

## ORIGINAL ARTICLE

# Long-term results in the treatment of fistula-in-ano with fibrin glue: a prospective study

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**Purpose:** This prospective study was done to analyze the efficacy of commercial fibrin glue application in the healing of patients with fistulas-in-ano from a long-term (mean 4.5 years) research period. **Methods:** This clinical trial of forty-six patients was performed during the period from January 2004 to February 2005. Thirty-nine men and seven women were treated for a fistula-in-ano with a commercial fibrin glue application. In the operating room, the patients underwent an anorectal examination under spinal anesthesia. The external and internal fistula tract openings were then identified. The fistula tract was curetted. Fibrin glue was injected into the external fistula opening until the fibrin glue could be seen coming from the internal opening. **Results:** The overall initial success rate was 86.95% (40/46). Recurrence rate was 41.30% (19/46). Two patients underwent a re-application with fibrin glue and the fistulas of these patients closed. The total recurrence rate was 36.95% (17/46). The long-term overall success rate was 63.04% (29/46). **Conclusion:** Fibrin glue application was thus found to be an easy, safe, acceptable, successful alternative treatment in the management of fistulas-in-ano. Choosing the patient correctly is very important because long (more than 4 cm) and non-ramificate fistula tracts usually close with commercial fibrin glue.

**Key Words:** Fistula-in-ano, Fibrin glue adhesive

## INTRODUCTION

Many techniques for fistula-in-ano treatment have been reported. The goal of surgical treatment of a fistula-in-ano is to heal the fistula tract with the lowest rate of recurrence while still maintaining continence. The standard surgical treatment of fistulas-in-ano is an anal fistulotomy, which involves laying open the fistula tract and any associated sphincter muscle. Despite being properly performed, fistulotomy wounds can have prolonged healing times which can result in contour defects around the anus and

they can also cause postoperative discomfort [1]. The other techniques (seton application, flap, etc) also have a long treatment period and are skilled operative techniques. In addition, Lunniss et al. [2] have shown that even a minimal division of the anal sphincter muscle during a fistulotomy can be associated with changes in fecal continence. Given these results, investigators have thus sought simpler sphincter muscle-sparing techniques to treat fistulas-in-ano [1].

Recently, the use of tissue adhesives or sealants in surgery has increased because of improved autologous and

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commercially available products [1,3-5]. Fibrin glue application can be a valuable adjunct to surgical procedures in the treatment of fistula-in-ano. Fibrin glue is a biological glue made up of fibrinogen and its multiple components [6]. The end product is a gel-like substance that can be used in surgery to achieve hemostasis and a water tight seal [7].

The purpose of this study was to ascertain the effectiveness of commercially available fibrin glue in closing fistula-in-ano at the long-term period.

## METHODS

This prospective clinical study was carried out on 47 patients undergoing commercial fibrin glue application in the Department of General Surgery in Gaziantep University Faculty of Medicine between January 2004 and February 2005. Any patients with intersphincteric fistulas, rectovaginal fistulas, Crohn's disease and fistulas-in-ano associated with chronic cavities, acute sepsis, or side-branches were excluded. To outline the extent of the fistulous tract, a fistulography was performed on patients with suspicious complicated fistulas. Patients with a ramification of the fistulae demonstrated by X-ray were excluded. One patient was excluded because of a follow-up problem. Forty-six patients were thus included in the study. Thirty-nine men and seven women were treated for a fistula-in-ano. Their mean age was 33 years (range, 16 to 59 years). The duration of persistent fistulae ranged from 4 months to 10 years. The patient characteristics and fistulae duration are shown in Table 1.

The study was designed and conducted according to the guidelines of the Helsinki Declaration [8] and was ap-

proved by the local ethics committee. Detailed informed consent was obtained from all patients.

Preoperatively, none of the patients complained of any degree of fecal incontinence. All patients were managed under normal inpatient procedures. Anamnesis was performed. A careful physical examination confirmed the diagnosis of fistulas-in-ano in each patient. Each patient was instructed to use a mechanical bowel preparation with polyethylene glycol or sodium phosphate, one day before the application of the fibrin glue injection. All patients received prophylactic parenteral antibiotics (cefuroxime, 1.5 g; ornidazole, 500 mg). The anorectal examination and fibrin glue application were performed in the operating room. The procedure was carried out under spinal anesthesia. Operating time was recorded between the injection of the spinal anesthesia and a visual of the glue bubble at the external orifice of the fistula.

