Clinical Trials of Medical Devices: Study Protocol

Name	EndoGel for endoscopic resection to treat early gastroenterological tumor and polyps
Medical Device	EndoGel
Specification	Gel-W Sodium Alginate 100mg (shortened to *Vials of white powder*) Gel-B Calcium Lactate 400mg (shortened to *Vials of blue power*)
Manufacturer	ITRI Active Pharmaceutical Ingredient Manufacturers/ Taiwan
Contract Giver	National Cheng Kung Hospital Project Investigator launched the clinical trials (IIT)
Code Number	July19th, 2017 Wei Shou Shi Zi No.1060013298
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Performed in accordance with *Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice* (ISO 14155-1, -2)	

Abstract

Endoscopic Submucosal Dissection (ESD) or endoscopic mucosal resection aims at dissecting mucosal lesions completely, which can only be applied in suitable appropriate patients and lesions. The standard operation procedure of ESD includes the following steps: marking of the lesions, repeated submucosal injections, lesion resections, repeated submucosal dissections and removal of lesions. Making use of various endoscopic devices will facilitate submucosal dissection of lesions swiftly and safely. Endoscopic mucosal resection is a similar procedure, involving submucosal injection of suitable solution; then, using snares to remove the lesions at one or several times piece by piece. In both situations, an ideal mucosal elevation can help doctors remove lesions effectively and safely without damaging the surrounding normal tissue. For these purposes, the solutions in the submucosa should be able to provide a thick submucosal fluid cushion, remain in the submucosal area long enough to allow the treatment procedures successfully completed, ESD or EMR, and to preserve the tissue specimen for pathological examinations.

Normal saline used to be the most widely-used solutions for submucosal injection. However, it can only sustain the submucosal cushion for a short period of time. To overcome the current limitations, more ideal solutions for submucosal injections are developed. Hyaluronic acid is now the most optimal solution for submucosal injection in Japan, but it is not covered by Health Insurance in many countries due to very expensive. As a result, we aim at developing a better solution for submucosal injection.

We produced a kind of new solution for submucosal injection, named EndoGel, a Class II medical device. This clinical trial aims at recruiting patients who are diagnosed with polypoid lesions in their esophagus, stomach or intestines. In these patients endoscopic dissection or endoscopic mucosal resection is considered the most appropriate treatment for them. In our clinical trial, we intend to inject EndoGel in the submucosal area of the targeted lesion in patients' esophagus, stomach or intestines to facilitate the performance of ESD. The purpose of this clinical trial is to

evaluate the safety and efficacy of using EndoGel in ESD and endoscopic dissection of superficial tumors.

I. Introduction

1.1 Background

The westernization of Asian diets has increased the incidence of polyps and early cancers of gastrointestinal tract in Taiwanese people. Accordingly, there is a sharp surge in the number of people who undergo regular health screenings. Also, the number of patients doing esophago-gastro-duodenoscopy (EGD), polypectomy resection and endoscopic submucosal dissection (ESD) increases remarkably. As evidences show that effective polypectomy in GI tract can prevent future cancer evolving from the previous polyps, the device to facilitate the preemptive technology is important, we invent our EndoGel for this purpose.

Normal saline is widely used as the solution for submucosal injection in endoscopic treatment. However, the fluid appears lost in the mists of time, and only maintains the submucosal cushion for a short period of time. The drawbacks make endoscopic surgeries more difficult, increasing the risks of harming deep mucosal tears while dissections. On the other hand, the loss of normal saline causes repeated injections and thus prolongs the time of endoscopic dissection. To overcome the current limitations, more ideal solutions for submucosal injection are developed. Hyaluronic acid is now the most optimal solution for submucosal injection, but it is not covered by Health Insurance and thus very expensive. As a result, it is not widely used by most countries around the world.

