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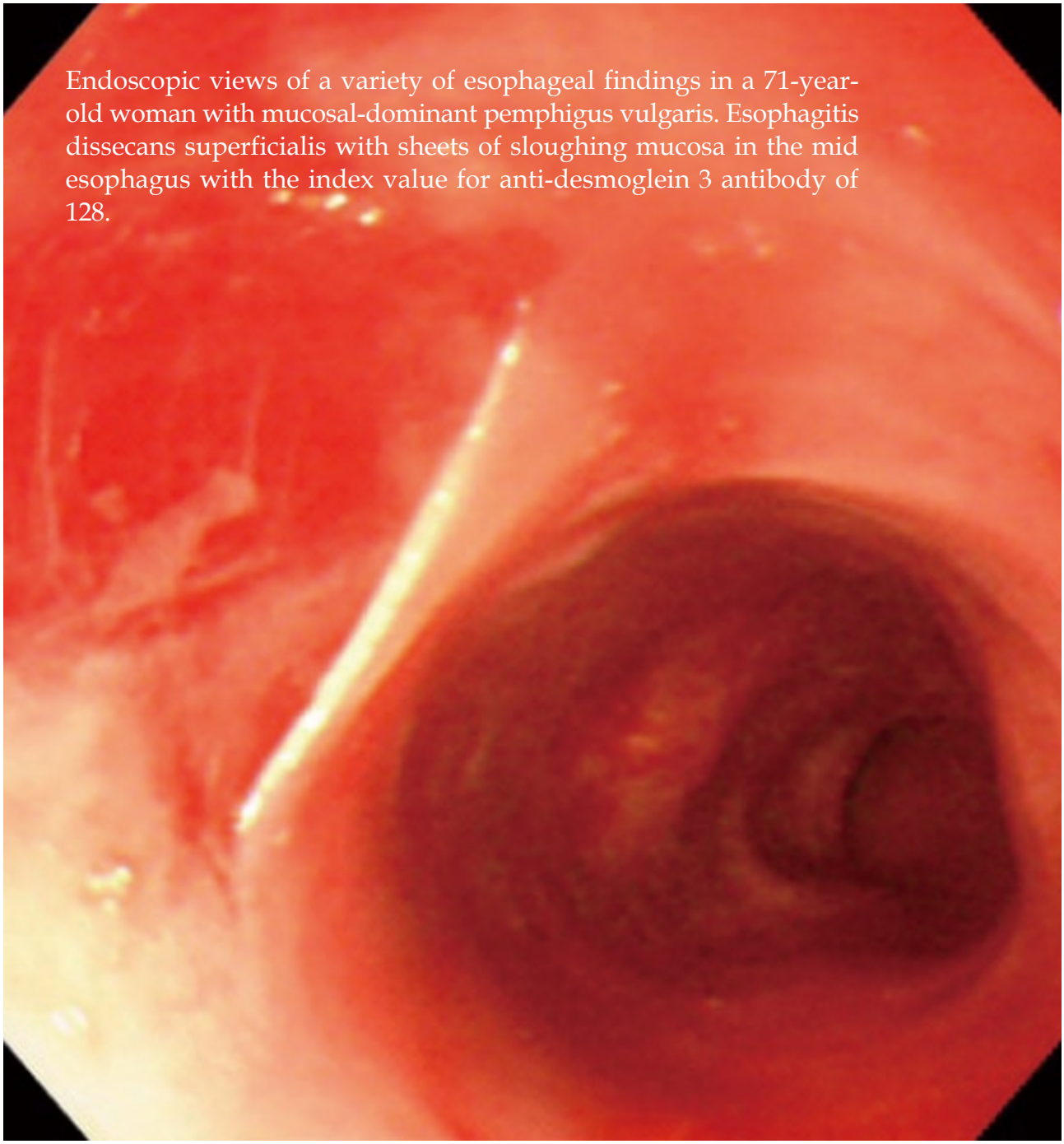

Endoscopic views of a variety of esophageal findings in a 71-year-old woman with mucosal-dominant pemphigus vulgaris. Esophagitis dissecans superficialis with sheets of sloughing mucosa in the mid esophagus with the index value for anti-desmoglein 3 antibody of 128.

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EDITORIAL

Contrast enhanced endoscopic ultrasound: More than just a fancy Doppler

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Abstract

Contrast enhanced endoscopic ultrasound (CEUS) is a new modality that takes advantage of vascular structure and blood flow to distinguish different clinical entities. Contrast agents are microbubbles that oscillate when exposed to ultrasonographic waves resulting in characteristic acoustic signals that are then converted to colour images. This permits exquisite imaging of macro- and microvasculature, providing information to help delineate malignant from non-malignant processes. The use of CEUS may significantly increase the sensitivity and specificity over conventional endoscopic ultrasound. Currently available contrast agents are safe, with infrequent adverse effects. This review summarizes the theory and technique behind CEUS and the current and future clinical applications.

Key words: Endoscopic ultrasound; Contrast enhancement; Microbubble

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INTRODUCTION

Endoscopic ultrasound (EUS) was a revolutionary development, which allowed gastroenterologists to see within the layers and beyond the gastrointestinal (GI) luminal tract. Since its beginnings in the early 1980s[1,2], developments have largely involved improvement in image quality, and the introduction of the curvilinear echoendoscope to allow for tissue sampling and "interventional" EUS[3-6]. EUS has established roles in the diagnosis of and therapy for a variety of gastrointestinal disorders, in particular cancer staging and pancreaticobiliary disorders.

The use of fine needle aspiration (FNA) provides a cytologic diagnosis which immensely improves the diagnostic accuracy over imaging alone[7-11]. This modality, however, comes with increased time for procedure, cost and risk[12-17]. New imaging modalities have been developed with the aim of improving imaging diagnostic capabilities, one of which is contrast enhanced ultrasound (CEUS). CEUS and endoscopic ultrasound (CE-EUS) use microbubble agents to enhance vascular patterns. In this article, we review the basic concepts of contrast enhancement and its clinical applications.

CONTRAST ENHANCED ENDOSCOPIC ULTRASOUND

Major vasculature structures are easily identifiable on

standard B-Mode imaging, and the addition of color and power Doppler helps to confirm vascular flow, along with direction and velocity of flow within the vessel. Capillary flow with low volume and very slow velocities cannot be seen with this standard imaging. The addition of "contrast" amplifies microvasculature flow to help define the vascular architecture, and hence to characterize the nature of a specific lesion.

BASIC PRINCIPLES OF ULTRASOUND CONTRAST AGENTS

Contrast enhancement involves the administration of an intravenous agent during the (endoscopic) ultrasound study. Contrast agents are microbubbles that respond to energy from sound waves in characteristic ways which aid in enhancing the distinctions between tissue types. First generation agents were agitated normal saline, radiologic contrast agents or the patient's own blood that was injected into a peripheral vein. These substances were limited in their clinical utility for two main reasons[18,19]. First, the larger size of the microbubbles formed with saline or blood were too large to cross the pulmonary circulation vessels (capillaries approximately 7 μm) thereby making them ineffective in the assessment of abdominal organs. Second, the rapid diffusion of air from the microbubble into the plasma resulted in a very short lifespan, thus limiting the time for tissue examination. These unfavorable properties fueled the development of second generation agents, designed to overcome the limitations of their early counterparts. Currently, several different agents are used (Table 1), all of which employ similar principles. All contain a shell designed to trap the gas and resist degradation or dissolution, resulting in a longer and more stable half-life. Heavier gases such as perfluorocarbons, as opposed to air, reduce leakage out of the shell into the surrounding plasma. Finally, microbubble size is decreased (range 1-7 μm) allowing their passage through the pulmonary circulation to the abdominal organs.

When microbubbles are exposed to ultrasound waves, they undergo compression and expansion that correlates with the peak and trough of the ultrasound wave[18,20]. This "oscillation" produces a strong acoustic signal that is recognized and represented as hyperechogenicity on the ultrasound image. This is in stark contrast to tissue, which is largely incompressible. The vibratory properties of microbubbles are dependent on its physical properties, including the type of gaseous agent used, and the surrounding shell. In addition to microbubble vibration, the significant impedimental difference between the bubble and surrounding tissue reflects the ultrasound wave back at this interface, thus permitting differentiation.

The oscillation of the microbubble is also directly dependent on the properties of the incident sound wave, of which the most important are the frequency and intensity of the incident wave. Microbubbles smaller than 7 μm oscillate most readily at 2-10 MHz, which serendipitously are the frequencies most often used in EUS. The mechanical index (MI) is a measure of the pressure fluctuations within an ultrasound pulse, and can be thought of as the power of the pulse. It is mathematically derived by dividing the maximum negative sound pressure by the square root of the sound frequency. The effect on microbubbles varies with the mechanical index (Table 2). With very low mechanical indices (< 0.1), microbubbles oscillate symmetrically resulting in a linear relationship between the signal and the emitted sound waves. At low mechanical indices (0.1-0.6), microbubbles resist compression more than expansion, thereby oscillating asymmetrically. This creates a non-linear relationship with the emitted sound waves and the detected signal is shown as multiples of the fundamental vibratory frequency. Similar to overtones on musical instruments, this is known as harmonics. Manipulating these harmonics allows for the differentiation of perfused from non-perfused tissue. With high MI (> 0.6), microbubbles are unable to resist compression and are destroyed. The release of the gas from the bubbles at this high MI results in a transiently intense echo signal.

Distinguishing the harmonics created by the microbubbles from those of the surrounding tissue can prove challenging. One method uses the instability of microbubbles at higher mechanical indices. Using color Doppler ultrasound, the disappearance of a previous signal at a high MI can be visualized and has been used to detect abnormalities such as metastatic liver lesions[21]. Specialized Doppler software known as Stimulated Acoustic Emission increases the resolution of lesions within the liver by de monstrating a color defect in areas of microbubble uptake against a highlighted normal liver and spleen. It is mainly

Table 1 Second generation contrast agents currently available

Contrast agent	Shell components	Gas	Mechanical index
Definity®	Phospholipid	Perfluoropropane	Low
Imagent®	Phospholipid	Perfluorohexane	Low
SonoVue®	Phospholipid	Sulfur hexafluoride	Low
Sonavist®	Polymer	Sulfur hexafluoride	Low
Sonazoid®	Lipid	Perfluorocarbon	Low
Optison®	Albumin	Perfluoropropane	Low
Sonogen®	Surfactant	Perfluoropentane	Low
Levovist®	Galactose/Palmitic acid	Air	High
Albunex®	Albumin	Air	High

Table 2 Effect of mechanical index on second generation microbubbles

Mechanical index	Effect on microbubble oscillation	Relationship between emitted sound waves and detected signal
Low (< 0.1)	Symmetrical	Linear
Moderate (0.1-0.6)	Asymmetrical	Non-linear
High (> 0.6)	Destruction	N/A

N/A: No detected signal as oscillation at the high frequency causes the microbubbles to burst.

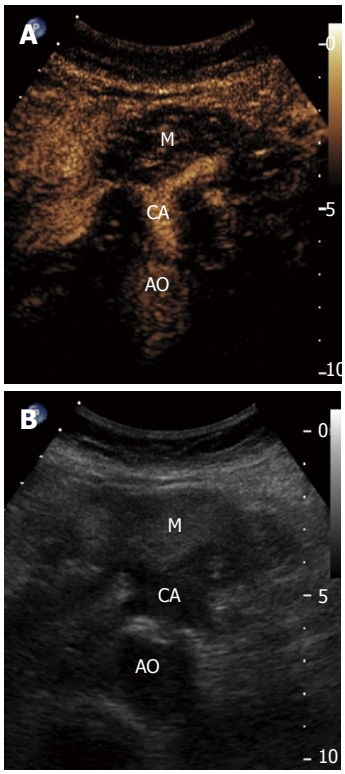

Figure 1 Transabdominal contrast enhanced ultrasound. A: Hypoechoic lesion in the head of the pancreas on traditional grey-scale ultrasound. B:Vascularity of this lesion after infection of Definity contrast agent. The ultimate diagnosis later proved to be pancreatic adenocarcinoma encasing the celiac axis. AO: aorta; CA: celiac axis; M: mass. Image courtesy of Dr. Stephanie Wilson, Department of Radiology, University of Calgary.

used with more fragile contrast agents such as Levovist and is limited by its inability to perform real time scanning due to rapid destruction of the agent[18]. The stability of newer generation microbubbles permits the formation of harmonics at lower frequencies. This helps distinguish the microbubbles from the surrounding tissue without destroying the microbubble at high MIs[22]. Filters are usually required to remove background signals at the expense of reduced spatial resolution.

Phase inversion mode (PIM) was developed in an attempt to maintain spatial resolution while detecting the harmonics of the microbubbles at low mechanical indices. In this modality, two impulses are sent, one being phase-inverted, and the returning emitted signals are summed. Linear signals (i.e. from surrounding tissue) are eliminated as signals received from the two impulses are 180° out of phase with a summation signal of 0, leaving only the non-linear signal of the microbubble to form the image[23,24]. Summing of multiple PIM signals is often required to account for increased noise at lower mechanical indices[25]. Phase inversion can be combined with traditional B-mode ultrasound such that the microbubble signal is displayed over a background B-mode image. Phase inversion mode with conventional Doppler (so called "Vascular Recognition Imaging") allows for visualization of flow through larger vessels simultaneously with slow-moving microbubbles in smaller vessels[26].

SAFETY ISSUES WITH SONOGRAPHIC CONTRAST AGENTS

While the second generation agents are generally safe, their administration does involve important potential risks and complications. The use of synthetic molecular components in the shells of these contrast agents poses a potential allergic or anaphylactic risk. *In vitro* studies have demonstrated a phenomenon termed "cavitation", whereby adjacent tissue is damaged with very high contrast agent concentrations and high sound energies[27]. Initially, during the low pressure phase of the ultrasound wave, fluid in the blood is pulled away from the microbubbles, creating a free air bubble. This bubble then collapses ("cavitates") in the high pressure phase of the wave releasing a large amount of energy resulting in increased the local temperature, release of free radicals, and lysis of neighboring cells. Importantly, this effect has not been demonstrated with the conventional concentrations and sound energies used. Finally, caution should be exercised in patients with ischemic heart disease with specific contrast agents (SonoVue®, Definity®, Optison®), as there have been reported cases of cardiac deaths during contrast echocardiogram studies[19].

