

Lumevis™: a new medical device to prepare patients for esophagogastroduodenoscopy. Experimental clinical study

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Abstract

Background. Esophagogastroduodenoscopy (EGDS) is the gold standard exam for upper gastrointestinal diseases. EGDS is very important in Early Gastric Cancer diagnosis and treatment but it is an operator-dependent exam and there are lots of factors that reduce its visibility (mucus, bubbles and foam).

Aim. The aim of our study is to evaluate if the use of Lumevis™ improves mucosa visualization during EGDS without increasing the examination time and complications' rate and comparing the differences in patients prepared with water or no intervention.

Materials and methods. we recruited 50 patients from 01/08/2020 to 31/08/2020 who came to our observation for epigastric pain, dyspepsia and gastroesophageal reflux (GERD). For each patient we evaluate the satisfaction of the procedure, vision quality, EGDS duration and the presence of bubbles following the administration of: nothing (group 1); 50 ml of water alone (W) (group 2); W + simethicone (S) 150 mg+N-acetylcysteine (NAC) 250 mg+10% acetic acid 2.5 ml (group 3); W+S 100 mg + NAC 300 mg + 10% acetic acid 2 ml (group 4); W + S 100 mg + NAC 200 mg + 10% acetic acid 1.5 ml (group 5).

Results. Our results suggest that the lesion detection rate improves with the use of simethicone, acetylcysteine and acetic acid prior to EGDS, although this needs to be studied prospectively.

Conclusions. Lumevis™ is proposed as a new product in the routine preparation of all patients who have to undergo an EGDS, raising the level in the quality of the exam. *Clin Ter 2021; 172 (1):e16-22. doi: 10.7417/CT.2021.2275*

Key words: esophagogastroduodenoscopy, early gastric cancer, simethicone, N-acetylcysteine, acetic acid, whitening effect, endoscopic visibility

Background

One of the major problems for the endoscopist during esophagogastroduodenoscopy (EGDS) is the presence of foam, bubbles, mucus and saliva, whether small or large, which can compromise correct endoscopic visibility, forcing in some cases the interruption examination and its repetition. This physiological condition of the gastric tract can hide any small lesions, compromising the validity of the diagnosis or

making the endoscopic evaluation of the resection margins of a lesion more complex.

In such cases there is the likelihood of underestimating the patient's real pathological condition (missed lesions), with repercussions in terms of oncological radicality and quality of life. For this reason, very often, when the presence of foam, bubbles / gas, mucus is found during EGDS, the operator carries out pressure washing of the gastric mucosa through the accessory channel of the instrument using a peristaltic pump (1,2).

Endoscopy of the upper gastrointestinal tract, like that of the lower gastrointestinal tract, requires optimal visualization of the mucosa. It is clear that endoscopic vision is often hindered by the presence of bubbles and foam: multiple aspirations alternating with intraprocedural washes are therefore necessary, which lengthen the time necessary for the endoscopic examination, exposing the patient to aspiration pneumonia. Simethicone (S) is often used to improve visibility during endoscopy and has been suggested by some clinical studies (3), just as N-acetylcysteine (NAC) is a long-known mucolytic substance (4-9).

The aim of our study is to determine whether the use of simethicone premedication in combination with N-acetylcysteine and acetic acid (Lumevis™) improves visualization of the mucosa during an upper gastrointestinal endoscopy without increasing the examination time and without increasing the incidence of complications during the procedure and comparing the differences in visualization of the gastric mucosa in patients prepared with simethicone + NAC + acetic acid at 10% or no intervention.

Materials and methods

For our study, duly authorized by the Palermo I Ethics Committee, conducted at the Digestive Endoscopy Outpatient Department of the University Hospital "P. Giaccone" in Palermo, we recruited, from 01/08/2020 to 31/08/2020, 50 patients who came to our observation for epigastric pain, dyspepsia and gastroesophageal reflux (GERD). Each patient underwent diagnostic EGDS and the satisfaction of

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the procedure, vision quality, duration of the examination and the presence of bubbles were evaluated following the administration of: 50 ml of water alone (W) (group 2); W + simethicone (S) 150 mg + NAC (S) 250 mg + 10% acetic acid 2.5 ml (group 3); W + simethicone 100 mg + NAC (S) 300 mg + 10% acetic acid 2 ml (group 4); W + simethicone (S) 100 mg + NAC (S) 200 mg + 10% acetic acid 1.5 ml (group 5). For the first (control) group, the procedures were performed without resorting to any solution (group 1). Table 1 shows the clinical-demographic characteristics of the enrolled patients.

