

Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano



Ann. Ital. Chir., 2010 81: 349-356

Roberto Cirocchi*, Alberto Santoro**, Stefano Trastulli*, Eriberto Farinella*, Giorgio Di Rocco**, Domenico Vendettuali**, Domenico Giannotti**, Adriano Redler**, Marco Coccetta*, Nino Gullà*, Carlo Boselli*, Nicola Avenia*, Francesco Sciannameo*, Antonio Basoli***

*Department of General Surgery, "Santa Maria Hospital", Terni, University of Perugia, Italy

**Department of Surgical Sciences, University of Rome "La Sapienza", Rome, Italy

***Department of General Surgery "P. Stefanini", University of Rome "La Sapienza", Rome, Italy

Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano

AIM: To evaluate the convenience in terms of recurrence and fecal incontinence rates of fibrin glue versus surgical treatment in the management of fistula-in-ano.

MATERIALS AND METHODS: Randomized controlled trials (RCTs) and non-randomized studies (CCTs) comparing conventional surgical treatment versus fibrin glue treatment in patients with perianal fistulae were identified using a pre-defined search strategy. The post treatment anal incontinence rate and the fistula recurrence rates between the two operations were compared by using the methods provided by the Cochrane Handbook for Systematic Reviews of Interventions. The lack of homogeneity of results between the different studies did not allow to analyze other secondary outcomes. Patients with cryptoglandular and Crohn's anal fistula were enrolled in the analysis. The employed fibrin glue came from commercial kits: Beriplast (Aventis Behring, Sussex, United Kingdom) and Tisseal or Tissucol (Baxter, Inc, Mississauga, Ontario). Surgical conventional treatment consisted of fistulotomy, placement of a cutting or loose latex seton and advancement mucosal flap closure. All patients were followed up at 6 and 12 weeks, the longest follow up was 6 months.

RESULTS: Two RCTs (106 patients) and 1 non randomized studies (232 patients) were identified. The recurrence rate is higher, although still not statistically significant, in those patients who underwent fibrin glue injection (44/81) versus conventional surgical treatment (108/230), (OR: 0.44; 95 %CI: 0.12-1.68; P=0,23). Furthermore in the analysis of the subgroup of RCTs alone there were not significant differences with the previous results of RCTs with CCT analysis (OR: 0.33; 95 %CI: 0.03-3.66; P=0,37). In the same way the analysis of the subgroup of RCTs with complex anal fistulae were not statistically significant and similar to the previous results regarding all type of fistulas (OR: 0.86; 95 %CI: 0.01-72.36; P=0.95). The analysis of post-operative anal incontinence showed no difference between the group who underwent fibrin glue injection (9/230) and the conventional surgical treatment group (10/81), (OR: 1.00; 95 %CI: 0.43-2.34; P = 1.00). A very low heterogeneity in the analysis was detected (Chi-square = 0.04 - P=0%).

CONCLUSION: Our statistical analysis does not show any significant statistical difference between fibrin glue treatment versus conventional surgical treatment for all perianal fistulae in terms of recurrence (P=0.23) and anal incontinence (P=1.00).

KEYWORDS: Anal fistula, Anal fistula plug, Fibrin glue, Fistulotomy, Meta-analysis.

Introduction

Surgery for fistula-in-ano is a challenge for surgeons. Westertep defined this challenge as "Anal fistulotomy

between Skylla and Charybdis" ¹. The majority of anal fistulae are simple and low (70%) ² and the treatment of these fistulae present a satisfactory outcome ³. Among the several post-operative complications the most important ones are represented by recurrence (0-14%) ^{1,4} and disturbance in anal continence (10-24%) ^{3,5}. However the incontinence in these patients frequently consists of loss of flatus control (25%) and soiling (31-44%), rather than severe faecal incontinence (11-17%) ^{3,5}. The different incidence of these complications depends on the fistula complexity, type of surgical treatment, completeness

Pervenuto in Redazione: Luglio 2010. Accettato per la pubblicazione Settembre 2010

