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**ORIGINAL PAPERS**

# Experimental study of hybrid-knife endoscopic submucosal dissection (ESD) *versus* standard ESD in a Western country

Joaquín de-la-Peña[1], Ángel Calderón[2], José Miguel Esteban[3], Leopoldo López-Rosés[4], David Martínez-Ares[5], Óscar Nogales[6], Aitor Orive-Calzada[7], Sarbelio Rodríguez[8], Eloy Sánchez-Hernández[9], Juan Vila[10] and Gloria Fernández-Esparrach[11]

*[1]Hospital Virtual Valdecilla. Santander, Spain. [2]Hospital Basurto. Bilbao, Vizcaya. Spain. [3]Hospital Clínico San Carlos. Madrid, Spain. [4]Hospital Lucus Augusti. Lugo, Spain. [5]CHU Vigo. Vigo, Spain. [6]Hospital General Universitario Gregorio Marañón. Madrid, Spain. [7]Hospital Galdakao-Usansolo. Vizcaya, Spain. [8]Hospital Unviersitario 12 de Octubre. Madrid, Spain. [9]Complexo Hospitalario de Ourense. Ourense, Spain. [10]Endoscopy Unit. Complejo Hospitalario de Navarra. Pamplona, Navarra. Spain. [11]Endoscopy Unit. Gastroenterology Department. Hospital Clínic. IDIBAPS, CIBEREHD. Universidad de Barcelona. Barcelona, Spain*

## ABSTRACT

**Background:** Endoscopic submucosal dissection (ESD) is an effective but time-consuming treatment for early neoplasia that requires a high level of expertise.

**Objective:** The objective of this study was to assess the efficacy and learning curve of gastric ESD with a hybrid knife with high-pressure water jet and to compare with standard ESD.

**Material and methods:** We performed a prospective non-survival animal study comparing hybrid-knife and standard gastric ESD. Variables recorded were: Number of *en-bloc* ESD, number of ESD with all marks included (R0), size of specimens, time and speed of dissection and adverse events. Ten endoscopists performed a total of 50 gastric ESD (30 hybrid-knife and 20 standard).

**Results:** Forty-six (92 %) ESD were *en-bloc* and 25 (50 %) R0 (hybrid-knife: n = 13, 44 %; standard: n = 16, 80 %; p = 0.04). Hybrid-knife ESD was faster than standard (time: 44.6 ± 21.4 minutes *vs.* 68.7 ± 33.5 minutes; p = 0.009 and velocity: 20.8 ± 9.2 $mm^2$/min *vs.* 14.3 ± 9.3 $mm^2$/min (p = 0.079). Adverse events were not different. There was no change in speed with any of two techniques (hybrid-knife: From 20.33 ± 15.68 to 28.18 ± 20.07 $mm^2$/min; p = 0.615 and standard: From 6.4 ± 0.3 to 19.48 ± 19.21 $mm^2$/min; p = 0.607). The learning curve showed a significant improvement in R0 rate in the hybrid-knife group (from 30 % to 100 %).

**Conclusion:** despite the initial performance of hybrid-knife ESD is worse than standard ESD, the learning curve with hybrid-knife ESD is short and is associated with a rapid improvement. The introduction of new tools to facilitate ESD should be implemented with caution in order to avoid a negative impact on the results.

***Key words:*** Endoscopic submucosal dissection. ESD. Hybrid-knife ESD. Water-jet assisted ESD. Experimental endoscopy.

## INTRODUCTION

Endoscopic submucosal dissection (ESD) is a curative therapeutic modality for gastrointestinal neoplasms. It was developed in Japan to achieve *en-bloc* resection of superficial neoplastic lesions (1-3). However, ESD has not yet been standardized, is technically difficult and time consuming, and requires a high degree of endoscopic skill for it to be performed safely. These limitations explain why the technique has only a limited use in Europe and the USA.

