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ENDOSCOPIC GASTRIC SUBMUCOSAL DISSECTION: experimental comparative protocol between standard technique and Hybrid-Knife®

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ABSTRACT - ***Background*** - Endoscopic treatment of superficial gastrointestinal tumors is routinely performed, however the advantages and shortcomings of submucosal pressure-jet dissection is still debated. ***Objective*** - Aiming to compare this technique with conventional submucosal dissection, a study was designed in pigs. ***Methods*** - Areas of the antral mucosa of the stomach with a diameter of 2 cm^2 (6 per animal) were marked, and resected by means of the hybrid-knife (experimental technique), and Flush-knife or IT-knife (controls). An ERBE ICC 300 electrosurgical unit was adopted. End-points were procedural time, complications, and quality of the resected specimen. ***Results*** - A total of 27 interventions were conducted in five animals. Time spent with the two options was quite short, and similar: 9.5±3.1 vs 8.0±3.0 minutes (P=0.21). Complications didn't differ (three per group, not significant), and removed specimen looked adequate in both circumstances. ***Conclusion*** - The hybrid-knife technique is an acceptable alternative to submucosal dissection, showing no difference compared to the standard technique taking into consideration the procedure, the presence of complications and the quality of the resected specimen.

HEADINGS - Stomach neoplasms. Dissection, instrumentation. Gastric mucosa. Swine. Surgical Instruments.

INTRODUCTION

Endoscopic submucosal dissection (ESD) of superficial gastrointestinal lesions is now a recognized alternative for en-bloc removal of several tumor modalities. Originally described in the stomach, it was subsequently expanded to the esophagus, colon and rectum as well.

ESD allows for reliable extirpation of noninvasive lesions, with a high degree of complete resection and low risk of recurrence[2]. Even relatively large superficial growths have been removed, and tumor invasion may be assessed by pathological analysis. This technique therefore complies with oncological requirements, as total en bloc removal, with investigation of resection margins is feasible.

Nevertheless, this is a relatively slow and cumbersome procedure, and much technical ability is required for safe and expedite performance. Preliminarily the mucosa is circumferentially cut, followed by dissection of the submucosa underneath the lesion. Hemorrhage and perforation are constant risks during such intervention, thus demanding frequent injection of saline to raise the mucosa, and create a safe space above the muscular layer.

There is some experimental evidence that jet dissection could be an advantageous technique, creating submucosal fluid "cushions", and uncoupling the tumor from underlying structures[3,6,7]. Within such framework, a hybrid instrument combining both an endoscopic knife and coagulator, and a high-pressure saline injector, might speed up the handling of ESD. Frequent accessory changes would be avoided, and a more straightforward approach could be adopted, thus benefitting the clinical outcome[12].

The hybrid-knife is commercially available, however protocols comparing its performance with standard dissection are scarce[9,10]. Aiming to compare such technique with conventional alternatives (Flush-knife and IT-knife), an experimental model in pigs was devised. The end-points were procedure duration and major complications (bleeding and perforation).

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METHODS

Compliance with ethical standards

The Institutional Animal Welfare Committee approved the study. "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985) were followed, as well as national guidelines for animal experimentation, as established by the Ethics Committee, Sao Paulo University Medical School, as well as by the Brazilian College of Animal Investigation.

Experimental design

This was a prospective, randomized, controlled experimental study in pigs.

Preliminary steps

Healthy male domestic pigs 3-4 months old (25-30 kg) were fasted during 24h before the procedure, only water with sugar being allowed during this period. General anesthesia with endotracheal intubation was conducted (ketamine 40 mg/kg followed by isoflurane 1%-4%). At the end of the procedure, animals were euthanized under anesthesia, employing KCl 19.1% injection.

Experimental endoscopic resection

The gastric antrum was selected, including both anterior and posterior wall. Areas of mucosa with a diameter of 2 cm^2 (6 per animal) were marked with coagulation points, and consecutively resected, mimicking a superficial tumor.

Conventional ESD: after marking and lifting the lesion, an initial mucosal incision was made besides a marker point. Circumferential dissection proceeded, with the help of manual saline injections, until complete lesion extirpation was achieved.

Hybrid-knife procedure: Marking and initial cutting were identical. However, the handy hydro dissection system, based on an axial water-jet channel, permitted more confident lifting and cutting of submucosal structures.

Equipment

For conventional ESD either Flush-knife (Fujifilm, Tokyo, Japan) or IT-Knife (Olympus, Tokyo, Japan) were employed. Submucosal saline infiltration was performed with a catheter injector. An ERBE VIO 300 D electrosurgical unit (Erbe, Tubingen, Germany) was adopted, with cutting adjusted to the Endocut mode, and coagulation to the Forced Coagulation mode. For the experimental resection a hybrid-knife model I (Erbe, Tubingen, Germany - Figure 1) was used, along with the pressure bomb ERBEJET 2. The electrosurgical unit and settings were the same as previously described.

