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Efficacy and Incontinence Rate of Biomaterials (Fibrin Glue and Fibrin Plug) in Comparison to Surgical Interventions in the Treatment of Perianal Fistula: A Systematic Review and Meta-analysis of Randomized, Controlled Trials

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Abstract: Anal fistula is an abnormal connection between the anal or rectal lumen and perianal skin that reduce quality of life. There are various surgical options for treatment with variable success rate. A novel treatment is to seal the fistula tract using biomaterials (fibrin glue and fibrin plug). Objective of this study was to evaluate the healing efficacy and incontinence rate of biomaterials (fibrin glue and fibrin plug) in comparison to surgical interventions in the treatment of cryptoglandular perianal fistula using meta-analysis of randomized controlled trials. PubMed, Scopus, Google Scholar and Web of Science were searched for clinical trial studies investigated the effects of biomaterials in the treatment of fistula-in-ano. Studies on patient with anal fistulae underwent fibrin glue, fibrin plug or other biomaterials application and surgical management for healing of fistula were included. Clinical response and incontinence were the key outcomes of interest. Six randomized placebo-controlled clinical trials consisting 315 patients in various arms met our criteria (comparing biomaterial with surgical interventions) and were included in the analysis. Pooling of data showed that effectiveness of biomaterials in comparison to surgical interventions was non-significant with relative risk (RR) of 0.73 (95% CI of 0.31-0.89, $p = 0.096$). The incontinence rate RR in biomaterials and intervention was also non significant with RR of 0.35 (95% CI = 0.05-2.28, $p = 0.27$). The included clinical trials had different follow-up durations, causes of fistula and method of intervention in treated patients. This meta-analysis demonstrates that the effectiveness and incontinence rate of biomaterials and conservative treatment is not significantly different.

Key words: Fistula, biomaterial, fibrin glue, fibrin plug, systematic review, meta-analysis

INTRODUCTION

Anal fistula is an abnormal communication between the anal or rectal lumen and perianal skin. It is common condition with profound negative impact on quality of life (Garcia-Aguilar *et al.*, 2000). From the pathophysiologic point of view, fistulas can be formed through different processes. According to the cryptoglandular hypothesis, it is believed that infection of the intersphincteric glands is the leading cause of anorectal fistula (Parks, 1961) but a variety of other conditions, such as trauma and neoplasia are also associated (Zmora *et al.*, 2003). In particular, Crohn's disease as a gastrointestinal inflammatory condition can cause fistulas which might

have resistance to conventional treatment (Rezaie *et al.*, 2005). Although several proposed Crohn's disease treatment modalities showed promising results (e.g., anti tumor necrosis factor), there are some with detrimental effects on fistula (e.g., corticosteroids) (Rezaie *et al.*, 2005; Nikfar *et al.*, 2011). For surgical treatment decision making, fistulas can be classified according to the level at which it transgresses the anal sphincter. Low transsphincteric fistulas involve the lower third of the external anal sphincter mechanism and are generally treated by fistulotomy with a high success rate for cure. In contrast, high transsphincteric fistulas involving the upper two thirds of the external sphincter remain a surgical challenge because incontinence will result from

the division of muscle involving more than one third of the sphincter (Chung *et al.*, 2009). There are various alternative surgical options for this latter type, namely, rectal advancement flap and seton drainage (Van Koperen *et al.*, 2008) but patients may complain of a prolonged healing period and major discomfort (Altomare *et al.*, 2011).

In the early 1990s, the treatment of perianal fistulae with autologous or commercial fibrin glue was suggested. This novel attractive approach uses the activation of thrombin to form a fibrin clot to mechanically seal the fistula tract. The clot undergoes gradual fibrinolysis while promoting tissue-healing processes to obliterate the fistula tract permanently (Aba-bai-ke-re *et al.*, 2010). Although this new therapy was promising at first, some drawbacks emerged. The liquid consistency of fibrin glue is not ideal for the purpose of closing anorectal fistulas, because it is easily extruded from the fistula tract during, for example, coughing and straining (Johnson *et al.*, 2006). To address these problems, fibrin plug as an alternative strategy to obliterate the fistula tract was developed. The plug material has inherent resistance to infection (Aba-bai-ke-re *et al.*, 2010), does not produce a foreign body reaction and becomes repopulated by its own tissue in a period of about 3 months (Van Koperen *et al.*, 2011).