The technique of ESD involves circumferential cutting of the mucosa surrounding the tumor followed by dissection of the submucosa under the lesion. The most time-consuming part of the ESD is the submucosal dissection where bleeding is frequently experienced and repeated injections of fluid are needed for maintaining an adequate submucosal cushion. Recent experimental trials demonstrate that a water-jet dissector allows rapid elevation of mucosal areas in the upper-gastrointestinal tract by creation of submucosal cushions (4-6). Therefore, the availability of a hybrid device that combines a cautery knife with a water jet in one instrument should simplify and accelerate ESD because submucosal injection and circumferential cutting and dissection of lesions as well as coagulation of bleeding can be performed with the same device without a

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*Correspondence:* Gloria Fernández-Esparrach. Endoscopy Unit. Hospital Clínic. c/ Villarroel, 170. 08036 Barcelona (Spain)
e-mail: mgfernan@clinic.ub.es

*De-la-Peña J, Calderón A, Esteban JM, López-Rosés L, Martínez-Ares D, Nogales O, Orive-Calzada A, Rodríguez S, Sánchez-Hernández E, Vila J, Fernández-Esparrach G. Experimental study of hybrid-knife endoscopic submucosal dissection (ESD) versus standard ESD in a Western country. Rev Esp Enferm Dig 2014;106:98-102.*

need for changing the instrument. These options should make the procedure quicker and may increase its safety and efficacy (7). Compared with EMR, the hybrid-knife ESD procedure time is significantly longer but there is a trend of shortening the procedure time with increasing experience (8). However, there are scarce experimental data and even less human experience with this device so far (9,10).

The aim of the present study was to evaluate the efficacy and learning curve of hybrid-knife gastric ESD and to compare it versus standard ESD in a porcine model.

## MATERIAL AND METHODS

### Study design

Twenty-four male pigs (Large White) weighing 35 to 40 kg were used to perform ESD in the stomach. The experimental protocols were approved by Valdecilla's Virtual Hospital and met the guidelines of regional governmental agency.

Ten endoscopists with experience in therapeutic endoscopy but with different levels of expertise in experimental ESD (*ex vivo:* median 6, range 0-30; *in vivo:* median 13, range 1-45) performed the procedures. Only 4 endoscopists had some experience in human cases. ESD with the hybrid technique was performed alternatively with the classic technique, starting always with hybrid ESD. Endoscopists worked by pairs. The complete procedure time was recorded as well as the tools used, the resected specimen size, number of marks included, number of perforations, number of different instruments needed, difficulties, and other adverse events.

ESDs were started in the greater antral curvature with a circumferential marking of a defined area (25 x 20 mm). When a pair of resections was done (one with each technique) we moved to the anterior antral wall, then to the posterior antral wall and afterwards to the upper part of the stomach.

### Animals

All procedures were performed with the animals placed in the left lateral decubitus position and under general anesthesia with endotracheal intubation and mechanical ventilation. Vital signs and physiological parameters were monitored during the procedures. The pigs were premedicated with a combination of tiletamine hydrochloride plus zolazepam hydrochloride (Zoletil©; Virbac España, Barcelona, Spain) and xylazine. Anesthesia was induced with propofol (6 mg/kg, i.v.) and maintained with continuous propofol infusion (20 mg/kg/h, i.v.). At the end of each session, animals were euthanized and necropsy was immediately performed.

### Devices

We used forward-viewing single channel gastroscopes (EG-2970K and EG-2985K, Pentax U.K. Limited) with a conical transparent cap attached to the tip. The modular VIO generator (VIO 300D; Erbe Elektromedizin, Tübingen, Germany) was used as surgical system.

For the hybrid-knife ESD we used a water-jet hybrid knife (Erbe Hybrid Knife®, Erbe Elektromedizin, Tübingen, Germany). For standard ESD we used a needle Knife with a 2.5 mm long needle (Splashneedle DN-D2718A, Pentax U.K. Limited) and an isolated knife with a 5 mm long active part located in a lateral position on a rotatable plastic catheter (Mucosectom, DP-D2518, Pentax U.K. Limited). The VIO mode ENDO CUT Q 2-4-1 was used for circumferential cutting and dissection. The argon plasma coagulation (APC) mode FORCED APC, 50 W was used for marking of lesions and FORCED COAG E2 45 W was used for coagulation of vessels. Dissection with electrocautery was alternated with submucosal fluid injection as many times as needed.

### Preparation of the targeted area

The areas for resection were defined in an oval shape with a size of approximately 25 mm in length and 20 mm in width in the antrum and body of the stomach. This size was selected because it represents the smallest area for which the technique of ESD is considered to be useful and has been used in other experimental studies (8). Clearly visible coagulation markers at 4-mm distances around the targeted area were set by an APC probe as described.

