

Original Article

Minimally invasive surgical management of complex anorectal fistula with biological plug: a meta-analysis

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Abstract: The ideal modality of complex anorectal fistula treatment usually has the merit of low recurrence rate, minimal incontinence, and improvement of patients' quality of life. The aim of this research is to provide a systematic review of the surgical management of complex anorectal fistula repaired with a biological plug. The related studies, including randomized controlled trials, controlled clinical trials, and observational studies collected in PubMed, Medline, Scopus, EmBase, Cochrane library, Springer link, Web of Science, and Medline databases from January 1995 to October 2015 were evaluated carefully. One thousand sixty-four cases of higher and lower complex anorectal fistula were analyzed. A literature research showed that a total of 96 full-text publications resulted from the related studies, among which 30 studies with 1,064 patients were tabulated in the qualitative and quantitative synthesis. The fistula closure rate of the procedure in these studies is 55.6% (confidence of interval range 51.9%-59.2%), whereas the recurrence rate is 43% (CI, 38.7-47.3%). The abscess formation rate is 7.8% (CI, 5.7-10.5%). Meanwhile, the extrusion rate of the plug is 13.6% (CI, 11-16.9%). Fistula closure is achieved by using the anal fistula plug in approximately 55.6% of patients with complex anal fistula. Further randomized, controlled, multicenter, double-blinded, clinical trials studying objective parameters of fistula healing are still needed to substantiate these findings. Standardized plug insertion technique and fixed perioperative parameters are also necessary.

Keywords: Fistula-in-ano, anal fistula plug, review, recurrence, complex

Introduction

Fistula-in-ano is an old and common disorder in general surgery. A simple laying-open procedure is effective for simple or low fistula. However, it also presents as a surgical hazard because of the high recurrence rate and risk of incontinence that may occur, especially in patients with a complex or higher, multiple-tract fistula. Surgery was considered a radical treatment of the disease. Although a broad spectrum of modalities has now been applied to clinical practice, it still needs to be standardized. The main purpose of management is to eradicate the internal and external opening with anorectal continence. Numerous surgical procedures, including fistulotomy, seton cutting procedure, and endoanal advancement, are reported as alternative therapeutic methods; nevertheless, conclusive information on the efficacy of the treatment and short- and long-term complications are still lacking. Some treatment methods may cause sphincter damage, fecal incontinence, or recurrence. According to some reports, cutting seton could reach a higher healing rate, from 80% to 100%. However, the concomitant fecal incontinence rate may rise as high as 60% [1-3].

Fistulotomy has been shown to be effective in 75% to 100% of patients, but it accompanies a 60% rate of incontinence, especially in complex fistulae [4-6]. Fistulotomy is now considered an improper option when the fistula tract incorporates a significant amount of the internal and external anal sphincter, as in many cases of high, complex, trans-sphincter fistulae [7, 8]. The mucosal advancement procedure is the best-established alternative method to fistulotomy, with reported success rates ranging from 37% to 89% [9, 11] and incontinence rates from 9% to 21% [9, 10] in experienced hands. The fibrin glue injection method presents a minimally invasive approach with a relatively high long-term recurrence rate of 69% to 100% [12-14].

To date, none of the single procedures can be considered a perfect standard, and for this rea-

son, a variety of novel surgical methods have been introduced that aim to improve efficacy. The biological plug can either be extracted from small intestinal mucosa in animals or completely synthesized. The application of a biological plug is now considered less invasive and to have a high success rate. Moreover, it is reproducible and easy to practice, thus requiring a short learning curve. High cost, extrusion, and antixenic reaction are among the disadvantages of biological plug practice. Several systematic reviews have been reported. However, they are less informative in terms of number of articles, content of sample, and type of the plugs. Therefore, in this systematic review, the published literature was comprehensively evaluated, focusing on the effectiveness and safety of the AFP plug in patients who have anal fistula.