Procedures were executed by six different endoscopists, one senior endoscopist with experience with ESD, two who completed their training – which included ESD practice – in a few years, and three second year endoscopy residents doing ESD training. Both animals and operators were randomized for each intervention, in order to avoid any bias. One random sample from each population was submitted to an experienced pathologist, for histological evaluation of depth and completeness of resection.

FIGURE 1. Hybrid-knife model I (courtesy of Anderson Bellangero, E. Tamussino & CIA LTDA - São Paulo)

End points

The following outcomes were considered: duration of the procedure, major complications (hemorrhage, perforation), and quality of the surgical specimen (complete in-depth removal).

Statistical analysis

The package OpenEpi 2.3 was employed[8]. Fisher`s Exact test was selected for categorical variables, along with Student`s *t* test for continuous measurements. A significance value of $P<0.05$ was adopted.

RESULTS

A total of 27 interventions were conducted in 5 animals, 13 with the conventional technique (controls) and 14 with jet dissection (hybrid-knife). Time spent with the two options was similar: 9.5±3.1 vs 8.0±3.0 minutes ($P=0.21$) (Table 1).

Number of complications was not different either: two bleedings and one perforation in the hybrid group, and three bleedings in the control pigs (Table 2). Also pathological analysis revealed few discrepancies. Area of the resected mucosa was similar, and only depth of mucosal resection was somewhat better with the standard procedure (525 vs 445 µ), even though both were histologically adequate (Figures 2 and 3).

TABLE 1. Procedural time

	Hybrid	Conventional	*P*
Intervention	14	13	-
Duration (mean/SD)	9.52/3.1 min	8/3.04 min	0.21*

SD: standard deviation. * Student's *t* test for independent samples.

TABLE 2. Complication risk

	Hybrid	Conventional	ARR/ARI	CI 95%	*P*
Bleeding	0.142	0.231	0.088	-0.205 - 0.381	0.46*
Perforation	0.071	0.000	-0.071	-0.206 - 0.064	0.51*

ARR: absolute risk reduction; ARI: absolute risk increase; CI: confidence interval. * Fisher's exact test.

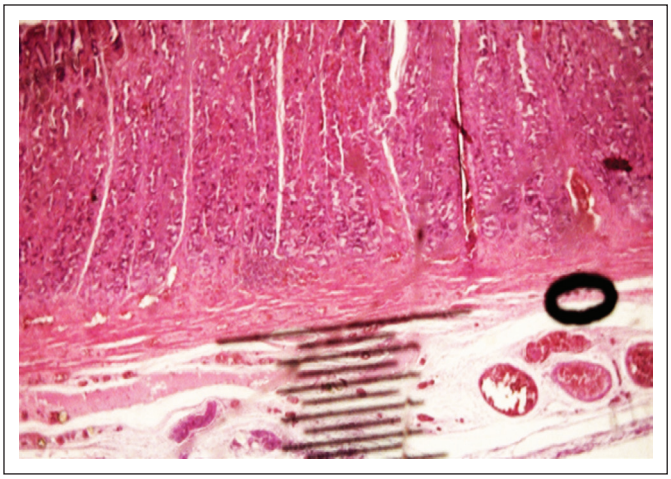

FIGURE 2. Gastric endoscopic submucosal dissection obtained with standard technique. Submucosal layer is 525 microns depth

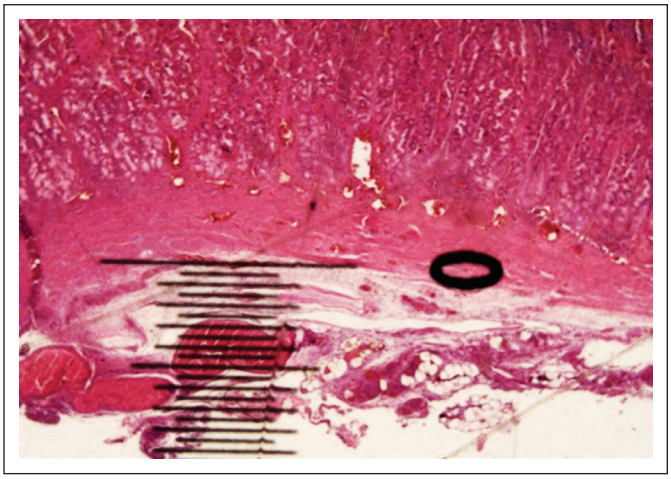

FIGURE 3. Gastric endoscopic submucosal dissection obtained with Hybrid-knife. Submucosal layer is 445 microns depth

DISCUSSION

The learning curve of ESD, including the hybrid-knife modality, is considered prolonged, hampering the acceptance of this endoscopic option, except in a few countries[5]. Nevertheless, the technique might avoid the need for more aggressive interventions. A somewhat related attempt to reduce submucosal electrosurgical knife manipulation relies on an inflatable balloon for blunt dissection. In an early experience with rectosigmoid colon in pigs, about 6 cm of mucosa was removed in 25 minutes, with an acceptable complication rate[11].

