# Use of a New Elastin Patch and Glue for Repair of a Major Duodenal Injury

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**Major duodenal injury with significant tissue loss causes high morbidity and mortality. Our new elastin based heterograft combined with small intestinal submucosa (SIS) and biodegradable glue could be used for repair of such defects. Twenty-four domestic pigs were anesthetized and underwent celiotomy. A 2 cm circular defect was created at the second portion of the duodenum with scissors, excising one–half of its circumference. Our elastin patch, combined with SIS, was applied to cover the defect using biodegradable cyanoacrylate glue and a few sutures. It was then covered with omentum. Animals were followed by weight gain, endoscopic evaluation, and upper GI barium studies. After 2–5 months, animals were sacrificed to obtain specimens. One failed in 3 days due to a technical problem, and one failed in 20 days due to an abdominal abscess. The other 22 animals (22/24, 91.7%) did well, gaining weight. Early endoscopic studies (5–14 d) showed an intact patch. Upper GI studies showed varying degrees of stenosis at the repair site at 3–4 months. Sacrifice after 2–5 months showed complete healing of the defect and a dissolved patch. Our new elastin patch material provides a reliable barrier for repair of duodenal injury, and the biodegradable glue provides quick and easy watertight tissue fusion for our patch. *ASAIO Journal* 2000; 46: 409–414.**

Surgical repair of major injury to the second portion of the duodenum with significant tissue loss requires innovative surgical techniques and is associated with significant morbidity and mortality.[1] Segmental resection and primary end-to-end anastomosis is not possible in this region due to its close proximity to the head of pancreas and connections with the common bile duct and pancreatic duct. Small defects can be repaired by primary closure, which will result in stricture of the duodenum, depending upon the amount of tissue loss. Large defects cannot be repaired this way; they will require innovative techniques, such as creation of a jejunal patch, duodenojejunostomy, serosal onlay patch, pyloric exclusion with gastrojejunostomy, or even pancreatico-duodenectomy. The last procedure is fairly extensive, and is not likely to be tolerated by acute trauma patients with multiple injuries. The first three procedures can be done, but they still require prolonged operative time involving additional bowel anastomosis, and are feasible only when the jejunum is intact. Pyloric exclusion is accompanied by prolonged external drainage of the duodenal content, which makes it difficult to manage fluid and electrolyte balance, and a high incidence of intra–abdominal infection, sepsis, and chronic fistula formation, predisposing the victim to prolonged intensive care, parenteral nutrition, hospitalization, and disability. This is due to the high content of electrolytes and digestive enzymes in the duodenal fluid, which comes mainly from bile and pancreatic excretion. As a result, prolonged leakage from the duodenum is associated with prolonged and extensive tissue loss and sepsis. Recent developments in antibiotics and intensive care has significantly reduced the mortality rate from this condition, but morbidity is still high. If we could develop a technique that can easily, quickly, and reliably close the duodenal injury without compromising the lumen, we can expect much faster recovery with fewer complications and less morbidity and mortality.

The elastin based heterograft we developed at the Oregon Medical Laser Center could be used to repair such a defect in the duodenum without compromising the lumen, need for other bowel anastomosis, or extensive resection. In our laboratory, this material was shown to be biologically inert, inducing minimal immunologic response, and resistant to infection and hydrochloric acid.

SIS has been experimentally used to replace arteries and veins with success,[2,3] and has been shown to serve as an excellent scaffold for the regeneration of tissue when used to repair the urinary bladder.[4–6] We speculated that the combined patch of elastin and SIS will serve as an effective physical and chemical barrier for duodenal contents owing to the property of elastin, whereas SIS serves as scaffold for tissue growth (**Figure 1**). Use of biodegradable cyanoacrylate glue was proposed to achieve a quick and easy way to secure the patch in place and provide watertight fusion instantly.