Patients <18 years of age, pregnant women, elderly over 65 years, patients with cystic fibrosis were excluded from the study. The study was carried out in double blind, as the

patients, auxiliary staff, endoscopist, nurses and data collectors were not informed about the contents of the bottle. For this purpose, all liquid solutions were prepared in opaque containers of similar appearance. Participants received the assigned solution 30 minutes prior to the procedure under the supervision of a physician. All patients, after having signed regular informed consent, received standard recommendations before the procedure: at least 8 hours of liquid and solid fasting and 72 hours of suspension of anti-secretory drugs. Local pharyngeal anesthetic solution was used immediately prior to the procedure. Endoscopic visibility was assessed in 4 districts (esophagus, gastric body, fundus and antrum) using a visual scale (4), grading from 1 to 4 points (Fig. 1): 1. no adherent mucus on the examined mucosa; 2. a small



Fig. 1. Degrees of visibility of the mucosa from conventional endoscopy. A: No sticky mucus; B: delicate mucus that does not obscure the view; C: A large amount of mucus that obscures vision and requires <30 mL of water to clear; D: Heavy adherent mucus that requires > 30ml of water for cleaning

Table 1. Clinical-demographic characteristics of the patients enrolled for the study

	Group 1 (no prep)	Group 2 (water 50 ml)	Group 3 (S 150 mg + NAC 250 mg + AA 10% 2.5ml)	Group 4 (S 100 mg + NAC 300 mg + AA 10% 2 ml)	Group 5 (S 100 mg + NAC 200 mg + AA 10% 1.5ml)
Number	10	10	10	10	10
Mean age (years)	45.3 ± 8.7	46.1 ± 7.9	44.9 ± 7.5	48.3 ± 6.8	45.3 ± 8.7
M:F ratio	1.4:1	1.5:1	1:1	1:1	1.5:1
Dyspepsia	50%	60%	80%	60%	80%
Epigastric pain	90%	80%	90%	90%	80%
GERD	60%	70%	60%	80%	50%
PPI	100%	90%	100%	100%	90%
Prokinetics	50%	60%	40%	50%	40%

amount of mucus on the mucosa that does not obstruct vision; 3. a large amount of mucus on the mucosa, which can be thoroughly washed with less than 50ml of water; 4. a large amount of mucus, which cannot be completely cleaned with up to 50 mL of water, and would require more water for flushing.

Results

The results were evaluated based on the patient's satisfaction, the quality of vision, the duration of the examination, the presence of bubbles, the detection of esophagitis, gastritis or duodenitis, and above all the identification of lesions <5 mm. We observed how compared to group 1 that took no preparation (Fig. 2), groups 3, 4 and 5 (prepared with oral intake of simethicone, NAC and acetic acid) had better

quality of vision, going from a value of 4/10 of group 1 to 9/10 of group 5. The percentage of lesions <5mm identified was equal to 0 in group 1 and also in group 2 (which took only water), on the contrary the patients of groups 4 and 5 endoscopists found lesions in the 20% of cases. In particular, a reduction in the duration of the exam was noted between group 1 and group 5, going from 6 minutes in group 1 to 5 minutes in group 5. No adverse reactions due to the procedure were detected during the study. No allergic reactions or aspirations of the upper respiratory tract were observed. There were no cardiovascular or endoscopic adverse events in patients during the study period from study drug administration to at least 120 minutes after completion of the UGE procedure. No late adverse reactions were reported. Results are reported in Table 2. From the data in the table and from Fig. 3-4 it can be seen how the use of the solution with 100 mg of simethicone and a quantity of NAC between 200 mg