Materials and methods

Study selection and data collection process

PRISMA statement guidelines were strictly followed in producing this systematic review [15]. The PICOS scheme was followed for reporting inclusion criteria. The articles published from January 1995 to October 2015 in PubMed, Medline, Scopus, EmBase, Cochrane library, Springer link, Web of Science, and Medline were searched by using such searching phrases as “controlled trials”, “controlled clinical trials”, “randomized”, “nonrandomized”, “anal fistula”, “fistula-in-ano”, “anal fistula plug”, “fistula plug”, “fistulotomy”, “fistulectomy”; “advancement procedure” and “seton”, etc. Only peer-reviewed articles were taken into consideration. Randomized, controlled trials, controlled clinical trials, and observational studies were included, too. No language or publication status restrictions were imposed. Patients from both genders, 18 years or older, with cryptoglandular and Crohn’s anal fistula were enrolled in this systematic review. Titles or abstracts of all identified studies were independently assessed. Full-text articles of potentially relevant studies were obtained for study. Disagreements were solved through discussion. Characteristics of trial participants, the inclusion and exclusion criteria for trials, type of intervention, and type of results were measured carefully.

Definition of fistula in ano

All patients who enrolled in this study were diagnosed with complex or trans-sphincter fistula. A fistula was defined as complex when it

occurred in high [supra-sphincter, extra-sphincter, or high trans-sphincter (track crosses > 30% to 50% of the external sphincter)] and anterior position in a female, with multiple tracts, or the patient suffered from preexisting incontinence, local irradiation, or Crohn’s disease. Fistulae with multiple tracts were defined as fistulae with single primary and multiple secondary openings. Plug extrusion was defined as the falling out of partial or complete plug in the postoperative period. Surgical success was achieved when clinical healing of the fistula in the anal tract occurred. In the case of multiple tracts, the procedure was considered successful only if all the tracts were clinically closed. The systematic review of all patients who underwent plug treatment for complex anal fistulae between January 1995 to October 2015 was undertaken. Fistulae were classified as simple or complex based on the previously described classification. Simple fistulae are defined as cryptoglandular and single-tract fistulae with no history of Crohn’s disease, whereas complex fistulae included high trans-sphincter fistulae-in-ano, recto-vaginal, horseshoe, multiple-tract fistulae, and supra-sphincter and recurrent fistulae in which conventional surgical techniques may impair patients’ continence.

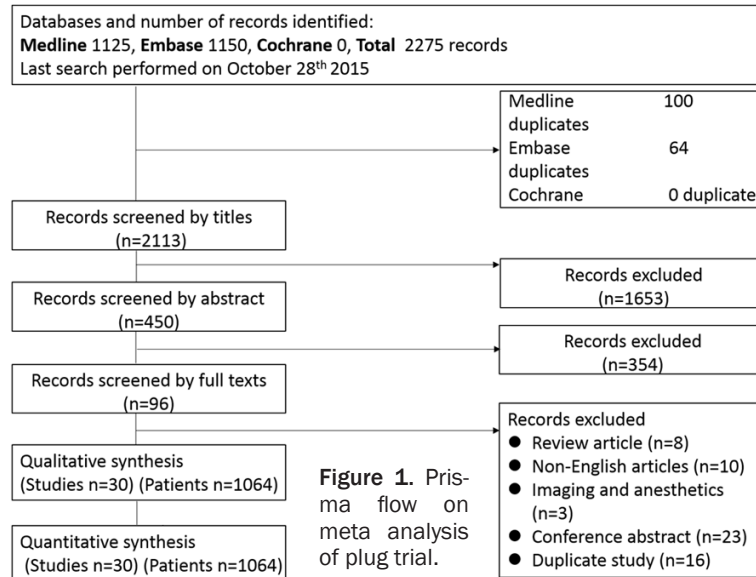
Inclusion and exclusion criteria

All randomized, nonrandomized controlled, non-controlled clinical trials focusing on AFP or comparing AFP with other treatment methods for anal fistulae with outcome report were included in this systematic review. Repeated AFP plug insertion, combined therapy using AFP plug, or other treatments were excluded. Abstracts, letters, case reports, comments, and conference proceedings were not included in this systematic review. Studies of recto-vaginal fistula treated by AFP were also excluded from this meta-analysis. Studies were excluded from this systematic analysis if the results of the treatments were not reported or it was impossible to calculate these from the published results. Trials comparing surgery (fistulotomy, advancement mucosal closure, and placement of seton) to fibrin treatment, anal fistula plug (AFP), or acellular dermal matrix (ADM) were also analyzed.

