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EDITORIAL

Prospects of polyglycolic acid sheets for the treatment of esophageal stricture after esophageal endoscopic submucosal dissection

Qing-Xia Wang, Rui-Hua Shi

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Abstract

Esophageal cancer is the seventh most common type of cancer and the sixth leading cause of cancer -related mortality worldwide. Endoscopic submucosal dissection (ESD) is widely used for the resection of early esophageal cancer. However, post-ESD esophageal stricture is a common long-term complication, which requires attention. Patients with post-ESD esophageal stricture often experience dysphagia and require multiple dilatations, which greatly affects their quality of life and increases healthcare costs. Therefore, to manage post-ESD esophageal stricture, researchers are actively exploring various strategies, such as pharmaceutical interventions, endoscopic balloon dilation, and esophageal stenting. Although steroids-based therapy has achieved some success, steroids can lead to complications such as osteoporosis and infection. Meanwhile, endoscopic balloon dilatation is effective in the short term, but is prone to recurrence and perforation. Additionally, esophageal stenting can alleviate the stricture, but is associated with discomfort during stenting and the complication of easy displacement also present challenges. Tissue engineering has evolved rapidly in recent years, and hydrogel materials have good biodegradability and biocompatibility. A novel type of polyglycolic acid (PGA) sheets has been found to be effective in preventing esophageal stricture after ESD, with the advantages of a simple operation and low complication rate. PGA membranes act as a biophysical barrier to cover the wound as well as facilitate the delivery of medications to promote wound repair and healing. However, there is still a lack of multicenter, large-sample randomized controlled clinical studies focused on the treatment of post-ESD esophageal strictures with PGA membrane, which will be a promising direction for future advancements in this field.

Key Words: Polyglycolic acid; Endoscopic submucosal dissection; Esophageal stenosis; Esophageal cancer; Steroids

Core Tip: Esophageal cancer is the seventh most common type of cancer and the sixth leading cause of cancer death worldwide. Endoscopic submucosal dissection (ESD) is considered a prominent method for early esophageal cancer resection. However, esophageal stenosis is a common complication of esophageal ESD. A novel hydrogel material, polyglycolic acid sheet, is safe and effective for the prevention of esophageal strictures after ESD.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) has become the preferred treatment method for early esophageal cancer, due to its high rate of lesion resection, which is conducive a more accurate pathological diagnosis after surgery[1]. Additionally, ESD causes lesser damage to patients and facilitating faster postoperative recovery compared to traditional surgery. However, it often involves resection of more than 3/4th of the esophageal mucosa, which frequently leads to post-operative esophageal stenosis[2]. Esophageal stenosis is indeed one of the long-term complications of esophageal ESD, often leading to dysphagia. This condition necessitates multiple endoscopic balloon dilatation (EBDs), considerably affecting patients' quality of life[3].

Currently, various strategies are available for treating esophageal strictures, yet each approach has its limitations. Although the effectiveness of oral steroids is well recognized, they potentially cause systemic side effects, such as osteoporosis, immunosuppression, diabetes, peptic ulcers, and infections[4]. Injection of triamcinolone acetonide (TA) has demonstrated good results, but local injection may injure the muscularis propria resulting in complications, such as delayed perforation[5]. Furthermore, the successful use of self-expanding coated metal stents for the prevention of post-ESD esophageal strictures has been reported; however, these stents are associated with the risks of bleeding, perforation, and migration[6].

In recent years, rapid advancements in tissue engineering have led to the introduction of hydrogel materials with controllable physicochemical properties and biocompatibility[7,8]. Polyglycolic acid (PGA) membranes, a type of hydrogel material, are increasingly being used for preventing post-ESD esophageal strictures[9,10]. Extensive endoscopic resections, often employed for the treatment of early esophageal neoplasia, can result in fibro-inflammatory strictures. The mechanisms behind post-ESD esophageal stricture formation are as follows: (1) Initial secretion of tissue invasive factors; (2) disruption of the protective barrier; and (3) activation of inflammatory pathways; and (4) inflammatory proliferation of myofibroblasts[11,12]. Creating a barrier over large exposed areas of submucosa after resection not only protects it from endoluminal stress factors but also shields the residual submucosa and muscularis propria while serving as a matrix for epithelial cell migration. Among the various wound-protective strategies, PGA sheets have shown the most convincing evidence with a 37.5% stricture rate and excellent safety[13].

CLINICAL IMPLICATIONS

PGA membranes serves as a biophysical barrier for covering wounds, as well as it facilitates delivery of medications to promote wound repair and healing[9,10]. Kim *et al*[14] reported good results in preventing esophageal strictures using PGA patches to cover postoperative defects. Sakaguchi *et al*[15] evaluated the application of PGA sheets with fibrin glue and found it to be an effective and safe method for preventing post-ESD esophageal stricture and reducing the need for EBDs. Sakaguchi *et al*[16] suggested that the administration of PGA and basic fibroblast growth factor suppresses myofibroblast activation in the acute phase, thereby preventing esophageal constriction. A randomized controlled trial conducted in 2018 reported a lower postoperative stricture rate (20.5%) with the application of PGA sheets for wound coverage in the coverage group than in the non-covered group[17]. Sakaguchi *et al*[18] proposed the efficacy of PGA combined with steroid injections for preventing post-ESD esophageal stenosis, revealing a significantly lower stenosis rate with the use of combination therapy than with PGA alone. A study by Iizuka *et al*[19] suggested that PGA sheets and fibrin glue are promising option for preventing esophageal stricture, showing similar efficacy to that of intralesional steroid injections. Hwang *et al*[20] reported favorable outcomes, noting that the stricture rate in the PGA group (12.5%) was significantly lower than that of the historical control group (66.7%). Yang *et al*[21] demonstrated that the combined PGA plus stent placement therapy yielded a lower occurrence and milder severity of post-ESD esophageal stricture than that of stent placement therapy alone in patients with early-stage esophageal cancer. Additionally, a recent study employed a triamcinolone-soaked PGA combined with a fully covered metal stent to prevent stricture after extensive dissection of the esophageal mucosa. The study demonstrated that the method is safe and may decrease the incidence of esophageal stricture and the number of EBD sessions required after large esophageal ESD[22].

However, Iizuka *et al*[23] suggested that PGA sheets do not reduce the incidence of esophageal strictures after ESD, proposing that potential reasons for this to be premature detachment of the PGA sheets and insufficient follow-up period.

CONCLUSION

A growing number of studies have demonstrated that PGA membranes can significantly reduce the rate of esophageal strictures after esophageal ESD, decrease the number of EBDs needed by patients, and improve their quality of life. Some studies have suggested that the efficacy of PGA membrane in preventing esophageal stricture after ESD is not superior to that of a local TA injection; however, this observation also reinforces the fact that PGA membranes indeed play a role in preventing esophageal stricture. The primary mechanism by which PGA membranes prevent esophageal strictures appears to be the physical protection of the wound, leading to a consequent reduction in inflammatory exudation.

To address the challenge of PGA membranes being easily dislodged numerous researchers have combined PGA membranes with fibrin glue or stent, achieving positive effects. Other researchers have used PGA membranes in combination with TA to prevent stenosis after ESD and have also achieved effective results. These combined treatments can address the shortcomings of monotherapy and enhance overall therapeutic effectiveness, thereby demonstrating the promising application potential of PGA membranes.

In conclusion, PGA sheets are safe and effective in preventing post-ESD esophageal strictures. However, a notable gap exists in the form of multicenter, large-sample randomized controlled clinical studies focusing on the treatment of post-ESD esophageal strictures with PGA membranes. Addressing this gap represents, a promising direction for future development in this field.

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EDITORIAL

Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions: Clinical significance

Xu-Peng Wen, Qi-Quan Wan

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Abstract

Transoral endoscopic resections in treating upper gastrointestinal submucosal lesions have the advantages of maintaining the integrity of the gastrointestinal lumen, avoiding perforation and reducing gastrointestinal fistulae. They are becoming more widely used in clinical practice, but, they may also present a variety of complications. Gas-related complications are one of the most common, which can be left untreated if the symptoms are mild, but in severe cases, they can lead to rapid changes in the respiratory and circulatory systems in a short period, which can be life-threatening. Therefore, it is important to predict the occurrence of gas-related complications early and take preventive measures actively. Based on the authors' results in the prepublication of the article "Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions," and in conjunction with our evaluation and additions to the relevant content, radiographs may help screen patients at high risk for gas-related complications. Controlling blood glucose levels, shortening the duration of surgery, and choosing the most appropriate surgical resection may positively impact the prognosis of patients at high risk for gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions.

Key Words: Complications; Endoscopy; Upper gastrointestinal tract; Nomogram; Clinical significance

Core Tip: Transoral endoscopic resection of upper gastrointestinal submucosal lesions is associated with gas-related complications, which are unavoidable and may increase patient burden and prolong the duration of hospitalization. A four-variable nomogram predicts the risk of gas-related complications after transoral endoscopic resection of upper gastrointestinal submucosal lesions, guiding endoscopists during clinical operations.

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INTRODUCTION

Here, we comment on the article by Yang *et al*[1] accepted in the recent issue of the *World Journal of Gastrointestinal Endoscopy*. We focus on the research actuality and clinical significance of the four-variable nomograms, namely diabetes, lesion origin, surgical resection method, and surgical duration for predicting gas-related complications in transoral endoscopic resections. Upper gastrointestinal submucosal lesions, as a gastrointestinal disorder, are smooth-surfaced elevated lesions and are common in elderly patients[2]. With the development and maturation of endoscopy and endoscopic ultrasonography examination techniques, as well as the increased health awareness of the population, the detection rate of gastrointestinal submucosal lesions in the digestive tract has increased dramatically[3,4]. Gastrointestinal submucosal lesions are often called subepithelial gastrointestinal lesions (SELs). SELs are an elevated lesion originating in the muscularis mucosae, submucosa, or lamina propria, and can also be extraluminal. Endoscopic techniques are the first line of investigation for the diagnosis of SELs. Recently, a rising number of gastrointestinal submucosal lesions were treated at gastroscopy[5,6]. The American Society for Gastrointestinal Endoscopy and National Comprehensive Cancer Network guidelines recommend endoscopic surveillance of asymptomatic lesions < 2 cm in diameter. However, larger lesions or those causing significant symptoms require immediate intervention[7].

For endoscopic treatment of SELs, the results of a large epidemiologic study suggested that the difference in disease-specific morbidity and mortality in patients with gastrointestinal stromal tumors < 2 cm in diameter was not statistically significant compared with those treated with surgical resection[8]. Therefore, in conjunction with clinical practice, some patients undergoing endoscopic techniques, an invasive investigation, show poor compliance with follow-up. Eendoscopic treatment can be performed in such patients who are unable to have regular follow-up and have a strong desire for endoscopic treatment. The techniques of transoral endoscopic resection include high-frequency electrocoagulation, endoscopic mucosal resection, endoscopic submucosal excavation, endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER), and endoscopic full-thickness resection. STER is a new technique developed based on transoral endoscopic esophageal sphincterotomy peroral endoscopic myotomy (POEM), which is also an extension of the ESD technique. The resection rate of SELs treated by STER is 84.9% to 97.5%[9,10].

Irregular tumor morphology, originating from the deep layers of the intrinsic muscular layer, intraoperative air insufflation, and operative time > 60 min are independent risk factors for the occurrence of major postoperative complications[11]. Of the complications that can occur after endoscopic treatment, gas-related complications are more common [12], but most of these complications are mild and can usually be self-absorbed or improved by conservative therapy, and the application of carbon dioxide (CO_2) gas throughout the operation can effectively reduce the severity of gas-related complications[13-15].

The main influencing factors leading to gas-related complications: (1) Depth of intrinsic myotomy; and (2) intra-tunnel pressure. They are mainly caused by gas entering the lumen outside the esophageal wall, entering the mediastinum to form mediastinal emphysema, infiltrating into the subcutaneous tissues to form subcutaneous emphysema, and entering the abdominal and thoracic cavities to form pneumomediastinum and pneumothorax. Usually, mild symptoms do not require treatment, but severe cases can lead to rapid changes in respiratory circulation for a short period, which can be life-threatening. At present, some progress has been made in domestic and international research on the mechanism and factors affecting the occurrence of gas-related complications during endoscopic operations, which may be related to the duration of the disease, previous treatment history, Eckardt's score, S-type esophagus, Ling's staging, the way of establishing the tunnel entrance, the width of the tunnel, the length of the tunnel, the duration of the operation, and the use of the hybrid knife. Many of these factors are still in disagreement[16-18]. It is crucial to predict the occurrence of gas-related complications, take proactive precautions, and determine the need for intraoperative emergency treatment, such as closed thoracic drainage and peritoneal puncture deflation.

Nomogram, a visual clinical predictive model, provides a scientific basis for clinical decision-making. This nomogram primarily visualizes the results of the regression equation, which is usually used for logistic regression or COX regression to draw multiple line segments in a specific proportion based on the regression results, so that an individual's risk of disease or survival probability can be easily calculated. Researchers have evaluated, validated, and compared risk factors for gas-related complications in the training cohort using univariate and multivariate analyses. Diabetes, lesion origin, surgical resection method, and surgical duration were incorporated into the final nomogram[1].

ACTUALITY OF GAS-RELATED COMPLICATIONS DURING TRANSORAL ENDOSCOPIC RESECTION OF UPPER GASTROINTESTINAL SUBMUCOSAL LESIONS

Gas-related complications were the most common complications, including the mediastinum and subcutaneous emphysema, pneumothorax, pneumoperitoneum, and even gas embolism. Currently, CO_2 is mainly used as a gas source for perfusion, which is a natural product of the organism's metabolism and has the characteristics of easy inhalation from the outside and excretion from the body, which can effectively prevent the occurrence of related complications and reduce the risk of surgery[19,20]. During the STER procedure, subcutaneous emphysema is identified by observing and palpating the skin of the patient's neck. Subcutaneous emphysema is often associated with mediastinal emphysema. On a computed tomography scan performed after the POEM procedure, the rate of capnoperitoneum or subcutaneous emphysema was 30%-57%[20]. A recent review of 19 studies, including approximately 1300 cases of POEM, found an overall incidence of gas-related complications of 36%. Complications were distributed as follows: Pneumoperitoneum 17%, pneumothorax 5%, mediastinal air 4%, and subcutaneous emphysema 10%[21]. In POEM, sigmoid-type esophagus was identified as an independent risk factor for gas-related complications, possibly due to an esophageal twist increasing the pressure into the tunnel[22].

Besides, the main influencing factors leading to gas-related complications: (1) Depth of intrinsic myotomy, and (2) intra-tunnel pressure. Notably, many patients have multiple concurrent gas-related complications, such as pneumothorax and pneumomediastinum. Although the incidence of gas-related complications is relatively high, most of these complications are minor and do not require therapeutic intervention. Using CO_2 instead of air to reduce the risk of gas embolism and pneumothorax is theoretical, as demonstrating a statistical advantage of CO_2 in reducing the incidence of such rare complications is challenging. However, since air aeration can have catastrophic consequences, the use of CO_2 is recommended because transoral endoscopic resection typically destroys large areas of mucous membranes, which normally acts as a barrier to air. Most studies suggest that prolonged CO_2 inflation should be relatively safe for upper and lower gastrointestinal endoscopy in sedated patients with normal respiratory status[12,13,15,23]. Based on autopsy findings, forensic experts found an open blood vessel at the base of a gastric ulcer in a patient who died of air embolism after a gastroscopy and recommended using CO_2 to inflate it. Improved quality of endoscopic recovery is another advantage of CO_2 infusion, which has been demonstrated in many randomized controlled studies only in patients undergoing colonoscopy[24] and endoscopic retrograde cholangio pancreatography[25]. We believe it is reasonable to extrapolate these findings to transoral endoscopic resection of upper gastrointestinal submucosal lesions.

CLINICAL SIGNIFICANCE OF FOUR-VARIABLE NOMOGRAM FOR PREDICTING GAS-RELATED COMPLICATIONS IN TRANSORAL ENDOSCOPIC RESECTIONS

Currently, there are no reliable prediction models for predicting major gas-related complications in patients with transoral endoscopic resections. Although several studies have developed nomograms to predict other complications in patients with transoral endoscopic resections, most are limited to predicting stenosis[26-28].

Therefore, in this study, the researchers retrospectively analyzed clinical data from 353 patients to identify predictors of gas-related complications in patients undergoing transoral endoscopic resection. The results showed that diabetes, lesion origin, surgical resection method and duration were independent predictors associated with gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions.