In the United States, methylcellulose being the primary material, a new solution for submucosal injections is invented. This solution is now approved to be a Class II medical device by FDA. But it is neither registered nor clinically-used in Taiwan due to its high cost and weak promotion. In the past, most doctors in Taiwan used normal saline with higher concentration (3%) or glucose solutions (20%, 30%, 50%) for submucosal injection. These solutions are easy to access and comparatively cheaper;

moreover, they remain in the submucosal area longer than normal saline does. However, inflammatory reactions usually occur at the spots where physicians inject these solutions. Consequently, most Taiwanese endoscopists now use Glycerol (10%) or Hyaluronic acid at patients' own expense as the solution for submucosal injection. But another problem rises; TFDA did not officially permit physicians to use these solutions in endoscopic surgeries. In other words, the cost of them is a grey area.

By contrast, our medical device, EndoGel, is composed of calcium lactate and sodium alginate, both of which have been widely used clinically in Taiwan. TFDA has approved the use of 0.3% alginate in 500ml for intravenous injection. As a result, sodium alginate is considered safe and applicable. Further, the Handbook of pharmaceutical excipient explicitly lists it as a GRAS substance, with LD50 (cat, IP): 0.25g/kg, LD50 (rabbit, IV): 0.1g/kg and LD50 (rat, IP): 0.25g/kg. Expectedly, we assume that the locally injected volume of alginate is below 50ml in single administration. If the patient is of 50 kg, the optimal dose of alginate for him/her is 0.01g/kg. Furthermore, alginate leaks from the wound after therapy.

Calcium lactate has also been used commonly in Taiwan for many years. It is used in the treatment of Hypocalcemia, Osteoporosis and Postmenopausal, and can be intravenously injected. Calcium lactate is also regarded as GRAS. Expectedly, we assume that the locally injected volume of alginate is below 50ml in single administration. If the patient is of 50 kg, the optimal dose of calcium lactate for him/her is 0.02g/kg.

After we mix sodium alginate and calcium lactate, the viscosity of the mixed solution increases due to cross-linking. Thus, the solution can create an optimal height of submucosal cushion with its high viscosity. The results of pre-clinical trials also manifested that the effect of this solution in submucosal elevation is equivalently good as that of Hyaluronic acid, and even better than that of Glycerol! Animal body ESD also showed the feasibility of this solution in submucosal elevation.

Consequently, we formally submitted an application for using this solution, named EndoGel, in submucosal injection; we also requested for the consent of TFDA

to conduct clinical trials for a class II medical device to investigate EndoGel. Besides, because *EndoGel* has been registered, we would change the name of the intervention as *AceGel* to prevent misunderstanding and other problems in the future.

1.2 Clinical Trial Guidance

This clinical trial is performed in accordance with *Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice* (ISO 14155-1, -2). Before we recruited the patients, we had sent all the documents such as proposals and clinical trial informed consents to IRB of National Cheng Kung University and TFDA, and consequently they have approved this case. Afterwards, we started to recruit patients with all the procedures in conformance with what has instructed in *Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice.*

During the recruitment process, IRB at National Cheng Kung University audited the relevant documents on August 31st, 2018, and provided us with instructions and suggestions.

II. Materials and Methods

2.1 Description of Medical Devices

EndoGel is a solution for submucosal injection. It can be used to lift gastric lesions when being injected into the submucosal areas during ESD or EMR. The submucosal cushions help endoscopists efficiently remove the lesions with electric probes or polypectomy snares, offering patients a less invasive option for gastrointestinal cancer treatment.

EndoGel is composed of calcium lactate and sodium alginate, both of which are considered “Generally recognized as safe” (GRAS). After mixing the two substances, the viscosity of the solution increases due to cross-linking. Hence, the solution can

serve as the submucosal injective solution used for treatments of early gastrointestinal cancer, and can effectively prevent surgical complications such as bleeding and perforation. Ideally, the suggested mixing ratio is 1:1, but ratios ranging from 0.5:1 to 2:1 can still successfully trigger gelation of the mixed solution. Besides, we dye calcium lactate blue to help endoscopists to mark the lesions to be removed. As a result, we suggest that the injection of Calcium lactate (the blue one) precedes the injection of Sodium alginate (the white one) during ESD or EMR. Or alternatively, endoscopists can use a double diameter syringe to inject the two solutions simultaneously to the targeted lesion.

