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Research Paper

Optimum management for complex anal fistula: A network meta-analysis of randomized controlled trials

Warsinggih [a,*], Citra Aryanti [a], Muhammad Faruk [b]

[a] Division of Digestive, Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[b] Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

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ABSTRACT

Background: Complex anal fistula has a high recurrence rate and disturbing surgical complications, which are frustrating for patients and challenging for surgeons. Although single or combined management methods have produced positive outcomes, no trials have simultaneously compared these therapies. Therefore, this study aimed to determine the management method for complex anal fistula with the lowest failure and complication rates.
Methods: This network meta-analysis (NMA) was registered in the international prospective register of systematic reviews (PROSPERO; CRD42023393349). Randomized controlled trials that analyzed complex anal fistula management were obtained from Medline, Scopus, and Cochrane using representative keywords. The primary outcome was the failure of anal fistulas to heal (including recurrences) after 6 to 12 months. The secondary outcome was fecal incontinence. All statistical analysis was conducted within the Bayesian framework using BUGSnet 1.1.0 in R Studio. A forest plot and league table were used to present the results.
Results: A total of 19 studies containing 15 interventions, 1844 subjects, and 104 pairwise comparisons were analyzed quantitatively. The lowest failure rates occurred with ligation of the intersphincteric fistula tract (LIFT) + Plug (RR 0.2; 95 % CI 0.01–2.65), LIFT + platelet-rich plasma (PRP) (RR 0.22; 95 % CI 0.01–2.89), and FSR (RR 0.26; 95 % CI 0.02–2.12) relative to drainage seton. LIFT combined with other management methods showed lower fecal incontinence rates than the other treatments.
Conclusion: The combination of LIFT with plug or PRP resulted in lower failure and complication rates in the management of complex anal fistula compared to the other methods tested.

Introduction

The phrase “complex anal fistula” refers to anal fistulas that are correlated with transsphincteric fistulas, pre-existing fecal incontinence, malignancy, radiation, and IBD and involve greater than 30 % of extrasphincteric, supra-sphincteric, horseshoe, external sphincter, branching, or recurrent fistulas [1]. The disease is challenging for both patients and surgeons due to its high recurrence rate and management complications [2].

In 2016, Bubbers et al. [3] proposed an algorithm for the management of complex anal fistulas that recommended draining setons. However, treatment failures were common; therefore, further management options were required that involved multiple procedures. The second option considered was an advancement flap, plug, or ligation of the intersphincteric fistula tract (LIFT), and if recurrence occurred after these two procedures, a draining/cutting seton or repeat flap or LIFT under general anesthesia was recommended [3]. Numerous surgical techniques for complex anal fistulas have been proposed, such as the rectal advancement flap, LIFT, anal fistula plug, fibrin glue, video-assisted anal fistula treatment (VAAFT), mesenchymal stem cell, laser, and fistula clip [4]. The VAAFT, laser, and fistula clip modalities are relatively new and randomized clinical trial (RCT) results for complex anal fistula are still limited.

The ideal management for anal fistulas depends on two principles: the eradication of sepsis and promotion of fistula tract healing by the closing of the tract and preservation of the sphincter complex and continence mechanism [5]. Thus, the goals of complex anal fistula repair are the reduction in recurrence and the avoidance of incontinence. This

* Corresponding author at: Division of Digestive, Department of Surgery, Faculty of Medicine, Hasanuddin University Makassar, Jalan Perintis Kemerdekaan KM 11, Makassar, Sulawesi Selatan, 90245, Indonesia.
E-mail addresses: kbd.warsinggih@gmail.com (Warsinggih), citra.aryanti@hotmail.com (C. Aryanti), muhammadfaruk@unhas.ac.id (M. Faruk).