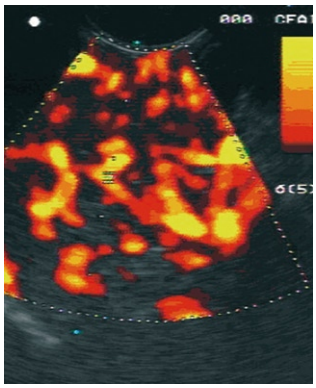

Figure 2 Contrast enhanced endoscopic ultrasound image using SonoVue injection of a focal pancreatic lesion. The region shows regular vascularization consistent with chronic pancreatitis. Image courtesy of Hocke M *et al*, *World J Gastroenterol* 2006[34].

CLINICAL APPLICATIONS

Pancreatitis and pancreatic neoplasm

The differentiation of chronic pancreatitis and pancreatic cancer is difficult when using traditional diagnostic tools. As chronic pancreatitis is an established risk factor for pancreatic adenocarcinoma, the differentiation between the two is of added importance in order to avoid unnecessary intervention and to instigate appropriate therapy. Transabdominal ultrasound has been a traditional diagnostic tool but is limited in its ability to differentiate these entities. Transabdominal contrast enhanced ultrasound offers significant advantages in discerning the etiology of pancreatic lesions (Figure 1). In the absence of chronic pancreatitis, conventional endoscopic ultrasound has a diagnostic accuracy of 85%-100% for pancreatic neoplasms[28]. In the presence of chronic pancreatitis the accuracy of EUS is markedly reduced, even in conjunction with FNA[29-31].

The use of a contrast agent is able to enhance the different vascular patterns of pancreatic neoplasms and chronic pancreatitis (Figures 2 and 3), in particular, more reliable discrimination of arterial and venous blood flow[32,33]. In differentiating focal pancreatitis from pan-

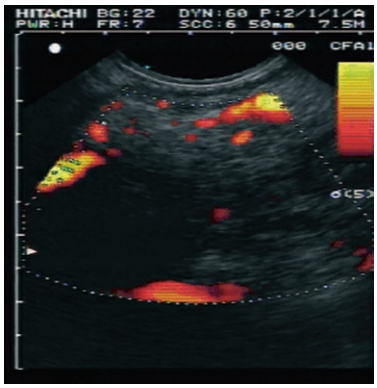

Figure 3 Contrast enhanced endoscopic ultrasound image using Sono Vue injection of a focal pancreatic lesion. This region shows irregular arterial vascularization suggestive of a malignancy (later proven to be ductal adenocarcinoma). Image courtesy of Hocke M *et al*, *World J Gastroenterol* 2006[34].

Table 3 Accuracy of contrast enhanced endoscopic ultrasound versus other imaging modalities

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Pancreatic neoplasm			
CEUS[31-35,60]	~ 91	~ 93	~ 92
EUS +/- FNA[8,47,60-70]	85-98	67-91	91-95
CT[61,63,64,71-73]	77-86	64-93	66
MRI[61,64,73-75]	85-99	60-95	79-81
Lymphadenopathy			
CEUS[54,60,76]	60	91	82-92
EUS +/- FNA[52,77-83]	68	86	75-99
CT[52,78,81-83]	33	75	51-74

CEUS: Contrast enhanced endoscopic ultrasound; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; CT: Computed tomography; MRI: Magnetic resonance imaging.

creatic cancer, contrast enhanced EUS has a sensitivity of 91% and a specificity of 93%, with positive and negative predictive values of 100% and 88% respectively[31,32]. These values are significant improvements over standard EUS imaging in this population. In general, pancreatic cancer is hypovascular on contrast color Doppler imaging whereas focal pancreatitis appears hypervascular. Hocke *et al*[34] performed a study using SonoVue to differentiate the vascular patterns of focal pancreatitis and pancreatic adenocarcinoma. Malignant lesions demonstrated absence of venous vessels and an irregular appearance to the arterial vessel architecture within the tumor. Vascularization of these malignant foci was visible only after the injection of a contrast agent. Conversely, chronic pancreatitis demonstrated both venous and arterial vessels with regular arterial microvascular architecture. This vascularity was visible on conventional Doppler assessment, prior to administration of a contrast agent. Using these criteria, the addition of contrast enhancement to conventional Doppler EUS improved the sensitivity from 73.2% to 91.1% and the specificity from 83.3% to 93.3%. CEUS offers improved accuracy over conventional imaging methods for the diagnosis of pancreatic neoplasms (Table 3). Levovist has also been used as a contrast agent for the differentiation of pancreatic cancer and chronic pancreatitis. In comparison to power Doppler EUS, contrast enhancement with Levovist has been shown to improve from 11% to 83.3% sensitivity for the detection oflesions smaller than 2 cm[35].

Detection of neuroendocrine tumors (NETs) of the pancreas may also be improved with contrast enhancement. NETs usually present as a small singular well demarcated lesion with echogenicity ranging from hypo to iso to hyperechoic[36-40]. Detection on standard EUS is at times problematic, in particular if they are isoechoic. Classically, however, these tumors are hypervascular; therefore the use of contrast enhancement would significantly improve EUS diagnostic capabilities[41]. In a small study of 37 patients with pancreatic lesions, Hirooka *et al*[42] showed contrast enhancement in 100% (n = 4) of islet cell tumors compared to 0% (n = 11) in adenocarcinoma lesions. The ability to distinguish an NET by imaging without the need for FNA is ideal for two reasons. First enucleation procedures for cure may be hampered if FNA is performed. Second, adequate tissue acquisition may be difficult in these small lesions. The decision for or against FNA depends on the individual patient, as there may be prognostic implications to cytology results[43].

The differentiation of malignant from benign cystic lesions of the pancreas is also at times problematic. Traditionally, FNA with fluid analysis for CEA was the single best test for the diagnosis of a mucinous neoplasm[44]. More recently, the addition of DNA analysis further increases the ability to determine a mucinous and/or malignant cyst[45]. Contrast enhancement may help in the diagnosis of mucinous cystic neoplasms, and in particular, help determine if a solid component/mural nodule appears suspicious for adenocarcinoma. In the study by Hirooka *et al*, 80% of intraductal papillary mucinous tumors displayed enhancement. Unfortunately the authors of this study did not offer pathologic correlation of these cystic lesions nor distinguish the proportion of these tumors with a solid component[42].

While metastases to the pancreas are rare, they remain an important entity in the differential diagnosis of a pancreatic nodule or mass. CE-EUS can play an important complementary role to tissue sampling through FNA. In a small study, 4 of 5 metastatic lesions in the pancreas displayed a hypervascular echogenic signal[46]. Whether metastatic lesions from different primary sites provide different CE-EUS signals remains to be seen.

Fine needle aspiration (FNA) remains a mainstay technique for obtaining tissue for the diagnosis of pancreatic lesions. It is doubtful that contrast enhanced imaging will replace tissue acquisition, and for cancer management in particular. In certain situations, however, contrast enhancement may help decide if FNA is warranted, in particular if surgical treatment and outcomes would be affected. Furthermore, while the positive predictive value of FNA approaches 100%[47], the negative predictive value only reaches 30%-44%[47,48]. This often necessitates a second EUS procedure for repeat FNA or a percutaneous biopsy[9,30,49]. As suggested by Giovanni, the high sensitivity and specificity of CE-EUS may reduce the need for repeat procedures if the initial FNA is negative[50].

Lymphadenopathy

EUS plays a pivotal role in the nodal staging of GI and mediastinal malignancies. Major differences in management are dependent on the accurate determination of malignant lymph nodes. In esophageal cancer, EUS has proven to be more accurate than CT scanning in detecting the presence of abnormal lymphadenopathy[51,52] with an overall accuracy for lymph node staging of approximately 75%. Standard EUS criteria for malignancy include size > 1 cm, hypoechoic, round shape, and sharp demarcation[53]. With FNA, the accuracy has been reported to be up to 99.4%[7]. The improved accuracy is important, as the presence of local metastatic lymphadenopathy remains one the most important predictors of survival, and is a determinant for adjuvant therapy and/or resectability. Hocke *et al*[54] compared contrast enhanced endoscopic ultrasound features of lymph nodes to fine needle aspiration. CE-EUS criteria for malignant lymph nodes were irregular appearance of vessels, and the sole presence of arterial vessels, whereas regular vessel appearance and presence of both arterial and venous vessels were used to identify benign lymph nodes. CE-EUS had a specificity of 91% but a sensitivity of only 60% in the differentiation of benign and malignant mediastinal lymph nodes. While CE-EUS improved the specificity in comparison to traditional EUS, low sensitivity prevents its ability to be used as the sole tool to discern malignant lymph nodes (Table 3). It may, however, be helpful for examining small nodes, or when FNA cannot be done due to intervening vasculature or tumor presence within the needle path.

Biliary diseases

Experience with CE-EUS for examination of biliary tract disorders is very limited. One study showed possible application to differentiating benign sclerosing cholangitis from cholangiocarcinoma[55]. In one small study of 14 patients, CE-EUS improved gall bladder tumor staging (T stage) accuracy from 78.6% to 92.9%[56]. Whether this will change patient management or translate into improved patient outcomes is unknown.

Tumour response and therapy

CE-EUS has been explored as a method of assessing treatment response in pancreatic lesions. Giday and colleagues, using a porcine model, demonstrated a marked difference in enhancement in ablated areas of the pancreas (no enhancement) compared to surrounding tissue (increased enhancement)[57]. In a novel experiment, Korpanty *et al*[58] created targeted microbubbles to vascular endothelial growth factor activated blood vessels that are seen in pancreatic neoplasms. The enhancement by these targeted microbubbles was significantly reduced with the use of anti-angiogenesis therapy, thereby providing a method of monitoring response to these agents.

The ability to target microbubbles allows the focused delivery of therapeutic substances within the bubbles to a specific site, which can then be released by a targeted ultrasound wave. Chemotherapeutic drugs within microbubbles can be released in a specific concentrated area by destroying the bubbles using high mechanical indices under real time ultrasound guidance[59]. Delivery in this fashion would provide more uniform delivery to specific, actively perfused areas of the tumor, compared to fine needle injection. Animal *in vivo* studies are still lacking. This technique is likely to gain popularity in the near future, given its specificity for the target tissue.

CONCLUSION

Contrast enhanced ultrasound is a newer technique that is gaining favor in the diagnosis and delivery of therapy in a variety of gastrointestinal disorders. Its ability to accurately differentiate diseased tissue from surrounding normal tissue will facilitate more accurate identification of lesions that were traditionally difficult to characterize. Multiple technological advances, including second generation microbubbles and phase inversion mode allow for improved spatial resolution, thereby increasing the accuracy of this modality in smaller and smaller lesions. Future directions for contrast enhanced endoscopic ultrasound will include complementary use with endoscopic elastography, which is another rapidly expanding field in endoscopic imaging.

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TOPIC HIGHLIGHT

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New endoscopy devices to improve population adherence to colorectal cancer prevention programs

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Abstract

Despite recent advances in medicine, colorectal cancer (CRC) remains one of the greatest hazards for public health worldwide and especially the industrialized world. It has been well documented with concrete data that regular screening colonoscopy aimed at early detection of precancerous polyps can help decrease the incidence of CRC. However, the adherence of the general population to such screening programs has been shown to be lower than that expected, thus allowing CRC to remain a major threat for public health. Various reasons have been suggested to explain the disappointing compliance of the population to CRC screening programs, some of them associated with colonoscopy per se, which is viewed by many people as an unpleasant examination. Governments, medical societies, individual gastroenterologists, as well as the medical industry are working in order to improve endoscopic devices and/or to improve standard colonoscopy. The aim is to improve the acceptance of the population for this method of CRC screening, by providing a painless and reliable examination of the colon. This review focuses on some of the latest improvements in this field.

Key words: New colonoscopes; Colonoscopy; Colorectal cancer screening; Technology

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INTRODUCTION

Despite recent developments in medical research including attempts to use blood, stool samples or imaging techniques (e.g. CT technology) to detect early cancer, colonoscopy remains the examination of choice in colorectal cancer (CRC) prevention. Regular screening colonoscopy aimed at early detection of precancerous polyps seems to reduce the incidence of CRC[1]. Although most studies that have proved the benefits of regular colorectal screening were based only on flexible rectosigmoidoscopy, they show a 60% reduction of CRC-associated deaths, provided screening was done before development of symptoms[2,3]. However, despite the proven benefits of endoscopic colon screening, patients worldwide seem to be un-

willing to adhere to screening programs, demonstrating an unacceptably low compliance rate. Studies including first-degree relatives of patients with colorectal cancer showed a compliance rate that ranged from 50% to 80%[4,5]. When examining the general asymptomatic population, compliance rates are even lower. Lack of symptoms, fear of detecting a tumour, embarrassment and discomfort that many patients believe accompany the procedure, difficulty in bowel preparation and even lack of knowledge or awareness of the benefits of regular colorectal screening are some of the main reasons that seem to prevent patients to adhere to screening programs[6]. Introduction of better sedation (including use of propofol) during colonoscopy seems to somewhat improve patient acceptance of colonoscopy[7]. However, the goal of an "easy" examination of the large bowel, that is widely accepted from the public still remains unfulfilled.

