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ORIGINAL ARTICLE

Preclinical evaluation of a novel thermally sensitive co-polymer (LiftUp) for endoscopic resection

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ABSTRACT

Introduction: Endoscopic resection techniques can successfully resect large lesions either in "en bloc" fashion or in "piece-meal" technique by using a submucosal injection solution. The aim of this study was to evaluate the safety of a novel injectable, containing thermally sensitive co-polymer from ethylenoxide and propylenoxide (LiftUp) used as submucosal injection solution.
Material and methods: We conducted an *in vivo* animal trial in the porcine model to evaluate the LiftUp gel in a preclinical setting and to study the effectiveness of mucosal lifting and the safety of the new injectable. In seven animals a total of 63 injections and endoscopic resections were carried out in different anatomical locations (esophagus, stomach and rectum). The resection sites were controlled endoscopically one and four weeks after resection and a histopathological evaluation of the resection sites was performed after four weeks.
Results: The application of LiftUp was safe and there were no negative effects on wound healing after injection and resection. A major procedural complication rate (defined as perforation and major haemorrhage) of 3.2% was registered, which undercuts the anticipated mean complication rate of 4–8%. Furthermore, there was no necessity of reinjection after the initial submucosal injection in 90.5% and no procedural complications in 98.8%. The histopathological examination of the tissue samples indicated normal wound healing with granulation tissue and epithelialisation.
Conclusion: The use of LiftUp as submucosal injection solution was feasible for different endoscopic resection techniques, with high and long-lasting elevation and fewer procedural adverse events than expected at trial planning. The new injectable is a practical advancement over the current state-of-the-art of submucosal injection and could fasten up the resection procedure and make endoscopic 'en bloc' resection safer.

Abbreviations: EMR: endoscopic mucosal resection; EU: European Union; ESD: endoscopic submuocsal dissection; ESGE: European Society of Gastrointestinal Endoscopy; HF: high frequency; ISGC: injectable submucosal gel cushion; OTSC: over-the-scope-clip

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ISGC; injectable submucosal gel cushion; LiftUp; endoscopic mucosal resection; endoscopic submucosal dissection; co-polymer; ESD; EMR; h-ESD; EMR+; feasibility study

Introduction

Endoscopic submucosal dissection (ESD) and endoscopic mucosa resection (EMR) are established minimally invasive techniques for dysplastic lesions and early gastrointestinal neoplasia [1,2]. Common adverse events of these two techniques are perforation and bleeding [3]. In these procedures an agent is injected into the submucosa, thereby creating a liquid-filled cushion. Thus, the overlaying tissue is lifted and the submucosal space widened for resection, protecting the underlying muscular layer.

A variety of different injection agents have been used in clinical practice, e.g. solutions of isotonic or hypertonic saline (NaCl), gelatine, hydroxyl-propyl-methylcellulose, hydroxyethylic starch (HAES), hyaluronate, glucose, dextrose, fructose, glycerine, Na-alginate, as well as mixtures of these components [4–6]. However, these agents diffuse relatively quickly into the surrounding tissue or leak from the dissection area. The cushion therefore dissolves quickly, which necessitates frequent re-injection, especially in ESD. Dependent on the ESD knife used a continuous exchange of dissection and injection devices is needed,

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leading to a considerable extension of the operating time [7]. LiftUp was developed and evaluated in this preclinical trial in order to provide a long-lasting stable submucosal fluid cushion. The new injectable is a promising injection solution for EMR/ESD because its viscosity is temperature-dependent. It is liquid at room temperature and is easily injectable into the submucosal layer. At body temperature (37 °C) it changes its viscosity to a gel-like state and forms a gel cushion, which remains stable for hours. Re-injection is not or less frequently necessary and the intended separation of the mucosal from the muscular layers as resection space is maintained for a longer period during the intervention. This potentially facilitates resection in EMR and ESD and may reduce adverse events related to insufficient mucosal lifting [3].