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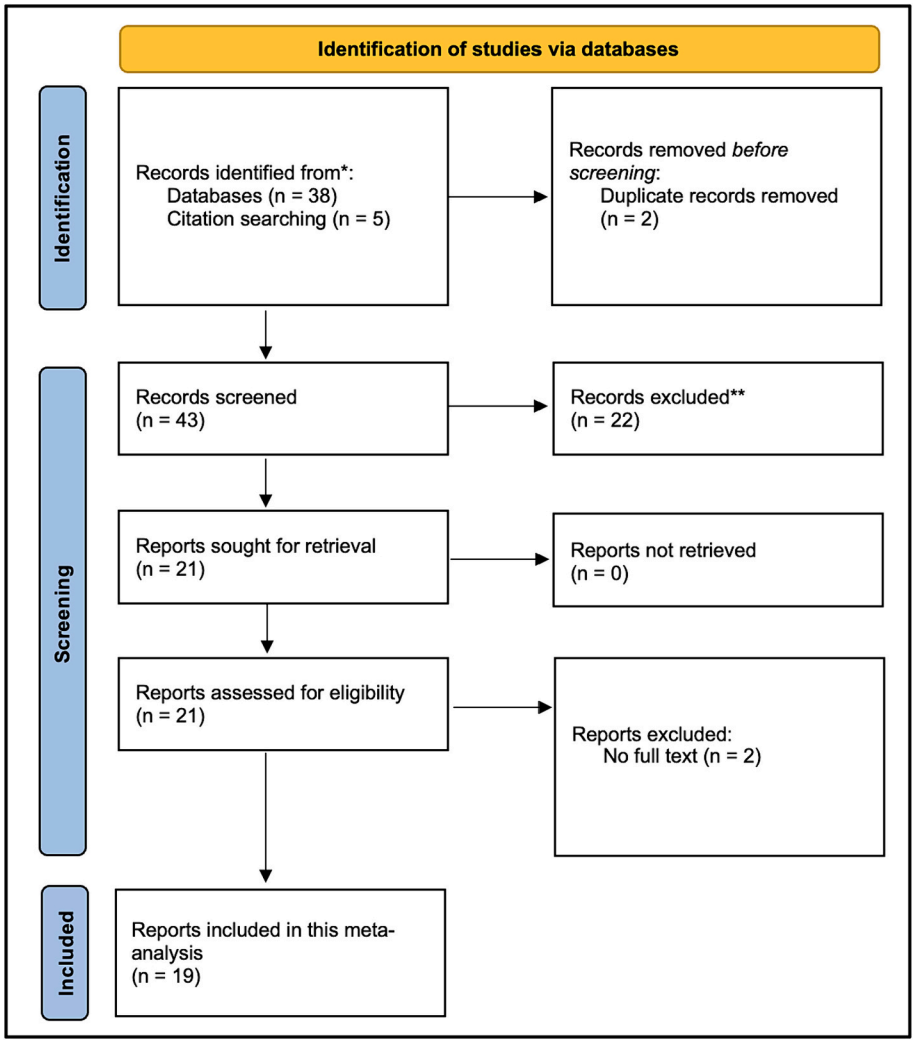

Fig. 1. PRISMA flow chart. The network meta-analysis and systematic review were conducted in compliance with PRISMA guidelines.

study aimed to determine the optimal intervention method for managing complex anal fistula with minimal recurrence and lower fecal incontinence complication rates.

Methods

This study used a network meta-analysis (NMA) to evaluate various treatments for complex anal fistula based on RCTs. The guidelines of the preferred reporting items for meta-analyses (PRISMA) with network meta-analyses (NMA) extension were used, and the study was registered with PROSPERO (Registration number: CRD42023393349).

Data sources

The electronic databases of the Cochrane Library, MEDLINE (PubMed), and Scopus were used to conduct the online systematic search. Along with the cited papers, the following websites were searched using Google Scholar. The search included studies up to January 2022.

Search strategy

A combination of words and a series of logic keywords related to complex anal fistula management were used. The Pubmed search was as follows: Search: (Complex [MeSH Terms] OR Transphincteric [MeSH Terms] OR High Sphincteric [MeSH Terms]) AND (Anal Fistula [MeSH Terms] OR Fistula [MeSH Terms]). Filters: Randomized Controlled Trials.

Eligibility criteria

The selected studies were required to meet the following inclusion criteria:

1. Involved adult patients with complex anal fistulas that compared at least two treatments,
2. Fulfilled the criteria of the randomized controlled trial, and
3. Included the full text of the article.

In addition, the exclusion criteria for the studies were as follows:

1. Studies that lacked a case-control design; those involving case reports, observational or retrospective studies, reviews, or animal research, and
2. Management studies that did not involve comparisons.

Data extraction and study selection

Two reviewers independently examined each citation. Irrelevant titles or abstracts were excluded and the reviewers obtained and assessed

Table 1
Characteristics of studies included in this network meta-analysis.

