

Initial Experience with Fibrin Glue Treatment of Anal Fistulae in Children

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Pediatric anal fistulae commonly result from recurrent perianal abscesses, of which nearly 50 per cent develop an anal fistula. The purpose of this study was to report the results of using fibrin glue to treat anal fistula in pediatric patients. Infants and children with recurrent perianal abscesses and anal fistulae were treated with either fistulectomy or fibrin glue. Demographic and clinical characteristics and outcomes were compared between the groups. A total of 34 children were included; 27 received fistulectomy (median age eight months) and seven received fibrin glue treatment (median age 14 months). No significant differences in demographic or clinical characteristics were found between the two groups (all, $P > 0.05$). Median follow-up duration was significantly higher in the fibrin glue group compared with that in the fistulectomy group (five months *vs* one month, $P = 0.003$). There was one recurrence in the fistulectomy group, and no recurrences in the fibrin glue group ($P = 1.0$). No complications occurred in either group. Fibrin glue treatment is a simple and effective treatment alternative in the management of anal fistula in children, offering the advantage of sphincter muscle-sparing and reduced risk of fecal incontinence.

ANAL FISTULAE ARE hollow canals lined with granulation tissue that form an abnormal connection between the anus and perianal skin, and are associated with considerable morbidity and discomfort.¹ Common causes of anal fistula include nonspecific anal gland infection, Crohn's disease, perforation by a foreign body, external trauma, tuberculosis, carcinoma, and immunodeficiency.²

About one individual in 10,000 in the general population will have anal fistulae annually, of which about 80 per cent are cryptoglandular fistulas, arising from abscesses after an initial anal gland infection.²

In children, anal fistulae almost always result from recurrent perianal abscesses; however, unlike in adults, the tracts in children occasionally run radially from the anal canal origin to the abscess site.³ Children account for 0.5 to 4.3 per cent of all patients presenting with perianal abscesses, and males are affected most frequently, mostly younger than two years of age.⁴

Surgical treatment using fistulotomy and fistulectomy is used most commonly to correct anal fistulae, and both procedures involve laying the fistula tract open entirely.⁵ However, although these procedures are considered relatively safe for simple distal fistulae,

they are associated with low efficacy rates, prolonged healing, and significant pain, and are only appropriate for patients with minimal risk to sphincter function; up to 20 per cent of adult patients may have postoperative continence disorders.⁶ After fistulectomy, the recurrence of anal fistula ranges from 16 to 70 per cent, and incontinence rates range from 0 to 40 per cent.⁷

Biological products are being used experimentally as sphincter-sparing and continence-protective methods for treating anal fistulae.⁸ Fibrin glue is a tissue sealant that activates fibrinogen to form a gel-like fibrin clot. It has been used for purposes such as sealing tissues, augmenting hemostasis, and facilitating the targeted delivery of drugs, and a 90 per cent efficacy rate is reported across applications.⁹ Abel et al.¹⁰ first reported the use of autologous fibrin glue for rectovaginal and complex anal fistulae in 1993. More recently, biological fibrin glue from donor plasma that has been treated to inactivate viruses has become available.^{11–14} With respect to fistula, the fibrin clot seals the fistula and helps fibroblasts to form a collagen network. By contrast to conventional fistulectomy, the administration of fibrin glue is a simple procedure that does not affect sphincter structure.¹⁴ Studies in adult patients have shown favorable results that are superior to conventional surgery in terms of closure of the fistula, patient comfort, undisturbed sphincter function, reduced overall hospital stay, reduced postoperative analgesia requirement, and the absence

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of complications, especially incontinence.^{9, 11, 14–18} However, no reports are available describing the use of this fibrin glue for treating anal fistula in children.

The purpose of the study was to evaluate the use and outcomes of fibrin glue for the treatment of pediatric anal fistula *versus* fistulectomy.