Apart from patient compliance, a good-quality of colonoscopy is necessary to provide all the benefits of endoscopic screening. In various studies, conventional colonoscopy seems to have a 5%-6% polyp miss rate for polyps greater than 1 cm, 13%-15% for polyps 5-9 mm and up to 25% for polyps smaller than 5 mm. Factors that influence the quality of colonoscopy in terms of polyp detection are withdrawal time, adequacy of bowel preparation and thorough inspection behind every intestinal fold[8,9]. Moreover, colonoscopy is a procedure that requires endoscopists with sufficient training, technical skills and experience. This, however, is not the case in every hospital, where colonoscopies might be performed by endoscopists of lesser experience. This was displayed in a recent British prospective study, that reviewed data from 9223 colonoscopies performed in 68 centers over a 4 mo period. Here the cecum intubation rates were rather low (76.9%, with an even worse adjusted rate of 56.9%) and definitely far from the expected 90%-94%[10]. The association between screening colonoscopy and reduction in CRC mortality rates seems to be due to reduction in left colon cancer deaths[11]. In two case-control studies, the relative risk of left-sided colon tumours after a negative colonoscopy was less than 0.2, while for right-sided colon tumours the relative risk ranged from 0.4 to 0.67[12,13]. These data point out that even regular colonoscopic screening has limitations in detecting all suspicious lesions. In order to overcome these problems and limitations, technical improvements to conventional colonoscopes and new devices are being developed, which aim to achieve colonoscopies of higher quality and thus to possibly increase the adherence of the public to CRC prevention programs. Initial data[7] seems to support the authors' view that improvement of the quality of colonoscopies in terms of accuracy and adenoma detection rates, might also contribute to increasing population adherence to CRC prevention programs. This may be either by "convincing" primary health care physicians to refer more patients to these programs or by influencing the public directly with high adenoma detection rates and low percentages of missed polyps, i.e. by showing that colonoscopy is the "gold standard" in colorectal screening, by far superior to alternative methods (e.g. CT- or MRI-colography). Therefore, in the following paragraphs we will focus not only on new endoscopic devices, but also briefly highlight technical innovations which bring improvements in visualization with standard endoscopes, as they might also prove to have a positive impact on the public's compliance with colorectal screening.

NEW TECHNOLOGY COLONOSCOPES

Aer-O-scope

This is a self-propelled, self-navigating, disposable endoscope. It consists of the following parts: (1) an electro-optical imaging capsule, containing a digital camera, which is implanted inside a balloon, called "scanning balloon"; (2) a workstation which helps the endoscopist inspect and control capsule movement during the examination; and (3) a supply cable that connects the workstation to the electro-optical capsule. This cable contains multiple channels and provides current, water and suction that are necessary during the examination. The examination begins by placing a silicone balloon (through a rectal introducer) into the patient's rectum. This rectal balloon is then inflated and seals the anus. Immediately after that, the scanning balloon is also inflated and CO_2 is introduced between the rectal and the scanning balloon. The pressures inside and behind the scanning balloon are controlled through electronic sensors and adjusted by the workstation computer. The pressure gradient that is created in this way can propel the scanning balloon inside the intestinal lumen. During its movement the scanning balloon adjusts its volume and shape according to the shape of the intestine, preventing patient discomfort. When the scanning balloon reaches the cecum, CO_2 behind the balloon is allowed to leave the colon through the rectal inductor, while new CO_2 is introduced, but this time between the scanning ballon and the cecum. This creates a pressure gradient in the opposite direction, which allows the endoscope to travel backward and simultaneously distends the colon in front of the camera. The inspection of the colonic mucosa is conducted during the endoscope's withdrawal, which is controlled by the endoscopist through the workstation's computer. Aer-O-scope has an omnidirectional imaging system, based on conical lenses and a mirror that provides simultaneous circumferential, backward as well as forward views, allowing inspection even behind mucosal folds. *Ex vivo* as well as *in vivo* porcine studies have shown that the Aer-O-scope reaches its maximal cable length (which is equivalent to that of the cecum in humans) in 80%-90% of the cases and has 98% sensitivity for detecting beads (i.e. markers that imitate polyps) greater than 2.5 mm. In another study performed in 12 healthy young volunteers who underwent both conventional colonoscopy and Aer-O-scope endoscopy, cecal intubation was achieved in 83% of the cases with both methods. This new colonoscopy device promises pain reduction during the examination, since Aer-O-scope does not create loops and the pressure

inside the colon is kept at lower levels than those of a conventional colonoscopy. Further human studies are, however, needed in order to prove the advantages of this endoscope, keeping in mind that the device is not currently endowed with a working channel[14-16].

Neoguide endoscopy system

Neoguide endoscopy system (NES) is an articulated endoscope comprising 16 segments of the same length. Each segment has the ability to bend in every direction. NES is handled as a conventional endoscope and is equipped with an external position sensor which measures the endoscope's insertion depth. The main computer combines data from the orientation of the tip of the endoscope and the external position sensor, regulating the shape of its segment to assume the shape of the colon, as it advances through the lumen. This endoscope adjustment to the shape of the colon leads to reduction of loop formation, which together with colon ligament stretching is the source of 90% of episodes of pain during colonoscopy. Eickhoff *et al* studied the forces that are exerted on the colonic wall and the displacement of the colon during conventional and Neoguide endoscopy, using model colons. NES was found to apply significantly less forces on the colonic wall and caused significantly less colon displacement and loop formation, whilst offering 3-dimentional, real-time imaging of the bowel[17]. In another human trial by the aforementioned team, loops were formed during NES endoscopy in only 4/10 patients and were successfully straightened with the help of the 3D imaging system[18]. However, despite satisfactory results displayed when using the NES-system (verified by both patients and physicians), large scale studies are needed to compare conventional colonoscopy with NES in terms of efficacy and safety.

Invendo colonoscope

The Invendo colonoscope is a single-use, motor-driven colonoscope, where all the push and pull manoeuvres of the endoscopist are replaced by a handheld device (Invendo Medical, Ltd., Kissing, Germany). It is a flexible colonoscope with a working length of 200 cm, endowed with an inner sheath (with a 10mm diameter). An outer sleeve is pulled over this inner sheath and inverted on each of the respective ends (at the biopsy port and just below the endoscope deflection) and attached to a propulsion connector. The connector is then locked into an endoscope-driving unit and the examination can then be started. Under handheld control by the physician, 8 drive-wheels in the endoscope-driving unit start to move in the selected direction. The wheels grip the inner side of the inverted sleeve, causing the inverted sleeve and inner sheath to move either forward or backwards The endoscope tip can be deflected electro-hydraulically 180° (at body temperature) in any direction by moving a joystick on the handheld device. The colonoscope has a working channel of 3.2 mm (therefore allowing use of a biopsy forceps through the channel). In the first pilot volunteer study on 34 patients the examination was performed in all cases without sedation and had to be interrupted in only 2 patients due to pain. The rest of the patients did not mention any significant discomfort during the examination. The cecal intubation rate was 82%, whereas the mean cecal intubation time was 20 min. Only 4/34 patients complained of abdominal bloating after the procedure[19].

Cathcam

Cathcam is a wire-guided, catheter-based method. It consists of a light, 160 cm long catheter (almost half the weight of the shaft of a colonoscope), which is guided by a looped guide-wire. It is also equipped with 6 light-emitting diodes, a 2.8 mm working channel, lens irrigation and air inflation systems. The hinged guide-wire passes through the 2.8 mm working channel of the catheter. A reusable micro-camera is then fitted on the tip of the catheter. A study conducted in live pigs showed 30% to 40% reduction in the peak force exerted on the colonic wall using Cathcam. A pilot safety and efficacy study included 13 volunteers who had failed to complete a conventional colonoscopy. For the first 5 of these patients, colonoscopy could be completed exclusively by Cathcam. However, the prototype Cathcam's tip could not be angulated and it was found difficult as well as time-consuming to manoeuvre the wire and the catheter through the left colon. For the rest of the patients conventional colonoscopy was performed up to the point where no further advancement of the scope was possible; at this point, the looped guide-wire was then inserted and advanced into the colon. The conventional colonoscope was then removed (leaving the guide-wire in place) and the Cathcam was advanced over the guide-wire, resulting in a rapid completion of the rest of the procedure. Twelve out of a total 13 patients thus completed the Cathcam colonoscopy. The patients were mildly sedated and only 2 complained of pain, while 8/13 mentioned pain in their previous conventional colonoscopy[20,21]. It seems that Cathcam has the potential to become an important tool for completion of difficult colonoscopies although some further modifications in its design will be necessary in order for Cathcam to become optimal for that purpose.

Pill cam colon

Pill Cam Colon capsule shares the same basic technology with the widely-used small bowel capsule (Pillcam SB). It is an endoscopic capsule of 31 mm length and a diameter of 11 mm. Each end of the capsule is enhanced with a microcamera which acquires images at a frame rate of 4 frames per second (2 images per camera). Its total operating time reaches approximately 10 h. Each camera contains an automatic lighting control and improved optics that provide a broad observation field (twice the coverage area and depth of field compared to those of Pillcam SB) (Figure 1). The colon capsule initially transmits images for only 5 min after its activation and then steps into a "sleeping" (also known as

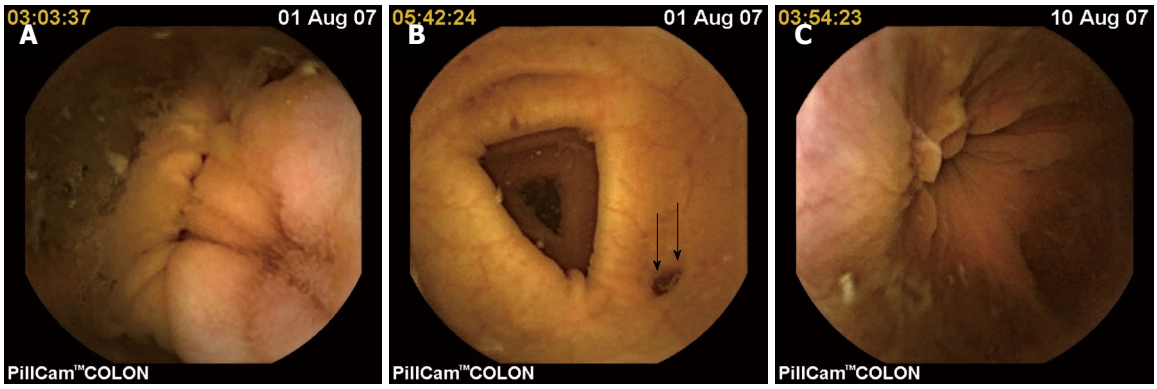

Figure 1 Pill cam colon capsule. A: a normal colon (cecum and ileocecal valve); B: A small colonic diverticulum in the colon transversum; C: The rectum with internal haemorrhoids (equivalent to a retroflex view with the standard colonoscope).

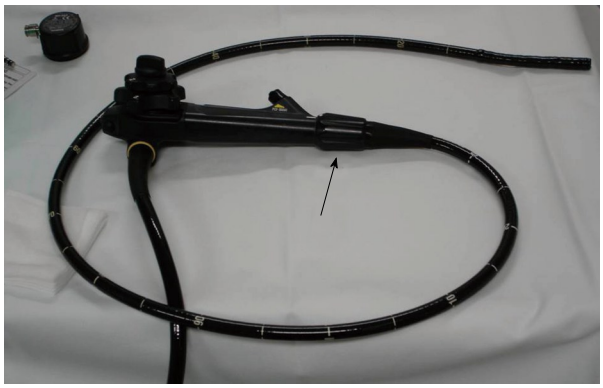

Figure 2 Variable stiffness colonoscope with the control ring to adjust stiffness (arrow).

"hibernating") mode in order to save energy as it travels through the small intestine. Two hours later it is automatically reactivated and starts transmitting images again. By this time the capsule has normally reached the terminal ileum in most patients. The rest of the system (sensors, data recorder and software) are similar to the small bowel capsule. Initial data that were published on the first-generation colon capsule, reported sensitivities in detecting polyps > 6 mm (compared to conventional colonoscopy which was used as gold standard) ranging between 50%-70%, whereas specificities were between 73%-100%[22,23]. A large recent prospective study, which included 328 patients with suspected or known colonic disease, compared colon capsule endoscopy with colonoscopy in detecting lesions of the large intestine. Sensitivity of the colon capsule for diagnosing polyps with a diameter of 6 mm or larger was 64%, whereas its specificity was 84%. In detection of advanced adenomas with a diameter of 10 mm or larger sensitivity and specificity were 64% and 98% respectively[24]. It was also clearly demonstrated in the same study that the sensitivity of the colon capsule depends on good bowel preparation, meaning the presence of clear fluid in the colon, which allows detailed inspection of the mucosa and quick movement of the capsule. This was clearly illustrated in the same study, by the fact that on patients with a good or excellent bowel preparation the sensitivity of the method in detecting advanced adenomas rose significantly up to 88% when compared to that of patients with a fair or poor preparation (here, the corresponding value reached a mere 44%)[24]. Moreover, a previous study had shown that intensive (each capsule examination was read 3 times) and trained capsule data reading improved the sensitivity and specificity from 50% and 83% respectively from the first reading to 70% and 100% after the third (i.e. "trained") reading[22]. It therefore seems that although the sensitivity of the colon capsule in colorectal screening is lower than that of standard colonoscopy, it can be increased by improving bowel preparation combined with careful reading of the colon capsule examination data. Moreover, an improved, second-generation colon capsule has already been developed. It was recently tested in a feasibility study across 5 centers, involving 104 patients (data from 98 were finally analyzed). Here, sensitivity for detection of polyps $\geqslant$ 6 mm was 89%, whereas for polyps $\geqslant$ 10 mm it was 88% (specificities were 76% and 89% respectively)[25]. These results suggest a potential for improved accuracy compared with the first-generation colon capsule system and seem to verify the high expectations of those who believe that the colon capsule can indeed be an alternative to conventional colonoscopy in screening for CRC. However, more prospective and comparative studies still need to be performed on this issue.

ECHNICAL IMPROVEMENTS AND DEVELOPMENT OF COLONOSCOPES

Variable stiffness colonoscopes

During the last decade colonoscopes with variable stiffness (VSC) have been used in a number of trials. VSCs possess a control ring that adjusts stiffness according to examination conditions (Figure 2). Decreased stiffness gives the endoscope the flexibility needed to traverse sharp angles or a fixed sigmoid colon, while increased stiffness provides adequate rigidity to overcome a loop formation and to straighten the colon. Several studies have been performed, providing conflicting results about the cecal intubation rate, the cecal intubation time, the use of ancil-

lary maneuvers and the need for sedation during colonoscopy with the use of VSCs[26-30]. A recent meta-analysis of randomized controlled trials that compared the pediatric or adult VSCs with standard adult colonoscopes (SAC) in adult patients, showed that VSC-colonoscopy increased cecal intubation rate, required less sedation (whether meperidine or midazolam) and caused less abdominal pain. However, there was no difference in use of ancillary maneuvers and in the time needed for cecal intubation[26]. It is clear that further trials are needed in order to evaluate VSC during procedures without sedation, in patients who previously failed to complete colonoscopy and among inexperienced endoscopists, both being situations where a more efficacious colonoscope is needed. A recent study compared cecal intubation time and patient discomfort using 3 different types of colonoscopes: the pediatric VSC, the non-magnifying adult VSC and the magnifying adult VSC in unsedated patients. Pediatric VCS (in spite of their smaller caliber) did not seem to reduce patient discomfort, but on the other hand had a longer intubation time (possibly due to their decreased rigidity deriving from their smaller diameter, which might make them more floppy). However, pediatric VCS remain important tools in examining a narrowed and fixed colon, especially in diverticular disease and intestinal adhesions[31].