## Methods

### *Elastin Patch*

An elastin patch was created from porcine aorta. After harvesting, it was preserved in 80% ethanol for 72 hours, after which it was fully digested by soaking in 0.5 M NaOH at 60°C with sonication. The digested aorta was cut into 4 × 4 cm patches, and two patches were pressed together at 121°C for 15 minutes to form one bilaminar patch. The patch was then packaged and sterilized at 121°C for 15 minutes.

Mechanical data of the patch follows. The tensile strength was measured by applying vertical traction on a 1 × 2 cm piece of the elastin patch until it was torn, using a Vitrodyne

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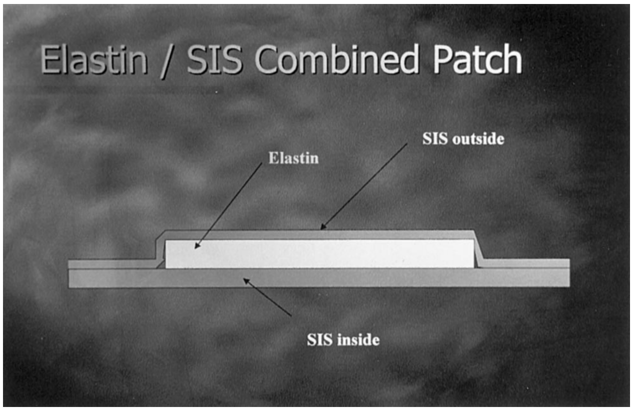


**Figure 1.** Schematic representation of the Elastin/SIS patch.

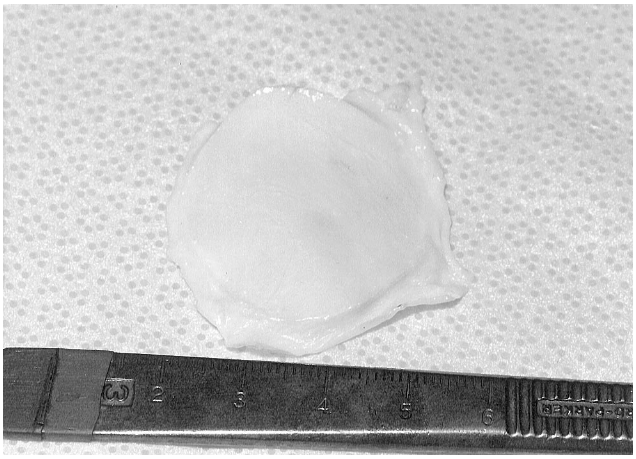

**Figure 2.** Photograph of the actual Elastin/SIS composite patch.

V1000 Mechanical Tester (Largo, FL). The average tensile strength was 432.9 ± 127.5 (N/m) (n = 4). In addition, 3-0 Vicryl suture (Ethicon, Inc., Somerville, NJ) was passed through the patch 3 mm from its edge, and traction was applied to test the suture holding strength, which was 78.13 ± 8.93 (g) (n = 4).

### *SIS Patch*

The SIS patch was made from a fresh intestinal segment of domestic swine. The tunica serosa and tunica muscularis were abraded by longitudinal wiping with a scalpel handle and moistened gauze. The remaining intestine is everted, and the tunica mucosa removed in the same manner. The tube was then inverted to its original orientation. This was rinsed with saline several times, placed in 10% Neomycin sulfate solution, and stored at 4°C. Decellularization was performed by immersing the SIS in 2 mM SDS solution and stirring with a magnetic bar for 1.5 hours. This was then washed in 0.01 M PBS (pH 7.0) for 5 minutes, which was repeated 3–4 times. Finally, the SIS was soaked in 0.01 M PBS (pH 7.0) with 10% Neomycin for storage.

### *Cyanoacrylate Glue*

Biodegradable Cyanoacrylate glue was provided by Poly-Med, Inc. (Anderson, SC). Gel composition was methoxypropyl cyanoacrylate (MPC) and L1 (copolymer of lactide, glycolide, and caprolactone).