Data extraction and result measurement

Detailed information on the enrolled subjects, type of the fistulae (single or multiple), underlying

Meta analysis of plug trial



ing disease (Crohn's disease), time of surgery, success rate, recurrence rate, plug extrusion rate, abscess formation rate, and incontinence rate were carefully collected and written into an Excel file, then tabulated into different categories. The data were analyzed and assessed separately by different reviewers to avoid mistakes and deviations. The names of the authors were not revealed. Any discrepancies were sorted out for discussions until the reviewers reached consensus. All data and results of statistical tests were extracted from the papers and entered in a data sheet for particular and specific evaluation. If the data was not specifically recorded or reported, it was regarded as missing or not reported, and no assumptions were made regarding the missing data. The fistula closure rate of the AFP procedure in fistula-in-ano was taken as the primary index for measurement of the curative effect. The secondary measurements were the recurrence rate, the plug extrusion rate, and abscess formation/sepsis rate, but analysis of some variables was not accurate due to the lack of a standard reporting format and high-quality data. These variables included the impact of seton insertion before the plug procedure, role of antibiotics, the effect of the procedure on incontinence, objective pain assessment after the procedure, and the efficacy of multiple plug procedures in the same patient. Successful treatment was defined as clinical healing of the fistula in the anal tract. In patients with multiple tracts, the procedure was considered successful only if all the tracts were closed.

Statistical analysis

Statistical analysis was performed in line with recommendations from the PRISMA statement and the Cochrane Handbook for systematic reviews. Data were presented in parametric and nonparametric pattern, depending on their presentation in the original publications. The Comprehensive Meta-Analysis software was used to generate the meta-analysis and forest plots by using a random effects model. Statistical analysis for categorical variables was performed by using the odds ratio (OR) as the summary

statistic. This ratio represents the odds of an adverse event occurring in a fistula plug or acellular dermal matrix group compared with the surgery (fistulotomy, advancement mucosal closure, and placement of seton) group.

Results

A total of 30 independent studies focusing on the anal fistula plug was retrieved (**Figure 2**), and the general information was tabulated (**Table 1**). Two randomized, controlled trials comparing AFP with any other treatment modality were found. Literature research resulted in a total of 96 full-text publications (**Figure 1**). Sixty studies, including 29 conference abstracts, 16 duplicate studies, 10 non-English publications, six review articles, and three technical communications were excluded. Thirty studies [16-46], with 1,064 patients, were assessed in a qualitative and quantitative synthesis. Among the reported 30 publications with 1,064 patients, the study types of reported articles included randomized/nonrandomized and controlled/non-controlled clinical trial and prospective study (**Table 1**). Patients were carefully screened for double reporting, and quantitative synthesis/meta-analysis was performed. Papers were tabulated in a qualitative synthesis and categorized into levels of evidence in accordance with the definition provided by the Centre of Evidence in Medicine at Oxford. The result showed that the fistula closure rate of the procedure in reported studies is 55.6% (CI 51.9%-59.2%). In contrast, the recurrence rate is 43%