Third eye

A new, retrograde-viewing, auxiliary imaging device that can be inserted in the working channel of conventional colonoscopes is the Third Eye (TE). As soon as the examination begins, a transparent cap is positioned on the distal tip of the colonoscope. The TE is then inserted through the colonoscope's working channel, as soon as the latter has achieved intubation of the cecum. Once in the cecum, the TE extends beyond the tip of the colonoscope. The device is angled and locked in such a way that it does not prohibit the antegrade view of the colonoscope. TE provides a parallel retrograde view during the withdrawal of the colonoscope. In the first safety and efficacy trial of TE, 38 polyps were detected in 24 patients. Thirty polyps were detected only in antegrade view, 4 polyps were detected in both views and 4 more polyps were detected exclusively in the retrograde view. One out of 4 polyps was an adenoma of 0.7 cm. The diagnostic yield of colonoscopy was increased by 11.8%. The device slightly increased the colonoscope withdrawal time (mean withdrawal time was 22 min), mainly because it has to be withdrawn and reinserted every time a polyp needs to be removed. TE is a promising device and a large study comparing it to conventional colonoscopy is expected[32].

Narrow–band imaging

Narrow-band imaging is an innovative optical technology that modifies the center wavelength and bandwidth of an endoscope light into a narrow band illumination of 415 ± 30 nm[33]. This provides a better visualization of the capillary pattern of the mucosa and could thus provide better visualization of colonic adenomas (Figure 3). So far, studies in Western countries have not shown significant differences in detection rate of adenomas between NBI and white light. The value of NBI may be in providing improved detection rates of adenomas for colonoscopists who experience low adenoma detection rates in white light[34]. Moreover, the interpretation of NBI images needs adequate training and its use for screening may be excessively time consuming and cost-ineffective[35]. NBI has shown its efficacy in distinguishing adenomatous from hyperplastic polyps. However, its role in adenoma detection, remains to be fully tested. In a recent prospective randomized study, NBI-assisted colonoscopy was compared to conventional white-light wide-angle colonoscopy in terms of adenoma detection. Here, NBI did not significantly improve adenoma detection but, interestingly, it seemed to induce a learning effect, improving adenoma detection in standard colonoscopy, i.e. helped to "train the eye" of endoscopists in detecting adenomas with standard colonoscopy[35]. Moreover, a recent large (1256 patients), randomized trial, performed in a homogeneous setting (6 private practices, experienced colonoscopists, CRC-screening patients) failed tfo demonstrate an objective benefit of NBI in adenoma detection[36]. Therefore the actual role and usefulness of NBI in screening colonoscopy still seems to require more validation studies.

Fujinon intelligent chromoendoscopy

Fujinon intelligent chromoendoscopy (FICE), also known as computed virtual chromoendoscopy, is a technique similar to NBI aimed at enhancing tissue surface structures[37] (Figure 4). FICE was used to increase adenoma detection rates during colonoscopy in a German series of 871 patients, comparing it with indigocarmine spraying[38]. However, the results did not differ statistically between the groups in terms of adenoma detection, procedure time or the differentiation between adenomas and non-neoplastic polyps.

Based on these and other similar data, it is the personal feeling of the authors that contrast enhancement in conventional imaging techniques will probably not contribute in reducing adenoma miss rates (at least of experienced colonoscopists).

CONCLUSION

The latest developments and variations of endoscopic devices, as well as the aforementioned improvements of conventional colonoscopes, may indeed play an important role in CRC prophylaxis, but a major factor that will judge their actual impact is the feasibility of their implementation in clinical practice, i.e. the question "which of these devises really works?". In fact, not all of them have yet proven their practicability. Some of them do not have working channels, which may not - currently- be a prerequisite when dealing with a capsule endoscope, but is certainly inacceptable when the devise in question is a "tube" endoscope. Others seem to have other flaws that have not allowed their production up to now. It should

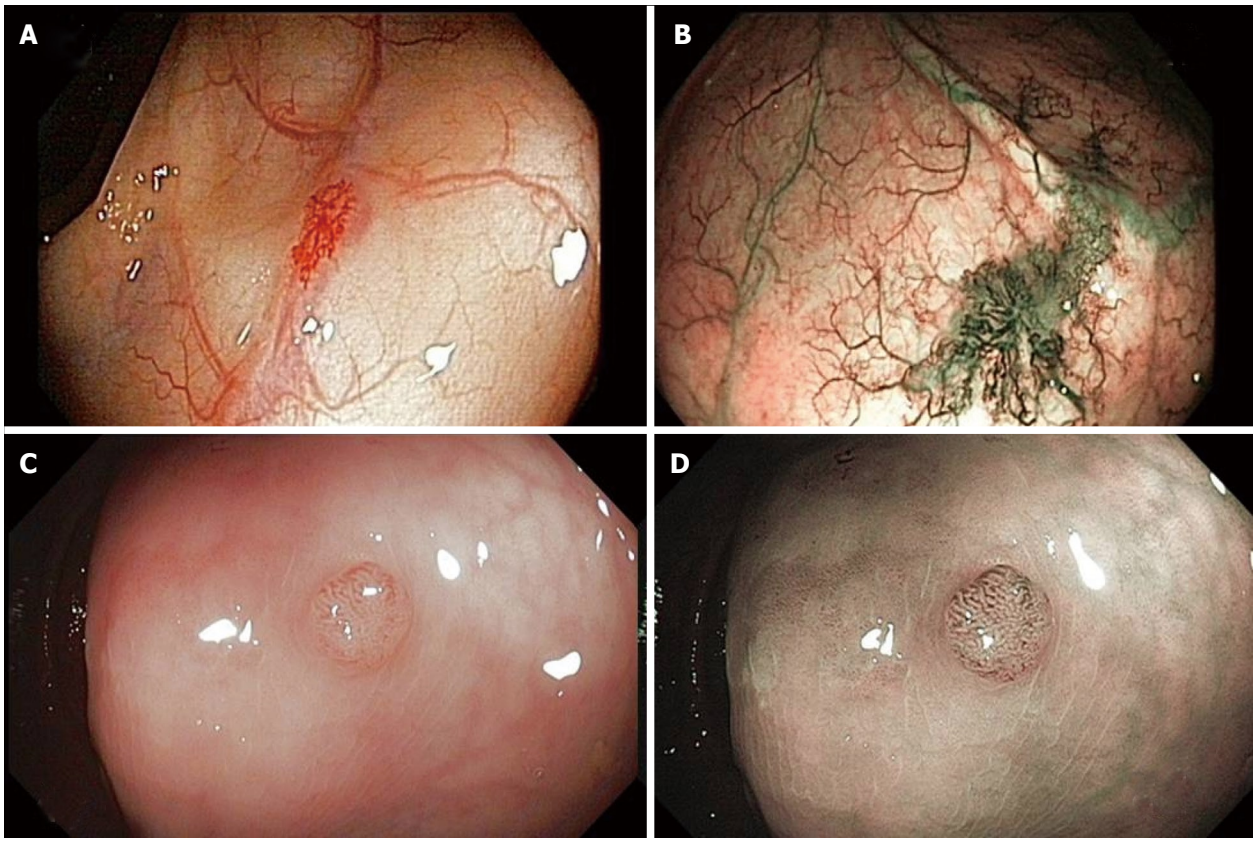

Figure 3 Visualization of colonic lesions. A: Angiodysplasias under standard view; B: Angiodysplasias under improved visualization with narrow–band Imaging (NBI); C: A colonic polyp displayed with standard colonoscopy; D: The same polyp with NBI.

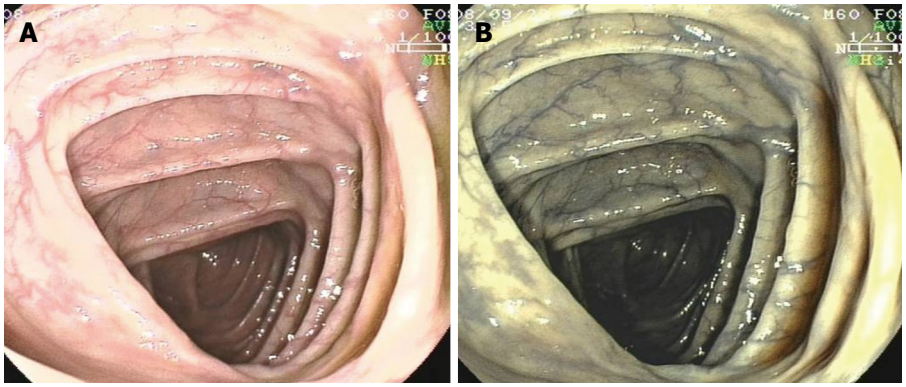

Figure 4 Visualization of the colon transversum. A: Under standard view; B: With Fujinon intelligent chromoendoscopy (FICE). Note the improved visualization of the capillary pattern of the mucosa with FICE.

be stressed that of all the new devises, the colon capsule seems to be a promising tool in CRC screening, as it is a painless, minimally-invasive method, which requires no bowel insufflation or sedation and could therefore play a significant role as an alternative to standard colonoscopy. Although in the initial studies, its sensitivity in the detection of polyps and advanced adenomas is currently lower than that of conventional colonoscopy, it can be increased by improving bowel preparation, combined with careful reading of the colon capsule examination data. Also, the new, second-generation colon capsule has already shown signs indicating that the capsule is probably the most promising endoscopic devise that can serve as an alternative to classical endoscopy for CRC screening. Another issue that deserves extra caution is costs: Most of these new technologic developments are - for the time being- rather expensive. However, the cost of a device can certainly not be finalized as long as it is still under development or in the experimental phase. By the time the product comes to production, prices can change. Another issue is cost-effectiveness, i.e. a devise might be expensive now but may eventually help reduce costs, e.g. by reducing mortality and morbidity from CRC and by reduction of hospital costs, lost working days *etc*. Therefore, despite the fact that most of these new devices are currently rather expensive, in the long run they might prove to be cost-effective. Once more, studies - this time questioning the cost-benefit rate of these devises- will be needed.

Finally, another factor that should not be underestimated is the role of the primary health provider. The

latter must be well-informed on the benefits that derive from screening colonoscopy in order to encourage the public to participate in CRC screening. Thus, the primary health physician can also act as another extremely effective "tool" to increase population adherence to CRC prevention programs. It is therefore the duty of medical associations, especially gastroenterological organizations to contribute to keeping the public, as well as primary health providers, informed on the benefits of examination of the colon to prevent CRC.

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GUIDELINES FOR CLINICAL PRACTICE

Esophagitis dissecans superficialis and autoimmune bullous dermatoses: A review

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Abstract

Esophagitis dissecans superficialis (EDS) is a rare and severe endoscopic finding characterized by sloughing of large fragments of esophageal mucosal lining. Although EDS has been reported in association with serious illnesses and certain medications, the pathophysiological association of autoimmune bullous dermatoses with EDS has gained remarkable attention. Among these dermatoses, pemphigus vulgaris and pemphigoid frequently present with various types of esophageal involvement including EDS. We review the pathophysiology and clinical features of this involvement with the presentation of our experiences. The importance of endoscopic evaluation of this entity is discussed.

INTRODUCTION

Esophagitis dissecans superficialis (EDS) is a rare endoscopic finding characterized by sloughing of large fragments of esophageal mucosal lining[1]. In Figure 1A, an endoscopic image in our institute shows the typical features of EDS with vertical fissures and sloughing of whitish superficial epithelium. In 1892, Rosenberg coined the term "EDS" to describe this entity[2]. Its usual symptoms are dysphagia, odynophagia and heartburn. Hematemesis or vomiting esophageal casts occurs rarely. The causes of EDS include idiopathy[1,3], medications (bisphosphonates[4], nonsteroidal anti-inflammatory drugs[1] and potassium chloride), hot beverages, chemical irritants, celiac disease[5], collagen diseases[6] and

autoimmune bullous dermatoses. Recently, the pathophysiology and strong relationship between EDS and autoimmune bullous dermatoses have gained remarkable attention. We review these topics with the presentation of our experiences.

PEMPHIGUS

Pemphigus is a rare autoimmune disease that causes blistering of the skin and oral mucosa. It is caused by antibody-mediated autoimmune reaction to desmogleins, desmosomal transmembrane glycoproteins of keratinocytes, leading to acantholysis[7,8]. There are two major types of pemphigus: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). There are two subtypes of PV: the mucosal-dominant type with mucosal lesions but minimal skin involvement and the mucocutaneous type with extensive skin blisters and erosions in addition to mucosal involvement[7]. Patients with PF have scaly erosions of the skin but not of the mucosa. The clinical phenotype of PV is determined by the distribution of desmoglein 1 and desmoglein 3[7]. The desmoglein compensation theory can explain the localization of blisters[7]. Desmoglein 3 is expressed throughout the oral mucosa but only in the basal and immediate suprabasal layers of epidermis. Conversely, desmoglein 1 is expressed throughout the epidermis more intensely in the superficial oral mucosa but weakly in the deep layers. Anti-desmoglein 1 or anti-desmoglein 3 autoantibodies inactivate only the corresponding desmoglein and functional desmoglein 1 or desmoglein 3 alone is sufficient for cell-cell adhesion[7,8]. In the mucosa therefore, desmoglein 1 is unable to compensate the loss of desmoglein 3 function because it is weakly expressed, particularly in the deep layer. This pathophysiology explains why anti-desmoglein 3 alone can cause blister formation in the mucosa. Patients with mucosal-dominant PV have anti-desmoglein 3 antibodies which cause mucosal blisters whereas those who also have anti-desmoglein 1 antibodies have skin involvement[7,8].