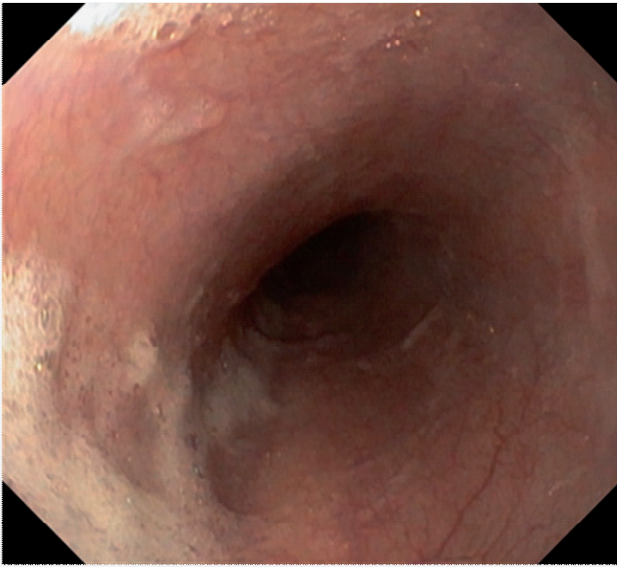


Fig. 2. Appearance of the mucosa without pre-endoscopic oral preparation

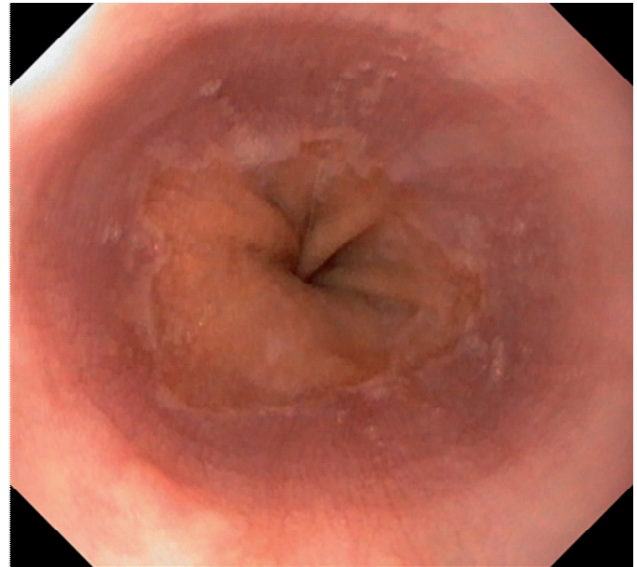


Fig. 3. Mucosa in patients who took Lumevis™ orally during pre-endoscopy preparation



Fig. 4. Another patient, on the left evident residues of mucus and bubbles in the untreated patient, on the right clear visibility of the mucosa in the same patient treated with Lumevis™

Table 2. Results

	Group 1 (no prep)	Group 2 (water 50 ml)	Group 3 (S 150 mg + NAC 250 mg + AA at 10% 2.5ml)	Group 4 (S 100 mg + NAC 300 mg) + AA at 10% 2 ml)	Group 5 (S 100 mg + NAC 200 mg) + AA at 10% 1.5ml)
Patient satisfaction	Not applicable	8/10	8/10	9/10	8/10
Vision quality	4/10	5/10	9/10	9/10	9/10
Exam duration (min)	6 ± 3	6 ± 4	6 ± 2	6 ± 2	5 ± 1
Bubbles	+++	++-	+-	Absent	Absent
Esofagitis	30%	40%	40%	30%	30%
Gastritis	60%	30%	20%	40%	40%
Duodenitis	20%	20%	30%	30%	30%
Lesions < 5 mm	0	0	30%	20%	20%

and 300 mg effectively favours vision during the endoscopic procedure, reducing the number of bubbles and ultimately the duration of the examination, and increasing the number of lesions < 5 mm diagnosed.