Methods

A prospective parallel study of fistulectomy *versus* fibrin glue treatment was conducted. The internal review board of Shin Kong Wu Ho-Su Memorial Hospital reviewed and approved the study protocol (Institutional Review Board #20140604R), and the parents or guardians of all patients provided signed informed consent to participate.

Infants and children with recurrent perianal abscesses (three or more times) who had been treated at our hospital from September 2009 to September 2015 with antibiotics and local care were eligible for inclusion in this study. Patients were referred from the outpatient pediatric department of our institution to the surgery department for possible surgical management. Surgery was not performed until the area had healed, and the fistula could be identified in the perianal area. Patients with a prior incision and drainage of an abscess were excluded from this study. Patients with a history of inflammatory bowel disease were also excluded.

Patients were treated consecutively after a decision was made by the parents regarding the method. Parents were informed of the associated risks of fistulotomy and fistulectomy, namely, that both involved risk of injuring the sphincter muscle and causing incontinence. The fibrin glue option was explained thoroughly, including the benefits of lower incontinence rate, undisturbed sphincter function, and greater safety as reported in adult studies. The parents or legal guardians of the children then made the decision of which procedure to perform.

Patient sex, age, fistula site, follow-up, complications, and final treatment outcomes were recorded. Surgery and evaluation of the patients was performed by the same pediatric surgeon. Complications were defined as rectal bleeding, perianal pain, local infection, and incontinence as described previously.¹⁸ Recurrence was defined as discharge, pain, and visualization or palpation of either an internal or external fistulous opening, as described previously.¹⁵

Fistulectomy

Fistulectomy was performed with patients in the lithotomy position and under general anesthesia. A

lubricated retractor was inserted in the anus to determine the origin of the fistula. The abscess is incised and drained. A silver probe was then gently inserted into the opening of the tract to visualize the opening in the anal canal. A scalpel or electrocautery was used to open the fistula tract, as previously described.¹⁸ Granulation tissue in the floor of the fistula or in the abscess cavity was curetted as necessary. The overlapping skin was excised to assure free drainage of the tract.

Fibrin Glue Treatment

Fibrin glue (TISSEEL[®]; Baxter Healthcare Corporation, Westlake Village, CA) treatment was performed in the operating room with patients under general anesthesia. An examination was performed to identify the external and internal opening of the fistula. Fibrin glue was not injected until an internal opening was clearly identified. A flexible narrow catheter of 3.5-mm diameter was inserted through the external opening through the fistula toward the internal opening. A double-chamber syringe was used to deliver the filler fibrinogen solution and thrombin solution, using an adjoining piece to connect the syringe with the 40-mm-long application cannula. The single-outlet design allows equal volumes of the two solutions to pass through the adjoining piece into the application cannula for thorough mixing. The fibrin glue (2 mL) was injected with simultaneous slow withdrawal of the catheter until the fistula was completely filled and both openings were sealed.

After the procedure, patients received a regular diet. Perioperative antibiotics were not routinely used. Most patients were discharged home on the day of surgery as described in previous studies.¹¹

Follow-up

All patients were seen in the outpatient department one day after surgery, with successive follow-up at one week and one month. Patients were then examined at three-month intervals until reaching at least two years follow-up observation.

Statistical Analysis

Categorical variables, including gender and recurrence, were presented as counts and percentages. Fisher's exact test was performed to compare the differences between the fistulectomy group and fibrin glue group. Because the sample size was small, continuous variables, including age and follow-up duration, were presented as medians and ranges; Mann-Whitney U tests were performed for the group comparisons. All

statistical analyses were performed by IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, NY). Two-tailed values of $P < 0.05$ indicated statistical significance.

Results

A total of 34 children were included in the study; 27 received fistulectomy and seven received fibrin glue treatment (Table 1). There were 26 males and one female in the fistulectomy group (median age eight months; range 1–180 months), and six males and one female in the fibrin glue group (median age 14 months; range 4–144 months). In infants and pediatric age patients, the location of the anorectal ring is not divided as in adult patients (submuscular, intersphincteric, infralevator, and supralevator) because the anorectal ring is not mature. Usually, only two locations are used for pediatric patients: low type (similar to intersphincteric in adult) and high type. All patients in this study were of low type.

