Efficacy of synthetic glue treatment of high crypoglandular fistula-in-ano

Efficacité du traitement des fistules anales cryptoglandulaires hautes par colle synthétique

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Summary

Objectives. — In France, seton drainage followed by fistulotomy is currently the standard treatment for high cryptoglandular fistula-in-ano. Biological or synthetic glues, such as Glubran\textsuperscript{2}, have been recently proposed for sealing the fistula tract. The purpose of this study is to determine the healing rate with glubran2 and to assess the functional outcome after cure of fistula-in-ano.

Patients and methods. — From July 2006 to July 2008, 34 patients (20 males; median age 48.5 years, range 22–55 years) with high cryptoglandular anal fistulas were treated with glubran2. Patients were seen for physical examination at 1, 3 and 6 months, then interviewed by telephone at 1 and 2 years, and in September 2009. The Fecal incontinence severity index (FISI) score was used to assess continence.

Results. — The healing rate at 1 month was 67.6% (23 patients); the fistula failed to heal in 11 patients. All 23 patients with a healed fistula remained recurrence-free, with no continence disorders noted, during the median 34-month follow-up period (range 21–43 months). One patient was lost to follow-up after 6 months.

Conclusion. — Glubran2 provides an effective treatment for high fistula-in-ano, with no change in continence. In future, a randomized comparison of this agent with fibrin glues should be useful.

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Résumé

Buts. — Actuellement, en France, le traitement de référence des fistules anales hautes d’origine cryptoglandulaires est un drainage sur séton puis une fistulotomie. Une alternative récente est
l'encollage du trajet fistuleux par colle biologique ou synthétique comme le Glubran® 2. Le but de ce travail était d'évaluer le taux de cicatrisation et les résultats fonctionnels des fistules anales hautes traitées par encollage au Glubran® 2.

Patients et méthodes. — De juillet 2006 à juillet 2008 : 34 patients, 20 hommes âge médian de 48,5 ans (22 à 85 ans) présentant une fistule anale haute cryptoglandulaire ont été traités par Glubran® 2. La colle était injectée par l’intermédiaire d’un cathéter dans le trajet préalablement cureté. Les patients étaient revus cliniquement à un, trois et six mois, puis étaient contactés téléphoniquement par l’équipe infirmière à un an puis tous les ans et en septembre 2009. La continence était évaluée par le Fecal Incontinence Severity Index (FISI).

Résultats. — À un mois, la fistule était fermée chez 23 patients (67,6 %), 11 patients étaient en échec. Aucun des 23 patients cicatrisés n’a récidivé, aucun trouble de la continence n’était observé sur un suivi moyen de 34 mois (21—43) (un patient était perdu de vue après six mois).

Conclusion. — L’encollage par Glubran® 2 est un traitement efficace des fistules anales hautes, sans altération de la continence. Une étude randomisée avec les colles biologiques semble justifiée.

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### Introduction

There are two conflicting objectives in the surgical treatment of fistula-in-ano: preservation of sphincter function to ensure post-cure continence; and elimination of suppuration, with healing of the primary orifice to avoid recurrence.

Most authors refer to the Parks classification [1], but we prefer the more practical method that divides fistula-in-ano into high and low fistulas (Fig. 1). Low fistulas cross the lower third of the external sphincter. They can be treated by fistulotomy in a one-stage operation with a good outcome, including a low recurrence rate and little effect on continence. For high fistulas, where a large portion of the tract runs through the sphincter, several surgical phases are required, including seton drainage followed by treatment of the fistula tract [2].

Conventional sphincter-sparing methods include the loose seton technique, widely used for fistula-in-ano with Crohn’s disease [3,4], advancement of mucosal flaps or dermal island flaps [5—7] and fistulotomy followed by sphincter reconstruction [8]. However, the development of glues and plugs has raised renewed interest in sphincter-sparing techniques [9,10]. In addition to their simplicity, these ‘‘modern’’ methods have the advantage of preserving sphincter function. According to the literature so far, the success rate with fibrin glue is 53% [11].

Tests with the recently available synthetic glue Glubran® 2 show a 70% healing rate after the primary glue injection and 90% after several injections [12]. Glubran 2 is composed of N-butyl-2-cyanoacrylate combined with a methacryloxy-sulfolane co-monomer, and is the only class-III synthetic device for internal use. It is a ready-to-use transparent pale-yellow glue that polymerizes rapidly on contact with blood or other biological fluids. The ‘‘cyano’’ moiety binds with proteins while the ‘‘acrylate’’ moiety enables polymerization. Their combined action leads to the formation of a watertight air-permeable film that favors tissue healing. Hydrolytic degradation is slow, taking 15 days to 6 months. Polymerization time depends on the quantity of glue injected. In general, the glue starts to polymerize 1—2 s after application and is complete in 60—180 s. One drop can cover a surface area of 1 cm², forming a thin adhesive film with high tensile strength [13].

This medical device can be used for all indications for biological glues without the risk of contamination related to the presence of a biological component, and with perfect traceability.

