의학박사 학위논문

돼지 모델에서 체중 감소를 위한

새로운 식욕억제 위장관 장치의 개발

Development of Novel Intra-gastric Satiety-inducing Devices

울산대학교대학원

의 학 과

나 희 경

돼지 모델에서 체중 감소를 위한

새로운 식욕억제 위장관 장치의 개발

지도교수 정 훈 용

이 논문을 의학박사 학위 논문으로 제출함

2019년 12월

울산대학교 대학원

의 학 과

나 희 경

나희경의 의학박사학위 논문을 인준함

심사위원장 김 도 훈 (인)

심사위원 정 훈 용 (인)

심사위원 최 기 돈 (인)

심사위원 안 지 용 (인)

심사위원 임 현 (인)

울 산 대 학 교 대 학 원

2019 년 12 월

Abstract

Introduction: Minimally invasive procedures can impact the treatment of obesity by bridging the gap between medical and surgical therapy. Therefore, we developed a device that can be placed under endoscopic guidance to reduce the rate of weight gain and promote weight loss and evaluated its safety and efficacy in a porcine model.

Methods: The intra-gastric satiety inducing device (ISD) is a modified partially covered self-expandable esophageal stent connected to a star-shaped disk part. Eight juvenile pigs were randomly divided into ISD (n=5) and control (n= 3) groups. The ISD was placed under endoscopic and fluoroscopic guidance and fixed to the pig's nose by a string. Animal behavior, body weight, serum ghrelin hormone, and the ISD position were monitored weekly. Four pigs were sacrificed 6 weeks after ISD placement or in case of complications. One pig had the ISD removed at 6 weeks and was followed up for an additional 4 weeks to check for rebound effects (rebound pig). Hematoxylin& eosin and Masson's trichrome staining, and immunostaining for the interstitial cell of Cajal (ICC) were performed after sacrifice.

Results: The ISD placement was technically successful in all pigs without any immediate complications. Two ISDs (40%) migrated at 4 and 5 weeks after placement and their data were included in the analysis at the respective time points. The ISD group had significantly lower median percentage weight gain ratio from week 1 to week 6 compared to the control group: 4% vs 26% at week 1 (p=0.025), 15% vs 47% at week 2 (p=0.025), 29% vs 49% at week 3 (p= 0.024), 49% vs 71% at week 4 (p=0.043), 56% vs 82% at week 5 (p=0.034), and 46% vs 88% (p = 0.05), respectively. The rebound pig showed a higher rate of weight gain compared to the control from week 7 to week 10: 105%, 126%, 142%, and 157% vs 97%, 99%, 102%, and 107%, respectively. The median ghrelin hormone levels in the ISD group from week 1 to week 6 were 20.9, 32.3, 28.3, 41.4, 47, 39.7 ng/L. The ISD induced reversible inflammatory changes

in the distal esophagus and the fundus of the stomach. The number of the ICCs (median, range) was lower in the ISD (3, 1-4) compared to the control (9.5, 7-16), and the rebound (11.5, 8-15) pigs.

Conclusion: The ISD reduces the rate of weight gain in juvenile pigs and induces reversible inflammation and tissue hyperplasia. The mechanism of action of the ISD may be related to pressure effect on the gastric fundus or alteration of gastric motility.

Key Words: Obesity, Weight loss, Intragastric satiety inducing device, Interstitial cells of Cajal

차 례

표 및 그림 목차

INTRODUCTION

Obesity has become international public health problem that affect the quality of life, increase the risk of illness and raises the health-care costs in the past 50 years.[1] Obesity affect more than one-third of adults in United State [2] and the prevalence of obesity worldwide has been increasing. It is associated with various comorbid condition such as hypertension, diabetes, dyslipidemia, coronary heart disease, sleep apnea, stroke and nonalcoholic fatty liver diseases and it is associated with an increased risk of all-cause mortality.[3]

Bariatric surgery remains the gold standard for the treatment of severe obesity. However surgical treatment is often related to high cost, adverse events, and low patient acceptance.[4] There has been a consistent need for less invasive intervention which can avoid or bridge to surgery. Various endoscopic treatment devices including intra-gastric balloons, duodenal-jejunal bypass sleeve, and duodenal mucosal resurfacing has been developed. These endoscopic bariatric therapies can offer the potential advantages of reversibility, repeatability, and cost effectiveness.[4]

Full sense device is reported as an effective method to induce satiety by compression on gastric cardia.[3,5] Unpublished animal and human study has shown that the device is useful to induce excess weight loss without serious complications.[5] However, the animal and clinical data has not been published recently and the device has not been commercialized nor approved for sale. Therefore, in this study, we aimed to develop a novel intra-gastric satiety-inducing device (ISD) to promote weight loss and evaluated its safety and efficacy in a porcine model.

MATERIAL AND METHODS

Animal study

A total of 8 pigs weighing 31.2–43 kg (median, 34.1 kg) were purchased from Orient Bio (Seongnam, Korea) and were randomized into two groups. Five pigs underwent ISD placement (ISD group). The remaining three weight- and age-matched healthy pigs were used as controls (control group). All pigs were fed regular chew (unrestricted supply) and maintained at 22 ± 2°C.

This study was approved by the Institutional Animal Care and Use Committee of our institution and conformed to U.S. National Institutes of Health guidelines for humane handling of laboratory animals.

