Antithrombotic drug use effect in the treatment of early gastric cancer by endoscopic submucosal dissection

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Abstract: This study was designed to investigate the efficacy and safety of endoscopic submucosal dissection (ESD) for treatment of early gastric cancer. In this study, we evaluated the effects of antithrombotic drugs on bleeding risk in patients with ESD. Meta analysis showed that the use of antithrombotic drugs before ESD can reduce the risk of postoperative bleeding, but the early recovery of the use of antithrombotic drugs, or combined with a variety of antithrombotic drugs will increase the risk of bleeding. Twenty-four lesions in 524 patients were treated using ESD, and treatment status and efficacy were observed. Patients received intravenous antibiotics 30 minutes before ESD to prevent infection. If infection occurred after ESD, according to susceptibility test results, patients were given sensitive antibiotics. The one-time en bloc resection rate of all 524 lesions was 100%, and the histologic curative resection rate was 100%. The average time of surgery was 48 min. The rate of mild acute bleeding was 4.2% (22/524), the incidence of postoperative abdominal pain was 54.2% (284/524), and no heavy acute bleeding, perforation, or delayed postoperative bleeding occurred. Endoscopic re-examination at 2 months revealed an ulcer healing rate of 100%. A 12-month follow-up revealed no local residue, relapse, or new lesions. ESD can increase the one-time en bloc resection rate and histologic curative resection rate, and is a safe and effective method for treatment of early gastric cancer.

Keywords: Early gastric cancer, endoscopic submucosal dissection, outcomes, cancer recurrence.

INTRODUCTION

Early gastric cancer refers to stomach cancer that has spread to the mucosal or submucosal layers (fig. 1 and fig. 2), regardless of the size of the lesion or whether there is lymph node metastasis (Cirak *et al.,* 2015; Cvetanovic *et al.,* 2015; Kim 2016; Libânio 2016; Sato *et al.,* 2016; Saragoni 2015). Recent research has shown that endoscopic submucosal dissection (ESD) treatment of early gastric cancer has similar efficacy as surgical laparotomy (fig. 3, fig. 4, and fig. 5), and allows most patients to avoid the risks of traditional surgical procedures and severe effects on quality of life after the procedure (Babacan *et al.,* 2015; Baikoussis *et al.,* 2015; Bal *et al.,* 2015; Bozkurt *et al.,* 2015; Buyukhatipoglu *et al.,* 2015; Balmadrid *et al.,* 2015; 2015; Bhatt *et al.,* 2015; Cho, 2015; Espinel *et al.,*2015). Our department used ESD to treat early gastric cancer and achieved good clinical outcomes. The efficacy and safety of ESD in treating early gastric cancer is summarized below.

Total resection of endoscopic submucosal dissection can be performed with larger lesions, the resection rate is as high as 80%, has been widely carried out in domestic and abroad, but the risk of bleeding was also increased, especially for cardiovascular and cerebrovascular diseases need taking antithrombotic drugs in patients with more attention to. There is no uniform understanding of the risk of bleeding anticoagulant drug increased after ESD, studies have shown that compared with the continuous application of antithrombotic drugs, never taking or preoperative stopping antithrombotic drugs can effectively reduce the risk of bleeding after ESD, but also some scholars believe that the effect of antithrombotic drugs on no significant postoperative bleeding ESD. A multi center study showed that there were more confusion and disagreement among the physicians about the use of antithrombotic drugs in ESD, and more often relied on their own clinical experience. At present, the main research is retrospective and observational studies, and there is a lack of specific drug withdrawal and recovery strategies. The aim of this study was to evaluate the effects of antithrombotic drugs on bleeding risk in patients with ESD.

