

Minimally invasive entero-enteral dual-path bypass using self-assembling magnets

Marvin Ryou¹ · Hiroyuki Aihara¹ · Christopher C. Thompson¹

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Abstract

Background A minimally invasive method of entero-enteral bypass may be desirable for treatment of obstruction, obesity, or metabolic syndrome. We have developed a technology based on miniature self-assembling magnets which create large-caliber anastomoses (incisionless anastomosis system or IAS). The aim of this study was to assess (a) procedural characteristics of IAS deployment and (b) long-term integrity and patency of the resulting jejunoleal dual-path bypass.

Methods Endoscopic jejunoleal bypass creation using IAS magnets was performed in 8 Yorkshire pigs survived 3 months. Procedure: The jejunal magnet was endoscopically deployed. However, the ileal magnet required surgical delivery given restraints of porcine anatomy. A 5-mm enterotomy was created through which the ileal magnet was inserted using a modified laparoscopic delivery tool. Magnets were manually coupled. Pigs underwent serial endoscopies for anastomosis assessment. Three-month necropsies were performed, followed by pressure testing of anastomoses and histological analysis.

Results Jejunoleal bypass creation using self-assembling IAS magnets was successful in all 8 pigs (100 %). Patent, leak-free bypasses formed in all animals by day 10. All IAS magnets were expelled by day 12. Anastomoses were widely patent at 3 months, with mean maximal diameter of 30 mm. At necropsy, adhesions were minimal. Pressure testing confirmed superior integrity of anastomotic tissue. Histology showed full epithelialization across

the anastomosis with no evidence of submucosal fibrosis or inflammation.

Conclusions Entero-enteral bypass using self-assembling IAS magnets is safe and technically feasible in the porcine model. IAS magnets can be rapidly delivered endoscopically or through a modified laparoscopic device. Expulsion of fused magnets avoids retention of prosthetic material. Anastomoses are widely patent and fully re-epithelialized. Three-month pressure testing reveals anastomotic tissue to be as robust as native tissue, while necropsy and histology suggests minimal/absent tissue inflammation. In human anatomy, a fully endoscopic jejunoleal bypass using IAS magnets may be feasible.

Keywords Incisionless anastomosis system (IAS) · Anastomosis · Magnetic anastomosis · Compression anastomosis · Surgical anastomosis · Side-to-side anastomosis · Dual-path bypass · Self-assembling magnets for endoscopy · SAMSEN · Endoscopic bypass · Endoscopic anastomosis · Intestinal anastomosis

A fully endoscopic method for creation of a durable intestinal bypass may be desirable for treatment of obesity, type II diabetes, and malignant obstructions [1–3]. Currently, intestinal bypasses are surgically created using staples or suture [4] and have been difficult to replicate endoscopically [5–8]. A third strategy based on compression anastomosis has been successfully applied endoscopically in animal studies [9–16], and magnetic compression in particular has also been utilized in a human trial as a minimally invasive treatment of malignant gastric outlet obstruction [17]. However, compression anastomoses have historically suffered from two major disadvantages: (1) They require days to form [18], and (2) transoral delivery

✉ Marvin Ryou
mryou@partners.org

¹ Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

of the device has restricted anastomosis size (in the literature, maximum diameter 1.4 cm) which in turn has limited long-term patency [19].

Our group has devised a purely endoscopic device and method for intestinal bypass creation (incisionless anastomosis system or IAS) using compressive force delivered by self-assembling magnets. These “smart” magnets are endoscopically delivered and self-assemble into an octagon capable of creating large-caliber anastomoses (Fig. 1A–D). When reciprocal octagonal magnets occupy adjacent lumens, they couple to form a portal for immediate bypass. Over several days, these magnets fuse, slough off, and are naturally expelled, leaving behind a large side-to-side anastomosis (i.e., dual-pathway anastomosis; Fig. 2A–D).