During the trials, the physicians who performed ESD and EMR with EndoGel pointed out a pivotal drawback; they found that due to the repeated injections of EndoGel, the pressure in syringes was so high that the duration of surgery was extended. To overcome this problem, we adjusted the concentration and ratio of the components in EndoGel to create the desired proportion which meets the physicians' need. The adjustment is shown in the following table;

EndoGel After Adjustment	
Component	Volume
Sodium alginate	100mg
Calcium lactate	400mg
EndoGel is a product used for endoscopic therapy. We suggest that physicians inject calcium lactate (the vial with blue powder) first and sodium alginate (the vial with white powder) later.	
How to dilute sodium alginate: First, infuse the sodium alginate powder with 10-20mL sterile water or normal saline. Second, shake the vial for 30 to 60 seconds until the solution is clear without floating particles on the surface. Afterwards, draw the solution to fill a 3mL syringe with a needle. The purpose of using a 3mL syringe is to reduce the resistance while injecting.	

How to dilute calcium lactate: First, infuse the calcium lactate powder with 10-20mL sterile water or normal saline. Second, shake the vial well and draw the solution out with a 10mL syringe with a needle.
How to use EndoGel: Fill the endoscopic aspiration syringes with calcium lactate and sodium alginate, and inject them respectively to the submucosal area of targeted lesions. Before injecting the second solution, fill the syringe with sterile water or normal saline to wash the residue solution within it away. If not, the remnant of calcium lactate is likely to become gel which obstructs the syringe when mixing with alginate.

2.2 Abstract of the clinical trial

Endoscopic Submucosal Dissection (ESD) is an endoscopic technique which aims at dissecting mucosal lesions completely. Speaking of ESD, it is of importance to select the appropriate patients and lesions. The standard operation procedure includes the following steps: marking of the lesions, repeated submucosal injections, lesion resections, repeated submucosal dissections and removal of lesions. Making use of various endoscopic devices will facilitate submucosal dissection of lesions swiftly and safely. Furthermore, an ideal mucosal elevation can also help doctors dissect lesions effectively. A suitable solution for submucosal injection can provide a thick submucosal fluid cushion, remain in the submucosal area long enough to securely allow ESD and preserve the tissue specimen which allows for pathological examinations.

Normal saline used to be one of the most widely-used solutions for submucosal injection. However, it can only maintain the submucosal cushion for a short period of time. To overcome the current limitations, more ideal solutions for submucosal injections are developed. Hyaluronic acid is now the most optimal solution for submucosal injection, but it is not covered by Health Insurance and thus very

expensive. As a result, our project aims at developing a better solution for submucosal injection.

Our project produced a kind of new solution for submucosal injection, named EndoGel. We have conducted in vitro and in vivo assays of pigs with EndoGel. The results showed no serious complications occurring to the pigs in vivo.

2.2.1 Goal of the clinical trial

The primary goal of this clinical trial is to evaluate the safety and efficacy of using EndoGel in ESD and endoscopic dissection of superficial tumors clinically.

