Approval Number: 202210059DIPA

National Taiwan University Hospital
Clinical Trial Protocol

* This protocol should include a "Clinical Trial Summary" on the cover page.

□Drug □Medical Device □Medical Technology■ Other: Purely Academic Research

I.Project Title

Difference in aerosol-generating amount between wired magnetic-assisted capsule endoscopy system and esophagogastroduodenoscopy examination of varices in biliary atresia patients

II.Principal Investigator

Dr. Jia-Feng Wu, Attending Physician / Professor

III.Co-Principal Investigator

Dr. Ping-Huei Tseng, Attending Physician / Professor

Dr. Chi-San Tai, Attending Physician / Lecturer

IV.Specific Aims

The goal of this clinical trial is to compare the safeness and effectiveness of traditional esophagogastroduodenoscope (EGD) and wired magnetically assisted capsule endoscopy (MACE) in the diagnosis of esophageal varices in biliary atresia (BA) patients.

V.English Abstract

Background and aims: Biliary atresia (BA) is the leading cause of chronic liver insufficiency, liver cirrhosis, esophageal varices, and liver transplantation in the world. Regular endoscope examination with prompt adjustment of therapeutic agents is key to avoid the occurrence of esophageal varices bleeding. During the pandemic of COVID-19, to offer a regular and safe endoscopy survey of esophageal varices in BA patients become a medical challenge issue in the world.

Our study aim to investigate the diagnostic utility and safety of a Magnetically Assisted Capsule Endoscopy (MACE) system as comparing with traditional esophagogastroduodenoscope (EGD) in BA patients for the esophageal varices survey. We also aim to clarify whether the MACE is a less aerosol -generating procedure than EGD during the survey of esophageal varices, and decrease the risk of SARS-CoV 2 transmission.

Methods: This is an open-labeled un-blind trail. We intend to include 25 BA patients > 6 years of age agree to receive MACE examination into the study group, and another 25 BA patients > 6 years of age

who will receive regular EGD into the control group. After the signature of the inform consent, they will enter this study. During the examination, a DR-528 Handheld Particle Counter (Met One Instruments, Inc., Grants Pass, OR) will be applied to detect aerosol generated during the examination. The compliance, diagnostic accuracy, and safety between study and control groups will be analyzed.

Scientific merits and anticipated results: The MACE was approved to achieve similar diagnostic accuracy and safety as EGD in adult population in Taiwan. Since subjects receiving MACE examination may close their mouth and have a face mask during the procedure, we intend to prove the MACE is an efficient, safe and less aerosol-generating procedure than EGD in BA patients this study. With the results of this study, we may offer the evidence of a safe and efficient examination during the pandemic of COVID-19 to protect the patients and medical staffs.

VI.Background Introduction & Significance

Research Purpose: Our study aims to investigate the diagnostic utility and safety of the Magnetically Assisted Capsule Endoscopy (MACE) system compared to traditional esophagogastroduodenoscopy (EGD) in the surveillance of esophageal varices in patients with biliary atresia (BA). Additionally, we seek to determine whether MACE generates fewer aerosols than EGD during the examination, thereby potentially reducing the risk of SARS-CoV-2 transmission.

General Background Information: Biliary atresia (BA) is one of the leading causes of chronic liver failure, liver cirrhosis, esophageal varices, and the need for liver transplantation during childhood worldwide (1-4). Statistically, approximately 50% of patients with BA develop portal hypertension, and 26.5% are at risk of gastrointestinal variceal bleeding (5-7). Esophageal variceal bleeding often results in significant complications and risks. In adult patients with chronic hepatitis, clinical indicators such as APRI, FIB-4, Extended BAVENO, or BAVENO VI are commonly used to help predict the presence of significant esophageal varices (8, 9). However, previous studies in BA patients have shown that these clinical indicators are not accurate in predicting the risk of esophageal varices in this population. Therefore, in clinical practice, physicians still rely on invasive esophagogastroduodenoscopy (EGD) to diagnose and assess the severity of esophageal varices. Based on the severity of the esophageal varices, physicians adjust medication dosages to reduce the risk of unexpected variceal bleeding and its associated complications.

Since the outbreak of SARS-CoV-2 in Wuhan, China in 2019, COVID-19 has continued to spread widely across the globe and has been confirmed as a direct contact and droplet infection disease. As of

June 2022, COVID-19 has resulted in nearly 541 million infections and over 6.3 million deaths worldwide. In Taiwan, it has caused 3.44 million infections and more than 6,000 deaths. Consequently, the pandemic has placed enormous pressure and strain on global healthcare systems. During the outbreak in Europe in 2021, it was reported that over 20% of healthcare workers in northern Italy were infected, severely disrupting normal medical operations and preventing patients with chronic illnesses from receiving necessary medical care (10).