Patients with diabetes mellitus (DM). DM is a chronic metabolic disorder in which prolonged episodes of hyperglycemia are common. Hyperglycemia can cause impairment and disruption of the normal function of many organs, including the gastrointestinal tract[29]. The pathogenesis of gas-related complications during transoral endoscopic resection in DM is complex, multi-factorial with motor dysfunction, glycemic control, autonomic neuropathy, and psychological factors, and is not well understood[30]. Previous studies have shown that the morphology and biomechanical properties of the gastrointestinal tract change during diabetes, such as increased wall thickness and hardness of the gastrointestinal tract[31]. The changes in stress distribution and wall stiffness likely alter the stress after the stop the way the mechanosensitive afferents. Consequently, the perception and motility of the intestinal tract will change as well. Therefore, the morphological changes and biomechanical remodeling are likely to affect function of mechanosensitive afferents in the gastrointestinal wall and further affect the motor and sensory function[32]. Some studies confirms that type 2 diabetes is an independent risk factor for esophageal foreign body perforation[33]. The underlying mechanism of diabetes-induced esophageal foreign body perforation may lie in impaired wound healing and neuropathy in DM patients. Neuropathy can cause abnormal esophageal movement in most people with diabetes, sometimes similar to diffuse esophageal spasm[33]. As the disease progresses, some minor injuries caused by foreign bodies tend to be repaired in non-diabetic patients, whereas diabetic patients are more prone to worsening injuries and a tendency to persistent stagnation, which may lead to serious complications such as gas-related complications or perforation and exacerbation of the disease. In part, this is the result of neuropathy. Therefore, future studies target neuropathy associated with diabetes. For example, we may be able to obtain data on the patient's glycosylated hemoglobin before the procedure, which could help determine whether poor glycemic control in diabetic patients increases the risk of gas-related complications or perforation.

Concerning lesion origin. Regarding the overall incidence of adverse complications, the prevalence was higher in esophagoscopy patients than in gastroduodenoscopy patients. Endoscopic procedure-related morbidity (*i.e.*, pneumomediastinum and subcutaneous emphysema) is the main reason for the differences shown, which may be related to

anatomical features such as lack of serosa in the esophagus and thin intestinal wall. The development of extended subcutaneous emphysema has been reported to be an enhancing factor for CO_2 retention during laparoscopic surgery and requires immediate attention to determine the presence of pneumothorax or pneumomediastinum, especially when the endoscopic procedure involves the chest[34]. In this case, patients with ESD require more careful attention. Some studies have shown that increases in $PaCO_2$ and the prevalence of adverse events were greater in patients undergoing esophagoscopy than in those undergoing gastroduodenoscopy[35]. As things stand, it is uncertain whether the degree of CO_2 retention may be different with different targeted organs for endoscopy.

Concerning surgical resection method. The incidence of gas-related complications during transoral endoscopic resection varies significantly depending on the surgical method. The main influencing factor leading to gas-related complications is the depth of myometrium propria incision. Due to the lack of serosal layer in the esophagus, to reduce the occurrence of gas-related complications, in early POEM, it is recommended to only incise the circular muscles to avoid damaging the longitudinal muscles. However, this method is less effective for some patients with severe symptoms [36]. To ensure long-term patient outcomes, a clinical study of more than 2000 POEM surgeries showed that total myotomy, namely total incision of the circular and longitudinal muscles from the stenosis to the subcardia, not only did it not increase the number of gas-related complications, but also significantly shortened the operative time compared with simple circular myotomy[22]. But subsequent studies have confirmed that the incidence of postoperative gastroesophageal reflux is higher with this method. Another influencing factor is the pressure inside the tunnel. To ensure tunnel expansion during surgery, the gas must be fed continuously. If the gas accumulates excessively in the tunnel, the increased pressure inside the tunnel will cause the gas to flow into the mediastinum through the airspace and lead to the accumulation of gas, which then enters the subcutaneous tissues. At present, the inverted T-shaped tunnel opening method has been established, *i.e.*, the first transverse incision is 0.5-0.8 cm, and then a longitudinal incision of about 1.0 cm is made at the anus side edge of the transverse opening, which on the one hand ensures that there is enough space in the surgical incision for the mirror to be easily accessed and for the gas and liquid to be smoothly discharged[37]. On the other hand, with a small transverse span, it is relatively easy to close the incision. on the other hand, the transverse span is small, so it is relatively easy to close the incision[37,38]. Simple longitudinal incision of the tunnel entrance will result in the endoscope being tightly encircled by the mucosa at the exit, and prolonged poor gas injection and drainage will keep the gas in the tunnel under high pressure, making it susceptible to gas-related complications[23]. Besides, during full myotomy, the integrity of the outer esophageal membrane should be preserved as much as possible.

Concerning surgical duration. The gastrointestinal tract rapidly absorbs CO_2, so prolonged surgical durations can still lead to gas-related complications. The duration of transoral endoscopic resections may be affected by various resection devices, traction techniques, and even submucosal injection of materials, which may further affect the results[39]. In addition, some studies have suggested that lesion fibrosis may alter transoral endoscopic resections duration[39,40]. As the duration of surgery increases, the rate of gas-related complications becomes higher and more severe. Second, it is worth considering whether the endoscopist's experience level is related to the duration of transoral endoscopic resections and ultimately, whether it leads to gas-related complications.

LIMITATIONS OF FOUR-VARIABLE NOMOGRAM FOR PREDICTING GAS-RELATED COMPLICATIONS IN TRANSORAL ENDOSCOPIC RESECTIONS

We acknowledged the limitations in the present study. First, while their four-variable nomogram showed promise, its performance could potentially be improved by incorporating additional clinical variables, such as presence of previous treatment history, how the tunnel portal is established and narrowness of the tunnel. A history of preoperative treatments such as: Dilation, surgery, which can cause adhesions in the submucosal layer and increase the difficulty of tunnel creation. Simple longitudinal incision of the tunnel entrance will result in the endoscope being tightly encircled by the mucosa at the exit, and prolonged poor gas injection and drainage will keep the gas in the tunnel under high pressure, making it susceptible to gas-related complications[23]. Additionally, the corresponding performance comparison against other well-established models is warranted. In future studies, many experiments are needed to further search for possible biomarkers to better predict the occurrence of gas-related complications in transoral endoscopic resections.

CONCLUSION

In summary, using a nomogram incorporating surgical duration, method of surgical resection, DM, and the lesion layer of origin to predict gas-related complications in transoral endoscopic resections is recognizable. Theoretically, a patient's preoperative gas intolerance may be a marker for the development of postoperative gas-related symptoms. Perioperative risk can be reduced through early prevention and intervention. However, there are many factors contributing to the development of gas-related complications during surgery, possibly involving the patient, anesthesia, and surgery, and the influence of these factors can continue to be investigated, and the predictive value can be confirmed by expanding the sample size. Future studies should evaluate the clinical value of preoperative gas provocation tests.

FOOTNOTES

Author contributions: Wan QQ designed the overall concept and outline of the manuscript; Wen XP contributed to the discussion and design of the manuscript; all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Case Control Study

Propofol sedation in routine endoscopy: A case series comparing target controlled infusion *vs* manually controlled bolus concept

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Abstract

BACKGROUND

Many studies have addressed safety and effectiveness of non-anaesthesiologist propofol sedation (NAPS) for gastrointestinal (GI) endoscopy Target controlled infusion (TCI) is claimed to provide an optimal sedation regimen by avoiding under- or oversedation.

AIM

To assess safety and performance of propofol TCI sedation in comparison with nurse-administered bolus-sedation.

METHODS

Fouty-five patients undergoing endoscopy under TCI propofol sedation were prospectively included from November 2016 to May 2017 and compared to 87 patients retrospectively included that underwent endoscopy with NAPS. Patients were matched for age and endoscopic procedure. We recorded time of sedation and endoscopy, dosage of medication and adverse events.

RESULTS

There was a significant reduction in dose per time of propofol administered in the TCI group, compared to the NAPS group (8.2 ± 2.7 mg/min *vs* 9.3 ± 3.4 mg/min; $P = 0.046$). The time needed to provide adequate sedation levels was slightly but significantly lower in the control group (5.3 ± 2.7 min *vs* 7.7 ± 3.3 min; $P < 0.001$), nonetheless the total endoscopy time was similar in both groups. No differences between TCI and bolus-sedation was observed for mean total-dosage of propofol

rate as well as adverse events.

CONCLUSION
This study indicates that sedation using TCI for GI endoscopy reduces the dose of propofol necessary per minute of endoscopy. This may translate into less adverse events. However, further and randomized trials need to confirm this trend.

Key Words: Sedation; Endoscopy; Propofol; Target controlled infusion; Non-anaesthesiologist propofol sedation; Adverse event

Core Tip: First, target controlled infusion (TCI) is claimed to provide an optimal sedation regimen. Secondly, little is known about the differences of time of sedation and propofol dosage between nurse-administered intermittent bolus propofol sedation and TCI. Thirdly, sedation using TCI for gastrointestinal (GI) endoscopy reduces the dose of propofol necessary per minute of endoscopy (8.2 ± 2.7 mg/min *vs* 9.3 ± 3.4 mg/min; $P = 0.046$). Fourthly, sedation using TCI for GI endoscopy could have an impact on propofol total dosage on prolonged endoscopy procedures. Fifthly, this may translate into less adverse events and higher safety when using TCI in prolonged procedures.

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INTRODUCTION

Many studies have addressed the safety and effectiveness of non-anaesthesiologist propofol sedation (NAPS) for gastrointestinal (GI) endoscopy[1-5]. A high dose of propofol has been recognized as an independent risk factor for sedation-related complications[6]. For the safe use of propofol during endoscopic procedures performed by non-anaesthesiologists, controlled comparisons between different methods of propofol administration are still needed.

One of the most frequent methods of propofol sedation in GI endoscopy is manual administration of boluses. This method may be sub optimal during long-lasting endoscopies[7]. Target Controlled Infusion (TCI) is a delivery system with an infusion mode that uses pharmacokinetic models (based on age, sex, height, weight and dosing history in the individual patient) to calculate infusion rates required to reach and maintain a desired target concentration in the target tissue of the brain. Ultimately, the system is claimed to provide a calculated optimal sedation regimen hence avoiding under- or oversedation[8-10].

The aim of the present study was to assess safety and performance, in terms of time of sedation and dosage of propofol during TCI sedation in comparison with nurse-administered intermittent bolus propofol sedation.

MATERIALS AND METHODS

Study cohort

Forty-five consecutive patients undergoing endoscopy under TCI propofol sedation were prospectively included from November 2016 to May 2017. These were compared to a historic cohort of sex and age-matched patients that underwent endoscopy with bolus-sedation ($n = 80$). These comparator patients were matched for type endoscopic procedure. Exclusion criteria were age under 18 years; pregnant and lactating women; American Society of Anaesthesiologists class IV; allergy to propofol, fentanyl, or benzodiazepine; and anticipated difficult airway.

Endoscopic procedures

Hospital faculty experienced endoscopists performed all endoscopic procedures in Table 1. Physical monitoring included heart rate, peripheral arterial oxygen saturation, and non-invasive blood pressure being monitored and recorded continuously with a bedside monitor. Blood pressure was recorded every 2 min. All patients received oxygen 2 L/min *via* nasal cannula throughout the procedure.

Drug administration and endpoint evaluation

Propofol was administered intravenously by using the Module Dependable Process Station TCI system (Fresenius Kabi, Bad Homburg, German) using the pharmacokinetic parameter set according to the Schnider model. The initial setting of the target blood concentration of propofol was set at 2.0 mg/mL. The predicted brain tissue concentration of propofol at

Table 1 Endoscopy list [*n* (%)]

Endoscopy	Bolus (*n* = 80)	TCI (*n* = 45)
Gastroscopy	7 (8.7)	3 (6.6)
Colonoscopy	18 (22.5)	9 (20.0)
Gastro/Colo	30 (37.5)	18 (40.0)
EUS	20 (25.0)	12 (26.7)
ERCP	5 (6.3)	3 (6.7)

TCI: Target controlled infusion; EUS: Endosonography ; ERCP: Endoscopic retrograde cholangiopancreatography.

each time point was calculated automatically and was shown on the monitor of the TCI pump. The primary plasma target concentration was set at 1.5 g/mL with the possibility to increase the target by 0.3 g/mL every two minutes to a maximum of 3.5 g/mL. this adjustment was made upon the patients response based on the Observers Assessment of Alertness/Sedation (OAA/S) score[11].

Historic comparator sedation protocol: Manual sedation was following the "20/2 rule"[12] with an induction bolus dose of 0.5-1.0 mg/kg of propofol (Disoprivan 1%) followed by titration of maximum 20 mg every 2 min. Low doses of fentanyl bolus (25-100 g) could be added at the discretion of the endoscopist in both sedation regimens.

Once patient lost verbal command and eyelash reflex (OAA/S scores < 2) endoscopy was started. The induction period was defined as the time from the start of propofol infusion to insertion of the endoscope. The procedure time was defined as the time of the first endoscope insertion until endoscope removal.

Adverse events

Adverse events were defined as hypoxemia (peripheral oxygen saturation less than 90 %), hypotension (drop of mean arterial pressure below 60 mmHg), bradycardia (drop heart rate below 50 beats per minute for more than 1 min), and tachycardia (rise of heart rate above 110 beats per minute for more than 1 min). If hypoxemia occurred during the sedation, we performed chin lift on the patient and increased the oxygen dose.

Primary endpoint

The primary endpoint of the study was the consumption of propofol (mg) during endoscopy evaluated as dose (mg) per time (min).

Secondary endpoints include time of induction, total sedation time and safety regarding adverse events during sedation. The primary hypothesis stated that the use of TCI sedation would decrease the use of propofol over time and therefore be associated with a safer sedation.

Statistical analyses

All statistical analyses were performed with Stata 12.0. Results are presented as mean ± (SD). Differences between groups were calculated with Student's *t*-test, Wilcoxon rank sum test and Chi^2 test whenever appropriate. A value of $P < 0.05$ was regarded as significant.

RESULTS

All patients successfully underwent smooth procedures and no severe adverse event occurred. The demographic characteristics of the study participants did not show significant differences between the TCI group and the control group with respect to sex (female: 57% *vs* 43%; $P = 0.67$) and median age (55.9 *vs* 56.2; $P = 0.17$).

Endoscopy characteristics are shown in Table 1 and did not differ significantly between groups ($P = 0.55$).

The average total propofol consumption did not significantly differ between the groups (378.6 ± 213.1 mg *vs* 340.07 ± 150.07 mg; $P = 0.59$). However, there was a significant reduction in dose per time of propofol administered in the TCI group, compared to the bolus group (8.2 ± 2.7 mg/min *vs* 9.3 ± 3.4 mg/min; $P = 0.046$, Figure 1).

The time needed to provide proper sedation level was slightly but statistically significantly lower in the control group (5.3 ± 2.7 min *vs* 7.7 ± 3.3 min; $P < 0.01$). Nonetheless, the total endoscopy time was not different (42.3 ± 19.3 min *vs* 43.5 ± 18.2 min; $P = 0.57$).

There were no significant differences in the number of interventions utilizing fentanyl (71.2% *vs* 73.3% $P = 0.8$). However, average dose of fentanyl being used was significantly less in the TCI as compared to the control group (59.14 ± 28.37ug *vs* 36.67 ± 16.52 g; P 0.01).

No difference between bolus-sedation and TCI was observed for the rate of adverse events (26% *vs* 24%; $P = 0.95$, Table 2).

We ran a subgroup analysis with either short (less than 30 min) or long (more than 1 h) exams, for which results are shown in Tables 3 and 4. We found no significant reduction of dosage per time in favour of the TCI group looking at longer exams (8.94 ± 3.21 mg/min *vs* 6.82 ± 2.44 mg/min; $P = 0.08$, Figure 2). A reduction in total propofol dose in favour

Table 2 Number and percentage of adverse events [*n* (%)]

	Bolus (*n* = 80)	TCI (*n* = 45)	*P* value
Total adverse events	21 (26.0)	11 (24.0)	0.95
Hypoxemia	3 (14.4)	4 (36.4)	
Hypotension	10 (47.6)	5 (45.4)	
Bradycardia	4 (19.0)	2 (18.2)	
Tachycardia	4 (19.0)	0	

TCI: Target controlled infusion.

Table 3 Subgroup analysis according to duration of endoscopy: Short endoscopy < 30 min

Variable (mean ± SD)	Bolus (*n* = 21)	TCI (*n* = 10)	Delta	*P* value
Induction time (min)	4.81 ± 1.67	5.8 ± 1.81	0.99	0.11
Total time (min)	20.62 ± 6.49	21 ± 4.71	0.38	0.65
Total dose (mg)	198.1 ± 69.19	204.4 ± 74.23	6.3	0.81
Dose/time (mg/min)	10.14 ± 3.25	9.87 ± 3.58	0.27	0.58

TCI: Target controlled infusion.

