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*Clinical Trials Study*

Detachable string magnetically controlled capsule endoscopy for the non-invasive diagnosis of esophageal diseases: a prospective, blind clinical study

a prospective, blind clinical study

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Abstract

BACKGROUND

Traditional esophagogastroduodenoscopy (EGD) as an invasive examination method can cause discomfort and pain in patients. In contrast, magnetically controlled capsule endoscopy (MCE) as a non-invasive method is being applied to the detection of the stomach and small intestine diseases, but its application in esophageal diseases is not widespread.

AIM

We aimed to evaluated the safety and efficacy of detachable string magnetically controlled capsule endoscopy (ds-MCE) in the diagnosis of esophageal diseases.

METHODS

Fifty subjects who had been diagnosed as esophageal diseases were prospectively recruited for this clinical study and experienced the examination of detachable string magnetically controlled capsule endoscopy and conventional esophagogastroduodenoscopy. The primary endpoints included the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of detachable string magnetically controlled capsule endoscopy in patients with esophageal diseases. Secondary endpoints were consisted of the visualization of the esophageal and dentate lines, as well as the subjects' tolerance to the procedure.

RESULTS

Using esophagogastroduodenoscopy as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of detachable string magnetically controlled capsule endoscopy for esophageal disease detection were 85.71%, 86.21%, 81.82%, 89.29%, and 86%, respectively. The detachable string magnetically controlled capsule endoscopy was more comfortable and convenient than esophagogastroduodenoscopy, with 80% of patients feeling that
detachable string magnetically controlled capsule endoscopy examination was very comfortable or comfortable, and 50% of patients believing that detachable string magnetically controlled capsule endoscopy examination was very convenient.

CONCLUSION
The ds-MCE had the same diagnostic effects as traditional EGD for esophageal diseases and showed more comfortability and convenience than EGD, providing a novel non-invasive method for esophageal diseases.

Key Words: Detachable string magnetically controlled capsule endoscopy; esophagogastrroduodenoscopy; non-invasive diagnosis


Core Tip: Our study showcases detachable string magnetically controlled capsule endoscopy (ds-MCE) as an innovative, non-invasive technique for esophageal diagnosis, matching the 86% accuracy of traditional EGD while significantly enhancing patient comfort. With 80% of patients reporting a favorable experience, ds-MCE stands to increase compliance and revolutionize the approach to esophageal disease management, offering a promising leap forward in gastroenterological diagnostics with minimal patient discomfort.

INTRODUCTION
Esophageal diseases including gastroesophageal reflux disease (GERD), Barrett’s esophagus, esophageal tumors pose a serious threat to human health. The long-term chronic inflammation is strongly associated with an increased risk of Barrett’s
esophagus and esophageal cancer\textsuperscript{2}. It is noted that most of the malignant cases can metastasize to distant sites, leading to poor prognosis\textsuperscript{3,4}. Consequently, early diagnosis of esophageal diseases is crucial for preventing the occurrence of esophageal cancer.

Esophagogastroduodenoscopy (EGD) is the "gold standard" for upper gastrointestinal diseases, allowing visualization of the mucosa and sampling, but EGD requires intubation, even anesthesia, resulting in poor compliance. Esophageal capsule endoscopy (ECE) is a well-tolerated and safe procedure\textsuperscript{5}, which was initially used to diagnose small intestinal diseases \textsuperscript{6}. In 2004, the first-generation ECE was authorized and acquired video images from both ends of the device at a rate of 2 frames/second/end\textsuperscript{7}. The second-generation ECE was approved in 2007 to provide improved image quality at 15 frames/second and high spatial resolution\textsuperscript{8}. A third-generation ECE featured a 174\textdegree angle of view and a 35 frames/second rate\textsuperscript{9} but failed to improve detection rates\textsuperscript{10}. ECE as a screening tool for esophageal diseases shows the medium sensitivity and specificity for 77\% and 86\% vs. EGD for 76\% and 90\%\textsuperscript{11}, but ECE has a high false-positive rate\textsuperscript{8}, making itself ineffective as an alternative to EGD. It was proposed in 2013 that a magnetically controlled capsule endoscopy (MCE) system was developed and approved in China\textsuperscript{12}, involving a capsule manipulated by an external magnetic field to visualize the mucosa. MCE is nearly equivalent to conventional EGD due to its diagnostic accuracy\textsuperscript{13} and high sensitivity in minor erosions\textsuperscript{12}. Another study demonstrates that the diagnostic accuracy of MCE in esophageal lesions can reach 86\% \textsuperscript{14}. Moreover, a detachable string magnetically controlled capsule endoscopy (ds-MCE) is developed to control the movement of the capsule, allowing direct and repeated observation of the esophagus \textsuperscript{15}.