Meta-analysis of Post-operative Extrusion Rate

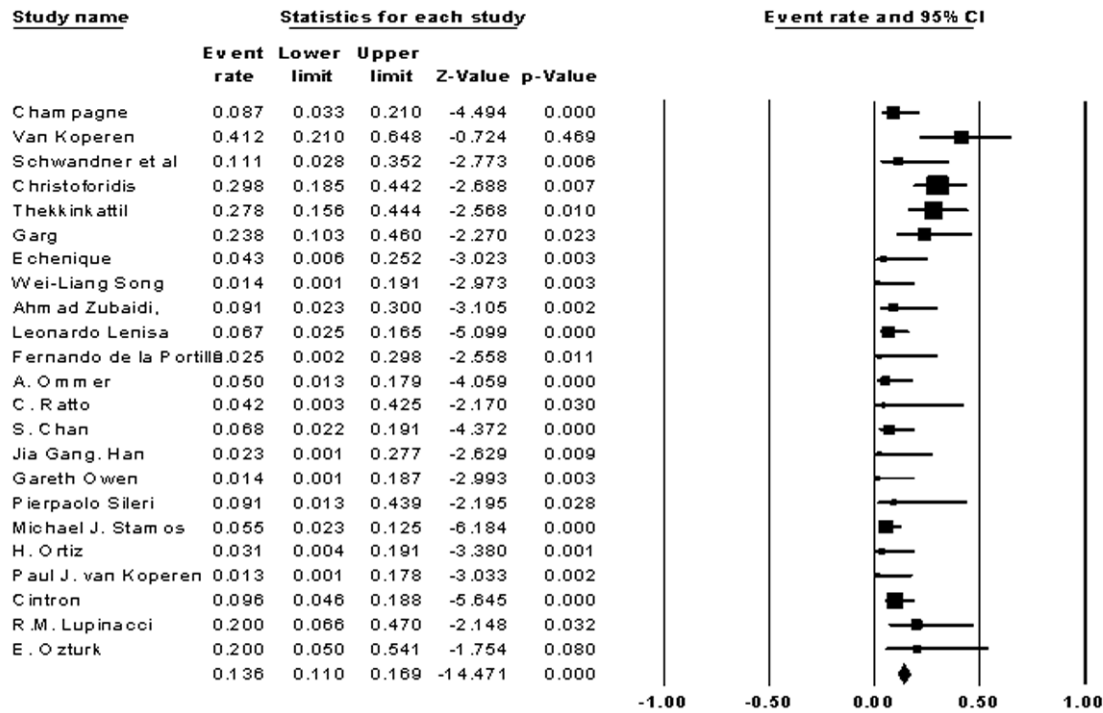


Figure 2. Meta analysis of postoperative extrusion rate of plug study.

(CI, 38.7-47.3%). The abscess formation rate is 7.8% (CI, 5.7-10.5%). Meanwhile, the plug extrusion rate is 13.6% (CI, 11-16.9%) (Figures 2-5). All patients underwent seton insertion drainage before plug surgery.

The median follow-up in these studies was 20.1 month, with the longest follow-up 93 months (Table 1). The baseline characteristics of patients were different in these studies. In addition, there was imbalance in surgical characteristics (learning curve, preoperative bowel preparation, use of prophylactic antibiotics, and standard plug operative techniques), which affected the success rate in different treatments. The reasons for the assumed risk (e.g., the median control group risk across studies) are provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). In addition, we searched six related meta-analyses or systematic reviews [47-52] about the anorectal fistula plug compared with other treatments. In these meta-analyses, the fistula closure rates of the AFP plug vary consid-

erably from 14% to 96%; four of these systematic reviews did not accord with the PRISMA statement.

Discussion

Fistula-in-ano is a common disorder in many people. Management of a complex anorectal fistula is challenging because both internal and external sphincters are involved in the fistula tract, and fecal continence could be impaired after surgery. Although fistulotomy is a simple procedure, and its efficacy is reported as high as 39%-75% [3-6], it is not recommended for trans-sphincter fistulae due to the high risk of postoperative incontinence. Various surgical approaches, such as the endo-rectal advancement procedure, loose-seton placement, and fibrin installation, have been applied to the management of complex anorectal fistulae. However, the recurrence rate and the risk of postoperative fecal incontinence of these procedures were extremely high.

Recently, a biological anal fistula is becoming an attractive surgical option for anorectal fistu-