IAS evolved from technology previously called self-assembling magnets for endoscopy (SAMSEN), which our group used for successful gastrojejunostomy creation in an acute porcine model [20] and durable jejunocolonic anastomosis in a survival porcine model [21]. The overarching aim of this particular study was to evaluate IAS for entero-enteral anastomosis creation in a long-term survival model. The specific aims of this study were (1) to evaluate the procedural characteristics of the refined IAS design; (2) time required for bypass to form; (3) short- and long-term safety; (4) 3-month patency; (5) integrity of the anastomosis as measured by burst pressure studies; and (6) histological characteristics of the anastomosis.

Methods and materials

This preclinical study focused on defining the procedural characteristics of IAS delivery and the characteristics of the resulting intestinal bypass. IAS technology was developed with the support of the Center for Integration of Medicine and Innovative Technologies (CIMIT; Boston, MA). IAS technology is now owned by GI Windows (W. Bridgewater, MA).

Incisionless anastomosis system

The incisionless anastomosis system (IAS) includes a pair of self-assembling magnetic octagons, each approximating the diameter of small bowel lumen. IAS components were constructed using neodymium–iron–boron rare earth magnets coated in a proprietary bio-safe material. IAS was designed for delivery through a colonoscope (Olympus CF-160AL; Olympus America Inc., Center Valley, PA; instrument channel 3.7 mm diameter).

Survival animal studies

This study was conducted with approval by the Institutional Animal Use and Care Committee at Pine Acres Research Facility (Norton, MA). Survival studies were performed in a total of eight juvenile Yorkshire pigs (30–40 kg).

Pigs were *nil per os* (NPO) 24 h preprocedure. Animals were initially sedated using intramuscular injection of Telazol, Xylazine, and Atropine. General anesthesia was used.

Enteroscopy was performed for IAS magnet deployment in the proximal jejunum, approximately 30–50 cm beyond the pylorus (Fig. 3). Anatomic constraints (i.e., corkscrew colon in pigs) precluded endoscopic delivery of the ileal IAS magnet; therefore, laparotomy was performed. A 5-mm ileotomy was created between two stay sutures using an electrocautery knife 100 cm proximal to the ileocecal valve. The ileal IAS magnet was then delivered through the ileotomy using a modified laparoscopic delivery device. The ileal IAS magnet was centered around the ileotomy and manually coupled with the jejunal IAS magnet.

All animals were recovered and underwent daily inspection to assess food intake and general appearance. All animals were fed a standard diet throughout. Animals were scoped every 3–5 days to evaluate the intestinal bypass which sometimes involved endoluminal instillation of Omnipaque contrast to perform a double-contrast study

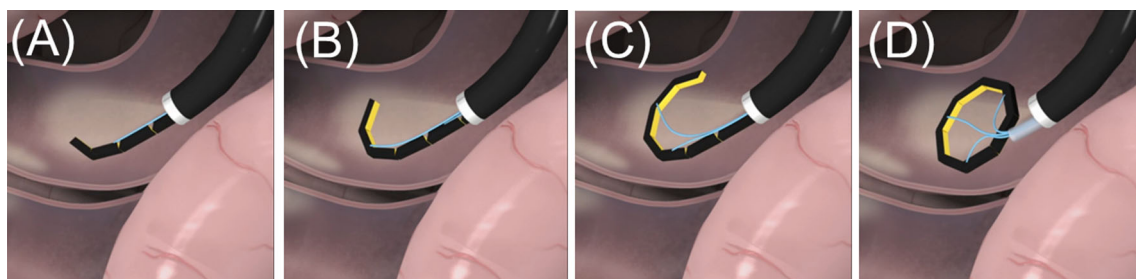


Fig. 1 A–D Sequential deployment of IAS magnet through instrument channel of colonoscope, progressing through linear configuration to final octagon configuration