### Standard ESD procedure

After the preparation of the targeted area, ESD was performed as described (11). We injected a mixture of Glycerol 50 % with saline and methylene blue to form an initial cushion and injections were frequently repeated to secure an appropriate lifting of the mucosal layer and separation from the muscle layer. Before cutting, a circumferential incision including all coagulation markers was performed as deep as possible. Dissection was started in the oral site using the needle knife and/or the mucosectome.

### Hybrid-knife ESD

The hybrid knife was alternately used for injection with the water-jet system and cutting as well as for coagulation of visible vessels as described (6). The fluid used was saline with methylene blue. The direction of dissection was targeted tangentially to the surface of the lesion at the submucosal layer to minimize the risk of perforation.

### Statistical analysis

The variables analyzed were: Number of ESD completed, number of ESD with all marks included (R0), size of specimens, time and speed of dissection and adverse events. The size of specimen was calculated with the formula $\pi \cdot A \cdot B/4$, where A was the larger diameter and B was the smaller diameter. To compare the variables between both techniques we use the Mann-Whitney test.

Data are expressed as mean and standard deviation. A p value < 0.05 was considered statistically significant. Statistical analysis was performed with the ‹‹R›› statistic program (12).

## RESULTS

We performed a total of 50 gastric ESD (30 hybrid-knife and 20 standard) with a mean of 7.2 ± 3.3 dissections per endoscopist. Forty-six (92 %) ESD were completed in only one piece (*en-bloc* resection rate of 92 %) without differences between techniques (Table I). In 3 cases in the hybrid-knife group, the resection was completed with a polypectomy snare.

We were not able to retrieve 3 specimens for the inspection of the margins. Therefore, in a per-protocol analysis, in 25 out of 43 cases (58 %), all the marks were included in the specimen (hybrid-knife: n = 12/27, 44 %; standard: n = 13/16, 81 %; p = 0.04) (Table I). None of the 3 cases in the hybrid-knife group that were completed with polypectomy snare were R0.

The size of the specimens was not different in both groups (hybrid-knife: 40.3 ± 13.2 mm; standard: 35.5 ± 10.9 mm; p = 0.826). There was a trend for the hybrid-knife ESD to be faster than the standard with a speed of 20.8 ± 9.2 $mm^2$/min *vs.* 14.3 ± 9.3 $mm^2$/min (p = 0.079) (Fig. 1).

Adverse events were not different among groups. There was an incidence of perforation of 4 (13 %) and 2 (10 %), respectively (p = 0.722). Dissection caused at least 1 bleeding event in 8 cases (16 %) but hemostasis could always be achieved by use of coagulation forceps (Table I).

The speed did not change with any of two techniques when comparing the first with the last round (hybrid-knife: from 20.33 ± 15.68 to 28.18 ± 20.07 $mm^2$/min; p = 0.615 and standard: From 6.4 ± 0.3 to 19.48 ± 19.21 $mm^2$/min; p = 0.607). The learning curve showed a rapid improvement in R0 rate in the hybrid-knife group (from 30 % to 100 % in the intention-to-treat analysis and from 33 % to 100 % in the per protocol analysis) whereas showed not differences with the standard ESD group (from 70 % to 60 % in the intention-to-treat analysis and from 87 % to 71 % in the per protocol analysis) (Table II).

**Table I. Comparative results of both techniques**

| | *Standard ESD n = 20* | *Hybrid-knife ESD n = 30* | *p* |
|---|---|---|---|
| Time of resection, min | 68.7 ± 33.5 | 44.6 ± 21.4 | 0.009 |
| Perforation | 2 (10 %) | 4 (13 %) | 0.723 |
| Cuts in the muscular layer | 3 (15 %) | 5 (17 %) | 0.835 |
| Marginal cuts | 4/16 (25 %) | 9/27 (33 %) | 0.505 |
| Hemorrhage | 4 (20 %) | 4 (13 %) | 0.479 |
| *En-bloc* ESD | 18 (90 %) | 28 (93 %) | 0.670 |
| *R0:* | | | |
| Intention-to-treat analysis | 13 (65 %) | 12 (40 %) | 0.04 |
| Per-protocol analysis | 13/16 (81 %) | 12/27 (44 %) | 0.04 |

