Polyglycolic acid and fibrin glue can be used as a serosa membrane substitute to close serosal defects

Kazuhiko KASUYA¹, Yuichi NAGAKAWA¹, Minako SUZUKI¹, Takahisa IKEDA¹, Hitoshi SAITO¹, Takashi OZAWA¹, Akihiko TSUCHIDA¹, Tatsuya AOKI¹, Takao ITO¹, Atsushi SOFUNI²

¹Department of Surgery, Tokyo Medical University
²Department of Internal Medicine, Tokyo Medical University

Abstract

Purpose. Recently, a new sealing technique using a polyglycolic acid felt and fibrin glue (PGA felt sealant) has been developed to close dural or pleural defects in neurosurgery and thoracic surgery. Our purpose was to evaluate whether the PGA felt sealant would be safe and effective for closure of the gastrointestinal serosal mural defect in the digestive tract surgery.

Method. We prepared an artificial gastrointestinal mural defect and artificial digestive fluids of pH 7.0 or pH 3.0. We measured the rupture pressure to compare the durability between the PGA felt sealant and fibrin glue sealant. On the basis of the experimental results, we performed an initial trial for the PGA felt sealant for suture reinforcement of gastrectaneous fistula closure.

Results. The PGA felt sealant and the fibrin glue sealant withstood pressure of over 300 and 107±13 mmHg in the pH 7.0 fluid, and 282±12 and 72±9 mmHg in the pH 3.0 fluid, respectively. In the clinical case, the patient could begin an oral intake 2 weeks after the fistula closure.

Conclusion. We concluded that the PGA felt sealant was suitable as a serosa membrane substitute to close fistulas accompanied with a mural defect.

Introduction

Gastric or intestinal fistula sometimes occurs as a postoperative complication of gastrointestinal (G.I.) surgery. If it associated with a large gut wall defect, the fistula does not close naturally, and becomes intractable. In such cases, although surgical suturing of the serous membrane is important for fistula closure, it is difficult when the mural defect is too large or the G.I. wall is fragile. Closures with insufficient suturing of the serous membrane often reopen. Fibrin glue is one of the most common absorbable materials and it is often used in open surgery or endoscopic treatment, such as for prevention of leakage of pancreatic juice from marginal pancreatic section, or leakage of fecal discharge from a chronic intractable anal fistula¹⁻⁹. Fibrin glue sealant has the advantage of filling up long or fragile fistulas and in cases of the fistulas which have long and complex thin branches like an ant's nest. In contrast, when serosa membrane suture is impossible because of bowel serosal defect such as in gastric or intestinal mural defects, the fibrin glue sealant is insufficient, because it dissolves and drains away easily in the digestive juice and disintegrates due to peristaltic movement of the
stomach or the small intestine. In particular, fibrin glue is useless for fistulas covered by mucosa brought out through a mural defect. We hypothesized that an absorbable scaffold was needed to apply the fibrin glue to a wide mural defect surface.

A new synthetic and absorbable felt made of polyglycolic acid (PGA) has been developed to reinforce pleural rips in thoracic surgery or to repair dural defects in neurosurgery. The PGA felt (Neovail®: Japan Medical Planning, Kyoto, Japan) plus the fibrin glue (Bolheal®: Teijin Pharma Limited, Tokyo, Japan) sealant was used to control air leakage as a pleural substitute. In addition to preventing puncture of the lung cut surface because of airtight strength the flexible PGA did not disturb lung expansion and was strongly resistant to airborne bacteria. In addition, PGA felt sealant completely stopped leakage of cerebrospinal fluid even under positive pressure when used as a dural substitute. We therefore hypothesized that the PGA felt sealant was suitable for closing fistulas with large gastric or intestinal mural defects. First, we evaluated the durability of the PGA sealant experimentally. Subsequently, we tried to use PGA felt as a durable substitute of a serosal membrane to close the fistula after gastrostomy.