Table 4 Subgroup analysis according to duration of endoscopy: Long endoscopy > 60 min

Variable (mean ± SD)	Bolus (*n* = 13)	TCI (*n* = 9)	Delta	*P* value
Induction time (min)	6.08 ± 5.15	9.44 ± 3.50	3.36	< 0.01
Total time (min)	73.30 ± 14.29	69.89 ± 8.95	3.41	0.89
Total dose (mg)	656.15 ± 291.42	484.67 ± 200.02	71.48	0.27
Dose/time (mg/min)	8.94 ± 3.21	6.82 ± 2.44	2.12	0.08

TCI: Target controlled infusion.

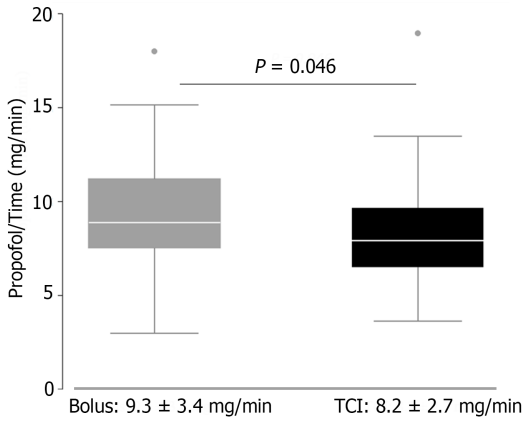

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Figure 1 Propofol dose/time (mg/min). TCI: Target controlled infusion.

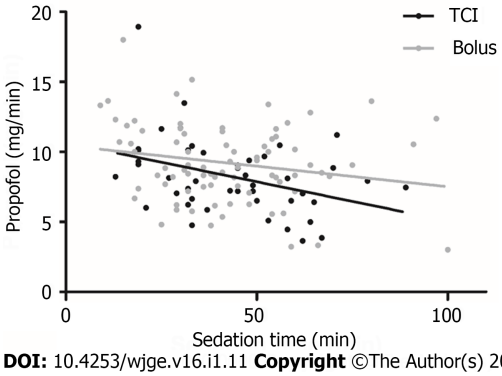

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Figure 2 Propofol dose/time (mg/min) over sedation time. TCI: Target controlled infusion.

of the TCI group was observed looking at longer exams; this did not reach statistical significance (656.15 ± 291.42 *vs* 484.67 ± 200.02; $P = 0.27$).

DISCUSSION

Propofol has been widely accepted as an ideal agent for endoscopy sedation because of the rapid onset of action and short recovery time[1,2]. However, propofol may cause cardiorespiratory inhibition necessitating providing of cardiorespiratory support with a ventilator until propofol is metabolized because there are no antagonists available. Thus, it is necessary to keep a balance between adequate sedation depth and minimized adverse effects. Intermittent bolus and continuous infusion are both alternatives for administration of propofol. However, the great variation in individual responses to propofol may be an important concern regarding safety during endoscopies[13].

During time-consuming endoscopic procedures, it may be difficult to obtain the optimal titration of drugs without increasing the risks of severe hypoxia, prolonged sedation and patient discharge after procedure[14].

Among different systems available for propofol administration, TCI uses a pharmacokinetic model to achieve and maintain a selected target plasma propofol concentration, through variation of the infusion rate, with a good predictive performance[8]. Previous studies on the use of TCI-based propofol administration demonstrated its feasibility and help in avoiding over- or under-sedation GI endoscopy[9,10]. Specifically, TCI-administered propofol sedation has been reported to achieve higher endoscopists satisfaction score, faster recovery of patients and more stable hemodynamic and respiratory conditions during endoscopy than manual infusion regimens particularly in hands of unexperienced training anaesthesiologists[15-17].

TCI-based propofol sedation has been evaluated in large series of various endoscopic procedures demonstrating safety and benefits[18,19].

The results of our study indicate that sedation using TCI for GI endoscopy reduces the dose of propofol necessary per minute of endoscopy. All procedures were carried out successfully and both methods of sedation were associated with adequate clinical sedation levels.

The occurrence of adverse events (around 25% in both groups) may seem high. However, we used very sensitive and conservative cut-offs to define adverse events, most of which were not severe or even life threatening. It is important to emphasie that our cohort didn't include any patients who would have increased risk for and/or require per se a higher dosage of propofol known as confounding factors such as: Primary Sclerosing Cholangitis, IV Drug users, bad experience in pervious endoscopy, patients with severe pain syndromes and/or being on opiates.

We also ran a subgroup analysis with either short (less than 30 min) or long (more than 1 h) exams, expecting to find better results with longer endoscopy procedure.

The analysis is therefore based on fewer results and the results did not reach statistical significance, but we found a trend tend towards reduction of dosage per time (2.12 mg/min) in favour of the TCI group. It may also be interesting to note that a reduction of total propofol dose of approximatively 170 mg in favour of the TCI group was found, even if this difference did not reach statistical significance because of the large variance.

Another advantage that was stated by the nursing staff is the convenience of the pump, allowing for more time and focus for the endoscopy nurse to help with the procedure if necessary, as well as the fewer manual interactions of the syringes, which reduces the risk of contamination.

Interestingly, significantly less fentanyl was used in the TCI group. This could be interpreted as a relative underuse of propofol in the bolus group, where the total amount of propofol would have been expected to be higher compared to the TCI group. It seemed that in the bolus group, at least some of the propofol was substituted by fentanyl.

CONCLUSION

In conclusion, our study indicates that sedation using TCI for GI endoscopy reduces the dose of propofol necessary per minute of endoscopy and this could have an impact especially on prolonged endoscopy procedures. This may also translate into less adverse events and higher safety when using TCI in prolonged procedures. However, further studies on large scale with prospective randomized-controlled design are needed to standardize sedation with propofol. With proper education, TCI sedation could then be implemented in routine endoscopy procedures.

ARTICLE HIGHLIGHTS

Research background

Non-anaesthesiologist propofol sedation (NAPS) for gastrointestinal (GI) endoscopy is safe and effective. Target controlled infusion (TCI) is claimed to provide an optimal sedation regimen by avoiding under or over-sedation.

Research motivation

Little is known about the differences of time of sedation and propofol dosage between nurse-administered intermittent bolus propofol sedation and TCI.

Research objectives

The aim of this study is to assess safety and performance of propofol TCI sedation in comparison with nurse-administered bolus-sedation.

Research methods

Forty-five patients undergoing endoscopy under TCI propofol sedation were prospectively included from November 2016 to May 2017 and compared to 87 patients retrospectively included that underwent endoscopy with NAPS.

Research results

Sedation using TCI for GI endoscopy reduces the dose of propofol necessary per minute of endoscopy (8.2 ± 2.7 mg/min *vs* 9.3 ± 3.4 mg/min; $P = 0.046$). Time needed to provide adequate sedation levels was lower in the control group. No differences between TCI and bolus-sedation was observed for mean total-dosage of propofol rate as well as adverse events.

Research conclusions

Sedation using TCI for GI endoscopy reduces the dose of propofol necessary per minute of endoscopy.

Research perspectives

Sedation using TCI for GI endoscopy could have an impact on propofol total dosage especially on prolonged endoscopy procedures. This may also translate into less adverse events and higher safety when using TCI in prolonged procedures.

FOOTNOTES

Author contributions: Sarraj R collected the dataset, wrote and designed the manuscript and figures; Vakilzadeh N provided support for the statistical analysis and figure design; Krupka N reviewed the manuscript and supported the submission; Theiler L and Wiest R designed the trial and implemented the TCI use in clinical practice and reviewed and the manuscript.

Institutional review board statement: The study was reviewed and approved by the Gesundheits-, Sozial-und Integrations direktion Kantonale Ethikkommission für die Forschung.

Conflict-of-interest statement: No conflict-of-internest to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at riad.sarraj@insel.ch. patient consent was not obtained but the presented data are anonymized and risk of identification is low.

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ORIGINAL ARTICLE

Clinical Trials Study

Bowel preparation protocol for hospitalized patients ages 50 years or older: A randomized controlled trial

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Abstract

BACKGROUND

The incidence and mortality rate of colorectal cancer progressively increase with age and become particularly prominent after the age of 50 years. Therefore, the population that is ≥ 50 years in age requires long-term and regular colonoscopies. Uncomfortable bowel preparation is the main reason preventing patients from undergoing regular colonoscopies. The standard bowel preparation regimen of 4-L polyethylene glycol (PEG) is effective but poorly tolerated.

AIM

To investigate an effective and comfortable bowel preparation regimen for hospitalized patients ≥ 50 years in age.

METHODS

Patients were randomly assigned to group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) or group 2 (4-L PEG). Adequate bowel preparation was defined as a Boston bowel preparation scale (BBPS) score of ≥ 6, with a score of ≥ 2 for each segment. Non-inferiority was prespecified with a margin of 10%. Additionally, the degree of comfort was assessed based on the comfort questionnaire.

RESULTS

The proportion of patients with a BBPS score of ≥ 6 in group 1 was not significantly different from that in group 2, as demonstrated by intention-to-treat (91.2% *vs* 91.0%, $P = 0.953$) and per-protocol (91.8% *vs* 91.0%, $P = 0.802$) analyses. Furthermore, in patients ≥ 75 years in age, the proportion of BBPS scores of ≥ 6 in

group 1 was not significantly different from that in group 2 (90.9% *vs* 97.0%, $P = 0.716$). Group 1 had higher comfort scores (8.85 ± 1.162 *vs* 7.59 ± 1.735, $P < 0.001$), longer sleep duration (6.86 ± 1.204 h *vs* 5.80 ± 1.730 h, $P < 0.001$), and fewer awakenings (1.42 ± 1.183 *vs* 2.04 ± 1.835, $P = 0.026$) than group 2.

CONCLUSION

For hospitalized patients ≥ 50 years in age, the bowel preparation regimen comprising 2-L PEG + 30-mL lactulose + a low-residue diet produced a cleanse that was as effective as the 4-L PEG regimen and even provided better comfort.

Key Words: Aged 50 years or older; Hospitalized; 2-L polyethylene-glycol + 30-mL lactulose + a low-residue diet; Comfort

Core Tip: Individuals ≥ 50 years in age require long-term and regular colonoscopies. Uncomfortable bowel preparation is the main reason preventing patients from undergoing regular colonoscopies. The 4-L polyethylene glycol (PEG) regimen is effective but poorly tolerated. We observed that the 2-L PEG + 30-mL lactulose + low-residue diet regimen was not inferior to the 4-L PEG regimen. The 2-L PEG + 30-mL lactulose + low-residue diet regimen was more comfortable than the 4-L PEG regimen. In patients ≥ 75 years in age, 2-L PEG + 30-mL lactulose + low-residue diet regimen was still effective.

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INTRODUCTION

The incidence and mortality rate of colorectal cancer (CRC) progressively increase with age and become particularly prominent after the age of 50 years[1]. Furthermore, approximately 90% of CRC cases and deaths worldwide are estimated to occur in this age group[1]. Therefore, the notably higher risk for CRC in the population of ≥ 50 years in age necessitates long-term and regular colonoscopies. Using laxatives is one of the most uncomfortable aspects of the colonoscopy procedure and is a major deterrent to patients adhering to regular colonoscopies[2]. Thus, effective and comfortable bowel preparation regimens are required to promote regular colonoscopies among patients ≥ 50 years in age.

A high-dose (4 L) regimen of water-mixed polyethylene glycol (PEG) yields a good bowel cleansing effect[3], but patients poorly tolerate it due to the high volume of water consumed. Alternatively, a low-dose bowel preparation regimen using 2 L of water mixed with PEG and ascorbic acid has been proposed to improve tolerability in adults[4]. However, the risk of inadequate bowel preparation is higher in adults ≥ 50 years in age than in younger individuals. Advanced age, increasing prevalence of constipation, diabetes, and hypertension are all risk factors for inadequate bowel preparation[3,5]. Moreover, individuals of ages 50 years or older have a higher prevalence of comorbidities and are more likely to be on antiplatelet or anticoagulant medications, resulting in an increased risk during the pericolonoscopy period. Consequently, they have a higher proportion of hospitalizations for colonoscopy compared to younger individuals. Hospitalization itself is considered a risk factor for inadequate bowel preparation[3,5]. Limited clinical studies have been conducted to clarify the effectiveness and comfort of low-dose bowel preparation regimens in hospitalized patients ≥ 50 years in age.

Reducing water intake to 2 L can improve comfort[4], while following a low-residue diet[6] and using lactulose as an adjuvant[7] can enhance the effectiveness of bowel preparation. Therefore, we proposed a bowel preparation regimen involving a mixture of 2 L of water with PEG and lactulose along with a low-residue diet for hospitalized patients ≥ 50 years in age who were undergoing colonoscopy. We aimed to evaluate the effectiveness, comfort, and safety of this method. These study results may contribute to supporting and improving decision-making in clinical practice.

MATERIALS AND METHODS

Study design and setting

This was a prospective, single-blinded (endoscopist) randomized controlled trial conducted in a tertiary care hospital in Beijing, China, which included patients who underwent colonoscopy at the endoscopy center. All colonoscopies were scheduled in the afternoon. No endoscopists used additional adjuvants or adjuvant devices to improve bowel preparation.

Patients

Patients admitted to the Geriatrics Department for planned colonoscopy from January 2022 to June 2022 were included in the study. The criteria for patients to be admitted for colonoscopy were as follows: (1) Presence of ≥ 2 comorbidities (such as diabetes, hypertension, chronic heart failure, coronary heart disease, chronic kidney disease, chronic obstructive pulmonary disease, *etc*); (2) colon polyp diameter ≥ 1 cm, requiring polypectomy; (3) history of colon polyps with a diameter ≥ 1 cm; and/or (4) history of inadequate bowel preparation. Patient inclusion criteria included: (1) Age ≥ 50 years; (2) indication for colonoscopy; and (3) willingness to participate in the study. Exclusion criteria included: (1) Age < 50 years; (2) inability to complete bowel preparation; and (3) unwillingness to enroll in the study. The study design was reviewed and approved by the Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University (approval No. TRECKY2021-227). The trial registration number is NCT05397158.

Randomization and group description

A random sequence of 312 individuals was generated using statistical software. Participants were allocated to either group 1 or group 2 in accordance with their order of enrollment, following the sequentially assigned random sequence numbers. In group 1, the patients received 30 mL of lactulose in the morning before the colonoscopy day and consumed a low-residue liquid diet for breakfast, lunch, and dinner. The patients were then provided with 2 L of water mixed with PEG electrolyte powder on the morning of the colonoscopy and fasted for breakfast and lunch. In group 2, patients were allowed to have a regular diet for breakfast and lunch the day before the colonoscopy and a fasted, enteral nutritional emulsion or low-residue liquid diet for dinner (depending on the patient's blood glucose and tolerance). They received 2 L of water mixed with PEG electrolyte powder in the afternoon before the colonoscopy. Then, the patients were administered 2 L of water mixed with PEG electrolyte powder on the morning of the colonoscopy and fasted for breakfast and lunch. The PEG electrolyte powder comprised PEG, sodium sulfate, sodium bicarbonate, sodium chloride, and potassium chloride.

Before bowel preparation, the physician explained the bowel preparation regimens to the patient and provided written bowel preparation instructions (Supplementary material) and a comfort questionnaire (Supplementary material). The questionnaire was completed by the patient and collected before the colonoscopy. Furthermore, the physician checked with the patient on the evening before the colonoscopy and on the morning of the colonoscopy to evaluate the bowel preparation. If the cleansing was poor and inadequate bowel preparation was predicted, 1 L of water mixed with PEG electrolyte powder was additionally provided on the morning of the colonoscopy, and the supplementation was recorded.

Pre-colonoscopy diet

This study provided the foods that the patients should consume before their colonoscopy. A low-residue liquid diet was defined as a diet with a total fiber intake of < 10 g/d[3]. Breakfast included whole milk, white bread, and boiled eggs, lunch consisted of rice porridge, and dinner comprised rice porridge and steamed eggs. An enteral nutritional emulsion was used as a residue-free liquid diet.

Assessment of bowel preparation

The endoscopists were blinded in this study, wherein two endoscopists reviewed the colonoscopy images (30-50 images per patient) and assessed bowel preparation using the Boston bowel preparation scale (BBPS)[8] (Supplementary material). According to the BBPS, the colon is divided into three segments: right colon, transverse colon, and left colon (descending and rectosigmoid colon)[9]. Adequate bowel preparation was defined as a BBPS score of ≥ 6, with a score of ≥ 2 for each segment[10,11].