Meta analysis of plug trial

Table 1. Characteristics of the included studies

Author's	Year of study	Type of study	Follow-up in months (range), Patients followed up (in %), Method of follow-up	Success/ Total patients	Sex M/F	No. of patients with Comple x fistula	No. of patients with Crohn's Disease	No. of Fistulas with multiple tracts	No. of Recurrent fistula	Extru- sion No. (%)	Ab- scess/ Sepsis No. (%)	Inconti- nence	Methodology assess- ment (Pre-op seton insertion, bowel prepara- tion, operative position, anesthesia, duration of admission)
1. Johnson et al [16]	2006	PCT	3.5 (3-4), 100%, C	13/15	11/4	15	0	6	NR	NR	NR	Improved	MBP, PJK, GA,
2. O'Connor et al [17]	2006	PS	10 (3-24), 100%, C	16/20	NR	20	20	7	NR	NR	NR	Improved	PSI (11/36 Tr), MBP, PJK, GA
3. Champagne et al [18]	2006	PS	12 (6-24), 100%, C+T	38/46	NR	46	0	7	NR	4 (9)	NR	Improved	PSI (9/55 Tr), MBP, PJK, GA
4. Ellis [19]	2007	RCS	6 (3-11), 100%, C+T	12/13	12/1	NR	0	NR	NR	NR	NR	Improved	PJK, LR or GA, DC
5. Van Koperen et al [20]	2007	PS	7 (3-9), 100%, C	7/17	12/5	17	1	1	12	7 (41)	NR	Improved	BE, L, LR or GA, DC
6. Schwandner et al [21]	2008	PS	9 (7-11), 95%, C	11/18	10/8	11	7	0	NR	2 (11)	NR	Improved	PSI (16/19 Pt) BE, L, LR or GA
7. Ky et al [22]	2008	PS	6.5 (3-13), 98%, C+T	24/44	27/17	20	14	10	8	NR	NR	Improved	BE, L, GA
8. Lawes et al [23]	2008	RCS	7.4 (NR), 100%	4/17	NR	NR	NR	NR	NR	NR	5 (29)	Improved	PJK, GA
9. Christoforidis [24]	2008	RCS	5 (1-11), 100%, C+T+MRR	18/47	26/21	NR	3	NR	NR	14 (22)	2 (4)	Improved	PSI (49/64 Tr), MBP-6, BE-41, PJK, LA or GA
10. Thekkinkattil [25]	2008	PS	11 (3-18), 100%, C	18/36	NR	36	NR	5	NR	10 (23)	NR	Improved	PSI (NR), BE, L, GA
11. Garg [26]	2008	PS	9 (6-18), 91%, C+T	15/21	20/1	21	0	8	14	5 (24)	1 (5)	Improved	L, LR
12. Echenique [27]	2008	RCS	10 (5-36), 100%, MRR	14/23	14/9	5	0	1	NR	1 (4)	3 (13)	Improved	PSI (18/23), MBP, PJK, SA
13. Wei-Liang Song [28]	2008	PS	34 (7-14 d), 100%	34/34	19/11	2	0	2	0	0	0	0	MBP
14. M. Adamina [29]	2014	PS	46 (4.8-68.4), 100%, C+T	46/46	30/16	19	0	19	26	NR	0	Improved	PSI
15. Ahmad Zubaidi [30]	2008	PS	22 (6-18), 100%, C	19/22	20/2	10	2	10	0	2	0	NR	PSI
16. Leonardo Lenisa [31]	2010	PS	60 (2-34), 100%, C	36/60	31/29	55	0	11	24	4	0	Improved	MBP
17. Fernando [32]	2011	PS	19 (12), 100%, C	7/19	18/1	NR	NR	NR	12	0	1	Improved	MBP
18. A. Ommer [33]	2013	PS	40 (NR), 100%, C	39/40	30/10	4	NR	NR	1	2	3	Improved	PSI, MBP
19. C. Ratto [34]	2012	PS	11 (5), 100%, C+EUS	8/11	4/7	10	0	10	3	0	1	Improved	PSI, BE
20. S. Chan [35]	2012	PS	44 (10.5), 100%, C	22/44	27/17	40	4	40	22	3	0	Improved	BE
21. Jia Gang. Han [36]	2012	PS	21 (12-15), 100%, C	20/21	19/2	NR	NR	NR	1	0	0	1	Oral BP
22. Gareth Owen [37]	2010	PS	32 (2-29), 100%, C	13/35	18/14	NR	3	NR	24	0	0	NR	PSI
23. Pierpaolo Sileri [38]	2011	PS	11 (9), 100%, C	10/11	3/8	11	5	NR	1	1	0	Improved	BE
24. Michael J. Stamos [39]	2015	PS	93 (NR), 34/93, C	3/91	71/22	86	NR	NR	3	5	11	Improved	BE, PSI
25. H. Ortiz [40]	2009	RCS	32 (NR), 100%, C	14/32	10/22	NR	NR	NR	14	1	2	NR	MBP
26. Ma-Mu-Ti-Jiang A ba-bai-ke-re [41]	2010	PS	ADM 5.7 (5.1-6.4), 100%, C ERAF 6.1 (5.9-6.5) 100%, C	75/90	ADM 24/21 ERAF 25/20	ADM 45 ERAF 45	NR	NR	ADM 2 ERAF 13	NR	NR	IMPROVED	BMP
27. Paul J. van Koperen [42]	2011	RCT	11 (5-27), 21/60, C, T, MRR	Plug 14/22 Adv 8/15	Plug 23/8 Adv 19/10	Plug 23 Adv 20	NR	NR	Plug 14 Adv 8	0	0	Improved	PSI, MBP
28. J. R. Cintron [43]	2013	PS	15 (NR), 75/75, C	28/73	45/28	72	8	NR	45	7	4	improved	PSI, MBP
29. R.M. Lupinacci [44]	2010	PS	6 (NR), 15/15, C	8/15	8/7	NR	3	NR	7	3	1	Improved	MBP
30. E. Ozturk [45]	2015	PS	24 (10-32), 10/10, C, T	7/10	6/4	10	NR	10	3	2	0	Improved	MBP

