free air under both hemidiaphragms (Figure 2). Following ERCP, laboratory test results were as follows: hemoglobin concentration, 10.7 g/dL white blood cell count, 7900 cells/μL; aspartate aminotransferase, 485 IU/L; alanine aminotransferase, 438 IU/L; total bilirubin, 0.9 mg/dL; alkaline phosphatase, 59 IU/L; C-reactive protein (CRP), 81 mg/L; amylase, 32 IU/L; and lipase 25.7 IU/L. Nil per os was initiated with peripheral parenteral nutrition, intravenous broad spectrum antibiotic administration, and nasogastric tube drainage.

Abdominal pain was relieved on the sixth day after the endoscopic treatment, and the amount of free air under both hemidiaphragms was decreased on the chest X-ray. The laboratory test results showed that liver function was normalized and the CRP level decreased to 32.3 mg/L. The patient remained symptom-free for 3 d, and was permitted to take sips of water on the ninth day after duodenal perforation. Although the serum CRP level did not increase, the chest X-ray showed increased free air under both hemidiaphragms two days later. A follow-up CT scan with oral contrast (Gastrografin) showed no contrast leakage, however, it did show moderate amount of pneumoperitoneum (Figure 3). To determine if surgery was needed, a surgeon was consulted and the decision was made to continue conservative management for one more week. Although the patient remained symptom-free during this one-week period, the second follow-up CT showed a small fistula, approximately 2 mm in diameter, communicating with the peritoneal cavity at the prior perforation site in the duodenum (Figure 4). The previous CBD stone was not observed, and we presumed the stone had passed spontaneously. The serum CRP level was nearly normalized. With patient and medical guardian's consent, a decision was made to perform endoscopic treatment before the operation. The secondary duodenal fistula was successfully closed using endoscopic treatment with additional clipping and fibrin glue (Greenplast®) injection (Figure 5). The free air under both hemidiaphragms significantly decreased the day after the endoscopic treatment, and the patient resumed a scheduled diet followed by a discharge three weeks after the development of duodenal perforation.

DISCUSSION

Although ERCP-related perforation is reported in less than 1% of cases, mostly due to sphincterotomy, perforation needs to be diagnosed immediately and treated promptly. Delays in the diagnosis and intervention of the perforation may lead to the development of sepsis and multiorgan failure, resulting in high mortality (8%-23%)[8-10]. The most commonly used classification of ERCP-induced perforations, suggested by Stapfer *et al*[11], is based on the mechanism of perforation and forecasts the need for surgery depending on the anatomic location and severity of injury. Another classification proposed

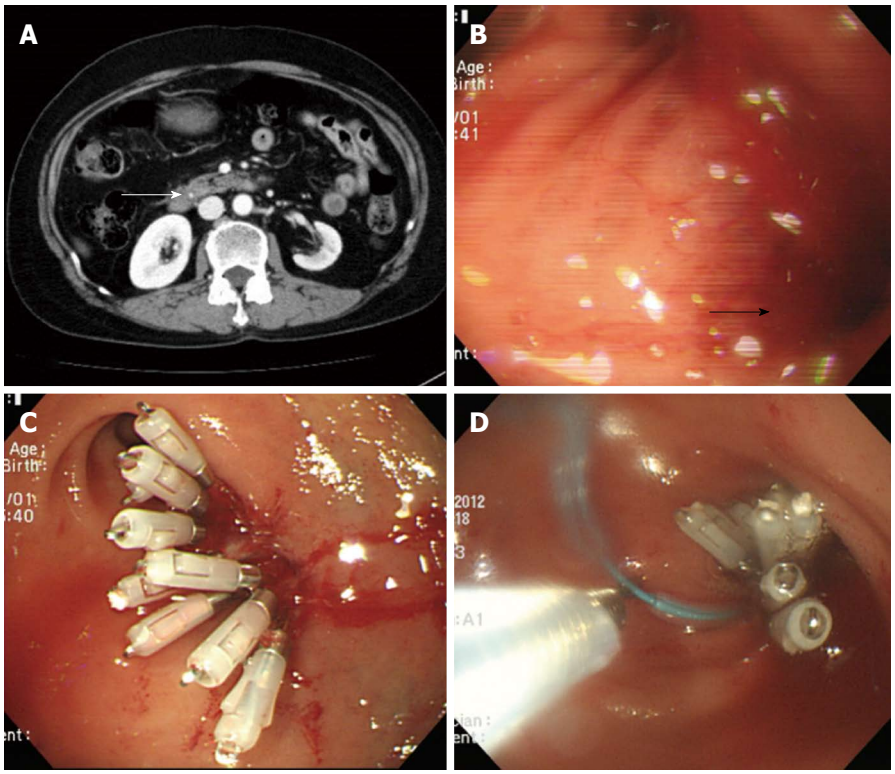

Figure 1 Initial abdominal computed tomography and endoscopic findings during endoscopic retrograde cholangiopancreatography. A: Computed tomography showed a small common bile duct stone (thin white arrow); B: During endoscopic retrograde cholangiopancreatography, a 10 mm-sized perforation developed in the lateral wall of the duodenal bulb during inadvertent rapid withdrawal of the duodenoscope (thick black arrow); C and D: Multiple hemoclips and an endoloop were immediately applied for the defect closure.