Author	Country	Age (mid) (years)	M/F	Follow-up (months)	Intervention	Failure	Wexner score	Incontinence
A ba-bai-ke-re (2010) [6]	China	45	49/31	6	Plug (ADM) ($n = 26$)	2	NA	1
					RAF ($n = 28$)	10		4
Abdelnaby (2019) [7]	Egypt	39	80/17	12	RAF (n = 49)	2	0 SD 1	1
					Drainage seton ($n = 48$)	4	0 SD 2	7
Altomare (2009) [8]	Italy	50	43/20	6	Cutting seton ($n = 25$)	3	NA	6
					Fibrin glue (Tissucol) ($n = 38$)	23		10
Bondi (2017) [9]	Norway	50	48/43	12	RAF ($n = 40$)	15	NA	NA
					Plug (Surgisis) ($n = 41$)	27		
de la Portilla (2019) [10]	Spain	49	37/19	12	Fibrin glue ($n = 32$)	10	NA	NA
					PRP ($n = 24$)	9		
Garcia-Arranz (2020) [11]	Spain	50	30/14	12	Fibrin glue (Baxter) + ASC (Autolog) ($n = 23$)	9	NA	NA
					Fibrin glue (Baxter) ($n = 21$)	7		
Garcia-Olmo (2009) [12]	Spain	43	24/25	12	Fibrin glue + ASC (n = 24)	7	NA	NA
					Fibrin glue (n = 25)	21		
Han (2016) [13]	China	36	190/38	6	LIFT + Plug (AEDM) ($n = 112$)	7	NA	NA
					LIFT ($n = 116$)	19		
Herreros (2012) [14]	Spain	49	127/56	6	ASC (Cellerix) ($n = 64$)	37	0.6 SD 0.9	7
					Fibrin glue (Baxter) + ASC (Cellerix) ($n = 60$)	36	2.3 SD 3.1	13
					Fibrin glue (Baxter) ($n = 59$)	36	1.4 SD 1.8	14
Jayne (2019) [15]	UK	45	132/108	12	Plug (Surgisis) ($n = 115$)	52	NA	NA
					Cutting seton (42)	15		
					Fistulotomy ($n = 16$)	4		
					RAF ($n = 17$)	8		
					LIFT ($n = 50$)	29		
Madbouly (2014) [16]	Egypt	43	42/28	12	LIFT (n = 45)	19	0.26 SD	4
					RAF ($n = 45$)	22	0.76	7
							0.34 SD 0.9	
Madbouly (2021) [17]	Egypt	41	59/39	12	LIFT-PRP ($n = 49$)	7	0 SD 2.5	7
					LIFT (n = 49)	17	0 SD 2	2
Molendijk (2015) [18]	Netherlands	NA	NA	6	ASC (Allogeneic) (n = 23)	9	NA	NA
					Placebo ($n = 9$)	6		
Omar (2019) [19]	Egypt	43	56/4	12	Drainage seton ($n = 30$)	4	0.56 SD 1.3	3
					Cutting seton (n = 30)	1	0.4 SD 1.1	2
Ortiz (2009) [20]	Spain	NA	NA	12	Plug ($n = 15$)	12	NA	NA
					RAF (n = 16)	2		
Panés (2016) [21]	Spain	38	116/96	6	ASC (Allogeneic) ($n = 107$)	36	NA	NA
					Placebo ($n = 105$)	49		
Rezk (2022) [22]	Egypt	38	48/22	6	LIFT (n = 35)	14	0	0
					LIFT + ASC (Autologous) ($n = 35$)	11	0	0
Sørensen (2021) [23]	Denmark	43	32/13	6	FSR ($n = 22$)	6	NA	NA
					VAAFT (n = 23)	15		
Yu (2022) [24]	China	39	104/16	12	Drainage seton ($n = 56$)	4	NA	6
					Cutting seton ($n = 55$)	5		25

Abbreviations: ASC: adipose-derived stem cells, AEDM: acellular or extracellular dermal matrix, PRP: platelet-rich plasma, RAF: rectal advancement flap, M/F: male/female.

the entire paper for the remaining citations. The consensus of a third reviewer was obtained to settle disagreements between the reviewers. The publication year, author's name, sample size, sex ratio, follow-up duration, and management type were evaluated.

Quality and risk of bias assessment

Using the Jadad scoring system, the methodological quality of each component study was evaluated. Only items with a score of three or greater were considered. The intra-class correlation coefficient was used to assess reviewer reliability. For randomized trials (RoB2), the Cochrane risk of bias tool was used to evaluate bias risk.