NR: not reported/cannot be concluded from the data provided; PCT: prospective nonrandomized controlled trial; PS: prospective study, RCS: retrospective case series. Follow-up methods: C-clinical examination; T-telephonic interview; MRR-medical records review. None of the studies employed the use of MRI (magnetic resonance imaging) or EUS (endo-anal ultrasound). PSI-preoperative seton insertion, Tr-tracts, Pt-patients. Preoperative bowel preparation: MBP-mechanical bowel preparation (preoperative); BE-bowel enema (preoperative) Operative Position--Lithotomy-L, Prone Jack Knife-PJK. Anesthesia--GA-General Anesthesia, LR-LoCo-regional, LA-Local anesthesia, Duration of Admission--DC= Day care.

Meta-analysis of Post-operative Recurrence Rate

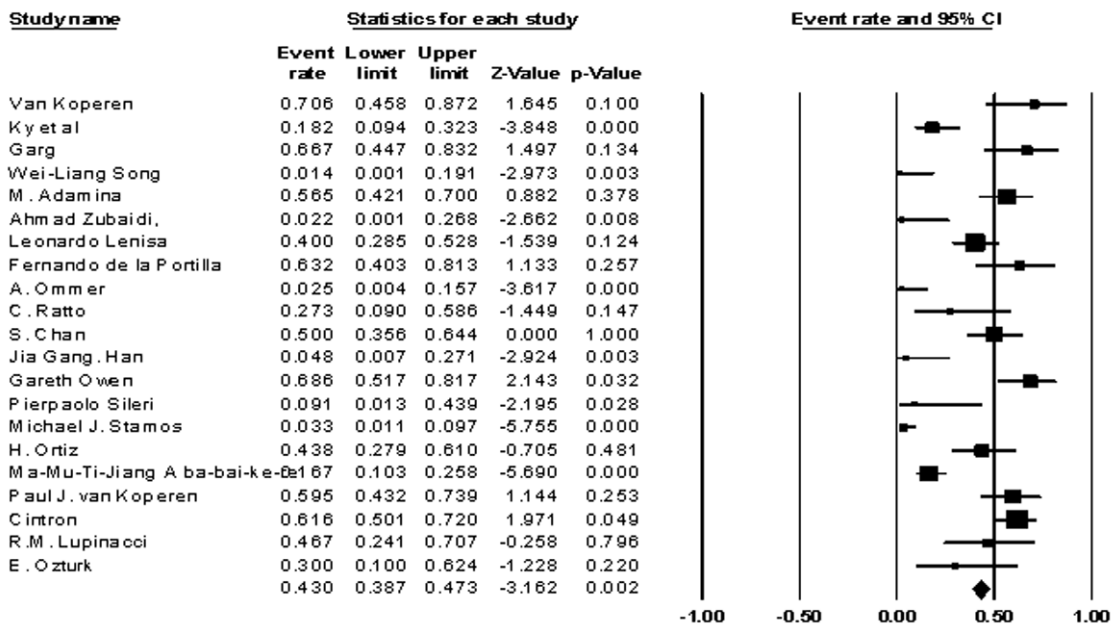


Figure 3. Meta analysis of postoperative recurrence rate of plug study.

