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REVIEW

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Fibrin glue for fistula-in-ano: the evidence reviewed

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Abstract Fibrin glue is increasingly used in the treatment of anal fistulae. This review aims to establish its long-term efficacy and clarify its role in this setting. A search of Medline and PubMed databases was performed from 1966 to 2004. Data were collated regarding the type of study, fistula aetiology and complexity, technical aspects of glue application, and short- and long-term healing rates. The majority of studies comprised prospective series with fistulae of mixed aetiology. The overall healing rate was 53% with a wide variation between studies (10%–78%). The only factor that could account for this diversity was fistula complexity, with series including a high proportion of complex fistulae reporting worse outcomes. The quality of data to assess the efficacy of fibrin glue in the treatment of anal fistulae is poor and further clinical trials are needed. Fistula complexity is the main factor that adversely influences long-term healing rates.

Key words Anal fistula • Fibrin glue

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Introduction

Anal fistulae are a common proctocological problem affecting 1 in 10 000 of the population [1]. The aim of fistula treatment is to achieve long-term healing without compromise of the continence mechanism. Surgical strategies to treat fistulae tend to be guided by their degree of complexity and their underlying aetiology. Whilst simple low fistulae may be adequately treated by fistulotomy alone with recurrence rates in single figures [2, 3], minor degrees of incontinence are still reported with rates varying widely from 0% to 50% [4]. Complex fistulae involving a substantial proportion of the sphincter complex are more difficult to treat. Cutting and loose setons [5], staged fistulotomy [6], and rectal and anodermal advancement flaps [7] have all been advocated. However, none are free of the complication of faecal incontinence, with minor incontinent rates for cutting setons reported between 0% and 63% [8–10], and up to 35% [7] for transanal advancement flaps.

In 1992, Hjortrup et al. [11] published the first series of perineal fistulae treated with fibrin glue. This novel approach offered a simple method of promoting fistula healing with maximal preservation of the continence mechanism. Initially, the application of this technique was hampered by the need to make autologous fibrin preparation, but in 1998 the licensing of commercial fibrin glues lead to a rapid increase in their utilisation. Early results were encouraging with high rates of fistula closure [12, 13], but as experience was gained questions began to be asked about the long-term efficacy of such treatment. The current literature contains over a dozen reports of fibrin glue in the treatment of fistula-in-ano. The evidence concerning its efficacy is conflicting with a wide variation in the reported healing rates.

The current article reviews the literature in an attempt to explain the reasons for this diversity and to clarify the role of fibrin glue in the treatment of fistulae-in-ano.

Materials and methods

Medline and PubMed databases were searched from 1966 to April 2004 using the categories 'rectal fistula' and 'fibrin tissue adhesive' together with combinations of the keywords 'fibrin', 'fibrin glue', 'fistula', 'fistula-in-ano' and 'anal fistula'. All original English language articles where a fibrin-based adhesive was used in the treatment of anal fistulae were retrieved. Articles involving single case reports, cancer-related fistulae, or perineal sinuses were excluded as were articles related to the use of fibrin glue in the treatment of other gastrointestinal fistulae. This strategy was combined with a manual search for articles and abstracts cited in the retrieved manuscripts. Care was taken to identify early studies which had subsequently been incorporated into later series to avoid duplication of data.

From the selected articles, data was retrieved regarding the type of study performed, the cohort size, the aetiology and complexity of the fistulae, the type of fibrin glue used, technical aspects of glue application, the length of follow-up, and the short- and long-term healing rates. A follow-up period of 12 months or greater was deemed necessary to determine long-term healing rates as almost all recurrences following fibrin glue are apparent within 3 months of treatment with only occasional recurrences detectable after 6 months [14].

Results

Our search retrieved 15 original articles on the use of fibrin glue in the treatment of fistula-in-ano. Three of these articles contained data that was subsequently incorporated into later series and were excluded. One study included patients treated by either fibrin glue alone or with a combination of fibrin glue and endoanal advancement flap [15]. In the present review only data from those patients receiving fibrin glue alone were included. Only one randomised clinical trial was found [16]. Nine articles described prospective cohort studies and two were retrospective reviews. Seven studies included follow-up of 12 months or greater. Of the twelve studies, only one selected exclusively fistulae of cryptoglandular aetiology whilst the remaining eleven included fistulae of mixed aetiology. Five studies included only complex fistulae.