**Table II. Learning curve in R0 rate with hybrid-knife and standard ESD**

| | *1st round* | *2nd round* | *3rd round* | *4th round* |
|---|---|---|---|---|
| *Hybrid-knife ESD* | | | | |
| Intention to treat | 3/10 (30 %) | 2/8 (25 %) | 3/8 (37 %) | 4/4 (100 %) |
| Per protocol | 3/9 (33 %) | 2/7 (29 %) | 3/7 (43 %) | 4/4 (100 %) |
| *Standard ESD* | | | | |
| Intention to treat | 7/10 (70 %) | 6/10 (60 %) | | |
| Per protocol | 7/8 (87 %) | 5/7 (71 %) | | |

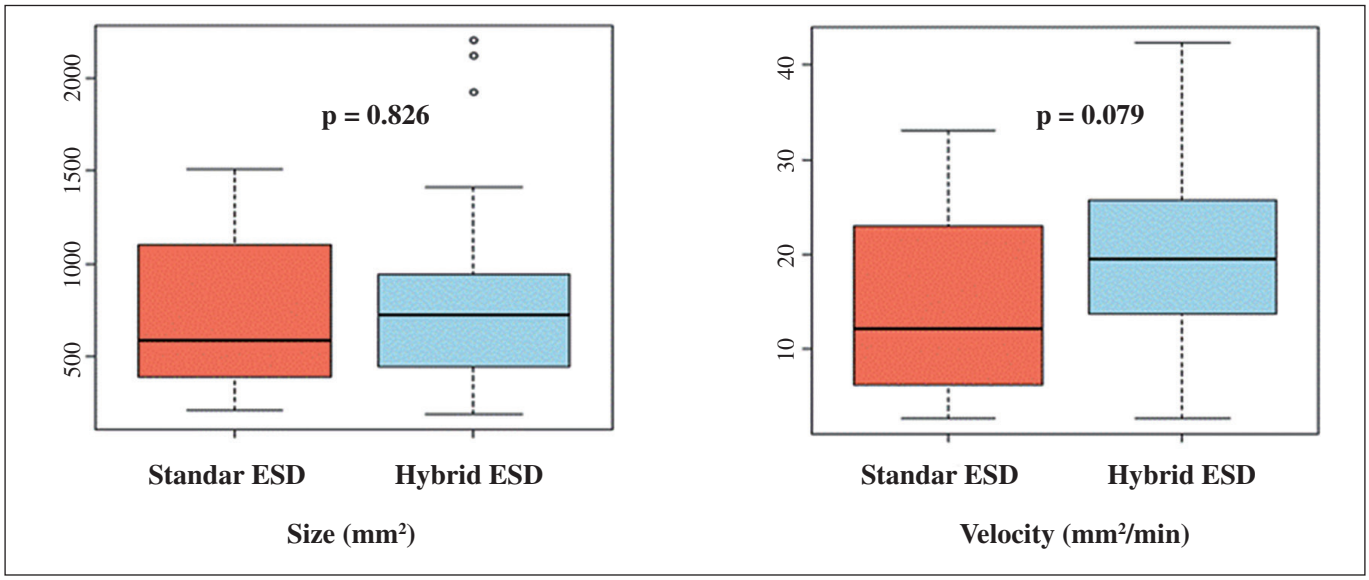


Fig. 1. Comparative results of size and speed of ESD.

## DISCUSSION

Initial impressions with the Erbe Hybrid Knife®, which combines an ultra-fine high-pressure fluid jet with an electrocautery needle, make this device an attractive tool for performing ESD (7-10). This device allows submucosal fluid elevation with a preselected pressure and subsequent cutting or coagulation, and seems to accelerate the ESD procedure because it avoids changes between lifting and cutting by using the same device. The feasibility of this new device has been assessed in animal stomach (4-6), colon (7), and esophagus (6,8) and there is initial experience in humans (9,10) but there is no information regarding the learning curve of ESD with hydrodissection technique.