Novel ISD and delivery system

The developed ISD was shown in Figure 1. It comprised two parts: a straight self-expanding metallic stent (SEMS) for the lower esophagus and a nitinol disc for the fundus of the stomach. The esophageal SEMS part was knitted from a 0.229-mm nitinol wire into a tubular configuration. When fully expanded, the SEMS part was 24 mm in diameter and 60 mm in length. Four flaps were attached to the upper end of the esophageal SEMS part to prevent migration. The distal end of the esophageal SEMS had 6 barbs (3 mm in length,) the proximal 20 mm was uncovered while the remaining 40 mm were covered by silicon. An anti-reflux valve was attached to the esophageal SEMS. To make the ISD removable, a drawstring of nylon monofilament was attached to the upper inner margin of the SEMS. The disc part was designed to be in direct contact with the fundus of the stomach to apply continuous pressure. It was a star-shaped flat mesh made from a 0.229-mm nitinol wire (diameter, 70 mm) and perpendicularly connected to the esophageal SEMS part by two pillars of nitinol wire (50 mm

in length) and the connection was covered by PTFE membrane. The ISD delivery system comprised a Teflon sheath (outer diameter, 9.3 mm; inner diameter, 8.3 mm; length, 70 cm), and a pusher catheter with a guiding olive tip. A hole was made 15 cm from the tip to allow passage of the strings after the ISD placement. The total introducer length was 120 cm. The ISD was fixed in pace by a polyester string. The string was passed through the nose of the pig and tied to a metal ring attached to the nasal bridge.

Techniques of ISD placement and removal

After 12 h of fasting and under the supervision of a veterinarian, the pigs were premedicated with 50 mg intramuscular ketamine. An endotracheal tube was placed, and anesthesia was administered by inhalation [0.5%–2% isoflurane (Ifran®; Hana Pharm. Co., Seoul, Korea) with oxygen (510 mL/kg per min) at 1:1]. All procedures were performed in the left decubitus position. An over-tube was placed through the mouth into the esophagus. An endoscope (CF-H260AI; Olympus Inc. Tokyo, Japan) was introduced through the over-tube into the stomach, and the suction of gastric secretions was performed by a gastroenterologist. A 0.035-inch guidewire (Radifocus M; Terumo, Tokyo, Japan) was passed through the working channel of the endoscope into the stomach. The endoscope was removed while retaining the guidewire, and the ISD delivery system was passed over the guidewire into the stomach by an interventional radiologist. Under fluoroscopic guidance, the pusher catheter was held in place with one hand, while the sheath was slowly withdrawn in a continuous motion with the other hand. The disc part was placed in the gastric fundus, and the connection part was placed in the lower esophagus, bridging the gastroesophageal junction (Figure 2). The two strings that are attached to the proximal part of the esophageal part of the ISD were passed outside the pig's mouth. A soft guidewire was passed from the each nostril to the mouth and the string was tied to the guidewire which was pulled through the nose. The strings were then fixed to a metal ring

attached to the nasal bridge. After the ISD deployment, its position was assessed by endoscopic and fluoroscopic examination. For the removal of the ISD, the drawstring was grasped and pulled into the sheath, and the entire device was collapsed by withdrawing the hook wire using fluoroscopic monitoring. If the ISD had migrated to the stomach, removal was performed under endoscopic and fluoroscopic guidance.

Follow-up

After ISD placement, the pigs could eat after recovery from the anesthesia. The amount of food intake was monitored three times per day. Weight and behavioral changes were monitored at 1-week intervals. The percentage of weight gain was calculated according to the following formula: percentage of weight gain (%) = (final weight − initial weight) / initial weight × 100. Plain radiographs of the abdomen were obtained at 1-week intervals to assess the ISD position. Endoscopic examination was performed 4 weeks after ISD placement to evaluate the ISD position and ISD-related side effects.

Histopathology and immunostaining

Four pigs from the ISD group and two from the control group were sacrificed 6 weeks after placement or in case of side effects. The remaining pig from the ISD group had the device removed at 6 weeks and was followed up for an additional 4 weeks to check for any rebound effects (rebound pig). All pigs were euthanized by the administration of an overdose of xylazine hydrochloride (Rompun; Bayer, Seoul, Korea). Surgical exploration followed by gross examination of the esophagus and stomach was performed. Specimens were then collected and fixed in 4% neutral buffered formalin for 24 hours at 4°C and then embedded in paraffin and sectioned. The slides were stained with hematoxylin and eosin and Masson's Trichrome.

Immunohistochemical staining for CD117 (CKIT, GTX33947; GeneTex, Irvine, Calif) was performed to assess the presence of interstitial cells of Cajal (ICC). Before staining, unstained 3μm sections were cut from neutral formalin-fixed, paraffin-embedded blocks and rehydrated using ethanol. Staining was performed in Genoss co., ltd by an automated Ventana Discovery (Ventana Medical Systems, Inc, Tucson, Ariz) per the manufacturer's protocol using a standard CC1 (EDTA pH 9) antigen retrieval and the DAB Detection Kit (Ventana Medical Systems, Inc). CD117 (CKIT) staining was first evaluated qualitatively for overall normal-appearing patterns and the number of CD117 (CKIT)-positive ICCs. CD117 positive ICCs were also quantified by counting positively stained cells per high power field (×400). For each slide, three high-power fields were counted and averaged

Statistical analysis

Data are expressed as the median (range). The differences between the groups were analyzed using Mann–Whitney U-test, as appropriate. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 23.0; SPSS, IBM, Chicago, IL, USA).