Variables collected

The following variables were recorded for the various aspects of the study: (1) Demographics of the study patients: Age, sex, lifestyle habits (including smoking and alcohol consumption), history of abdominopelvic surgery, comorbidities, and nutritional status (including body mass index, blood hemoglobin, and serum albumin); (2) Bowel preparation: Patient's diet, type and dosage of laxatives administered, and interval between the last dose of laxatives and colonoscopy; (3) Colonoscopy: BBPS score of each bowel segment and the presence/absence of polyps, adenomas, or tumors (confirmed based on pathological examination); (4) Comfort: Comfort questionnaire results, including comfort score from 0 to 10, sleep duration on the night before colonoscopy, number of awakenings during sleep on the night before colonoscopy, and presence of bowel incontinence during bowel preparation; and (5) Safety: Laboratory test results of serum potassium, sodium, calcium, and creatinine and plasma B-type brain natriuretic peptide (BNP) before and after bowel preparation.

Outcomes

The primary outcome was to compare the percentage of adequate bowel preparation in each bowel segment and the whole colon in group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) with that in group 2 (4-L PEG) as well as to compare the mean BBPS scores in each bowel segment and the whole colon between the two groups. The secondary outcome was to compare the difference in the comfort and safety of bowel preparation between group 1 and group 2.

Statistical analysis and sample size

Continuous variables were expressed as mean ± SD, while categorical variables were represented as count (percentage). Continuous variables were compared using the student's *t*-test or rank sum test, whereas the χ^2 test was used to compare

the categorical variables between the two groups. A P value of < 0.05 was considered significant. SPSS version 26 (IBM Corp, Armonk, NY, United States) was used for all statistical analyses.

Non-inferiority analysis was employed to determine whether the efficacy of the regimen of 2-L PEG + 30-mL lactulose + a low-residue diet was not inferior to that of the 4-L PEG regimen. According to the pre-experimental results and a previous study[12], the non-inferiority margin between the two bowel preparation regimens was set at 10%. A total of 22 patients per group was needed based on a type I error of 2.5%, power of 80%, and dropout rate of 10%. In this study, we intended to conduct a subgroup analysis on the population ≥ 75 years in age. In the preliminary experiment, this subgroup constituted approximately 15%-20% of the total population. To achieve a targeted subgroup sample size of 22 individuals per group, a final inclusion of 146 participants per group was determined. The analysis was performed using intention-to-treat and per-protocol approaches. We used the CONSORT reporting guidelines, with the CONSORT checklist published[13].

RESULTS

This study included 350 patients admitted to the Geriatrics Department for proposed colonoscopy between January 2022 and June 2022. Among these patients, 312 participated in the randomized grouping, from which 8 patients were excluded because of missing data. Ultimately, 148 patients were included in group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) and 156 in group 2 (4-L PEG). Further, 2 patients in group 1 and 1 patient in group 2 were excluded because they were administered an additional 1 L of PEG due to predicted inadequate bowel preparation. Figure 1 shows the flow chart of the study.

A total of 148 patients were included in group 1 (2-L PEG + 30-mL lactulose + a low-residue diet), with an age range of 52-88 years. Additionally, 156 patients were enrolled in group 2 (4-L PEG), with ages ranging from 50-92 years. No statistical differences in sex, age, lifestyle habits, history of abdominopelvic surgery, most comorbidities, or nutritional status were found between the two groups. Compared with the patients in group 2, those in group 1 had a significantly longer interval (4.71 ± 1.248 *vs* 4.26 ± 1.315, P = 0.003) between the last dose of laxatives and colonoscopy. Table 1 shows the complete demographic information.

Analysis of bowel preparation

The results of the bowel preparation assessment in both groups were compared based on the intention-to-treat analysis (Table 2). The proportion of BBPS scores of ≥ 2 in the right colon (75.7% *vs* 74.4%, P = 0.791), transverse colon (98.0% *vs* 95.5%, P = 0.379), and left colon (100.0% *vs* 99.4%, P = 0.379) as well as the proportion of BBPS scores of ≥ 6 in the whole colon (91.2% *vs* 91.0%, P = 0.953) in group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) did not differ significantly from those in group 2 (4-L PEG). Similarly, the mean BBPS scores of the right colon, transverse colon, and left colon as well as that of the whole colon showed no differences between groups 1 and 2.

The results of the bowel preparation assessment in the two groups were further compared using per-protocol analysis (Table 2). Group 1 and group 2 did not demonstrate significant differences in the proportion of BBPS scores of ≥ 2 in each segment as well as in the proportion of BBPS scores of ≥ 6 in the whole colon. Furthermore, no differences were observed between groups 1 and 2 in terms of mean BBPS scores of each segment as well as that of the whole colon.

Detection rates of polyps, adenomas, and tumors

Based on the intention-to-treat analysis, the detection rates of polyps (73.0% *vs* 66.7%, P = 0.232), adenomas (56.8% *vs* 46.8%, P = 0.082), and tumors (4.1% *vs* 3.2%, P = 0.684) were not significantly different between group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) and group 2 (4-L PEG) (Table 2).

The results of the per-protocol analysis also showed no significant differences in the detection rates of polyps, adenomas, and tumors between group 1 and group 2 (Table 2). Therefore, the bowel preparation regimen of 2-L PEG + 30-mL lactulose + a low-residue diet was not inferior to the 4-L PEG regimen for detecting polyps, adenomas, and tumors.

Bowel preparation in patients ≥ 75 years in age

A total of 55 patients were of ages 75 years or older, among which 22 were in group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) and 33 in group 2 (4-L PEG). The two groups showed no differences in sex, age, history of abdominopelvic surgery, constipation, laxatives, diabetes mellitus, hypertension, nor nutritional status (body mass index, blood hemoglobin, and serum albumin) (Table 3).

As revealed in Table 3, the proportions of BBPS scores of ≥ 2 in the right colon, transverse colon, and left colon as well as the proportion of BBPS scores of ≥ 6 in the whole colon in group 1 were not significantly different from those in group 2 (Table 3). Thus, in the case of patients ≥ 75 years in age, the bowel preparation efficiency in group 1 was not inferior to that in group 2.

Comfort and safety assessments

Our results showed that group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) had higher comfort scores (8.85 ± 1.162 *vs* 7.59 ± 1.735, P < 0.001), longer sleep duration (6.86 ± 1.204 h *vs* 5.80 ± 1.730 h, P < 0.001), and fewer awakenings (1.42 ± 1.183 *vs* 2.04 ± 1.835, P = 0.026) on the night before the colonoscopy than group 2 (4-L PEG). Furthermore, compared with group 2, group 1 showed a reduced incidence of bowel incontinence during bowel preparation; however, this difference was not significant (Table 4). Therefore, patients in group 1 experienced better comfort than those in group 2.

Table 1 Demographics of the study patients, *n* (%)

Characteristics	Group 1[1], *n* = 148	Group 2[2], *n* = 156	*P* value
Age in yr	65.76 ± 7.843	66.99 ± 9.337	0.377
Male sex	100 (67.6)	105 (67.3)	0.961
Lifestyle habits			
Current smoking	30 (20.3)	33 (21.2)	0.849
Smoking history	63 (42.6)	66 (42.3)	0.963
Current drinking	34 (23.0)	35 (22.4)	0.911
Drinking history	40 (27.0)	41 (26.3)	0.883
History of abdominopelvic surgery	41 (27.9)	56 (36.1)	0.125
Comorbidity			
Constipation	19 (12.8)	25 (16.0)	0.430
Drugs for constipation	7 (4.7)	10 (6.4)	0.524
Diabetes	64 (43.2)	74 (47.4)	0.463
Hypertension	86 (58.1)	89 (57.4)	0.903
Chronic heart failure	2 (1.4)	4 (2.6)	0.728
Coronary heart disease	19 (12.8)	34 (21.8)	0.040
Chronic kidney disease (≥ stage 2)	99 (66.8)	89 (57.0)	0.280
Chronic obstructive pulmonary disease	6 (4.1)	8 (5.1)	0.655
Nutritional status			
BMI in kg/m^2	24.325 ± 3.049	24.569 ± 2.936	0.718
Hemoglobin in g/L	135.91 ± 15.903	135.30 ± 15.906	0.675
Albumin in g/L	39.542 ± 3.0895	39.469 ± 3.7827	0.710
Interval between last dose of laxatives and colonoscopy in h	4.71 ± 1.248	4.26 ± 1.315	0.003

[1]Group 1: 30 mL of lactulose on the day before the colonoscopy, three meals with a low-residue liquid diet, and 2 L of water mixed with polyethylene glycol on the colonoscopy day.
[2]Group 2: Regular diet for breakfast and lunch, fasting or a low-residue liquid diet for dinner, and 2 L of water mixed with polyethylene glycol (PEG) on the day before the colonoscopy; 2 L of water mixed with PEG on the colonoscopy day.
Data are mean ± SD or *n* (%). BMI: Body mass index.

The alterations in the levels of serum electrolytes (potassium, sodium, and calcium), serum creatinine, and plasma BNP before and after bowel preparation in group 1 were slight and not different from those in group 2 (Table 5). Thus, the two bowel preparation regimens had no significant effect on the electrolyte levels nor renal or cardiac function, with no significant difference between the two groups.

DISCUSSION

Globally, the morbidity and mortality rates of CRC gradually increase with age and become particularly pronounced in individuals ≥ 50 years in age[1]. Hence, adults ≥ 50 years in age require regular colonoscopies. Our study results showed that the bowel preparation regimen comprising a low dose of 2-L PEG + 30-mL lactulose + a low-residue diet had a good bowel preparation effect along with comfort and safety profiles for patients ≥ 50 years in age. Furthermore, we observed that in the subgroup of patients ≥ 75 years in age who were at higher risk of inadequate bowel preparation, the 2-L PEG + 30-mL lactulose + a low-residue diet regime was not inferior to the 4-L PEG regimen.

In the subgroup analysis of individuals ≥ 75 years in age, group 1 exhibited a slightly lower percentage of adequate bowel preparation in the right colon compared to group 2, without statistical significance. This observation might be attributed to a longer time interval between the administration of the final bowel preparation agent and the colonoscopy procedure in group 1 compared to group 2. Furthermore, this study included a limited number of patients ≥ 75 years in age, and there was a disparity in the sample sizes between the two groups, which needs to be addressed in future studies. Therefore, further research is necessary to gain a more comprehensive understanding of the effectiveness of a low-dose

Table 2 Comparison of the degree of cleansing of the bowel preparation regimens and colonoscopy findings between groups 1 and 2, *n* (%)

Variables	Group 1[1]	Group 2[2]	*P* value
Intention-to-treat analysis	*n* = 148	*n* = 156	N/A
Right BBPS score ≥ 2	112 (75.7)	116 (74.4)	0.791
Transverse BBPS score ≥ 2	145 (98.0)	149 (95.5)	0.379
Left BBPS score ≥ 2	148 (100.0)	155 (99.4)	0.247
Global BBPS score ≥ 6	135 (91.2)	142 (91.0)	0.953
Mean BBPS in the right colon	1.92 ± 0.634	1.92 ± 0.727	0.861
Mean BBPS in the transverse colon	2.73 ± 0.489	2.68 ± 0.556	0.539
Mean BBPS in the left colon	2.64 ± 0.483	2.58 ± 0.507	0.395
Mean BBPS in the whole colon	7.28 ± 1.167	7.18 ± 1.346	0.676
Polyp detection rate	108 (73.0)	104 (66.7)	0.232
Adenoma detection rate	84 (56.8)	73 (46.8)	0.082
Tumor detection rate	6 (4.1)	5 (3.2)	0.684
Per-protocol analysis	*n* = 146	*n* = 155	N/A
Right BBPS score ≥ 2	112 (76.7)	116 (74.8)	0.705
Transverse BBPS score ≥ 2	143 (97.9)	148 (95.5)	0.234
Left BBPS score ≥ 2	146 (100.0)	154 (99.4)	0.331
Global BBPS score ≥ 6	134 (91.8)	141 (91.0)	0.802
Mean BBPS in the right colon	1.93 ± 0.629	1.92 ± 0.726	0.924
Mean BBPS in the transverse colon	2.73 ± 0.488	2.68 ± 0.555	0.556
Mean BBPS in the left colon	2.64 ± 0.483	2.58 ± 0.508	0.354
Mean BBPS in the whole colon	7.30 ± 1.159	7.19 ± 1.347	0.639
Polyp detection rate	106 (72.6)	103 (66.5)	0.247
Adenoma detection rate	83 (56.8)	72 (46.5)	0.071
Tumor detection rate	6 (4.1)	5 (3.2)	0.674

[1]Group 1: 30 mL of lactulose on the day before the colonoscopy, three meals with a low-residue liquid diet, and 2 L of water mixed with polyethylene glycol on the colonoscopy day.
[2]Group 2: Regular diet for breakfast and lunch, fasting or a low-residue liquid diet for dinner, and 2 L of water mixed with polyethylene glycol (PEG) on the day before the colonoscopy; 2 L of water mixed with PEG on the colonoscopy day.
Data are mean ± SD or *n* (%). BBPS: Boston bowel preparation scale; N/A: Not applicable.

bowel preparation regimen in achieving adequate preparation of the right colon in older individuals.

Comorbidities gradually increase with age in individuals ≥ 50 years in age. Multiple previous studies on bowel preparation have excluded patients with chronic kidney disease, chronic heart failure, long-term laxative use, long-term antiplatelet drug and anticoagulant drug use, or inflammatory bowel diseases[14,15]. In contrast, the present study included patients with such conditions, which reflected the real clinical practice situation. This makes the resulting findings more informative for clinical settings. In this study, notable differences were observed between the two groups of patients in terms of the proportion of individuals with concurrent coronary heart disease and the time interval between the administration of the final bowel preparation agent and the colonoscopy procedure. These differences might be attributed to the relatively small sample size in the study. In the future, it is necessary to further expand the sample size to reduce the influence of confounding factors on the study results.

Compared with fasting, a low-residue diet leads to better tolerance and patient compliance, leading to more patients being willing to review colonoscopy[6,16]. Previous studies also suggest that a longer low-residue diet (*e.g.*, 3 d) before colonoscopy provides no additional benefit to bowel cleansing[17]. In the commonly used clinical method of 4 L of water mixed with PEG, there are no restrictions on breakfast and lunch on the day before the colonoscopy. Hence, in group 2 (4-L PEG), patients were allowed to consume a regular diet for breakfast and lunch on the day before the colonoscopy, while their dinner options were either a low-residue liquid diet or fasting, depending on the presence or absence of diabetes in each individual patient.

Table 3 Demographics and bowel preparation efficiency in patients ≥ 75 years in age in groups 1 and 2, *n* (%)

Characteristics	Group 1[1], *n* = 22	Group 2[2], *n* = 33	*P* value
Age in yr	79.36 ± 4.22	81.03 ± 4.19	0.149
Male sex	15 (68.2)	25 (75.8)	0.537
History of abdominopelvic surgery	8 (36.4)	15 (45.5)	0.503
Comorbidity			
Constipation	6 (27.3)	8 (24.2)	0.800
Drugs for constipation	2 (9.1)	3 (9.1)	1.000
Diabetes	12 (54.5)	14 (42.4)	0.378
Hypertension	17 (77.3)	24 (72.7)	0.848
Nutritional status			
BMI in kg/m^2	24.16 ± 2.88	24.29 ± 2.53	0.542
Hemoglobin in g/L	128.50 ± 15.88	125.12 ± 16.39	0.203
Albumin in g/L	38.60 ± 4.05	37.88 ± 4.19	0.600
Bowel preparation efficiency			
Right BBPS score ≥ 2	16 (72.7)	27 (81.8)	0.641
Transverse BBPS score ≥ 2	22 (100.0)	32 (97.0)	1.000
Left BBPS score ≥ 2	22 (100.0)	33 (100.0)	N/A
Global BBPS score ≥ 6	20 (90.9)	32 (97.0)	0.716

Data are mean ± SD or *n* (%).
[1]Group 1: 30 mL of lactulose on the day before the colonoscopy, three meals with a low-residue liquid diet, and 2 L of water mixed with polyethylene glycol on the colonoscopy day.
[2]Group 2: Regular diet for breakfast and lunch, fasting or a low-residue liquid diet for dinner, and 2 L of water mixed with polyethylene glycol (PEG) on the day before the colonoscopy; 2 L of water mixed with PEG on the colonoscopy day. BBPS: Boston bowel preparation scale. BMI: Body mass index; N/A: Not available.