Our previous study showed that MCE is a safe and non-invasive endoscopic examination with a highly accurate detection rate for gastric and small intestinal diseases\textsuperscript{16}. In the present study, ds-MCE was applied for detection of esophageal diseases and we found that ds-MCE had the same diagnostic effects as traditional EGD for esophageal diseases and showed more comfortability and convenience than EGD, providing a novel non-invasive method for esophageal diseases.
MATERIALS AND METHODS

METHODS

Study design
This was a prospective, blinded, self-controlled clinical study conducted at Shanghai Sixth People's Hospital from November 29th, 2019 to September 20th, 2021. The study was approved by the Ethics Committee of Shanghai Sixth People's Hospital (No. 2019-082-2).

Study participants
The participants aged 18-75 years with previously diagnosed esophageal diseases were eligible for this clinical study. Patients with one of the following conditions were excluded: 1) no surgical condition or refusal to undergo any abdominal surgery; 2) intracorporeal pacemaker; 3) intracorporeal implantation of electronic devices such as cochlear implants, magnetic metal drug infusion pumps, neurostimulators, and magnetic metal foreign bodies; 4) women during pregnancy; 5) dysphagia, known or suspected gastrointestinal obstruction, stricture, and fistula, significant gastrointestinal bleeding, history of gastrointestinal surgery or history of abdominal surgery with altered gastrointestinal anatomy, history of abdominal radiation; 6) contraindication to electro-gastroscopy; 7) other conditions that the investigator believes exist that are not appropriate for this study. All subjects understood and agreed to the study protocol and voluntarily signed the informed consent form.

Procedures
After obtaining informed consent, each subject underwent a ds-MCE followed by EGD which was the standard diagnostic method for comparison with ds-MCE. The EGD operating and diagnosing physicians were unblinded to the ds-MCE operating and reviewing physicians. The procedure for this study was shown in Figure 1.

The ds-MCE (specification: NU-1/CEE-1) consisting of a MCE system and a single-use detachable string (Figure 2) was provided by Shanghai Ankon Medical Technology Co, Ltd (Shanghai, China). The examiner only took one capsule to complete the upper
gastrointestinal examination. The detachable string of the single-use capsule endoscope was connected to one end of the capsule and the other end was attached to a syringe, which moved the capsule up and down to examine the esophagus. Following the examination of the esophagus, the air was injected through the syringe to separate the capsule from the string, and the capsule was then inserted into the stomach to examine the stomach and small intestine.

**Study outcomes and definition**
The detection of esophageal lesions by ds-MCE and EGD was recorded separately, and EGD was used as the gold standard for the diagnosis of esophageal diseases. The primary endpoints of this study included: sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of ds-MCE for esophageal disease detection (Table 1). 1) Sensitivity: The probability of a positive EGD and a positive MCE result, which was an indicator of the ability to detect a positive result in this test. 2) Specificity: The probability of a negative EGD and a negative MCE, which was an indicator of the ability to detect a negative result. 3) Predictive value: including positive and negative predictive values. The higher the value, the more likely it was to estimate the probability of the subject having the disease or not. 4) Diagnostic accuracy: the probability that ds-MCE was consistent with EGD findings.

Secondary endpoints: 1) Esophageal visualization: the ability to clearly capture and preserve images of the upper, middle, and lower esophagus. 2) Dentate line visualization: clear capture of the dentate line images. 3) Subject tolerance: participants completed a questionnaire to assess their level of comfort with EGD and ds-MCE, with ratings ranging from 0 to 4 (0 = very comfortable; 1 = comfortable; 2 = tolerable; 3 = uncomfortable; 4 = very uncomfortable); the ease of inspection score ranges from 0 to 3 (0 = very convenient; 1 = convenient; 2 = inconvenient; 3 = very inconvenient). This study evaluated the safety of the subjects by counting the incidence of adverse events and complications during and after capsule endoscopy and EGD.

