

External Pancreatic Fistulas Resistant to Conventional Endoscopic Therapy: Endoscopic Closure With N-Butyl-2-Cyanoacrylate (Glubran 2)

M. Mutignani
A. Tringali
E. Khodadadian
L. Petruzzello
C. Spada
G. Spera
P. Familiari
G. Costamagna

External pancreatic fistulas may follow abdominal surgery or injury. While most respond to conservative management or endoscopic intervention, others might require surgery for complete healing. We report four cases of patients with external pancreatic fistulas that failed to respond to conservative management and drainage. N-butyl-2-cyanoacrylate surgical glue (Glubran 2)

was directly injected into the fistulous tract. The fistulas closed within 24 hours of the Glubran 2 injection in three cases (75%). In patients with external pancreatic fistulas that fail to respond to conservative and endoscopic drainage, injection of Glubran 2 directly into the fistulous tract may lead to closure, thus avoiding the need for surgical intervention.

Introduction

External pancreatic fistula (EPF) has been reported to occur in the setting of surgery for abdominal trauma, acute and chronic pancreatitis, and pancreatic cancer [1–2]. In 40–90% of cases, the fistula heals with conservative management [2–5], but where there is no response, endoscopic drainage or surgical bypass or resection might be needed. While endotherapy is less invasive and safer than surgical intervention, it may be unsuccessful in the presence of ductal stricture or obstruction [6].

N-butyl-2-cyanoacrylate (Histoacryl) has been used for suture reinforcement [7], arteriovenous embolization [8], endoscopic treatment of bleeding gastroduodenal ulcers and varices [9] and occlusion of external biliary fistulas refractory to endoscopic drainage [10]. Glubran 2 (General Enterprise Marketing, Viareggio, Lucca, Italy) is a new cyanoacrylate surgical glue composed of N-butyl-2-cyanoacrylate and methacryloxysulfolane monomer; the longer radical chain has a lower temperature of polymerization than Histoacryl which results in lower toxicity [11,12] and less inflammatory reaction [13]. Glubran 2 carries the CE mark and can be used for endoscopic treatment of pancreatic fistulas as stated in the manufacturer's instructions.

Methods

All our patients gave informed consent for the injection of Glubran 2 directly into the pancreatic duct. Endoscopic retrograde cholangiopancreatography (ERCP) was carried out with the patient in the supine position for better imaging of the pancreatic ducts. Biliary and pancreatic sphincterotomies facilitated access to the pancreatic duct and reduced pancreatic ductal pressure. A mixture of 1–2 ml of Glubran 2 and 1–2 ml of contrast (Lipiodol; Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected directly into the fistulous tract using an ERCP catheter with a radiopaque marker (GC-5; Wilson-Cook Inc., Winston-Salem, North Carolina, USA) to visualize the site of injection under fluoroscopy; before the injection the catheter was flushed with 5% glucosate to avoid polymerization in the catheter.

A nasopancreatic drain was left in place and a check pancreatography was performed 24–48 hours later to evaluate fistula healing.

Institution

Digestive Endoscopy Unit, Catholic University, Rome, Italy

Corresponding Author

G. Costamagna, M.D. · Digestive Endoscopy Unit · Università Cattolica del Sacro Cuore · A. Gemelli University Hospital · Largo A. Gemelli 8 · 00168 Rome · Italy · Fax: +39-06-30156581 · E-mail: gcostamagna@rm.unicatt.it

Submitted 13 January 2004 · Accepted after Revision 7 April 2004

Bibliography

Endoscopy 2004; 36 (8): 738–742 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0013-726X
DOI 10.1055/s-2004-825672

Table 1 Details of the four patients and their treatments

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	21	21	56	73
Sex	Male	Female	Male	Female
Fistula				
Etiology	Open splenectomy	Laparoscopic splenectomy	Open splenectomy	Left colectomy
Location	Pancreatic tail	Pancreatic tail	Pancreatic tail	Pancreatic tail
Pancreatic duct transection	No	Yes	No	Yes
Duration of unsuccessful conservative treatment, months	3	6	1	9
Mean fistula output, ml/day	50	200	100	150
Glubran 2, ml	1	1	1	2
Lipiodol, ml	1	1	1	2
Outcome	Healing of fistula (24 hours)	Healing of fistula (24 hours)	Healing of fistula (24 hours)	Persistence of fistula
Complications	-	-	Bleeding from the sphincterotomy	-

Case reports

Details of the patients and the treatments instituted are given in Table 1.