2.2.2 Design of the clinical trial

2.2.2.1 Experiment design

We aim at recruiting 12 patients who are diagnosed with gastrointestinal superficial tumors to conduct clinical trial therapies. EndoGel is the solution used for submucosal injection for all candidates. The usage of EndoGel is listed below;

1. Infuse 10-20mL normal saline into the vial with blue powder of calcium lactate. Shake the vial well and then draw the solution out with a 10mL syringe with a needle.
2. Infuse 10-20mL normal saline into the vial with white powder of sodium alginate. Shake the vial well until no floating particles can be seen on the surface. Draw the solution out with a 3 mL syringe with a needle. Mix the two solutions in conformance with the suggested mixing ratios given in **section 2.1**.
3. Fill the endoscopic aspiration syringes with calcium lactate and sodium alginate, and inject them respectively to the submucosa beneath targeted

lesions. Before injecting the second solution, fill the syringe with sterile water or normal saline to wash the residue solution within it away. If not, the remnant of calcium lactate is likely to become gel which obstructs the syringe when mixing with alginate.

4. After mixing the two substances, the viscosity of the solution increases due to cross-linking. EndoGel will create a submucosal cushion with an optimal height. Remove the lesions with electric probes or polypectomy snares by dissecting the elevated cushion.

The administered dose and injection times of EndoGel can be determined based on the size of lesions and the height of submucosal cushions. Physicians will perform the endoscopy surgery in endo rooms or operation rooms after clinical assessment. The standard operation procedure includes the following steps;

Endoscopic submucosal dissection (ESD):

(1). Mark the perimeter of the lesion with cautery.

(2). Inject the lifting agent to the submucosa around the perimeter of the lesion. In this trial, the lifting agent is the mixed solution of alginate and calcium lactate.

(3). Incise the elevated submucosa and circumferentially cut the perimeter of the lesion with an electrosurgical knife.

(4). Dissect the submucosa beneath the lesion by an electrosurgical knife until the lesion is completely resected.

(5). Manage any complications such as intraprocedural bleedings and perforations.

(6). Make sure there is no bleedings or perforations after the dissection of lesions. If so, do the appropriate management. If not, ESD is officially completed.

Endoscopic mucosal resection (EMR):

(1). Formulate a resection strategy. Make sure the lesions could be successfully removed via snare excision.

(2). Inject the lifting agent to the submucosa around the lesion. In this trial, the lifting agent is the mixed solution of alginate and calcium lactate.

(3). Use polypectomy snares to excise the lesions.

(4). Manage any complications such as intraprocedural bleedings and perforations.

After the therapy, we will monitor the vital signs of the patients in wards or endo rooms. We carry out the medical observation in order to react promptly to any immediate adverse events occurring to the patients, such as delayed bleedings and perforations. We will also conduct long term follow-up hematology tests to monitor the GOT and GPT of the patients.

2.2.2.2 Indicator of end point

1. Complete resection rate of the gastrointestinal superficial tumors.
2. Follow-ups of wound-healing conditions. Evaluate whether the lifting agent causes any local tissue damage.
3. The incidence of complication is lower than 5% within one month.

2.2.3 Ethical considerations

Patients' willingness to participate in clinical trials is respected. They have the freedom to decide whether they want to join the trials or not. They are also entitled to withdraw the clinical trial agreement at any time during the trial with no specific reasons. In addition, physicians won't be unpleasant and biased against the patients. Moreover, the project investigator and sponsors also have the right to terminate the clinical trials.

2.2.4 Data quality assurance

Physicians will try their best to avoid anti-information drugs such as NSAID, which will mislead the interpretation of treatment effects on those who join this clinical trial during observation period.

2.2.5 Patient Population

2.2.5.1 Inclusion/exclusion criteria

The inclusion criteria:

A. patients over 20 years old
B. patients who are diagnosed with superficial tumors or polyps via endoscopy
C. patients with tumor/polyp size over 10mm
D. patients who never undergo endoscopic therapy before
E. patients with the polyps of no deep submucosal invasion or metastasis

The exclusion criteria:

A. patients with other advanced malignant neoplasm
B. patients with low white blood cell count (WBC<2,000μL), or patients with low platelet count (platelet count < 50,000/μL) or abnormal blood coagulation
C. patients who are currently using anticoagulant and can't stop using the drug

D. patients whose major organ dysfunction and thus being considered inappropriate to participate the trial

E. patients who are diagnosed with deep submucosal invasion or metastasis

F. patients who fail to do follow-up endoscopy evaluations

G. patients who are allergic to the compositions of our product (sodium alginate or calcium lactate)

H. patients who don't sign the consent form of participation of this trial

2.2.5.2 Sample size

Period: from the time when IRB approved this trial to December, 2018

12 patients will be recruited.