In this systematic review, we used meta-analysis to study surgery and biomaterials that are used for the management of fistula and rate of incontinence.

MATERIALS AND METHODS

Data sources: PubMed, Scopus, Google Scholar and Web of Science were searched for studies that investigated efficacy of fibrin glue and fibrin plug in treatment of fistulas. Data were collected from 1966 to June 2012. The search terms were: “fistula”, “perianal fistula”, “fibrin glue”, “fibrin plug” and “fibrin sealant”. The search was restricted to English literature. Reference lists of the retrieved articles were also reviewed for additional applicable studies. Randomized controlled clinical trials comparing the fibrin glue, fibrin plug or other biomaterials with surgical management for healing of fistula were taken into consideration. The Crohn’s disease fistulas and

those caused by other causes such as trauma and post-operation were excluded. The title and abstract of each article was reviewed to eliminate duplicates, reviews, case studies and uncontrolled trials. Data were extracted in terms of patients’ characteristics, incontinence and treatment outcome.

Study selection: All controlled clinical trials that investigated the effect of biomaterials (fibrin glue and fibrin plug) on perianal fistula were considered. Response of fistula to the agent and its incontinence rate were the key outcomes of interest. The response is defined as complete closure.

Studies and abstracts that were presented at meetings were also considered. Two reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies, uncontrolled trials, trials did not have desired outcomes and trials published in languages other than English. Reviewers independently extracted data on type of study, therapeutic regimens, time of exposure and outcome measures. Disagreements were resolved by consensus.

Assessment of trial quality: Jadad score, which indicates the quality of the studies based on their description of randomization, blinding and dropouts (withdrawals) was used to assess the methodological quality of trials (Jadad, 1998) (Table 1). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis: Data from selected studies were extracted in the form of 2x2s by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using StatsDirect software version 2.7.8. Standardized effect size and 95% confidence intervals (95% CI) were calculated using Der Simonian-Laird (for random effects) method. The Cochran Q test was used to test heterogeneity and $p < 0.05$ considered significant. In case of heterogeneity or including too few studies in analysis, the random effects model was used. Funnel plot was used as publication bias indicator.

Table 1: Jadad quality score of randomized controlled trial included in the meta-analysis

Study	Randomized	Blinding	Withdrawal described	Total
Lindsey <i>et al.</i> (2002)	2	0	1	3
Ortiz <i>et al.</i> (2009)	2	0	1	3
Van Koperen <i>et al.</i> (2011)	2	2	1	5
Van der Hagen <i>et al.</i> (2011)	2	0	1	3
Aba-bai-ke-re <i>et al.</i> (2010)	2	1	1	4
Altomare <i>et al.</i> (2011)	2	0	1	3

RESULTS

We reviewed 8862 abstract and titles (Fig. 1), of which, 8846 were excluded on the basis of title and abstract irrelevancy or duplication. Therefore, 16 studies were scrutinized in full text, of which, 6 (Lindsey *et al.*, 2002; Ortiz *et al.*, 2009; Aba-bai-ke-re *et al.*, 2010; Altomare *et al.*, 2011; Van der Hagen *et al.*, 2011; Van Koperen *et al.*, 2011) were considered eligible and met inclusion criteria for systematic review and were included in meta-analysis. Of excluded studies, one was retrospective, one studied enterocutaneous fistulas, one studied Crohn's disease fistulas and seven had no applicable results (different types of glue, comparing glue with plug, studying surgery with and without glue). The incontinence has been assessed with different scoring systems. The quality of eligible studies was assessed by Jadad score (Jadad, 1998). Four (Lindsey *et al.*, 2002; Ortiz *et al.*, 2009; Altomare *et al.*, 2011; Van der Hagen *et al.*, 2011) out of 6 studies received Jadad score 3. One study received Jadad score of 4 (Aba-bai-ke-re *et al.*, 2010) and one 5 (Van Koperen *et al.*, 2011) (Table 1).