Table 4 Comparison of degree of comfort between groups 1 and 2

Variable	Group 1[1], *n* = 60	Group 2[2], *n* = 82	*P* value
Comfort score	8.85 ± 1.162	7.59 ± 1.735	< 0.001
Sleep duration in h	6.86 ± 1.204	5.80 ± 1.730	< 0.001
Number of awakenings	1.42 ± 1.183	2.04 ± 1.835	0.026
Incontinence (%)	4 (6.7)	11 (13.4)	0.196

Data are mean ± SD or *n* (%).
[1]Group 1: 30 mL of lactulose on the day before the colonoscopy, three meals with a low-residue liquid diet, and 2 L of water mixed with polyethylene glycol on the colonoscopy day.
[2]Group 2: Regular diet for breakfast and lunch, fasting or a low-residue liquid diet for dinner, and 2 L of water mixed with polyethylene glycol (PEG) on the day before the colonoscopy; 2 L of water mixed with PEG on the colonoscopy day.

Laxative agents can be categorized into two main types: isotonic and hyperosmotic. Previous studies have shown that hyperosmotic laxatives can significantly increase the risk of deteriorating renal function[18]. Furthermore, in patients with inflammatory bowel disease, using hyperosmotic laxatives can increase the risk of worsening mucosal lesions associated with bowel preparation[19]. Therefore, the safer PEG-based isotonic laxative was chosen for this study of patients ≥ 50 years in age. Moreover, our results suggested that neither high doses (4 L) nor low doses (2 L) of PEG had a significant effect on electrolyte (potassium, sodium, and calcium) levels nor renal or cardiac function.

Lactulose, the adjuvant used in this study, is commonly used to treat constipation by promoting bowel movements. Previous studies in patients with constipation have demonstrated that the bowel preparation effect of PEG combined with lactulose is better than that of PEG alone[7]. Moreover, lactulose has a good taste and does not require large amounts of water in a short period. Thus, it can reduce the symptoms such as abdominal distension and nausea and

Table 5 Comparison of laboratory test results before and after bowel preparation between groups 1 and 2

Variables, before and after bowel preparation	Group 1[1], *n* = 51	Group 2[2], *n* = 53	*P* value
Serum potassium in mmol/L	0.277 ± 0.288	0.275 ± 0.343	0.809
Serum sodium in mmol/L	1.804 ± 2.498	1.566 ± 2.508	0.878
Serum calcium in mmol/L	0.015 ± 0.117	0.018 ± 0.099	0.435
Serum creatinine in μmol/L	1.678 ± 6.110	3.832 ± 6.805	0.093
Plasma BNP in pg/mL	3.851 ± 30.264	8.0417 ± 64.987	0.216

Data are mean ± SD. BNP: B-type brain natriuretic peptide.

[1]Group 1: 30 mL of lactulose on the day before the colonoscopy, three meals with a low-residue liquid diet, and 2 L of water mixed with polyethylene glycol on the colonoscopy day.

[2]Group 2: Regular diet for breakfast and lunch fasting or a low-residue liquid diet for dinner, and 2 L of water mixed with polyethylene glycol (PEG) on the day before the colonoscopy; 2 L of water mixed with PEG on the colonoscopy day.

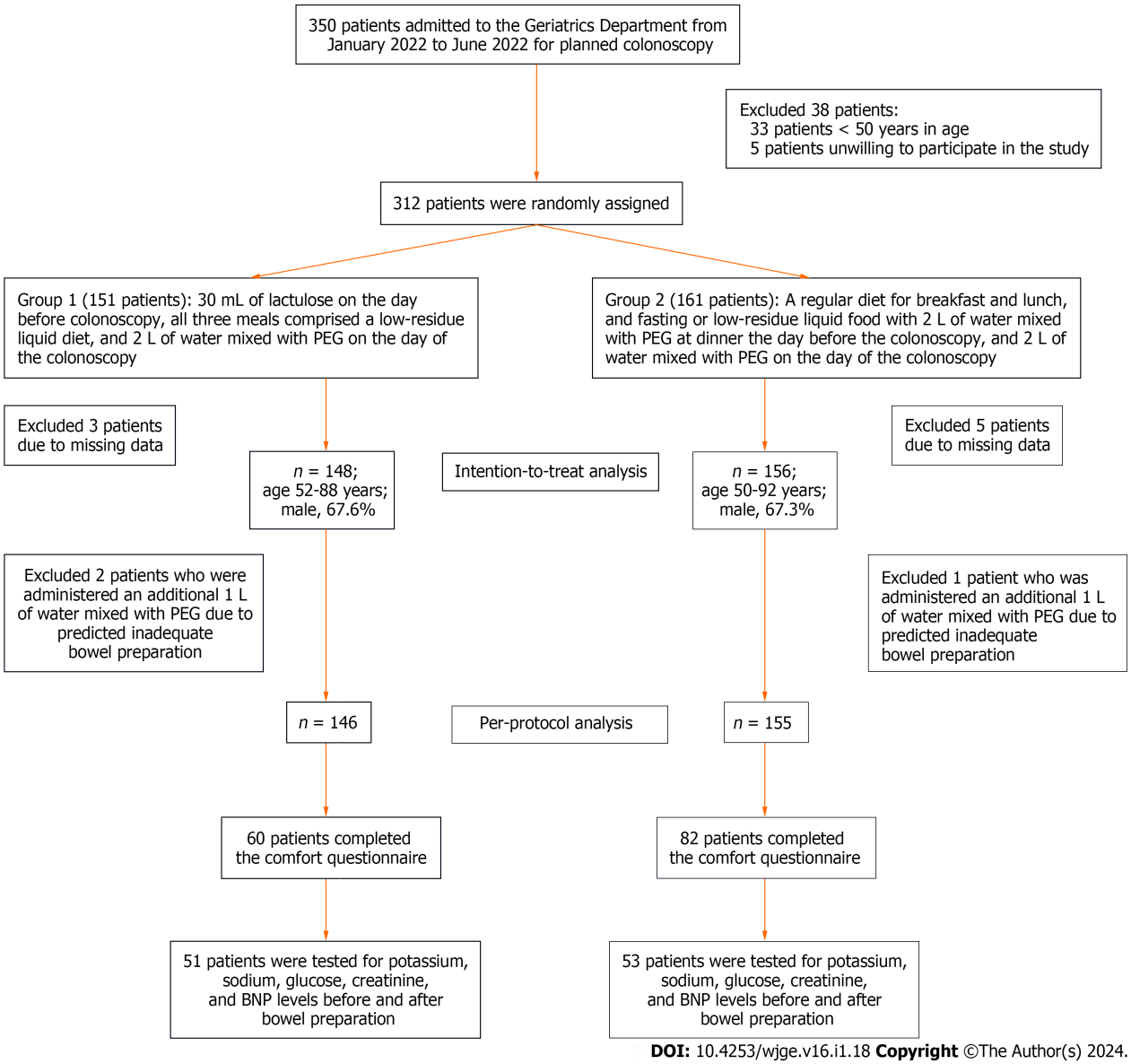

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Figure 1 Flow chart of the study. BNP: B-type brain natriuretic peptide; PEG: Polyethylene glycol.

improve patient tolerance.

In this study, BBPS was used to assess bowel preparation. The bowel preparation of the regimen was assessed after the endoscopist completed flushing and suction. The effectiveness and reliability of this scale have been confirmed by large sample-size studies[20].

Studies have demonstrated that an interval of 3-5 h between the last dose of laxatives and colonoscopy is optimal for good bowel preparation quality, with a minimum interval of at least 2 h[21]. However, the current study was limited by the number of endoscopists and scheduling of the colonoscopies. Thus, some patients had an interval of > 5 h between the last dose of laxatives and colonoscopy. The patients in group 1 (2-L PEG + 30-mL lactulose + a low-residue diet) had a significantly longer interval (closer to 5 h) between the last dose of laxatives and colonoscopy than those in group 2 (4-L PEG) (4.71 ± 1.248 *vs.* 4.26 ± 1.315, $P = 0.003$). Nevertheless, our results demonstrated that the 2-L PEG + 30-mL lactulose + a low-residue diet regimen was still not inferior to the 4-L PEG regimen for bowel preparation.

Regarding comfort during bowel preparation, previous studies have used the incidence of nausea and vomiting as an assessment indicator[15] but have not evaluated the sleep situation and fecal incontinence on the night before the colonoscopy. The present study highlighted that the 2-L PEG + 30-mL lactulose + a low-residue diet regimen resulted in longer sleep duration, fewer awakenings, and a reduced incidence of fecal incontinence than the 4-L PEG regimen on the night before the colonoscopy. Additionally, the overall comfort score was higher with the 2-L PEG + 30-mL lactulose + a low-residue diet approach than in the 4-L PEG regimen, suggesting better patient tolerance that may promote long-term regular colonoscopy participation.

The study results also indicated good bowel preparation in older adults (age ≥ 75 years) using a low dose of laxatives (2-L PEG + 30-mL lactulose + a low-residue diet). However, the comfort and safety parameters in this subgroup were not evaluated due to the limited number of patients available. Therefore, further studies should be conducted to assess bowel preparation in the older population of ≥ 75 years in age.

This study exclusively included hospitalized patients. However, in other countries, a portion of patients may choose outpatient colonoscopy examinations based on local circumstances. Due to the relatively short duration of hospital stay for the participants in this study, their clinical characteristics resembled those of outpatient cases. Therefore, the results of this study may be applicable to outpatient populations.

CONCLUSION

Patients ≥ 50 years in age require long-term and regular colonoscopies due to the notably higher CRC morbidity and mortality rates. The bowel preparation regimen of low-dose (2 L) PEG combined with lactulose and a low-residue diet was comparable with the high-dose (4 L) PEG regimen for bowel cleansing and even provided better comfort.

ARTICLE HIGHLIGHTS

Research background

The incidence and mortality rates of colorectal cancer (CRC) progressively increase with age, and this rise is particularly prominent after the age of 50 years. Therefore, the population ≥ 50 years in age requires long-term and regular colonoscopies. Uncomfortable bowel preparation is the main reason that prevents patients from undergoing regular colonoscopies. The bowel preparation regimen of 4-L polyethylene glycol (PEG) is effective but poorly tolerated.

Research motivation

Reducing water intake to 2 L can improve comfort, while following a low-residue diet and using lactulose as an adjuvant can enhance the effectiveness of bowel preparation. Therefore, we proposed a bowel preparation regimen involving a mixture of 2 L water with PEG and lactulose along with a low-residue diet for hospitalized patients ≥ 50 years in age who were undergoing colonoscopy.

Research objectives

This study aimed to evaluate the effectiveness, comfort, and safety of a 2-L PEG + 30-mL lactulose + low-residue diet regimen.

Research methods

Non-inferiority analysis was employed to determine whether the efficacy of the regimen of 2-L PEG + 30-mL lactulose + a low-residue diet was not inferior to that of the 4-L PEG regimen. The analysis was performed using intention-to-treat and per-protocol approaches. The primary outcome was to compare the percentage of adequate bowel preparation in each bowel segment and the whole colon in group 1 with that in group 2 as well as to compare the mean Boston bowel preparation scale scores in each bowel segment and the whole colon between the two groups. The secondary outcome was to compare the difference in the comfort and safety of bowel preparation between group 1 and group 2. The comfort assessment included comfort score, sleep duration on the night before colonoscopy, number of awakenings during sleep on the night before colonoscopy, and the presence of bowel incontinence during bowel preparation. Safety assessment included laboratory test results of serum potassium, sodium, calcium, and creatinine and plasma B-type brain natriuretic

peptide before and after bowel preparation.

Research results

The bowel preparation regimen comprising a low dose of 2-L PEG + 30-mL lactulose + a low-residue diet had a good bowel preparation effect along with comfort and safety profiles for patients ≥ 50 years in age. Furthermore, in the subgroup of patients ≥ 75 years in age who were at higher risk of inadequate bowel preparation, the 2-L PEG + 30-mL lactulose + a low-residue diet regime was not inferior to the 4-L PEG regimen.

Research conclusions

In patients ≥ 50 years in age, the bowel preparation regimen comprising 2-L PEG + 30-mL lactulose + a low-residue diet produced a cleanse that was as effective as that yielded by the 4-L PEG regimen and even provided better comfort.

Research perspectives

Patients ≥ 50 years in age require long-term and regular colonoscopies due to their notably higher CRC morbidity and mortality. The bowel preparation regimen of 2-L PEG + 30-mL lactulose + a low-residue diet is comparable with the high-dose (4 L) PEG regimen for bowel cleansing and even provides better comfort. These study results may contribute to supporting and improving decision-making in clinical practice.

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FOOTNOTES

Author contributions: Liu Q, Chen YW, and He Y designed the study; He Y, Cui LJ, and Guo ZH conducted the study; He Y and Cui LJ collected the data; He Y, Chen YW, Cao K, and Liu Q analyzed the data; He Y and Chen YW drafted the manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University (Approval No. TRECKY2021-227).

Clinical trial registration statement: This study is registered at ClinicalTrials.gov, registration number NCT05397158 (https://clinicaltrials.gov/ct2/show/NCT05397158).

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

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ORIGINAL ARTICLE

Observational Study

Safety and efficacy of modified endoscopic ultrasound-guided selective N-butyl-2-cyanoacrylate injections for gastric variceal hemorrhage in left-sided portal hypertension

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Abstract

BACKGROUND

Gastric variceal hemorrhage is one of the primary manifestations of left-sided portal hypertension (LSPH). The hemorrhage is fatal and requires safe and effective interventions.

AIM

To evaluate the clinical safety and efficacy of modified endoscopic ultrasound (EUS)-guided selective N-butyl-2-cyanoacrylate (NBC) injections for gastric variceal hemorrhage in LSPH.

METHODS

A retrospective observational study of patients with LSPH-induced gastric variceal hemorrhage was conducted. Preoperative EUS evaluations were performed. Enrolled patients were divided into modified and conventional groups according to the NBC injection technique. The final selection of NBC injection technique depended on the patients' preferences and clinical status. The technical and clinical success rates, operation time, NBC doses, perioperative complications, postoperative hospital stay, and recurrent bleeding rates were analyzed, respectively.

RESULTS

A total of 27 patients were enrolled. No statistically significant differences were observed between the two groups regarding baseline characteristics. In comparison to patients in the conventional group, patients in the modified group demonstrated significantly reduced NBC doses (2.0 ± 0.6 mL *vs* 3.1 ± 1.0 mL; P = 0.004) and increased endoscopic operation time (71.9 ± 11.9 min *vs* 22.5 ± 6.7 min; P < 0.001). Meanwhile, the two groups had no significant difference in the technical and clinical success rates, perioperative complications, postoperative hospital stay, and recurrent bleeding rates.

CONCLUSION

Modified EUS-guided selective NBC injections demonstrated safety and efficacy for LSPH-induced gastric variceal hemorrhage, with advantages of reduced injection dose and no radiation risk. Drawbacks were time consumption and technical challenge.

Key Words: Endoscopic ultrasound; Selective; N-butyl-2-cyanoacrylate; Gastric varices; Hemorrhage; Left-sided portal hypertension

Core Tip: Gastric variceal hemorrhage is a severe and critical complication of left-sided portal hypertension (LSPH). Endoscopic ultrasound (EUS)-guided interventions are emerging endoscopic treatments with diagnostic and therapeutic potential. Our study revealed that EUS-guided selective N-butyl-2-cyanoacrylate injection is a safe and effective treatment alternative for patients with LSPH-induced gastric variceal hemorrhage, with reduced N-butyl-2-cyanoacrylate doses and satisfactory technical and clinical success rates.

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INTRODUCTION

Left-sided portal hypertension (LSPH) is caused by splenic vein stenosis, thrombosis, or obstruction, with pancreatic diseases as the most common etiology[1,2], among which pancreatitis and pancreatic tumors account for the leading causes of LSPH[3,4]. Clinical symptoms of LSPH are attributed to an increase in the pressure gradient between the portal vein and the inferior vena cava[5]. Gastric variceal hemorrhage is one of the primary manifestations and the foremost cause of emergency department visits in LSPH patients[6], first described in 1969[7]. Given normal liver function and no obvious clinical symptoms in LSPH patients, gastric varices (GV) have received little attention, and their hemorrhage can be unexpected and fatal[8]. Thus, safe and effective interventions are required.

