

Paolo Barillari
Luigi Basso
Antonella Larcinese
Paolo Gozzo
Marileda Indinnimeo

Cyanoacrylate glue in the treatment of ano-rectal fistulas

Accepted: 23 December 2005
© Springer-Verlag 2006

P. Barillari (✉) · L. Basso ·
A. Larcinese · P. Gozzo ·
M. Indinnimeo
Department of Surgery
"Pietro Valdoni",
University of Rome "La Sapienza"
Medical School,
Policlinico "Umberto I",
viale del Policlinico 155,
00161 Rome, Italy
e-mail: paolo.barillari1@tin.it
Tel.: +39-06-49972167

Abstract *Background and aims:* The management of anal fistula is debatable. Although several procedures have been described, none of them is free from complications, such as anal incontinence and anal pain. The purpose of this study was to evaluate the employment of a glue composed of *N*-butyl-2-cyanoacrylate and methacryloxysulfolane (Glubran 2) to treat fistula-in-ano. *Patients and methods:* Twenty-one patients (14 men and 7 women) with cryptoglandular anal fistula were enrolled in the study and treated as day-cases. Fistulas were assessed both clinically and by trans-rectal endosonography with a rotating 10-MHz 360° endoscopic probe. Assessment of continence was also performed. The fistula tract was identified, curetted and washed-out with normal saline and hydrogen peroxide; then the glue was injected from the syringe nozzle through a catheter previously inserted into the fistula. Additional treatments were performed when the first failed. *Results:* Five of seven simple fistulas (71.4%) healed with primary glue treatment; the other two needed sec-

ond and third injections, and both healed. Ten of 14 (71.4%) complex fistulas healed with primary treatment; of the other four patients, one showed signs of intolerance to cyanoacrylate, which required re-intervention to remove the applied glue. In the second patient, treatment was successful after a second session; in the third case, three glue injections were required; while the fourth patient was lost at follow-up after three unsuccessful sessions. The ratio of cumulative healing with only one treatment was 15/21 (71.4%), and the ratio of overall healing after more than one session was 19/21 (90.2%). There was no sign of recurrence of the disease after 18 months of follow-up. *Conclusion:* Cyanoacrylate glue seems to be ideal to treat fistula-in-ano, as it is a safe, cost-effective, repeatable and muscle-sparing technique. The incidence of recurrence is low, and post-procedure complicated fistulas or perianal abscesses were not reported.

Keywords Cyanoacrylate glue · Ano-rectal · Fistulas

Introduction

Management of fistula-in-ano is both challenging and controversial. Inter-sphincteric and low trans-sphincteric fistulas usually heal well after simple fistulotomy, although sometimes, fecal or permanent gas incontinence may occur [1, 2]. In contrast, many surgical options have been

suggested to treat high trans-sphincteric, supra-sphincteric or extra-sphincteric fistulas, because these are associated with significant incontinence if treated by simple fistulotomy. Several procedures, such as staged fistulotomy using the placement of a cutting seton, mucosal advancement flaps, island flap anoplasty and combined seton-double flap procedures, have been described [3, 4]. Although these

techniques minimise incontinence compared to simple fistulotomy, they are associated with significant patient discomfort and pain, require admission to a hospital, may take several months to heal and do not completely reduce the risk of incontinence.

Fibrin glue seems to be, in many ways, the ideal treatment for fistula-in-ano [5]. The technique is simple, repeatable and does not affect the sphincteric musculature. When injected into a fistula, the fibrin clot seals the fistula tract and enhances migration and activation of fibroblasts and, thus, collagen deposition. Different studies have reported conflicting success rates (range=10–85%), which have been attributed to differences in the etiology, complexity of the fistulas reported in each series, variations in technique, duration of follow-up, different types of fibrin sealant (autologous or commercial), fibrinogen concentration of the glue, employment of a fibrinolytic inhibitor or addition of powdered collagen to create a “cement mixture” [6].

The aim of the present study was to evaluate the employment of *N*-butyl-2 cyanoacrylate together with methacryloxysulfolane (Glubran 2) to treat fistula-in-ano.