### *Surgical Method*

Twenty-four domestic pigs were anesthetized, intubated, and underwent celiotomy using sterile technique. The second portion of the duodenum was mobilized and was brought out of the wound. A circular defect 2 cm in diameter was made on the second portion of the duodenum, excising one-half of its circumference. A circular Elastin patch with a diameter of 3 cm was sandwiched between a 4 × 4 cm SIS sheet using biodegradable cyanoacrylate glue (**Figures 1 and 2**). This composite patch was placed over the duodenal defect using the same glue (**Figures 3 and 4**), and a few interrupted sutures were used to anchor the patch in place to avoid migration of the patch in case the glue fails (**Figure 5**). This was further covered by omentum to provide a vascular supply to the area of repair, which we speculated would help with healing (**Figure 6**). The celiotomy was closed, anesthesia was withdrawn, and the pig was extubated. The pigs were allowed to resume regular feed-

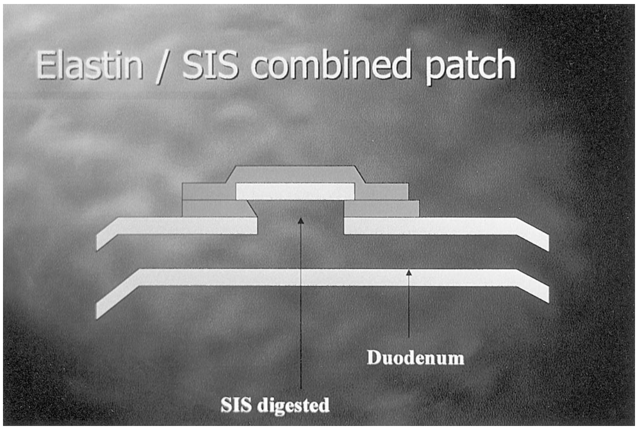


**Figure 3.** Schematic representation of the Elastin/SIS composite patch applied to the hole in the duodenum.

**Figure 4.** The hole in the duodenum and application of the glue.

**Figure 5.** Photograph of the Elastin/SIS composite patch applied.

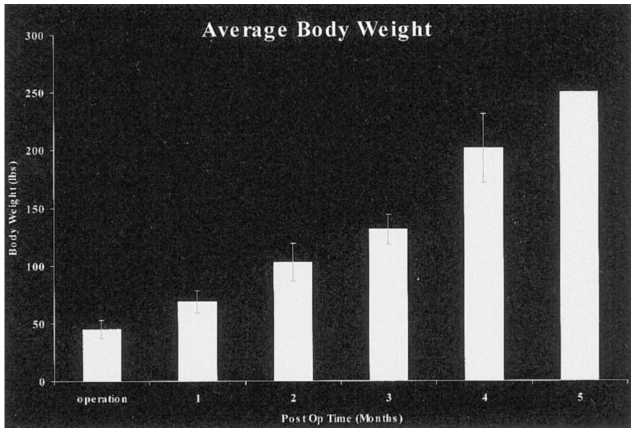


**Figure 7.** Average body weight of the animals. Significant weight gain was observed every month. (t-test, $p < 0.05$).

ing soon after surgery, typically within the first hour after extubation. They were followed by clinical observation, weight gain, endoscopic studies, and barium swallow studies. Two to five months after surgery, the pigs were sacrificed to obtain the specimens, which were submitted for histologic examination. No antibiotics or antacids were given after surgery. Animal experiments were conducted strictly following the guidelines set by the Institutional Animal Care and Use Committee of the Oregon Health Sciences University.

## Results

One animal had to be sacrificed at 3 days after surgery; the patch had already partially dehisced with free leakage of the bowel content. This was most likely due to the technical problem of failing to glue that area of the patch.

Another animal had to be sacrificed at 3 weeks after surgery. This animal developed an abscess confined to the retroperitoneal space, due to what appeared to be a perforation through the repaired site. The duodenal defect was still 2 cm in diameter and covered with thick fibrous tissue, which had a perforation into the abscess cavity. Fragments of elastin were observed within the fibrous scar. The internal surface of the scar was covered with a thin layer of regenerated mucosa.