In recent years, the widespread use of digestive endoscopy in clinical practice has led to a gradual shift in patient preference towards minimally invasive endoscopic techniques, especially in the field of endoscopic ultrasound (EUS)[9,10]. EUS has demonstrated convenience and promise in diagnostic procedures and hemostatic interventions for GV due to the combined function of endoscopy and ultrasound[11]. Moreover, EUS-guided GV therapy offers a safer and more practical alternative than the conventional therapy of endoscopic N-butyl-2-cyanoacrylate (NBC) injection[12,13].

Based on previous studies, we reported a modified EUS-guided selective NBC injection procedure in a patient with LSPH-induced gastric variceal hemorrhage[6]. The preliminary advantages of this modified procedure included reduced NBC doses, radiation avoidance, and a firmer obliteration effect with fewer rebleedings caused by glue ulcers[6]. We conducted this retrospective study in our single center to verify these clinical values and provide more basis for future research on EUS-guided GV treatment.

MATERIALS AND METHODS

Study design and study population

This retrospective study received approval from the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. We retrospectively reviewed qualified LSPH patients from the First Affiliated Hospital of Chongqing Medical University from October 2019 to September 2023. All enrolled patients were diagnosed with LSPH-induced gastric variceal hemorrhage and received endoscopic NBC injections. Written informed consent was obtained from all the patients before each endoscopic procedure. Exclusion criteria included previous endoscopic hemostasis, severe organ dysfunction, or other conditions unsuitable for endoscopic procedures.

Endoscopic interventions

The final selection of NBC injection technique types (modified EUS-guided selective NBC injection or conventional endoscopic NBC injection) depended on the patients' preferences and clinical status. Patients electing conventional endoscopic NBC injection constituted the conventional group and received conventional sandwich injection[14], while patients electing modified EUS-guided selective NBC injection formed the modified group and received selective NBC injection under EUS guidance (Linear Pentax echoendoscope, Hoya Co., Tokyo, Japan) (Figure 1)[6].

Postoperative follow-up and data collection

The technical and clinical success rates, operation time, NBC doses, perioperative complications, and postoperative hospital stay were collected from inpatient medical records and analyzed. The follow-up records were reviewed 1, 3 and 6 mo after the NBC injections. Recurrent upper gastrointestinal hemorrhage rates were derived from the routine outpatient follow-up at the Gastroenterology Department. Only patients with complete medical records were included.

Data analysis

Continuous variables and categorical were expressed as means ± SD and *n* (%), respectively. Unpaired Student's *t* test and Mann–Whitney *U* test were used for continuous variables, while the χ^2 and Fisher's exact tests were performed for categorical variables. Statistical analyses were performed using SPSS 23.0, and statistical significance was defined as $P < 0.05$.

RESULTS

Patient characteristics

This study preliminarily enrolled 30 patients. However, some participants underwent splenectomy or had both modified EUS-guided selective NBC injection procedures and conventional endoscopic NBC injection procedures during the follow-up period and, therefore, were excluded. Thus, the final number of qualified participants in the conventional and modified groups was 16 and 11, respectively (Figure 2). Significant differences were not observed between the two groups regarding baseline characteristics (Table 1). The median age was 46.6 (range 24.0–68.0) years for the modified group and 47.9 (range 29.0–68.0) years for the conventional group. Seven patients in the modified group (63.6%) and 11 in the conventional group (68.8%) were male ($P = 0.78$). In all enrolled patients, the three most common causes for LSPH-induced GV hemorrhage were, in order, walled-off necrosis (12/27, 44.4%), pancreatic pseudocyst (8/27, 29.6%) and pancreatitis (5/27, 18.5%). Eight patients in the modified group (72.8%) and 12 in the conventional group (75.0%) were diagnosed with walled-off necrosis or pancreatic pseudocyst ($P = 0.93$) (Table 1).

Safety and efficacy of endoscopic procedures in two groups

Technical success was defined as successful injection and absolute occlusion of the targeted GV, while clinical success was defined as the resolution or improvement of gastric variceal hemorrhage. The technical success rate was 100% for both types of injection procedures, and clinical success rates were 90.9% and 100% in the modified and conventional groups, respectively ($P = 0.41$). The technical and clinical success rates were not significantly different between the groups (Table 2).

Perioperative complications included ectopic embolization, local venous thrombosis, extravascular injection, severe new-onset bleeding following the needle removal, and the early appearance of glue ulcers[15,16]. In comparison to patients in the conventional group, patients in the modified group demonstrated significantly reduced NBC doses (2.0 ± 0.6 mL *vs* 3.1 ± 1.0 mL; $P = 0.004$) and increased endoscopic operation time (71.9 ± 11.9 min *vs* 22.5 ± 6.7 min; $P < 0.001$). Meanwhile, the perioperative complications, postoperative hospital stay, and recurrent bleeding rates for patients in the modified group were 0%, 4.4 ± 1.6 d, and 9.1%, respectively, *vs* 6.3%, 5.8 ± 2.2 d, and 18.8% for those in the conventional group. The two groups had no significant difference in the perioperative complications, postoperative hospital stay, and recurrent bleeding rates (Table 2).

DISCUSSION

This present study built on our prior research and compared the safety and efficacy of a modified EUS-guided selective NBC injection procedure for gastric variceal hemorrhage in LSPH with conventional endoscopic NBC injection procedures. To the best of our knowledge, no similar studies had previously been reported in the literature.

Our result revealed consistency with previous research that LSPH was most common in patients with pancreatic disease, especially those with walled-off necrosis and pancreatic pseudocyst[17,18], which occurred because of the anatomical proximity between the splenic vein and the pancreas[6]. Therefore, regular follow-ups should be scheduled for LSPH patients to reduce unexpected and fatal bleeding. Moreover, when considering endoscopic minimally invasive procedures, sufficient attention to intraoperative and postoperative bleeding should be paid to patients with pancreatic pseudocysts or walled-off necrosis[2,19].

Although endoscopic NBC injection was recommended with great clinical value in achieving hemostasis in LSPH patients[20], conventional injection procedures have striking defects in identifying varices below the gastric mucosal layer, locating culprit vessels during massive gastric hemorrhage, and reducing possible operation-related complications,

Table 1 Study population and comparison of two groups, *n* (%)

Value	Modified group (*n* = 11)	Conventional group (*n* = 16)	*P* value
Age (yr)	46.6 ± 11.6	47.9 ± 10.2	0.756
Gender			1.000
Female	4 (36.4)	5 (31.3)	
Male	7 (63.6)	11 (68.8)	
Etiology			0.932
Pancreatitis	2 (18.1)	3 (18.8)	
Pancreatic pseudocyst	4 (36.4)	4 (25.0)	
Walled-off necrosis	4 (36.4)	8 (50.0)	
Pancreatic tumors	1 (9.1)	1 (6.2)	

Table 2 Endoscopic operation and follow-up data of two groups, *n* (%)

Value	Modified group (*n* = 11)	Conventional group (*n* = 16)	*P* value
Technical success rates	11/11 (100)	16/16 (100)	
Clinical success rates	10/11 (90.9)	16/16 (100)	0.407
Operation time (min)	71.9 ± 11.9	22.5 ± 6.7	< 0.001
NBC doses (mL)	2.0 ± 0.6	3.1 ± 1.0	0.004
Perioperative complications			1.000
Ectopic embolization	0/11 (0)	0/16 (0)	
Local venous thrombosis	0/11 (0)	0/16 (0)	
Extravascular injection	0/11 (0)	0/16 (0)	
Severe new-onset bleeding	0/11 (0)	1/16 (6.3)	
Early appearance of glue ulcers	0/11 (0)	0/16 (0)	
Postoperative hospital stay (d)	4.4 ± 1.6	5.8 ± 2.2	0.072
Recurrent bleeding			0.624
Rebleeding in 1 mo	0/11 (0)	0/16 (0)	
Rebleeding in 1-3 mo	0/11 (0)	1/16 (6.3)	
Rebleeding in 4-6 mo	1/11 (9.1)	2/16 (12.5)	

including ectopic embolization and extravascular injection[21-23]. These deficiencies also place new demands on further developments of endoscopic procedures. EUS is a productive and promising approach to perform real-time ultrasonic scanning and interventions for GV, perforating feeding veins, portal vein and its tributaries, and collateral circulation[11, 24]. EUS-guided NBC injection in GV patients revealed superior clinical outcomes than conventional endoscopic injection dual to properties of NBC dosage reduction, better obliteration, and fewer recurrences and rebleedings[13,25].

We applied this modified EUS-guided selective NBC injection in LSPH-induced gastric variceal hemorrhage patients, and we found that it was, first and foremost, safe and effective in this retrospective study in our single center. Safety is the primary premise and final goal of exploring technical development. Compared with conventional endoscopic injection, this modified procedure did not increase the incidence of perioperative complications, nor would it prolong the patient's hospital stay. Meanwhile, more cases were included in this study to verify our previous research and testify to the benefits of NBC dosage reduction and its consequent reduced medical cost and complications[6]. Reducing glue-related complications focuses on effectively minimizing the injection dose, including endoscopic clips-assisted injection, balloon-occluded retrograde transvenous obliteration (BRTO), combined deployment of embolization coils and cyanoacrylate, and our modified procedure[26-28]. Each of these above procedures has its own advantages and applicable population. The modified procedure in our study can locate the puncture site more accurately in real time; the injection depth and angle can be precisely controlled; the injection can be timely terminated through observing the real-time flow blocking effect; and it can help avoid extravascular injection and reduce the total injection dose; avoid radiation exposure during the combined coil deployment or BRTO; and reduce related medical costs. It is also worth noting that the operation time was significantly longer in the modified group than in the conventional group. We considered that was

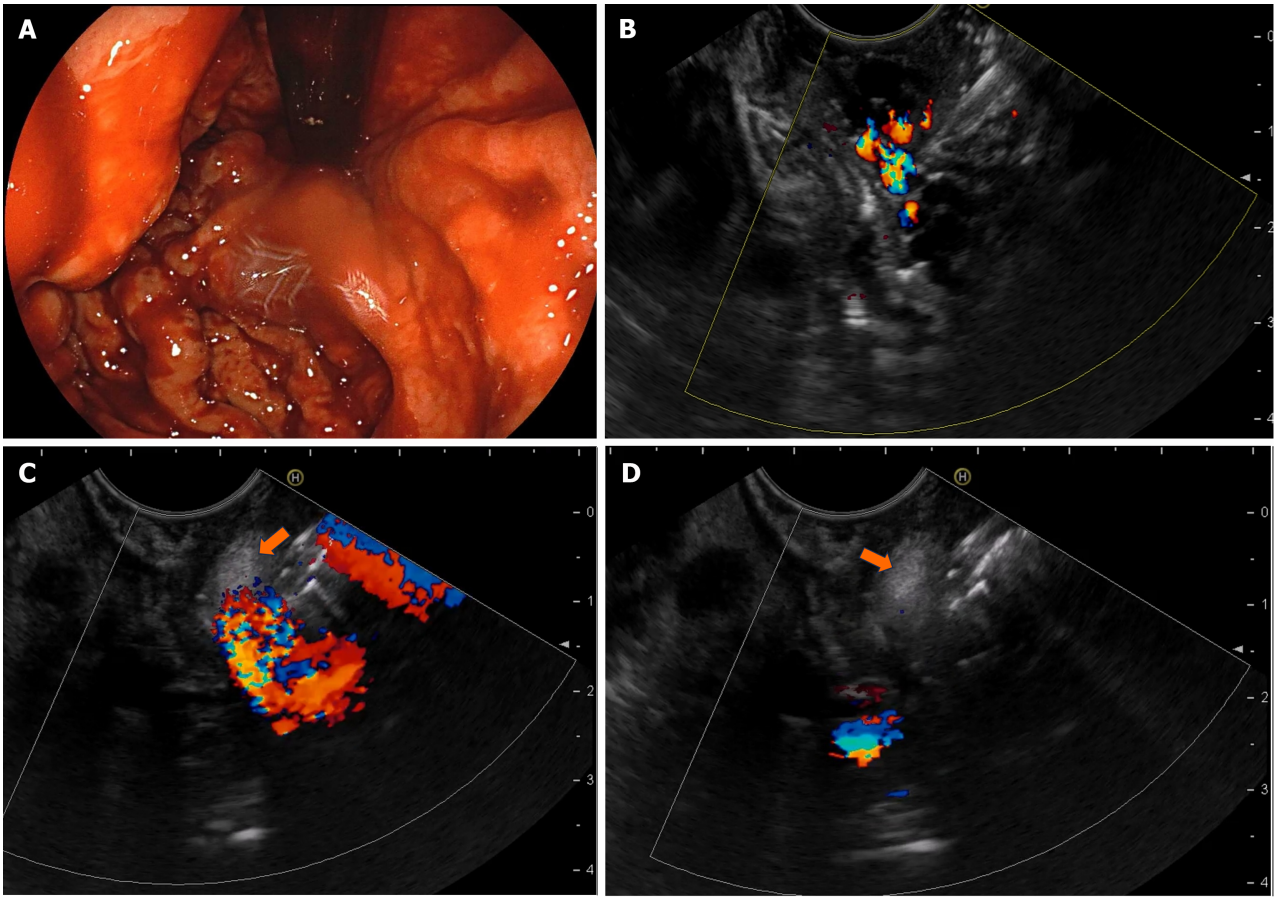

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Figure 1 Endoscopic procedure for patients in modified group. A: Gastroscopy revealed gastric varices (GV) with active bleeding; B: A confluence of GV was identified and selected as the injection site; C: N-butyl-2-cyanoacrylate (orange arrow) was injected into the selected gastric varix; D: Hyperechoic fillings (orange arrow) and decreased blood flow signals were observed after injections.

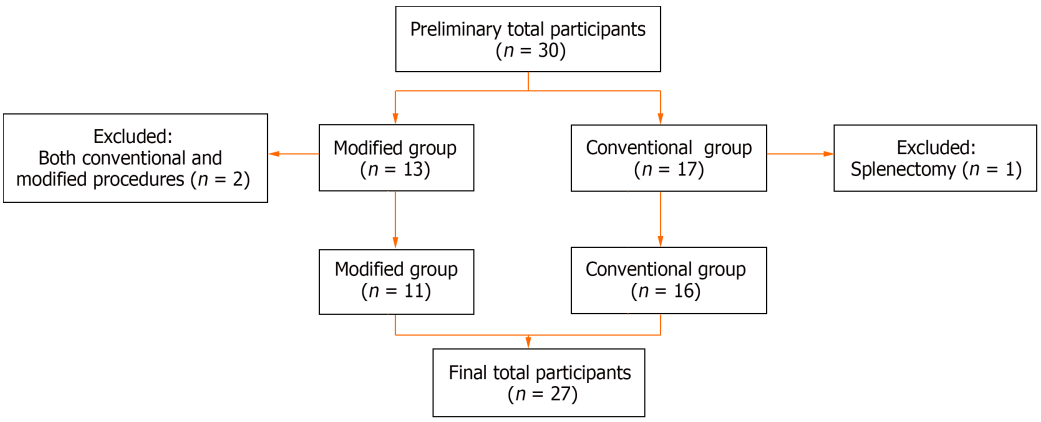

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Figure 2 Flowchart of patients included in the study.

relevant to time consumption in confirming the ideal puncture site during the EUS procedure. Therefore, this method is currently unsuitable for endoscopic centers lacking relevant experience, nor is it applicable for critically ill patients with unstable vital signs who need urgent endoscopic hemostasis.

EUS technology and equipment have not been satisfactorily popularized in many Asian regions, and there is still a significant training demand for many endoscopic interventional operations, including EUS-guided GV procedures[29]. Compared to these more difficult and time-consuming EUS-guided GV procedures, the technique and equipment required for conventional injection are more accessible to acquire and, therefore, cannot be discarded[30]. It was also noticed in the inclusion phase of this study that two patients shifted from the original modified procedure to the conventional method in their follow-up endoscopic treatment. We presume that this was because of the advantages of the

conventional operation in reducing difficulties and operation time. Consequently, a multidisciplinary discussion team is a widely recommended approach to selecting the most appropriate individual treatment.

There were three main limitations. First, this was a retrospective observational study. Our findings are limited by the study design, and future prospective randomized controlled studies are needed. Second, this was a single-center study, and EUS-guided operations are noticeably affected by technical conditions and experience levels. In the future, multicenter studies involving more endoscopy centers in multiple tertiary hospitals are needed. Third, the sample size was small and had a specific regional characteristic. On the one hand, the small number of enrolled patients was because LSPH is a rare cause of GV and consequent hemorrhage[31,32]. On the other hand, since the our endoscopic center is a regional center for treating severe pancreatitis, most patients included in this study had complications such as pancreatic pseudocyst or walled-off necrosis, which may have had an unavoidable impact on the results. Therefore, future studies need to include more LSPH patients with varied causes.