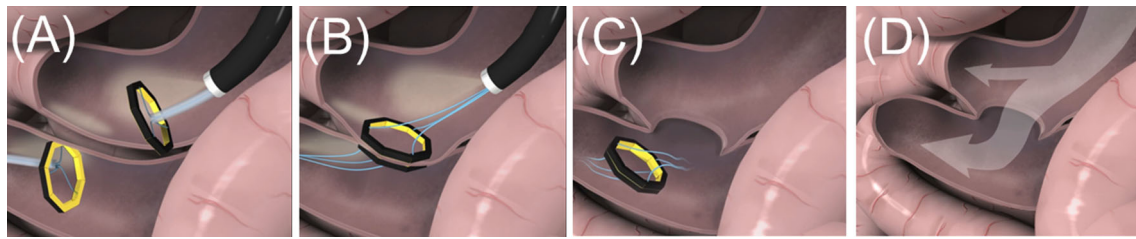


Fig. 2 A–D Coupling of two IAS magnets residing in separate, adjacent lumens. Note Suture lines are cut, and after several days, a dual-path bypass forms. The coupled magnets are naturally expelled

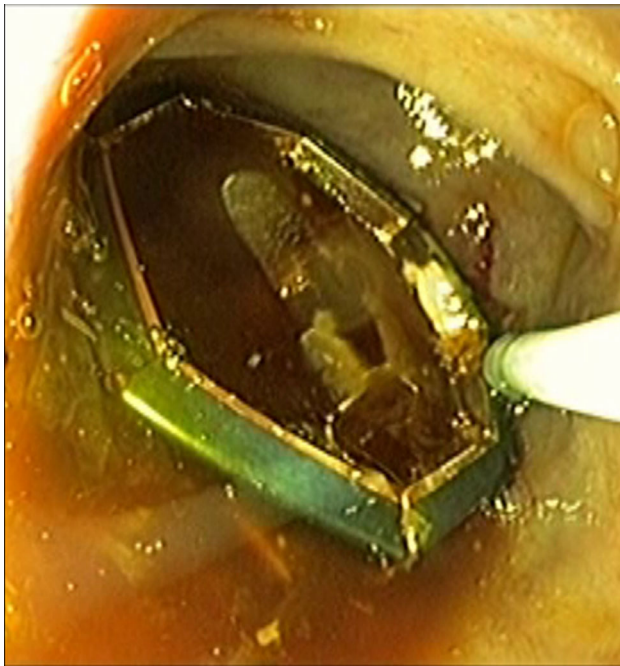


Fig. 3 Endoscopic view of fully formed IAS magnet

for evaluation of anastomotic leak. Fluoroscopy was also used to confirm expulsion of magnets.

In order to confirm reversibility of bypass, the final three pigs underwent surgical resection of their anastomoses and re-establishment of intestinal continuity at 3 months. First, the jejunio-ileal anastomosis was removed by incising the small intestine longitudinally with an electrocautery knife. Then, two stay sutures were placed at the margin of defect, in the middle of incision line. Finally, transverse closure was performed on the defects by layer-to-layer running suture with 4–0 absorbable suture. These animals were survived for another 2 weeks. Laparoscopic reversal with linear stapler was considered, but it was deemed more important to resect the anastomosis en bloc for subsequent burst pressure studies and histological analysis.

Final endoscopic evaluation and necropsies were performed at 3 months in the first five pigs, and 3.5 months for the final 3 pigs. The peritoneal cavity and the anastomosis

were grossly inspected for the presence or absence of adhesions. Adhesions were scored on a scale of 0 to 3 according to a previously published scoring system applied to a similar porcine survival model [22]. A score of 0 represented no adhesions, one represented filmy avascular adhesions, two represented dense or vascular adhesions, and three represented dense and vascular adhesions. The anastomosis was then resected en bloc, and the diameter of the anastomosis was recorded. Subsequently, the anastomosis was subjected to underwater air pressure testing using previously published methodology [23]. Sites of tissue failure were recorded. Finally, the tissue was fixed in formalin for histological evaluation.

Results

Survival animal studies

All eight pigs underwent successful IAS magnet deployment, magnet self-assembly, and coupling of reciprocal IAS magnets (Fig. 4). All pigs recovered without incident.