RESULTS

Technical outcomes

The ISD placement was technically successful in all cases (100%, n = 5) without procedure-related adverse event. Two ISDs (40%, 2/5) migrated at 4 and 5 weeks and was successfully removed under endoscopic and fluoroscopic guidance with no adverse event. The remaining ISDs removal was successful 6 weeks after placement under endoscopic and fluoroscopic

guidance. The pigs were immediately sacrificed and their data included in the analysis at the respective time points. The remaining three ISDs were removed 6 weeks after placement; two pigs were immediately sacrificed and one pig (the rebound pig) was followed up for additional 4 weeks.

Weight changes

The ISD group had significantly lower median percentage weight gain from week 1 to week 6 compared to the control group (Table 1 and Figure 3(a)); 4% vs 26% at week 1 (p=0.025), 15% vs 47% at week 2 (p=0.025), 29% vs 49% at week 3 (p= 0.024), 49% vs 71% at week 4 (p=0.043), 56% vs 82% at week 5 (p=0.034), and 46% vs 88% (p = 0.05), respectively. The rebound pig showed a higher rate of weight gain compared to the control from week 7 to week 10; 105% vs 97% at week 7, 126% vs 99 % at week 8, 142% vs 99% at week 9, 157% vs 107% at week 10, respectively (Figure 3(b)).

Gross and histopathological changes

Gross and histopathological changes were shown in Figure 4 and 5. SEMS induced tissue hyperplasia was seen at the proximal end of the esophageal part of the ISD, submucosal chronic inflammatory cell infiltration was seen at its distal end, and epithelial hyper-keratinization was seen at the gastroesophageal junction. In the rebound pig, the esophagus showed partially subsided tissue hyperplasia, and regression of the inflammation and the epithelial hyper-keratinization.

The cardia and fundus of the stomach in contact with the disc part showed superficial ulceration, inflammatory cell infiltration, hyperplasia of the submucosal lymphoid follicles, and in one pig there was an area of small abscess formation. The rebound pig showed residual submucosal lymphoid hyperplasia with mucosal erosions.

ICC Immunohistochemistry

The ISD pig showed qualitative decrease in the ICCs as demonstrated by CD117 (CKIT) staining. The median number of the ICCs per high-power field was lower in the ISD pig (3; range = 1 - 4) as compared with the control (9.5; range = 7 – 16), and the rebound (11.5; range = 8 - 15) pigs (Figure 6). No appreciable inflammation involving the myenteric ganglia on review of the hematoxylin and eosin–stained slides.

DISCUSSION

In this study, ISD showed significantly decelerate weight gain during six weeks follow-up period which is consistent with our previous pilot study.[6] When we removed ISD, the pig showed a higher rate of weight gain compared to the control pigs. ISD seems to be effective to reduce weight gain in juvenile pigs. It is technically feasible in all cases and safe. In our previous study, migration is the main problem of the stent and the migration rate of the fully covered type is up to 100%. Therefore, we modified stent design to prevent migration such as changing the proximal portion as uncovered portion and addition of bars and flaps. Modified ISD decreased the migration rate from 100% to 40%. Vomiting and reflux caused by ISD is another problem in the pilot study. We added anti-reflux flap valve inside the ISD and no cases of reflux or aspiration event was reported during the follow-up period.

The main finding of our study is the inhibition of weight gain in the growing juvenile pigs after the ISD placement. Interestingly, even though the animal behavior was not significantly changed after the ISD placement, the pigs in the ISD group tended to eat less than those in the control group (albeit we could not accurately measure the amount of daily food intake). When the ISD was removed, the rebound pig had rapid rate of weight gain that even exceeded the

rate of the control pig. This means that as long as the ISD is in place, there is a tendency of early satiety and less weight gain, and we assume that this effect would induce weight loss in the case of obesity.

In the ISD group, the esophagus showed mild tissue hyperplasia at the proximal end of the stent, with inflammatory cell infiltration and epithelial cell hyperplasia near the gastroesophageal junction. Submucosal lymphoid follicular hyperplasia were notably increased in ISD pig. Histologic changes seems to be caused by mechanical irritation of the ISD and the changes were reversible after ISD removal. On histological evaluation to assess the effect of the ISD on the stomach, we found that the number of ICC in the fundus of ISD pig decreased compared to control pig. ICC are known as being located less densely in the fundus and the fundus contains only intramuscular ICC.[7-9] ICC contribute to several important function in the GI tract including generation of electrical slow wave activity, coordination of pacemaker activity, and mechanosensation to stretch of GI muscle.[9,10] We infer that the decreased number of ICC is caused by motility restriction and inflammation of the disk portion. The decrease of ICC leads to additional loss of the effective contraction and relaxation of the fundus. Previous study reported that the stomach resected for severe gastroparesis revealed hypoganglionosis, neuronal dyspepsia and decreased myenteric and intramuscular ICC.[11] In our study, the number of ICC increased after removal of ISD. ICC is known as having high degree of plasticity.[12] Trans-differentiation and apoptosis have been proposed as mechanism of ICC loss. Some study group have reported that ICC can transdifferentiate into a fibroblast/smooth muscle phenotype not expressing Kit and after the removal of the insult, ICC can transdifferenate back into a Kit expression ICC after the removal of the insult.[13,14]

The ISD did not induce major side effects (e.g. severe bleeding, perforation, or gastric outlet obstruction requiring surgical intervention). However, mechanical irritation by the uncovered proximal part induced tissue hyperplasia, as expected, that was regressing in the rebound pig.