The diagnostic hallmark of PV is acantholysis with bulla formation in the suprabasal region and the pathognomonic "a row of tombstones-like" basal cell layer[9]. Immunological examinations confirm the diagnosis[10]. For direct immunofluorescence (DIF) to show intercellular IgG and C3 deposits, a biopsied specimen should be placed in special media and commercially available systems are applied to indirect immunofluorescence (IIF). Until recently, DIF or IIF was the standard method of detecting antibodies that bind to the keratinocytes. However, recent studies have shown that enzyme-linked immunosorbent assay (ELISA) to detect anti-desmoglein 1 and anti-desmoglein 3 antibodies is much simpler and more quantifiable than immunofluorescence[7]. ELISA scores which show parallel fluctuations with the activity of PV are useful for monitoring disease activity[7]. The treatment consists of systemic steroids, megadose pulse steroids, immunosuppressive drugs, plasmapheresis and intravenous immunoglobulin. Topical treatment is applied to reduce pain and to prevent and treat secondary infections. In refractory PV, rituximab, a chimeric monoclonal antibody against CD20, can be applied[10].

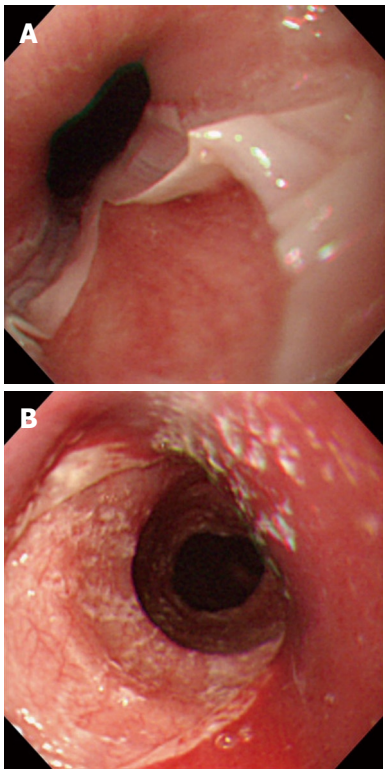

Figure 1 Endoscopic view of esophagitis dissecans superficialis. A: With diffuse sloughing mucosa of the lower esophagus in a 76-year-old woman presenting hematemesis, and the cause was idiopathic; B: with longitudinal sloughing mucosa from upper to mid esophagus in a 67-year-old woman with mucocutaneous type pemphigus vulgaris, note fine whitish fragments of sloughed mucosa, and the index value for anti-desmoglein 3 antibody by enzyme-linked immunosorbent assay was over 1280 (normal value < 7).

ASSOCIATION OF EDS AND PV

The oral mucosa and skin are common sites of PV and other mucosal surfaces with stratified squamous epithelium such as nasopharynx, esophagus, conjunctiva, anus and vagina are also involved[10]. Oral lesions precede skin lesions in 70% of PV cases and when skin is already involved, concomitant oral lesions are encountered in 90% of cases[11]. As for esophageal involvement, prevalence of esophageal involvement was considered quite rare because of the little recognition of the importance of esophageal lesions of PV among dermatologists and inexperience of such lesions for most endoscopists. Such involvement may be under-recognized or misdiagnosed as peptic esophagitis. Since the first case of esophageal involvement of PV was reported by Raque *et al*[12] in 1970, such cases have been increasingly reported. Esophageal symptoms of PV patients include dysphagia, odynophagia, heartburn, regurgitation, chest pain and hematemesis[11-16]. Recent endoscopic studies have shown a relatively higher incidence (46%-87%) of esophageal lesions among PV patients than ever expected[13-16]. The studies have indicated a strong correlation between esophageal symptoms and endoscopic detection of esophageal involvement. Endoscopic features range from mild to severe forms including local erythema, red erythematous longitudinal lines, blisters, erosions, ulcers and EDS. It has been obvious that dysphagia and odynophagia may indicate esophageal involvement by PV; therefore, endoscopy is

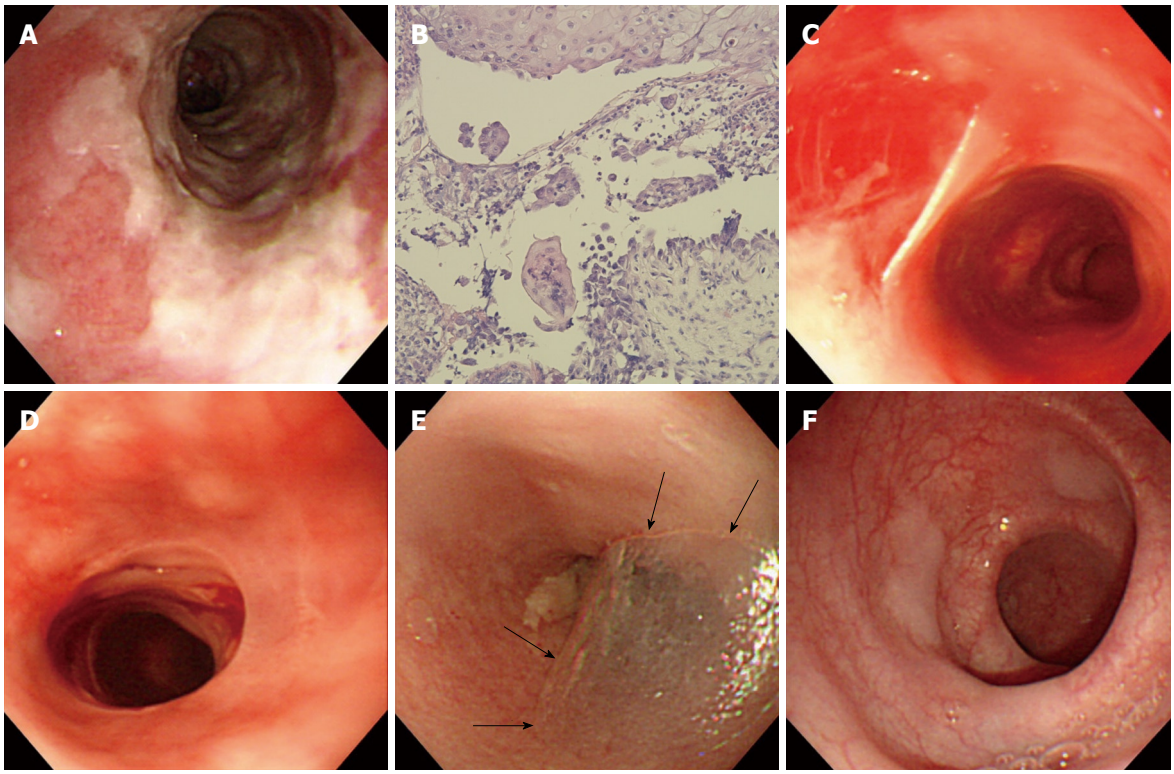

Figure 2 Endoscopic views of a variety of esophageal findings in a 71-year-old woman with mucosal-dominant pemphigus vulgaris. A: Note esophagitis dissecans superficialis with extensive reddish erosion of the entire esophagus and whitish sheets of sloughed mucosa with the index value for anti-desmoglein 3 antibody of 1620; B: Histopathological examination of the esophageal mucosa, showing separation at the suprabasal level of epithelium. Note the formation of a row of tombstones-like basal cells that remain attached to the basement membrane (H&E, × 100); C: Esophagitis dissecans superficialis with sheets of sloughing mucosa in the mid esophagus with the index value for anti-desmoglein 3 antibody of 128; D: Sheets of sloughing mucosa presenting esophageal webs in the upper esophagus; E: A bulla (arrowheads) in the upper esophagus with the index value for anti-desmoglein 3 antibody of 145; F: Several slightly raised whitish blisters scattered in the lower esophagus.

indicated for esophageal symptoms. PV patients with exclusive esophageal involvement have been reported[17]. In addition, endoscopic examination is helpful to distinguish PV lesions from candidal, herpetic and peptic esophagitis which are frequent in PV patients receiving steroids and immunosuppressive drugs. It is also helpful to detect gastroduodenal peptic diseases before high dose steroid therapy.

Among various esophageal lesions in PV, dramatic presentations of EDS with vomiting esophageal casts were documented before the endoscopic era[18,19]. Six cases of EDS associated with PV have been well documented in the English literature[18-23]. Four out of six cases underwent endoscopy at the initial episode. Endoscopic features of EDS have included stripped mucosa with bleeding[20], total desquamation of the esophageal mucosa without bleeding[21], long linear mucosal break[22] and vertical fissures and circumferential cracks with peeling, whitish mucosa with extensive bleeding and exudating esophagitis[23]. A typical endoscopic image of EDS associated with PV in our institute is shown in Figure 1B. Our patient had mucocutaneous type PV and remains well with immunosuppressive treatment. In Figure 2, sequential endoscopic images of various esophageal lesions including EDS in another patient with PV in our institute are depicted. The control of her disease activity was difficult despite intensive treatment and thus characteristic findings of diffuse erosion, EDS, bulla and webs appeared within a short period. There was a female predominance of the cases including our cases[23]. Cesar *et al*[23] have indicated that EDS associated with PV is an acute event and does not imply worsening of PV because PV was either in partial or total remission in reported cases. However, through our experience shown in Figure 2, we believe that EDS may be an acute on chronic event and a severe form of esophageal lesions in PV. As mentioned before, ELISA scores of anti-desmoglein 3 show parallel fluctuations with the activity of esophageal lesions of PV.

There have been some concerns about endoscopic examination for patients of PV because of the potential risks of causing trauma to fragile esophageal mucosa by endoscopic procedure[24] and positive Nikolsky's sign, stripping of the apparently normal mucosa on withdrawal of the biopsy forceps[25-28]. Trattner *et al*[29] have documented that DIF studies of the biopsied esophageal mucosa were positive for PV lesions even in the normal macroscopic appearance of the esophagus in PV patients. Therefore, most PV patients may have the potential risk of positive Nikolsky's sign in the esophagus. With respect to those risks, most endoscopic examination has been undertaken safely in skilled hands[14,16,30]. For the treatment of esophageal PV lesions and/or the prevention of po-

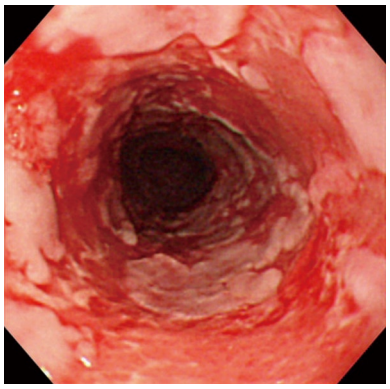

Figure 3 An endoscopic view of an 84-year-old man with mucous membrane pemphigoid. Note esophagitis dissecans superficialis with extensive reddish erosion of the entire esophagus and whitish sheets and fragments of sloughed mucosa.

tential injury after biopsies, mucosa-protecting agents and antacid agents may be helpful in addition to steroids. It is mandatory that endoscopists give the pathologists adequate biopsy specimens which include basement membrane but it is sometimes difficult to perform such a biopsy because of the tangential position of endoscope and biopsy forceps inside the esophagus. Galloro *et al*[30] have indicated that a commercially available rocking biopsy forceps provide adequate sampling which leads to demonstrating suprabasal acantholysis and making the definite diagnosis of esophageal involvement. Performing biopsies at the junction between floor and roof of the blister and adjacent, not blistering mucosa is also recommended[30].

ASSOCIATION OF EDS AND PEMPHIGOID

EDS may also present in other autoimmune bullous dermatoses including pemphigoid. Pemphigoid is a group of autoimmune subepithelial blistering diseases, subclassified into mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid and bullous pemphigoid (BP)[31]. MMP is characterized by linear deposition of IgG and complement factor 3 along epithelial basement membrane zone resulting in subepidermal blisters and erosions[31]. Mucous membrane involvement is common, primarily of the oral mucosa and conjunctiva, but may also include the nasopharynx, esophagus and genital mucosa[32]. Esophageal bullae or erosions occur in 8 percent of cases[32]. Esophageal symptoms with pemphigoid are similar to those with PV. Since the first case of EDS of MMP was reported by Foroozan *et al*[33] in 1967, such cases have been rarely reported[34]. These lesions heal with scarring, leading to the formation of webs and strictures[35,36]. Esophageal webs represent an early stage of the involvement whereas strictures are more likely to represent an advanced stage secondary to scarring and fibrosis[37], sometimes requiring endoscopic dilatation or surgery[38,39]. An endoscopic image of extensive EDS associated with MMP in our institute is shown in Figure 3. BP is characterized by subepidermal blisters forming large, tense bullae. Sites involved include the oral cavity, anus and genital mucosa. Although the involvement of esophagus is much less common with pemphigoid than pemphigus[32], certain cases of BP have reminded us that diseases of the "outside" skin may also be manifest on the "inside" skin of the esophagus[40-43]. We should be aware that endoscopic contact may cause esophageal bullae in BP[42,43]. Treatment of pemphigoid mainly consists of steroids.

CONCLUSION

Autoimmune bullous dermatoses such as PV and pemphigoid frequently present with various types of esophageal lesions including EDS, a severe form of the involvement. Recognition of the esophageal involvement in PV and pemphigoid may alter the management, requiring close teamwork between dermatologists and endoscopists. As the esophageal mucosa is fragile with potential Nikolsky's sign, endoscopic examination should be performed carefully in skilled hands for esophageal symptoms to evaluate the correct diagnosis and allow prompt treatment.

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REVIEW

Anesthesia and sedation in pediatric gastrointestinal endoscopic procedures: A review

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Abstract

Gastrointestinal (GI) endoscopic procedure has become an essential modality for evaluation and treatment of GI diseases. Intravenous (IV) sedation and General Anesthesia (GA) have both been employed to minimize discomfort and provide amnesia. Both these procedures require, at the very least, monitoring of the level of consciousness, pulmonary ventilation, oxygenation and hemodynamics. Although GI endoscopy is considered safe, the procedure has a potential for complications. Increased awareness of the complications associated with sedation during GI endoscopy in children, and involving the anesthesiologists in caring for these children, may be optimal for safety. Belonging to a younger age group, having a higher ASA class and undergoing IV sedation were identified as risk factors for developing complications. Reported adverse events included inadequate sedation, low oxygen saturation, airway obstruction, apnea needing bag mask ventilation, excitement and agitation, hemorrhage and perforation. A complication rate of 1.2% was associated with procedures performed under GA, as compared to 3.7% of complications associated with IV sedation. IV sedation was seen to be independently associated with a cardiopulmonary complication rate 5.3% times higher when compared to GA. GA can therefore be considered safer and more effective in providing comfort and amnesia.