Meta-analysis of Success Rate of Procedure

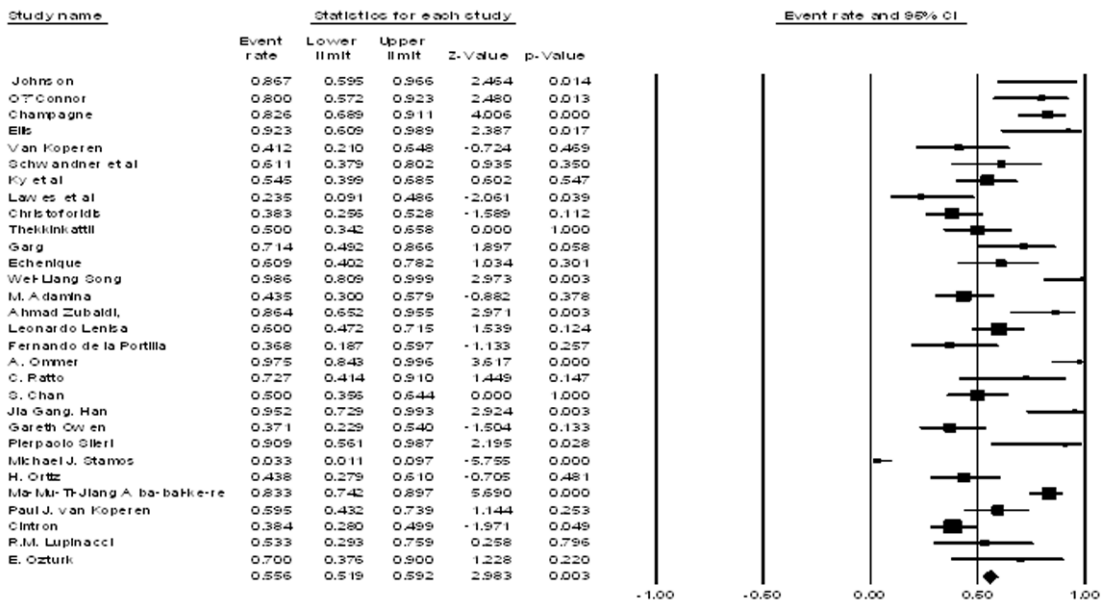


Figure 4. Meta analysis of success rate of plug study.

la patients. More attention has been paid to this sphincter-preserving technique, which aims to prevent the high incontinence rate after conventional surgery. An anal fistula plug can securely close the primary opening, thus enabling the surgeon to eradicate the fistula tract

with minimal damage to the sphincter. A theoretical advantage of this kind of plug is based on the surgical suturing of the internal opening of the fistula and complete closing of the fistula tract. Different medical centers and hospitals have reported their preliminary results of this

Meta-analysis of Post-operative Abscess Formation Rate

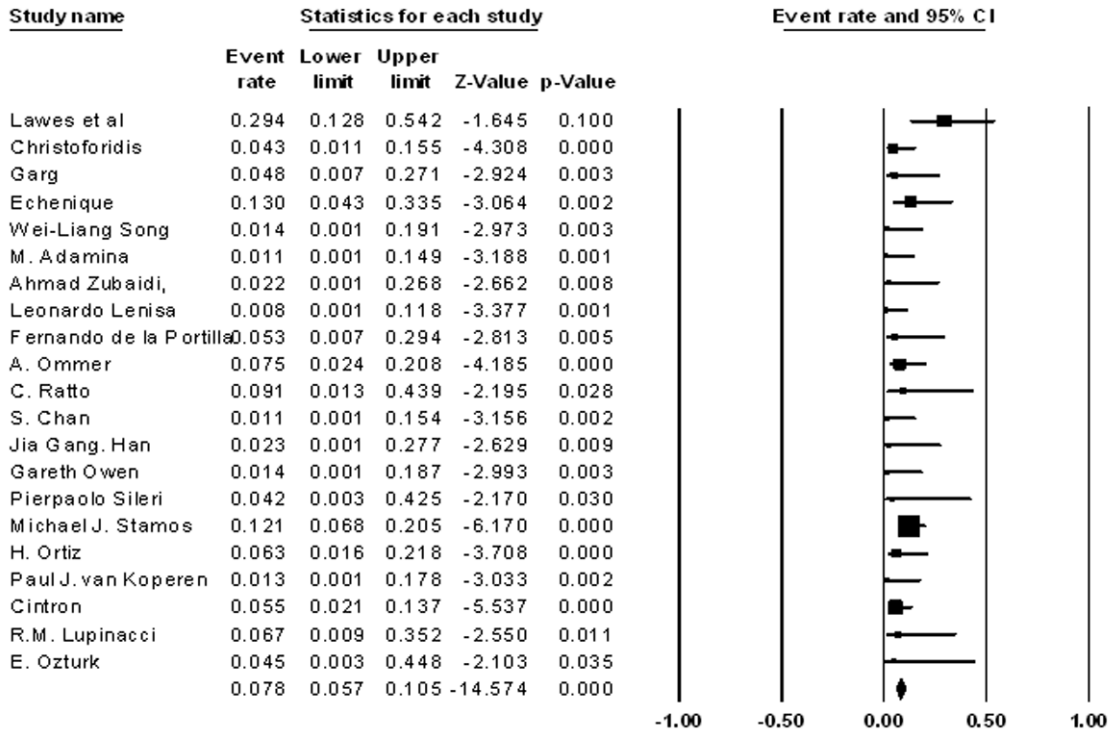


Figure 5. Meta analysis of postoperative abscess formation rate of plug study.