Patients and methods

Twenty-one consecutive patients (age range = 24–63; sex = 14 males and 7 females) with cryptoglandular anal fistula were enrolled into our prospective study at the Department of Surgery “Pietro Valdoni”, University of Rome “La Sapienza” Medical School, Italy. Permission was obtained from the local ethical committee. The technique was thoroughly described to each patient, and informed consent was consequently obtained. In all cases, Crohn’s disease and rectovaginal fistulas were previously ruled out by means of medical history, clinical presentation and anatomical assessment. After careful inspection of the anus and the perianal area confirmed the presence of an anal fistula, all patients were scheduled for out-patient surgery and treatment with *N*-butyl [2] cyanoacrylate *N*-butyl [2] cyanoacrylate (monomer) and methacryloxysulfolane (monomer) (Glubran 2, GEM S.r.l., Viareggio, Italy). Pre-operatively, fistulas were assessed both clinically and by means of trans-rectal endosonography with a rotating 10-MHz 360° endoscopic probe (diameter, 1.7 cm) (B&K Medical, Gentofte, Denmark) to evaluate the complexity of the tract and its relationship with the ano-rectal sphincteric complex. A baseline assessment of continence was made with documentation of incontinence scores (Cleveland Clinic incontinence questionnaire) [7]. Pre-operatively, a draining seton was inserted and left in place for at least 15 days prior to the procedure, and oral cephalosporin associated to metronidazole was given 5 days beforehand.

Cyanoacrylate glue treatments were performed as day-cases in the operating room, with patients under spinal anesthesia or sedation with intravenous midazolam and

monitored for intra-operative control of pain. All patients had full mechanical bowel preparations the day before the procedure. In the operating room, the patients were placed in the Lloyd–Davies (lithotomy) position, and the perianal skin was prepared with povidone iodine. An Eisenhammer retractor was then inserted in the anal canal, and the previously placed draining seton was removed. The internal (primary) and external (secondary) openings of the anal fistula were carefully identified and the track was thoroughly curetted and washed-out with normal saline and/or diluted povidone iodine irrigation. The cyanoacrylate glue was retrieved from storage at 4°C, and kept at room temperature for 2 h. The offending anal gland at the internal opening was first identified, destroyed using mono-polar diathermy and eventually loosely sutured with a figure-of-eight stitch using 3-0 Vicryl (Ethicon, Pomezia, Italy).

A 6-French urothelial catheter with no needle was inserted into the fistulous tract from the external opening toward the internal opening and as far as it was possible to progress. The glue was then slowly injected from the syringe nozzle through the catheter. Once “bubbling” of glue was noticed at the loosely sutured primary opening, the catheter was slowly and gently withdrawn while the glue was still injected, until the catheter emerged at the external opening, where another “bubbling” of glue was eventually seen at the perianal skin. Most polymerisations of the glue occurred within approximately 60 s, during which the patients felt a mild sensation of “heat”. No dressing was applied and, after 2 h, all patients were discharged. Oral ciprofloxacin, 500 mg, and metronidazole, 500 mg, both twice daily for 10 days, were prescribed. Post-operatively, the patients were instructed to avoid strenuous physical activity for 7 days and showers rather than baths were recommended for 10 days. Multiple daily sitz baths were also suggested. The patients were re-examined every 2 weeks for the first 2 months, and then every 3 months. If the fistula failed to heal with primary treatment at a 4-week follow-up, a second glue treatment was performed. Post-treatment maximum resting, squeeze pressures and incontinence scores were assessed 12 weeks following the procedure. The patients were always asked to complete a satisfaction score, rated on a 5-level Likert scale as either “poor”, “fair”, “good”, “very good” or “excellent” [7], and a pain score, rated on a visual analogue scale ranging from 0 (no pain) to 10 (maximum pain ever experienced), and report their work-time and productivity loss.

Results

The durations of symptoms ranged from 3 to 72 months (median=16 months). Fourteen patients had complex fistulas (high trans-sphincteric) and seven had simple

fistulas (low trans-sphincteric). Only one patient presented pre-operative symptoms of incontinence.

Five of seven simple fistulas (71.4%) healed with primary glue treatment. The other two simple fistulas received second and third glue injections and both eventually healed. Ten of 14 complex fistulas (71.4%) healed with primary glue treatment. Of the other four patients, one showed signs of intolerance to cyanoacrylate consisting of severe redness and serous discharge, which required re-intervention 10 days later to remove the applied glue. The second patient treatment was successful after a second session; in the third case, three glue injections were required, while the fourth patient was lost at follow-up after three unsuccessful sessions. At follow-up, all patients always received careful rectal examinations by one of the authors. The ratio of cumulative healing with only one treatment was 15/21 (71.4%), and the ratio of overall healing after more than one treatment was 19/21 (90.2%). None of the patients had impairments of baseline continence scores, and maximum resting and squeeze pressures did not significantly change from baseline records. The mean satisfaction score was 8.5, the main pain score was 2.8 and all patients returned to work within 3 days. No complications such as hemorrhages or perianal abscesses ever developed. Mean follow-up was 18 months (range = 6–28 months, median=16 months), and not one of the 19 successfully treated patients showed recurrence of the fistula.