By day 10 in all animals, central tissue necrosis had created a patent bypass within the coupled magnets

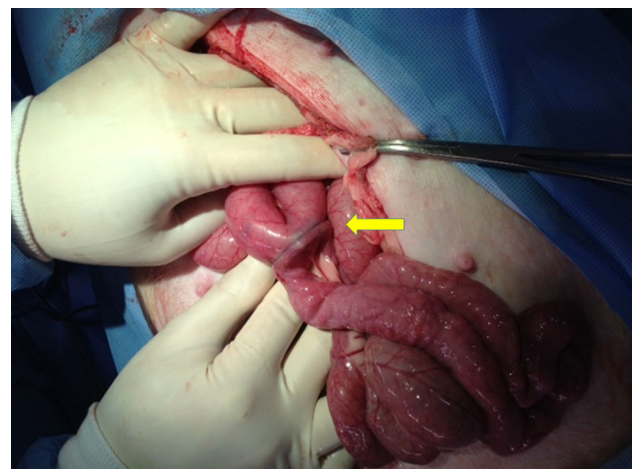


Fig. 4 Jejunio-ileal IAS magnets after manual coupling (yellow arrow) (Color figure online)

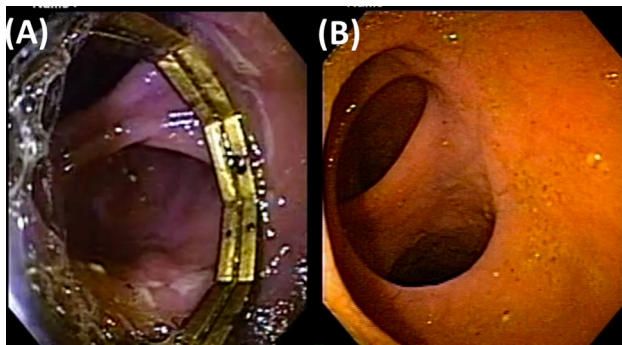


Fig. 5 **A** Endoscopic view at day 10. Both IAS magnets have coupled, and entero-ental anastomosis has been created. **B** Day 90. Coupled magnets have been spontaneously expelled, and anastomosis is fully formed

(Fig. 5A). The anastomosis was robust enough to allow for deep scope passage, and double-contrast studies demonstrated the absence of anastomotic leak in all animals.

By day 90 in all animals, the fully fused IAS magnets had sloughed off and had been naturally expelled, leaving behind a fully patent anastomosis. The anastomosis rim appeared to be completely re-epithelialized (Fig. 5B). Deep endoscopic exploration again showed a widely patent dual-path bypass.

The three pigs that underwent surgical reversal at day 90 recovered without incident. They were able to eat a liquid diet the next day, an ad lib diet at postoperative day 3, and resumed their preoperative growth rates.

Postmortem analysis

All eight pigs exhibited adhesions involving the laparotomy incision, but minimal to absent adhesions at the anastomosis. All adhesions at the anastomosis were scored zero (absent) or one (filmy avascular adhesions) (Fig. 6).

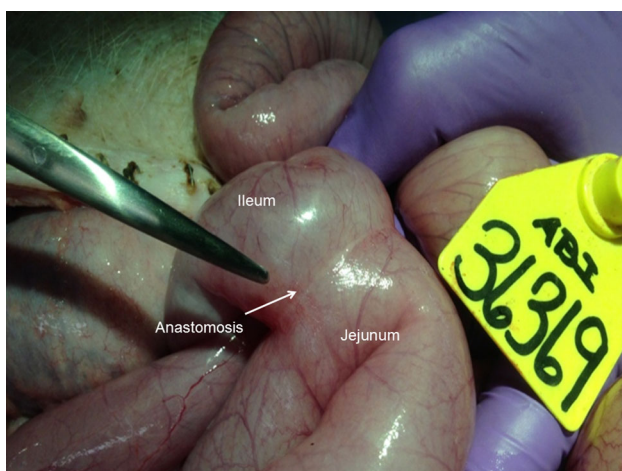


Fig. 6 Necropsy at 3 months. Clean anastomosis without adhesions

Additionally, there was no evidence of hemorrhage or abscess. The mean diameter of the anastomosis was 30 mm (27–35 mm). Upon pressure testing, the site of tissue failure was native tissue and not anastomotic tissue in all eight specimens (Fig. 7). Gross examination of the anastomoses showed intact mucosal surfaces with no evidence of ulceration, fissures, strictures, or abscess formation. Histological analysis demonstrated virtual absence of active inflammation as well as minimal fibrosis and scar formation, all consistent with a well-healed anastomotic site (Fig. 8).