Key words: Gastrointestinal; Endoscopy; Pediatrics; Sedation; General anesthesia

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INTRODUCTION

Gastrointestinal (GI) endoscopic procedure has become an essential modality for evaluation and treatment of gastrointestinal diseases. Intravenous (IV) sedation and General Anesthesia (GA) have been employed by anesthetists and non- anesthetists to minimize discomfort and provide amnesia. The American Society of Anesthesiologists (ASA) has published guidelines for the safe conduct of sedation during GI endoscopy[1,2]. Conscious sedation has been widely accepted as primary sedation for children undergoing these procedures[3]. However, regardless of the sedation regimen used, the overall immediate non-fatal hypoxia-related reversible complication rate of pediatric GI endoscopic procedures is 2.3%[4]. The American Academy of Pediatrics Committee on Drugs and The Joint Commission on Accreditation on HealthCare Organizations (JCAHO) have published guidelines to ensure safety and to reduce the risks associated with sedation in pediatric GI endoscopic

procedures[5,6]. Children often become agitated and restless, thus increasing the risk of complications associated with the procedures. GA is considered safe and effective in providing comfort and amnesia. However, GA requires expertise and has been viewed as not being cost effective[3].

There exists a great variation in sedation practice for pediatric endoscopy. Increased awareness of the com plications associated with sedation during GI endoscopic procedures in children, the institution of modern monitoring modalities to identify these complications, and the involvement of the anesthesiologists in looking after these children in, or outside, the operating room may be optimal for the safety of these patients[7]. The JCAHO has made it mandatory to provide the same standard of care and monitoring for children who undergo sedation or GA for these procedures[6].

AIMS AND OBJECTIVES

The aims and objectives of providing care during IV sedation or GA on children for these procedures are: (1) To allow the children to tolerate the unpleasant procedures with amnesia; (2) To allow the children to remain motionless, in order to prevent complications; (3) To ensure safety by provision of standard monitoring and care by adequately trained staff; (4) To provide high quality and cost effective care; and (5) To ensure early discharge from the facility to home.

SEDATION GUIDELINES

The American Society of Anesthesiologists Task Force[1] defined "Sedation and Analgesia" as a state that allows patients to tolerate unpleasant procedures while maintaining adequate cardiorespiratory function and the ability to respond purposefully to verbal commands and/or tactile stimulation. The Task Force decided that the term "Sedation and Analgesia" more accurately defines this therapeutic goal than does the commonly used but imprecise term "Conscious Sedation".

The purpose of these guidelines is to allow clinicians to provide their patients with the benefit of sedation and analgesia while minimizing the associated risks. Sedation and analgesia allows patients to tolerate unpleasant procedures by relieving anxiety, discomfort or pain. In children and uncooperative adults, sedation and analgesia may expedite the conduct of procedures that are not particularly uncomfortable but require the patient to remain motionless. Excessive sedation and analgesia may result in cardiac or respiratory depression that must be rapidly recognized and appropriately managed to avoid the risk of hypoxic brain damage, cardiac arrest or death. Conversely, inadequate sedation and analgesia may result in undue patient discomfort or injury because of lack of cooperation or adverse physiologic response to stress. The following practice guidelines for safe conduct of the GI endoscopic procedures were recommended by the ASA Task Force and have been found to improve patient satisfaction, increase clinical benefits and reduce adverse outcomes: (1) A pre - procedure patient evaluation (history, physical examination, laboratory evaluation); (2) A pre - procedure preparation of the patient (counseling, fasting); (3) Patient monitoring (level of con sciousness, pulmonary ventilation, oxygenation, hemody namics); (4) Contemporaneous recording of monitored parameters (such as level of consciousness, respiratory function, hemodynamics); (5) Availability of a staff person dedicated solely to patient monitoring and safety; (6) Education and training of sedation and analgesia providers; (7) Availability of appropriately sized emergency and airway equipment as well as trained staff; (8) Use of supplemental oxygen; (9) Use of multiple sedative and analgesic agents; (10) Titration of sedative and analgesic medication to achieve the desired effect; (11) Administration of sedative/analgesic agents by the intravenous route; (12) Availability of reversal agents (e.g. naloxone, flumazenil); (13) Post-procedure monitoring (during stay in a recovery facility, post-discharge); and (14) Special regimens for patients with special problems (e.g. including the uncooperative, the very old or the very young, those with severe cardiac, pulmonary, hepatic, renal, or central nervous system disease, those with morbid obesity, those exhibiting sleep apnea, pregnant patients, drug or alcohol abusers,: emergency and unprepared patients, and those with metabolic and airway difficulties).

RISK STRATIFICATION

During pre - procedure evaluation of children, one must attempt to stratify the patients as per the ASA classification. Thakkar *et al*[4] found that, the younger the age group, the higher the ASA class and IV sedation as risk factors for developing complications. Selection of patients according to this risk stratification may help to prevent or reduce complications associated with the procedure[8].

ASA Class 1 status (Healthy Children) and ASA Class 2 status patients (mild systemic illness such as asthma under good control) can be considered for IV sedation. ASA Class 3 status patients with severe systemic disease must be evaluated on an individual basis, and should be considered either for IV sedation or GA. ASA class 4 status patients with severe systemic disease which is a constant threat to life, and ASA class 5 status patients who are moribund patients and not expected to survive 24 h with or without the operation, must be considered for GA.

SEDATION LEVEL

Definitions of sedation levels have been published by the American Society of Anesthesiologists[2], and are as follows.

Moderate sedation/analgesia (conscious sedation)

A drug- induced depression of consciousness, during

which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep sedation/analgesia

A drug- induced depression of consciousness, during which patients cannot be easily aroused but respond purposefully to repeated or painful stimulation. The ability to maintain ventilator function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia

A drug- induced loss of consciousness, during which patients are not arousable, even by painful stimulation. The ability to maintain independent ventilator function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug- induced depression of neuromuscular function. Cardiovascular function may be impaired.

Monitoring during sedation and general anesthesia

Whatever the sedation method (IV Sedation or GA) is used, the care- givers need to be vigilant in their monitoring to avoid adverse events leading to fatalities. JCAHO has recommended mandatory uniform monitoring standards for children undergoing these procedures with either IV sedation or GA. The standard procedures as per the ASA Task Force guidelines include monitoring the following[1].

Level of consciousness: The response of patients to commands serves as a guide to their level of consciousness. Patients who respond as reflex withdrawal to painful stimuli are likely to be deeply sedated, approaching a state of general anesthesia. The members of the Task Force support the contention that monitoring the level of consciousness reduces risk and the overall cost.

Pulmonary ventilation: The primary cause of morbidity associated with sedation/analgesia is drug- induced respiratory depression, thus monitoring of respiratory function reduces the risk of adverse outcomes associated with sedation and analgesia. This can be monitored by observation of spontaneous respiratory activity or auscultation of breath sounds. In situations where patients are separated from care- givers, automated apnea monitoring (by detection of exhaled Carbon dioxide) may decrease the risk.

Oxygenation: Published data suggest that early detection of hypoxemia through the use oximetry during sedation and analgesia decreases the likelihood of adverse outcomes such as cardiac arrest and death. The Task Force members agree that hypoxemia during sedation and analgesia is more likely to be detected by oximetry than by clinical assessment alone. However, oximetry is not a substitute for monitoring respiratory function.

Hemodynamics: It is the opinion of the Task Force members that sedation/analgesia may blunt the appropriate autonomic compensation for hypovolaemia and the procedure related stress. Regular monitoring of vital signs reduces risk and cost. The Task Force members suggest the use of continuous electrocardiography (ECG) monitoring in patients with hypertension, cardiac disease or dysrhythmias. They suggest ECG monitoring is not generally required in patients without cardiac disease.

Blood pressure should be determined before sedation and analgesia is initiated, and at regular intervals during the procedure.

ROLE OF BISPECTRAL INDEX MONITORING

Bispectral index (BIS) monitor is a processed electroence phalogram (EEG) parameter that measures the hypnotic effect of anesthetic and sedative drugs. The com puter produces a single numeric value (0-100). Its manu facturer claims that a BIS score of 40-60 indicates general anesthesia, < 40 indicates deep anesthetic state, 61-70 indicates deep sedation, 71-90 indicates conscious sedation and > 90 indicates an awake state. The goal is to give an objective quantitative assessment of level of hypnosis. This has been validated in pediatric general anesthesia[9] and has also been validated as a measure of sedation in spontaneously breathing children aged less than 12 years[10]. Motas *et al*[11] used BIS and the University of Michigan Sedation Scale to assess depth of sedation. They concluded that there was a wide variation in depth of sedation attained and the goal of sedation was not achieved. They considered use of sedation by non-anesthesiologists as a therapeutic failure. They speculated that BIS may prove to be more suitable monitor than scoring systems that require interaction with the patient for assessment during the procedure.

ROLE OF PULSE OXIMETRY

Pulse oximetry is a valuable tool to pick up oxygen desaturation which could be due to poor respiratory effort in children undergoing IV sedation. However, oxygen desaturation is a relatively late sign of depressed ventilation, especially in the presence of supplemental oxygen. Malviya *et al*[12] picked up desaturation in 5.5% of patients and achieved a reduction in bad outcomes. Hypoxemia secondary to depressed respiratory activity is the most important risk factor for near misses and death during sedation for children undergoing procedures. Early detection may be valuable in avoiding morbidity and mortality in pediatric sedation procedures.

ROLE OF CAPNOGRAPHY

In the presence of supplemental oxygen, detection of hypoventilation by pulse oximetry alone may be delayed, with disastrous consequences. In children undergoing endoscopy with conscious sedation, microstream capnography has been shown to reveal hypoventilation in some patients when it was not detected by routine elec tronic monitoring and clinical assessment[13]. In a graphic assessment of respiratory activity with sidestream capnography, Vargo *et al*[14] reported episodes of apnea or disordered respiration detected by capnography. With simultaneous respiratory rate measurements obtained by means of capnography and auscultation with a pretracheal stethoscope, the authors verified that capnography was an excellent indicator of respiratory rate. They concluded that apnea and disordered respiration commonly occurs during therapeutic upper GI endoscopy and frequently precedes the development of hypoxemia. Potentially important abnormalities in respiratory activity remain undetected with pulse oximetry and visual assessment.

ADVERSE EVENTS DURING SEDATION AND GENERAL ANESTHESIA

Although GI endoscopy is generally considered safe, the procedure does have a potential for complications. The safety of children undergoing the procedure under sedation has long been an issue of concern, especially after a death associated with pediatric sedation in a dental practice was reported[15].

Motas *et al*[11] in a prospective study of children undergoing sedation by non-anesthesiologists for various procedures reported failure to achieve sedation in 12%-28% using BIS or the University of Michigan Sedation Scale respectively as a monitor of sedation.

Malviya *et al*[12], in another prospective study involving 1140 children sedated by a non-anesthesiologist for various procedures, reported a 20.1% incidence of adverse events. These included inadequate sedation, low oxygen saturation, airway obstruction, apnea needing bag mask ventilation, and excitement and agitation.

Lightdale *et al*[16] prospectively reviewed more than 2300 endoscopic procedures and reported agitation, respiratory events, incomplete procedures, hemorrhage and perforation as adverse events. Agitation was significantly associated with endoscopist- administered sedation.

Mamula *et al*[17] in a retrospective review of conscious sedation in children also reported approximately 20% incidence of non-life threatening adverse events.

Levis *et al*[18] reported a 20% incidence of recall in children following esophago-gastroduodenoscopy, thus increasing their level of anxiety and reluctance to accept subsequent procedures.

Thakkar *et al*[4], in a cross sectional retrospective study of 10236 upper GI endoscopic procedures in 0-18 year-old children reported an overall immediate complication rate of 2.3%. IV sedation with Midazolam, Fentanyl, Meperidine or Ketamine was used in 46% of procedures, whereas 54% procedures were performed under GA. Cardiopulmonary complications were reported in 79.9% of procedures, gastrointestinal complications were reported in 18% of procedures, whereas in 5.9% of procedures complications such as prolonged sedation, drug reaction or rash were reported. All complications were non-fatal and most were hypoxia- related and rever sible. They identified a younger age, higher ASA class, female sex and IV sedation as risk factors for developing complications. A complication rate of 1.2% was associated with procedures performed under GA as compared to a 3.7% incidence associated with IV seda tion. After adjusting with all other variables, they reported IV sedation to be independently associated with a cardiopulmonary complication rate 5.3% times higher when compared to GA.

IV SEDATION AND ANESTHESIA REGIMENS FOR PEDIATRIC GI ENDOSCOPY

The most common IV sedation regimen for pediatric GI endoscopy is the use of an opioid and a benzodiazepine combination to achieve analgesia and amnesia so that children tolerate the procedure well. Although mostly safe regimens were reported, it was found that the attending physician, whether an endoscopist, nurse assistant or an anesthesiologist must exercise extreme caution while administering the sedation to children for GI endoscopy. The best regimen is the use of IV agents because of their reliability, efficacy and easy titration to achieve the end point. However, monitoring during the procedure is essential.

MIDAZOLAM

Midazolam is water-soluble and a more readily metabolized drug. It is presented as a clear solution of pH 3.5, and after injection the chemical structure undergoes modification, increasing its lipid solubility, thus enhancing its diffusion into the central nervous system (CNS). Onset of action is rapid (usually within 90 sec) and it has a relatively short duration of action. It has an initial distribution half- life of 7-20 min and the elimination half-life of 2 h.

It is metabolized in the liver and excreted in the urine. Its main metabolite (1 hydroxymidazolam) has some pharmacological activity but undergoes rapid conjugation, thus limiting any effect.

Midazolam has a high affinity for the benzodiazepine receptors in the CNS and possesses classic hypnotic, an xiolytic, amnesic and anticonvulsant properties. It produces marked anterograde amnesia. It is administered in a dose of 0.05-0.15 mg per kilogram IV, in 2-3 divided bolus doses, each bolus dose to be given over 1-2 min. Its peak effect comes in 2-3 min and lasts for up to 45 min.