The product, manufactured by GEM S.r.l. [via dei Campi 2, PO Box 427, 55049 Viareggio (LU)] in Italy, has a CE label (Fig. 2) and is currently marketed in France by Nipro Biocorp Biopole 63360 Saint-Beauzire, France.

The purpose of the present study was to assess the healing rate, early morbidity and effect on anal continence of glubran 2 synthetic glue for the treatment of high cryptoglandular fistula-in-ano.

### Patients and methods

From July 2006 to July 2008, all patients with high cryptoglandular fistula-in-ano, except those with Crohn’s disease or a vaginal orifice, were invited to choose between two proposed treatments: an endorectal advancement flap or the injection of synthetic glue. Patients were informed of the following arguments for the choice of treatment: the endorectal advancement flap provides a high healing rate, but at the cost of more complex surgery and longer postoperative follow-up compared with the simplicity of synthetic glue injection, which probably offers a somewhat lower healing rate, but allows rapid recovery of activity.
Surgical technique

Glubran 2 was injected after a period of drainage with a loose seton (Ethiloop, 1.3 mm, Johnson and Johnson Medical Ltd) for 6 to 8 weeks and resolution of fistula discharge (Fig. 3). Preoperative preparation included an evacuation enema, and the surgical procedure was performed under general anesthesia. The fistula tract was curetted, then washed out with an iodine—hydrogen peroxide solution before deep electrocoagulation of the internal orifice. Petroleum jelly was used to protect the mucosa of the lower rectum. A catheter was inserted into the fistula tract via the external orifice for slow glue injection. When the glue appeared at the internal orifice, the catheter was slowly withdrawn while expressing glue until the external orifice was reached. Oral antibiotic prophylaxis was given postoperatively (ciprofloxacin 1 g/day, metronidazole 1 g/day) for 7 days. Patients remained in hospital overnight for postoperative surveillance. At discharge, all activities (except bathing and strenuous exercise for 15 days) were authorized.

Follow-up

Continence was assessed pre- and postoperatively using the Fecal incontinence severity index (FISI). Patients were reviewed at 1, 3 and 6 months. Physical examination looked for signs of unhealed fistula, fecal incontinence and/or anal leakage. Patients completed the FISI at each clinical visit [14].

A nurse also contacted each patient for telephone interviews 1 and 2 years after the procedure, and in September 2009. A standardized questionnaire was used to collect data on anal pain, perianal discharge, changes in continence or FISI score, and leakage or soiling. These data are summarized in Tables 1 and 2.

Results

Thirty-four consecutive patients (20 males, 14 females; median age 48.5 years, range 22—85 years) presenting with a high fistula-in-ano chose the glue treatment. At 1 month, the fistula had completely healed in 23 symptom-free patients (healing rate = 67.6%). These results were still present at 3 and 6 months, and none of these patients experienced a recurrence. One patient who had achieved full cure was lost to follow-up after 6 months. Continence was not affected, as the patients’ pre- and postoperative FISI scores remained unchanged.

There were 11 cases of failure: one patient accepted two successive glue injections, but the fistula still failed to heal.

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<th>Table 2</th>
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<td>Patient’s follow-up</td>
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Twenty-two of the 23 patients whose fistula had healed were contacted at 1 and 2 years, and in September 2009, for a telephone interview. The standardized questionnaire showed that none of the patients who had achieved a full cure complained of fecal incontinence or leakage. Median follow-up time was 34 months (range 21—43 months; Table 2).

Early complications, as revealed by anal pain, were noted in six patients: in three of these patients, pain was related to a cone of excess glue at the external orifice that was removed at the follow-up visit, after which symptoms resolved rapidly; in two other patients, pain was caused by chemical burns of the anal canal, but symptoms resolved rapidly; and in one patient, morphine was required to relieve pain caused by ulceration of the internal orifice that had healed slowly (complete healing was noted at 10 weeks).

The cost of the procedure is low. The glubran 2 injections cost less than €150 per patient, and patients were in hospital for only one night. Patients were able to resume their occupational activities rapidly and were simply advised to avoid strenuous exercise for 15 days.

**Discussion**

Before using this product, we performed a PubMed search online using the following keywords: cyanoacrylate; glubran; glubran 2; synthetic glue. The search returned 4079 references. This suggests that chemical glues are widely used in a large number of specialties for their hemostatic properties, their ability to close fistulas and to treat vascular malformations. No cases of long-term intolerance have been reported, which can be explained by the hydrolytic degradation of the product [13].

In France, the most popular treatment for high cryptoglandular fistula-in-ano is currently seton drainage, followed a few weeks later by sphincter section either via laid-open fistulotomy or the cutting seton technique. The present approach has the advantage of being a simple procedure that offers a high healing rate, with a less than 1% rate of recurrence [15]. Section of the sphincter is, nevertheless, a compromise that has deleterious effects on anal continence. In their review of the literature, Ommer et al. [16] reported incontinence in 0—64% of patients; however, incontinence scores are rarely reported, explaining in part the wide range of the results. Not surprisingly, the severity of incontinence depended on the thickness of the sphincter section.