Healing rates

The 12 studies included a combined total of 378 patients (Table 1). Overall, fibrin glue treatment resulted in healing in 200 patients (53%). Several studies included patients who had undergone repeat glue application after a first failure. Where it was possible to extract the data, this appears to have had little effect on the combined healing rate, increasing it to 213 of patients (56%). Healing rates varied widely between the studies, from 10% to 78%. The initial enthusiasm for fibrin glue is readily appreciated when the data is viewed in terms of early and late follow-ups. Sentovich [17] and Cintron et al. [18] reported early series with healing rates of 85% and 81%, respectively, which were subsequently modified to 60% and 61% in later larger series [14, 19]. In addition, Buchanan et al. [20] reported initial healing in 17 (77%) of 22 fistulae but only 3 (14%) remained healed on long-term follow-up. These studies underline the importance of long-term follow-up in determining fistula healing rates.

Fistula aetiology

Most of the series include fistulae of mixed aetiology but with cryptoglandular fistulae accounting for the majority.

Table 1 Healing rates following fibrin glue treatment for fistula-in-ano

Reference	Year	Patients, n	Follow-up, months	Healing rate, %	Healing after re-glue, %
Loungnarath et al. [22]	2004	39	26	31	33
Tinay, El-Bakry [23]	2003	18	8	78	NA
Buchanan et al. [20]	2003	22	14	14	14
Zmora et al. [15]	2003	24 (G)	12	33	
		13 (G +F)		54	NA
Sentovich [19]	2003	48	22	60	69
Lindsey et al. [16]	2002	19	3	42	63
Chan et al. [27]	2002	10	6	60	NA
Cintron et al. [14]	2000	79	12	61	NA
Partlj et al. [21]	2000	69	28	74	NA
Venkatesh, Ramnujan [12]	1999	30	26	50	60
Aitola et al. [28]	1999	10	6	10	NA
Abel et al. [13]	1999	10	7	50	60

G, fibrin glue alone; *G+F*, fibrin glue plus advancement flap; *NA*, not available or unable to determine

Only the two series by Buchanan et al. [20] and Patrlj et al. [21] dealt exclusively with cryptoglandular fistulae. Comparison of the healing rates in terms of aetiology is made difficult by the small numbers of non-cryptoglandular fistulae included in most studies. In the large study by Cintron et al. [14], cryptoglandular fistulae had a healing rate of 63% compared to 36% for fistulae of other aetiology, but fistula aetiology failed to predict successful healing on logistic regression analysis. This trend is supported by the smaller study by Venkatesh and Ramnujan [12] who achieved healing rates of 80% in cryptoglandular fistulae compared to a complete absence of healing in patients with Crohn's disease or HIV infection. Contrary to these findings, Sentovich [19] described similar healing regardless of aetiology, with rates of 72% for cryptoglandular, 80% for Crohn's, and 57% for other miscellaneous fistulae, whilst Loungnarath et al. [22] found healing in 23% of cryptoglandular, 31% of Crohn's and 75% of anastomotic fistulae on long-term follow-up. Only the study by Zmora et al. [15] reported better healing in non-cryptoglandular fistulae (50%), but their success rate for cryptoglandular fistulae was particularly low (20%). No study was able to establish a statistically significant difference in healing rates based on fistula aetiology, which is probably due to the relatively small numbers involved. However, healing in HIV-associated fistulae appears to be universally poor.