Patient 1

1 month after splenectomy following a car accident this patient developed a peripancreatic fluid collection requiring external percutaneous drainage, which resulted in an EPF with an average output of 40–50 ml/day. He did not respond to conservative therapy and was admitted to our hospital for endoscopic management 3 months later.

Magnetic resonance pancreatography with secretin stimulation (S-MRP) revealed a fistulous tract in the tail of the pancreas. During ERCP a nasopancreatic drain was placed to decrease the pressure in the pancreatic ductal system. However, the fistula output did not decrease. A second ERCP 2 days later a 7-Fr, 18-cm customized stent was placed in the pancreatic duct. The fistula initially closed but reappeared 5 days later. At ERCP, the stent was found to be displaced distally and was removed. Under fluoroscopic control Glubran 2 and Lipiodol were directly injected into the fistulous tract. The fistula closed within 24 hours of the injection as confirmed by pancreatography through the nasopancreatic drain. 8 months later the patient's general condition was good and S-MRP showed a normal pancreatic duct without evidence of an EPF or peripancreatic fluid collection.

Patient 2

A young woman sustained abdominal injury in a motorbike accident and underwent laparoscopic splenectomy. After surgery she developed an EPF with output averaging 200 ml/day. After 6 months of unsuccessful conservative management, the patient was admitted to our hospital for endoscopic therapy.

S-MRP revealed transection of the pancreatic duct in the tail region with a fistulous tract at the site of the transection. At ERCP a 6-Fr nasopancreatic drain was placed without effect on the fistula output. During a second ERCP, the fistulous tract and the duct

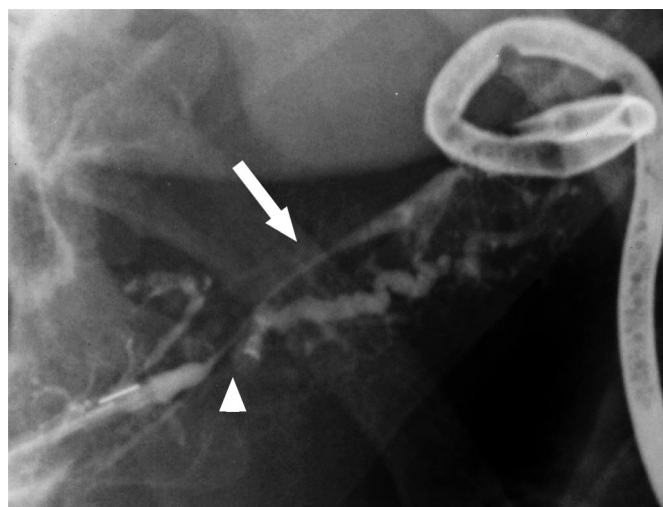


Figure 1 Patient 2: pancreatography showing the fistulous tract (arrow) and the pancreatic stump upstream of the rupture (arrowhead) of the main pancreatic duct.

upstream of the stricture were well visualized (Figure 1). Glubran 2 and Lipiodol were injected under fluoroscopic control directly into the fistulous tract with the aim of closing the distal pancreatic stump upstream of the rupture (Figure 2). The fistula completely closed within 24 hours as confirmed by check pancreatography through the nasopancreatic drain (Figure 3). The abdominal drain was removed, but 2 days later the patient developed pain in the left hypochondrium and fever. S-MRP showed a 1.5-cm fluid collection in the tail of the pancreas. The patient was successfully treated with intravenous antibiotics. 5 months later S-MRP showed a normal pancreatic duct downstream of the rupture and mild dilatation of the short ductal segment above it (Figure 4).