Inflammatory reactions were found both in the esophagus and fundus of the stomach, which were fully reversible after removal. Additionally, the fundus showed superficial ulceration and hyperplasia of the normally present submucosal lymphoid follicles [15]. While the lymphoid hyperplasia was still evident in the rebound pig, we believe that it would have regressed if the follow-up period was extended. In one pig, a small abscess was found in the submucosa of the fundus of the stomach. We presumed that an element of ischemia, rather than just chronic irritation, is the most plausible explanation. Apparently, too much pressure was exerted while pulling back the disc part to the fundus during the ISD placement (to ensure proper positioning), which resulted in pressure ischemia. This pig had the ISD in place for six weeks, and no obvious changes in its behavior were noted compared to the other pigs.

There are several limitation in this study. First, the number of the pigs was too small to perform robust statistical analysis. Secondly, we did not include the sham group to differentiate the effect of ISD from that of the stent itself. Third, the ISD was not evaluated in obese pigs to investigate its effect on weight loss. These limitations should be addressed in further studies.

CONCLUSION

We developed a new intra-gastric device reducing the rate of weight gain in juvenile pigs. ISD placement is technically feasible and safe in juvenile pigs. It induces reversible inflammatory reaction and tissue hyperplasia in the esophagus and fundus of the stomach. The mechanism of action may be related to pressure effect on the gastric fundus or alteration of gastric motility.

REFRENCES

1. Bray GA, Fruhbeck G, Ryan DH, Wilding JP. Management of obesity. Lancet (London, England) 2016;387:1947-56.

2. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. Jama 2010;303:235-41.

3. Abu Dayyeh BK, Edmundowicz SA, Jonnalagadda S, et al. Endoscopic bariatric therapies. Gastrointestinal endoscopy 2015;81:1073-86.

4. Abu Dayyeh BK, Kumar N, Edmundowicz SA, et al. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies. Gastrointestinal endoscopy 2015;82:425-38.e5.

5. PM. New endoscopic stent can lead to 100% EWL. Bariatic News c2012.

6. Park JH, Bakheet N, Na HK, et al. A Novel Full Sense Device to Treat Obesity in a Porcine Model: Preliminary Results. Obesity surgery 2019;29:1521-7.

7. Hirst GD, Beckett EA, Sanders KM, Ward SM. Regional variation in contribution of myenteric and intramuscular interstitial cells of Cajal to generation of slow waves in mouse gastric antrum. The Journal of physiology 2002;540:1003-12.

8. Mazet B, Raynier C. Interstitial cells of Cajal in the guinea pig gastric antrum: distribution and regional density. Cell and tissue research 2004;316:23-34.

9. Al-Shboul OA. The importance of interstitial cells of cajal in the gastrointestinal tract. Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association 2013;19:3-15.

10. Yin J, Chen JD. Roles of interstitial cells of Cajal in regulating gastrointestinal motility: in vitro versus in vivo studies. Journal of cellular and molecular medicine 2008;12:1118-29.

11. Zarate N, Mearin F, Wang XY, Hewlett B, Huizinga JD, Malagelada JR. Severe idiopathic gastroparesis due to neuronal and interstitial cells of Cajal degeneration: pathological findings and management. Gut 2003;52:966-70.

12. Huizinga JD, Zarate N, Farrugia G. Physiology, injury, and recovery of interstitial cells of Cajal: basic and clinical science. Gastroenterology 2009;137:1548-56.

13. Faussone-Pellegrini MS, Vannucchi MG, Ledder O, Huang TY, Hanani M. Plasticity of interstitial cells of Cajal: a study of mouse colon. Cell and tissue research 2006;325:211-7.

14. Torihashi S, Nishi K, Tokutomi Y, Nishi T, Ward S, Sanders KM. Blockade of kit signaling induces transdifferentiation of interstitial cells of cajal to a smooth muscle phenotype. Gastroenterology 1999;117:140-8.

15. Driessen A, Van Ginneken C, Creemers J, et al. Histological and immunohistochemical study of the lymphoid tissue in the normal stomach of the gnotobiotic pig. Virchows Archiv 2002;441:589-98.

TABLE

Table 1. Percentage changes in body weight of the ISD and the control groups

	Control (n=3)	ISD (n=5)	*p* value
Week 1	26 (24-28)	4% (-5 to 9)	0.025
Week 2	47% (44-48)	15% (12-23)	0.025
Week 3	49% (46-50)	29% (15-41)	0.024
Week 4	71% (70-79)	49% (13-60)	0.043
Week 5 †	82% (81-94)	56% (15-73)	0.034
Week 6 ‡	88% (84-95)	46% (8-72)	0.05

Values are presented as median (range).

