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Fibrin Glue Injection a Promising Option in the Treatment of Patients with Anal Fistula

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ABSTRACT

Background: *Fistula in ano is a public perianal illness and as a long-lasting inflammatory illness which does not cure naturally. There are several surgical procedures for treatment of fistula in ano, but these surgical interventions have little degrees of success, long time of wound healing after surgery and prolonged pain, especially in complex and difficult fistulas are observed. Novel sphincter-saving methods have been used in the management of perianal fistula in order to evade the risk of fecal incontinence. Among them, the fibrin adhesive method is popular because of its ease and repeatability.* ***Objective:*** *The objective of the present study is to evaluate the effect of fibrin-glue injection in the treatment of anal fistula (low/high as well as primary/secondary).* ***Method****: A prospective, planned experiment was conducted on 322 patients who were established to have fistulas in ano. They were assessed by sorting them into high fistula (172/322) and low anal fistula type (150/322). The fibrin glue was instilled in their anal tracts. The character of the anal tract, whether it was simple or complex and primary or secondary, was analyzed. The outcome in terms of a postoperative discharge (failure) was noted at 3 months, 6 months, 9 months, 1 year, and 2 years.* ***Results****: Total 322 patients were involved in this study. The general success rate was 275/322 (85.4%) after a mean follow-up of 1.5 years. All patients with a complex fistula (for low/high fistula, primary/secondary) had failure of healing (success rate 0%) either through first or second injection of fibrin-glue while all patients with simple fistula had successive rate of healing (for low/high fistula, primary/secondary) either through first or need the second injection of fibrin-glue. None of the patients had postoperative continence problems, and no other complications were noted.* ***Conclusion****: Fibrin glue is a novel attractive approach, easy, safe, minimally invasive, repeatable and cost effective for treatment of anal fistula simple (low/high and primary/secondary) and promising option for treatment of high fistula, and do not have a role for healing the complex anal fistula.*

Keywords: Fistula in-ano, Fibrin glue injection, Non-invasive technique

INTRODUCTION

A fistula in ano is a long-lasting inflammatory condition which does not cure naturally. The conventional management, which involves antibiotic therapy against the Gram-negative organisms and anaerobic bacteria, may affect in the acute and early phase of the anal disease, surgery remains the elective management. About 3 major aims in the management are involved; the first one is to eliminate the fistula duct as a source of infection, discharge, and sepsis. The second one is to avoid relapse and the third is to heal the fistula tract with the less rate of recurrence while still preserving continence preserve anal function [1]. Many surgical methods have been designated at present to accomplish these goals such as the addition of a seton, fistulotomy, fistulectomy, excision of crypts and anal glands, cauterization of the tract, implantation of an antibiotic chain, and more recently anal or rectal advancement flap. These techniques have low rates of effectiveness, long postoperative wound curing and protracted pain especially in complex and difficult fistulas [2-4]. Currently, according to the latest anal fistula treatment guidelines of American Society of Colon and Rectal Surgeons (ASCRS), it clearly pointed that it was equally important for treated patients in healing anal fistula and maintaining anal function, meanwhile it also must be balanced among the degree of sphincter incision, cure rate, and postoperative anal function. Accordingly, surgeons are still looking for better alternative methods for the treatment of anal fistula [5].

Recently, one of the suggested alternatives technique is the use of Fibrin glue injection. Fibrin glue is tissue cement that mimics the final phases of the natural clotting cascade. The sealant degrades as the fibrotic reaction progresses,

ultimately getting fully replaced by the natural tissue. Therefore, no foreign body exists and the track scars are purely closed [6,7]. Fibrin gluing of anal fistulas is simple and applicable. The mentioned aspects make this technique an extremely appropriate treatment choice. Fibrin tissue cement was first effectively used as a hemostatic factor in the early 1900s [8]. Although prior to 1998, the operative technique for fibrin glue as a treatment method of anal fistula in the United States was done using autologous fibrin sealant, nowadays most surgeons use commercially synthesized fibrin glue when gluing anorectal fistulas. This adhesive gives a unique healing result by sparing the sphincter muscles and accordingly avoiding incontinence. It also drops the patient distress and loss of the business hours. It is easy and applicable and an unsuccessfulness does not compromise the further treatment options [9]. But one of the communal problems related to the use of fibrin glue for anorectal fistulas is the infection chance, typically at the site of the exterior or secondary opening [10].

PATIENTS AND METHODS

This prospective surgical experiment has been conducted on 322 patients undertaking commercially available fibrin adhesive used in the Surgical Department at Al-Diawaniyah Teaching Hospital in Diawaniyah City, between January 2015 and February 2018. Any patients with intersphincteric fistulas, recto-vaginal fistulas, Crohn's disease and fistulas-in-ano accompanied by chronic holes, acute sepsis, or side branches were omitted. To sketch the size of the fistulous tract, a fistulography was done on patients with doubtful complicated fistulas. Patients with a ramification of the fistulae confirmed by X-ray were omitted. About 300 men and 22 women were treated for a fistula-in-ano. Their mean age was 45 years (range, 20 to 60 years). The period of persistent fistula ranged between 3 months to 1 year.