All applications were performed by the same surgical team on each patient. During the examination, under spinal anesthesia in the prone jackknife position the fistula was probed gently to identify any external and internal fistula tract openings. The external and internal openings of the fistula tract were identified in all patients. The length of the fistula tract was measured (according to the length of probe in the fistula tract) and noted. We planned the comparison of the length of the fistula tract of the 'recurrence' patients and the 'treatment' patients. The tract was curetted with polyester tape (white braided fiber, pre-cut lengths 1/8" wide; Sherwood Medical, St. Louis, MO, USA), which was tied with a few knots on itself. Extensive debridement was unnecessary, but the granulation tissue was removed, then cleaned out with normal saline. The fibrin glue from a commercial kit was retrieved from storage at 4°C and then allowed to reach room temperature over an approximately one-hour period. The fibrin glue was prepared according to the manufacturer's recommendations (Beriplast P, Aventis Behring, Marburg, Germany). In short, the fibrin glue consisted of two components: fibrinogen concentrate and thrombin. Fibrin glue mimics the last step of blood clotting. Factor XIII is added as an adjuvant and stabilizes the fibrin monomers. Aprotinin is added as an adjuvant and prevents fibrinolysis.

Fibrin glue was then instilled into the fistula tract by

**Table 1.** Patient characteristics and fistulae duration

Patient characteristics	Value
Gender, n (%)	
Male	39 (84.78)
Female	7 (15.21)
Age, mean (range)	33 yr (16-59 yr)
Fistula duration	
Minimum	4 mo
Maximum	10 yr

way of an external opening so its tip was seen emerging from the internal opening into the anal canal. The injection was performed through a double-channel tube (syringe) with an infant feeding tube (Size, 5 or 6 F; Romsons International, Nunhai, India), which was prepared according to the fistula tract length, and with the anal retractor in place. The tube had been introduced to the bottom of the fistula-in-ano and then was continuously withdrawn during the injection so that the fistula was completely filled with fibrin glue (this generally required less than 1 commercial fibrin glue product, consisting of approximately 2 mL glue). If the tract was long, two fibrin glue products were prepared and used. Once a bubble of instantly solid glue was seen at the internal opening, it was considered that the first part of the tract was filled. Then both the feeding tube and the syringe were slowly and steadily withdrawn while the glue continuing to be discharged. This application filled the tract with glue until the tube emerged at the external opening, where another bubble of glue was seen on the perianal skin. No dressing was applied on the external opening. The glue was allowed to become even more stable and solid over a little less than approximately one minute, and the anal retractor was removed, while being careful not to catch the internal bubble on the retractor and thus dislodge the plug.

Postoperative analgesic requirements were followed up. Complications were considered early if the occurrence was within one month of application, and late if the occurrence was after one month. The postoperative oral intake was restricted for one day. Thereafter, the patients were placed on a liquid diet for 24 hours and then gradually advanced to a regular diet. They received oral cefuroxime (250 mg twice daily) and ornidazole (500 mg a day) for one week. The length of hospital stay for each patient was also recorded. Patients were discharged the first day after their fibrin glue application. Sitz baths were prohibited for fear of dislodging the fibrin glue plug.

All patients were evaluated at each follow-up visit. Questions included whether they had any perirectal drainage, pain, or evidence of a failed fistula closure. It is generally considered that if the application was successful, then the effect of the treatment is immediate, with either a complete cessation or a significant reduction in

drainage. The patients were asked a series of questions regarding their experience of the length of limitation in normal activities and work. Physical examinations were also conducted with each subsequent clinic visit. Outpatient and telephone visit follow-up examinations were performed for all patients ranging from 4 to 5 years with a mean of 4.5 years. Therefore telephone visits were particularly useful in the long-term. If the fistula failed to heal with primary treatment fibrin glue at follow-up or had healed and then subsequently recurred, the patient was invited for another glue treatment if appropriate. Repeated fibrin glue injections were re-applied when there was a failure of treatment or clinical recurrence provided the patient agreed. Patients were instructed to notify their physicians if they suspected a recurrence anytime during their postoperative course.