CONCLUSION

Modified EUS-guided selective NBC injections demonstrated safety and efficacy for LSPH-induced gastric variceal hemorrhage, with advantages mainly in reducing injection dose and having no radiation risk. The drawbacks included that the procedure was time-consuming and technically challenging to perform. Therefore, this procedure is recommended for complicated patients in experienced endoscopy centers.

ARTICLE HIGHLIGHTS

Research background

Left-sided portal hypertension (LSPH) is often secondary to pancreatic diseases, including pancreatitis and pancreatic tumors. Given normal liver function and no obvious clinical symptoms in LSPH patients, gastric varices (GV) have received little attention.

Research motivation

To study the clinical value of our previously reported modified endoscopic ultrasound (EUS)-guided selective N-butyl-2-cyanoacrylate (NBC) injection procedure in patients with LSPH-induced gastric variceal hemorrhage.

Research objectives

To evaluate and compare the clinical safety and efficacy between modified EUS-guided selective NBC injections and conventional endoscopic NBC injection procedures for gastric variceal hemorrhage in LSPH.

Research methods

LSPH patients from the First Affiliated Hospital of Chongqing Medical University were retrospectively reviewed and analyzed from October 2019 to September 2023. The technical and clinical success rates, operation time, NBC doses, perioperative complications, postoperative hospital stay, and recurrent bleeding rates of the modified and conventional groups were analyzed.

Research results

The technical success rate was 100% for both types of injection procedures, and clinical success rates were 90.9% and 100% in the modified and conventional groups, respectively (P = 0.41). In comparison to patients in the conventional group, patients in the modified group demonstrated significantly reduced NBC doses (2.0 ± 0.6 mL *vs* 3.1 ± 1.0 mL; P = 0.004) and increased endoscopic operation time (71.9 ± 11.9 min *vs* 22.5 ± 6.7 min; P < 0.001). Meanwhile, the perioperative complications, postoperative hospital stay, and recurrent bleeding rates for patients in the modified group were 0%, 4.4 ± 1.6 d, and 9.1%, respectively, *vs* 6.3%, 5.8 ± 2.2 d, and 18.8% for those in the conventional group.

Research conclusions

The modified EUS-guided selective NBC injection procedure demonstrated reduced injection dose and no increased perioperative complications compared to conventional endoscopic NBC injection procedures. Thus, it is safe and effective in treating patients with LSPH-induced gastric variceal hemorrhage.

Research perspectives

This present study built on our prior research and compared the safety and efficacy of a modified EUS-guided selective NBC injection procedure for gastric variceal hemorrhage in LSPH with conventional endoscopic NBC injection procedures. EUS-guided advanced endoscopic procedures will undoubtedly be the future direction of endoscopic treatment.

FOOTNOTES

Author contributions: Zeng Y, Yang J and Zhang JW conceptualized and designed the research; Zeng Y and Yang J performed the literature search, analyzed the data, and wrote the original manuscript; Yang J and Zhang JW performed the endoscopic procedures and edited the final manuscript; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Adverse events associated with the gold probe and the injection gold probe devices used for endoscopic hemostasis: A MAUDE database analysis

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Abstract

BACKGROUND

Gastrointestinal (GI) bleeding accounts for over half a million admissions annually and is the most common GI diagnosis requiring hospitalization in the United States. Bipolar electrocoagulation devices are used for the management of gastrointestinal bleeding. There is no data on device-related adverse events for gold probe (GP) and injection gold probe (IGP).

AIM

To analyze this using the Food and Drug Administration (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database from 2013 to 2023.

METHODS

We examined post-marketing surveillance data on GP and IGP from the FDA MAUDE database to report devicerelated and patient-related adverse events between 2013-2023. The MAUDE database is a publicly available resource providing over 4 million records relating to medical device safety. Statistical analyses were performed using IBM SPSS Statistics V.27.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Our search elicited 140 reports for GP and 202 reports for IGP, respec-tively, during the study period from January 2013 to August 2023. Malfunctions reportedly occurred in 130 cases for GP, and actual patient injury or event occurred in 10 patients. A total of 149 patients (74%) reported with Injection GP events suffered no significant consequences due to the device failure, but 53 patients (26%) were affected by an event.

CONCLUSION

GP and IGP are critical in managing gastrointestinal bleeding. This study of the FDA MAUDE database revealed the type, number, and trends of reported device-related adverse events. The endoscopist and support staff must be aware of these device-related events and be equipped to manage them if they occur.

Key Words: Hemostasis; Gastrointestinal bleeding; Endoscopy; Device failure; Bipolar coagulation; Cautery; Risks

Core Tip: Gold probe (GP) and injection gold probe (IGP) are critical in managing gastrointestinal bleeding. This study of the Food and Drug Administration Manufacturer and User Facility Device Experience database revealed the type, number, and trends of reported device-related adverse events. Our search elicited 140 reports for GP and 202 reports for IGP, respectively, during the study period from January 2013 to August 2023. Malfunctions reportedly occurred in 130 cases for GP, and actual patient injury or event occurred in 10 patients. 149 patients (74%) reported with IGP events suffered no significant consequences due to the device failure, but 53 patients (26%) were affected by an event. The endoscopist and support staff must be aware of these device-related events and be equipped to manage them if they occur.

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INTRODUCTION

Gastrointestinal (GI) bleeding accounts for over half a million admissions annually and is the most common GI diagnosis requiring hospitalization in the United States[1]. Lesions with high-risk stigmata, which are associated with high rates of recurrent bleeding (50% to 80%) and result in significant morbidity if treated with medical therapy alone. Thus, the latest American College of Gastroenterology (ACG) guidelines recommend endoscopic therapy for ulcers with active spurting or oozing and nonbleeding visible vessels. The management of nonvariceal upper GI bleed (UGIB) has evolved tremendously with the advent of therapeutic endoscopic hemostasis devices and techniques. Studies have shown that thermal contact devices such as bipolar electrocoagulation and heater probes decrease the incidence of re-bleeding compared with no endoscopic therapy[2].

Overall, devices used to achieve hemostasis using thermal therapy were safe. The serious adverse events associated with these devices include uncontrollable bleeding and perforation[3]. Pooled data showed that the rate of bleeding that required urgent surgery was 0.3%, and perforation was 0.5%[4].

The gold probe (GP) and injection gold probe (IGP) (Boston Scientific Corp., Natick, Mass.) are two commonly used devices to achieve endoscopic hemostasis. IGP can deliver an injection as well as thermal therapy. No data on device-related adverse events for these devices used routinely to achieve endoscopic hemostasis is available.

Thus, we aimed to evaluate the events associated with using Gold Probe and Injection Gold Probe using the Food and Drug Administration (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database from 2013 to 2023.

MATERIALS AND METHODS

We examined post-marketing surveillance data on GP and IGP from the FDA MAUDE database to report devicerelated and patient-related adverse events. The MAUDE database is a publicly available resource providing over 4 million records relating to medical device safety. The MAUDE database has medical device reports (MDRs) submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as healthcare professionals, patients and consumers (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm#fn1).

It consists of four primary (Master Event, Device, Patient, Text) and two supplemental (Device Problems and Problem Code Descriptions) file types, which, when combined, provide a detailed account of an adverse event or product problem report. Healthcare professionals have used MAUDE to review events associated with specific products or procedures. Several articles referencing MAUDE have been published analyzing adverse events specific to a particular outcome, product, or body system. It is publicly available online and de-identified. Therefore, no institutional review board approval was required for this study.

Outcomes and statistical analysis

We queried the MAUDE database from January 2013 to August 2023. The MAUDE web search feature is limited to adverse event reports within the past ten years. The data was analyzed for device issues and patient adverse events. The

primary outcome measure of this study was the failure modes of the endoscopic diathermy *Gold Probe™* (Ò Boston Scientific) and injection diathermy *Injection Gold Probe™* (Ò Boston Scientific). Secondary outcomes included significant complications associated with device failure. The MAUDE database cannot capture the utilization of IGP in the United States; therefore, the actual incidence rate of each failure or complication type cannot be assessed. Categorical variables were presented as numbers; all statistical analyses were performed using IBM SPSS Statistics V.27.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Our search elicited 140 reports for GP and 202 reports for IGP, respectively, during the study period from January 2013 to August 2023. The procedure type for GP use was esophagogastroduodenoscopy (47) followed by colonoscopy (25), bronchoscopy (7), endoscopic retrograde cholangiopancreatography (ERCP) (6), enteroscopy (3), missing procedure information (52), Table 1. The procedure types for IGP were esophagogastroduodenoscopy (174) followed by colonoscopy (16), ERCP (11), and enteroscopy (1), Table 2.

Primary outcomes outlining failure modes for the GP and IGP is outlined in Tables 3 and 4. GP failure modes were failure to deliver energy (107), followed by material separation or fracture of the probe tip (28), arcing (1), missing component (1), bent tip (1), and detachment of device (2). IGP failure modes were failure to deliver energy (115), followed by material separation or fracture of the probe tip (34), crack (9), device detachment (27), material puncture (5), and mechanical problems (12).

Malfunctions reportedly occurred in 130 cases for GP, and actual patient injury or event occurred in 10 patients. In assessing secondary outcomes, no deaths were reported, although two patients experienced prolonged hemorrhage and two fiberoptic endoscopes were damaged by the device; 7 patients required a secondary procedure to retrieve the detached probe. Most patients with a reported GP event suffered no significant consequences due to the device failure (93%), but 7% required a second procedure or experienced prolonged stay or discomfort, Table 5. Most patients reported with IGP events (74%) suffered no significant consequences due to the device failure, but 26% of patients were affected by an event (prolonged hemorrhage, need for a secondary procedure due to a detached probe), Table 6. Reports by year decreased significantly after 2017 for both GP and IGP, Table 7.

DISCUSSION

Our study comprehensively analyzes events reported with GP and IGP from 2013 to 2023. For both GP and IGP, the most reported problem is the "failure to deliver energy." Investigating the root cause of this recurrent issue with these devices is imperative. If user error is identified as a significant factor, offering additional training to the healthcare professionals using these devices and refining the user guidelines would be beneficial.

The significantly higher number of reported events with IGP devices than with GP devices is noteworthy. While a higher usage frequency might contribute to the increased reporting, the pronounced rate of patient-related adverse events stemming from IGP failures cannot be dismissed lightly. Especially concerning are instances requiring repeat procedures, as they amplify the risk profile for patients and accentuate the resource burdens on healthcare institutions.

The manufacturer for the GP and IGP reports patient-related adverse events, including perforation, bleeding, aspiration pneumonia, and septicemia/infection, and reports a potential electrical hazard to the patient and operator with possible adverse including fulguration, burns, stimulation, and cardiac arrhythmia[5]. However, there have been no studies so far that have looked at the device-related events that could occur with GP and IGP. Our study is the first to analyze the device-related events reported. It sheds light on device-related complications, thus enhancing the existing knowledge pool crucial for daily clinical applications. Data regarding other bipolar devices was sparse and thus a comparative analysis could not be done.

The 2021 ACG guidelines for managing UGIB strongly recommend endoscopic hemostatic therapy with bipolar electrocoagulation, heater probe, or injection of absolute ethanol for patients with UGIB due to ulcers. Several studies have proven the efficacy and overall safety of GP and IGP to manage gastrointestinal hemorrhage[2,6,7]. The safety and efficacy of bipolar devices have been also established while managing lower GI bleeding[8,9]. GP and IGP are Bipolar devices used to manage GI bleeding during endoscopy. Given the ubiquity of these bipolar devices in clinical scenarios, endoscopists, and auxiliary staff must be apprised of potential device-related pitfalls.

Interestingly, the findings of this study also suggest that there was a decline in the events for both IGP and GP from 2017. Endoscopists familiarity with the device and adequate training in its usage, and manufacturer's improvement of the quality of the device could have led to fewer events. Usage of other hemostatic devices could have also contributed to this. Over-the-Scope Clips (OTSC) has been shown to be as effective as standard therapy in non-variceal upper gastrointestinal bleeding since 2017[10]. OTSC has also proven effective in large ulcers up to 5 cm[11], with a high success rate of hemostasis (80%) even in recurrent bleeding and has also competed with GP and IGP as first line hemostatic method since 2017[12].

At around the same time, hemostatic aerosolized powders such as TC 325 (Hemospray) have become part of the hemostatic armamentarium available to the endoscopist, especially effective in the setting of diffuse mucosal bleeding[13, 15].

Table 1 Reported procedure type in which gold probe was used

Procedure	Number
Bronchoscopy	7
Colonoscopy	25
Esophagogastroduodenoscopy	47
Enteroscopy	3
Endoscopic retrograde cholangiopancreatography	6
Missing	52
Total	140

Table 2 Reported procedure type in which injection gold probe was used

Procedure	Number
EGD	174
Colonoscopy	16
ERCP	11
Enteroscopy	1
Total	202

EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Failure Modes of gold probe (Primary Outcomes)

Failure mode	Number	Percentage
Arcing	1	0.7
Component missing	1	0.7
Detachment of device component	1	0.7
Electrical connector broke during use	1	0.7
Failure to deliver energy	107	76.4
Material separation	28	20.0
Tip bent (from packaging)	1	0.7
Total	140	100.0

Table 4 Failure modes of injection gold probe (Primary Outcomes)

Failure mode	Number	Percentage
Crack	9	4.5
Material separation	34	16.8
Device detachment	27	13.4
Failure to deliver energy	115	56.9
Material puncture/hole	5	2.5
Mechanical problem	12	5.9
Total	202	100.0

Table 5 Events affecting patients with gold probe failure (Secondary Outcomes)

Events	Number
Bowel burn	1
Hemorrhage/Bleeding	1
Prolonged hospital stay	1
Removal requiring a second procedure	7
Total	10

Table 6 Events affecting patients or equipment with injection gold probe failure (Secondary Outcomes)

Events	Number
Prolonged hemorrhage	2
The secondary procedure to retrieve the detached probe	48
Probe damaged scope	3
Total	53

Table 7 Reports by year (2013-2023)

Year	MAUDE reports for gold probe	MAUDE reports for injection gold probe
2013	32	38
2014	32	36
2015	17	33
2016	26	30
2017	14	23
2018	3	6
2019	3	9
2020	2	8
2021	4	7
2022	1	5
2023	6	7
Total	140	202

MAUDE: Manufacturer and User Facility Device Experience.

These newer hemostatic technologies may have contributed to a decline in use of IGP and GP since 2017. It's also conceivable that the manufacturing process may have effectively addressed the prior device failure reports to redesign and improve quality control hence leading to a decline in the device malfunction/failure reports since 2017.

Guidelines for non-variceal upper gastrointestinal bleeding have emphasized that epinephrine injection needs to be combined with a secondary hemostatic modality and hence IGP use may have increased over GP use. IGP conveniently uses both injection and thermocoagulation sequentially without interruption to introduce another hemostatic method endoscopically. This may have contributed to increase in IGP use over GP and consequently higher device malfunction reports[15].

This study has limitations. The MAUDE web search feature is limited to adverse event reports within the past ten years. This passive surveillance system has its limitations. There is a potential for submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to under-reporting of events, inaccuracies in reports, lack of verification that the device caused the reported event, and lack of information about the frequency of the device use.

CONCLUSION

GP and IGP are critical in managing gastrointestinal bleeding. This study of the FDA MAUDE database revealed the type, number, and trends of reported device-related adverse events. The endoscopist and support staff must be aware of these device-related events and be equipped to manage them if they occur.

ARTICLE HIGHLIGHTS

Research motivation

Gold probe (GP) and gold probe (GP) are vital in managing gastrointestinal bleeding, yet they present notable risks. Awareness of these risks is essential for endoscopists and support staff. The study highlights the need for improved device safety and better management strategies in case of device failure.

Research objectives

The analysis revealed 140 reports for GP and 202 reports for IGP, with the majority of device failures being attributed to the failure to deliver energy. While most events did not lead to significant patient consequences, a notable proportion (26% for IGP) resulted in adverse outcomes like prolonged hemorrhage or the need for secondary procedures.

Research methods

The study utilized post-marketing surveillance data from the Food and Drug Administration (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database, analyzing reports for GP and IGP from January 2013 to August 2023. Statistical analyses were performed using IBM SPSS Statistics V.27.0 to identify primary and secondary outcome measures.

Research results

The primary objective is to evaluate the events associated with the use of GP and IGP, specifically focusing on the types and frequencies of device failures and their impact on patient outcomes.

Research conclusions

The motivation for this research stems from the lack of comprehensive data on device-related adverse events for GP and IGP, devices commonly used in managing gastrointestinal bleeding, despite their widespread clinical use.