Patient 3

A patient who had chronic lymphatic leukemia for 12 years underwent splenectomy for splenomegaly. At 2 months after surgery he developed a peripancreatic fluid collection near the tail

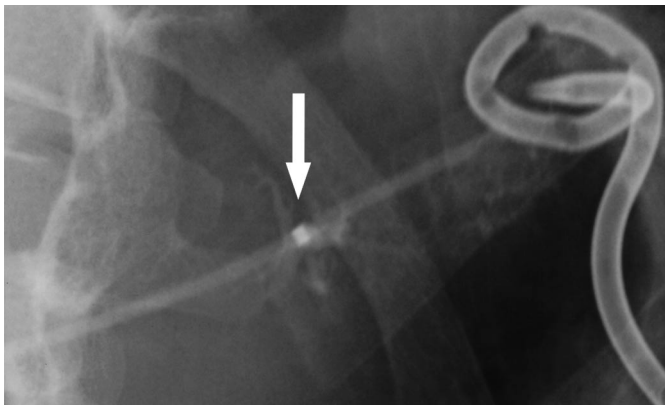


Figure 2 Patient 2: direct injection of Glubran 2 and Lipiodol into the fistulous tract. The radiopaque marker of the catheter is visible (arrow).



Figure 3 Patient 2: check pancreatography through the nasopancreatic drain 24 hours after Glubran 2 injection. There was complete closure of the fistula without opacification of the pancreatic tail upstream of the rupture of the main pancreatic duct.

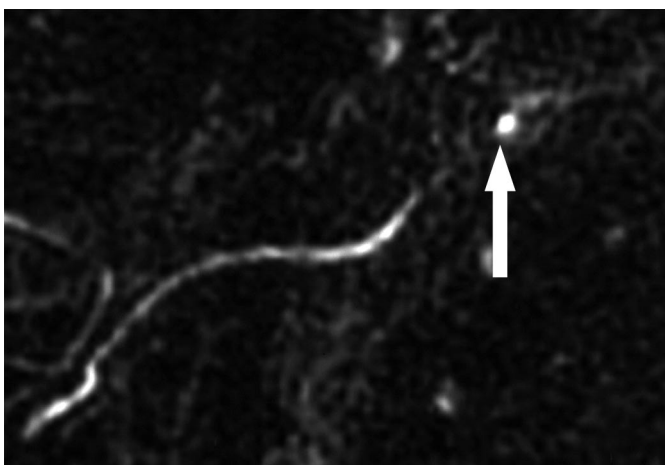


Figure 4 Patient 2: 5 months later, magnetic resonance pancreatography with secretin stimulation shows a normal pancreatic duct downstream of the rupture and mild dilatation of the short ductal segment above the rupture.



Figure 5 Patient 3: pancreatography showing a pancreatic fistula in the tail of the pancreas.

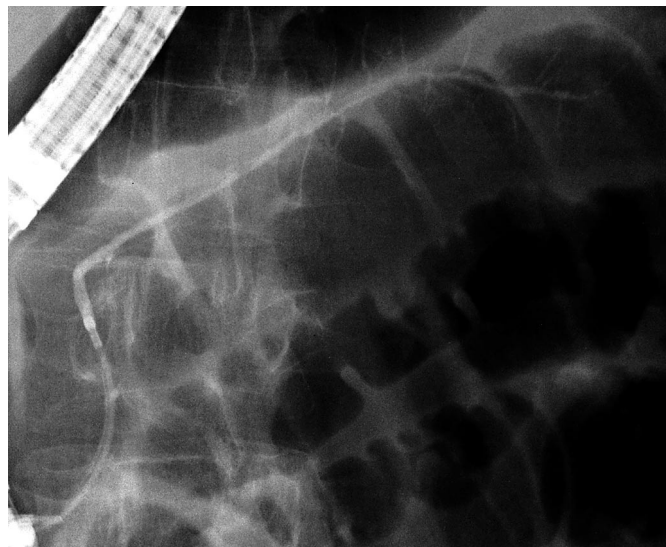


Figure 6 Patient 3: complete closure of the pancreatic fistula after Glubran 2 and Lipiodol injection.

of the pancreas that was drained surgically, and resulted in an EPF with a mean output of 100 ml/day, and 1 month later he was referred to our unit for an attempt at endoscopic treatment.