†One ISD migrated; ‡One ISD migrated

ISD, intra-gastric satiety-inducing device

FIGURES

Figure 1. Photograph of the ISD showing the proximal uncovered end with the nylon monofilament attached, the anti-migration flaps (white arrows), the barbs (white arrowheads), the valve-like antireflux membrane, the connection pillars (black arrows), and the disc part.

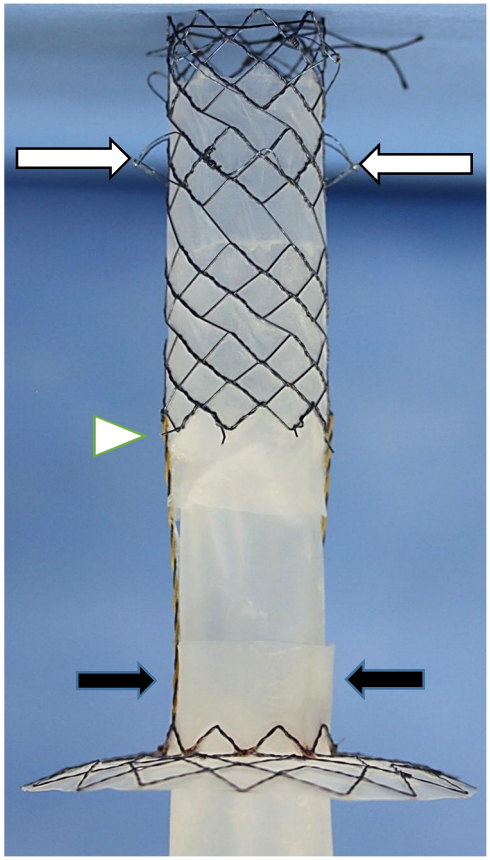
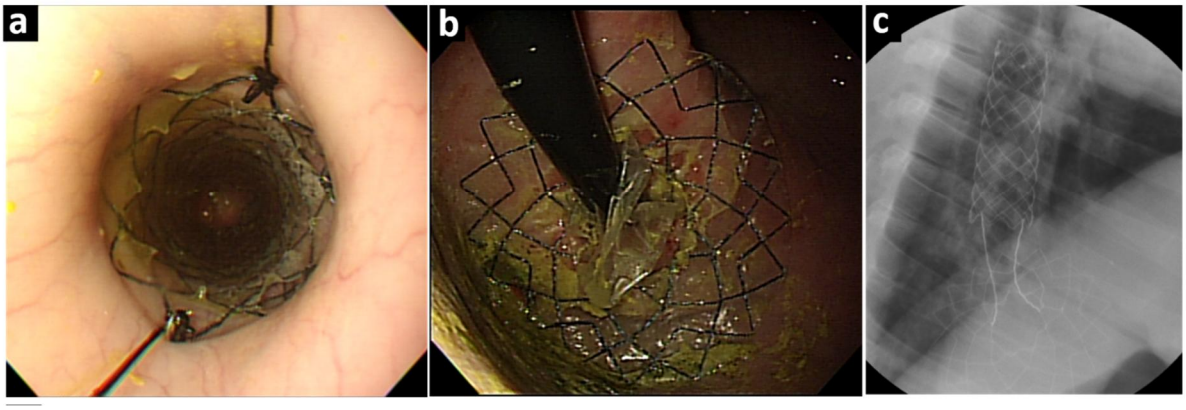


Figure 2. Images of inserted intra-gastric satiety-inducing device

a, b. Endoscopic images showing the proximal and distal ends of the ISD

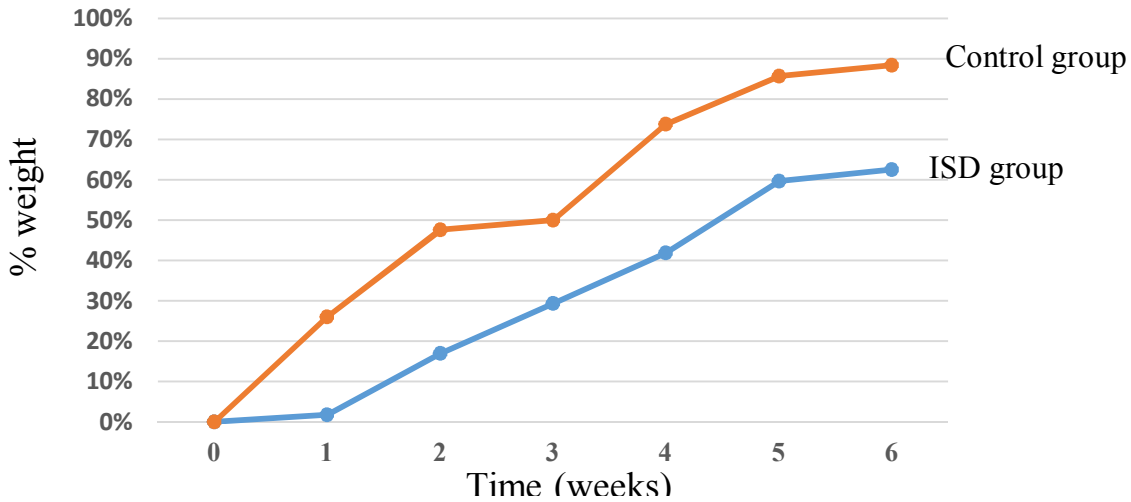
c. Lateral fluorosopic image showing the ISD immediately after placment.