**Statistical analysis**
Statistical analysis of the data was conducted with SPSS 26.0 and Graphpad prism 9. All hypothesis tests were performed at a two-sided 5% level of significance. Continuous variables were summarized using descriptive statistics. In the case of variables with a normal distribution, mean and standard deviation were taken, and in the case of variables with a skewed distribution, median and interquartile spacing were taken. The Kruskal-Wallis test was used for comparison between groups.

RESULTS

RESULTS

Patient characteristics
A total of 50 subjects (average age of 53.26 years; 46% female) were included, of whom 48 patients had a history of esophagitis, 1 patient had a history of Barrett's esophagus, 2 patients had a history of esophageal hiatal hemia, 8 patients had superficial gastritis, and 2 patients had atrophic gastritis. The demographic data of the 50 subjects were described in Table 2.

Diagnostic accuracy and safety of ds-MCE
50 participants successfully performed ds-MCE, and did not experience any adverse reactions or device defects associated with ds-MCE or EGD. A total of 21 cases (42%) of esophageal diseases were detected by EGD and 22 cases (44%) by ds-MCE. Among them, 3 subjects were diagnosed with esophageal diseases by EGD, but were negative by ds-MCE; while 4 subjects were diagnosed with the esophageal disease by ds-MCE, but were negative by EGD. The detection of specific esophageal diseases was shown in Supplementary Table 1.

Using EGD as the gold standard, the sensitivity of ds-MCE in detecting esophageal disease was 85.71% (95%CI: 62.64%, 96.24%), the specificity was 86.21% (95%CI: 67.43%, 95.49%), the positive predictive value was 81.82% (95%CI: 58.99%, 94.01%), and the negative predictive value was 89.29% (95%CI: 70.63%, 97.19%), and diagnostic concordance was 86% (95%CI: 72.64%, 93.72%) (Table 3). Meanwhile, ds-MCE was also
capable of clearly capturing and preserving pictures of the upper, middle, and lower esophagus and the dentate line with 100% integrity (Figure 3).

Assessment of the comfort and convenience of ds-MCE

The perceived comfort of the subjects undergoing EGD and ds-MCE examination was assessed by questionnaire form. The overall comfortable level of EGD was lower than that of the ds-MCE examination. Among them, 40 patients (80%) perceived that it was very comfortable or comfortable to undergo a ds-MCE examination, but only 19 patients (38.7%) perceived that it was very comfortable or comfortable to perform EGD. In addition, there were 7 patients (14.3%) who considered undergoing EGD to be uncomfortable or very uncomfortable, and the data were statistically different between the two sets ($p < 0.0001$). Regarding the convenience of the ds-MCE examination, 25 patients (50%) found it very convenient and no patient found it inconvenient (Figure 4. and Table 4).

DISCUSSION

The evolution of diagnostic modalities in gastroenterology is driven by the twin requirements of improving patient comfort and expanding clinicians’ diagnostic capabilities. In this context, the development of ds-MCE represents a detection innovation offering patients a less invasive option and improving compliance with recommended diagnostic procedures. Our clinical study evaluated the safety and effectiveness of ds-MCE, a novel capsule endoscopy technology, for diagnosing esophageal diseases. Our findings confirmed the clinical utility of ds-MCE as a feasible, accurate, and safe non-invasive diagnostic modality that may provide tremendous benefits in terms of patient comfort and diagnostic value.

Our study identified specific patient populations that stand to benefit from the ds-MCE detection. These included individuals at lower risk for esophageal pathology who did not require tissue sampling, such as those undergoing routine surveillance for conditions like Barrett's esophagus. Furthermore, ds-MCE presented a safer diagnostic option for patients at increased risk of complications from traditional endoscopy or
sedation, including the elderly, pregnant women, and those with hemodynamic instability. This might meet the growing demand for patient-friendly diagnostics that minimize discomfort and risk.

The unique design of ds-MCE features a steerable capsule endoscope tethered by a detachable cord, which facilitates detailed examination of targeted esophageal areas. The ds-MCE has demonstrated enhanced visualization rates across various esophageal segments, including the Z-line, with one study reporting significantly higher rates compared to standard MCE. This ability to obtain high-quality mucosal images without anesthesia represents a significant advance in patient-centered care, especially for those who are averse to traditional endoscopy, confirming the results of previous studies. Comparative analysis with existing technologies such as the N-scope demonstrates that ds-MCE can enhance the patient experience by minimizing discomfort. However, direct comparative studies are needed to confirm these claims.