Since conventional esophagogastroduodenoscopy (EGD) has been confirmed as a respiratory droplet-generating medical procedure (11), healthcare workers performing EGD during the COVID-19 pandemic are at risk of being exposed to patient infections during the examination (12). In response, international medical societies have developed guidelines recommending appropriate personal protective equipment (PPE) for endoscopists, pre-procedural COVID-19 screening, requirements for the endoscopic environment, and prioritization criteria for urgent versus elective endoscopic procedures during the pandemic (13-20). Elective and surveillance EGDs were often recommended to be postponed or deferred. During the pandemic in Taiwan, limitations in hospital bed availability, healthcare workforce shortages, and patient anxiety also led to the postponement or deferral of many routine endoscopic examinations. However, in patients with biliary atresia (BA), regular endoscopic surveillance and appropriate medical adjustment have been validated as crucial strategies to prevent unexpected esophageal variceal bleeding (21). Delaying routine endoscopic surveillance and medical interventions in BA patients may increase the risk of unexpected variceal bleeding and life-threatening events. In addition, during periods of severe COVID-19 outbreaks, patients often hesitated or declined routine medical examinations, further leading to disease progression and deterioration.

Therefore, how to balance the medical needs of patients with biliary atresia (BA) and ensure that they receive necessary endoscopic examinations during the pandemic, while protecting both patients and endoscopy personnel from COVID-19 infection to maintain the proper functioning of healthcare systems, has become an important medical issue. Magnetic-assisted capsule endoscopy (MACE) is a novel design that utilizes a disposable, externally magnetically controlled capsule connected by a tether to guide its movement through the gastrointestinal tract (22, 23). Previous studies conducted in Taiwan have already demonstrated the safety and diagnostic accuracy of MACE for upper gastrointestinal examinations (22, 23), while also avoiding the risks associated with anesthesia. Although MACE requires swallowing a tether, its invasiveness remains significantly lower than that of conventional endoscopy. Preliminary studies have shown favorable safety and patient acceptance (22, 23). During the examination, the patient swallows the capsule similarly to taking a pill, and can keep their lips closed and wear a mask throughout the procedure.

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This study aims to evaluate whether MACE can achieve diagnostic performance comparable to traditional EGD in detecting esophageal varices in BA patients, while reducing aerosol generation during the procedure, thereby protecting both patients and endoscopy personnel from the risk of SARS-CoV-2 infection.

VII.Reference

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VIII.Experiment Designs & Methods

(I.) Patient eligibility

A. Inclusion criteria:

(A.) Biliary atresia patients > 6 years old

(B.) Vital signs are stable

(C.) Without acute gastrointestinal bleeding

B. Exclusion Criteria:

(A.) Patients with metal implants, metal stent, artificial joints, bone plates, and bone screw

(B.) Patients with electronic devices, such as pacemakers, cochlear implants, or other

implanted electronic medical devices

(C.) Throat or esophageal obstruction leading to dysphagia patients

(D.) Consciousness disturbance patients unable to swallow

(E.) Patients with acute upper gastrointestinal bleeding

(F.)Patients with platelet lower than 40K or PT INR > 1.5

(II.)Design of experiments:

A.Study Design: Prospective open-label trial.

B. Trial Procedure:

(A.) Endoscopic Examination

In this study, 25 patients aged 6 years or older with biliary atresia undergoing Magnetic-Assisted Capsule Endoscopy (MACE) for esophageal varices survey will be enrolled as the "study group," while another 25 patients aged 6 years or older with biliary atresia undergoing conventional esophagogastroduodenoscopy (EGD) for esophageal varices survey will be enrolled as the "control group."Both groups will prospectively enter the study after providing informed consent and signing the consent form. All patients will fast appropriately according to endoscopic examination guidelines before the procedure.Patients undergoing conventional EGD may choose to receive conscious sedation based on clinical needs.Patients undergoing MACE will be advised to keep their lips closed and wear a surgical mask during the examination.We will compare clinical parameters between the two groups, including examination completion rate, pain perception during the procedure, safety, and willingness to undergo the same examination again in the future.

(B.) Droplet Particle Measurement

During examinations in both the "study group" and the "control group," we will use the MET ONE airborne particle counter [DR-528 Handheld Particle Counter (Met One Instruments, Inc., Grants Pass, OR)], placed on a platform at the same horizontal level as the patient lying flat, to simultaneously measure the number of droplet particles generated during the procedure.We will then compare the differences in droplet particle counts between the two groups.The primary endpoint of this study is to analyze the

difference in the number of droplet particles generated during the examinations between the "study group" and the "control group."The secondary endpoints are to analyze the examination completion rate, pain perception during the procedure, safety, and willingness to undergo the same examination again between the two groups.