In addition, tunnel dissection has been reported as a possible solution, for experimental lesions in the esophagus and stomach. In a comparative protocol[4], marked mucosal circles in pigs were lifted by means of a submucosal tunnel, created by the endoscope itself. Protected by a transparent cap, the instrument was introduced underneath the mucosa by means of a proximal opening, and gently pushed until the distal (exit) cut, with the help of periodical insufflation. Thus, most of the desired mucosa was teared free from the underlying muscle layer, rendering it relatively simple to complete the intervention and extract the specimen. In a small series including gastric antrum, fundus and esophagus, procedural time was not different from conventional ESD (around 30 minutes). Only in the esophagus was tunnel dissection quicker that the traditional approach. Occasional complications and incomplete resections were noticed[4].

The swine model is convenient, as anatomy is comparable to the human, and costs are affordable[1]. Within such context, this investigation revealed no conspicuous differences between the pressure-injection technique and the conventional one. Neither alternative was more challenging than the other, and despite occasional complications, en bloc resection was successful in all circumstances. Results also favorably compare to other suggestions like tunnel and balloon dissection[4,11], especially regarding consumed time, which was 2-3 times shorter than with the competing procedures. The hybrid-knife may thus be considered a valid alternative for ESD.

This protocol suffers from weaknesses. Animals and dissections were not plenty, and pathological examination was preliminary. Depth of dissection is not a primary outcome in our study, although we know that this is an important finding, as one of the quality criteria of the resection in gastric ESD is the adequate amount of submucosal tissue in the resected specimen. Unfortunately, we don't have a pathology laboratory linked to the experimental surgery lab, and were able to send only a random sample of each group for analysis of the depth of dissection. This did not allow a proper statistical comparison between the results of both methods. The medical team was also heterogeneous, which could explain the registered complications; however, this might also be viewed as one of the strengths of the design. It was desired to demonstrate that even insufficiently trained professionals, such as second year residents, could perform submucosal dissection, often described as a complex and time-consuming procedure.

CONCLUSION

In an experimental investigation in pigs, endoscopic mucosal resection in the gastric antrum employing either a conventional knife, or the hybrid-knife procedure, no differences emerged concerning duration and safety of the procedure. Depth of dissection was also apparently similar,

although evidence is preliminary. Various professionals including second-year residents could generally complete both modalities in less than 10 minutes. Further studies with larger samples are recommended, in order to fully explore the therapeutic potential of ESD, both employing standard and high-pressure mucosal injections.

Authors' contribuitions

Mendonça EQ: main author. Zuretti LS: data collection and organization. Panzani T: data collection and organization. Sulbaran M: procedure execution. Sakai CM: procedure execution. Sakai P: procedure execution and expert advisor.

Mendonça EQ, Zuretti LS, Panzani T, Sulbaran M, Sakai CM, Sakai P. Dissecção endoscópica submucosa gástrica: protocolo experimental comparativo entre a técnica convencional e o Hybrid-Knife®. Arq Gastroenterol. 2016,53(3):192-5.

RESUMO - ***Contexto*** **-** O tratamento endoscópico de tumores gastrointestinais superficiais é realizado rotineiramente, no entanto as vantagens e deficiências da dissecção submucosa com jato de pressão ainda é debatido. ***Objetivo*** - Visando comparar esta técnica com dissecção submucosa convencional, um estudo foi realizado em suínos. ***Métodos*** - Áreas da mucosa antral do estômago com um diâmetro de 2 cm^2 (um total de 6 por animal) foram marcadas, e a ressecção através do hybrid-knife (técnica experimental), e do Flush-knife ou IT-knife (controles). Uma unidade eletro cirúrgica ERBE ICC 300 foi adotada. Os desfechos foram: tempo do procedimento, complicações e qualidade da amostra ressecada. ***Resultados*** - Um total de 27 intervenções foram realizadas em cinco animais. O tempo gasto com as duas técnicas foi curto e semelhante: 9,5±3,1 vs 8,0±3,0 minutos (*P*=0,21). As complicações não diferiram (três por grupo, não significativas), e amostras retiradas foram adequadas em ambas as circunstâncias. ***Conclusão*** - A técnica de hybrid-knife é uma alternativa aceitável para dissecção submucosa, demonstrando não haver diferença em comparação à técnica convencional levando em consideração o tempo de procedimento, a presença de complicações e a qualidade da amostra ressecada.

DESCRITORES - Neoplasias gástricas. Dissecação, instrumentação. Mucosa gástrica. Suínos. Instrumentos cirúrgicos.

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