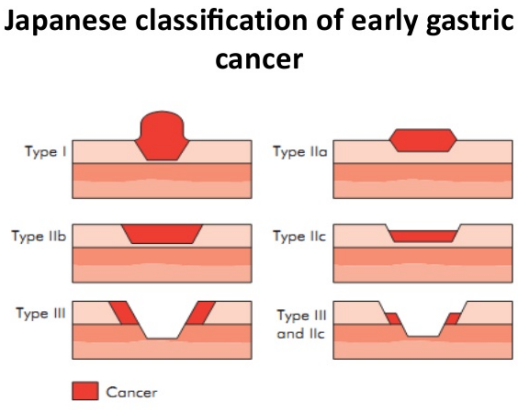

Fig. 1: Early gastric cancer classification

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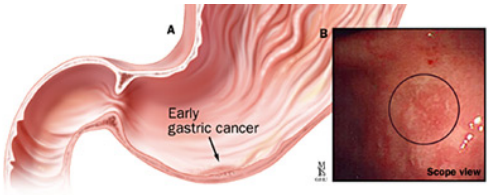

Fig.2: Early gastric cancer founded by endoscopy

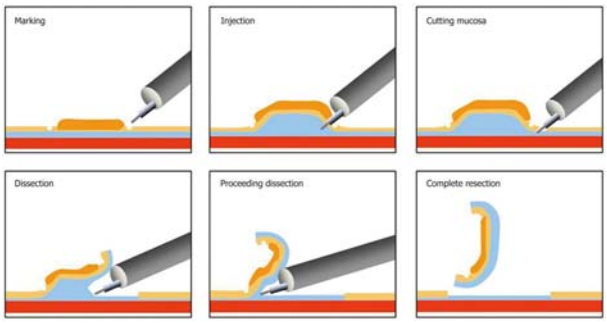

Fig. 3: Image of endoscopic submucosal dissection

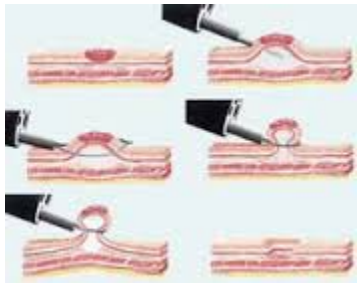

Fig. 4: Endoscopic submucosal dissection

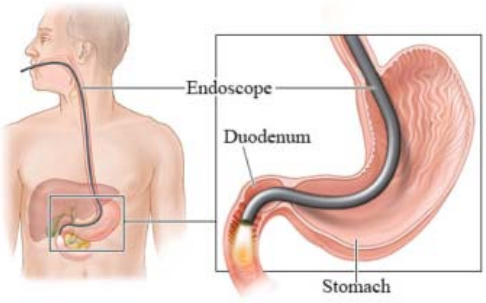

Fig. 5: Gastroscopy

In the practice of pharmacy, promulgated by the State Pharmaceutical Administration Department of drug research, production, circulation, use and Drug Administration and other relevant laws and regulations, rules and regulations is to ensure that all relevant units to normalize their pharmaceutical basis and guidelines (Altorki, 2016; Bergmann, 2016). The position and function of its own, also called in to ensure that these laws and regulations, rules and regulations formulated seriously at the same time, it is necessary for new ideas, new phenomena and new methods in pharmacy practice, make a scientific and systematic study and analysis of its theoretical basis, to more fully legal laws and regulations regulate the pharmacy the behavior of the corresponding departments (Chen *et al.,* 2009; Cahill *et al.,* 2015). The pharmaceutical logistics, on the one hand, provides a rare opportunity for the medical and health industry, the traditional medical industry to re shuffle the various interest groups on the other hand, also put forward a great challenge to China's current pharmaceutical laws and regulations.