**Methods**

We prepared two types of artificial digestive juice and an artificial G.I. mural defect to test the PGA felt sealant durability under conditions in the digestive organ (Fig. 1). The artificial intestinal juice was composed of 0.85% (W/V) of sodium chloride (Wako Pure Chemical Industries, Ltd. Tokyo, Japan), 0.1% (W/V) of mucin (Sigma Aldrich Corp. St Louis MO, USA), 0.04% (W/V) of trypsin (Wako), pancreatin (Wako) and 0.06% (W/V) of GAM broth (Nissui Pharmaceutical Co. Ltd. Tokyo, Japan) adjusted at pH 7.0 by sodium hydroxide and the artificial gastric juice was composed of 0.85% (W/V) of sodium chloride (Wako), 0.1% (W/V) of Mucin (Sigma) and 0.04% (W/V) of Pepsin (Sigma) adjusted to pH 3.0 by hydrochloric acid. A special plastic cylinder 10 cm in diameter with a valve for pressurization in the side was made as an artificial G.I. tract. We poured 10 ml of type juice into the bottom of the cylinder then placed a rabbit skin with a 5-mm hole, on the upper part of the cylinder. The hole represented an artificial mural defect and it was closed by a PGA felt patch with 0.4-μm diameter pores. We covered the PGA felt patch for a minute with 1 ml of the fibrinogen and then sprayed it with fibrin glue consisting of thrombin and fibrinogen on it. In the control study, only fibrin glue, without a PGA felt patch, was used. The cylinder was then slowly turned upside down. As a result, artificial digestive fluid came in contact with the PGA felt sealant, or in the case of the control, the fibrin glue. The cylinder was then incubated at 37°C for one hour. After 1 hour we applied air pressure through the side valve of the cylinder, and measured the maximum pressure until the sealant ruptured, to assess the strength of each type of seal. The maximum pressure means a difference between one atmospheric pressure (760 mmHg) and the internal pressure in the cylinder. The experiment was performed using the PGA sealant and the fibrin glue sealant in the artificial gastric fluid or in the intestinal fluid three times each. These values were expressed as the mean ± standard deviation (SD).

**Statistical analysis**

Differences between the statistical values of PGA felt sealant and fibrin glue sealant were evaluated by Welch's test.

---

**Fig. 1** An illustration of a cylinder with a valve for pressurization in the side, rabbit skin with a 5-mm hole on the upper parts as a serosal defect of an artificial G.I. tract. We poured an artificial digestive fluid into the bottom and then closed the hole by the PGA sealant (left). The cylinder was then slowly turned down and incubated at 37°C for one hour to contact the PGA felt sealant and the fluid (center). We applied air pressure through the side valve of the cylinder, and measured the maximum pressure until the sealant ruptured (right).
Results

With exposure to the artificial digestive juice at pH 7.0, the mean rupture pressures of the control consisting of fibrin glue alone were $107\pm13\text{ mmHg}$. However the PGA felt sealant remained intact to over $300\text{ mmHg}$ ($p<0.01$). At over $300\text{ mmHg}$, while the PGA sealant remained unbroken, air leaks developed between the rabbit skin and the side of the cylinder. The mean rupture pressure of the PGA felt sealant after exposure in artificial gastric juice at pH 3.0 was $282\pm12\text{ mmHg}$, while that of the fibrin glue sealant was $72\pm9\text{ mmHg}$ ($p<0.01$) (Fig. 2).

A 60-year old woman who had complete obstruction of the duodenum and hydro-peritoneum due to peritoneal carcinomatosis of gallbladder cancer underwent gastrostomy to drain the gastric juice. However, a gastric mural defect and a dead space below the wound developed at 6 weeks after the operation (Fig. 3a). CT revealed edema of the gastric wall and fluid around the fistula (Fig. 3b). Because no serous membrane could be used for mechanical patching of the gastric wall defect, conventional suturing closure would have been difficult because of gastric and bowel adhesions. Therefore, we performed surgical closure of the mural defect by the

![Graph showing maximal rupture pressures of PGA sealant (white bar) and the fibrin glue sealant (gray bar).](image)

Fig. 2 A maximal rupture pressures of PGA sealant (white bar) and the fibrin glue sealant (gray bar).