Discussion

Every year, over 1.7 million EGDS are carried out in Italy, practically about 30 per thousand inhabitants: EGDS is the most common method for the diagnosis and treatment of diseases of the upper gastrointestinal tract, also offering a unique opportunity to identify early neoplastic lesions. The improved technologies today have made it possible to operate such lesions by means of mucoresection and submucosal resection. A necessary prerequisite for such techniques is early diagnosis. It has been seen that the experience of the performer and the sharpness of the image have the greatest influence in the diagnosis of injuries in the early stages. Before an EGDS, a fasting period of 6 hours is classically indicated (10). However, even with this period of fasting, sometimes the visualization of the mucosa, especially in the stomach, is impaired by gastric mucus. In addition, the salivary glands inside the mouth produce, under normal conditions, about 1-2 liters of saliva per day, which, swallowed in the stomach, appears as a dense and whitish foam, which can hide any subcentimetric gastric lesions and/or duodenals otherwise clearly visible during endoscopic examination. To overcome this problem, in addition to continuous aspiration, the use of water and simethicone-based washes is widely used in clinical practice, carried out through the operating channels of the endoscope. However, this technique proved to be harmful both for the patient, increasing the risk of infections, and for the instruments themselves, residing simethicone crystals in the accessory channels. Furthermore, the timing will be longer and there will also be the risk of causing both gastric distension and aspiration of this liquid due to the reduction of the bronchial esophagus reflex and the high levels of liquid used in the washing. Since early cancer diagnosis has a major impact on its potential curability, mass screening programs have been implemented in Japan for some time. Although the true effect of this approach on mortality is poorly defined, some studies conducted in

Japan favor endoscopic mass screening, particularly with the advent of new minimally invasive procedures such as endoscopic mucosal resection for tumors detected in the early stages (11,12).

In Japan, about 50% of cancers are diagnosed early. In the United States early diagnosis is possible in 5-10% of patients (13). Vague symptoms of the upper gastrointestinal system may be present 6-12 months before the diagnosis of early gastric cancer (EGC), or may not be present at all. In Japan the presence of this vague symptomatology is often investigated further through endoscopic and factual investigations, the 5-year survival for gastric cancer is 10% in Western countries and 50% in Japan (14). In East Asia, many patients are now diagnosed while still asymptomatic thanks to the screening program that has been running since 1960. Early Gastric Cancer detection has recently increased in Korea and Japan. This is thanks to screening by means of optical fiber gastroscopy and other investigations of the upper gastrointestinal tract. It is assumed that this is the main proponent of the decrease in mortality trends. The "missed diagnosis" is configured as an erroneous presumption of health with respect to the diagnostic outcome. Failure to diagnose esophageal and/or gastric cancer after EGDS is well documented, with studies reporting rates ranging from 4% to 13% (15). Negative initial endoscopy is a relatively common occurrence among patients who have subsequently developed carcinoma (16). 11.3% of tumors of the upper intestinal tract (UGI) were lost on endoscopy in the 3 years prior to diagnosis (17). In a meta-analysis published in Endoscopy International Open 2014 (02: E46-E50) the two Anglo-Saxon gastroenterologists Shyam Menon and Nigel Trudgill, saw how out of ten studies including 3,787 patients in Japan, United Kingdom, Finland and Australia, fail a diagnosis or do not detect Upper gastrointestinal neoplasm (UGI) was a common occurrence, occurring approximately 7% of the time at one year at diagnosis, and up to approximately 12% of the time at 3 years prior to diagnosis (18). The general prognosis of gastric cancer is generally poor due to late presentation and diagnosis. If diagnosed early, the prognosis of gastric cancer is excellent and curative endoscopic resection may be possible without the need for surgery (19). The sharpness of the field of observation during EGDS is therefore very important both in the diagnostic screening