Purpose of animal trial and study endpoints

The primary purpose of this pre-clinical study was to demonstrate that injection of LiftUp allows effective mucosal lifting for EMR/ESD (efficacy) and has no negative effect on wound healing after injection and resection of the mucosa and/or submucosa (safety). The secondary purpose was to demonstrate that the ease of use of the injectable is technically comparable to other established injection solutions used. Based on the study purpose the following endpoints were set forth.

Primary endpoint

- Complication-free wound healing at the resection site at seven days and at four weeks of follow-up, defined as normal endoscopic and histological findings of healing.

Secondary endpoints

- Technical feasibility of submucosal injection and proper mucosal lifting, defined as complication-free submucosal injection and adequate mucosal lifting for subsequent resection.
- Necessity of re-injection during the procedure after initial submucosal injection.
- Major procedural adverse events (perforations, major bleeding/delayed bleeding, infection).

Material and methods

Study population and statistical methods

All animal experiments were performed according to the institutional guidelines for the care and use of animals. The animal protocol aimed to minimize pain or discomfort of the animals. The protocol was approved by the regional German government institution in charge (Approval Number C1/15, approved on September 9, 2015). From November 2015 until September 2016, endoscopic resection in combination with the use of LitfUp was performed in seven pigs (German Landrace), mean live weight: 48.6 kg, range: 44.9–56.5. Before interventions, all animals were endotracheally intubated and had general anesthesia.

During the study period, the test variables produced by the experiments were to be compared to accepted data in the literature in order to avoid two-arm-testing for animal protection reasons. The primary test variable was the measured combined complication rate of the injection of LiftUp in the animal model. The adverse event rate was defined as the acute adverse event rate during the intervention as well as the complications during the healing process. The literature variable was determined from a systematic literature search for complication rates in ESD. In European/American articles, ESD was taken to represent the most advanced 'state of the art' mucosal removal in endoscopy and Non-Japanese literature was chosen to reflect the clinical practice in endoscopy within the EU [8–15], since Japanese authors normally have broader experience in this technique, which was inaugurated in Japan. The adverse event rates identified in these published studies were combined into a study-specific overall adverse event rate if these had not already been specified in the respective articles. The specified or calculated study-specific overall complication rates were summarized in a mean complication rate, weighted according to the individual case numbers. The weighted total complication rate for ESD determined from the literature was 18.5% with a confidence interval of 95% between 13.8% and 23.8% [9]. From the experience of the involved physicians and developers of LiftUp, a total complication rate of 4–8% was estimated as realistically expectable for this animal study. The complication rate was assumed to be lower than commonly reported, given the technical advantage of more durable mucosal lifting associated with the use of the material as an injection agent with temperature-dependent viscosity and given the possibility to also conduct other resection techniques than ESD.

To calculate the required number of cases for the study, the following assumptions were taken: The following calculation of the number of required test animals was performed using a binominal test. With this test, an observed value (= determined combined