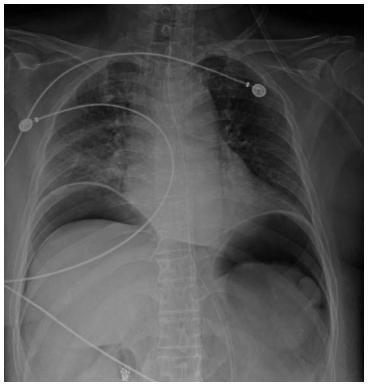

Figure 2 Chest X-ray after endoscopic retrograde cholangiopancreatography. The scan shows a large amount of pneumoperitoneum below both the hemidiaphragms.

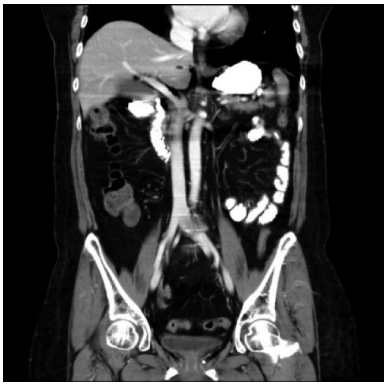

Figure 3 Follow-up abdominal computed tomography after duodenal perforation. No contrast leakage was detected into the peritoneum at the periduodenal lesion after endoscopic treatment; however, a moderate amount of pneumoperitoneum was present.

by Howard *et al*[12] categorizes ERCP-induced perforation into three types: guidewire, periampullary, and duodenal perforation.

The treatment of post-ERCP perforation should be determined based on the type, the severity of the leak, and clinical manifestations. In our case, the perforation was classified as type I using Stapfer's classification. Type I injury is caused by the endoscopic tip or insertion tube resulting in a large perforation requiring immediate surgery. However, if immediate treatment by endoscopic technique is not possible, conservative management with close monitoring may be a better option[9-11]. Sphincterotomy-related, guide-wire-related, or stent-related perforations can be treated by the endoscopic method with adequate ductal drainage above the perforation site[9,11]. In previous case reports, ERCP-related duodenal perforations were managed successfully with the use of endoclips[5,13]. However, adequate closure required inclusion of the bowel wall submucosal layer, which clips cannot reliably ensure. The patients need to be carefully selected, since the method is applicable to small, early detected,

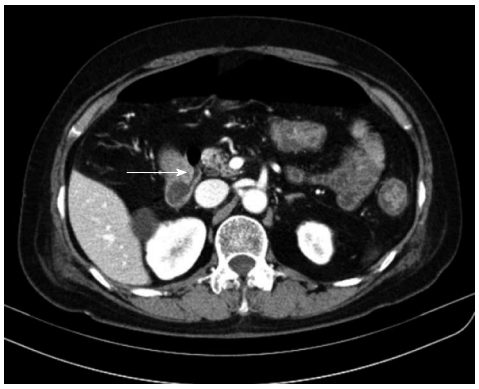

Figure 4 Second follow-up abdominal computed tomography after duodenal perforation. The scan shows a small fistula communicating with the peritoneal space, at the previous perforation site in the duodenal bulb (arrow), and absence of a common bile duct stone.

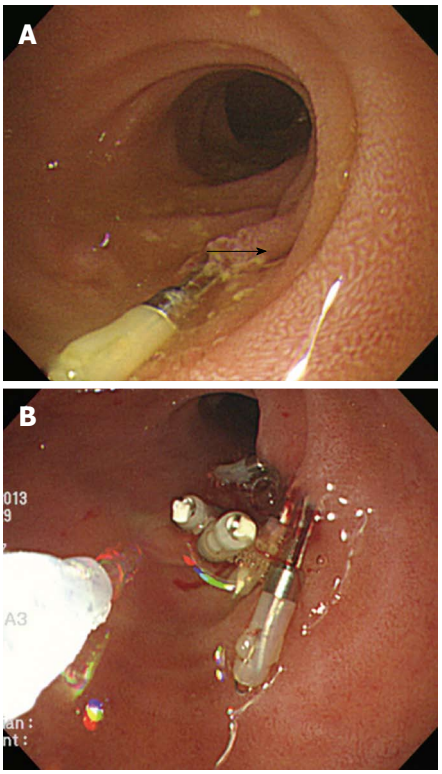

Figure 5 Endoscopic findings of the second endoscopic closure. A: A suspicious fistulous opening was detected at the previous perforation site (arrow); B: An application of additional multiple hemoclips and fibrin glue injection was successfully performed at the site of the suspicious fistulous opening.

and well-defined perforations, which meet all the criteria for conservative management such as the absence of abdominal signs and fluid collections.