The remaining 22 animals did very well, giving a success rate of 91.7% (22/24). They were able to resume oral feeding within the first hour after surgery, and showed significant weight gain every month (t-test, $p < 0.05$), following the normal growth curve of domestic pigs (**Figure 7**). One animal was sacrificed at 7 weeks, one at 2 months, 11 at 3 months, 7 at 4 months, and two at 5 months.

Endoscopic study was performed at 1 and 2 weeks after surgery. The patch was easily identified in the second portion of the duodenum, occupying up to one–half of its circumference. The duodenum was easily inflatable by injecting air, allowing the endoscope to pass through the area of repair and suggesting no mechanical obstruction (**Figure 8**).

Upper GI contrast studies were also performed to evaluate the function of the duodenum. Early after surgery (1–2 weeks), the repair site showed flat stiffening, but no significant stricture or obstruction to the passage of contrast (**Figure 9**). Late studies (more than 2 months after surgery) showed varying degrees of stricture of the repair site.

Gross specimens from the sacrificed animals showed complete healing of the repair site with mucosal coverage as early

**Figure 6.** Completed repair with omentum wrapping.

**Figure 8.** Endoscopic view of the repair site after 5 days.

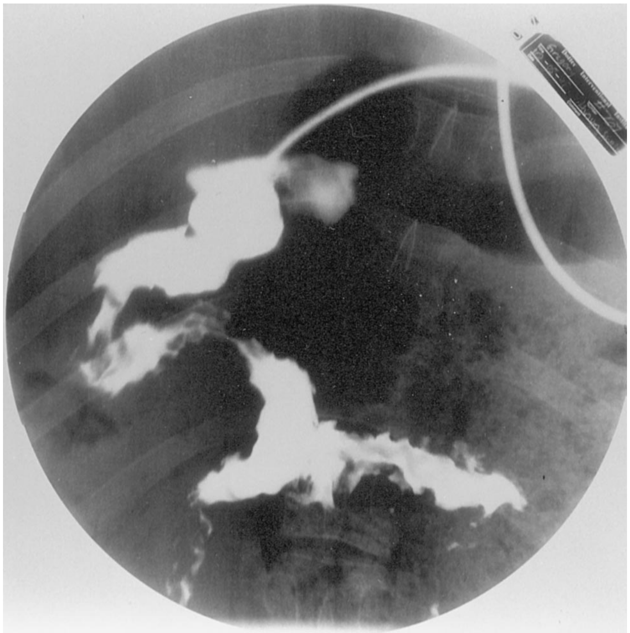

**Figure 9.** Barium study of the duodenum 2 weeks after repair. Flat stiffening of the repair site without obstruction is seen.

as 7 weeks, which had the appearance of a healed ulcer. There were varying degrees of hypertrophic circular tissue around the center of healing, causing mechanical obstruction that seemed to start resolving after 5 months (**Figure 10**).

Histology of the specimens after 7 weeks showed a completely healed duodenal wall with mucosal regeneration in the center (**Figure 11**). Submucosal tissue had also regenerated, with incomplete regeneration of the muscular layer. Nerves were found in the center of the regenerated tissue. Submucosal tissue showed marked hyperplasia around the regenerated tissue, which corresponds to the hypertrophic circular tissue on the gross specimen. There was no remnant of elastin or SIS identified in the specimen.


**Figure 10.** Gross specimen of the duodenum 3 months after the repair. A completely healed repair site is seen on the left side.