Discussion

The IAS was designed with an eye toward retaining the advantages of compression anastomosis (i.e., lower bleeding and leak rates, lower inflammation and stricture rates, higher mechanical strength) while mitigating the major historical limitations of (1) prolonged time for formation and (2) short-term patency. First, to address the time limitation, IAS magnets were designed to self-assemble into reciprocal pairs of octagonal frames which, if desired, could serve as a portal for immediate endoscopic access. Alternatively, after a few days, the coupled magnets would slough off into the enteral stream and leave behind a robust anastomosis. Second, to address short-term patency, which is a function of magnet size limitations inherent to per-oral delivery (cricopharyngeus), the IAS magnets were designed to self-assemble into much larger macro-configurations that could yield anastomotic calibers approaching the diameter of the small bowel itself, if not larger.

We had previously demonstrated proof-of-concept of self-assembling magnets in an acute animal study for



Fig. 7 Hematoxylin and eosin (H&E) stain of anastomosis at 3 months. Full re-epithelialization without evidence of acute inflammation

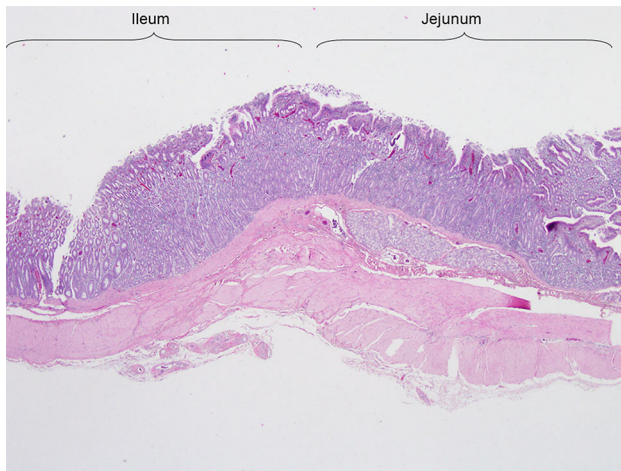


Fig. 8 Pressure testing set-up with digital pressure gauge

immediate gastrojejunostomy creation [21] as well as a survival animal study for jejunocolonic anastomosis [22]. In the current animal survival study, we proved that a durable entero-enteral anastomosis could be created using IAS magnets. Furthermore, we proved that the resulting anastomoses were characterized by the following critical features: (1) absence of bleeding, (2) absence of leaks, (3) long-term patency, (4) equivalent if not superior strength compared to native tissue, and (5) the absence of residual foreign material to cause fibrosis or inflammation.

Given the use of magnets, certain precautions need to be followed. First, patients will not be able to undergo magnetic resonance imaging (MRI) studies until expulsion of IAS magnets is confirmed. Second, the use of endoscopic instruments with stainless steel or other ferromagnetic composition will require care around the magnets to avoid inadvertent capture. Notably, standard endoscopes appear to function normally in the presence of IAS magnets.

The main limitations of this present work include small numbers and animal subjects. Additionally, this protocol required surgical assist for ileal magnet deployment given the constraints of porcine anatomy. Nevertheless, we believe the ileal magnet can be delivered endoscopically in human anatomy, but this will have to be born out in a clinical study.

In summary, this study presents successful creation of large-caliber, durable entero-enteral anastomoses using self-assembling IAS magnets in a porcine survival model. While this study utilized a combined endoscopic/surgical strategy for IAS magnet delivery and coupling, a fully endoscopic approach may be feasible in humans.

Acknowledgments The incisionless anastomosis system was developed with the support of the Center for Integration of Medicine and Innovative Technologies (CIMIT; Boston, MA).

Compliance with ethical standards

Disclosures Marvin Ryou, MD: equity interest, GI Windows. Hiroyuki Aihara, MD, Ph.D.: No conflict of interest. Christopher C. Thompson, MD, MHES: equity interest, GI Windows.

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