Correspondence to: Stefano Trastulli, Junior Specialist Physician, Department of General Surgery, University of Perugia, "Santa Maria Hospital", Via Tristano di Joannuccio, 05100 Terni, Italy (e-mail: stefano.trastulli@hotmail.it).

and length of follow up ⁶. The gold standard of more complex fistulae is the endorectal advancement flap repair ^{7,8} although the outcome is still poor ⁹. In the last decade, the fibrin glue and anal fistula plug has been considered an alternative to a surgical approach in the treatment of these complex anal fistulae ¹⁰⁻¹⁴. Several studies report the potential benefits of such a simple, safe, painless procedure and with a more comfortable wound management ¹⁵. We already highlighted the importance of fibrin glue treatment as a newer sphincter-saving approach in our previous systematic review in 2009, in which a longer and more accurate follow-up and further research were already recommended for a more appropriate evaluation ¹⁵. The recent publication of new Randomized Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs) prompted us to carry out a new systematic review in order to define the role of the fibrin glue in the treatment of the perianal fistulas-in-ano in terms of recurrence and incontinence rate.

Materials and methods

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We searched for published Randomized Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs), without language restrictions, using the following electronic databases: Cochrane Central Register of Controlled Trials (January 2010); MEDLINE (1966 to January 2010); EMBASE (1980 to January 2010); Science Citation Index (1981 to January 2010); ISI Proceedings (1990 to January 2010); Zetoc (searched January 2010); CINAHL (1982 to January 2010); Clinicaltrials.gov (searched January 2010). The literature researches were carried out using the following medical subject headings (MeSH) and free text words: "rectal fistula"; "perianal fistula"; "anal fistula"; "fistula-in-ano"; "fibrin adhesive"; "fibrin glue"; "fibrin sealant". We also checked the reference lists of all the identified studies. Furthermore we also collected the abstracts presented to the following international scientific societies: American College of Surgeons (2000 to 2009), American Society Colon-Rectal Surgeons (1991 to 2009), Italian Society of Surgery (1985 to 2009), Italian Society of Colorectal Surgery (2006 to 2009) and the *Courrier de colo-proctologie*.

DATA EXTRACTION

Three authors (RC, ST and AS) assessed titles or abstracts of all the studies identified by the initial search, excluding the irrelevant studies. Full text articles of potentially relevant studies and any studies with unclear methodology were obtained. All these studies were assessed by the three authors as to whether they met the inclusion criteria for this review, and the methods of ran-

domization and the adequacy of allocation concealment were evaluated.

OUTCOMES OF INTEREST

The main analyzed outcome was the recurrence rate of fistula; the secondary outcome was the anal incontinence. The lack of homogeneity of results between the different studies did not allow to analyze more secondary outcomes: clinical healing rate, complications, changes in baseline incontinence score and maximum resting and satisfaction scores, pain scores and days off work.

INCLUSION CRITERIA

We included RCT and CCT comparing conventional surgical treatment versus fibrin glue treatment in patients with perianal fistulas. Patients older than 18 years with cryptoglandular and Crohn's anal fistula were enrolled in the analysis. The employed fibrin glue only came from commercial kits: Beriplast (Aventis Behring, Sussex, United Kingdom) and Tisseal or Tissucol (Baxter, Inc, Mississauga, Ontario). All patients underwent surgery with general or spinal anesthesia. The fistula tract was irrigated with hydrogen peroxide solution. Fibrin glue was inserted in the fistula tract by the external opening while the internal opening was closed with a suture or with a "blob" of instant solid glue. Surgical conventional treatment consisted of fistulotomy, placement of a cutting or loose latex seton and performing an advancement mucosal flap closure. All patients were followed up at 6 and 12 weeks; the longest follow up period was 6 months. The primary endpoint of the trial was the fistula healing.