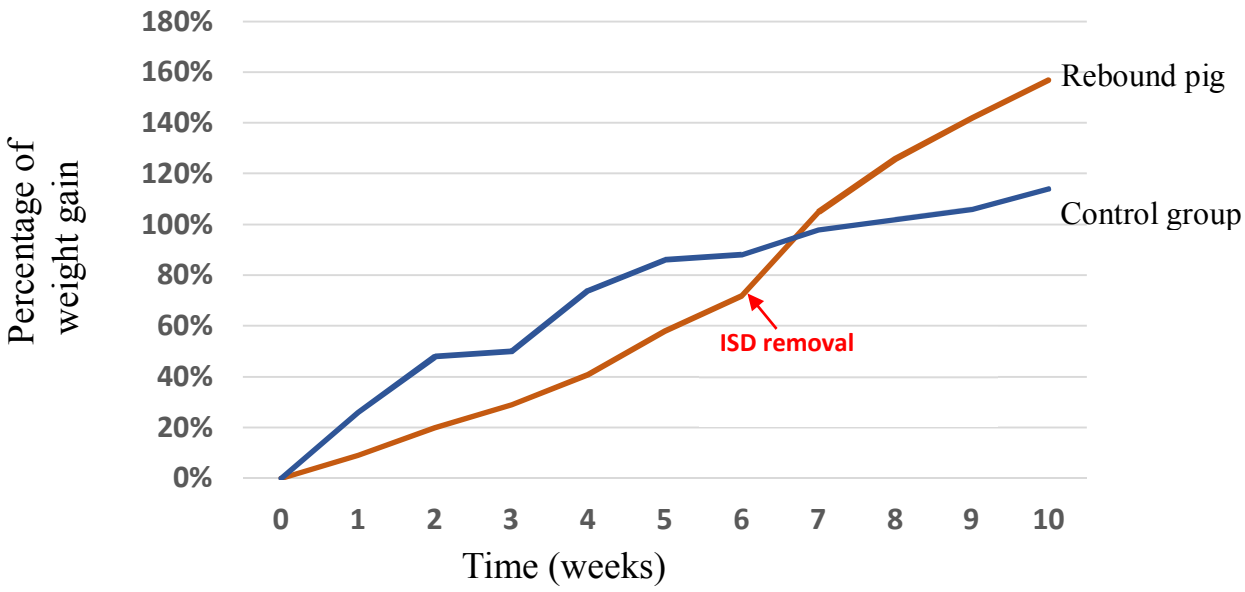
ISD, intra-gastric Satiety-inducing Device

Figure 3. Percent of weight gain ratio during the follow-up periods (a) Line graphs showing the percentage weight change in the ISD group compared with the control group over 6 weeks (b) the percentage weight change in the rebound pig compared with one of the control pigs over 10 week.

(a)



(b)



ISD, intra-gastric Satiety-inducing Device

Figure 4. Representative photographs obtained immediately after autopsy. **(a)** The ISD is in place while the stomach is empty and the fundus collapsed over the disc part (arrows**). (b)** Stomach is full of water (arrowheads pointing to the site of the disc part). **(c)** Opened esophagus and upper stomach after removal of the ISD. **(d)** Opened stomach showing an inside view of the disc part in relation to the gastroesophageal junction (asterisk) and to the porcine gastric diverticulum (arrow).