This is the first comparative study of the performance and learning curve of hybrid-knife ESD *versus* standard ESD in porcine stomachs. Differently from other previous studies reported, procedures were performed by several endoscopists with limited preliminary experience of ESD in experimental models and only anecdotal experience in human cases. *En-bloc* resection rate was good with both techniques but R0 resection rate was lower than expected especially with the hybrid-knife technique. Compared with the Japanese reports, the European experience with ESD is scarce and with lower resection rates even when using the standard technique (13,14). In a recently published German study, R0 en bloc resection with standard technique for all lesions (early gastric cancers and adenomas) was reported in 74 % of cases. Resection rates were lower in patients with early gastric cancer with expanded criteria of the Japanese Gastric Cancer Association (68.6 %) (13). In the only report of hybrid-knife ESD for gastric lesions in humans, Schumacher et al. included 29 consecutive patients with early gastric neoplasia that met the expanded criteria and the *en-bloc* resection and R0 rates were 90 % and 64.3 %, respectively. One explanation for the lower rate found in our study could be that endoscopists felt more confident when performing hybrid-knife ESD resulting in a fast and inaccurate technique. A different explanation could be an underestimation due to failure of coagulation spots identification on the specimen. Our hypothesis is that the high pressure of the water-jet could delete the peripheral marks by edema and we suggest placing the coagulation marks more than 4 mm far from the lesion when using a high-pressure fluid jet knife. In any case, endoscopists were able to modify the approach and the learning curve showed a rapid improvement up to 100 % in the fourth attempt with the hybrid-knife technique.

Similar results were reported in a recent retrospective analysis of the outcome of 80 classic ESD procedures in humans (15). The results indicated that the procedure could be performed effectively and safely after 40 cases, with a significant shortening of the procedural time during the learning curve. Because the endoscopist's experience affects the outcome of ESD and it is difficult to overcome a flat learning curve in Western countries due to a low rate of detection of early gastric cancers, it is essential to practice and improve the skills in animal models.

The learning-curve effect was very notable with the hybrid-knife technique. These results are in line with those reported by Neuhaus et al. (8) using the hybrid-knife for performing ESD in the colon of pigs but the main difference with our study is that procedures were exclusively done by two endoscopists with ESD experience in experimental and clinical settings.

Many methods have been developed to prevent perforation, but the fundamental principle that applies to all methods is that the mucosa is elevated by submucosal in-

jection of fluid. Normal saline solution is the most commonly used to create a submucosal fluid cushion but it diffuses quickly. Therefore, to lengthen the duration of elevation, one alternative is to use higher concentrations of saline and solutions with high viscosity (16-19) or to facilitate the repetition of fluid injection with the hybrid knife. Previous experimental trials did not show that the water jet itself can cause perforation and this potential risk may be overcome avoiding directing the water jet to the resection bed. Additionally, the thermal and mechanical damage of the resection bed is less pronounced when using the hybrid-knife ESD technique because the amount of fluid injected is higher and the water jet of the hybrid-knife can also be used for tissue-sparing blunt dissection of the submucosa. In our study, the perforation rate with the hybrid-knife technique was higher than the 5.5 % previously reported by Yahagi et al. (7) but was not different from the observed incidence with the classic ESD. We also used the hybrid-knife for short bursts of coagulation of visible vessels or minor bleedings and intensive use of electrosurgery was avoided to minimize the risk of perforation. All bleedings could be managed by use of the coagulation mode in both groups.

This study has several limitations. First, the study has not a randomized design and because the two techniques were performed alternatively, the endoscopists were not blind to the type of ESD. Second, it has been performed in a porcine model with a limited number of experiments that prevent to evaluate the learning curve individually for each endoscopist, experience or location. A study with a high number of procedures should be desirable but has several ethical issues. Third, due to the different speed of the techniques, the number of lesions resected with hybrid technique was higher than with the standard one. Fourth, although we aimed to create lesions with an area of 20-25 mm, measurements of the resected specimens revealed smaller or larger areas in several cases. These differences could be explained by inadequate marking of lesions because we did not use any template but the size of lesions resected was not different with the two techniques. Fifth, standard ESD was performed with two different knifes and it is known that each device has its own learning curve.

In summary, this first prospective and comparative study demonstrates that despite the initial decrease in R0 with hybrid-knife ESD, the learning curve with the hybrid-knife technique is short and shows a rapid improvement. Therefore, the introduction of new tools to facilitate the implementation of ESD should be performed with caution in order to avoid a negative impact on the results.