No significant differences in demographic or clinical characteristics were found between the two groups (all, $P > 0.05$). Median follow-up duration was significantly higher in the fibrin glue group compared with that in the fistulectomy group (five months *vs* one month, $P = 0.003$). There was one recurrence in the fistulectomy group (success rate 96%) and no recurrences in the fibrin glue group (success rate 100%) ($P = 1.0$). No complications occurred in either group. The characteristics of seven children who received fibrin glue treatment are summarized in Table 2.

TABLE 1. Patient Demographic Characteristics and Treatment Results

	Fistulectomy	Fibrin Glue	P Value
Number	27	7	
Gender			0.374
Male	26 (96.3%)	6 (85.71%)	
Female	1 (3.7%)	1 (14.29%)	
Age (months)	8 (1–180)	14 (4–144)	0.522
Follow-up (months)	1 (1–7)	5 (1–26)	0.003
Result	Healed	Healed	
Recurrence rate	1 (3.7%)	0 (0%)	1.000
Complications	None	None	

Discussion

The present study showed that fibrin glue was effective for the treatment of anal fistulae in children two months to 12 years of age. The success rate was 100 per cent and no complications occurred. To the best of our knowledge, this is the first study examining the use of fibrin glue to treat anal fistulae in children.

In pediatric patients who are more than one year of age, anal fistulae are difficult to heal after only incision and drainage of an abscess. Anal fistulae have been considered the result of a crypt abscess that has extended to the perianal skin, but it may also result from a perianal abscess.¹⁹ However, the exact etiology of anal fistulae is not known. It has been suggested that they can be congenital in children. It has also been proposed that androgen excess may stimulate the sebaceous glands and induce a secondary infection with subsequent perianal abscess and fistula.^{20–22} An anal fistula is usually located between the internal and external sphincter or penetrates the sphincter to open on the perianal skin, and the fistula tract is usually located lateral to the anus. Unlike in adults, Goodsall's rule does not apply in infants; the fistula typically extends radially from the skin opening to the anal canal at the involved crypt.

Published studies since the early 2000s have reported success with fibrin glue therapy in adults with anal fistulae. Results of studies we reviewed demonstrated success rates in adults ranging from 61 to 83.3 per cent, with mean follow-up ranging from 6 to 22 months (Table 3).^{13, 14, 16, 23, 24} Differences in the success rates may be because of patient selection and differences in the quality of autologous *versus* commercial fibrin glue because autologous fibrin glue may not form as strong a plug as the commercial preparation.¹⁸ Nevertheless, the procedure is superior to conventional surgical treatment and shows the best results when used for primary, single-tract, low anal fistulas.²⁵ A study on the long-term results of fibrin glue reported that in case of failed fibrin glue treatment, the procedure can be repeated and fistulotomy or other treatment methods can be adopted if failure occurs again.¹⁴

Fistula characteristics also have great influence on the success of fibrin glue treatment among adults, but

TABLE 2. Characteristics of Seven Children with Anal Fistulae Treated with Fibrin Glue

Age	Sex	Fibrin Glue type	Fistula Site	Fibrin Glue Treatment	Final Outcome
6 months	Male	Commercial	3 o'clock	Once	Healed
4 months	Male	Commercial	3 o'clock	Once	Healed
14 months	Male	Commercial	9 o'clock	Once	Healed
14 months	Male	Commercial	3 o'clock	Once	Healed
8 months	Male	Commercial	3 o'clock	Once	Healed
2 months	Male	Commercial	3 o'clock	Once	Healed
12 years	Female	Commercial	9 o'clock	Once	Healed