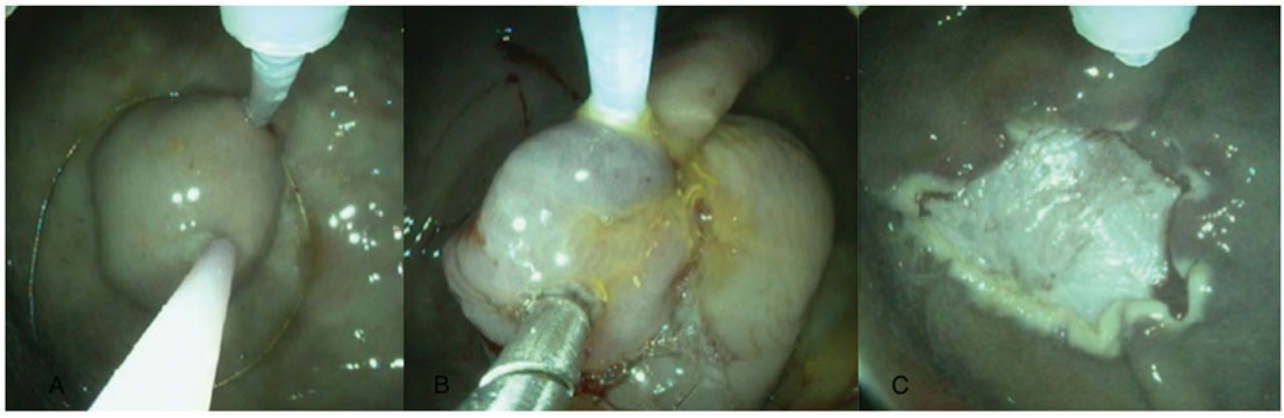

Figure 1. A-C: EMR + using Traction Polypectomy Snare and OTSC® Anchor.

adverse event rate) is compared to an expected value (= literature value).

For calculating, an α-error of 5% was assumed and for the 'power' of the test 80% were defined. As a theoretical value, 18% was set and the required number of cases was calculated using different effect intensities with respect to an expected overall complication rate of 4–8%. Nine injection and resection procedures were assumed feasible and were planned per animal.

The calculation showed that an anticipated mean complication rate of 6% would require 63 resections and therefore seven animals.

LiftUp for submucosal injection

The new injectable for elevation of the mucosa is a composition of distilled water, co-polymer from ethylenoxide, propylenoxide and sodium chloride. The co-polymer has a thermo-gelling behavior and increases its viscosity after being injected into the tissue at body temperature (37 °C, maximum viscosity). This behavior is used to provide a long lasting lifting effect at level of the submucosal layer. In this condition, the new substance does not diffuse and remains between submucosal fibers. The injection solution passed biocompatibility testing performed in compliance with the relevant norm ISO 10993.

Due to a higher viscosity compared to other injection fluids, a manometric inflation device (Accura Medizintechnik GmbH, Karben, Germany, Ref.no. 8610230S) was used to facilitate quick delivery of the material through the injection needle (needle length 6 mm, needle diameter 0.7 mm), providing a pressure of up to 20 bars.

Per injection and resection site an amount of 5–10 mL ISGC was injected. The injected material was then let in place for ~5 min to form the desired gel-like configuration. Then endoscopic resection was performed. Additionally, transmural injection of 10 mL of ISGC through the wall of the lower esophagus into the mediastinum was performed in six animals. This was done in order to assess whether LiftUp has adverse effects in case of accidental transmural injection.

Resection methods

Conventional piecemeal EMR, EMR+ (Figure 1 A–C] using a grasp-through-snare technique with a double channel endoscope or an additional external working channel, conventional ESD and hybrid ESD (h-ESD) in which remaining tissue at the distal side of the specimen was cut with a snare were performed [7,16]. The range of alternative techniques was offered to assess practical feasibility of injection with the new material in a variety of procedural options in interventional endoscopy.

The resection site was marked with high-frequency coagulation using either an ESD knife, the tip of a snare or a coagulation probe. The targeted resection size was ≥2 cm.

Results

Technical feasibility

LiftUp could be injected into the submucosa in all cases without any adverse events. After the given waiting time, it gelled completely and an adequate lifting effect could be achieved (Figure 2]. Resections of the mucosa or submucosa using the described techniques were possible in all of the animals at all locations.

Procedure results

In total 70 injections and resections (EMR, EMR+, ESD or h-ESD) were performed by four experienced

