A PROSPECTIVE STUDY TO EVALUATE THE EFFICACY OF FIBRIN GLUE IN FISTULA-IN-ANO

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Abstract

BACKGROUND AND AIMS: Fistulotomy remains the gold standard for the treatment of both low and high anal fistulae. The invasive nature of this modality and the associated risk of incontinence following fistulotomy have propelled the search for alternatives. We present our results after a 12 month follow-up of the instillation of fibrin glue in both low and high fistulae in ano including complicated cases such as post-surgery recurrence and horseshoe shaped fistulae.

MATERIALS AND METHODS: Thirty patients were enrolled in the study as day cases after prior informed consent. This study was cleared by the appropriate ethics committee. Patients underwent a thorough clinical work-up including a digital rectal examination and proctoscopy. An MRI was done in patients with a history of previous fistula surgery or for those in whom the internal opening was not palpable. The fistula tracts were irrigated with saline. Reconstituted fibrin glue was then injected into the fistula using a proprietary injector. Patients were followed up regularly in the outpatient department over the next year.

RESULTS: Of the 30 patients, 14 had a low fistula and 16 had a high fistula, with 6 previously operated cases in the latter group. A cumulative success rate of 87.5% (14/16) and 100% (14/14) was noted in the high and low fistulae sub-populations respectively. Five of the six patients with prior fistula surgery also healed completely.

CONCLUSIONS: Fibrin glue instillation is an efficacious, minimally invasive and potentially sphincter sparing alternative to surgery with promising results in patients with complex fistulae and post fistula surgery recurrence.

KEYWORDS: fistula-in-ano, fibrin glue, incontinence
INTRODUCTION

Fibrin glue was first used in surgery at the beginning of the last century [1] and has been used for the treatment of anal fistulae since the early 1980s. Variable success rates have been reported ranging from 31-85% [2-11]. The reasons cited for this variable result include the mixed fistula groups, varied aetiology, sourcing of data from numerous centres and a lack of standardization of technique. The application of fibrin glue has increased manifold ever since the United States Food and Drug Administration (US-FDA) approved its use and marketing in 1998.

Fibrin glue offers a means of achieving the twin aims of fistula surgery i.e. tract ablation and preservation of continence. The wave of initial reports aroused much interest in this new modality but numerous disappointing long term results dampened this enthusiasm [2-4, 15, 16].

This study attempted to evaluate the use of fibrin glue for complex fistulae and previously operated cases. Prospective evaluation was done and the results after one year follow up are presented.

METHODS

Thirty consecutive patients who presented with fistula in-ano to the outpatient department of surgery in a tertiary care teaching hospital were enrolled in the study. Enrolment was done regardless of the type of fistula and cases included those with low fistula in-ano and complex fistulae (high fistula, horseshoe shaped tract, post fistula surgery recurrence). High anal fistulae were defined as those running through the upper two thirds of the external sphincter complex as depicted on MRI. Exclusion criteria were the extremes of age (younger than 18 years and older than 70 years), diabetes mellitus, anal abscesses and pregnancy. Patients were explained about the procedure, and an informed consent was taken. Patients who had purulent discharge were given appropriate antibiotics according to the pus culture report till the cessation of discharge which normally took 7-10 days. Fibrin glue was not instilled in the presence of purulent discharge.

Each patient was examined pre-operatively with a thorough digital rectal examination (DRE) and proctoscopy. Although routine imaging was not done, those previously operated, those with multiple external openings and patients
without a palpable internal opening on digital examination underwent an MRI of the pelvis to delineate the course and complexity of the tract (Figure 1). No bowel preparation was given. Patients were treated as day care cases without any type of anaesthesia.

**Technique**

In the operation theatre, the patient was placed in dorsal lithotomy position, the buttocks were strapped apart and the perianal skin was first cleaned and draped. A lubricated 8 F infant feeding tube was inserted into the external opening till the extrusion of the tube into the anal canal from the internal opening. Once the tip of infant feeding tube was felt inside the anal canal, the tube was slightly withdrawn so that tip lay flush with the internal opening. Following this, the tract was irrigated thoroughly with normal saline (Figure 2). Any granulation tissue at the opening was debrided.

In this study, tissue glue (TISSEEL, Baxter, UK) was used, the components of which include human protein concentrate, synthetic fibrinolysis inhibitor solution, human thrombin and calcium chloride solution. A preparation time of 20 minutes was required as per the manufacturer’s instructions and the components of the glue were pre-loaded into syringes attached to the DUPLOJECT™ injector.