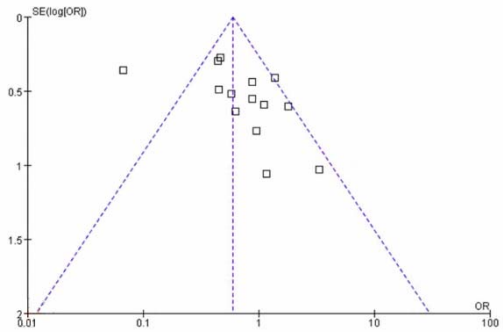

Fig. 6: Funnel plot

In China traditional mode of pharmaceutical logistics, pharmaceutical drug dealers and related units are in various regions for hospitals, pharmacies, clinics do delivery `, overlapping business relations, is a relatively chaotic model is formed in the process of logistics mode of modern medicine and primary logistics mode reflects the various pharmaceutical companies the druggist, products collected by the logistics center, logistics center of downstream customers around the do distribution trend (Dindo *et al.,* 2004; Ghoneum *et al.,* 2015). Compared with the traditional mode of pharmaceutical logistics, modern pharmaceutical logistics can reduce the cost, reduce the business management of pharmaceutical retail terminal purchase cost and improve enterprise credit, solve the long-term medical arrears, increase market concentration, reduce the cost of sales orders, centralized, standardized management, reduce the risk and restore the smooth flow of public traffic, formation through the sharing of logistics facilities, logistics and financial system combined with the formation of network operation, promote the enterprise growth efficiency, and increase market share.

However, due to the modern logistics model is the role of the logistics provider in the middle route of the pharmaceutical logistics, and the logistics can share the benefits of resource sharing and the resource sharing. In addition, also relates to drug flow regulation, various drugs in regulating season through their quest to reduce the total transportation cost, enhancing the efficiency, but also timely research and adjust the relevant legal norms, effective protection of these new roles, new situation and new problems, to ensure the healthy and sustainable

development(Liu,2013; Hu, 2013). At present, scholars began to study medicine logistics, but there is little literature from the medical logistics supply chain management perspective, the pharmaceutical industry of different interest groups linked to the system to study its effect on drug supervision and management.

MATERIALS AND METHODS

General materials

From January 2012 to December 2014, our department performed ESD on 524 patients with early gastric cancer as determined by endoscopy and pathologic diagnosis. Among the 524 patients, 321 were male and 203 were female, and their ages ranged between 40 and 71 years with an average of 56.4 years. Three lesions were in the cardia, five were in the angular incisure, and sixteen were in the antrum. The lesions ranged in size between 1.5-5.0 cm with an average size of 3.6 cm. One lesion had an endoscopic grade of I, sixteen had an endoscopic grade of IIa, one had an endoscopic grade of IIb, and six had an endoscopic grade of IIa + IIC. EUS was performed before the procedure on patients with IIC to confirm that the pathologic change was limited to the mucosal and submucosal layers (Cetinkunar *et al*., 2015; Chapoy-Villanueva *et al*., 2015; Chen *et al*., 2015). The primary indications for ESD are: (1) non-ulcerated, undifferentiated intramucosal carcinoma with tumor diameter ≤ 20 mm; (2) non-ulcerated, differentiated mucosal pain regardless of lesion size; (3) differentiated intramucosal carcinoma with tumor diameter ≤ 30 mm accompanied with ulceration; (4) non-ulcerated, differentiated sm1 submucosal carcinoma with tumor diameter ≤ 30 mm (Dagher *et al*., 2015; Duzagac *et al*., 2015). Approved by the ethics committee of the hospital, all patients signed informed consent before surgery.