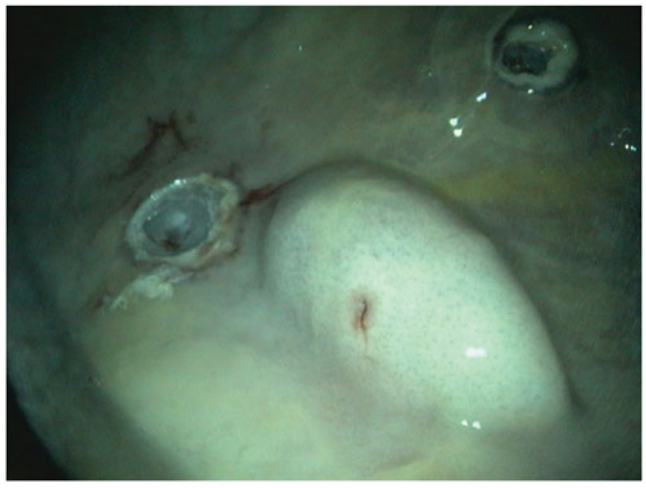

Figure 2. Stable lifting after ISGC (LiftUp) injection.

Table 1. Procedure outcomes.

Organ	Esophagus	Stomach	Rectum	Total
EMR	–	9 (14.3 %)	17 (27.0 %)	26 (41.3 %)
EMR+	–	21 (33.3 %)	4 (6.3 %)	25 (39.7 %)
ESD	2 (3.2 %)	9 (14.3 %)	–	11 (17.5 %)
h-ESD	1 (1.6 %)	–	–	1 (1.6 %)
Total number of resections	3 (4.8 %)	39 (61.9 %)	21 (33.3 %)	63
Transmural injection	6	n/a	n/a	6
Mean submucosal injection (mL)	18	9.4	4.5	10.7
Mean submucosal re-injection (mL)	0	0.45	1.0	0.5

endoscopists. One animal was euthanized in the initial pilot phase due to a perforation occurring during resection in the colon and loss of stool into the abdominal cavity due to insufficient relaxation of the animal during the procedure. This animal was excluded from the study and the protocol was amended to further exclude procedures in the colon, due to the thin wall in the porcine animal model under which procedures were deemed as technically non-standardizable. Hence, seven animals with a total of 63 resection areas were taken into account for further evaluation. Forty-two procedures were performed in the upper, and 21 in the lower gastrointestinal tract. In the upper gastrointestinal tract injections and resections were located in the esophagus (4.8%) and the stomach (61.9%); in the lower gastrointestinal tract in the rectum (33.3%) (Table 1). Most of the resections were performed via EMR (41.3%) and EMR+ (39.7%). ESD was performed in 11 cases (17.5%), h-ESD in only one case (1.6%). The size of the resected specimens varied between 1.6 and 4.8 cm. Re-injection of LiftUp after an initial submucosal injection was only necessary in six of the 63 resection cases. Detailed endoscopic data are depicted in Table 1.

Adverse procedural events

As mentioned above, in one animal a perforation into the peritoneal space was noted during resection. When clipping the perforation, stool accidentally passed the perforation area due to a peristaltic wave. It is noteworthy that laxation and bowel cleaning in the porcine animal model are more difficult to accomplish and are not animal friendly. Thus, bowel preparation and cleanliness in the animal experiment does not meet the standard of human endoscopy. The animal was euthanized and excluded from the study.

In two animals one perforation occurred during mucosal resection. Both were treated endoscopically using Over-the-Scope Clips (OTSC; Ovesco Endoscopy, Tuebingen, Germany) according to the study protocol. Follow-up endoscopy showed persistent closure of the perforation without any further problems. In six of 63 resections, mucosal resection sites were treated prophylactically with OTSCs to avoid potential delayed haemorrhage due to increased vascularisation of the resection area [17].

Minor active bleedings during resection were treated endoscopically according the study protocol. Major intra-procedural blood loss or delayed bleeding

Table 2. Overview of adverse events and additional intra-procedural measures.