Discussion

During the last decade, conservative treatment of perianal fistulas by employing fibrin glue has become popular because it is safe, repeatable and muscle-sparing [6–12]. On the other hand, a high recurrence rate has been reported, with consequent development of more complicated fistulas or abscesses. Many different techniques and several different types of fibrin glue have been used in multiple studies. Recurrences are reported to occur in up to 59% of cases [13], while a study by Park et al. showed no significant differences in a group of 43 patients treated with tissue fibrin sealant compared to autologous fibrin glue [14]. In any case, treatment with fibrin glue has mainly been advocated to treat complex fistulas, while its role in simple tracks is debatable [15]. With regard to bowel preparation, no substantial differences are reported in studies where a full bowel cleansing prior to the procedure was performed, as compared to patients who did not receive any bowel preparation. However, it can be speculated that a thorough pre-operative bowel cleansing helps to minimise the occurrence of bowel movements within the first 24–36 h, thus reducing the risk of early glue

extrusion. Cyanoacrylate glue was first synthesised in 1949 by Ardis, and was first employed in surgery in 1959 by Coover [15]. Later, a non-histotoxic form, butyl-2-cyanoacrylate, was developed, with excellent tissue gluing properties even in non-dry environments. During the 1960s, cyanoacrylate was employed in Vietnam on wounded American soldiers, mainly to stop bleeding. It has recently been used mainly by orthopaedic surgeons [16], ophthalmologists [17], neurosurgeons [18], urologists [19] and endoscopists [20]. Cyanoacrylate (Glubran 2) is a straw-coloured and clear liquid, contained in 1-ml, ready-to-use vials, to be stored in a cool environment, not exceeding +4°C. On contact with biological tissues in a moist environment, cyanoacrylate rapidly polymerises to create a thin elastic film bearing high tensile strength, which guarantees firm adherence of tissues. The film easily tailors to the planes and tissues of application, is totally water-resistant, and is not impaired by the presence of blood or organic fluids. After polymerisation, a suture needle may easily perforate the film because the process does not give rise to glassy aggregates. The polymerisation time varies in relation to the type of tissue where the glue is applied, the amount and nature of the fluids present and the amount of product employed. When correctly applied, the glue begins solidification within 1 or 2 s and completes the process within 60 or 90 s. The glue reaches its maximum mechanical strength upon completion of this reaction. Once solidification has occurred, the glue no longer possesses adhesive properties so that tissues or surgical gauzes may be safely employed in the operative field with no risk of undesirable adhesion. Polymerisation occurs at a temperature of approximately 45°C. The placement of a loose stitch through the internal/primary opening of the fistula prior to the injection of glue is important. This allows the glue to be injected under some pressure, thus filling any secondary tracts. Furthermore, cyanoacrylate is less dense than fibrin glue; as a result, it can reach even extremely thin secondary tracts and still “bubble” through the stitch on the primary opening. The authors believe that both pre-operative and peri-operative insertion of a draining seton are useful for a good outcome. The seton should be left in place for at least 15 days prior to the procedure, allowing good drainage and “cleansing” of the fistula so that the glue itself can later work in a relatively “clean” environment. Peri-operative employment of oral cephalosporin associated to metronidazole (for 15 days) should minimise the occurrence of secondary infections of the tract. In contrast to fibrin glue, cyanoacrylate is not reabsorbed but stays in place as an inert foreign body, initially giving the impression of a “hard string” which follows the tract of the fistula itself. However, no patient complained from this initial sensation of a “hard string”, which eases with time.

Due to our short-term follow-up, we are not able to achieve definitive conclusions regarding the natural history of cyanoacrylate, which is likely to stay as an inert substance during the following years. In only one case, we observed intolerance to the injected glue, which had to be removed. A method to assess intolerance to the compound should possibly be developed. In our research, satisfactory overall healing rates after one (71.4%) and two or three treatments (90.2%) were achieved. All patients were treated as day-cases and discharged soon after the procedure had been completed, which minimised the overall cost of treatment, as compared to more aggressive surgical approaches which may require long post-operative hospitalisations.

Conclusions

Cyanoacrylate can be employed to treat fistula-in-ano, as its use is easy, safe, cost-effective and all that is required in case of recurrences is a second or third session. Its efficacy seems to be at least comparable to that of fibrin-based glues. However, only further, larger series, studies with longer follow-ups and randomised trials will help to better show the place of cyanoacrylate in the modern treatment of ano-rectal fistulas.