Operating procedure

Prior to surgery, all patients signed an informed consent form and were informed regarding the surgical procedure and benefits and risks of the procedure. (1) First, 0.1-0.4% indigo carmine dye was used to demarcate the tumor boundary, and then a Flex knife or needle-knife was used to mark about 5 mm outside the tumor boundary. (2) A mixture of 10% glycerol, 5% fructose, epinephrine, indigo carmine, and normal saline was injected into the submucosa. (3) After fully lifting the pathologic area, it was pre-cut using a Flex knife or needle-knife, and an IT Knife or Flex knife was used to make a circular incision along the boundary marking. If the tumor was small, a snare was used to dissect the lesion. If the tumor was larger, accompanied by ulceration, had an atypical morphology, or was located in the angular incisure or other areas difficult for snare resection, submucosal dissection was performed. During the procedure, additional submucosal injection was performed as needed to maintain full lifting of the lesion and clear visualization during dissection. (4) Visible blood vessels in the mucosal wound surface were preventively closed during hemostatic forceps, argon plasma coagulation, or other methods. Larger exposed blood vessels were closed with hemostatic clips. Finally, sucralfate was sprayed on the wound surface to protect the wound and prevent bleeding (Guan *et al.,* 2015; Gunaldi *et al.,* 2015; Guo *et al.,* 2015; Gu *et al.*, 2015).

Meta analysis method

At the same time, we used Meta to investigate the effects of antithrombotic drugs on postoperative bleeding after endoscopic submucosal dissection (ESD). By reading the title and abstract of the literature, the relevant literatures were excluded, and then screened by the inclusion criteria and exclusion criteria. Inclusion criteria: the object of study for the treatment of ESD patients, comparing research methods for the use of antithrombotic drugs (including antiplatelet and anticoagulant drugs) and without the use of antithrombotic drugs, or the difference between the use of different methods. Without the use of antithrombotic drugs is defined as never taking or withdrawal before surgery has more than 30 d; continuous use of antithrombotic drugs is defined as disabled or disabled during the operation time of less than 7 d; discontinuation of antithrombotic drugs is defined as preoperative discontinuation of the drug more than 7 d, but less than 30 d. Effect index was used to evaluate the risk of bleeding after ESD,≤2D was defined as the early hemorrhage, ≥3D was defined as delayed hemorrhage. This study included a total of 15 papers, are observational studies (Cho *et al.* 2012; Suzuki *et al.*2014; Goto *et al.* 2010; Koh *et al.*2013; Sanomura *et al.* 2014; Lim *et al.* 2012; Yoshio *et al.* 2013; Ono *et al.* 2009; Takeuchi *et al.* 2013; Mukai *et al.* 2012; Miyahara *et al.* 2012; Mannen *et al.* 2010; Okada *et al.* 2011, Takizawa *et al.* 2008; Tokioka *et al.* 2012). Among them, 3 articles used antiplatelet drugs alone, and the other 12 were using antiplatelet drugs and anticoagulant drugs.

Histologic assessment of treatment efficacy

Lack of cancer cells at the resection margin was considered complete curative resection. Possible cancer cells at the resection margin were considered possible curative resection. Absence of either of these statuses is considered a lack of histologic curative resection.

Complications

Complications primarily included abdominal pain, bleeding, laceration, and gastrointestinal tract stricture. Mild acute bleeding indicates continuous intraprocedural oozing or spraying bleeding for 1 min or more which was successfully controlled with the endoscope. Heavy acute bleeding indicates active intraprocedural oozing or spraying bleeding that was difficult to control with the endoscope and required termination of the procedure

Table 1: ESD data of the 524 patients

Variable	Data
Time (median and range)	51 min (45-200 min)
One-time en bloc resection rate	100% (524/524)
Histologic curative resection rate	100% (524/524)
Pathology data Well-differentiated adenocarcinoma	349
Moderately differentiated adenocarcinoma	175
Intramucosal carcinoma	452
Submucosal carcinoma	72

Table 2: Complication data

Variable	Data
Mild acute bleeding	22 (4.2%)
Abdominal pain	284(54.2%)
Heavy acute bleeding,	0
Perforation	0
Delayed postoperative bleeding	0

and/or blood transfusion therapy. Delayed bleeding indicates clinical signs of bleeding after the procedure and/or hemoglobin levels decreasing more than 20 g/L (Han *et al.,* 2015; Hou *et al.,* 2015; *Jia et al.,* 2015; Kertmen *et al.,* 2015; Kong *et al.,* 2015; Kouloulias *et al.,* 2015).