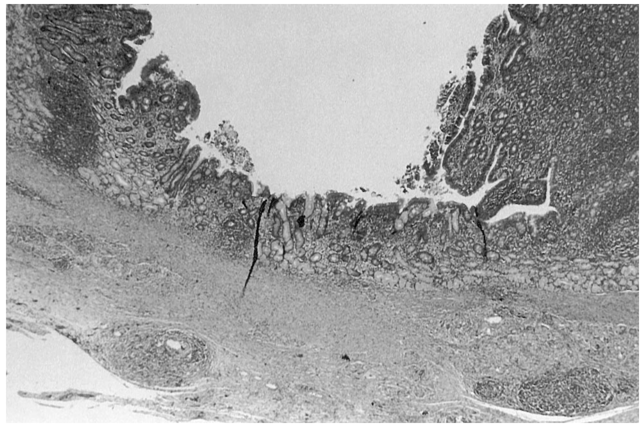

**Figure 11.** Histology of the healed repair site after 3 months. Regeneration of all the layers is observed.

## Discussion

Major duodenal injury with significant tissue loss is a serious injury that is very difficult to manage.[1] It requires innovative surgical techniques, and has a high morbidity. In treating a trauma victim with penetrating injury to the duodenum who most likely has coexisting serious associated injuries to the liver, pancreas, great vessels, and/or other parts of the bowel, the chances of survival are expected to improve when a surgeon can perform a definitive and reliable repair in a short amount of time. Primary repair is feasible only in relatively small injuries. Duodenal exclusion techniques still leave bile and pancreatic excretions to drain through the duodenal defects, causing chronic fistulas that will cause electrolyte imbalance, maldigestion due to the nonphysiologic state of the GI tract, and possible intra–abdominal abscess and sepsis. Although the mortality has decreased recently owing to improvement in intensive care and antibiotics, the morbidity and cost of care remains high, and patients suffer prolonged disability. More definitive procedures, such as pancreatico–duodenectomy, are too extensive for use in most critically injured patients, and are not tolerated. Jejunal patch and duoneno–jejunostomy require long operating times and are feasible only when the victim has an intact jejunum; it also involves additional bowel resection and anastomosis.

The duodenal patch repair we developed can be performed very easily, quickly, and reliably. The elastin patch is designed to provide a reliable barrier for 1 to 2 weeks while tissue regeneration and growth into the SIS takes place. This new regenerated tissue will, in turn, serve as an effective barrier, while the remaining elastin is completely digested in 4 to 6 weeks. Because the elastin patch itself is biodegradable by digestive enzymes in the duodenum, the risk of immunologic response and infectious complication from the patch are minimal. SIS is well integrated in the regenerated tissue and eventually disappears. This material, which is almost pure collagen, is an excellent scaffold for tissue growth.

Our preliminary experiment indicates, however, that the SIS inside the elastin is completely digested by the duodenal contents within a few days (**Figure 12**). Elastin, on the other hand, is much more durable, and serves as an effective barrier for 2 to 4 weeks.

Biodegradable cyanoacrylate glue was used to simplify the

**Figure 12.** Gross specimen of the duodenum 1 week after repair. The SIS and dyed glue inside the elastin is digested.

operative repair and to provide an immediate watertight seal against the duodenal enzymes. One critical problem that we faced with our pure elastin patch was that the material was quite fragile, lacking mechanical strength. Although not impossible, it was technically demanding to place a suture through this material without laceration. Placing this patch with glue made it much simpler and easier, and the initial mechanical strength of the tissue fusion was quite satisfactory.

Two animals did not survive the long-term experiment. One of them never regained GI continuity after surgery and had to be sacrificed after 3 days. There was a leak at the distal medial corner of the patch, most likely due to technical failure. We either failed to apply the glue in this corner or failed to apply the patch before the glue dried out. The original glue had no color and was transparent, but later a dyed glue was used to visually identify the glued area.

The other animal started to deteriorate 2 weeks after surgery, losing appetite and body weight. At sacrifice on the 20th day, we found that the animal had developed a retro-peritoneal abscess. The area of defect was covered with thick fibrous tissue, which had a 3 mm hole connecting it to the abscess cavity. Histology showed fragments of elastin in the fibrous scar, and the inner surface was covered with thin regenerated mucosa. This animal had a relatively large hole in the duodenum, and inadequate tissue fusion between the bowel edge and the patch was felt to be the cause of early dehiscence.