Organ	Esophagus	Stomach	Rectum	Total[a]
Major adverse events				
Perforation	0	1	1	2 (3.2 %; 95 % CI, 0.7 – 9.8 %)
Major bleeding/delayed bleeding	0	0	0	0 (0 %; 95 % CI, 0 – 3.9 %)
Stenosis	0	0	0	0 (0 %; 95 % CI, 0 – 3.9 %)
Intra-procedural measures				
Preventive intra-procedural clipping of the resection base	2	1	3	6 (9.5 %; 95 % CI, 4.4 – 19.3 %)
Intra-procedural hemostasis using clipping	0	4	0	4 (6.3 %; 95 % CI, 2.5 – 15.2 %)

Confidence intervals (95%) were calculated according to the method by Jeffreys as recommended for small sample size[18].
[a]Refers to a total number of 63 resections.

during follow-up, defined as overt bleeding or a drop in haemoglobin of >2g/dL, did not occur.

In general, no detectable adverse events occurred during injection of ISGC and the clinical course of the animals after the procedure was uneventful for the follow-up period. Table 2 summarizes the adverse procedural events during the interventions [18].

We registered a total rate of adverse events of 3.2% (= 2 cases of perforation) which undercut the expected range of 4–8% assumed by experienced endoscopists for such procedures.

Follow-up

The first follow-up endoscopy was routinely performed seven days after the initial procedure and showed nearly complete epithelialization of the resection areas in all animals. Signs of progressive ulceration could not be detected. Clipped areas had a regular endoscopic and macroscopic appearance and had healed well. Throughout the entire observation period of the animals no clinical symptoms or adverse events, such as bleeding or infection, did occur. Four weeks after the initial procedure a second endoscopy was performed followed by euthanasia and autopsy by midline laparotomy and access to the thoracic cavity via the diaphragm. All intervention areas in the esophagus, stomach and rectum appeared macroscopically normal and showed normal healing of the epithelium. Scars showed no abnormalities, and stricture formation did not occur, especially not in the esophagus. Furthermore, in the abdomen no signs of peritonitis, adhesions or other pathologies were visible. The amount of LiftUp intentionally injected through the esophageal wall into in the lower mediastinum was not detectable anymore and there were no mediastinal pathological findings upon autopsy.

In one animal a 1.5 cm clinically inapparent abscess was observed at the level of the left hepatic lobe at autopsy. The abscess was not located close to any resection site. In direct consultation with the consulting veterinarian present during the autopsy, the abscess was assigned to unknown causes, as spontaneous abscess can regularly be found in the pig. There was also no anatomical relation to the intentionally injected LiftUp through the esophageal wall.

Histo-pathological assessment

In total, 57 samples of the resection areas, preserved in 4% formalin solution were obtained for histological work-up. The remaining six resection sites were macroscopically not detectable anymore due to apparently complete healing and a macroscopically invisible scar. Hence, no specimens were retrieved for histology in these latter cases.

After fixation in formalin, dehydration and clearing all tissue samples were embedded in paraffin wax and resulting paraffin blocks were cut into sections of approximately 5 µm using a microtome. Tissue sections were stained with hematoxylin and eosin (HE), and analyzed. All tissue samples analyzed showed microscopically normal wound healing with granulation tissue, scar formation and epithelialization. Single tissue samples showed a still incomplete epithelialization at the level of the mucosal defect, which is expectable after an observation period of 28 days. Single samples showed no scarring (-), others more extensive mucosal scarring (+++). The extent of scarring seems correlated to the size of the tissue resected, the location of the resection as well as the wall-thickness of the organ. Scar formation was more pronounced in the stomach than in the rectum.

In 18 of the 57 tissue samples analyzed microscopic foreign-body-granulomata were detected. Generally, foreign body granuloma occurs as tissue reaction on a foreign body stimulus due to exogenous or endogenous material. The cause of foreign body

granulomata in our tissue samples was found to be pig chow residues. Foreign body constituents within LiftUp could be excluded due to the pure liquid composition of the solution. The animals had received animal chow (containing ground corn and fiber) already a few hours after the initial intervention. Thus, food residues were deposited on the open wound surfaces and sometimes were histologically found surrounded by subordinated foreign body giant cells. Due to the type of the foreign body it can be assumed that the material would have been degraded in the further course of wound healing. The findings correspond to normal reactions after endoscopic mucosal resection and did not have a negative impact on wound healing.