![Image showing a wide face fistula.](image)

Fig. 3 A wide face fistula was shown on the abdomen at 6 weeks after the gastrostomy. It was crested by gastric mucosa brought and through a mural defect (a). Abdominal CT revealed edema of the gastric wall (arrow head) and fluid around the fistula (b).

![Diagram showing the cross section of the gastric fistula, mucosal removal and suturing, and PGA sealant.](image)

Fig. 4 The illustration of the cross section of the gastric fistula (left), the mucosal removal and the mucosal suturing (center) and the PGA sealant as a serosa membrane substitute for mucosal suture reinforcement (right).
demucosation using the automatic device and reinforced it with the PGA sealant (Fig. 4). We initially lifted the edematous gastric mucosa up by suturing with 3-0 vicryl, and then cut and removed the mucosa by an Endo-GIA auto-suturing 3 staple lines, (Blue cartridge, Ethicon, Johnson and Johnson Corp, Tokyo, Japan). We trimmed the 0.15-mm thick PGA felt to an area 5 mm wider than the surgical margin and then placed it over the wound, and covered it with 1 ml of the fibrinogen solution, and finally sprayed the remaining fibrin glue. The PGA felt became solidly elastic like rubber within 5 minutes after the fibrin glue spraying. The wound was closed by conventional mattress sutures. The PGA felt and the fibrin glue continued to fill in subcutaneous space until at least a week after the operation (Fig. 5a). The patient could begin to eat normally 2 weeks after the operation with no complications. The solid fibrin glue under the wound was absorbed within four weeks, and the subcutaneous dead space disappeared (Fig. 5b).

Discussion

We set out to determine whether our PGA sealant method could be effective in compensating for serosal defects. It is well known that surgical suturing of the serous membrane is an important method to close fistulae with gastric or intestinal mural defects. However, it is sometimes not an option to use serosa membrane to patch defects, because bowel adhesion is often too great or the tissue is too fragile to allow suturing of the serosal membrane around the fistula (as in a bowel serous defect). We therefore require an absorbent material which has resistance to bacterial infection as a serosa membrane substitute. We evaluated whether the gastrointestinal mural defect healing could be achieved by the film in terms of the durability and degree of closeness. The PGA felt has already been used as a pleural substitute in thoracic surgery6-8, and as a dural substitute in neurosurgery9-11. Success was enhanced because the softness of the PGA felt facilitated adhesion to an irregular surface. Furthermore, PGA felt induced inflammatory cell permeation and neo-vascularization and adjusted to the healing environment9,10. In cases of digestive mural defect, flexibility and strength of films even in acid liquid environment are essential. Experiments on intensity durability materials of the film in an acid underwater environment have not been reported. Terasaka et al.9,10 reported that the PGA felt sealant yielded a resistance pressure of 110±37 mmHg under experimental arid conditions, and they concluded that the PGA sealant was suitable as a dural substitute. Our experimental results resembled those of Terasaka10,11, and showed that PGA felt maintained constant strength even when the PGA felt sealant was soaked in digestive juice.

There are two membranous forms of PGA material, a mesh type and a felt type. The PGA mesh and the fibrin glue has already been used for repair of esophageal perforation12. However, esophagus and the stomach and intestines vary in terms of biological environment. Peristaltic movement of the stomach or the bowel is usually stronger than that of the esophagus. Furthermore, PGA for the stomach or bowels is exposed to digestive juice which is more acidic and exposure is longer than in the esophagus. Because PGA felt is superior in water-repellence and flexibility than PGA mesh, the PGA felt sealant has replaced PGA mesh as materials for dural or pleural substitutes6-12. In the present case, the adhesive property of the fibrin glue and bowel wall was maintained despite the peristalsis of the stomach, due to outstanding expandable ability of the PGA felt, because the PGA felt is made of a synthetic absorbable fiber and allows cellular permeation, tissue ingrowth and neovascularization8,11. It is as yet unclear exactly when the PGA sealant begins to be replaced by connective tissue, and when it is absorbed in surrounding tissue. We showed that the PGA felt recommend radiologically detectable for longer than one week (Fig. 5a), and it was absorbed by 4 weeks in the present case (Fig. 5b). One week is long enough for the
healing process of the surgical margin. These clinical findings demonstrated that the PGA sealant completely covered the surgical margin and withstood the strong pressure caused by gastrointestinal peristaltic movement. Thus, in the present situation in which primary suturing closure might well have been insufficient, the PGA sealant was advantageous in comparison for the fibrin glue which is more easily absorbed.