RESULTS

The ESD group underwent surgery for 45-200 min with an average of 48 min. The one-time en bloc resection rate was 100%, and the histologic curative resection rate was 100%. Postoperative pathology: 349 patients with well-differentiated adenocarcinoma, 175 patients with moderately differentiated adenocarcinoma; 452 patients with intramucosal carcinoma, and 72 patients with submucosal carcinoma, as show in table 1.

The rate of mild acute bleeding was 4.2% (22/524), the incidence of postoperative abdominal pain was 54.2% (284/524), and no heavy acute bleeding, perforation, or delayed postoperative bleeding occurred, as show in table 2. There was one case of antral stricture after EGC procedure in the antrum, but there were no symptoms of gastrointestinal tract obstruction. No heavy acute bleeding, postoperative delayed bleeding, or gastrointestinal tract laceration occurred. Endoscopic re-examination at 2 months revealed an ulcer healing rate of 100%.

Follow-up at 12 months revealed no local residue, relapse, or new lesions. In the Meta analysis, the object of study for ESD treated patients, comparative research methods for the use of antithrombotic drugs (including antiplatelet and anticoagulant drugs) and without the use of antithrombotic drugs, or the difference between the use of different methods. Without the use of antithrombotic drugs is defined as never taking or withdrawal before surgery has more than 30 days; continuous use of antithrombotic drugs is defined as disabled or disabled during the operation time of less than 7 days; discontinuation of antithrombotic drugs is defined as preoperative discontinuation of the drug more than 7 days, but less than 30 days. Effect of indexes for the risk assessment of bleeding after ESD, which is less than 2 days is defined as early bleeding, defined as more than 3 days delayed hemorrhage.

Heterogeneity among the studies ($P < 0.00001$, $I2=75\%$), using random effects model. The Meta analysis results showed that discontinuation of antithrombotic drugs were risk of bleeding (8.19%, 114/1 392) higher than that of never taking antithrombotic drugs (group 5.28%, 472/8 938), but no statistical significance (OR=0.67, 95%, CI: 0.40 ~ 1.11, P=0.12) , as show in fig. 7. ESD 2 days after the operation is resumed the use of antithrombotic drugs. The subgroup analysis showed that postoperative withdrawal of more than 7 days, discontinuation of antithrombotic drugs were risk of bleeding (6.21%, 41/660) and never taking antithrombotic drugs (6%, 354/5, 896) showed no significant difference (OR=0.99 95%, CI: 0.71~1.39, P=0.97), as show in fig. 8. And after 2 days recovery of antithrombotic drug use, discontinuation of antithrombotic drugs were risk of bleeding (9.97%, 73/732) was significantly higher than that of never taking antithrombotic drugs (group 3.88%, 118/3 042), and the difference was statistically significant (OR=0.32, 95% CI: 0.11 - 0.96, P=0.04), as show in fig. 9.

There are 3 articles evaluated the combination evaluated the combination of 2 or more than 2 kinds of antithrombotic drugs with 1 kinds of antithrombotic drugs affect the risk of bleeding after ESD, the results