The glue was instilled using the DUPLOJECT™ injector attached to an infant feeding tube. The cannula was slowly withdrawn while the glue was still being injected until the catheter tip appeared at the external opening. Eventually, the external opening was covered by a drop of glue which became white on setting thus signalling the end of the procedure (Figure 3). None of the openings were sutured. The patient was kept immobile for 15 minutes and then allowed to leave the operating room as it takes 3–5 min for the glue to adhere firmly to the surrounding tissue and 10 min to reach 70% of its maximum strength (full strength occurs after 2 hours) [2]. Patients were prescribed a combination of ciprofloxacin and ornidazole for 5 days to take care of any residual infection in the fistulous tract. Infection causes a premature and accelerated lysis of the fibrin clot prior to the invasion of fibroblasts and establishment of healing.
The patients were instructed to eat a normal diet but stool softeners were prescribed as most had a history of constipation. The site was to be kept dry and toilet paper was to be used (Indian toilet habits necessitate the use of water for ablution). Patients were asked to report for follow-up to the outpatient department at 2, 4, 12 weeks and every 2 months thereafter. Patients were taken up for a repeat injection if the symptoms recurred at any follow-up visit. A fistula which failed to close 2 weeks after the second instillation of fibrin glue was taken as failure of treatment. If the fistula reappeared 4 weeks after closure it was defined as recurrence.

RESULTS

Thirty patients (24 men and 6 women) with a mean age of 38.4 years (range 24 to 65 years) were included in this study. Patients presented with the complaints of persistent discharge, pain or bleeding per rectum. The mean duration of symptoms was 15.6 months (range 3 to 30 months). Six patients had been operated previously (fistulectomy), of whom one had undergone two procedures. Four patients had a horseshoe shaped tract.

Fourteen patients had a low fistula and sixteen had a high fistula. None of the patients had pre-procedure incontinence. Four patients had two external openings and both were communicating as evidenced by MRI findings and a free passage of irrigation fluid and glue to the contralateral opening on table. Of the group, five patients had active infection and had been prescribed a course of antibiotics prior to glue instillation.

The following results were obtained during a follow up period of one year (Table 1)-
**TABLE 1: PATIENT OUTCOMES**

<table>
<thead>
<tr>
<th></th>
<th>TOTAL NUMBER (30)</th>
<th>NUMBER OF INSTILLATIONS OF GLUE</th>
<th>RECURRENCE AFTER 6 MONTHS</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW FISTULA IN-ANO</strong></td>
<td>14</td>
<td>10</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td><strong>HIGH FISTULA IN-ANO</strong></td>
<td>16</td>
<td>10</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abscess (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Failure (1)</td>
</tr>
</tbody>
</table>

Of the 14 patients with low fistula in-ano, 4 patients required more than one instillation of the glue for complete healing of the tract. There were no recurrences at 1 year. Sixteen patients had high fistulae and of them, 6 had been previously operated. Four of the previously operated cases had horseshoe shaped tracts (revealed well by MRI) and one of these patients required two applications of the glue. All fistulae initially healed satisfactorily, but on prolonged follow up, one of the patients developed a perianal abscess and another presented with a recurrence after 6 months of follow up. Thus, cumulatively, 87.5% (14/16) of the complex fistulae and 100% (14/14) of the low, simple fistulae healed.

Successful treatment was defined as complete obliteration of the tract and no signs of perianal sepsis. There were two recurrences (6.67%) of the 30 patients who underwent fibrin glue ablation and one of them presented as an abscess following the second cycle of glue instillation.

The infection subsided after deroofing the abscess. This particular patient had a high fistula in-ano and had a history of anal sepsis prior to the procedure.

There were no complications related to allergy to the glue components. All patients were ambulatory post procedure and returned to activities of daily living the next day. The ratio of cumulative healing at the end of the first year of follow-up after more than one injection was 93.3% (28/30) and the patients were satisfied with this modality of treatment. As opined by Adams [11],
when a fistula does close for at least 6 months, it appears to be a durable closure.

**DISCUSSION**

Anorectal fistulae represent a challenge to the surgeon. “Successful treatment” denotes an eradication of the primary tract. The traditional method of fistulotomy described by John of Arderne in the 14th century A.D. brings with it the risk of incontinence. Even with a “safe” fistulotomy, 30% of patients complain of some degree of incontinence and 20% develop recurrent fistula/abscess [14]. Other procedures have been devised such as the use of a seton, advancement flap procedures or attempts to occlude the fistula track by biological substances to circumvent the aforementioned complications. Autologous or commercial fibrin glue has been used to heal anorectal fistulae since 1991 as a sphincter-sparing alternative although the transanal rectal advancement flap continues to be the treatment of choice for high fistulae [21]. Despite its ease of application and the minimally invasive nature of this modality, it is yet to become popular. This could be because a consensus has not been reached regarding its status in the armamentarium of treatment options for fistula in-ano.