2.2.6 Clinical management and settings of clinical treatments

After the preparation and patient evaluation for a safe endoscopy, endoscopists will decide to perform ESD or EMR on the patients in accordance with their health condition. During the surgery, the administered dose of EndoGel can be determined based on the size of lesions and the height of submucosal cushions.

After the therapy, we will monitor the vital signs of the patients in wards or endo rooms. We carry out the medical observation in order to react promptly to any immediate adverse events occurring to the patients, such as delayed bleedings and perforations. We will also conduct long term follow-up hematology tests to monitor the GOT and GPT of the patients. Patients can leave hospital in 7 days if they are well recovered. They should also do follow-up examinations to see if there are any complications or adverse events.

All patients will receive the endoscopic follow-up examinations 4 weeks after the endoscopic surgery to evaluate the wound-healing conditions and to check if there is

local recurrence. Patients should go back to the outpatient clinic to do follow-up examinations after the first week and the sixth week.

2.2.7 Variance of this trial

Compared to the traditional endoscopy without using EndoGel, use of EndoGel in endoscopy can still risk complications such as bleedings and perforations. Generally, we can stop bleeding by using hemostatic clips to close perforation. A few serious cases may need the help of interventional radiological or surgical physicians. Physicians should also pay attention to the potential complications in the follow-up examinations.

Within the recommended dose of this product, it is still likely to cause allergies; however, no other serious side effects are known.

2.2.8 Drug therapy/ Clinical management

Patients will get preventative antibiotics before the endoscopy. If there is any complication such as perforation happening during endoscopy, physicians will stop bleeding by using hemostatic clips to close perforation. Patients are not allowed to eat for several days and will be given antibiotics and intravenous parental nutrition after endoscopy. They are fasted until they don't have abdominal pain or fever. Further, if they don't have any abnormal symptoms after eating, they can bring oral antibiotics home. On the other hand, if bleeding occurs during the treatment, endoscopic hemostats and hemostatic clips will be used to stop bleeding; if there is delayed bleeding, blood transfusion therapy, endoscopic hemostasis, transarterial embolization, or surgical intervention may be used depending on the severity.

Endoscopic resection of the specimen will be sent to the pathological examination; if a cancer is discovered, physicians will decide whether the patient should undergo additional surgeries based on the relevant pathological features (such as tumor clearance, cell differentiation, submucosal invasion, and lymphatic invasion).

A Follow-up examination will be arranged 4 weeks after surgery. The examination will assess the condition of wound healing to see if there is any residual polyp tissue at the wound or other places. If so, it will be removed and sent for testing.

2.2.9 Subsequent observation care

Patients will come back to the outpatient clinic after the first week of surgery to see if there is any side effect. They will also do the follow-up endoscopy within 4 weeks to check the wound-healing conditions and if there is any local recurrence. After the 6^{th} week, patients will return again for their check-up.

2.2.10 Statistical analysis

2.2.10.1 Hypotheses

This trial is designed to be a single-armed and non-contrast experiment. We aim to evaluate the safety of EnodGel in the clinical use.

2.2.10.2 Sample size

The purpose of the study is not to compare this new treatment with traditional ones, and thus there is no statistical test to calculate the appropriate number of samples as in the case of general clinical trials. Instead, a small number of samples have been evaluated to test the safety, which is like what researchers do in Phase I Study. Therefore, we recruited 12 patients in total.

2.2.10.3 Methods for statistical analyses

Descriptive statistics are used to analyze the data in this study.