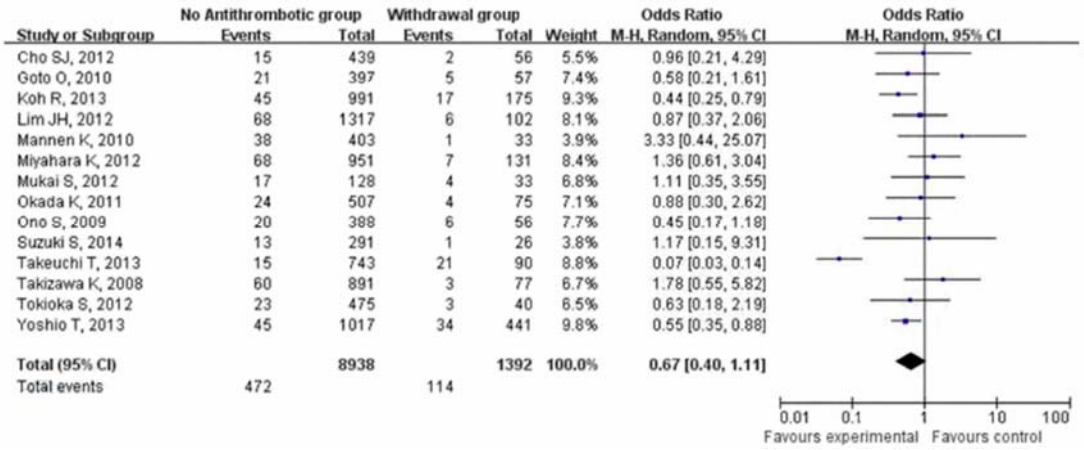

Fig. 7: Risk of bleeding after ESD surgery (Discontinuation of antithrombotic drugs with Not taking antithrombotic drugs)

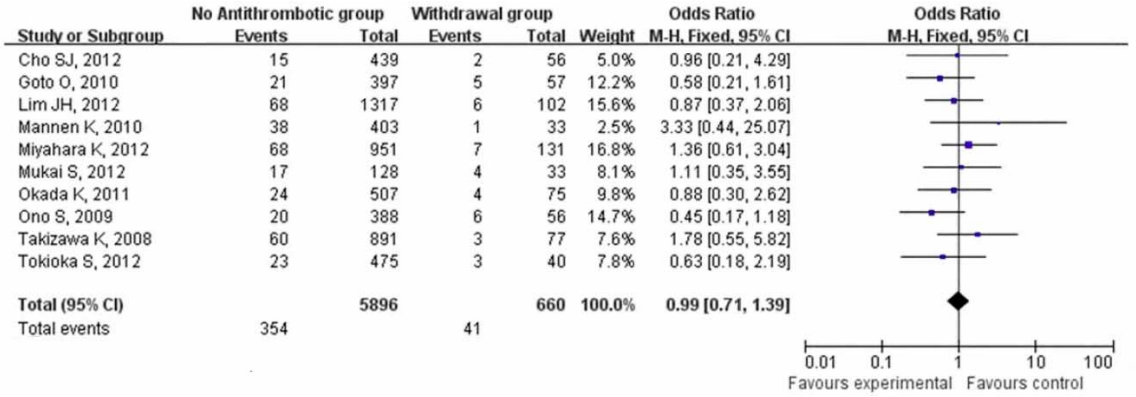

Fig. 8: Risk of bleeding after ESD surgery (discontinuation of more than 7D)

combined with antithrombotic drug group bleeding risk (13.31%, 39/293) was significantly higher than that of the single group (6.30%, 26/413), there was statistical and the difference (OR=2.13, 95% CI: 1.22~3.72, P=0.008) as show in fig. 10.

DISCUSSION

Bleeding is a common and serious complication of ESD, intraoperative bleeding can be found and treated in a timely manner, but the late postoperative bleeding, treatment is not timely, may cause serious consequences. With the aging of society, cardiovascular and cerebrovascular diseases gradually increased, taking antithrombotic drugs in patients with more and more, therefore, more and more attention for the risk of ESD patients treated with taking antithrombotic drugs. There is a lack of a unified understanding of the effects of anticoagulation or antiplatelet drugs on postoperative bleeding in patients with ESD. The results showed that the use of antithrombotic drugs in ESD did not significantly increase the risk of postoperative bleeding,
The preoperative discontinuation of antithrombotic drugs more than 7 d can greatly reduce the risk,and there was no significant difference with those who had never used antithrombotic drugs. But further research has found that even before operation was discontinued antithrombotic drugs, the risk of delayed bleeding is still higher than never use of antithrombotic drugs, which may be related to the postoperative recovery use of antithrombotic drugs related.