phase and in the therapeutic phase. For this reason, very often, when the presence of foam, bubbles / gas, mucus is found during the EGDS, the operator performs a washing of the gastric tract using the peristaltic pump through the accessory channel of the instrument. This wash-out procedure with aqueous solution under pressure (waterjet), however, does not allow a complete cleaning of the gastric tract, with consequent accumulation of liquid that must be aspirated and with inevitable lengthening of operating times. The addition of anti-foam and / or anti-mucus additives in the washing liquids (20) over time can alter the functionality of the endoscope washing channels due to any deposits that cannot be removed and, even worse, make sterilization ineffective (21). The American Journal of Infection Control reports a study on simethicone residues inside the endoscopes despite the treatment (22). During this study designed to evaluate the effectiveness of endoscope reprocessing, a borescope was used to examine the lumen and ports of the same endoscope (23). Inside, a viscous, white residual fluid was observed. This fluid is simethicone. Simethicone solutions commonly contain sugars and thickeners, they can contribute to microbial growth and biofilm development. The researchers observed that after reconditioning, more fluid droplets remained inside the ports and channels. Tests in infrared spectroscopy found that the viscous, white, opaque fluid observed in patient-ready reprocessed gastrointestinal endoscopes had properties compatible with simethicone-based products. Elements included in simethicone are carbohydrates and other substances that could support microbial growth and biofilm development (24). In the Journal of Gastroenterology and Hepatology, Dr. Chang et al. have seen how taking simethicone orally before EGDS is more convenient than using it via endoscopic flow; as regards costs, patient compliance and patient preparation, premedication with 100 mg of simethicone diluted in 100 ml of water before the EGDS is suggested. Adding NAC to the simethicone suspension in 100 ml of water reduces the need for endoscopic washings. In patients who are unable to take large amounts of fluid, good mucosal visibility can be achieved with a 5 ml suspension of simethicone given 30 minutes before gastroscopy (25). To improve the visualization of the gastric mucosa, a valid alternative to washing during the examination is therefore to administer an oral solution of antifoam and mucolytic agents prior to endoscopy. N-Acetylcysteine - classically defined NAC or more simply Acetylcysteine - is the N-Acetyl derivative of the more common amino acid L-Cysteine, with mucolytic action. The mucolytic activity of acetylcysteine is probably due to its ability to split disulfide bridges (-SS-) typical of many cyclic proteins present in mucus (mucoproteins). It has also been hypothesized that NAC inhibiting sodium absorption make the secretions of the lumen more hydrated and therefore fluid (26). The most frequently observed adverse reactions following the use of N-Acetylcysteine are: nausea, vomiting, diarrhea, migraine and skin rash (27). The use of N-Acetylcysteine is contraindicated in patients with cystinuria or with known hypersensitivity to the active substance or to structurally related active substances (28). There are no medical contraindications for pregnant or breastfeeding women, but in these cases it will be recommended based on the doctor's discretion.

The use of acetic acid (AA) in the digestive tract was first reported in 1998 by Guelrud and Herrera, to help identify small islets of Barrett's epithelium following ablative therapy. The technique has been used in gynecology since 1993 in which acetic acid was used on the cervix to highlight dysplastic areas during screening for cervical intraepithelial neoplasia (29). The use of acetic acid in the medical field is very ancient and varied, recognizing in particular its antifungal and generally local antiseptic role. From a search on PubMed, 22659 articles are found from 1925 to today. If its use is restricted to the most recent chromoendoscopy in the screening of esophagus-gastric precancerous diseases which is carried out only in a few centers, since 1998 only 31 scientific articles have been published on PubMed. AA is a weak acid (pH 2.5) taken diluted orally and has a first contact cleansing effect, helping to eliminate the surface layer of mucus by breaking the disulfide bonds of the glycoproteins. Secondly, it produces a reversible and short-term denaturation of the intracellular proteins of the cytoplasm which, by making the cytoplasmic fluid opaque, gives rise to the so-called whitening vinegar effect. This phenomenon, still unclear, is therefore characterized by an increase in the opacity of the mucosal surface with masking of the submucosal capillaries responsible for the characteristic rosy color of the mucous membranes. Upon reaching the stromal capillaries, the AA causes vascular congestion, leading to focal erythema but this is barely visible due to the overlying opaque mucosa (whitening vinegar effect). This focal redness becomes visible after the temporary whitening effect disappears and was first described by Longcroft-Wheaton as a strong predictor of neoplastic transformation. The exact mechanism remains unclear but it is believed that the difference in aceto-bleaching reaction between non-neoplastic and neoplastic mucosa is due to the difference in the nucleocytoplasmic ratio between non-neoplastic and neoplastic cells. The low cytoplasmic content of neoplastic cells allows them to lose the aceto-whitening effect more quickly than non-neoplastic cells with the appearance of focal lesions typical of neoplastic transformations. The novelty of the new medical product unique in the world lies in the fact that it collects together the three constituents mentioned above (simethicone, N-acetylcysteine and acetic acid) in a syrup with a pleasant taste that, administered half an hour before the EGDS, cleans the stomach of saliva residues, foamy, gas and mucus bubbles that reduce visual acuity during the examination. In addition, acetic acid, in addition to cleansing the stomach of mucus by breaking the disulfide bridges of glycoproteins, greatly enhancing the action of N-Acetylcysteine also gives rise to the whitening effect on the mucosa which makes dysplastic areas in Barrett's disease more evident. In endoscopy, simethicone aspirated from a bottle is generally diluted "empirically" in a container of water and injected into the patient's stomach through the endoscopic water channels or again, injected directly through the endoscopic port by means of a syringe. In 2018, the Journal of the Canadian Association of Gastroenterology published a statement on the impact of Simethicone in endoscopic investigations, prepared by doctors Amine Benmassaoud and Josée Parent (30). It is established that although not routinely used in clinical practice as a preparation for upper or lower endoscopic procedures, simethicone is frequently mixed in