Three randomized controlled trials of healing rates with rectal flaps were reviewed by Malik and Nelson [17], and Gustafsson and Graf [5] reported a 57% healing rate with mucosal flaps and noted that antibiotic prophylaxis did not significantly alter the results. For Ho and Ho [6], the healing rate was 90% using a dermal flap or fistulotomy. Perez et al. [8] compared the advancement flap with fistulotomy followed by reconstruction. The healing rate was better than 90% in both groups, with no significant differences in incontinence and manometric data. Overall, the success rate is variable for advancement flaps, ranging from 40 to greater than 90% [18—20].

The conventional sphincter-sparing methods are expected to preserve anal continence. In fact, in their review of the literature, Ommer et al. [16] reported that the rate of incontinence after lowering the mucosal rectal flap ranged from 0—42%. Zimmerman et al. [7] described deterioration of continence in 30% of patients treated with a dermal flap. According to Perez et al. [8], fistulotomy followed by sphincterorrhaphy in the same operation is also a source of minor changes in continence for 12.5% of patients.

The relative complexity of these surgical techniques limits their use. Dissection of the highly ramified fistula tract can be difficult, the postoperative surveillance period is relatively long (4—8 weeks) and patients must wait for healing before resuming their former activities. However, two recent sphincter-sparing techniques using glue or an absorbable plug to seal the fistula tract have been described. According to a review of prospective studies reported by Garg et al. [21], the success rate with plugs ranges from 35 to 87%, with follow-up times ranging from 3.5 to 12 months. Ky et al. [22] found this rate to decline rapidly: from an 84% success rate at 3—8 weeks down to 54.6% at 6.5 months. In addition, plugs are expensive at around €800 but, in their cost-analysis study, Adamina et al. [23] found that the overall cost of fistula-in-ano is lower when treated with a plug compared with a rectal flap.

According to the meta-analysis reported by Swinscoe et al. [11], the overall healing rate with fibrin glues is 53—ranging from 10 to 78% in a series that included a large proportion of high fistulas reporting less favorable rates—and the rate persists over time. From an economic point of view, treatment with fibrin glue is comparable to treatment with glubran 2, as the cost of the drugs or medical device are less than €150.

Rapid resumption of occupational activities is an advantage compared with the flap technique, even though strenuous exercise is contraindicated for 15 days. So far, two publications have reported results with glubran 2. Jain et al. [24] reported their experience with 20 patients. The fistula healed in 17 cases after the first injection, and the second injection was successful for two other patients. Barillari et al. [12] reported on 24 patients—14 with high fistulas and 10 with low fistulas. Their healing rate was five out of seven (71.4%) for low fistulas and 10 out
of 14 (71.4%) for high fistulas, with no continence disorders. A second injection was successful in four other patients.

The present study is only the second to report results with Glubran 2 for high fistula-in-ano. Our small, non-comparative, series was recruited at a single center and was followed-up for a median period of 34 months (range 21—43 months). This is, nevertheless, the largest series reporting on a homogenous population of patients with high cryptoglandular fistula-in-ano, excluding Crohn’s disease and vaginal orifices. Healing was achieved in 67.6% of our patients, a rate comparable to the 71.4% reported by Barillari et al. [12]. However, unlike those authors, who also reported 90% healing after two or three injections, only one patient in our study accepted a second injection, which proved to be unsuccessful.

All procedures were performed under general anesthesia. However, for de Paradis et al. [25], injection of fibrin glue under locoregional anesthesia enabled a significantly higher success rate.

According to Barillari et al. [12], patients were free of continence disorders, as were our patients, whose FISI scores remained unchanged 6 months later. When questioned about this issue during the telephone interview conducted in September 2009, 22 patients reported being free of any leakage or discharge. The median overall follow-up duration (clinical visit and telephone interview) was 34 months (range 21—43 months).

In the present study, the observed complications were noted early on and could have been avoided. An excess amount of glue was injected in three cases, which highlighted the importance of avoiding glue overflow onto the mucosa or skin. There were also two cases of anal canal burns, which most likely would have been avoided by sufficient protection with petroleum jelly.

There was, however, one case in which the glue caused ulceration. Burns and, more rarely, tissue necrosis with formation of deep ulceration are the recognized adverse effects of synthetic glues [26]. The polymerization reaction is exothermic, producing a temperature of 45°C locally but, in the presence of an excess amount of glue, the polymerization time is longer, thus possibly explaining the ulceration. However, this also suggests that the risk—benefit ratio needs to be more carefully examined.

Conclusion

Glubran 2 is a low-cost, easy-to-apply method for the treatment of fistula-in-ano that allows rapid recovery of prior activities, a satisfactory rate of healing and no change in fecal continence. In future, a comparative study vs fibrin glues should be undertaken. Early on in our study, there were minor inconveniences that could have been avoided with a rigorous operational protocol. We did, however, observe one serious complication, which prompted us to evaluate each patient according to the expected advantages of the technique compared with the risks involved.

Conflict of interest

The authors report no conflict of interest.

References