EXCLUSION CRITERIA

The studies were excluded from the analysis if: 1) the outcomes of interest were not reported for both techniques, 2) it was impossible to extrapolate or calculate the necessary data from the published results, 3) there was considerable overlap between authors, centers, or patient cohorts evaluated in published literature. Moreover the studies in which fibrin glue was used in the flap repair of anal fistulas were also excluded from this review. An additional exclusion criteria was represented by rectovaginal and trauma anal fistulae.

ASSESSMENT OF THE METHODOLOGICAL QUALITY OF THE STUDIES

RC, ST and AB registered whether the Authors of the trials used a sample size calculation, or they made their analysis using an intention-to-treat method. The method-

logical quality of the trials was assessed independently by RC, ST and AS. The review authors followed the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions. Differences of opinion between the Authors' extracting data were solved by discussion. AB cooperated as arbitrator when different opinions persisted.

MEASURES OF TREATMENT EFFECT

Dichotomous data were analyzed for relative risk ratio (RR), odds ratio (OR), and the absolute results were measured with the risk differences. For these measures of effectiveness 95% CI (95% confidence interval) was calculated. The Mantel-Haenszel method was used for the meta-analysis. Results were presented on a forest plot graph.

ASSESSMENT OF HETEROGENEITY

Chi-squared test was used for heterogeneity assessment.

STATISTICAL ANALYSIS.

We used Review Manager 5 to conduct the meta-analysis.

Results

ELIGIBLE STUDIES

There are currently four RCTs¹⁶⁻¹⁹ and one CCT²⁰ with a large series of patients comparing conventional surgi-

cal treatment *versus* fibrin glue treatment in patients with perianal fistula. In two RCTs^{17,18} we found a considerable overlap between authors, centers, and patient cohorts. Greco's study is an abstract presented to the 2nd National Congress of Italian Society of Colorectal Surgery (SICCR) (Verona, Italy, 2007, 15-17 October), for this reason we excluded Greco's study from this systematic review, while Altomare's study is a recent article published on Colorectal Disease. Moreover a RCT in which fibrin glue was used in the flap repair of anal fistulas¹⁹ (Tables I-II) was also excluded.

RESULTS FROM ANALYSIS

The recurrence rate is higher, although not yet statistically significant, in those patients who underwent fibrin glue injection (44/81) versus conventional surgical treatment (108/230) (54.32% *vs* 46.95%) (OR: 0.44; 95 %CI: 0.12-1.68; *P*=0,23) (Fig. 1). In this analysis there is a relevant heterogeneity (Chi-square = 7.94 - *I*²=75%) (Fig. 1) and for the OR calculation we used the M-H Random test instead of the fixed one.

We performed a subgroup analysis for RCTs alone and one for patients with complex anal fistulas; for this reason we excluded the CCT of Chung and 13 simple anal fistulas treated by Lindsey. The results of the subgroup analysis of RCTs alone are not statistically significant and are similar to the previous results of RCTs and CCT (OR: 0.33; 95 %CI: 0.03-3.66; *P*=0,37) (Fig. 3). In this subgroup analysis there is a higher relevant heterogeneity (Chi-square = 6.78 - *I*²=85%) (Fig. 4).

The results of the subgroup analysis of RCTs alone with complex anal fistulae are not statistically significant and are similar to the previous results of all types of fistu-

TABLE I - Characteristics of the studies considered in this systematic review

Author/Year	Type of study	Patients	Treatment
Lindsey 2002 ¹⁶	RCT	13 simple anal fistulas (low anal fistulas) and 29 complex fistulas	23 fistulotomies <i>vs</i> 19 fibrin glue injections
Chung 2009 ²⁰	CCT	232 high trans-sphincteric anal fistulas	27 fistula plugs, 23 fibrin glue injections, 86 seton drains, 96 flap advancements
Altomare 2009 ¹⁸	RCT	64 trans-sphincteric anal fistola	25 cutting setons <i>vs</i> 39 fibrin glue injections

TABLE II - Characteristics of the studies excluded from this systematic review.