On admission the patient was in poor general condition due to sepsis. He refused S-MRP because of claustrophobia, and underwent ERCP during which a pancreatic fistula in the tail of the pancreas was identified (Figure 5). Glubran 2 and Lipiodol were injected under fluoroscopic control directly into the fistulous tract. The next day he had melena, and duodenoscopy showed bleeding from the sphincterotomy that was successfully treated endoscopically. The EPF closed within 24 hours (Figure 6). The patient died 35 days later from progression of the leukemia.

Patient 4

A woman underwent left colectomy for colonic cancer, and 1 week later she developed a peripancreatic fluid collection that was drained percutaneously resulting in an EPF with a mean output of 150 ml/day. Fistulography showed rupture of the main pancreatic duct at the body-tail level. Conservative treatment was ineffective, and 9 months later the patient was referred to our unit for endoscopic treatment.

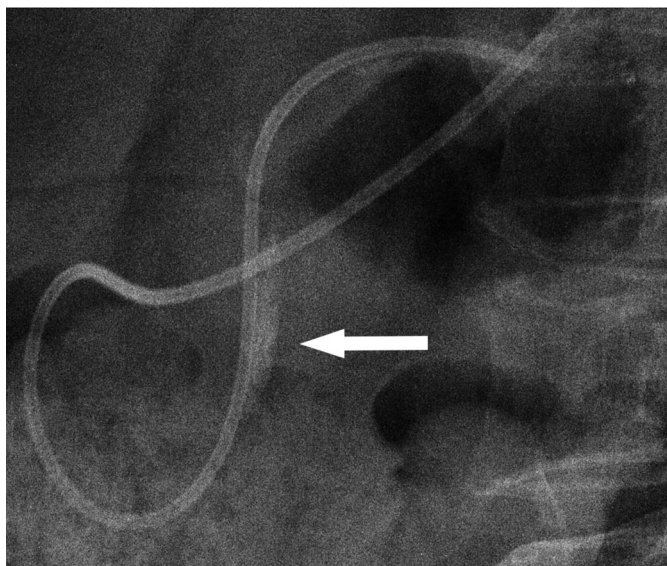


Figure 7 Patient 4: plain radiograph taken before the check pancreatography through the nasopancreatic drain shows an oval radiopaque foreign body in the pancreatic duct (arrow).

At ERCP a 7-Fr, 12-cm pancreatic stent was placed with the proximal end outside the fistulous tract draining the pancreatic duct upstream of the rupture. The fistula healed within 10 days, but 1 month later the EPF reappeared and the patient was readmitted. The pancreatic stent was removed, and Glubran 2 and Lipiodol were injected to obliterate the pancreatic stump upstream of the rupture. Follow-up pancreatography was done through the nasopancreatic drain 2 days later. Notably, a plain radiograph, taken before the pancreatography, showed an oval radiopaque foreign body in the pancreatic duct (Figure 7). Air was then injected through the nasopancreatic drain and the mixture of Glubran 2 and Lipiodol was ejected into the duodenum (Figure 8). Pancreatography showed obliteration of the pancreatic stump downstream of the rupture while the duct upstream was not sealed by Glubran 2 because of persistence of the fistula. 1 month later, a 5-cm peripancreatic fluid collection was detected on computed tomography (CT) scan. The patient underwent endoscopic ultrasound-guided pancreaticogastrostomy with placement of a 10-Fr stent near the pancreatic stump upstream of the rupture, and the fistula healed within 24 hours. The patient's general condition was good 4 months later.