Before the surgery, none of the patients have any grade of fecal incontinence. Patients were treated with normal measures, anamnesis was done. An alert clinical inspection clearly stated the judgment of fistulas-in-ano in the patient. The confirmatory diagnosis of the high anal fistulas was done, depending on a digital result, when the canal prolonged above the ano-rectal ring and on fistulography, while the contrast enhances internal ring which was seen in the rectum and low anal fistulas with the internal opening below the ano-rectal ring depending on Parks sorting [11]. The patients who had reserved no medication for their signs of fistula were well-thought-out as primary and those who had unsuccessful preceding surgical management were classified as secondary.

Fistulograms were performed for all patients to look for any holes and the number of other expenses (single or multiple) in a fistula. Each patient was educated to take a mechanical GIT preparation with polyethylene glycol or sodium phosphate, one day earlier the use of the fibrin adhesive inoculation. Patients were informed to use prophylactic antibiotics (cefuroxime: 1.5 g; or nidazole: 500 mg). The anorectal inspection and fibrin cement were done in the surgical room. The procedure has been conducted under regional anesthesia. Time has been noted from the injection of the regional anesthesia until the appearance of the glue bubble at the exterior opening of the fistula. During the inspection, by using spinal anesthesia in the prone jackknife location the fistula was probed carefully to identify if there were external or internal fistula tract openings. The extent of the fistula canal was measured and noted. The tract has been 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 ties on itself. The tract should then be carefully debrided without undue dilatation and widespread debridement was needless, the granulation tissue was detached, and then splashed with normal saline hydrogen peroxide. Fibrin adhesive from a kit was recovered from storage at 4°C and it then keeps reaching the room temperature.

The fibrin adhesive has been organized depending on the manufacturer's recommendations (Beriplast P, Aventis Behring, and Marburg, Germany). Briefly, the fibrin adhesive was composed of 2 components: fibrinogen concentrate and thrombin. Fibrin adhesive simulates the final phase of blood clotting. Factor XIII is supplementary which act as an adjuvant and stabilizes the fibrin. Aprotinin is added as an adjuvant and avoids fibrinolysis. The end result is a gel-like ingredient that can be used in surgery to reach hemostasis and water resist seal. After that the fibrin adhesive was filled into the fistula by way of an exterior opening thus, its tip has been seen emerging from the internal opening into the anal canal. The inoculation was done through a double-passage tube (syringe) with an infant feeding tube (Size, 5 or 6 F; Romsons International, Nunhai, Indıa), which was organized based on the fistula extent, and with the anal retractor in place. The tube had been existing to the bottom of the fistula-in-ano and then has been constantly removed during the injection. Thus, fistula has been totally filled with fibrin adhesive. Once a bubble of immediately solid glue has been gotten at the internal opening, it was reflected that the first portion of the tract has been filled. After that, both serving tube and the syringe were gradually and progressively removed while the cement ongoing to

be discharged. This procedure fills the area with adhesive until the tube appeared at the outside opening, while the bubble of glue should be seen on the perianal skin. The glue was left to convert into the firm and solid for 5-10 minutes and the anal retractor was removed, despite the fact being alert not to touch the internal bubble on the retractor which leads dislodge of the plug. Postoperative pain-killer was required. Problems were remarked early if the happening was within 1 month of operation, and late if it appears within more than 1 month. The post-operative oral consumption was controlled for 24 hours. Subsequently, patients were retained on a watery diet for 24 hours and then slowly progressive to an even diet. Patients acknowledged taking oral cefuroxime (250 mg twice daily) and ornidazole (500 mg a day) for 1 week. The duration of hospital stay for each patient was also noted. Patients were quite the first day after their fibrin glue solicitation. Sitz baths were forbidden. Patients were assessed at each check-up appointment. Inquiries comprised if they had any perirectal drainage, pain, or evidence of unsuccessful fistula management. It is usually reflected that the procedure was successful.

Patients have inquired a set of answers concerning their struggles of the extent of restraint in normal events and work. Clinical inspections were also done with each succeeding clinic visit. Outpatient and phone checkups were achieved for all patients ranging from 1-2 years with a mean of 1.5 years. If the fistula was unsuccessful to heal with first management trial with fibrin glue or had healed and then consequently recurred, the patient was invited for additional adhesive treatment. Recurrent fibrin glue injections were re-applied when there was a disappointment of treatment or clinical repetition provided the patient agreement. Patients were trained to notify their physicians if they supposed reappearance anytime during their postoperative course. The patient was included in the present study and categorized into the following as shown in Table 1.