Author/Year	Type of study	Patients	Treatment
Greco 2007 ¹⁷	RCT	77 trans-sphincteric anal fistola	32 cutting setons <i>vs</i> 38 fibrin glue injections
Ellis 2006 ¹⁹	RCT	232 high trans-sphincteric anal fistulas	30 advancement flap repair alone <i>vs</i> 28 advancement flap repair with fibrin glue

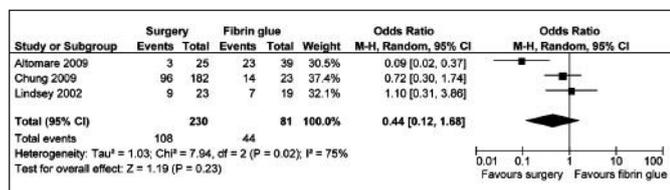


Fig. 1: Analysis of RCTs and CCT for recurrence of fistula-in-ano: conventional surgical treatment *versus* fibrin glue treatment in patients with anal fistula (Events: number of fistula-in-ano recurrence; Total: number of treated patients).

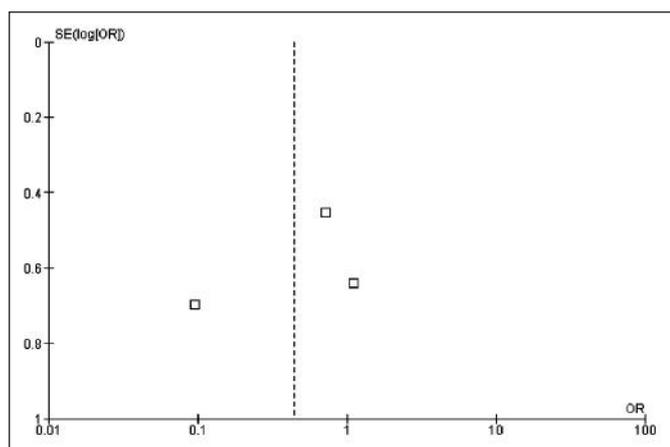


Fig. 2: Funnel plot of the analysis of RCTs and CCT for recurrence of fistula-in-ano: conventional surgical treatment *versus* fibrin glue treatment in patients with anal fistula.

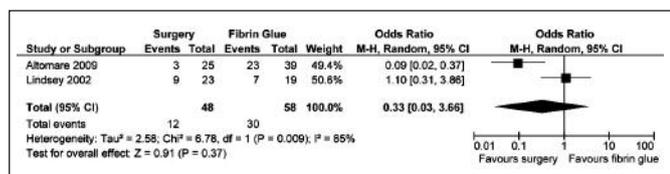


Fig. 3: Subgroup analysis of only RCTs for recurrence of fistula-in-ano: conventional surgical treatment *versus* fibrin glue treatment in patients with anal fistula (Events: number of fistula-in-ano recurrence; Total: number of treated patients).

lae (OR: 0.86; 95 %CI: 0.01-72.36; $P=0.95$) (Fig. 5). In this subgroup analysis we found a higher relevant heterogeneity (Chi-square = 13.60 - $I^2=93\%$) (Fig. 6). The analysis of post-operative anal incontinence showed only some cases of minor incontinence and no difference between the two groups: 9/230 in conventional surgical treatment group (3.91%) *versus* 10/81 in fibrin glue injection group (12.34%) (OR: 1.00; 95 %CI: 0.43-2.34; $P = 1.00$) (Fig. 7). In this analysis a very low heterogeneity was detected (Chi-square = 0.04 - $I^2=0\%$) (Fig. 8).