Being water-soluble, it takes three times as long for midazolam to reach a peak electroencephalographic effect as compared to fat-soluble diazepam[19]. The importance of this observation is that one must wait at least 3 min between IV doses to avoid "Stacking" of its effect. Midazolam must always be used with caution when administered with opioids because of the potential for respiratory depression.

FENTANYL

This is the most commonly used narcotic in infants and children. It has a rapid onset of action of about 30 sec, and a brief duration of action of 30-45 min. Termination of the effect of low doses of fentanyl results primarily from redistribution. Fentanyl is used for sedation in a dose range of 1-5 microgram per Kilogram in 0.5-1.0 micro gram per Kilogram bolus doses given every 3 min till the desired effect is achieved. The drug must be injected slowly to avoid chest wall rigidity associated with rapid administration. Fentanyl is metabolized in the liver. Fentanyl-induced bradycardia may need treatment with a vagolytic drug such as atropine.

REMIFENTANIL

Remifentanil is the most recent opioid available for use as an analgesic in a hospital setting. It is broken down by non-specific plasma and tissue cholinesterases, thus the importance of maturation of renal and hepatic function is minimal. Thus the half life of remifentanil in infants and adults does not differ, and is independent of the duration of infusion. Its action is therefore very brief. Bolus doses of remifentanil are associated with hypotension, bradycardia and chest wall rigidity. For safety reasons, the drug should be administered only by continuous infusion in a dose of 0.1 microgram per kilogram per minute.

Remifentanil has been shown to have propofolsaving effect, thus allowing a lower dose of propofol to be used for the maintenance of anesthesia[20]. A combination of remifentanil and propofol is considered safe, effective and acceptable for sedation in children under going gastrointestinal endoscopy[21]. However, the authors recommend the use of this combination by an experienced anesthesiologist in a hospital setting, as the combination may result in apnea and the need to control the airway.

PROPOFOL

Propofol is a substituted phenol derivative, metabolized rapidly in the liver to water soluble compounds which are excreted by the kidneys. After a single bolus injection, propofol levels rapidly decrease in the blood as a result of redistribution and elimination. Its initial distribution half-life is 2-8 min, and its elimination half-life varies from 1-3 h. The context-sensitive half-life of propofol for infusions lasting up to 8 h is less than 40 min. The time to peak effect is 90-100 sec after a dose of 2.5 mg per Kilogram. A dose of 2-3 mg per Kilogram is needed for induction of GA in children and an infusion of 50-150 microgram per Kilogram per minute for maintenance, in combination with an opioid or Nitrous oxide. Abu-Shawan I and Mack D in a small study of 42 procedures used a dose of 50-80 microgram per Kilogram per minute of propofol in combination with 0.1 microgram per Kilogram per minute of remifentanil[21]. The authors recommend this combination for sedation in children in a hospital setting in presence of an anesthesiologist. When compared with midazolam for sedation, propofol provides equal or better control and more rapid recovery[20].

CONCLUSION

A review of the relevant literature in Pubmed and Medline regarding use of IV sedation and GA for GI endoscopy in children, showed that GA is considered safe and effective,especially in developing countries where the level of monitoring and postanesthesia care may not be optimal. However, in developed countries with better moni toring, the use of IV sedation in children undergoing GI endoscopy may be considered safe.

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Lubiprostone used with polyethylene glycol in diabetic patients enhances colonoscopy preparation quality

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Abstract

AIM: To assess the additive effect of lubiprostone on the quality of colon preparation in diabetics given single-dosed polyethylene glycol electrolyte (PEG) for colonoscopy.

METHODS: This was an investigator-initiated, single-center, single-blinded prospective trial comparing the efficacy of L + PEG to PEG alone on colon preparation quality in diabetics undergoing screening colonoscopy. The study was approved by our institution's IRB. The PEG was given as a single-dose to address patient-compliance concerns voiced by our IRB with split-dosing. All patients received only clear liquids the day prior to colonoscopy. Experimental group (Grp L) received PEG + 1 dose L 2 h prior to and 2 h after PEG completion. Control group (Grp C) received only PEG the evening prior to the colonoscopy. Patients were randomly assigned to one of the 2 groups. The endoscopist was blinded to which colon prep was given and all colonoscopies were complete. Upon colonoscopy completion, the endoscopist rated the colon prep-quality by a validated 5-point Likert scale (1-excellent to 5-inadequate).

RESULTS: Sixty patients were enrolled in the study; 30 Grp L and 30 Grp C. Overall, patients were excluded due to study non-completion in 12 (41%) Grp L and 5 (17%) Grp C, $P = 0.04$. Average colon preparation score Grp L = 2.47 and Grp C = 3.00, $P = 0.09$. Although this was not statistically significant, there was a trend towards improved colon prep in Grp L. Statistical significance may have been achieved if completion rates had been similar between both study groups.

CONCLUSION: Use of 2-L capsules with PEG resulted in a trend towards improved colon prep over PEG alone in diabetic patients when given as a single-dose regimen.

Key words: Lubiprostone; Polyethylene glycol; Diabetes; Colonoscopy; colon preparation

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INTRODUCTION

Colonoscopy allows visualization of the entire colon and is indicated to identify etiologies of anemia, bleeding or inflammation in the gastrointestinal (GI) tract. Currently, colonoscopy is also the procedure of choice for colon cancer/polyp screening and surveillance[1]. Colon preparation cleansing quality determines the difficulty, speed and completeness of colonoscopy, especially in terms of lesion detection[2]. The impact of adequate colon preparation also has important cost implications as poor bowel cleansing results in shortened interval between colonoscopies, longer procedure times, decreased patient satisfaction and increased lesion miss rates[3]. The current types of colon preparations available are either larger volume polyethylene glycol electrolyte (PEG)-based or smaller volume sodium phosphate-based preparations. Despite the same efficacy between PEG *vs* sodium phosphate-based preparations according to a meta-analysis of randomized-controlled trials[4], sodium phosphate-based preps have been associated with fluid overload, electrolyte abnormalities (transient increase in serum sodium and phosphorus and decrease in calcium levels) and acute phosphate nephropathy in diabetic patients, even with normal renal function[5-8]. Thus, PEG-based colon cleansing solutions are the most commonly used colonoscopy preparations for diabetic patients. A large population-based study has shown diabetes to be an independent risk for colon cancer compared to the general population[9]. However, recent data has shown that diabetic's bowel cleansing with PEG-based prep is not as efficient as non-diabetic's[10]. PEG (Nulytely) is an osmotically-balanced bowel cleansing regimen that may be safely administered to patients with electrolyte imbalances, advanced liver disease and those with poorly compensated congestive heart failure and renal failure[11]. A 4 liter volume of PEG is taken orally in its entirety the evening before colonoscopy or as a split-dose (each 2 liters the night before and 5 h prior to colonoscopy). Lubiprostone (Amitiza, Sucampo Pharmaceuticals, Inc., Bethesda, MD; Takeda Pharmaceuticals America, Inc., Deerfield, IL) is a locally acting type-2 chloride channel activator which causes intestinal fluid secretion resulting in softened stool and increased intestinal transit without the loss of either net intravascular fluid or electrolytes[12]. Lubiprostone is currently approved by the US Food and Drug Administration (FDA) at a 24 mcg dose taken twice daily orally for chronic idiopathic constipation in adults and an 8mcg dose taken twice daily orally for irritable bowel syndrome with constipation in women $\geqslant$ 18 years old[13]. Long term use of lubiprostone causes no clinically significant changes in serum electrolyte levels[13]. Lubiprostone has been safely used in diabetic patients and is only contraindicated in patients with known or suspected mechanical GI obstruction. In addition, lubiprostone should be avoided in pregnant patients and is a category C medication[13]. A prior trial with non-diabetics using a 24 mcg lubiprostone capsule (L) given in a single dose with split-dose PEG showed improvement in prep quality[14]. The purpose of our study was to assess whether the addition of lubiprostone to a single-dose of 4 liters of PEG the evening before colonoscopy would affect the quality of colon preparation in diabetics.

MATERIALS AND METHODS

This was an investigator-initiated, single-center, single-blinded prospective trial comparing the efficacy of L + PEG to PEG alone on colon preparation quality in adult-onset diabetic mellitus (AODM) undergoing screening colonoscopy. This study was approved by our institution's IRB prior to implementation.

Participants

We prospectively offered enrollment to all adult-onset diabetic outpatients who were referred to the Gastroenterology clinic at the Medical College of Georgia in Augusta, Georgia for a screening colonoscopy from July, 2008 to March, 2010. Patients were at least 50 years of age with known AODM. The study participants were enrolled in the trial by one of two Gastroenterology attending physicians or a Gastroenterology fellow. Women must have been post-menopausal or surgically sterile. Patients had to be able to read and write in English and give a valid, informed consent. Patients with the following characteristics were excluded from the study: suspected acute or chronic pseudo-obstruction, active GI hemorrhage, known inflammatory bowel disease, chronic diarrhea, prior colonic resection, acute diverticulitis, known colonic mass, clinical evidence of decompensated liver disease, renal disease or patients on dialysis, current or previous use of lubiprostone and allergy to lubiprostone.

Randomization

Subjects were assigned to the Control group (Grp C) or Experimental group (Grp L) on an odd/even basis. After research informed consent had been obtained, subjects were given a study ID numbered 1 through 60. Subjects with an odd number were assigned to Grp C while subjects with an even number were assigned to Grp L. Subjects were then given a randomization package by the hospital research pharmacist consisting of the preparation orders, supplies, instructions and the date of their procedure by the investigator obtaining informed consent. The endoscopists were blinded to which preparation was given.

Colon-cleansing methods

All patients received 4 liters of PEG preparation (*Nulytely*, Braintree Laboratories, Inc., Braintree, MA; 420 g polyethylene glycol 3350, 5.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride and one optional 2.0 g flavor pack) given as a single-dose to address patient compliance concerns voiced by our IRB with split-dosing. In addition, all patients received only a clear liquid diet the day prior to colonoscopy. Grp L received PEG plus 2 lubiprostone capsules, 1 capsule the 2 h prior to PEG and 1 capsule 2 h after PEG completion.

Table 1 Modified Ottawa bowel preparation scale

Score	Definition
1-excellent	Small volume of clear liquid or great than 95% of the colonic mucosal surface seen
2-good	Large volume of clear liquid covering 5%-25% of the surface, but greater than 90% of surface seen
3-fair	Some semisolid stool that could be suctioned or washed away, but great than 90% of surface seen
4-poor	Semisolid stool that could not be suctioned or washed away but great than 90% of the surface seen
5-inadequate	Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning; repeat preparation and colonoscopy needed

Bowel cleansing score ranging from excellent to inadequate and description of each score.

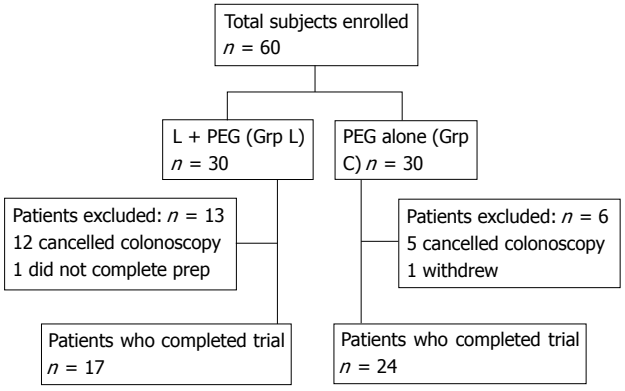

Figure 1 Patient flow chart. Schematic diagram of patients throughout the trial. (see attached JPEG). Grp L: Experimental group; Grp C: Control group.

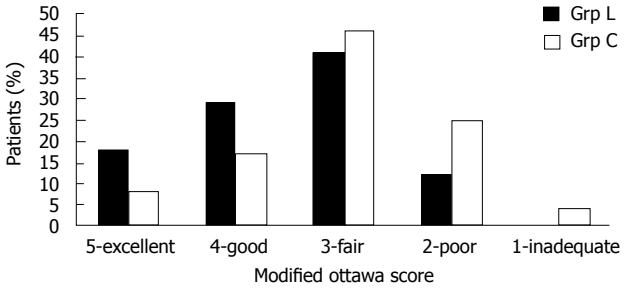

Figure 2 Endoscopist's evaluation of bowel cleansing. Comparison of bowel preparation quality among the 2 study groups using a modified ottawa score. Grp L: Experimental group; Grp C: Control group.

Grp C received only PEG the evening prior to colonoscopy. The study's sponsor prohibited a placebo-pill to be given in Grp C (a single-blinded trial). All patients were instructed to start drinking the PEG solution around 6pm the evening before their colonoscopy and ingest about 8 oz every 10 min until completion of 4 liters.

Colonoscopy

All the colonoscopies were carried out in the endoscopy center at the Medical College of Georgia. The colonoscopies were performed by two experienced endoscopists using the Olympus colonoscopes (Olympus Optical Co., Tokyo, Japan). A complete colonoscopy was defined as reaching the cecum which was determined by visualization and documentation of the ileocecal valve and appendiceal orifice. Patients either received moderate conscious sedation by administering a combination of fentanyl and midazolam intravenously or monitored anesthesia care with diprivan.

Primary outcome

The primary measured endpoint of this study was the quality of colon cleansing preparation as rated by a blinded endoscopist using a validated 5-point Likert scale[15].

Evaluation of colon cleansing

One of two gastroenterology attending physicians graded all the bowel preparations upon completion of the colonoscopy and was blinded to what bowel cleansing prep the patient had taken. The colon prep quality was rated based on global colon assessment using a modified Ottawa bowel preparation scale with 1 being excellent and 5 considered inadequate (Table 1).

Statistical analysis

The study was designed to determine whether L + PEG improved colon prep quality in AODM patients undergoing screening colonoscopy *vs* PEG alone. It was expected that at least 100 patients would complete the trial. A sample size of 100 patients would detect a 30% difference in the percentage of patient with excellent (1) or good (2) prep quality with 89% power and a two tailed *P* value of 0.05. However, due to loss of funding from the pharmaceutical company, the study was terminated early. The quality of colonoscopy preparations was compared using chi-square statistics. Exact methods were used if there were small or zero cell counts.