The main domains of the RoB2 assessment tool include random sequence generation, effect of assignment, missing outcome data, measurement of the outcome, and selective outcome reporting. The measures for these domains were classified as "high," "some concerns," or "low" and the outcomes were used to determine the overall risk of bias. Minimal risk was assessed when all domains returned low risks. The bias assessment was classified as having "some concerns" if issues were identified in at least one category that were not classified as high risk. A high risk of bias score was obtained if a domain was deemed to be at high risk or if numerous domains were detected as showing some concerns. In addition, raters examined the studies for any potential biases, including those relating to publication or sponsorship. If insufficient details were available to allow for a clear assessment of bias, the trial authors were contacted.

Outcomes

The primary outcome in this study was the failure of anal fistulas (including recurrence) to heal in 6–12 months. The secondary outcome was the fecal incontinence rate.

Statistical analysis

Network meta-analyses (NMA) facilitate the statistical combination of direct and indirect evidence by synthesizing trial findings from treatments that constitute a connected network. Each statistical analysis was conducted using the Bayesian framework and BUGSnet 1.1.0, and the results were assessed using Markov chain Monte Carlo simulation.

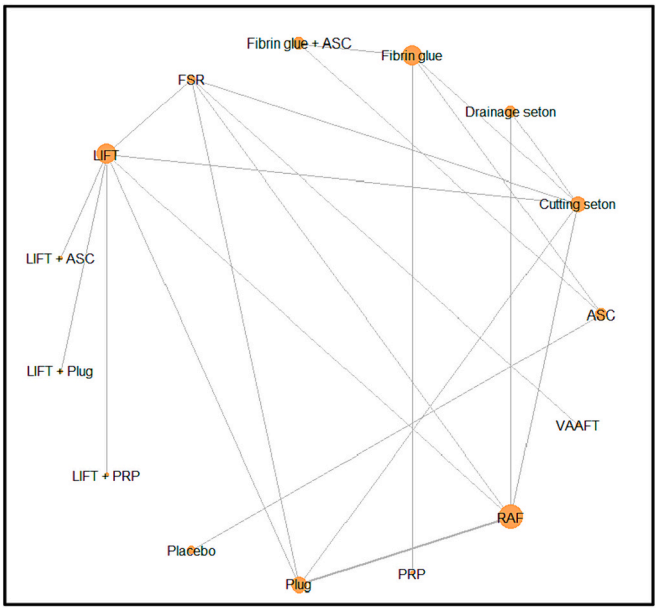

Fig. 2. Network plot of trials comparing complex anal fistula interventions.

To evaluate the fitness of the model, we compared the residual deviation with the number of unconstrained data points. Similar values indicated a sufficient fit of the model. Deviance information criteria (DIC) were used to choose between the models; smaller values signified a better fit and a difference of more than five points was significant. The Gelman and Rubin criteria, as well as a trace plot inspection, were used to evaluate convergence. NMA also allows treatments to be ranked in a SUCRA plot based on their ability to produce a given result. For each intervention, statistically significant outcomes were computed and presented in a league table and forest plot.

Results

Literature search

Fig. 1 shows the results of the literature search and study selection, which identified 43 records. Five additional records were included that were detected by hand searching. Of the total, 22 studies were excluded after title screening and 2 lacked full-texts and were excluded, yielding 19 studies for the final analysis. Table 1 provides a summary of the procedure.

A total of 19 studies with 15 interventions, 1844 subjects, and 104 possible pairwise comparisons were included in this study. A network plot of trials comparing complex anal fistula inventions is shown in Fig. 2.

A random model was employed for the analysis in this study. The DIC is considerably lower in a random effects model. Five items were identified as the main causes of the poor fit of the model based on the fixed effects model. A single outlier was evident in the random effects model, which warrants further investigation (Fig. 3a and b). By fitting a random effects inconsistency model and contrasting it with the random effects consistency model, we evaluated the consistency of the network. The data showed a general agreement between the two models and were positioned on the y and x lines with the exception of three or four points (Fig. 3c). Therefore, the random effects and consistency models were appropriate.