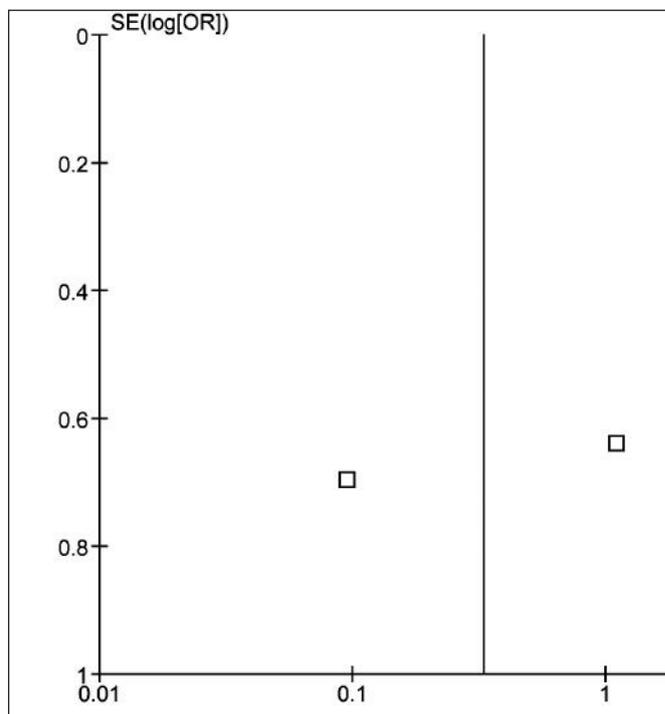


Fig. 4: Funnel plot of the subgroup analysis of only RCTs for recurrence of fistula-in-ano: conventional surgical treatment *versus* fibrin glue treatment in patients with anal fistula.

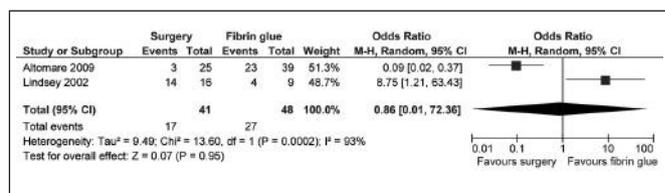


Fig. 5: Subgroup analysis of only RCTs with complex anal fistulas for recurrence of fistula-in-ano: conventional surgical treatment *versus* fibrin glue treatment in patients with anal fistula (Events: number of fistula-in-ano recurrence; Total: number of treated patients).

Discussion

In the last two decades new techniques such as fibrin glues and anal fistula plugs have been introduced as an alternative approach to surgery in the treatment of fistula-in-ano in order to lower the incidence of recurrence and post-operative fecal incontinence after surgery. Since the first report in 1991, fibrin glue injection has become increasingly used because it is simple and repeatable²¹; the success rate is improved by repeated injections and does not interfere or compromise subsequent surgical options²². Moreover the prolonged discomfort associated with wound dressing after surgery is avoided²³. The first published studies on the use of fibrin glue in the treatment of the anal fistulae^{24,25} reported very high healing rates but more recent trials do not evidence the same high rates for this technique^{26,27}.

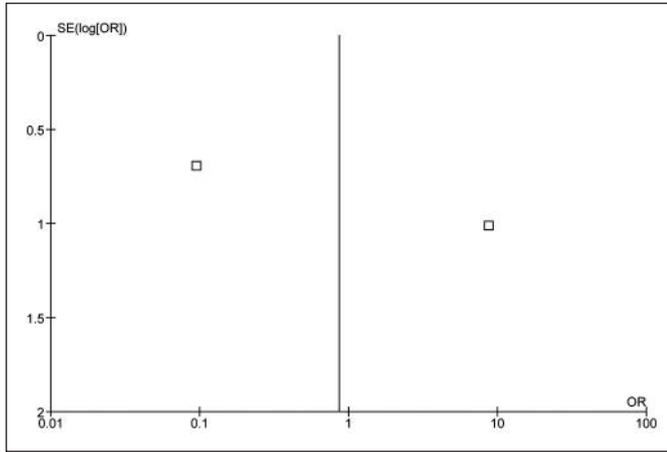


Fig. 6: Funnel plot of the subgroup analysis of only RCTs with complex anal fistulas for recurrence of fistula-in-ano: conventional surgical treatment versus fibrin glue treatment in patients with anal fistula.