Generally, absorbent material is superior in antibacterial properties in comparison with non-absorbable material, for the former does not allow tissue ingrowth. The latter remaining in living tissue induces bacterial infection. However, the absorbent material generally cannot preserve the sufficient strength in comparison with the non-absorbable material. It is important to know how long the absorbent material maintains its strength. Because there are PGA products of various thickness, we can choose them as necessary for the purpose and can estimate the period until absorption.

Recently, new absorbent connective matrices have been developed. Balcom et al. reported a synthetic hydrogel scaffold which was composed of an aqueous solution of a copolymer of polyethylene glycol acylated end groups. Girard et al. reported a patching technique with an acellular dermal matrix (AlloDerm: LifeCell, Branchburg, New Jersys, USA) as a biological scaffolding for an intestinal serosal defect and fistulas in patients with open peritoneal cavities. Their purpose was similar to that of the present report by using an absorbable scaffold and glue for the repair of organ defects. More new matrices or scaffold materials will be developed in future.

In summary, we have demonstrated that the PGA felt sealant was clearly superior to the fibrin glue in the artificial digestive juice experimentally, and we succeeded in the repair of a potentially refractory fistula with a defect in the gastric serosa membrane. These results showed that the PGA sealant was suitable as a serosa membrane substitute for suture reinforcement in cases with fragile tissues such as gastrocutaneous or enterocutaneous fistula.

Acknowledgement

The authors are indebted to Prof. J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this manuscript.

References

消化管の代用様膜としての吸収性ポリグリコール酸フェルトの検討

柏谷和彦１) 永川裕一1) 鈴木美奈子1)
池田隆久1) 斉藤満1) 小澤隆1)
土田明彦1) 青木達哉1) 糸井隆夫2)
祖父尼淳2)

1)東京医科大学外科学第三講座
2)東京医科大学内科学第四講座

背景: 消化管の瘻孔の閉鎖では様膜・縫合線合が重要である。しかし様膜欠損部が大きいなどの理由で縫合線合が不十分なとき、瘻孔は再開口してしまうことが多い。吸収性ポリグリコール酸フェルト＋フィブリノン綱による閉鎖（PGA法）は柔軟性がよく、肺切除面の空気漏れ防止に有用とされる。

目的: 消化管の瘻孔の閉鎖に際し、PGA feltが代用様膜として使用できるかを検討した。

方法: 呷皮膚に欠損部を作成し、同部位をPGA法とフィブリノン綱単独（FG法）にて閉鎖した後、人工腸液（pH 7.0）・人工胃液（pH 3.0）に37℃で1時間暴露した。その後、耐圧実験を行った。

結果: 人工腸液暴露下では、PGA法300 mmHg圧で2時間耐圧し、FG法は107 mmHgであった。人工胃液ではPGA法282 mmHgまで耐圧し、FG法では72 mmHgであった。

臨床例: 60歳の女性の胃瘻状態に対し、吻合器による粘膜縫合閉鎖後に代用様膜としてPGA法を施行した。臨床例において瘻孔閉鎖に成功した。

考察: 消化管瘻孔は腸液や胃液に曝されることで、閉鎖に難渋する。PGA法は消化液に暴露後もフィブリノン綱単剤よりも閉鎖強度も著しく増加した。その理由としてフェルト状のシートの柔軟性の高さ、また面での閉鎖が有利であったと考えられた。PGAには線維芽細胞の走化性もあり、物理的な閉鎖の後、生体面からも治癒効果を誘導したと考えられた。

＜キーワード＞ポリグリコール酸フェルト、代用様膜、縫合補助、胃皮膚瘻

( 6 )