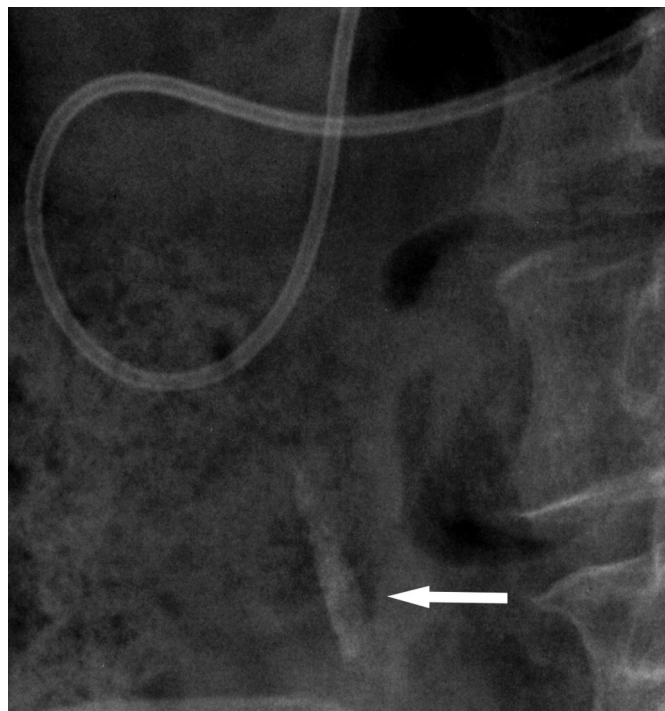


Figure 8 Patient 4: the mixture of Glubran 2 and Lipiodol was ejected into the duodenum (arrow) when air was injected through the nasopancreatic drain.

Discussion

While the incidence of EPF is 4–6% after pancreatic surgery, it increases to 33% in cases of surgery for abdominal injury [14,15]. Although some patients respond to conservative management, others might require endoscopic drainage [16] or surgical Roux-en-Y pancreaticojejunostomy, fistulojejunostomy, or distal pancreatectomy when the tail of the pancreas is affected [15,17] (Table 2).

With regard to conservative treatment, a retrospective study showed that postoperative EPF healed with conservative management for 11 weeks in 86% of cases, while inflammatory EPF closed after 22 weeks in only 53% of cases [18]. With intravenous octreotide, low-volume EPFs (< 100 ml/day) healed after an average of 12 ± 7 days, while high-volume fistulas (> 100 ml/day) required a mean of 28 ± 27 days [3].

Table 2 Results of studies of conservative, surgical, and endoscopic treatment of external pancreatic fistulas

Authors (year)	Type of treatment	Cases, n	Mean fistula output, ml/day	Success rate, %	Mean time to fistula healing, days	Complications, %
Howard et al. (1998) [18]	Conservative	15 (postoperative) 15 (inflammatory)	–	86 53	77 154	–
Bassi et al. (2000) [3]	Conservative	6 (low-output) 12 (high-output)	97 448	100 83	12 28	–
Bassi et al. (2000) [15]	Surgical	17	359	70	1	30
Costamagna et al. (2001) [6]	Endoscopic	16	205	75	9	–
Boerma et al. (2000) [16]	Endoscopic	15	125	87	10	–
Present series	Glubran 2	4	125	75	1	25

A surgical approach was used by Bassi et al., who described 17 patients with EPF who underwent fistulojejunostomy. While 12 patients had an uneventful postoperative course, four patients had postoperative complications that responded to conservative management [15].

Conventional endoscopic treatment by means of endoscopic drainage has been reported to be a safe and effective first-line therapy for patients with EPF who do not respond to conservative therapy. The main goal of endotherapy is to reduce the pressure in the pancreatic duct and bypass any existing ductal disruption. To achieve this, biliary and/or pancreatic sphincterotomy may be done followed by placement of a nasopancreatic drain. However, the EPF may fail to heal in the presence of stricture, obstruction, or ductal disruption [6].

In a recent paper, we reported the use of endoscopic therapy in 16 patients with postsurgical EPF in whom conservative management had failed. The fistula healed in 11/12 patients in whom a nasopancreatic drain could be placed. The fistulas closed after a mean time of 8.8 days. No complications related to the endoscopy were observed [6].

In this report we have described a new endoscopic approach.

In the first two cases reported here, the fistulous tract was not seen during the first ERCP but was clearly evident during the repeat ERCP guided by S-MRP. During the second ERCP, forceful contrast injection closer to the site of the fistula clearly delineated the fistulous tracts.

In patient 1, the small caliber of the pancreatic duct did not allow placement of a drain of adequate size. In the second patient, the presence of a ductal stricture with upstream ductal transection probably impeded fistula closure after the nasopancreatic drain was placed. After Glubran 2 injection and removal of the percutaneous drain this patient developed a small fluid collection in the tail of the pancreas, but a pseudocyst did not develop because the pancreatic duct upstream of the rupture was closed with Glubran 2.