Study or Subgroup	Surgery		Fibrin glue		Weight	Odds Ratio		Odds Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Allomare 2009	6	25	10	39	56.0%	0.92 [0.29, 2.94]			
Chung 2009	0	162	0	23		Not estimable			
Lindsey 2002	9	23	7	19	44.0%	1.10 [0.31, 3.86]			
Total (95% CI)		230		81	100.0%	1.00 [0.43, 2.34]			
Total events:		15							
Heterogeneity:		Chi ² = 0.04, df = 1 (P = 0.83); I ² = 0%							
Test for overall effect:		Z = 0.01 (P = 1.00)							

Fig. 7: Analysis of RCTs and CCT for incontinence: surgical treatment versus fibrin glue treatment in patients with anal fistula (Events: number of clinical incontinence; Total: number of treated patients).

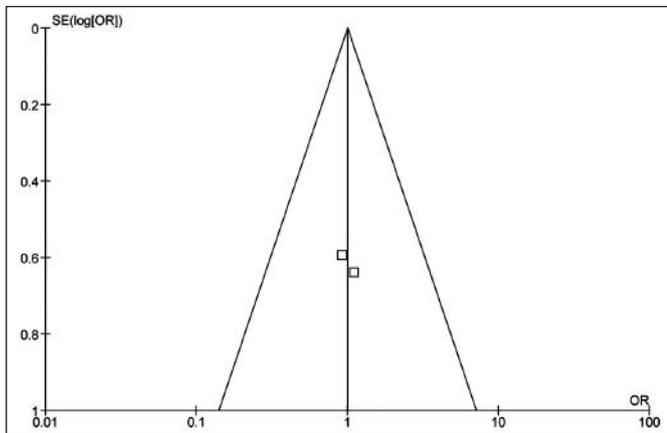


Fig. 8: Funnel plot of the analysis of RCT and CCT for incontinence: surgical treatment versus fibrin glue treatment in patients with anal fistula.

In a review of the literature²¹ the reported healing rates in patients with simple fistula treated with fibrin glue, ranged from 10% to 74%, with a mean of 50%. The importance of longer and more accurate follow-up evaluation in patients treated with fibrin glue was pointed out by different authors, in agreement with other studies in which recurrences were observed up to one

year later, being this the only way to demonstrate significant healing rates decreases.

A decrease in healing rate from 85%, 81%, and 77%, to 60%, 61%, and 14%, respectively, has been reported by other authors^{11,22,28} in patients with a long-term follow-up evaluation at 2 years. On the contrary, a higher healing rate ranging from 60% to 78%, was reported in studies dealing with simple fistulae, while those reporting exclusively complex fistulae showed lower success rates, ranging from 14% to 50%.

Shorter fistulae (<3.5 cm) tend to recur more often than longer fistulae (>3.5 cm), with rates of 54% versus 11%, respectively, due to the fact that shorter fistulae do not hold the glue as well as longer-tract fistulae do²⁹. Swinscoe *et al*²¹ confirmed this in their review.

However, most of the published studies were retrospective, while prospective ones were non-randomized clinical trials comparing fibrin glue injection with surgical approach.

The aim of our study was to compare the results of the surgical treatment versus fibrin glue treatment in patients with anal fistula. We could find only two RCTs¹⁷⁻¹⁸ and one CCT²⁰ in literature. The statistical analysis of these studies results does not show any statistically significant difference between fibrin glue treatment versus conventional surgical treatment for all fistulas-in-ano as far as concerns recurrence ($P=0.23$) and anal incontinence ($P=1.00$).

Our statistical analysis (RCTs + CCT or RCTs alone) does not confirm the poor long-term results in patients who underwent fibrin glue treatment rather than surgery. Surgical conventional treatment (fistulotomy, seton, flap advancement repair) does not show significant lower incidence of recurrence compared with fibrin glue treatment ($P=0.23$ for RCTs + CCT or $P=0.37$ only for RCTs). Similar results are present in the subgroup with complex anal fistulae ($P=0.95$); in these patients the fistula tract incorporates a significant portion of the sphincter muscles and the surgical treatment is a challenge for postoperative continence. Furthermore fibrin glue treatment did not show any advantage in terms of anal incontinence ($P=1.00$).