Complex versus simple fistulae

Several of the studies compared healing rates between simple and complex fistulae, although the definition of complex is somewhat arbitrary due to the lack of any standardised classification. Again the data are somewhat controversial. Cintron et al. [14] reported high healing rates in simple fistulae, with 82% for intersphincteric and 62% for transsphincteric, but only 40% for complex fistulae. However, the complex fistulae were of mixed aetiology including Crohn's and HIV-associated fistulae. Lindsey et al. [16] attempted to standardise the assessment of fistula complexity by the use of preoperative endoanal ultrasound and structured surgical assessment. In this small randomised trial, no difference in healing rates was detected in terms of fistula complexity with 3 of 6 (50%) simple fistulae and 9 of 13 (69%) complex fistulae healing following fibrin glue application.

Overall, studies that included simple fistulae [14, 19, 21, 23] reported high rates of healing with figures in the region of 60%–78%, whilst those that dealt exclusively with complex fistulae [12, 13, 15, 20, 22] reported lower healing rates in the range of 14%–50%. Although it was not always possible to determine the proportion of simple and complex fistulae and their respective healing rates in many studies, the series have been classified into those that dealt with exclusively complex fistulae and those that included patients with both complex and simple fistulae (Table 2). Healing was achieved in 35.5% of patients in studies that included only complex fistula as compared to 62.9% of patients in studies that included both simple and complex fistulae ($p<0.001$). This crude analysis suggests that fistula complexity does have an effect on healing rates and may explain the diversity in reported results.

Fistula track length

Only two studies compared healing rates in terms of fistula track length and these present conflicting data. In Partlj et al.'s study [21], a healing rate of 88.9% was achieved for fistulous tracks greater than 3.5 cm compared to 45.8% for shorter tracks. In contrast, Cintron et al. [14] reported better healing in shorter fistulae; fistulae that failed to heal had a mean length greater than 4 cm while healed fistulae had a mean length of 2.8 cm. These two studies differed in the composition of their respective cohorts, with Partlj et al.'s series being comprised exclusively of cryptoglandular fistulae whilst Cintron et al.'s series included fistulae of mixed aetiology.

Composition of fibrin glue

The majority of studies used commercially available fibrin glue products (Tissel, Viguard, Beriplast, and other unspecified products). Two studies used exclusively autologous fibrin preparations and two used a combination of

Table 2 Fistula healing in studies that included only patients with complex fistulae compared to studies that included those with both simple and complex fistulae. Chi-squared test, $p<0.001$

	Complex only	Simple and complex	Total
Healed	49 (35.5)	151 (62.9)	200 (52.9)
Not healed	89 (64.5)	89 (37.1)	178 (47.1)
Total	138 (100)	240 (100)	378 (100)

Table 3 Healing rates classified according to type of fibrin glue preparation

Reference	Glue type	Initial healing rate, %
Loungnarath et al. [22]	Tissel	31
Tinay, El-Bakry [23]	Tissel	78
Zmora et al. [15]	Tissel	33
Patrlj et al. [21]	Tissel (+ cefuroxime)	74
Aitola et al. [28]	Tissel	10
Sentovich [19]	Tissel (90%)	60
	Autologous (10%)	40
Cintron et al. [14]	Tissel (30%)	58
	Viguard (37%)	69
	Autologous (33%)	54
Lindsey et al. [16]	Beriplast	42
Hjortrup et al. [11]	Beriplast	50
Buchanan et al. [20]	Unspecified	14
Chan et al. [27]	Unspecified	60
Venkatesh, Ramnujan [12]	Autologous	50
Abel et al. [13]	Autologous	50

commercial and autologous preparations (Table 3). No differences in the healing rates are discernable as regards the type of fibrin preparation employed. In particular, Cintron et al. [14] compared Tissel, Viguard, and autologous preparations each in approximately one-third of 79 fistulae and found no significant difference in the healing rates.

Bowel preparation and antibiotics

Bowel preparation, either full mechanical preparation or rectal enema, was used in 8 of the 12 studies. No difference in the healing rates is appreciable between those using and those not using bowel preparation. Eight of the studies used antibiotic prophylaxis as part of their fibrin glue regimen. Six of these used a prophylactic parenteral dose, whilst Patrlj et al. [21] attempted antibiotic sterilisation of the fistulous tract prior to gluing. Again, the large number of simple fistulae in the Partlj et al. study makes it difficult to assess the effects of rigorous track sterilisation on fistula healing. No overriding trend is appreciable between those studies that employed antibiotic usage and those that did not.