Fibrin glue is an activated mixture of a solution containing fibrinogen, factor XIII, fibronectin and aprotinin. Factor XIIIa also cross-links with fibrin and fibronectin which are present in the sealant mixture which then cross-link with collagen in the surrounding tissue [8]. When applied to an anal fistula, the fibrin clot seals the track and stimulates the migration, proliferation and activation of fibroblasts. Via the bridging action of fibronectin it serves as a matrix for ingrowing fibroblasts and pluripotent endothelial cells [9], which take on the function of normal repair-promoting cells after fibrin degradation. The clot is lysed within 1-2 weeks by plasmin. Fibroblasts are activated and gradually invade the site, laying down collagen which sets the stage for healing of the fistula [20]. Failure of this leads to a recurrence.

The reported success rate in the treatment of complex fistulae is approximately 14% with most recurrences occurring within 3 months of treatment [4, 6]. Despite this, the patients reported high levels of satisfaction due to the low morbidity of the procedure [10]. A review in 2005 looked at the current evidence in the usage of fibrin glue. There was a large variation in the healing
outcomes (10–78%) with an overall healing rate of 53% due to differences in fistula aetiology and complexity. High failure rates were associated with complex fistulae [16].

This study included 16 patients with high fistulae (53.3%) of which 25% had a horseshoe tract. Previously operated patients represented 20% of the patients undergoing fibrin glue ablation. Healing after the primary application was 66.7% and the cumulative rate of healing was high i.e. 87.5% at the end of a 12 month follow up with a high rate of reported patient satisfaction. This correlates with a 2004 study by Jurczak et al [3], who used fibrin glue to seal trans-sphincteric and supra-sphincteric fistulae in 39 patients with a success rate of 83.9%.

As regards the methodology, we did not actively curette the tract. Only the excess granulation tissue at the mouth of the cutaneous opening was removed. Thorough irrigation was done with normal saline. Other studies have used Volkmann spoons and brushes [7], irrigation with hydrogen peroxide and disinfection with rifamycin solution [18] and an endoscopy channel cleaning brush [19] among others.

The internal opening was not sutured in this series although Sentovich [8] reported on a prospective series of 48 patients (75% of cryptoglandular origin) treated with fibrin glue where the procedure was combined with closure of the internal opening with a figure of eight suture. A recurrence rate of 31% was noted after a median follow-up of 22 months. The suture apparently prevents extrusion of clot during the high pressures generated within the anal canal during defaecation. Loungnarath et al [4] also reported on 39 patients with perianal fistulas treated with fibrin glue. While the overall recurrence rate was 69%, 4 of the 6 patients whose internal opening was closed had a recurrence (33%). However, there was no significant difference in the success rate in a prospective randomized study which compared fibrin glue with suture closure of the internal opening compared with fibrin glue instillation alone [17].

Of the complications noted, one patient developed an anal abscess and went on to develop a recurrence. Two cases complained of mild serosanguineous discharge from the fistula site post procedure but both eventually healed definitively. This is in concordance with literature, with sepsis and abscess formation being the oft quoted complications [7]. All our patients received post-operative antibiotics in view of the fact that most had prior infection.
Interestingly, a few small, prospective studies have showed that the addition of antibiotics to the glue for local application has little effect on healing rates [14, 15].

Fibrin glue was found to be effective even for complex fistulae and operated cases in this study. Reported success rates for complex fistulae are 14%. Previous published studies have stated “prior surgery” as an exclusion criterion [16, 17] but we attempted to give this subgroup the benefit of this therapy. A second and seldom, a third, instillation increased the success rates and this has been documented by other researchers as well [10, 12].

CONCLUSION

Success rates with fibrin glue are lower than conventional surgery, but this sphincter-sparing approach is a simpler, less time consuming, painless alternative which can administered on an out-patient basis. The only rate limiting factor is preparation of the actual glue, the technicalities of which can be mastered within a short span of time. This study did not select cases traditionally thought suitable for this modality (e.g. simple, low fistulae) and fortunately, the results in complex fistulae and previously operated cases were quite encouraging although the authors concur that a larger study population and a longer follow up period is required to reliably establish this modality as a first line therapy for this group of patients.

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