TABLE 3. *Published Studies of Fibrin Glue Treatment for Adult Anal Fistula*

Study	Fibrin Glue Type	Year	Number of Patients	Success Rate(%)	Follow-up
Cintron et al. ¹⁶	Commercial Autologous	2000	79	61	Mean 12 months
Park et al. ¹³	Commercial	2000	29	69	Mean 6 months
Lindsey et al. ²³	Commercial	2002	42	63	Mean 17 months
Sentovich ¹⁴	Commercial Autologous	2003	48	68.8	Mean 22 months
Maralcan et al. ²⁴	Commercial	2006	36	83.3	Mean 54 weeks

anal fistulae in children do not vary in classification; nearly all arise from recurrent perianal abscesses.³ It also seems reasonable that the success rate of treating complex and recurrent anal fistula would be lower. It is especially difficult, *e.g.*, to find the original fistula canal whether a recurrent fistula is located at a high level.^{10, 17, 18} In addition, a relatively small infection within the fistula tract may dislodge the fibrin glue plug, which leads to failed treatment. We provided specific wound care instructions to the parents of all our patients such that the wounds were kept clean (saline rinses) but not excessively wet (*e.g.*, no soaking in a bathtub), and the application of local antibiotic ointment as necessary.

A range of biological products and approaches are now being used to treat anal fistulae, including fibrin glue, fibrin plugs, adipose derived stem cells, and the mucosal advancement flap (MAF).²⁶ Closure rates and/or success rates vary by technique. The instillation of autologous adipocyte stem cells is an innovative technique that inhibits the immune response and inflammation with success rates of 57, 52, and 37 per cent depending on the use of stem cells alone, with fibrin glue, or fibrin glue alone, respectively, but without significant differences between these approaches.²⁶ The MAF technique uses endorectal/endoanal flaps to close the internal ring either with or without closing the tract itself, with success rates ranging from 77 to 100 per cent.²⁷ Göttgens et al.²⁸ reported that a combination of MAF with platelet-rich plasma resulted in a long-term closure rate of 83 per cent.

Coverage using a porcine-derived fibrin plug was introduced by Robb et al.²⁹ in 2004. However, the procedure can be difficult to perform with closure rates varying from 14 to 87 per cent.²⁷

The complications of fistulotomy and fistulectomy have long been noted and include rectal bleeding, perianal pain, local infection, delayed healing, and the most significant and common complication, anal incontinence.³⁰ Investigations of fistula management in infants and children, however, do not report rates of recurrence and complications comparable with those in adults. For example, evaluation of the long-term effects of seton placement in 95 infants younger than one year demonstrated five to six weeks healing time

and only one case of recurrence.³¹ Charalampopoulos et al.³² found that incision and drainage of perianal abscesses in children was effective without significant perianal sepsis and suggested that fistulas in children can be treated successfully using fistulotomy because complex fistulas are so uncommon. However, biological alternatives offer a low-risk option, and studies of adults treated with fibrin glue showed reproducible results with a short learning curve and minimal morbidity.^{32, 33} Results of a large multicenter study of adults with cryptogenic perianal fistula reported that of 60 patients treated with fibrin glue, six had recurrence, four needed additional surgery, and two received antibiotics for infection, but none had incontinence.³⁴

Data from a comprehensive study of the clinical characteristics of anal fistula in infants suggested that although the management of pediatric perianal abscesses and anal fistulae is still controversial, conservative treatment has excellent outcomes compared with surgical treatment.³⁵

Limitations

This study has the limitation of a small sample and relatively short follow-up. The lack of randomization in the series may also have influenced the results, although the two groups were comparable.

Conclusions

Fibrin glue treatment is a simple and effective treatment alternative for the management of anal fistulae in children. It offers the advantage of sparing injury to the sphincter muscle and avoids the risk of complications associated with fistulectomy or fistulotomy. This procedure is easy for surgeons to learn and perform. Because previous research on the use of fibrin glue involved adults and studies of children are lacking, the present study is consequently the first involving children and presents preliminary results. Further prospective investigation is needed to establish the feasibility and effectiveness of fibrin glue treatment for pediatric anal fistulae, including a larger sample from multiple centers and longer term follow-up.

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