Table 1 Characteristic of patients study

Patients Characteristics (Total n=322)	Number/Percentage
Male	300 (93%)
Female	22 (6.8%)
Duration of fistula	3 month-1 year
Length of fistula	4 cm-10 cm
Follow up	At 3 months,6 months, 9 months, 1 year and 2 years

The anal fistula was categorized into the low/high, primary/secondary anal fistula groups according to Park's classification as shown in Table 2 [8].

Table 2 Type of fistula according to patients study

Type of fistula	No (%)	Primary No (%)	Secondary No (%)
Low fistula	150 (46.6%)	140 (93.3%)	10 (6.7%)
High fistula	172 (53.4%)	150 (87.2%)	22 (12.8%)
Total	322 (100.0%)	290 (90.1%)	32 (9.9%)

In addition to the above classification (low/high fistula type) we categories these fistulae into subdivision like simple and complex. The word "complex" anal fistula is an adaptation of the novel Parks cataloging, talk about to those fistulas in which management by a traditional open technique would end in a remarkable loss of continence. An anal fistula of cryptoglandular origin may be defined as compound when the path marks more than 30% to 50% of external sphincter (high transsphincteric or suprasphincteric fistula), when is anterior in a female or has numerous tracks [11] (Table 3).

Table 3 Type of fistula according to simple or complex

Simple or complex	Number /Total (%)
Simple fistula	275/322 (85.4%)
Complex fistula	47/322 (14.6%)

Ethical Considerations

Each patient included in this plan signed an informed consent form, detail of the method and agent used with the possible failure of this option and was approved by the ethics committee of the Medical Research Institute.

Statistical Analysis

SPSS version 16 and Microsoft Office Excel 2007 were used in the analysis of these data, chi-square test and Fisher exact test were used to study the association between any two nominal variables. The p-value of less than or equal to 0.05 was considered significant.

RESULTS

Effective management is well-defined as the lack of any discharge or abscess till the time of the last follows up. While the failure rate or recurrence rate means an initial throwing out of the fibrin adhesive from the internal opening, insistent sepsis in the anal tract or an inadequate elimination of the tract with fibrin adhesive or the development of a perianal abscess.

Clinicopathological Characteristics

In the present study, the patients were categoried into 2 groups: high fistula group, 110 out of the 172 fistulas were successfully healed after the first attempt. The unhealed fistula tracts were a re-again second injection, which healed only 20 out of 62 patients. The total success rate, by the end of follow up period, was 130 out of 172 cases (75.5%).

In the low fistula groups, 140 out of the 150 fistulas healed after the first attempt and 5 of the 10 which were healed after the second injection. The achievement rate at the end of follow-up was 275 (85.4%), as shown in Table 4.

Table 4 Successive rate of healing fistula in-ano after the first or second injection of fibrin-glue

Fistula type (n=322)	Successive rate after the first injection	Successive rate after the second injection	Total number success after follow up	Failure rate
Low fistula	140/150 (93.3%)	43743	145/150 (96.7%)	5/150 (3.3%)
High fistula	110/172 (64%)	20/62	130/172 (75.5%)	42/172 (24.5%)
Total	240	25	275/322 (85.4%)	47/322 (14.6%)

The recurrence or failure rate was 10 out of 150 in low fistula and 62 out of 172 in the high fistula. Only 5-patients out 10 cases of low fistula and 20 cases of high fistula were successfully treated after the second injection of fibrin-glue and these all cases were simple in type.

The final and total failure rate at end of follow-up period of the present study were 42/172 (24.5%) in the high fistula groups. While in low fistula groups, only 5/150 (3.3%) were failed and there was no healing, as shown in Table 4.

The total number of failure healing of fistula in ano after fibrin-glue injection (1^{st} and 2^{nd} injection) was about 47 (14.6%) out 322 cases (include 5 cases of low fistula and 42 cases of high fistula), all failure cases were complex type fistula, as shown in Table 5.

Table 5 Failure rate according to types of fistula

Type of fistula	Simple fistula failure	Complex fistula failure
Low	0/145	43590
High	0 /130	42/42
Total	0/275	47/47

Association between Healing of Fistula and Sex of Patients

The result of the present study showed that there was no statistical significance correlation between fistula healing and sex of patients ($p>0.005$).

Correlation between Healing of Fistula with Age of Patients

The result of the present study showed that the mean age of patients was 45 years that range from 25 years to 60 years. The fistula of patients with young age group was healed earlier than older age groups and there was a major difference in respect of mean age between cured and unsuccessful patients ($p<0.005$).

Association between Fistula Healing by Fibrin Glue and High/Low Type

The total number and rate of successive fistula healing were higher in low fistula type in comparison to high fistula type and the differences were statistically significant from that high fistula ($p<0.05$) as shown in Table 6.