plug. We found only six meta-analyses or systematic reviews [47-52] about this kind of plug compared with other treatments. These systematic analyses provide certain useful information on the role of anorectal fistula plugs in the treatment of anal fistulae. However, four of these systematic reviews did not accord with the PRISMA statement or had some deviations throughout the analysis. In these meta-analyses, the fistula closure rates of the AFP plug varied considerably, from 14% to 96%, which makes it hard for the doctors to choose an optimum treatment for a patient.

This meta-analysis has been performed according to the PRISMA statement and accomplished PRISMA 2009 checklist and clearly supported the final result of plug for the treatment of complex fistulae-in-ano. Our results showed that the fistula closure rate of the plug procedure in complex fistulae is 55.6% (confidence of interval range 51.9%-59.2%). In contrast, the recurrence rate is 43% (CI, 38.7-47.3%). The abscess formation rate is 7.8% (CI, 5.7-10.5%). The plug extrusion rate is 13.6% (CI, 11-16.9%).

There were several reasons for the different results shown in this systematic review. First, although combined surgery with fistulotomy or mucosal advancement flaps was used, it failed to produce accurate results for the plug alone. Second, variables such as operative technique or surgeons' experience may influence the success rate because the techniques associated with the anal fistula plug were not standardized. Third, factors such as preoperative bowel preparation, anti-TNF medication in Crohn's disease, and preoperative seton use; prophylactic antibiotic administration, operative position, anesthesia type, careful preparation for the anorectal fistula tracts before surgery, and postoperative care might all affect the outcome of the operation.

Postoperative follow-up is an important aspect of the results of plug research. In these plug studies, postoperative follow-up duration varies greatly; the median follow-up time was 20.1 months, with the longest follow-up time 93 months. The follow-up periods are different, and studies with 6 weeks or less follow-up failed to provide an accurate success rate.

One of the limitations of this systematic review lies in the unsatisfactory scope of research because of the small number of randomized controlled studies available. Although healing rate remains uncertain and controversial, the conventional surgery is still the first choice for anorectal fistula. Some studies considered the plug treatment a minimally invasive, repeatable, sphincter-sparing, and cost-effective method, but high postoperative recurrence should be taken into consideration. Some studies included in this systematic review reported the extrusion of the plug after a certain number of days after surgery. Poor wound closing technique might be partially attributed to the extrusion. This meta-analysis showed that patients with multiple tracts appear to have poorer recovery than those with a single fistula tract. The closure rate of the fistula tract in these patients was also higher than the cure rate, because the tracts with plug insertion were healed much more commonly than those without plug insertion. In some studies, surgical technique and devices should be modified to insert the plug successfully into the fistula tract in patients with complex fistulae [46].

Although same material is used in AFP plug and ADM, the use of these biological materials can be an alternative. Only limited data was available in these trials, and it is hard to evaluate the efficacy of different materials during the follow-up periods because the basic parameters vary greatly. Fistula closure is achieved by using the anal fistula plug in approximately 55.6% of patients with complex anal fistula. Further randomized, controlled, multicenter, double-blinded, clinical trials that study the objective parameters of fistula healing are still needed to substantiate these findings. A standardized plug insertion technique, with fixed perioperative parameter, is also necessary.

In addition, the data included in this systematic review were based on an unclear etiology and unidentified fistula classification of complex fistula. The surgical outcomes from different treatments of different fistulae (including Crohn's disease, pouch-vaginal fistulae, recto-vaginal fistulae, or other types of fistula) were various [53]. Therefore, it is necessary to standardize the classification and associated treatment options. Standard definition, standard surgical technique, and standard identification of patients' status are also required to clarify and improve this systematic review.

We summarized the success rate of the anal fistula plug in treating complex anal fistulae by analyzing the related study publications from 1995 to 2015. The main aim of this research was to conclude the efficiency of the anal fistula plug in the treatment of complex anal fistulae. We found that fistula closure is achieved by using the anal fistula plug in approximately 55.6% of patients with complex anal fistula. Further randomized, controlled, multicenter, double-blinded, clinical trials that study the objective parameters of fistula healing are still needed to substantiate these findings.

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Disclosure of conflict of interest

None.

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