(C.) Project Period: 11/01/2022-12/31/2026 (MM/DD/YYYY)

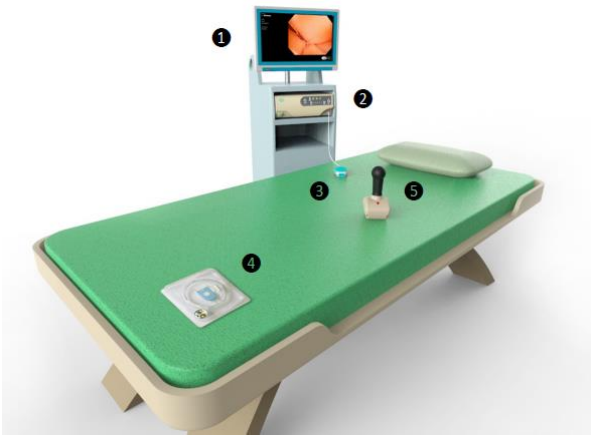
IX.Required Medications or Medical Equipment and Quantities

(I.) Magnetically Assisted Capsule Endoscopy (InsightEyes EGD): 50 sets

(II.) Aries E500i Image Processor (including power cable) / Aries E500i (Model: FG-270-0008, Quantity: 1)

(III.) InsightEyes Image Connector / InsightEyes EGD Dongle (Model: DG-001T, Quantity: 1): A connector that links the InsightEyes EGD to the image processor.

(IV.) InsightEyes MFN Magnetic Controller / InsightEyes MFN (Model: FG-270-0001, Quantity: 1): A magnetic device used to manipulate and adjust the positioning angle of the InsightEyes EGD.



Stationary equipment: ❷Arise E500i Image Processor ❶ Medical-grade monitor (not included in this product) ❸ InsightEyes Image Connector

Controller: ❺ InsightEyes MFN Magnetic Controller

Single-use medical devices: ❹InsightEyes EGD

The above equipment has been approved by the Taiwan Food and Drug Administration (TFDA) under Medical Device Permit No. 006509.

(V.) MET ONE airborne particle counter [DR-528 Handheld Particle Counter (Met One Instruments, Inc., Grants Pass, OR)]

X.Format of medical record forms: Study personnel will use separate case report forms (CRFs).

XI.Methods for Data Collection, Processing, Evaluation, and Statistical Analysis

(I.) Collect and record the enrolled patients' basic information (including sex, age, height, weight, past medical history, and medication history), vital signs, pain index, blood test results within the past three months, and transient elastography values.

(II.) Document the examination results of both the Magnetically Assisted Capsule Endoscopy (MACE) and conventional esophagogastroduodenoscopy (EGD), including the presence of esophageal varices and bleeding sites.

(III.) Record the patients' acceptance of the examination and any adverse effects.

(IV.) Record the particle count measurements obtained using the MET ONE Airborne Particle Counter [DR-528 Handheld Particle Counter (Met One Instruments, Inc., Grants Pass, OR)].

XII. Statistical Analysis and Sample Size Calculation

We will analyze the results using STATA (version 17) and MedCalc (version 20) statistical software. Continuous variables will be analyzed using the Student t-test or Mann-Whitney U test to assess differences between the "study group" and the "control group." Categorical variables will be analyzed using the Chi-square or Fisher's exact test. A p-value of <0.05 will be considered the threshold for statistical significance.For the sample size calculation, we assume that the study group will wear surgical masks for the examination, which have an approximate filtration efficiency of 87-90%. Based on a 95% confidence interval and a 5% margin of error, we estimate that enrolling 50 subjects (25 in the study group and 25 in the control group) will provide sufficient power to detect statistically significant results.

XIII. Adverse Reactions and Management

To date, there have been no reported adverse events associated with the InsightEyes EGD wired magnetically controlled capsule endoscopy. In the event that the patient experiences choking, suffocation, or other adverse reactions during capsule ingestion, the physician will immediately discontinue the examination and retrieve the capsule endoscope.

XIV. Principal Investigator and Co-Investigators' Academic and Professional Background, Publications, and Training

Please refer to the e-REC system for detailed information on the academic background, professional

experience, publications, and training of the research personnel.

XV. Responsibilities and Task List of Trial Personnel

Title	Name	Responsibilities and Scope of Work
PI, Attending Physician / Professor	Jia-Feng Wu	Study conception and execution, patient recruitment and assessment
Co-I, Attending Physician / Professor	Ping-Huei Tseng	Study conception and execution, patient recruitment and assessment
Co-I, Attending Physician / Lecturer	Chi-San Tai	Study conception and execution, patient recruitment and assessment

XVI.Subject Information and Informed Consent Form Format

Please refer to the e-REC system for the subject informed consent form.

XVII.Preclinical data

None.

XVIII.Potential Physical and Psychological Risks and Benefits

None.

XIX.Potential Financial Risks and Benefits

Each participant will receive a nutritional supplement allowance of NT$2,000.

XX.Conflict of Interest

None.

XXI.Ownership of Research Outcomes

The research outcomes will be jointly owned by the Principal Investigator and Insight Medical Solutions Co., Ltd.

XXII.Funding Source

This is an investigator-initiated study partially sponsored by the manufacturer.

XXIII.Other Information

None.

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Estimated Budget Table

Item	Amount (NTD)	Description
Participant Transportation Fees	100,000	Transportation reimbursement
Research Nurse / Assistant Fees	682,000	
Publication-Related Expenses	50,000	English editing and submission fees
Hospital Administrative Fee	30,000	
Total	862,000	