Table 6 Association between fistula healing by fibrin glue and high/low type

Type	Healing	Failure	P-value
Low	145/150 (96.7%)	5/150 (3.3%)	<0.05
High	130/172 (75.5%)	42/172 (24.5%)	

Association between Simple/Complex Type Fistula and Healing by Fibrin Glue Injection

All cases with simple fistula (265/265, 100%) were healed after first or after the second injection by fibrin-glue while all cases of complex type (47/47, 100%) were failed healing or recurrence. And the differences were statistically significant when compared ($p<0.05$) as shown in Table 7.

Table 7 Association between simple /complex type fistula and healing by fibrin glue injection

Type	Healing	Failure	p-value
Simple	265/265	0/265	<0.05
Complex	0/47	47/47	

The most important benefit in this technique was that none of the healed fistula (high/low fistula, primary/secondary) had any fecal or gas incontinence, itching, in the follow-up period, after this treatment. The mean hospital stay was one day. No one of the patients required painkillers for pain relief. There was no complication associated with the submission of fibrin glue. All of the patients restarted normal activities within 2-3 days. All patients could be back to work within 5-7 days.

DISCUSSION

Fistula in-ano yields persistent anxiety on the patient as well as on the surgeon. Many surgical choices for the handling of anal fistulas have been well-known, which have the objective of curative the fistula duct, with less relapse. The measures like a fistulotomy, lead to a high rate of fecal and gas incontinence. Other ways like a set on insertion and recent methods like advancement flaps have been compared with the standard fistulotomy, but no particular technique has yet considered the gold standard for fistula healing [12]. Consequently, it is sensible to look for other ways of treating fistulas in-ano.

Fibrin adhesive submission has proved to be better than traditional surgery in relations of patient relief, uninterrupted sphincteric job, drop in time of hospital stay, less painkiller needed and faster yield to normal activities with less operative trauma and no complication [12,13].

In this study of 172 high anal fistulas and 150 low anal fistulas has investigated the outcome after using fibrin adhesive in the anal canal of the patients. Primary and secondary fistulas were involved and also classified into simple and complex.

The mean age (45 years) in the presented study was similar to other studies and a male preponderance was noted in the present study similar to other studies [14,15].

In the present study, all cases with simple fistula (in low and high fistula type) were healed while all cases with complex fistula failed to heal. The successive rate in the low anal fistulas was higher than the high anal fistula, and these result of the present study could be a majority of low fistula were a simple type. These results were similar to the result of other studies of Mishra, et al., Göktürk, et al., and Jean-Charles, et al., [14-16].

The recurrence or failure rate at end of follow-up period in the present study, was 47 (14.6%) out of 322 cases, and all these cases which were complex type and these result was like to the relapse rates in the other studies and the management unsuccessfulness in the present study were initiated by an early expulsion of the fibrin clot from the internal opening, a insistent sepsis in the anal canal or an imperfect elimination of the fistula with fibrin glue [14-17]. It had been recommended in the past, that suturing of the internal opening prohibited the expulsion of the clot, but numerous current trials have proved that there was no significant change in the curative rate, with such technique [16-19].

In the current study, there was an important advantage of the second injection for all cases of a simple fistula which

were not cured after the first instillation of fibrin-adhesive and this outcome could have some methodical errors throughout the first trial. These results were similar to other studies, a significant benefit of the second injection for simple fistula failed after the first try [17,20,21]. While other study noticed, that there was no benefit of the second injection of fibrin glue in simple fistula [14].

A fistulectomy is considered as the procedure of choice for simple low type fistula in ano while high anal fistulas (simple or complex) are among the most difficult complication faced in colorectal surgery and surgical option carry the risk of both recurrence and or incontinence. Therefore, the treatment of high fistula (simple/complex) by fibrin glue resolved the problem of surgical technique and was considered as a promising option and superior to surgical technique.

The final results of the present study showed no advantage of fibrin-glue injection among the complex and multiply branched fistulas. These results were similar to results of other studies [17,20,21].

The current study does not show any prevalence of fecal or gas incontinence in any of the preserved patients as also in all the comparable trails and all the patients could conduct duty after the 1st day. Yet, this handling is harmless and does not need more surgical management [17], it may remarkably have a restricted role in designated highly compound cases in which sphincter damage is highly expected. In this condition, patients should be evidently advised about the failure rate anticipated with the technique and the possible need for further management.

CONCLUSION

Fibrin glue is a novel attractive approach, easy, safe, minimally-invasive, repeatable and cost-effective for the treatment of simple (low/high, primary/secondary) anal fistula. In addition to the traditional surgical techniques, in terms of the patient relief, less period of hospital stay, less pain and the complications and adverse reactions minimized. Fibrin-glue injection is considered the promising option for treating the simple (low/high, primary/secondary) anal fistulas.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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