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## REFERENCES

1. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-9.
2. Miyamoto S, Muto M, Hamamoto Y, Boku N, Ohtsu A, Baba S, et al. A new technique for endoscopic mucosal resection with an insulated-tip electrosurgical knife improves the completeness of resection of intramucosal gastric neoplasms. Gastrointest Endosc 2002;55:576-81.
3. Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, et al. Advantage of endoscopic submucosal dissection in comparison to endoscopic mucosal resection for early gastric cancer. Gastrointest Endosc 2006;64:877-83.
4. Kaehler GF, Sold MG, Fischer K, Post S, Enderle M. Selective fluid cushion in the submucosal layer by water jet: Advantage for endoscopic mucosal resection. Eur Surg Res 2007;39:93-7.
5. Lingenfelder T, Fischer K, Sold MG, Post S, Enderle MD, Kaehler G. Combination of water-jet dissection and needle-knife as a hybrid knife simplifies endoscopic submucosal dissection. Surg Endosc 2009;23:1531-5.
6. Fernández-Esparrach G, Matthes EL, Maurice D, Enderle M, Thompson CC, Carr-Locke DL. A novel device for endoscopic submucosal dissection that combines water-jet submucosal hydrodissection and elevation with electrocautery: Initial experience in a porcine model. Gastrointest Endosc 2010;71:615-8.
7. Yahagi N, Neuhaus H, Schumacher B, Neugebauer A, Kaehler GF, Schenk M, et al. Comparison of standard endoscopic submucosal dissection (ESD) versus an optimized ESD technique for the colon: An animal study. Endoscopy 2009;41:340-5.
8. Neuhaus H, Wirths K, Schenk M, Enderle MD, Schumacher B. Randomized controlled study of EMR versus endoscopic submucosal dissection with a water-jet hybrid-knife of esophageal lesions in a porcine model. Gastrointest Endosc 2009;70:112-20.
9. Takeuchi Y, Uedo N, Ishihara R, Iishi H, Kizu T, Inoue T, et al. Efficacy of an endo-knife with a water-jet function (Flushknife) for endoscopic submucosal dissection of superficial colorectal neoplasms. Am J Gastroenterol 2010;105:314-22.
10. Schumacher B, Charton JP, Nordmann T, Vieth M, Enderle M, Neuhaus H. Endoscopic submucosal dissection of early gastric neoplasia with a water jet-assisted knife: a Western, single-center experience. Gastrointest Endosc 2012;75:1166-74.
11. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, et al. A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. Gastrointest Endosc 1999;50:560-3.
12. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2012. ISBN 3-900051-07-0. Available at: http://www.R-project.org/
13. Probst A, Pommer B, Golger D, Anthuber M, Arnholdt H, Messmann H. Endoscopic submucosal dissection in gastric neoplasia – experience from a European center. Endoscopy 2010;42:1037-44.
14. Farhat S, Chaussade S, Ponchon T, Coumaros D, Charachon A, Barrioz T, et al. Endoscopic submucosal dissection in a European setting: A multi-institutional report of a technique in development. Endoscopy 2011;43:664-70.
15. Choi IJ, Kim CG, Chang HJ, Kim SG, Kook MC, Bae JM. The learning curve for EMR with circumferential mucosal incision in treating intramucosal gastric neoplasm. Gastrointest Endosc 2005;62:860-5.
16. Fujishiro M, Yahagi N, Kashimura K, Mizushima Y, Oka M, Enomoto S, et al. Comparison of various submucosal injection solutions for maintaining mucosal elevation during endoscopic mucosal resection. Endoscopy 2004;36:579-83.
17. Fujishiro M, Yahagi N, Kashimura K, Matsuura T, Nakamura M, Kakushima N, et al. Tissue damage of different submucosl injection solutions for EMR. Gastrointest Endosc 2005;62:933-42.
18. Conio M, Rajan E, Sorbi D, Norton I, Herman L, Filiberti R, et al. Comparative performance in the porcine esophagus of different solutions used for submucosal injection. Gastrointest Endosc 2002;56:513-6.
19. Fernández-Esparrach, Shaikh S, Cohen A, Ryan MB, Thompson CC. Efficacy of a reverse phase polymer as a submucosal injection solution for EMR: A comparative study. Gastrointest Endosc 2009;69:1135-9.