The included trials covered 163 patients for biomaterial arm and 152 patients for surgical interventions. The data on patients' characteristics, type of biomaterial, follow up duration, incontinence rate measuring tool, successful treatment definition and the type of intervention on the other arms of treatment and outcomes of interest are shown in Table 2-4.

Effect of biomaterials in comparison to surgical interventions in treatment of anal fistulae:

The summary for Relative Risk (RR) of efficacy of biomaterials in comparison to surgical interventions in patients with anal fistulae for six included trials (Lindsey *et al.*, 2002; Ortiz *et al.*, 2009; Aba-bai-ke-re *et al.*, 2010; Altomare *et al.*, 2011; Van der Hagen *et al.*, 2011; Van Koperen *et al.*, 2011) was 0.73 with 95% CI = 0.31-0.89, non-significant RR (p = 0.096, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 2b) and could not be combined, thus the random effects for individual and summary of effect size for RR was applied (Table 3). Regression of normalized effect vs. precision for all included studies for RR of efficacy in patients with anal fistulae among biomaterials vs. surgical interventions was -3.43 (95% CI = -8.16 to 1.3, p = 0.12) and Kendall's test on standardized effect versus variance indicated tau = -0.2, P= 0.47 (Fig. 2c).

Incontinence after treatment with biomaterials in comparison to surgical interventions in patient with anal fistulae:

In Table 4, the summary for Relative Risk (RR) of incontinence after treatment with biomaterials in comparison to other surgical interventions in patients with anal fistulae for two included trials (Aba-bai-ke-re *et al.*, 2010; Van der Hagen *et al.*, 2011) was 0.35 with 95% CI = 0.05-2.28, a non-significant RR (p = 0.27, Fig. 3a). Cochrane Q test for heterogeneity indicated that the studies are not heterogenous