Rabaud and others[7–9] have reported successful results of duodenal patch repair using their elastin biomatrix, impregnated with antibiotics and pancreatic enzyme inhibitors, in 10 rabbits and 3 dogs. Unfortunately, the results with large animal models and the histologic data were ambiguous. Our patch is virtually made of pure elastin without impregnation by any enzyme inhibitors or antibiotics. Preliminary studies to test its resistance against hydrochloric acid *in vitro* showed no degeneration after 1 week. Duodenal content, however, is a mixture of bile, pancreatic enzymes, hydrochloric acid, ingested food, and microorganisms. Pancreatic digestive enzymes, such as elastase, could rapidly degenerate the elastin patch. Whereas the enzyme inhibitor, Elgin C, strongly inhibits the solubilization of human aortic elastin by human pancreatic elastase, the efficacy of the inhibitor sharply decreases if elastase is reacted with elastin for a prolonged time.[10]

*In vitro* studies to investigate how our patch was going to behave *in vivo* seemed futile. Not all of the pancreatic enzymes are commercially available, and they are quite unstable *in vitro*. These enzymes are also activated by contact with duodenal mucosa and bile. In addition, we needed to know the patch's fate after several weeks rather than several days. For these reasons, we decided to proceed with an *in vivo* study without further preliminary *in vitro* studies.

Use of a biomaterial patch to repair the GI tract has never been reported in clinical experience, but the results of this *in vivo* experiment are very promising. Collet *et al.*[11] reported their clinical experience, using elastin biomatrix to reinforce the bowel anastomosis in 18 cases, with two unrelated deaths and two postoperative fistulas. These clinical data were obtained from critically ill patients without controls, making it impossible to draw any conclusion from their experience.

Surgical experiments were typically performed 30 minutes from skin to skin. The actual time required for the duodenal repair itself was less than 15 minutes. No other bowel resection or anastomosis is required, and our animals could resume oral feeding immediately after they recovered from anesthesia. For trauma victims with penetrating injury to the duodenum this is an ideal treatment because the surgical time is minimal and recovery is fast, eliminating the need for prolonged hospitalization with antibiotics and intravenous hyperalimentation.

Our major concern with this repair was late stricture of the repair site. We postulated that the repaired site functioned as an ischemic bowel wall, which would heal by contraction rather than regeneration. In our experience, it seems to heal by both regeneration and contraction, leaving a mild to moderate degree of stenosis, but not as severe as one would expect from healing by contraction alone. The center of the healed scar showed evidence of mucosal regeneration. There was always a circular ridge of hypertrophied mucosa or submucosal tissue around the center, which also seems to contribute to the mechanical constriction of the duodenal lumen. This was most prominent at 3 months, and the two animals examined after 5 months showed a tendency toward resolution, although objective quantification was not possible. We postulate that this "ridge" is caused by the early degeneration of the glue, which allows the glued edge of the duodenum to fall into the lumen, exposing this part to the duodenal content. This circular edge will undergo inflammatory changes, resulting in a hypertrophied circular scar. To eliminate this problem, we will need to develop glue that can function *in vivo* for 2 to 4 weeks. The glue we are using (GF-62) is composed of methoxypropyl cyanoacrylate (MPC) and L1 (Copolymer of lactide, glycolide, and caprolactone). Methoxypropyl cyanoacrylate with other modifiers result in higher adhesive strength than isobutyl cyanoacrylate when used to approximate soft tissues.[12] The use of cyanoacrylate glue to repair the injury may also be contributing to resistance against infection.[13]

## Conclusion

Our new elastin patch material provides a reliable barrier to repair a major tissue defect in the second portion of the duodenum. By combining this patch with SIS, we could obtain a fairly strong material that is resistant to infection and digestive enzymes, allowing the tissue to heal from the outside.

The modified cyanoacrylate glue provides quick and easy water tight tissue fusion for our patch. Further modification to prolong its function over 2 weeks is desired, which is likely to reduce the degree of stricture at the repair site.

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