RESULTS

A total of 60 patients were enrolled and randomized in the clinical trial; 30 in Grp L and 30 in Grp C (Figure 1). Overall, 13 patients were excluded in Grp L and 6 patients in Grp C. In Grp L, 12 patients (41%) cancelled their procedure and 1 did not complete the prep. In Grp C, 5 patients (17%) cancelled their procedure and 1 withdrew from the trial. The no-show rate between Grp L and Grp C was statistically significant ($P = 0.04$).

The quality of the bowel preparation as evaluated by the endoscopist for each study group is shown in Figure 2. Overall, 8 out of 17 patients (47%) in Grp L had an excellent or good colon prep quality versus 6 out of 24 patients (25%) in Grp C ($P = 0.14$). The average colon preparation score in Grp L was 2.47 and 3.00 in Grp C ($P = 0.09$).

Unfortunately, in order to achieve a statistical significance of ⩽ 0.05 an anticipated effect (f^2) of 0.37 would have had to have been achieved (f^2 = 0.18 in this study). Although this trial did not show statistical significance, there was a trend towards improved colon prep quality in Grp L.

There were no serious adverse events associated with this study. However, 1 patient in Grp L had a known history of paroxysmal atrial fibrillation and was in normal sinus rhythm during the time of study enrollment but was in atrial fibrillation with controlled rate the morning of colonoscopy. All of the colonoscopies were complete, except 1 in Grp C due to inadequate prep quality.

DISCUSSION

Colonoscopy remains the preferred method for colon cancer and polyp screening and a successful procedure requires adequate bowel preparation[16]. The ideal colon preparation should allow consistent and reliable visualization of the colonic mucosal surface with a safety profile that is acceptable for all types of patients. Unfortunately, no current bowel cleansing preparation meets these criteria[14].

Our study is the first to evaluate the use of lubiprostone in combination with a more practical single-day PEG regimen on the effect of bowel prep quality in diabetics undergoing screening colonoscopy. Use of 2 lubiprostone 24 mcg capsules with a PEG single-dose regimen resulted in a trend towards improved colon preparation versus PEG alone in patients with AODM. Statistical significance may have been achieved if completion rates had been similar between both study groups. It is also possible that even higher doses of lubiprostone will be required to achieve better colon prep-quality in diabetics when single-dose PEG is used.

This study does have some limitations. Firstly, it was performed at a single-center and was only single-blinded. The study's sponsor prohibited a placebo-pill to be given in Grp C. Secondly, previous studies have shown improved bowel cleansing with split-dose PEG[16] but, due to concerns voiced by our IRB regarding patient compliance with a split-dose PEG, we had to use single-dose PEG in our trial. Lastly, the original trial was powered for a sample size of 100 patients in order to achieve statistical significance; however this trial was terminated early due to loss of funding from the pharmaceutical company. Thus, it is possible that a type Ⅱ error could have occurred because the study group was insufficiently powered. Statistical significance may have been achieved if the trial had been fully completed.

In conclusion, this study showed that there is a trend towards improved colon prep quality in diabetic patients undergoing screening colonoscopy who received a combination of L + PEG versus PEG alone. Given that 2 doses of lubiprostone has an average retail cost under $9.00 US, combining lubiprostone to standard PEG may be a reasonable and cost-effective option to achieve better bowel cleansing in difficult to prep adult-onset diabetic patients[17]. In addition, with almost no adverse events reported, adding lubiprostone may be a viable option to achieve optimal bowel prep in diabetics especially if split-dose PEG is used. A larger double-blinded trial will be required to further evaluate these findings. The medical community must continue to develop safe, effective and well tolerated methods for bowel cleansing in order to maximize the effect of colon cancer/polyp screening.

COMMENTS

Background

Diabetic patients may have difficulty in obtaining acceptable colonoscopy preparation quality.

Research frontiers

Achievement of superior colonoscopy preparation quality is of utmost importance to allow for colonic lesion detection in colonoscopy. Research is ongoing to provide patients colonoscopy preparation medication regimens that are easily taken while achieving preparation quality for patient compliance and wide-spread clinical application.

Innovations and breakthroughs

Addition of Lubiprostone to polyethylene glycol–based colonoscopy preparations may enhance colonoscopy preparation quality in a diabetic population that is difficult to prep.

Applications

Future larger studies utilizing lubiprostone with other patient populations and colonoscopy preparation regimens will need to be performed to confirm that lubiprostone is a cost-effective adjunctive medication in colonoscopy preparation.

Terminology

Lubiprostone (*Amitiza, Sucampo Pharmaceuticals, Inc., Bethesda, MD; Takeda Pharmaceuticals America, Inc., Deerfield, IL*) is a locally acting type-2 chloride channel activator which causes intestinal fluid secretion resulting in softened stool and increased intestinal transit without the loss of either net intravascular fluid or electrolytes.

Peer review

The article should be accepted as initial, innovative research utilizing lubiprostone to improve colonoscopy preparation in the difficult to prep diabetic population. However, the reviewers noted that conclusions drawn from the study's result would be limited by its small sample size.

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CASE REPORT

Endoscopic treatment of a large colonic polyp as a cause of colocolonic intussusception in a child

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Abstract

Colocolonic intussusception is an uncommon cause of intestinal obstruction in children. The most common type is idiopathic ileocolic intussusception. However, pathologic lead points occur approximately in 5% of cases. In pediatric patients, Meckel's diverticulum is the most common lead point, followed by polyps and duplication. We present a case of recurrent colocolonic intussusception which caused colonic obstruction in a 10-year-old boy. A barium enema revealed a large polypoid mass at the transverse colon. Colonoscopy showed a colonic polyp, 3.5 centimeters in diameter, which was successfully removed by endoscopic polypectomy.

Key words: Colocolonic intussusception; Juvenile polyp; Endoscopic treatment; Large colonic polyp

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INTRODUCTION

Colocolonic intussusception is an uncommon cause of intestinal obstruction in children[1,2]. The most common type is idiopathic ileocolic intussusception. On rare occasions, in less than 3% of cases, colocolonic intussusception occurs and is usually associated with no pathologic lead point[3,4].

The pathologic lead point occurs in only 5% of intussusception cases, and is usually present in older children[1,5]. The most common pathologic lead point is Meckel's diverticulum, followed by small bowel polyps and intestinal duplications[2,6].

We present a case of colocolonic intussusception in a 10-year-old boy. The patient had as pathologic lead point a large polyp which was completely removed by endoscopic surgery. The pathological result confirmed a juvenile colonic polyp.

CASE REPORT

A 10-year-old boy was admitted to the Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine at Siriraj Hospital due to recurrent episodes of intussusception. In a provincial hospital, he presented

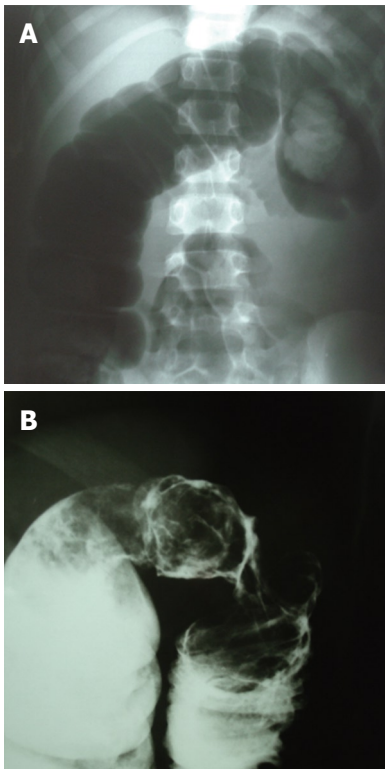

Figure 1 Plain abdominal film. A: Completed colonic obstruction on the left side of the colon; B: Barium enema revealed a colonic mass at the splenic flexor after successful reduction.

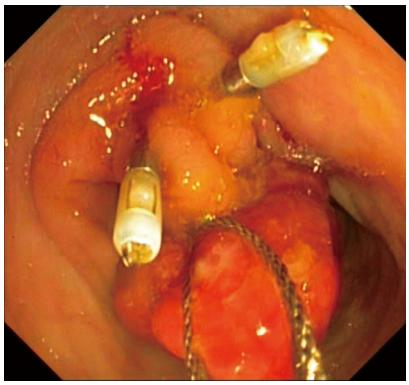

Figure 2 At the transverse colon, a huge colonic polyp with mucosal invagination confirmed that it was acting as a leading point. Snare polypectomy was applied after successful vascular control with two hemoclips.

with a one-day history of colicky abdominal pain and bloody stool. Abdominal ultrasonography was performed, and confirmed the diagnosis of intussusception. After hydrostatic reduction failed, he underwent a laparotomy for manual reduction. The patient recovered and was discharged from the hospital on the day 5.

8 d after the operation, colicky pain recurred as well as the bloody stool. A plain abdominal film showed colonic obstruction near the splenic flexure of the colon (Figure 1A). Colocolonic intussusception was successfully reduced by hydrostatic pressure. A barium enema revealed a mucosal lesion at the splenic flexure of the colon (Figure 1B). The patient was then referred to our hospital.

He underwent an elective colonoscopy 1 wk later. A large pedunculated polyp, measuring 3.5 centimeters in diameter, was detected at the transverse colon and polypectomy was successfully performed (Figure 2). The pathologic finding revealed a juvenile polyp (Figure 3). The child recovered and has done well ever since.

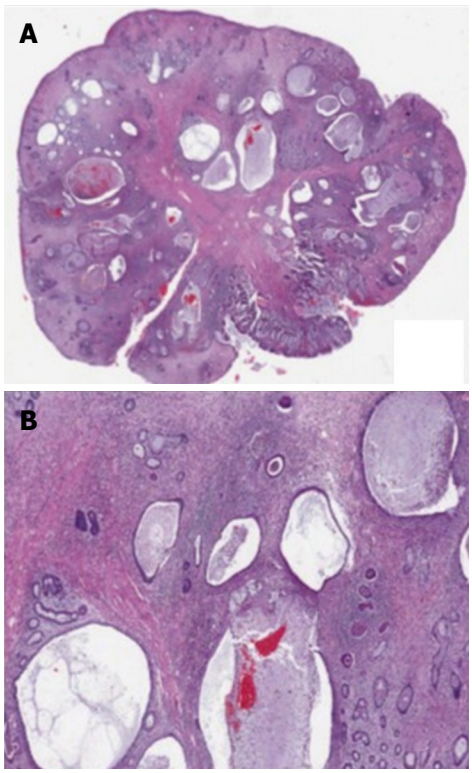

Figure 3 The whole mouth capture shows a polypoid mass, with edematous stroma, inflammation, and ulceration. A: Multiple dilated mucous glands and mucin lakes are noted; B: The dilated mucous glands and stromal inflammation (× 2).

DISCUSSION

Although intussusception has been reported in all pediatric age groups, 75%-90% of the cases occur within the first 2 years of life[6]. Most of the presentations of intussusception are of the idiopathic ileocolic type[4,6,7]. Only 5%-6% of these patients have pathologic lead points[1,2,4]. The incidence of pathologic lead points increases with age and recurrent episodes. Intussusception which occurs outside the ileocolic junction appears to have a higher incidence of pathologic lead points and requires surgical management such as a bowel resection[4]. This patient should have been initially suspected to have a pathological lead point with the development of recurrent colocolonic intussusception.

The approach to patients with intussusception due to a pathological lead point is similar to that of patients in the idiopathic group, as it may at first be difficult to diagnose them from standard management procedures, such as presenting history, physical examination and a plain film. A contrast enema reduction is the first line of the management, unless the patient shows signs of secondary peritonitis. Lead points which are caused by diffuse mucosal lesions benefit from this approach. Some of them (non-pathological lead points) are associated with inherent existing conditions such as hereditary angioneurotic edema[8]. A careful review of post-evacuation films should be performed in cases where there is a strong possibility of a pathologic lead point[9]. In

the colocolonic intussusceptions group, colonoscopy is indicated in order to identify a lead point in the colon. Endoscopic treatment, such as polypectomy, can safely be performed when removable mucosal lesions are present[3,10]. This intervention can reduce unnecessary or invasive surgery. However, pediatric colonoscopy requires sedation and/or a general anesthetic, as opposed to a barium enema which, in good pediatric radiology hands, can be just as effective for diagnosis and further information.

A juvenile colonic polyp can act as a lead point for colocolonic intussusception[3]. Juvenile polyps usually occur in first decade of life. The usual presenting symptom is painless hematochezia[11,12]. Although a solitary lesion is often benign, malignant transformation can occur in juvenile polyposis syndrome when the number of juvenile polyps is greater than 5[12]. A complete colonoscopy plays a crucial role in distinguishing juvenile polyposis syndrome from a solitary polyp. Surveillance colonoscopy is recommended in those who have multiple polyps and precancerous lesions.

In conclusion, recurrent colocolonic intussusception in a school-age patient is rare and usually due to a pathologic lead point. Goals for the treatment are the reduction of intussusception and searching for and finding a lead point. Radiologic reduction is a useful initial treatment. However, it is seldom successful in reducing a colocolic intussusception, an intussusception in an older child, and/or a recurrent intussusception, all of which are symptoms of an intussusception caused by a pathological lead point. A careful review of post-evacuation films is helpful. Colonoscopy is a non-invasive and effective tool in searching for intraluminal lesions in the colon such as polyps, which can be simultaneously removed.

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Meetings

Events Calendar 2010

January 25-26
Tamilnadu, India
International Conference on Medical Negligence and Litigation in Medical Practice

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

February 11-13
Fort Lauderdale, FL, United States
21th Annual International Colorectal Disease Symposium

February 26-28
Carolina, United States
First Symposium of GI Oncology at The Caribbean

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-17
Landover, Maryland, United States
12th World Congress of Endoscopic Surgery

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

April 28-May 01
Dubrovnik, Croatia
3rd Central European Congress of surgery and the 5th Croatian Congress of Surgery

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 15-19
Minneapolis, MN, United States
American Society of Colon and Rectal Surgeons Annual Meeting

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

June 20-23
Mannheim, Germany
16th World Congress for Bronchoesophagology-WCBE

August 28-31
Boston, Massachusetts, United States
10th OESO World Congress on Diseases of the Oesophagus 2010

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 11-12
La Jolla, CA, United States
New Advances in Inflammatory Bowel Disease

September 16-18
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18th United European Gastroenterology Week

October 29-November 02
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November 13-14
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Instructions to authors

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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