Research perspectives

This study investigates the device-related adverse events associated with the use of GP and IGP in endoscopic hemostasis, leveraging data from the FDA's MAUDE database over a decade (2013-2023).

Research background

The findings underscore the need for ongoing surveillance, device improvement, and consideration of emerging hemostatic technologies. Further research into device design and usage guidelines could enhance safety and efficacy in clinical practice.

FOOTNOTES

Author contributions: Suresh Kumar VC contributed to conceptualization, design, manuscript writing, and editing; Aloysius M contributed to design, statistical analysis, manuscript writing, and editing; Aswath G contributed to manuscript review and editing.

Institutional review board statement: This is a de-identified database-based study thus it was determined that no ethical approval/IRB is required.

Informed consent statement: For this study, we utilized a de-identified database, specifically the FDA's Manufacturer and User Facility Device Experience (MAUDE) database, which contains anonymized and publicly available data. Given the retrospective and de-identified nature of the data analyzed, this study did not involve direct interaction with patients or access to identifiable patient information. Consequently, in accordance with ethical guidelines and research standards, informed consent was not required for this database-based study.

Conflict-of-interest statement: There are no conflicts of interest to report.

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Observational Study

Upper gastrointestinal bleeding in Bangladeshi children: Analysis of 100 cases

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Abstract

BACKGROUND

Upper gastrointestinal bleeding (UGIB) is defined as bleeding that occurs proximal to the ligament of Treitz and can sometimes lead to potentially serious and life-threatening clinical situations in children. Globally, the cause of UGIB differs significantly depending on the geographic location, patient population and presence of comorbid conditions.

AIM

To observe endoscopic findings of UGIB in children at a tertiary care center of Bangladesh.

METHODS

This retrospective study was carried out in the department of Pediatric Gastroenterology and Nutrition of Bangabandhu Shiekh Mujib Medical University, a tertiary care hospital of Bangladesh, between January 2017 and January 2019. Data collected from hospital records of 100 children who were 16 years of age or younger, came with hematemesis, melena or both hematemesis and melena. All patients underwent upper gastrointestinal endoscopy (Olympus CV 1000 upper gastrointestinal video endoscope) after initial stabilization. Necessary investigations to diagnose portal hypertension and chronic liver disease with underlying causes for management purposes were also done.

RESULTS

A total of 100 patients were studied. UGIB was common in the age group 5-10 years (42%), followed by above 10 years (37%). Hematemesis was the most common presenting symptom (75%) followed by both hematemesis and melena

(25%). UGIB from ruptured esophageal varices was the most common cause (65%) on UGI endoscopy followed by gastric erosion (5%) and prolapsed gastropathy (2%). We observed that 23% of children were normal after endoscopic examination.

CONCLUSION

Ruptured esophageal varices were the most common cause of UGIB in children in Bangladesh. Other causes included gastric erosions and prolapsed gastropathy syndrome.

Key Words: Bangladeshi; Children; Endoscopy; Upper gastrointestinal bleeding; Esophageal varices

Core Tip: Various etiologies are responsible for upper gastrointestinal bleeding. However, we found a wide range of etiologies including non-gastrointestinal causes in Bangladeshi children.

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INTRODUCTION

Gastrointestinal (GI) bleeding is not uncommon in children. When the source of bleeding is proximal to the ligament of Treitz, it is defined as upper gastrointestinal bleeding (UGIB) and when distal to the ligament of Treitz as lower gastrointestinal bleeding[1]. UGIB varies greatly in presentation and may provoke anxiety in the child, caregivers and healthcare providers. UGIB presents commonly as hematemesis, melena or both hematemesis and melena. Hematemesis is defined as vomiting of blood that may be bright red or coffee-ground color, small or large volume and may be associated with clots. A fistful of clots is nearly equivalent to 500 mL of blood[2]. Melena is black, tarry stool, and 60 mL of blood is the minimum quantity to produce melena. Blood is present for at least 6 h in the intestine[3]. UGIB is infrequent in children with an estimated incidence of 1-2/10000 per year[4], where the majority are self-limiting[5]. Significant UGIB is infrequent and remains a management challenge to clinicians.

Etiology of UGIB in children is diverse, and causes vary by age, geographical location and associated comorbidities[6, 7]. In older children and adolescents, significant causes of UGIB include variceal bleeding and peptic ulcer disease. Foreign body ingestion is rare in older children and adolescents. Common etiologies in infants are Mallory-Weiss tear and reflux esophagitis. Other common causes in neonates include swallowed maternal blood and milk protein allergy[7].

Management of patients with UGIB depends on an underlying cause, severity of bleeding and hemodynamic status of patient. There is a paucity of data regarding the etiology, mode of presentation and endoscopic findings of UGIB in children of Bangladesh. The purpose of the study was to observe endoscopic findings of 100 cases of UGIB admitted in the Department of Pediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University, a tertiary care hospital of Bangladesh.

MATERIALS AND METHODS

This retrospective observational study was carried out in the department of Pediatric Gastroenterology of Bangabandhu Sheikh Mujib Medical University of Bangladesh. Data were collected from hospital records after approval from the departmental ethical committee. In total, 100 children who were 16 years of age or younger presented with hematemesis and/or melaena and underwent upper GI endoscopy after stabilization of vitals within 24-48 h. Patients who underwent sedation by parenteral midazolam and pethidine with preparations for resuscitation were included in this series. Patients who were older than 16 years of age or presented with bright red per rectal bleeding were excluded. Upper GI endoscopy was completed by an expert pediatric gastroenterologist of the same department with an Olympus CV 100 video endoscope model. All patients were treated according to the standard departmental protocol. Blood for grouping (ABO and Rh), routine complete blood count, and in selected cases blood liver biochemistry (alanine transaminase, serum albumin, prothrombin time) with Wilson's disease/autoimmune hepatitis panel were done. Stool for occult blood, along with Doppler ultrasonography of the abdomen for ascites, liver echotexture, portal vein thrombosis/cavernous malformation, diameter/pressure and splenomegaly were completed for all patients according to the departmental protocol. The study was approved by the departmental Ethics Committee. Statistical analyses were performed using frequency, means, standard deviations and proportions.

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Figure 1 Example of grade 4 esophageal varices.

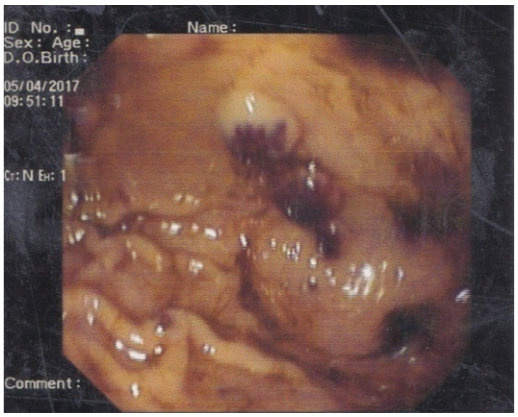

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Figure 2 Blue rubber bleb nevus in the stomach.

RESULTS

A total of 100 children underwent UGI endoscopic evaluation during the study period. Among them, 62 were male (62%), and 38 (38%) were female. The mean age of the patients was 9 ± 4.25 years. Altogether, 22% of patients were younger than 5-years-old, 42% of patients were between 5-years-old and 10-years-old, and 36% of patients were above 10-years-old (Table 1). We observed that 15% of patients were admitted with impending shock (hypotension, tachycardia, cold clammy skin) from hematemesis and/or melena and needed volume resuscitation. Among the studied patients, 30 presented with isolated hematemesis, 2 presented with isolated melaena, and 68 presented with combined hematemesis and melaena (Table 1).

At endoscopy, 65% of patients had esophageal varices and required endotherapy like variceal ligation/sclerotherapy (Figure 1). We observed that 12% of patients had non-variceal bleeding, and 23% of patients had normal UGI endoscopic findings. Among the 12 patients who had non-variceal bleeding, 5 patients had gastric erosion, 1 patient had features of gastroesophageal reflux disease, 1 patient had nonconclusive findings but was ultimately diagnosed with hemophilia, 1 patient had features of blue rubber bleb nevus syndrome (Figures 2 and 3), 1 patient had a Mallory-Weiss tear, 2 patients had prolapsed gastropathy (Figure 4), and 1 patient with an eroded posterior duodenal artery from a duodenal ulcer underwent emergency laparotomic ligation of the eroded posterior duodenal artery (Table 2).

There were no patients with UGIB that was caused by foreign body ingestion. UGIB was caused in 65% of patients by variceal bleeding from ruptured esophageal varices. Among them, 47 patients were ultimately diagnosed with extrahepatic portal hypertension, and 18 patients were diagnosed with chronic liver disease (CLD). The etiology of CLD included Wilson's disease (12 patients), post-Kasai procedure for biliary atresia (1 patient), autoimmune hepatitis (1 patient), congenital hepatic fibrosis (1 patient), and cryptogenic (3 patients). The cause was idiopathic in 23 cases.

Table 1 Demographic characteristics of the patients, *n* = 100

Variable	Value
Age in yr	
< 5	22 (22)
5-10	42 (42)
> 10	36 (36)
Mean ± standard deviation	9.0 ± 4.5
Sex	
Male	62 (62)
Female	38 (38)
Presentation	
Hematemesis	30 (30)
Melena	2 (2)
Hematemesis and melena	68 (68)

Data are *n* (%) unless otherwise indicated.

Table 2 Upper gastrointestinal endoscopic findings of the patients, *n* = 100

Variable	Value
Normal	23 (23)
Esophageal varices	65 (65)
Extrahepatic PHTN	47 (47)
CLD with PHTN	18 (18)
Non-variceal causes	
Gastric erosion	5 (5)
GERD	1 (1)
Hemophilia	1 (1)
BRBNS	1 (1)
MWT	1 (1)
PGS	2 (2)
Duodenal artery erosion	1 (1)

Data are *n* (%). BRBNS: Blue rubber bleb nevus syndrome; CLD: Chronic liver disease; GERD: Gastroesophageal reflux disease; MWT: Mallory-Weiss tear; PGS: Prolapsed gastropathy syndrome; PHTN: Pulmonary hypertension.

DISCUSSION

In the current study, the male to female ratio was 1.6:1, which is similar to another study of UGIB in children[6]. A recent study by Dubey *et al*[8] showed that UGIB was more common in the 5-10 year age group (71.4%). We also found that the majority of children (42%) were in the 5-10 year group.

Variceal bleeding from portal hypertension was the most common cause (65%) of UGIB in this study. In another study, portal hypertension accounted for 95% of cases[9]. The variceal bleeding rate of our study was very high in comparison to 10.6% in the Western hemisphere (South America and North America)[5,10,11]. These differences may be explained by referral bias (*i.e.* the majority of non-variceal bleeding cases were managed in non-tertiary healthcare centers, while variceal bleeding cases were referred to our tertiary care center). In addition, geographic variation of disease states resulting in UGIB may play a factor.

Among the variceal bleeding cases, extrahepatic portal hypertension was the major cause in 47% of patients, whereas 18% of patients were diagnosed with CLD with portal hypertension. Extrahepatic portal hypertension was also found to

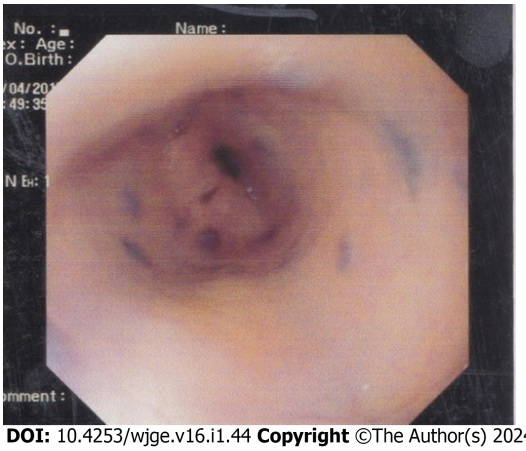

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Figure 3 Blue rubber bleb nevus in the lower end of the esophagus.

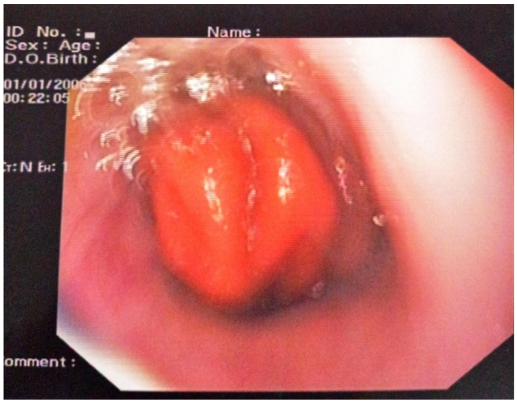

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Figure 4 Prolapsed fundus of the stomach in the esophagus.

be a common cause (46%) of variceal bleeding in another study from a neighboring country[9,12]. In a study from India, 16.1% of cases of UGIB were caused by CLD with portal hypertension, which is similar to our findings (18%)[8]. Our study showed that Wilson's disease was the most common cause (12%) of CLD with portal hypertension and may be related to the burden of consanguineous marriage and/or referral bias. We found that 3% of UGIB cases were due to cryptogenic CLD with portal hypertension, which may be explained by the lack of modern laboratory facilities to diagnose metabolic liver diseases other than Wilson's disease.

During the evaluation of the 100 children with UGIB, we found that 12% of children had non-variceal bleeding. Among them, gastric erosion was found in 5% of cases, which is similar (9%) to another study from India[12]. This may be partially explained by parents using self-medication (nonsteroidal anti-inflammatory drugs/traditional medications) during minor trauma, high fever, *etc.* Other endoscopic diagnosis were blue rubber bleb nevus syndrome, Mallory-Weiss tear, prolapsed gastropathy syndrome, and posterior duodenal artery erosion from duodenal ulcer. In our series, there were 23 idiopathic cases, which is similar to the findings from Mittal *et al*[12]. Cleveland *et al*[6] also found normal or doubtful sources on endoscopy in 42% of their cases. Normal UGI endoscopy findings may suggest minor mucosal lesions or extra GI sources (*i.e.* swallowed blood).

CONCLUSION

Upper GI endoscopic evaluation of children with UGIB showed ruptured esophageal varices were the most common cause of UGIB in Bangladesh.

ARTICLE HIGHLIGHTS

Research background

Upper gastrointestinal bleeding (UGIB) is defined as bleeding that occurs proximal to the ligament of Treitz and can

sometimes lead to potentially serious and life-threatening clinical situations in children. The etiology of UGIB in children is diverse and causes vary with age, geographical location and associated comorbidity.

Research motivation

There is a paucity of data regarding the etiology, mode of presentation and endoscopic findings of UGIB in children of Bangladesh.

Research objectives

The purpose of the study was to observe endoscopic findings of 100 cases of UGIB that were admitted in the Department of Pediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University, a tertiary care hospital of Bangladesh.

Research methods

This retrospective observational study was carried out in the department of Pediatric Gastroenterology of Bangabandhu Sheikh Mujib Medical University of Bangladesh. Data were collected from hospital records after approval from the departmental ethical committee. In total, 100 children who were 16 years of age or younger presented with hematemesis and/or melaena and underwent upper gastrointestinal endoscopy after stabilization of vitals within 24-48 h. Patients who were older than 16 years of age or presented with bright red per rectal bleeding were excluded. All patients were treated according to the standard departmental protocol. The study was approved by the departmental Ethics Committee. Statistical analysis were performed using frequency, means, standard deviations and proportions.

Research results

A total of 100 patients were studied. UGIB was most common in the 5-10 years age group (42%), followed by those older than 10 years (37%). Hematemesis was the most common presenting symptom (75%) followed by both hematemesis and melena (25%). UGIB from ruptured esophageal varices was the most common cause (65%) on upper gastrointestinal endoscopy followed by gastric erosion (5%) and prolapsed gastropathy (2%). We observed that 23% of patients had a normal endoscopy.

Research conclusions

Upper gastrointestinal endoscopic evaluation of children with UGIB showed that ruptured esophageal varices were the most common cause of UGIB in Bangladesh. Non-gastrointestinal causes like hemophilia may also present with gastrointestinal bleeding.

Research perspectives

Further multicenter studies should be conducted to determine non-gastrointestinal causes of UGIB.

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FOOTNOTES

Author contributions: Mazumder MW designed the research study and performed the research; Benzamin M analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the departmental Ethics Committee of the Department of Pediatric Gastroenterology and Nutrition of Bangabandhu Shiekh Mujib Medical University (Approval No. BSMMU/Ped. Gastro/2023/122).

Informed consent statement: As this was a retrospective study, consent from parents/patients was unnecessary.

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