The analysis of the mean Wexner's score for incontinence is poor after surgical treatment (seton treatment) (1.79 to 5.1) ($P=0.0017$) versus fibrin glue treatment (0.66 to 0.49) ($P=0.07$); these data are supported by the results of anal manometry: mean pre and postoperative resting and squeezing anal pressure are significant poorer in the seton group (69 vs 62 mmHg, $P=0.0011$, and 120 vs 100 mmHg, $P=0.0043$, respectively) compared to fibrin glue treatment (75 vs 72 mmHg and 120 vs 120 mmHg, respectively)¹⁸. From these heterogeneous results, we not only need to compare the number of patients with incontinence, but also the mean of pre and after treatment Wexner's score for incontinence and the results of anal manometry (mean pre and postoperative resting and squeezing anal pressure). In the clinical practice, rou-

tine pre-operative manometry doesn't seem to have any predictive role in the occurrence of post-operative incontinence⁵, while it plays a very important role in this investigation. The main limitation of this trial is the low number of randomized patients, which does not allow to obtain significant statistical meta-analysis results. Other important limitations are the lack of radiological healing proven by a pelvic MRI and the absence of an adequate 6 month-follow up³⁰, stating that all recurrences after fibrin glue treatment appear within 3 months and only rarely after 6 months¹¹; in addition, the apparent closure of external skin wound does not always mean complete healing²⁸.

The results of the evaluation of the anal fistula plug seemed to be superior to fibrin glue not only because it eradicates the problem of slippage of the material from the fistula tract but also because of the supposed benefit derived from the activity of the plug as a good medium or matrix for human tissue regeneration.

Conclusion

In literature there are only three RCTs¹⁶⁻¹⁸ and one CCT²⁰ comparing surgical versus fibrin glue treatment in patients with anal fistula. Our statistical analysis does not show any significant statistical difference between the fibrin glue treatment versus conventional surgical treatment for all fistulas in ano in terms of recurrence ($P=0.23$) and anal incontinence ($P=1.00$). In the subgroup of complex anal fistulae, the results are similar between the two groups ($P=0.95$). However, the limited collected data do not support the use of fibrin glue and this review underlines the need of new RCTs with a higher number of patients, adequate follow-up and other secondary outcomes such as Wexner's score for incontinence and the results of anal manometry (mean pre and postoperative resting and squeezing anal pressure). It is important to note that there are only two available randomized controlled clinical trials comparing fibrin glue with the classic techniques^{17,18}. The advent of anal fistula plug seems to be superior to fibrin glue because it eradicates the problem of slippage of the material from the fistula tract³¹⁻³³. There is also the added benefit of the plug acting as a good bridging medium or matrix for human tissue regeneration. Definitive evidence of the advantages of the new technologies compared with traditional interventions relies on future randomized control studies to be conducted.

Competing interests

The Authors state that none of the authors involved in the manuscript preparation has any conflicts of interest towards the manuscript itself, neither financial nor moral conflicts. Besides, none of the authors received support

in the form of grants, equipment, and/or pharmaceutical items.