Radical gastric cancer surgery and lymph node dissection have been considered the treatment of choice for early gastric cancer (Apostolakis *et al*., 2015; Aldeas *et al*., 2015; Zhou *et al*., 2015; Lv *et al*., 2015; Liu *et al*., 2015; Sun *et al*., 2015; Luo *et al*., 2015; Hou *et al*., 2015; Tao *et al*., 2015; Shi *et al*., 2015). Radical surgery for intramucosal carcinoma and submucosal carcinoma have a postoperative 5-year survival rate as high as 98%, but the complication rate and mortality rate of radical surgery are as high as 30% and 5% respectively (Lee *et al*., 2015; Liapis *et al*., 2015; Li *et al*., 2015;). After radical surgical resection, symptoms such as early satiety, swallowing difficulty, reflux, and abdominal discomfort are common complications, and quality of life is similar to radical surgery during the progression stage of gastric cancer (Antonova *et al*., 2015; Antonova *et al*., 2015; Avci *et al*., 2015;). Studies have already confirmed endoscopic treatment is appropriate for early gastric cancer with a

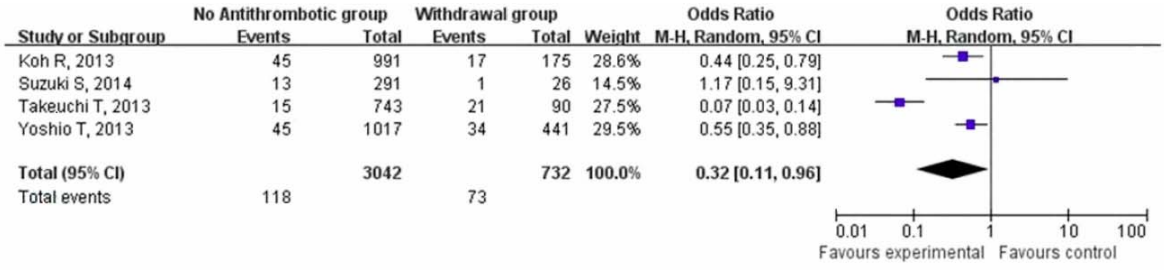

Fig. 9: Risk of bleeding after ESD surgery (discontinuation 2D)

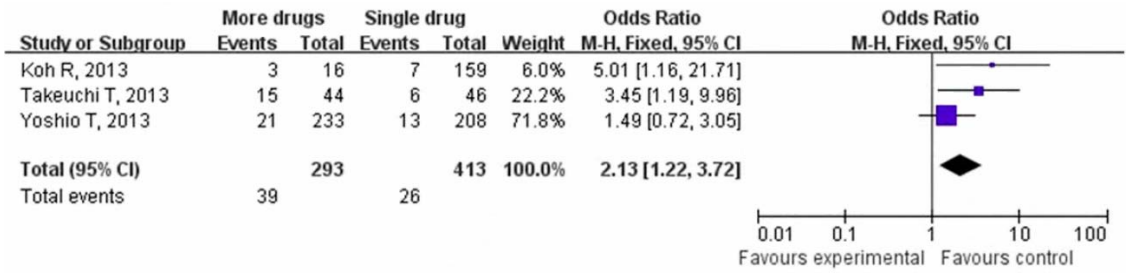

Fig. 10: Combined antithrombotic drugs

very low rate of lymph node metastasis (Damyanov *et al*., 2015; Divani *et al*., 2015; Gkialas *et al*., 2015 ;).