ISD, intragastric satiety inducing device

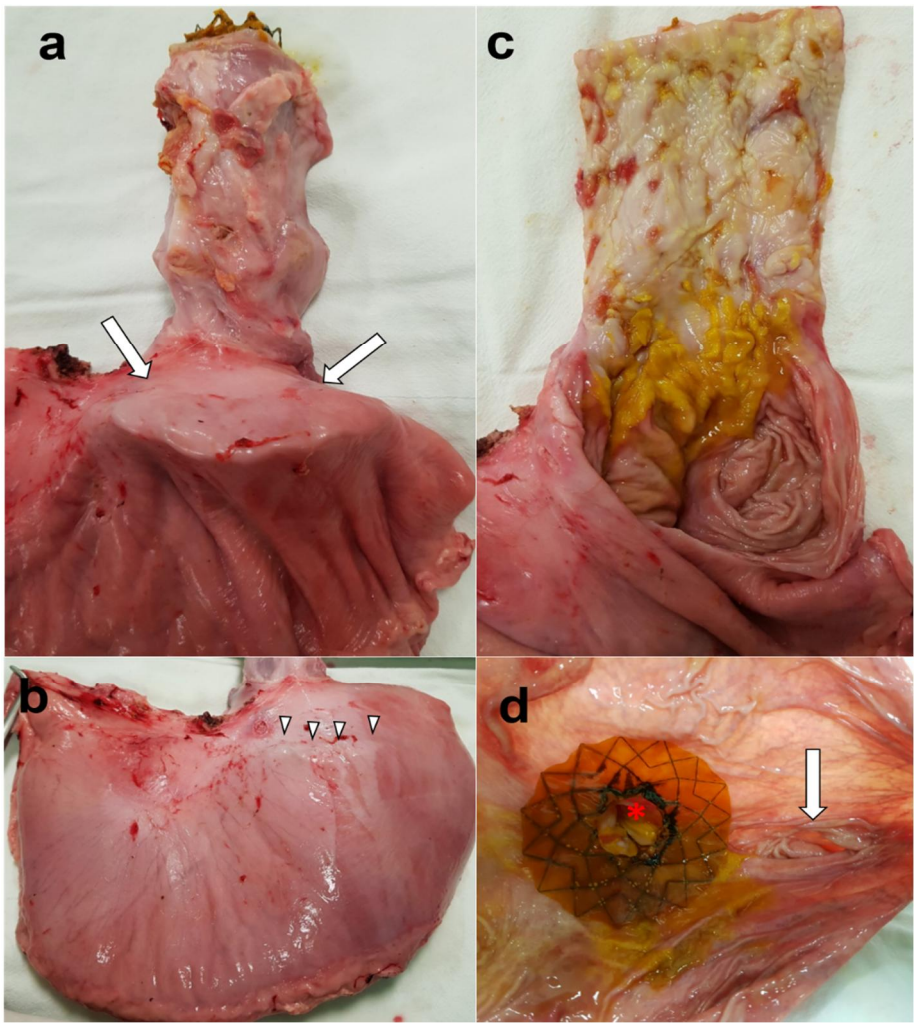


Figure 5. Representative histological images from the esophagus in contact with the esophageal SEMS of the ISD (X 40). The upper row shows MT stained slides from the proximal part with prominent tissue hyperplasia represented by the blue color seen in the ISD group compared to the control group and the rebound pig. The middle row shows H&E stained slides from the middle part with submucosal inflammatory infiltration in the ISD group (arrows) compared to the control group and the rebound pig. The lower row shows H&E stained slides from the gastroesophageal junction with epithelial hyperkeratinization (arrow) in the ISD group; note the lymphoid follicles (arrowheads) at the gastric side in the rebound pig.

H&E, hematoxylin and eosin; ISD, intragastric satiety inducing device; MT, Masson trichrome's; SEMS, self-expandable metal stent

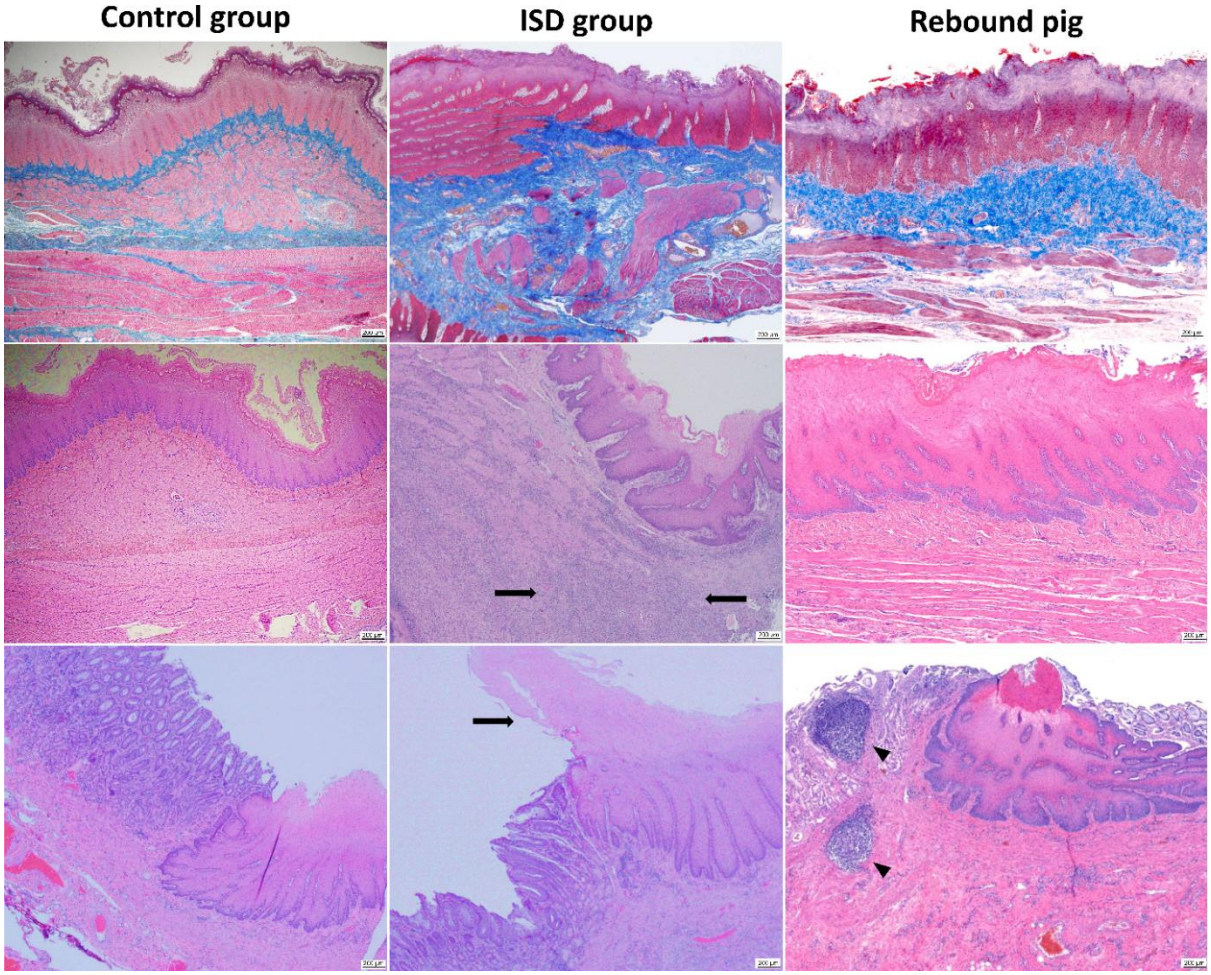
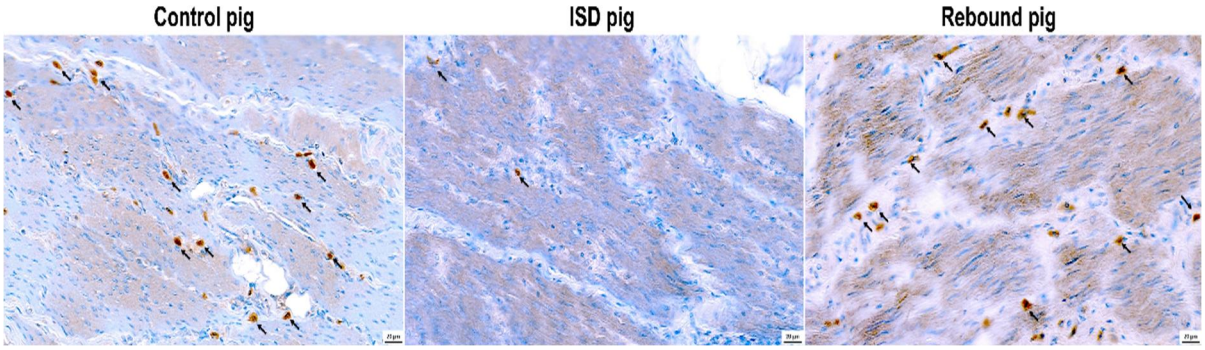