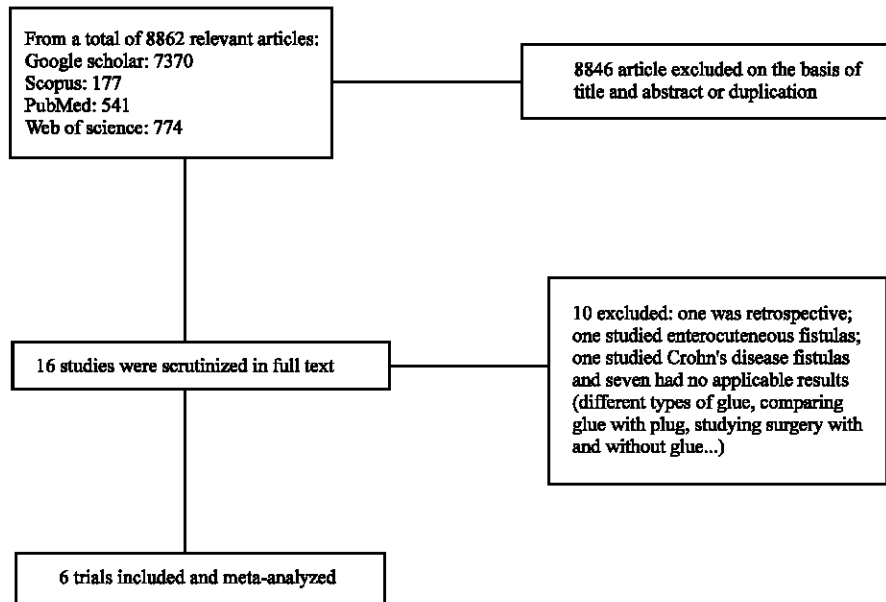


Fig. 1: Flow diagram of the study selection process

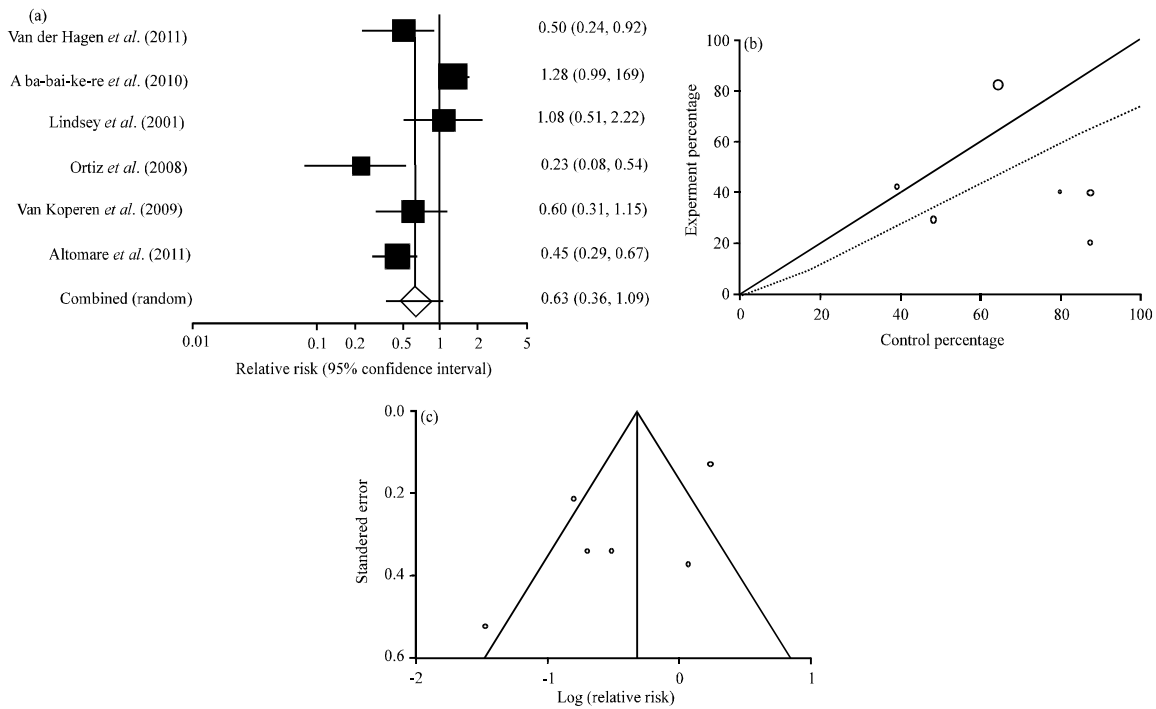


Fig. 2(a-c): (a) Individual and pooled relative risks, (b) Heterogeneity indicators and (c) Publication bias indicators for efficacy in the studies considering biomaterials comparing to surgical interventions in patients with anal fistulae

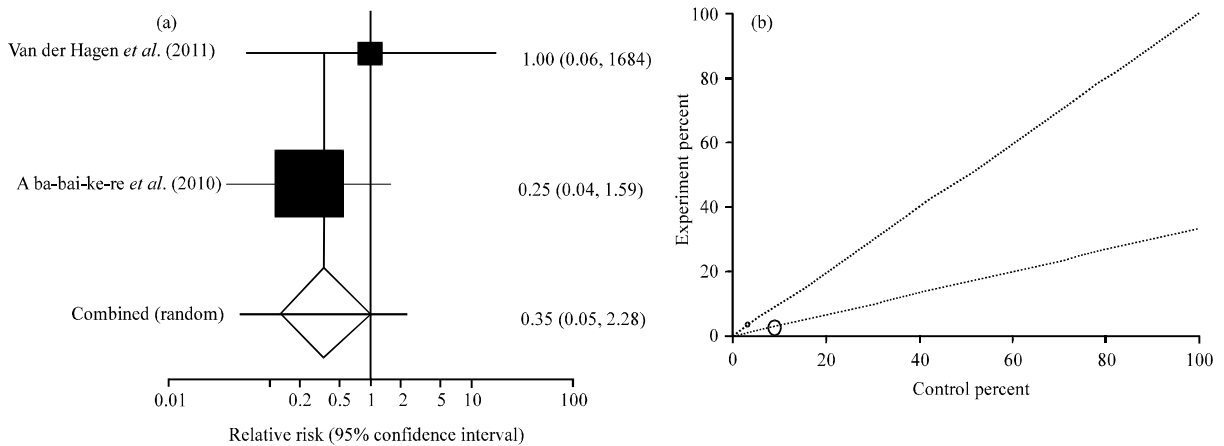


Fig. 3(a-b): (a) Individual and pooled relative risks for the outcome of “incontinence” and (b) Heterogeneity indicators for the outcome of “incontinence” in the studies considering biomaterials comparing to surgical interventions in patients with anal fistulae

($p = 0.54$, Fig. 3b) and could be combined but because of too few included studies, the random effects for individual and summary of effect size for RR was applied. Regression of normalized effect vs. precision for all included studies for RR of incontinence due to treatment in patients with anal fistulae among biomaterials vs. surgical interventions could not be calculated because of too few strata.