Discussion

Established endoscopic resection techniques such as ESD and EMR are accepted worldwide for the removal of dysplastic lesions and early neoplasia in the upper and lower GI tract [7]. For these procedures mucosal elevation is an essential step to keep complication rates low and simplify an oncologically correct en-bloc resection of the lesion. Frequent adverse events during endoscopic resection include bleeding, perforation, infection and thermal injury [19]. Recently, the use of viscous submucosal injection solutions has been described as safer and faster than saline solution, due to their longer presence at the site of injection [20].

The current state for injection solutions are isotonic saline, glucose or glycerol solution, hydroxyethyl starch or sodium hyaluronate [5,21,22]. The recently published ESGE guidelines request the following qualities for the ideal submucosal injectate: sustainable lifting effect, enabling en-bloc or oligo-piecemeal resection, low costs, wide availability and few adverse events [23,24]. Saline solution is widely used for ESD and EMR but nevertheless multiple injections are often needed to maintain a submucosal cushion. The lifting effect has only short duration and normally diminishes in the time frame of five minutes. This may lead to the necessity of repetitive injections and potentially to a longer and riskier resection procedure [6].

A Japanese study compared saline solution, glycerine solution, dextrose solution and two hyaluronic acid solutions for EMR and investigated the potential tissue damage of the different injection agents [25]. The authors demonstrated that hypertonic solutions caused cell dehydration and possible damage of the resected specimens as well as an impaired healing of the artificial ulcer [25] at the resection site. In a systemic review and meta-analysis Ferreira et al. showed that in clinical practice sodium hyaluronate and normal saline seem to be equivalent concerning complete resection rates [6]. Which submucosal injection solution is the optimal for endoscopic resection remains unclear. There is still need for further research in this field to optimize resection technique and speed.

The results of our preclinical *in vivo* study in the procine animal model demonstrate the efficacy and safety of ISGC for different endoscopic resection techniques (ESD, EMR, EMR + and h-ESD). The intention of the trial was not to compare the effect of LiftUp with other injectables, although this would be interesting future research. The primary endpoint of the study, a complication-free wound healing at the resection site at four weeks of follow-up, defined as normal histopathological findings, was reached in all 57 cases. The analyzed tissue samples showed microscopically normal wound healing with granulation tissue, scar formation and epithelialization. Submucosal injection was technically easy and resulted in satisfactory mucosal lifting in all cases. The total major adverse event rate was 3.2% in this study, which undercut the expected range of 4–8%. Other types of major adverse events did not occur.

Secondary endpoints, no necessity of re-injection after initial submucosal injection and no major procedural adverse events were reached by 90.5% and 96.8%, respectively. We believe that this constitutes a technical advancement over the current state-of-the-art of submucosal injection with other injection solutions, commonly flattening out within a few minutes and requiring re-injection. Because of its high viscosity and gel-like appearance at body temperature, LiftUp leads to a pronounced submucosal cushion, lasting longer and making the resection procedure technically easier. For complex resection techniques such as ESD, this could potentially shorten the learning curve in the future [7,26].

In conclusion, the present study demonstrates the suitability of LiftUp for submucosal injection. It lasts longer in the submucosal layer due to its thermos-viscous properties. It did not show negative influence on post-procedural defect healing and histology after its use was found normal in all cases. Further studies are warranted, ideally comparative trials to show its superiority to other injection solutions. LiftUp may potentially increase en bloc resection rates with less total adverse events and accelerate endoscopic resection due to persistent submucosal space creation.

Disclosure statement

Edris Wedi received travel cost support from Ovesco Endoscopy AG. Timo Weiland and Stefanie Freidinger are employees of the contract research organization novineon CRO who was in charge of trial management. Thomas Gottwald and Marc Schurr hold management positions with Ovesco Endoscopy AG. Chi-Nghia Ho and Gabor Conrad are employees of Ovesco Endoscopy AG. The other authors have no conflicts of interest or financial ties to disclose.

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