## RESULTS

Over a five-year period, 46 consecutive patients were treated with commercial fibrin glue. The cause of the fistula-in-ano was cryptoglandular in all patients. All of the patients had one fistula tract. Forty-two (91.30%) of the fistulas were transsphincteric, and 4 (8.69%) were suprasphincteric. The average length of the fistula tracts were 5.4 cm with a range from 4.1 to 13.2 cm.

Our initial success rate was 40 of 46 closures (86.95%). They were transsphincteric and suprasphincteric, 37 (88.09%) and 3 (75.00%), respectively. A second injection was needed in six patients (13.00%) because fistulas recurred between 2 and 9 weeks. All recurrence cases were transsphincteric except one. All recurrence patients were offered another attempt at fistula sealing using fibrin glue. Only two patients accepted the second application. One of these had a low transsphincteric fistula, and the other had a high transsphincteric fistula. These two patients underwent a second application of fibrin glue, thus resulting in a total resolution of the symptoms and a healing of the fistulous tracts. Repeated fibrin glue treatments were successful for both patients.

The other 4 patients refused the second fibrin glue application. They elected another technique. They under-

went a seton-fistulotomy as these fistulas were high trans-sphincteric types.

In total, 19 recurrences were observed initially. Another application was recommended to these patients. Two patients were accepted. In these two patients, the second application was successful. Seton was applied to the remaining 17 cases. These setons were ended with seton fistulotomy sooner than 4 weeks. In 4 cases, the setons were changed 3 times each for sufficient drainage. The treatments were completed with seton fistulotomy at approximately the 12th week. For almost all recurred patients, the length of the tract was about 4 cm. The earliest recurrence was the at 2nd week. The last recurrence was in the first year.

None of the patients developed incontinence. No mortality was observed. The mean follow-up was 4.5 years with a range of 4 to 6 years. The mean length of operations was 16 minutes with a range from 14 to 29 minutes. The mean hospital stay was 1 day. None of the patients needed analgesics for pain relief. There was no complication related to the application of commercial fibrin glue. All of the patients resumed normal activities within 48 hours. All patients could return to work within 7 days. The recurrence rate was 41.30% (19/46) initially. Two patients underwent re-application and treatments were successful. At the end of the long-term period (mean 4.5 years) the total recurrence rate was 36.95% (17/46). Initially, the recurrence rates were higher than those in following months. So, the curve of Kaplan Meier reflected these findings (Fig.

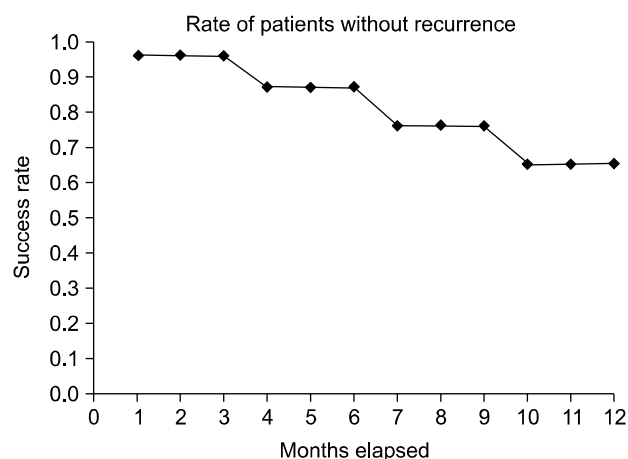


Fig. 1. Kaplan Meier curve for recurrence cases

1). The Kaplan-Meier estimator (named after Edward L. Kaplan and Paul Meier), also known as the product limit estimator, estimates the survival function from life-time data. In medical research, it may be used to measure the fraction of patients living for a certain amount of time after treatment. We calculated the Kaplan-Meier estimator for the recurrence and then graphed them as Fig. 1. We calculated the one way analysis of variance (ANOVA) to find the statistical differences between 2 groups to compare the lengths of the fistula tracts. One way ANOVA result is 61,70. And  $P < 0,01$ . Test results show statistically significant relationships between the 2 groups. So our results say these two groups are different from each other. The overall success rate was 63.04% (29/46). Fistula treatment results are shown in Table 2.