References

1. Garcia-Aguilar J, Belmonte C, Wong DW, Goldberg SM, Madoff RD (1998) Cutting seton versus two-stage seton fistulotomy in the surgical management of high anal fistula. *Br J Surg* 85: 243–245
2. Schouten WR, Zimmerman DD, Briel JW (1999) Transanal advancement flap repair of trans-sphincteric fistulas. *Dis Colon Rectum* 42:1419–1423
3. Mizrahi N, Wexner SD, Zmora O et al (2002) Endorectal advancement flap: are there predictors of failure? *Dis Colon Rectum* 45:1616–1621
4. Pescatori M, Mungo M, Guarino E (2002) Combined seton–double flap procedure for complex high anal fistula. *Tech Coloproctol* 6:71
5. Redl H, Schlag G (1986) Properties of different tissue sealants with emphasis on fibrin-based preparations. In: Schlag G, Redl H (eds) *Fibrin sealant in operative medicine*. Springer, Berlin Heidelberg New York, pp 27–38
6. Loungnarath R, Dietz DW, Mutch MG, Birnbaum EH, Kodner IJ, Fleshman JW (2004) Fibrin glue treatment of complex anal fistulas has low success rate. *Dis Colon Rectum* 47:432–436
7. Jorge JM, Wexner SD, James K, Nogueras JJ, Jagelman DG (1994) Recovery of anal sphincter function after the ileoanal reservoir procedure in patients over the age of fifty. *Dis Colon Rectum* 37:1002–1005
8. Kavadas V, Barham CP, Finch-Jones MD, Vickers J, Sanford E, Alderson D, Blazeby JM (2004) Assessment of satisfaction with care after inpatient treatment for oesophageal and gastric cancer. *Br J Surg* 91:719–723
9. Romanos GE, Strub JR (1998) Effect of Tissucol on connective tissue matrix during wound healing: an immunohistochemical study in rat skin. *J Biomed Mater Res* 39:462–468
10. Hwang TL, Chen MF (1996) Randomized trial of fibrin tissue glue for low output enterocutaneous fistula. *Br J Surg* 83:112
11. Cellier C, Landi B, Faye A et al (1996) Upper gastrointestinal tract fistulas: endoscopic obliteration with fibrin sealant. *Gastrointest Endosc* 44: 731–733
12. Aitola P, Hiltunen KM, Matikainen M (1999) Fibrin glue in perianal fistulas—a pilot study. *Ann Chir Gynaecol* 88:136–138
13. Zmora O, Mizrahi N, Rotholtz N, Pikarsky AJ, Weiss EG, Nogueras JJ, Wexner SD (2003) Fibrin glue sealing in the treatment of perineal fistulas. *Dis Colon Rectum* 46:584–589
14. Park JJ, Cintron JR, Orsay CP et al (2000) Repair of chronic ano-rectal fistulas using commercial fibrin sealant. *Arch Surg* 135:166–169
15. Lindsey I, Smilgin-Humphreys MM, Cunningham C, Mortensen NJM, George BD (2002) A randomized, controlled trial of fibrin glue vs. conventional treatment for anal fistula. *Dis Colon Rectum* 45:1608–1615
16. Yilmaz C, Kuyurtar F (2005) Fixation of a talar osteochondral fracture with cyanoacrylate glue. *Arthroscopy* 21:1009
17. Sharma A, Kaur R, Kumar S, Gupta P, Pandav S, Patnaik B, Gupta A (2003) Fibrin glue versus *N*-butyl-2-cyanoacrylate in corneal perforations. *Ophthalmology* 110:291–298
18. Wakhloo AK, Perlow A, Linfante I, Sandhu JS, Cameron J, Troffkin N, Schenck A, Schatz NJ, Tse DT, Lam BL (2005) Transvenous *n*-butyl-cyanoacrylate infusion for complex dural carotid cavernous fistulas: technical considerations and clinical outcome. *Am J Neuroradiol* 26:1888–1897
19. Aslan G, Men S, Gulcu A, Kefi A, Esen A (2005) Percutaneous embolization of persistent urinary fistula after partial nephrectomy using *N*-butyl-2-cyanoacrylate. *Int J Urol* 12:838–841
20. Ryu SH, Moon JS, Kim I, Kim YS, Lee JH (2005) Endoscopic injection sclerotherapy with *N*-butyl-2-cyanoacrylate in a patient with massive rectal variceal bleeding: a case report. *Gastrointest Endosc* 62:632–635