In the third patient, Glubran 2 injection into the fistulous tract was chosen as the first-line treatment to obtain early closure of the fistula because of the poor general condition of the patient.

In patient 4, a peripancreatic fluid collection was still present at the time of Glubran 2 injection; perhaps the glue did not reach the pancreatic stump upstream of the rupture because it diffused into the cavity.

Glubran 2 injection directly into the fistulous tract is safe and the risk of complete closure of the main pancreatic duct is low, as shown in patient 4. Controlled clinical trials are needed to inves-

tigate the injection of Glubran 2 as a first-line treatment in cases of EPF that do not respond to conservative or conventional endoscopic treatment. S-MRP or fistulography prior to ERCP is recommended to delineate the anatomy of the pancreatic duct and the location of the fistula.

References

- Kozarek RA, Traverso LW. Pancreatic fistulas: etiology, consequences and treatment. *Gastroenterologist* 1996; 4: 238–244
- Ridgeway MG, Stabile BE. Surgical management and treatment of pancreatic fistulas. *Surg Clin N Am* 1996; 76: 1159–1173
- Bassi C, Falconi M, Salvia R et al. Role of octreotide in the treatment of external pancreatic pure fistulas: a single-institution prospective experience. *Langenbecks Arch Surg* 2000; 385: 10–13
- Martineau P, Shwed JA, Denis R. Is octreotide a new hope for enterocutaneous and external pancreatic fistulas closure? *Am J Surg* 1996; 172: 386–395
- Gullo L, Biliotti G, Pezzilli R et al. Effect of octreotide (SMS 201-995) on meal-stimulated pancreatic secretion in three patients with external pancreatic fistula. *Am J Gastroenterol* 1991; 86: 892–894
- Costamagna G, Mutignani M, Ingrosso M et al. Endoscopic treatment of postsurgical external pancreatic fistula. *Endoscopy* 2001; 33: 317–322
- Quinn J, Wells G, Sutcliffe T et al. A randomized trial comparing octylcyanoacrylate tissue adhesive and sutures in the management of lacerations. *JAMA* 1997; 277: 1527–1530
- N-BCA Trail Investigators. N-butyl cyanoacrylate embolization of cerebral arteriovenous malformations: results of a prospective, randomized multi-center trial. *Am J Neuroradiol* 2002; 23: 748–755
- Dhiman RK, Chawla Y, Taneja S et al. Endoscopic sclerotherapy of gastric variceal bleeding with n-butyl-2-cyanoacrylate. *J Clin Gastroenterol* 2002; 35: 222–227
- Seewald S, Groth S, Sriram PVJ et al. Endoscopic treatment of biliary leakage with n-butyl-2 cyanoacrylate. *Gastrointest Endosc* 2002; 56: 916–919
- Vinters HV, Galil KA, Lundie MJ et al. The histotoxicity of cyanoacrylates. A selective review. *Neuroradiology* 1985; 27: 279–291
- Montanaro L, Arciola CR, Cenni E et al. Cytotoxicity, blood compatibility and antimicrobial activity of two cyanoacrylate glues for surgical use. *Biomaterials* 2001; 22: 59–66
- Levrier O, Mekkaoui C, Rolland PH et al. Efficacy and low vascular toxicity of embolization with radical versus anionic polymerization of n-butyl-2-cyanoacrylate (NBCA). An experimental study in the swine. *J Neuroradiol* 2003; 30: 95–102
- Becker RJ, Bass RT, Zajtchuk R et al. External pancreatic fistula following abdominal injury. *Arch Surg* 1967; 95: 556–566
- Bassi C, Butturini G, Salvia R et al. A single-institution experience with fistulojejunostomy for external pancreatic fistulas. *Am J Surg* 2000; 179: 203–206
- Boerma D, Rauws EA, van Gulik TM et al. Endoscopic stent placement for pancreaticocutaneous fistula after surgical drainage of the pancreas. *Br J Surg* 2000; 87: 1506–1509
- Ilse I, Larsson J, Lindstrom E. Surgical management of pure pancreatic fistulas. *Hepatogastroenterology* 1994; 41: 271–275
- Howard TJ, Ock CE, Sarkar J et al. Contemporary treatment strategies for external pancreatic fistulas. *Surgery* 1998; 124: 627–632