## DISCUSSION

Over the years, many papers have been published on the use of fibrin glue in different specialties of surgery. The use of fibrin glue in the treatment of fistulas-in-ano was first reported in the early 1980's with reasonable results [9,10]. Since 1991, several articles have been published with favorable results using fibrin glue for the treatment of fistulas-in-ano [11-13].

Complications following a surgical repair for fistula-in-ano can be devastating for patients. Flatus incontinence may be a minor complication for the surgeon but it could be very embarrassing for the patient [14]. Therefore, it is prudent to look for other ways in treating fistulas-in-ano. Fibrin glue application has been shown to be superior to conventional surgery in terms of patient comfort, undisturbed sphincteric function, reduced overall hospital stay, reduced postoperative analgesia requirement and

Table 2. Treatment results

Fistula type	Total no. of cases	Initial success rate	Overall success rate
Transsphincteric	42 (91.30)	37 (88.09)	26 (61.90)
Suprasphincteric	4 (8.69)	3 (75.00)	3 (75.00)
Total	46 (100)	40 (86.95)	29 (63.04)

Values are presented as number (%).

faster return to normal activities with minimum operative trauma and no complication [7,14,15]. Some studies which were performed using conventional surgery techniques reported fistula treatment rates from 44 to 78 percent [15]. The overall success rate may be low but an acceptable rate for success in this study.

Although this study has a limited number of patients it has a long follow-up period. It was thought these results could be important to support former, optimistic studies and new planning studies. The patients tolerated the injection procedure very well, and there were no complications resulting from this treatment, and no patient had any change in continence. In addition, no wound pain or discomfort was observed. The results regarding the advantages of fibrin glue were similar to those found in the literature.

The heterogeneity of the clinical trials made direct comparisons difficult. If our results are compared with other similar studies, then some differences exist between the results (Table 3) [1,3,15-21]. These differences, however, may be explained by their patient selection, their exclusive use of autologous fibrin glue that has a lower fibrinogen concentration, differences in the standardization of these products, which may thus not form as strong a plug as the

commercial fibrin sealant may have, also contributed to their lower success rate. Furthermore, fistula characteristics are important factors combined with differences of complex or recurrent, primer and solitary, long or short. It is certainly possible that the success rate for treating complex and recurrent fistulas-in-ano is indeed, lower, because these types of fistulas have a lot of ramifications. Finding the original fistula tract can also be difficult if it is a high level recurrent fistula. In addition, it is also possible that the application techniques may differ. Certainly a relatively small infection within the fistula tract could dislodge the fibrin glue plug and thus result in treatment failure. In this study, all patients had fistulas-in-ano with a cryptoglandular origin. Commercial fibrin glue was used. All of the fistulas were non-complex, primer, solitary. Fistulas were long (average length of fistula tract was at least 5.4 cm). Furthermore, in this study, no abscess or infection was observed. A preoperative mechanical bowel preparation was performed. Preoperative antibiotic prophylaxis, curettage and washing with normal saline of the fistula tract locally were also performed. Oral antibiotics were also continued during the one-week postoperative period. The overall success rate was thus thought to be satisfactory as a result of the above reasons (fibrin glue ad-

**Table 3.** Data of published studies of fibrin glue treatment for fistulas-in-ano

Study	Year	Fibrin glue type	Fistula type (etiology or simple-complex)	Success rate, n (%)		Follow-up
				n	(%)	
Maralcan et al. [3]	2006	Commercial	Cryptoglandular	36	83.30	Mean 54 wk
Singer [21]	2005	Commercial	Complex	75 (3 group)	25.00 44.00 35.00	Mean 27 mo
Loungnarath [20]	2004	Commercial	Complex	39	31.00	Median 23 mo
Sentovich [15]	2003	Commercial autologous	Different (cryptogl. 75%)	48	68.80	Median 22 mo
Lindsey et al. [17]	2002	Commercial	Different (simple 31%)	42	63.00 (simple + complex) 59.00 (cryptogl.) 50.00 (simple)	Median 17.1 mo
Chan et al. [18]	2002	Commercial	Simple	10	60.00	Mean 26.4 wk
Sentovich [1]	2001	Commercial autologous	Different (cryptogl. 65%)	20	85.00	Mean 10 mo
Park et al. [16]	2000	Commercial	Different (simple+complex)	29	69.00	Mean 6 mo
Cintron et al. [19]	2000	Commercial autologous	Different (cryptogl. 89.9%)	79	61.00	Mean 12 mo
Present study	2011	Commercial	Cryptoglandular	46	63.04	Mean 4.5 yr

vantages).