the water pump to disperse the remaining bubbles during the examination. This makes it a ubiquitous product in an endoscopy unit (30). Unfortunately, it has been noted that simethicone residues, sedimented in the accessory channels of endoscopes, can potentially contribute to the formation of biofilms and lead to microbial growth. Biofilm formation is an important factor in microbial colonization and has been implicated in the outbreak of post ERCP bacteremia (31). The residual simethicone crystals can only be viewed through inspection, and not during a regular checkup, using a borescope (32). The elimination of crystals is only possible through mechanical cleaning after the connector has been removed and the channel has been opened (33). In 2018 Olympus issued a statement to suppliers, acknowledging that simethicone-based products may be difficult to remove from endoscopes when used in high concentrations despite strict adherence to reprocessing instructions. Olympus therefore recommended that if simethicone is needed, it should be used at the lowest possible concentration to achieve the desired effect or given purely orally during preparation.

Conclusions

Considering that to date stomach cancer is the second cause of mortality from malignant neoplasia, it is necessary to maximize efforts to identify suspected lesions of malignant progression. To this end, secondary surveillance programs such as endoscopic screening are useful as they allow for prompt action. To improve the diagnostic (through the correct identification of early lesions) and therapeutic (in the case of EGC) outcome, it will be appropriate to use all the precautions to improve the vision of the lumen and beyond. Our study has some obvious limitations: we cannot compare endoscopic visibility measurements for each patient before premedication to evaluate the impact of individual preparations (only 2 subjects, excluded from the study, underwent 2 upper endoscopies, one before and one after administration of the solution: the results, although not statistically significant, suggest a better visualization of the mucosa after the oral administration of simethicone, acetylcysteine and acetic acid. Our results suggest that the lesion detection rate improves with the use of simethicone, acetylcysteine and acetic acid prior to EGDS, although this needs to be studied prospectively. Our results also show that the oral use of simethicone, acetylcysteine and acetic acid before EGDS improves the visibility of the mucosa and reduces the need for water to almost zero, which can

increase the diagnostic yield of EGDS. In light of all this, the results obtained and the deep-rooted and extensive literature were inspired to try to create a medical device that can be administered exclusively orally before the EGDS called Lumevis™ which simultaneously contained the products promoting mucolysis (NAC and Ac Acetic) and salivary fluidization (simethicone) therefore capable of improving visibility during endoscopy. To this effect is added the aforementioned vinegar-whitening effect which helps to reveal precancerous gastric esophagus. The combination of simethicone, N-acetylcysteine and acetic acid allows, according to the well-known pharmacological principle, to reduce the dose of each component (enhancing effect), and to work synergistically to improve the diagnostic sensitivity of EGDS. Table 3 describes all the advantages on its use. Lumevis™ is proposed as a new product, which will lead to a Copernican revolution consisting in the routine preparation of all patients who have to undergo an EGDS, raising the level in the quality of the exam.

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Table 3. Potential advantages with the preparation of the patient through the intake of 50 ml of oral solution containing simethicone, N-Acetylcysteine and 10% acetic acid

Absence of washing with reduction of aspiration pneumonia
Faster and more accurate tests
Improved screening for precancerous lesions of the esophagus-gastric joint and stomach
Improvements in patients' health and quality of life
Savings on the SSN
Improvement of instrument sterilization with reduction of transmitted infections
Durable instrument efficiency

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