All relative efficacy data for each potential pair of interventions was included in the league table (at the 95 % confidence interval). The league table (Fig. 4) shows a hazard ratio scale with corresponding values. No significant differences in failure rates were noted among interventions relative to drainage seton. The lowest failure rates were shown by the LIFT + Plug (RR 0.2; 95 % CI 0.01–2.65), LIFT + platelet-rich plasma (PRP) (RR 0.22; 95 % CI 0.01–2.89), and FSR (RR 0.26; 95 % CI 0.02–2.12) relative to the drainage seton. The highest failure rates occurred with fibrin glue + ASC (RR 2.9; 95 % CI 0.18–41.34), ASC only (RR 2.33; 95 % CI 0.11–41.98), and PRP only (RR 2.23; 95 % CI 0.09–46.37) relative to the drainage seton (Fig. 4). The highest rates of incontinence post-surgery were found with the fibrin glue + ASC and PRP interventions, while the lowest rates were found in combinations involving the LIFT interventions (Fig. 5).

Discussion

Anal fistulas, specifically complex anal fistulas, are challenging conditions for surgeons to manage because of their high recurrence rates and postoperative risks of fecal incontinence. Currently, no standardized procedure exists for managing complex anal fistulas [25]. According to guidelines published by the American Society of Colon and Rectal Surgeons in 2022, complex anal fistulas are frequently treated with phased, definitive surgery to remove the fistula after a draining seton is used to control local sepsis [26]. An alternative would be to gradually divide the fistula and any related anal sphincter while maintaining a cutting seton *in situ* that is occasionally tightened [Grade recommendation: weak recommendation according to low-quality evidence (Grade 2B/C)]. Proceeding with a fistulotomy for complex fistulas should be carefully considered due to the significant postoperative incontinence in 10–40 % of patients [27].

This NMA showed that LIFT, combined with other interventions (Plug or PRP), showed the most favorable results (Fig. 6). This method had the lowest failure and fecal incontinence complication rates. This result was comparable to that of a systematic review by Zahra et al. (2022) [28], which found that closure of the intersphincteric fistula tract

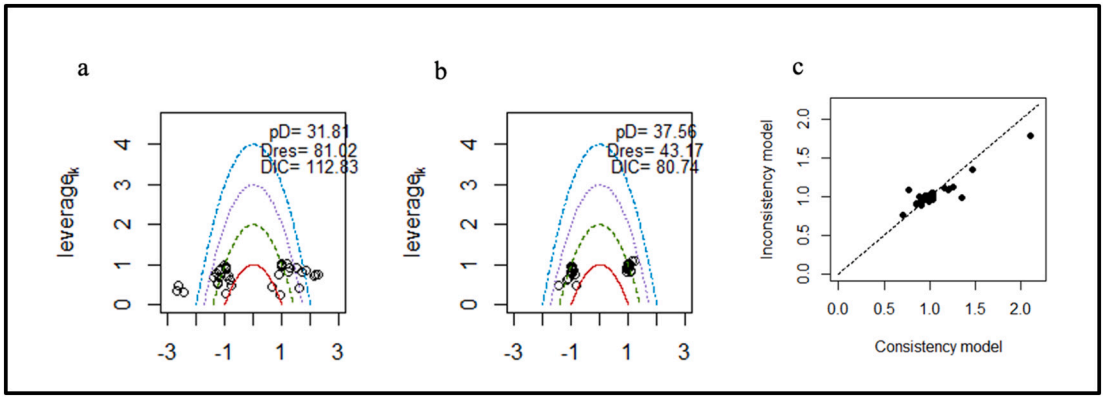

Fig. 3. Fixed-effects model (3a), random-effects model (3b), and consistency and inconsistency agreement graph (3c).