There were few possible failure factors, all or some of which may play a role in faster fibrin clot dissolution and failure. There are several possible explanations that may contribute to failures following sealing: lack of radiologic tests of fistula and fistulography to detect the extent of the fistula, a narrow communication between the fistula and the intestine that may still have been present, a short, straight tract makes it impossible for the fibrin glue to be retained adequately in the tract for any length of time, technical problems due to lack of experience and a failure of antibiotics to eradicate all bacteria trapped in the clots in the fistula [6-13]. There were 6 early recurrences in this study. It was suspected that in recurrent cases, the most probable causes were considered to be misdiagnosis or incorrect examination of the fistula tract preoperatively, technical problems, early oral intake postoperatively or infection in the tract. We have also observed that short fistula tracts respond poorly to fibrin glue injections, and the fistula tract length was approximately 4 cm in most of the recurrent cases. We found that the commercial fibrin glue succeeded more in cases longer than 4 cm with solitary fistulas during the five-year follow-up period. We thought there might also be technical problems in first few cases due to a lack of experience. It was also thought that early postoperative oral intake and the prediction of an infection in the tract might dislodge the fibrin glue plug. Two recurrent cases were also treated with second applications in this study. The total number of recurrences was 17. Despite impressive early results, we saw the success rate drop at the end of the follow-up period. However, this result is good because fibrin glue has many advantages, the most important of which is continence.

Whether fibrin glue can cure all types of fistulae remains controversial [11]. High anal fistulas are among the most difficult problems faced in colorectal surgery. A fistulotomy is not advised for these fistulas, because treatment and continence are competing priorities, and fistulotomy leads to an unacceptable risk of incontinence. In this study, long solitary non-ramificate fistula tracts tended to show good results with fibrin glue.

Fibrin glue in the treatment of fistulae-in-ano has been previously explored and the availability of commercial fi-

brin glue has also improved [3,16-18]. As a result, the success and recurrences rates were thus considered to be acceptable. However, long-term results were lower than our preliminary results.

Fibrin glue represents a new option in the management of the various types of fistulas-in-ano [19,22]. It has enjoyed recent success in a series of selected patients. Healing rates of up to 80 percent for cryptoglandular have also been reported (usually preliminary results). It can heal fistulas without jeopardizing anal continence, and if it fails, it can be repeated several times if required. Additionally, it does not preclude or alter subsequent treatment options [19]. Our practice and results are also similar to those reported in the literature.

In conclusion, fibrin glue injection is a feasible, valuable, effective treatment alternative in the management of fistula-in-ano. This procedure is easy for surgeons to learn and perform. The most important advantage is avoiding the risk of complications associated with fistulotomy or other techniques. It is minimally invasive and allows for a resumption of normal activities within a short time, for most patients.

In this study, we reported a 63.04% success rate in closing fistulas-in-ano with a sphincter muscle-sparing technique using fibrin glue over the long period. This technique has many advantages as mentioned above. This study also indicates that fibrin glue application is a simple, easily applicable, repeatable and safe for the treatment of fistula-in-ano. Thereafter, we should not only consider the success rate of commercial fibrin glue but the very important advantage of the muscle sparing techniques. It must be thought of as a preliminary option particularly for cryptoglandular and long fistulas. We think that some points must be observed with fibrin glue in anorectal fistulas for success. The most important factors are: fistula to be cryptoglandular, to be solitary and long tracted, to prepare the bowel completely, to apply single dose parenteral antibiotics preoperatively and followed by five days per oral at postoperative period, to restrict oral nutrition postoperative first day and to feed after second day step-by-step, to forbid sitting bath, to scrape the granulation tissue with a knotted nylon tape or similar techniques, to clean the tract with saline after curettage, and to

avoid technical failure during the preparation of fibrin glue back table.

However, future investigations may be necessary to determine the most effective fibrin glue type and the optimal application technique to improve these results. Comparative studies also must establish which technique is most suitable on first application.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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