Figure 6. Representative CKIT-stained slides (X 400) from the fundus of the stomach demonstrating decreased numbers of the interstitial cells of Cajal in the ISD pig compared to the control and the rebound pigs. Arrows indicate CKIT-positive interstitial cells of Cajal.



국문요약

연구목적: 본 연구에서는 돼지 모델에서 식욕 억제를 위한 위장관 장치를 개발하고 체중감소 효과와 안정성을 평가하는 것을 목적으로 한다.

연구 방법: ISD 는 자가 팽창성 식도 스텐트로 식도에 거치 되는 부분인 관 구조와 위 저부에 위치하는 디스크 부분의 2 부분으로 구성된다. 40kg 정도의 8 마리의 돼지를 각각 식욕억제 위장관 장치 (Intra-gastric satiety-inducing device, 이하 ISD) 삽입군 (5 마리)와 대조군 (3 마리)로 무작위 할당하여 실험한다. 삽입군은 내시경 및 투시 영상을 통하여 삽입하며, ISD 이동 방지를 위하여 스텐트의 근위부에 2 개의 줄을 연결하여 돼지의 비강으로 빼서 고정한다. 체중 변화 및 혈청 ghrelin 수치, ISD 의 위치를 주 1 회씩 6 주간 확인한다. ISD 군은 6 주후 내시경을 확인한 후 안락사하며, ISD 군 중에서 한마리는 스텐트 제거 후 체중 증가율을 확인하기 위하여 추가적으로 4 주 더 추적관찰 한다. 조직은 각각 식도와 위식도 접합부, 기저부로 나누어 병리 검사를 시행한다. Interstitial cell of Cajal (ICC) 의 수를 확인하기 위하여 c-kit 면역 염색을 시행한다.

연구결과: ISD 삽입군에서 모두 급성 합병증 없이 성공적으로 삽입이 이루어졌다. 5 마리중 2 마리는 각각 4 주차와 5 주차에 스텐트 이동이 확인되었다. ISD 군의 경우 대조군에 비하여 각각 1 주차 4% vs 26% (p=0.025), 2 주차 15% vs 47% 2 (p=0.025), 3 주차

29% vs 49% (p= 0.024), 4 주차 49% vs 71% (p=0.043), 5 주차 56% vs 82% (p=0.034), and 6 주차 46% vs 88% (p = 0.05)으로, 체중증가율이 낮음을 보여주었다. 6 주차에 스텐트를 제거한 돼지는 대조군에 비하여 가파른 체중 상승 추세를 보였다. ISD 군의 ghrelin hormone levels 은 1 주차 20.9, 2 주차 32.3, 3 주차 28.3, 4 주차 41.4, 5 주차 47, 6 주차 39.7 ng/L 이었다. ISD 군에서 스텐트 근위부 는 경도의 조직 과형성 및 염증 세포 침윤, 점막하 림프여포 증식 소견을 보여주었다. ICC 수는 ISD 에서 3/HPF(range 1-4), 대조군 9.5/HPF (range 7-16), rebound pig 11.5/HPF (range 10-15)로 ISD 군에서 낮았다.

결론: 새로이 고안된 ISD 는 돼지모델에서 체중 증가를 낮추는 데 효과적이며 안전한 방법이다.

중심단어: 비만, 체중 감소, 식욕억제 유발 장치, interstitial cell of Cajal