In the last 20 years, endoscopic mucosal resection (EMR) is already widely used to treat early gastric cancer, but EMR treatment of lesions >1.5cm in size or complicated by ulcers or scar tissue have one-time en bloc resection rates of less than 50%. The local relapse rate when 2, 3, or 4 or more lesions are resected are 6%, 26%, and 24% respectively, and postoperative confirmation of the depth of gastric cancer invasion is difficult. Therefore, the Japanese Gastric Cancer Association limited EMR treatment to be appropriate for differentiated, non-ulcerated, <20 mm uplift, ≤1 cm flat, or concave early gastric cancers (Gao *et al*., 2015; Gatzidou *et al*., 2015;). In 1994, the Japan National Cancer Center Hospital designed and began using the IT Knife to treat early gastric cancers, and from this point ESD become more and more broadly used to treat early gastric cancers (Luo *et al*., 2015; Lykoudis *et al*., 2015;).

Comparing ESD, EMR and other endoscopic methods with laparatomic procedures reveals the following benefits (Carvajal *et al*., 2015; Caziuc *et al*., 2015; Cetean *et al*., 2015 ; Li *et al*., 2015; Emir *et al*., 2015; Zhang *et al*., 2015; Huang *et al*., 2015): (1) Individualized treatment and strong targeting. Individualized ESD treatment programs can be prepared based on the location, size, shape and histologic classification of the lesion, ensuring the thorough resection of the tumor as well as preserving normal tissue and function to the greatest extent. (2) Less trauma, well tolerated by patients. The large trauma of laparotomy and the need for anesthesia is more demanding on the overall physical condition of the patient (e.g. heart and lung function, etc.). Because ESD involves fewer traumas and reduces patient suffering, it is beneficial for patient recovery and can be appropriate for patients who cannot tolerate or are unwilling to undergo laparotomy (such as elderly patients). (3) The same patient can undergo many ESD treatments, and treatment of multiple locations can take place at once. ESD can address multiple primary tumors, and is especially optimized for multiple primary tumors involving the gastrointestinal tract. (4) ESD can obtain complete histopathologic markers under non-surgical conditions, thereby elucidating the nature, invasion depth, and differentiation status of the lesion, determining whether lymphatic or vascular invasion exists, and predicting whether high-risk factors such as lymph node metastasis exists, benefiting clinical selection of the correct treatment regimen and sparing unnecessary surgical treatments. (5) Compared to EMR, ESD can dissect tumors with relative large area, irregular shape, or combined with ulceration or scarring en bloc from the muscular layer, significantly reducing tumor residue and relapse (Abu 2017; Fang and Ruan 2017; Liu *et al*. 2017; Takahashi 2017).

In this study, except for the occurrence of mild acute bleeding and mild postoperative upper abdominal pain, there were no complications such as heavy acute bleeding, gastrointestinal tract perforation, or postoperative delayed bleeding. Endoscopic follow-up at 2 months after ESD revealed an ulcer healing rate of 100%, and follow-up at 12 months revealed no local residue, relapse, or new lesions.

Along with many types of flexible endoscopes, many types of knives, electromagnetic fixation technologies, and many models of ERRB electronic endoscopy

systems and their attachments have been rapidly introduced and used in the clinic. Currently, ESD is the procedure of choice for early gastric cancer in Japan, Korea, and other East Asian countries. Preliminary results of ESD treatment of early gastric cancer are promising, but this treatment still has strict treatment indications, with weaknesses such as highly demanding endoscopic operation technique, and long-term clinical efficacy still requires further assessment (Breitenbuecher *et al*., 2015; Bruera *et al*., 2015; Bulut *et al*., 2015; Lin *et al*., 2015; Nishida *et al*., 2015; Longcroft-Wheato *et al*., 2015; Zhong *et al*., 2015).

CONCLUSION

The Meta analysis showed that the use of antithrombotic drugs before ESD can reduce the risk of postoperative bleeding, but the early recovery of the use of antithrombotic drugs, or combined with a variety of antithrombotic drugs will increase the risk of bleeding. Further randomized controlled studies are needed to confirm the specific strategies for stopping the drug. ESD is a method for one-time en bloc resection without needing traditional surgical procedures, and can achieve precise, histopathologically diagnosed, safe, and effective treatment method for early gastric cancer.

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