The design of ds-MCE allows for extended examination times within the esophagus, which is a substantial improvement over traditional capsule endoscopy, which often provides limited esophageal imaging due to rapid transit. The limitations inherent in current methods underscore the need for innovation in diagnostic endoscopy. The ds-MCE system in our study addressed the limitations by offering extended visualization of the esophageal mucosa, and was particularly advantageous for assessing areas that are traditionally challenging to evaluate using standard endoscopic techniques.

Despite the promising results, we acknowledged that our study had some limitations. First, patients with esophageal or gastric varices, commonly found in the lower esophagus, were not included, leaving it unclear about whether their presence would alter the interpretation of the dentate line by ds-MCE. Second, most of the subjects in this study were older adults with high levels of anxiety, and it need be investigated about whether the comfort ratings would be similar in younger individuals. Third, this pilot study only recruited adults and did not address the potential challenges of capsule ingestion in groups known for high rates of swallowing difficulties, such as children. Fourth, ds-MCE takes longer time than EGD, with median
examination times of 14.3 minutes vs 6.2 minutes, respectively. Fifth, as a non-invasive procedure, ds-MCE does not provide histological samples or therapeutic options, and considerations should be weighed within the broader clinical workflow and diagnostic strategy.

The clinical significance of false negatives in diagnosing esophageal pathology, especially for high-risk lesions like early-stage malignancies, is profound. Although the sensitivity shown in our study is encouraging, the observed false negative rate of approximately 15% necessitates a cautious approach when considering ds-MCE for the detection of such critical conditions. Rigorous evaluation of the diagnostic accuracy of ds-MCE is required in subsequent research efforts. Prospective, multicenter studies with larger sample sizes and the inclusion of high-risk patient groups are essential to validate our findings. Such studies should also perform head-to-head comparisons with established gold-standard diagnostic procedures to firmly establish the reliability and clinical applicability of ds-MCE.

CONCLUSION

In summary, our study positions ds-MCE as a viable alternative to conventional EGD, with comparable efficacy in detecting esophageal lesions and the potential to improve patient compliance in clinical settings. The continuous improvement and development of capsule endoscopy technology is expected to revolutionize the detection and management of upper gastrointestinal pathology. To fully realize ds-MCE's potential, future studies will be broadened to include diverse patient groups, such as children and the elderly, ensuring robust and generalizable results. Investigation into the cost-effectiveness of ds-MCE and its integration into standard diagnostic algorithms will be pivotal for its widespread adoption in clinical practice. Preliminary cost analysis models, accounting for potential reductions in anesthesia use and increased patient throughput, can offer valuable insights into ds-MCE's economic viability. Through these coordinated research efforts, ds-MCE is likely to redefine the paradigm of esophageal disease diagnosis in the coming years.
ARTICLE HIGHLIGHTS

Research background
Esophagogastroduodenoscopy (EGD), while the gold standard for diagnosing esophageal diseases, is invasive and can cause patient discomfort. Magnetically controlled capsule endoscopy (MCE) offers a non-invasive alternative, yet its application for esophageal conditions remains limited.

Research motivation
This study was motivated by the need to enhance patient compliance and comfort during esophageal examinations, while maintaining high diagnostic accuracy.

Research objectives
The primary aim was to assess the safety and diagnostic efficacy of detachable string magnetically controlled capsule endoscopy (ds-MCE) in identifying esophageal diseases.

Research methods
A prospective, blinded, self-controlled clinical study was conducted, comparing ds-MCE with EGD across various diagnostic parameters and patient tolerance levels in 50 subjects with known esophageal diseases.

Research results
ds-MCE demonstrated diagnostic accuracy comparable to EGD (86%) and was preferred by patients, with 80% reporting a comfortable or very comfortable experience.

Research conclusions
ds-MCE is an effective and patient-friendly diagnostic tool for esophageal diseases, offering a non-invasive alternative to traditional EGD with similar diagnostic outcomes.
Research perspectives

Further studies should expand the patient demographic to validate ds-MCE's utility across various populations and evaluate its cost-effectiveness for broader clinical adoption.
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