DISCUSSION

The results of this meta-analysis indicate that biomaterials are not more effective than conventional surgical therapies in treating fistulas. Study results for incontinence in biomaterials vs. interventional treatment can be pooled in two studies (Aba-bai-ke-re *et al.*, 2010;

Table 2: Characteristics of studies included in the meta-analysis

Study	Biomaterial	Control group	Comment	Trial follow up duration	Successful treatment definition	Incontinence measuring
Lindsey <i>et al.</i> (2002)	Glue (Beriplast®, Aventis Behring, Sussex, UK)	Fistulotomy, seton and flap	Data on continence extracted on 12th week. Rectovaginal fistulas are excluded	12 weeks	Complete cessation of fistula discharge	Cleveland Clinic incontinence questionnaire
Ortiz <i>et al.</i> (2009)	Lyophilized porcine submucosal plugs (Surgisis®)	Endorectal anal flap	Plug as the biomaterial. Anovaginal or rectourethral fistulas and Crohn's fistulas are excluded	12 months	Absence of abscess arising in the area and no obvious evidence of fistulation	Not studied
Van Koperen <i>et al.</i> (2011)	Lyophilized porcine submucosal plugs (Surgisis®)	Mucosal advancement flap	Plug as the biomaterial. One complication in each group. Crohn's fistulas are excluded.	12 months	Fistula closure	Colorectal functional outcome (COREFO), Wexner and Vaizey scales
Van der Hagen <i>et al.</i> (2011)	Glue	Advancement flap	All patients had seton for 3 months before study. Data for effectiveness of the biomaterial extracted after the primary glue. Rectovaginal and Crohn's fistulas are excluded. Two patients with incontinence healed by surgery and three in biomaterial group	3 months for healing rate (and 12 months for incontinence)	No drainage of the previous external opening with and without finger compression and when the external fistula orifice(s) was healed and asymptomatic	Vaizey scales
Aba-bai-ke-re <i>et al.</i> (2010)	Plug (acellular dermal matrix) (J. Y. ®)	Endorectal anal flap	Plug as the biomaterial. Complex and Crohn's fistulas are excluded.	5 months	Closure of all external openings, absence of drainage without further intervention and no abscess formation	Vaizey scales
Altomare <i>et al.</i> (2011)	Glue (Tissucol®)	Seton	Data for effectiveness of the biomaterial extracted after the primary glue (8 months). Complex and Crohn's fistulas are excluded	12 months	Complete cicatrization of the fistula and the absence of any clinical signs of perianal sepsis after at least 1 year	Wexner's grading scale

Table 3: Outcomes of clinical trials for surgical Interventions vs. Biomaterials.

Study	Successful treatment rate	
	Interventions	Biomaterials
Van der Hagen <i>et al.</i> (2011)	12/15 (80%)	6/15 (40%)
Aba-bai-ke-re <i>et al.</i> (2010)	29/45 (64.44%)	37/45 (82.22%)
Lindsey <i>et al.</i> (2002)	9/23 (39.13%)	8/19 (42%)
Ortiz <i>et al.</i> (2009)	14/16 (87.5%)	3/15 (20%)
Van Koperen <i>et al.</i> (2011)	14/29 (48.28%)	9/31 (29.03%)
Altomare <i>et al.</i> (2011)	21/24 (87.5%)	15/38 (39.47%)

Table 4: Outcomes of clinical trials on incontinence.