Our patient was immediately treated with endoscopy using multiple hemoclips and fibrin glue injection despite the perforation being relatively large (approximately 10 mm) for endoscopic closure. Although the endoscopy went well, a persistent secondary duodenal fistula, communicating with the peritoneal cavity, was observed on repeat CTs. Furthermore, free air was detected under the hemidiaphragms, despite the lack of extravasation of the contrast and the typical abdominal pain associated with the condition. An explanation for the free air is that it leaked from the fistula.

Gastrointestinal fistulas that result from surgery, disease, or trauma, are first treated medically. This includes parenteral nutrition and bowel rest, as well as control of infection, correction of electrolyte imbalance, and local care of the fistula tract. Patients with obstruction of the intestinal lumen downstream of the fistula or patients who have a persistent fistula, which fails to close after prolonged medical treatment, require surgical treatment[4,6]. Recently, various endoscopic approaches have been proposed for managing gastrointestinal leaks caused by fistulas, including fibrin glue injection, endoclip positioning, suturing devices, stent insertion, and endoluminal vacuum devices[14-16].

Fibrin glue, a formulation made up of glue and thrombin, is applied by a double injector system to repair tears. Mixing of these two components results in a fibrin coagulum formation with a short onset time. Fibrin injection can be used for sealing only very small leaks (< 5 mm diameter) not connected to the cavities, and in the absence of abscesses[17]. In a retrospective analysis of 52 patients with fistulas and anastomotic leakages in the gastrointestinal tract, endoscopic treatment was successful in 56% of cases. The success rate for fibrin glue application as the sole endoscopic therapy was 37%[16]. In short, endoscopic treatment with fibrin glue should be considered as a valuable option for treating fistula and anastomotic leakage of the gastrointestinal tract.

Standard clips are widely used in endoscopy for mechanical hemostasis following post-procedural bleeding. The importance of their role in endoscopic closure of small perforations, immediately following polypectomy or mucosectomy, is widely recognized. However, data on the endoclip efficacy in treating post-surgical leaks and fistulas are variable. Furthermore, the low closure strength of endoclips limits their use in scarred and hardened post-surgical tissues. To overcome this limitation, a new over-the-scope clip system (OTSC; Ovesco Endoscopy AG, Tubingen, Germany), consisting of a large nitinol clip loaded on the tip of the endoscope, has recently been developed. This device enables capturing of a large amount of tissue, powerfully compressing and approximating the margins of a lesion, thus favoring its healing[14,18].

CBD stones, especially the small ones, may pass spontaneously in a significant number of patients[19,20]. The absence of a stone in the patient's CBD on follow-up CT could be explained by its spontaneous passage. Contrast leakage was not observed at the previous perforation site after endoscopic closure on the second follow-up CT. However, the leakage of air into the peritoneal space could have occurred through the secondary small fistula due to prior inadequate closure. Consequently, delayed formation of a secondary fistula should be considered in the presence of long-term, fluctuating free air under the diaphragm, viewed on abdominal imaging, following the

endoscopic treatment.

In summary, despite the initial endoscopy treatment with hemoclips and an endoloop, a secondary persistent duodenal fistula developed due to incomplete previous endoscopic closure of the duodenal perforation after ERCP. Additional clipping and fibrin glue injections were successful in closing of the fistula.

COMMENTS

Case characteristics

Diffuse abdominal discomfort after endoscopic closure of the endoscopic retrograde cholangiopancreatography (ERCP)-related perforation with no specific symptom six days after ERCP.

Clinical diagnosis

Failure or inadequacy of endoscopic treatment for ERCP-related duodenal perforation.

Differential diagnosis

Residual common bile duct stone or periduodenal abscess formation at the perforation site was possible.

Laboratory diagnosis

C-reactive protein was elevated after ERCP-related perforation followed by a decrease six days after endoscopic treatment.

Imaging diagnosis

A secondary duodenal fistula formation into the peritoneal cavity on abdominal computed tomography (CT) due to inadequate primary endoscopic treatment for ERCP-related perforation.

Treatment

After failed endoscopic closure of the ERCP-related duodenal perforation and the secondary fistula formation at the perforation site on abdominal CT 16 d after ERCP, a rescue endoscopic treatment with hemoclips and fibrin glue was successfully achieved, and persistent free air on chest X-ray disappeared a day after the rescue treatment.

Related reports

The retroperitoneal duodenal perforation after biliary sphincterotomy led to development of the secondary duodenal fistula, refractory to laparotomy and drainage with conservative treatment, which was successfully managed with biliary self-expandable metallic stent insertion.

Term explanation

Fibrin glue, a biologic tissue adhesive, is made up of fibrinogen and thrombin, and has been used endoscopically for the treatment of bleeding, fistulas, and anastomotic leak.

Experiences and lessons

Clinicians should consider the possibility of a secondary fistula formation into the peritoneal cavity, due to the presence of persistent fluctuating free air on chest X-ray after endoscopic treatment of a bowel perforation.

Peer review

A very clear and concise case presentation. Well-structured and correctly documented. It is an interesting experience and we appreciate for sharing it with the readers.

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