Discussion

The use of fibrin glue in the treatment of anal fistulae, particularly complex fistulae, has an obvious appeal. It is a simple, safe technique that can facilitate fistula healing with minimal discomfort or risk of incontinence to the patient. Early results of glue application were encouraging and led to the widespread dissemination of the technique. However, as experience was gained it became apparent that the use of fibrin glue was not the panacea it first promised. Several recent reports have described disappointing long-term outcomes that bring into question the original enthusiasm for the technique.

The aim of this article was to review the current literature on fibrin glue in anal fistulae to determine the realistic outcomes that can be expected and to guide future practice. It is now 12 years since the first publication on the use of fibrin glue in perineal fistulae [11] and there is still a paucity of good quality data in the literature upon which to make concrete recommendations. Only one randomised trial which allocated 19 patients to either fibrin glue or conventional treatment has been published, making formal systematic review impossible. The remaining 11 publications that we retrieved consisted of prospective series or retrospective reviews.

Interpretation of the data is made difficult by a number of factors. The majority of studies included fistulae of mixed aetiology and varied in their methodology for track preparation, glue application, and postoperative care. Several of the studies included small numbers of patients and provided only short-term follow-up. Few studies attempted to standardise fistula classification by either surgical assessment or the use of preoperative radiological imaging, and many failed to provide precise criteria of fistula healing. All this makes it difficult to tease out individual factors that may account for the diversity in the healing rates.

In an attempt to identify factors that may account for the diversity in success rates, we looked at various factors

that may influence fistula healing. The type of fibrin glue, the use of preoperative or intraoperative antibiotics and mechanical bowel preparation did not appear to affect fistula healing. The only factor that appears to influence healing is the complexity of the fistula, with studies that included exclusively complex fistula having a significantly lower healing rate than those that included both simple and complex disease. The three large studies with long-term follow-ups by Sentovich [19], Cintron et al. [14] and Partlj et al. [21] all reported healing rates in excess of 60% but contained significant numbers of cryptoglandular intersphincteric and transsphincteric fistulae. The majority of intersphincteric and many transsphincteric fistulae do not incorporate substantial amounts of sphincter muscle and are 'simple' by definition. In such cases, fistulotomy poses little risk to major incontinence, is quick and easy to perform, and provides good patient satisfaction and long-term healing rates [2, 24]. In contrast, complex fistulae can be difficult to treat with a significant risk to continence irrespective of the method employed.

Although fibrin glue has the advantage of minimal risk to continence, it appears to offer little benefit over existing techniques in terms of complex fistulae healing. The reasons for this are unclear. Complex fistulae involve a substantial proportion of the sphincter muscle and often included secondary tracts and horse-shoe extensions. The internal opening of complex fistulae is more likely to lie within the high pressure zone of the anorectum canal than in simple fistulae and adequate closure of this opening appears to be paramount in achieving successful fistula healing. This is well illustrated by the popularity of mucosal advancement flap techniques in the treatment of complex fistulae, which can produce fistula healing in 64%–75% of cases [25–27]. It is unlikely that fibrin glue alone is adequate for this role. In only one study by Sentovich [19] was a concerted attempt made to deal with the internal opening by means of suturing. This strategy might have been expected to bestow some benefit, but whether suture closure is an adequate means of dealing with the internal opening is debatable.

The precise role of fibrin glue in the treatment of anal fistulae remains unclear due to the lack of good quality clinical trials. Further well-designed studies are required to answer the many questions that remain. Although fibrin glue is associated with satisfactory rates of healing in simple fistulae, is it really better than conventional fistulotomy? Does fibrin glue have a role in the treatment of complex fistulae given its low healing rates and the reasonable results achievable with mucosal advancement flaps? Is it possible to identify factors that predict failure following fibrin glue treatment? Until such time as more complete data is available, it seems appropriate that fibrin glue will remain a treatment option for both simple and complex fistulae given its unparalleled safety profile. However, patients should be warned of the rates of failure and the possible need for subsequent procedures.

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