Riassunto

Molte tecniche chirurgiche sono state e vengono utilizzate per il trattamento delle fistole perianali. Ognuna di queste, tuttavia, si accompagna ad un certo rischio di complicanze post-operatorie: incontinenza anale (10-44%) e recidiva della fistola (0-14%). L'incidenza di queste complicanze dipende principalmente dalla complessità della fistola e dal tipo di tecnica chirurgica usata. Negli ultimi anni l'utilizzo della colla di fibrina per il trattamento delle fistole perianali è stata sempre più frequentemente utilizzata in alternativa alla chirurgia. Il trattamento con colla di fibrina ha diversi vantaggi rispetto alla chirurgia: non si associa ad importante dolore post-operatorio e, permettendo di risparmiare l'apparato sfinteriale anale, causa raramente incontinenza. Ai vantaggi sopra descritti vanno contrapposti gli svantaggi: le recidive, inizialmente molto basse, tendono poi ad aumentare con l'estensione del periodo del follow-up. Molti degli studi da cui derivano le evidenze sopra descritte sono retrospettivi o prospettici non randomizzati o includono soltanto delle piccole serie di pazienti. Altro elemento sfavorevole riscontrato in molti studi è la notevole eterogeneità, soprattutto nella tipologia di fistole trattate. Tali carenze hanno reso fino ad oggi di difficile interpretazione le reali potenzialità che questo presidio può avere nel trattamento delle fistole perianali. Lo scopo di questa metanalisi, è quello di confrontare, alla luce delle recenti pubblicazioni, i risultati ottenuti con il trattamento chirurgico versus quello con iniezione di colla di fibrina nel trattamento delle fistole perianali. RCT e CCT che comparano il trattamento chirurgico versus quello con colla di fibrina in pazienti con fistola perianale sono stati identificati e selezionati usando una strategia di ricerca predefinita. Per le analisi statistiche è stato utilizzato il programma Review Manager 5. Sono stati inclusi nella metanalisi due RCT per un totale di 106 pazienti (Altomare 2009, Lindsey 2002) ed un CCT per un totale di 223 pazienti (Chung 2009). Sono stati inclusi nell'analisi pazienti di età superiore o uguale ai 18 anni con fistole ad eziologia cripto ghiandolare o secondarie a Morbo di Crohn. La colla di fibrina utilizzata negli studi selezionati è quella presente nei kit commerciali (Beriplast o Tissel/Tissucol) e i trattamenti chirurgici consistono nella fistulotomia, applicazione di setone o "mucosal flap closure". Il periodo massimo di follow-up è stato di 6 mesi.

L'incontinenza anale post trattamento e i tassi di ricorrenza delle fistole dopo i due diversi approcci sono stati confrontati usando la metodologia proposta dal Cochrane Handbook for Systematic Reviews of Interventions. La carenza di omogeneità tra gli studi selezionati non ha permesso di valutare ulteriori outcomes.

I tassi di ricorrenza sono risultati elevati, anche se non statisticamente significanti, nei pazienti sottoposti ad iniezione di colla di fibrina (44/81) rispetto al trattamento chirurgico convenzionale (108/230), (OR: 0.44; 95 %CI: 0.12-1.68; $P=0,23$). La sub-metanalisi dei soli RCT non ha ugualmente dimostrato una significativa differenza rispetto all'analisi degli RCT più CCT per ciò che concerne la ricorrenza (OR: 0.33; 95 %CI: 0.03-3.66; $P=0,37$) così come quella degli RCT con fistole anali complesse rispetto a tutti i tipi di fistola (OR: 0.86; 95 %CI: 0.01-72.36; $P=0,95$).

L'analisi del tasso di incontinenza post operatoria non mostra differenze tra il gruppo di pazienti sottoposti ad iniezione di colla di fibrina (9/230) versus il gruppo di pazienti sottoposti ad intervento chirurgico (10/81), (OR: 1.00; 95 % CI: 0.43-2.34; $P = 1.00$).

La nostra metanalisi non mostra nessuna significativa differenza tra il trattamento con colla di fibrina e quello chirurgico convenzionale delle fistole perianali sia in termini di ricorrenza che di incontinenza anale post-operatoria. L'esiguità del campione in analisi impone la necessità di nuovi studi clinici randomizzati e soprattutto una valutazione post-trattamento per periodi di follow-up più lunghi in cui venga valutata anche la guarigione radiologica delle fistole e in cui l'incontinenza anale venga valutata pre e post operativamente con il Wexner's score e la manometria anale.

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