Study	Incontinence rate	
	Interventions	Biomaterials
Van der Hagen <i>et al.</i> (2011)	0/15 (0%)	0/15 (0%)
Aba-bai-ke-re <i>et al.</i> (2010)	4/45 (8.89%)	1/45 (2.22%)

Van der Hagen *et al.*, 2011) and the other studies have not reported the results in number of patient. The two studies were homogenous and showed that although incontinence rate was higher in interventional-treated patients in comparison to biomaterials, no significant difference was observed.

Whatever the cause, fistula is one of the challenging parts of proctology. Some studies have shown that although surgery in problematic in Crohn's disease related fistulas, there are effective medical treatments (e.g., broad spectrum antibiotics, immunomodulators, anti-inflammatory agents) which target disease complex

pathologic pathways (Rezaie *et al.*, 2006; Rahimi *et al.*, 2006, 2007; Nikfar *et al.*, 2010). In contrast, surgery has been remained the mainstay of treatment in most of other types of fistulas. In evolution of surgical techniques, incontinence after cutting Seton and fistulotomy, especially in high perianal fistulas, led to the development of more sphincter-conserving techniques, which include fistulectomy, advancement flaps and the use of loose Setons (Buchanan *et al.*, 2003). Even these new techniques carry a risk of incontinence, although much lower in the hands of skillful surgeon. Fibrin glue has been used in surgery for several years, but recently, glue

and its new alternative, fibrin plug have been used to treat perineal fistulas, with variable rates of success. Initial enthusiasm because of short-term success rate after this new treatment had been tampered by delayed fistula recurrence which has even occurred after skin healing (Buchanan *et al.*, 2003). Although there are meta-analyses studying the effect of fibrin glues and plugs in fistula (Cirocchi *et al.*, 2009, 2010; Garg, 2009; O'Riordan *et al.*, 2012), this is the first meta-analysis that reports the efficacy and incontinence rate of biomaterials (including fibrin glue and fibrin plug) in comparison to surgical interventions in randomized controlled trials.

In the recent years, biomaterials have been studied extensively. While some studies found fibrin glues and plug ineffective in comparison to conventional treatments (Ortiz *et al.*, 2009; Altomare *et al.*, 2011; Van der Hagen *et al.*, 2011; Van Koperen *et al.*, 2011), there are others indicating its effectiveness (Aba-bai-ke-re *et al.*, 2010). Some studies have found that the type of fistulas might be important in success rate. In study of Lindsey *et al.* (2002), fibrin glue was effective in complex fistula but not in simple ones. In four studies, the biomaterials were not effective in high, complex, or trans-sphincter fistulas (Ortiz *et al.*, 2009; Altomare *et al.*, 2011; Van der Hagen *et al.*, 2011; Van Koperen *et al.*, 2011) compared to the interventional treatment. In contrast, in one study (Aba-bai-ke-re *et al.*, 2010) it has well healing effect on aforementioned type of fistula. Some other studies have been focused on biomaterial effectiveness in combination to other treatment modalities. Ellis and Clark (2006) used fibrin glue as an adjunct to flap repair but failed to show any significant different. In another study, Singer and colleagues (Singer *et al.*, 2005) state that adding antibiotics to the biomaterials is not recommended. In one new study, Garcia-Olmo *et al.* (2009) compared fibrin glue with fibrin glue plus 20 million expanded adipose-derived stem cells and found promising results from latter study group with about four times increase in healing rate.

As a limitation of this meta-analysis, the included clinical trials had different follow-up durations, causes of fistula and method of intervention in treated patients. All of aforementioned limitations were inevitable because every study has its own inclusion and exclusion criteria and protocol. A fair criticism of this study is extracting the results of first fibrin glue application in studies which the reglue outcomes were also available. This was done in order to make the outcome similar to the other studies for which, according to protocol, the study ended after the first fibrin glue treatment.

CONCLUSION

In conclusion, the results of this systematic review showed that, from the point of view of effectiveness and incontinence rate, there is no significant different in biomaterials and conventional surgical interventions in fistulas. But the easier application in outpatient clinic, risk of viral transmission (although very low), risk of biomaterials extrusion and relatively high economic impact of biomaterials should be considered when making decision for selecting proper treatment modality. In addition, although there were no significant different in the incontinence rate, further clinical trials are needed for more accurate results.

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