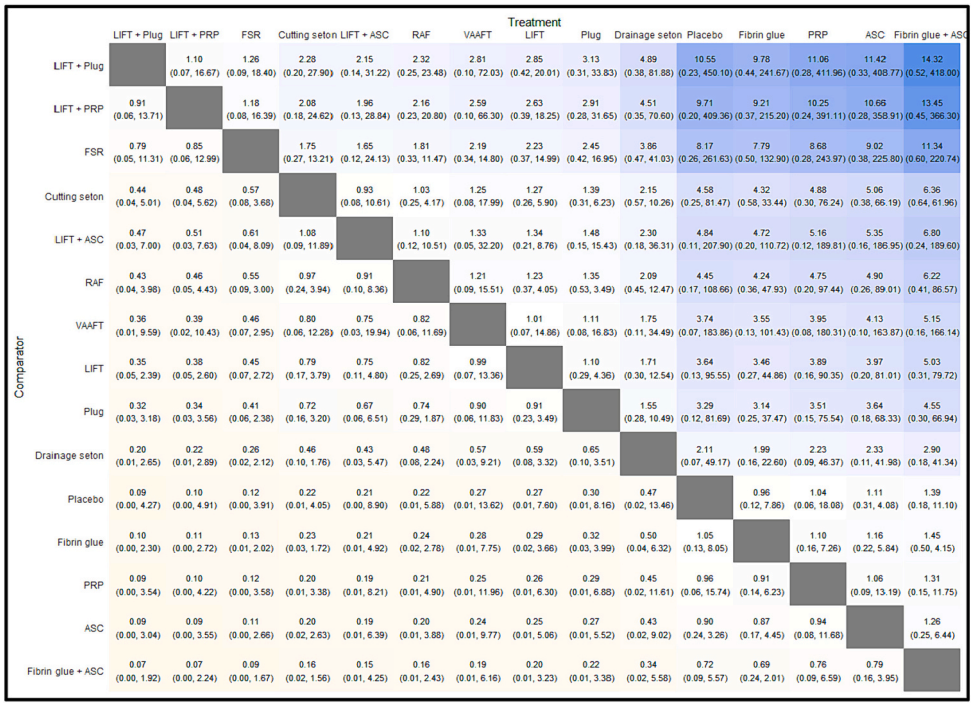

Fig. 4. League table showing the results of the network meta-analyses comparing the failure rates of all complex anal fistula interventions, including relative risk (RR) and 95 % confidence intervals.

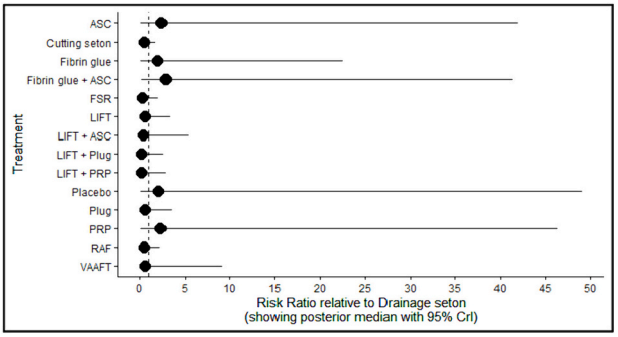

Fig. 5. Forest plot showing incontinence complication rates among all interventions for complex anal fistula relative to the drainage seton.

was a novel and potentially effective treatment for complex anal fistulas. However, the authors of this review could not recommend those findings because of insufficient data.

LIFT was first introduced in a study by Rojanasakul et al. (2007) [29], which was considered a breakthrough in managing perianal fistulas. LIFT ligation was performed at the fistula tract close to the internal opening. This technique effectively controlled the contamination of fecal material into the fistula tract, which promoted healing. Thus, the LIFT method combines two principles: closing the internal orifice with minor sphincter damage and removing the contaminated cryptoglandular tissue through the intersphincteric approach. The anal sphincters are not divided; therefore, there is no risk of fecal incontinence [30].

There are some limitations to this study. First, the surgeons differed in each study, which can cause bias in the data analysis. Second, only RCTs in the English language were included. However, as far as we are aware, this was the first NMA that compared all techniques for the treatment of complex anal fistulas. More RCTs are required to further the results of the next NMA.

Conclusion

Combining LIFT with plug or PRP was the most favorable technique for managing complex anal fistulas. This method was associated with lower failure and complication rates.

Ethical approval

Not applicable.

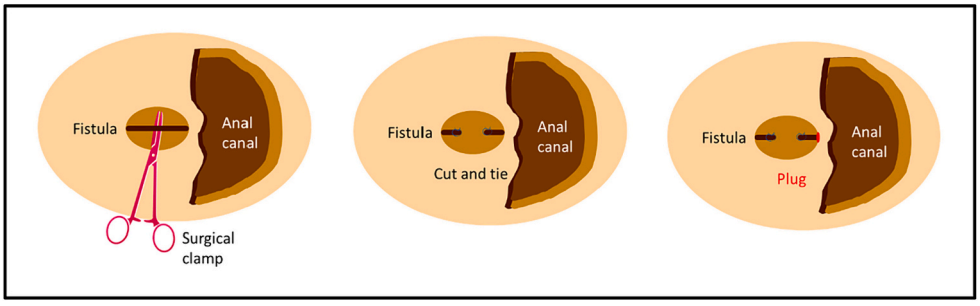

Fig. 6. LIFT and plug.

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CRediT authorship contribution statement

Warsinggih: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Citra Aryanti:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Muhammad Faruk:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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