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REVIEW

Operative and medical treatment of chronic anal fissures-a review and network meta-analysis of randomized controlled trials

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Abstract Anal fissures are a common problem and have a cumulative lifetime incidence of 11%. Previous reviews on anal fissures show inconsistent results regarding post-interventional healing and incontinence rates. In this review our aim was to compare the treatments for chronic anal fissures by incorporating indirect comparisons using network meta-analysis. The PubMed database was searched for randomized controlled trials (RCTs) published between 1975 and 2015. The primary outcome measures were healing and incontinence rates after lateral internal sphincterotomy (LIS), anal dilatation (DILA), anoplasty and/or fissurectomy (FIAP), botulinum toxin (BT) and noninvasive treatment (NIT). Random effects network meta-analyses were complemented by fixed effects and Bayesian models. The present analysis included 44 RCTs and 3268 patients. After a median follow-up of 2 months, the healing rates for LIS, DILA, FIAP, BT and NIT were 93.1, 84.4, 79.8, 62.6, and 58.6% and the incontinence rates were 9.4, 18.2, 4.9, 4.1, and 3.0%, respectively. Compared with NIT, the odds ratio (OR) [95% confidence interval (CI)] for healing after LIS, DILA, FIAP and BT was 9.9 (5.4−18.1), 8.6 (3.1−24.0), 3.5 (1.0−12.7) and 1.9 (1.1−3.5), respectively, on network meta-analysis. The OR (95% CI) for incontinence after LIS, DILA, FIAP and BT was 6.8 (3.1−15.1), 16.9 (6.0−47.8), 3.9 (1.0−15.1) and 1.6 (0.7−3.7), respectively. Ranking of treatments, fixed effects and Bayesian models confirmed these findings. In conclusion, based on our meta-analysis LIS is the most efficacious treatment but is compromised by a high rate of postoperative incontinence. Given the trade-offs between the risks and benefits, FIAP and BT might be good alternatives for the treatment of chronic anal fissures.

Keywords Network meta-analysis · Chronic anal fissures · Noninvasive treatment · Lateral internal sphincterotomy · Botulinum toxin

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Introduction

Anal fissures are longitudinal tears in the squamous epithelium of the anal canal distal to the dentate line, and in up to 90% of cases they are located on the posterior midline [1]. Fissures are classified into an acute and a chronic form and into primary and secondary fissures based on their pathogenesis. Chronic fissures are defined by both or either chronology and morphology. The criteria are duration of symptoms for longer than 8 weeks, the presence of a sentinel pile, a skin tag or an ulcer with exposed internal sphincter fibers [2]. The exact pathogenesis of primary fissures remains uncertain, but a core point is hypertonicity of the internal anal sphincter [3], which leads to local ischemia [4]. Furthermore, inflammation and pain induce ongoing hypertonicity, giving rise to a vicious circle [2]. Therefore, the aim of treatment strategies is to reduce the sphincter tone with either medical agents, such as glyceryl trinitrate (GTN), calcium channel blockers (CCB) and botulinum toxin, or surgical interventions, such as lateral internal sphincterotomy (LIS).

With a lifetime risk of 11%, anal fissures are a common problem in routine medical care [5]. Patients' quality of life can be significantly reduced due to massive discomfort or severe pain [6, 7]. Complications from a lack or inadequacy of treatment include abscess, fistula and incontinence. Thus, it is important to have therapeutic options that are efficient and safe.

LIS is often claimed to be the gold standard therapy for chronic anal fissures. The latest American guidelines are supported by level 1a evidence for LIS due to its high efficiency compared with other therapies, particularly medical treatment [8]. However, the debate on postoperative fecal incontinence remains. A recent meta-analysis of 22 randomized controlled trials (RCTs) analysed long-term disturbances in continence after LIS and found an overall incontinence rate as high as 14% [9]. Earlier, in 2011 and 2012, Nelson et al. performed two separate meta-analyses in which they assessed medical treatment in one [10] and considered the operative treatment of chronic anal fissures in the other [11]. Surgical treatment was demonstrated to be far more effective than medical treatment, with a pooled healing rate of 89%. These authors reported that medical therapy had a chance of cure that was "only marginally but significantly better" than placebo; however, there was a risk of recurrence in the range of 50%. LIS was the most efficient therapy, and it was less likely to result in treatment failure than was fissurectomy. With respect to continence disturbance, there was no significant difference between the procedures.

In summary, the outcomes and side effects of the treatments for chronic anal fissures reported in the literature are inconsistent. Previous meta-analyses were performed using standard pairwise methods and were thus limited to direct comparisons. The recently developed network meta-analyses can perform indirect comparisons of interventions that have not been studied head-to-head and enable investigators to statistically estimate the relative efficacy between every intervention included in the network [12, 13].

The aim of the study reported here was to analyse the established invasive and noninvasive treatments for primary chronic anal fissures in adults with respect to healing, incontinence, and long-term treatment failure rates, including the latest RCTs and incorporating indirect comparisons by using network meta-analysis.

Methods

The present network meta-analysis was conducted according to the guidelines and checklist of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension Statement for Reporting of Systematic Reviews: Incorporating Network Meta-analyses of Health Care Interventions [14]. Each process step in the literature search, study selection, data extraction and quality assessment was performed independently and crosschecked by two reviewers (S.E. and L.M). Discrepancies were resolved by consensus in the presence of a third investigator (R.W.).

Eligibility criteria

Randomized controlled trials published between January 1975 and 7 October 2015 were considered. Language was not a reason for exclusion. RCTs studying the treatment of primary chronic anal fissures in adults were selected if they had at least two interventional arms receiving one of the following treatments: open, closed or unspecified LIS (LIS), fissurectomy and/or anoplasty (FIAP), anal dilatation (DILA), botulinum toxin injections (BT) or noninvasive treatment (NIT). NIT included the following treatments: oral or local application of isosorbide mononitrate, isosorbide dinitrate and GTN, CCB and conservative treatment (local anesthesia, local hydrocortisone or ointment).

The rationale for the clustering of treatments was the small difference in fissure persistence and postoperative risk of incontinence between open and closed LIS reported in previous research [11]. Fissurectomy and anoplasty both remove bradytrophic scar tissue and secondary morphologic transformations of the fissure and were therefore clustered under FIAP. Patients who received conservative treatment were summarized under NIT in accordance with previous reviews, which found that medical therapy is marginally better than placebo [10].

RCTs were included only if they provided information on at least one of the outcome measures defined below.

Data items and extraction of outcomes data

Healing rates and post-interventional incontinence rates were defined as the main outcome measures. To assess the long-term treatment failure rates, a no-success rate (defined as fissures that did not heal + recurrent fissures + fissures treated by further interventions to achieve healing) was computed as a secondary outcome measure. Healing was defined by either or both clinical and morphological criteria (painlessness and complete epithelization of the fissure, respectively). Incontinence was defined as post-interventional newly emerged fecal soiling and/or incontinence to flatus or liquid or solid stool.

Information sources and search

The literature search was completed on 7 October 2015. The Medline (PubMed) database was searched using the following search terms: "fissure in ano" [MeSH terms] OR ("fissure" [All Fields] AND "ano" [All Fields]) OR "fissure in ano" [All Fields] OR ("anal" [All Fields] AND "fissure" [All Fields]) OR "anal fissure" [All Fields]. The "related article" function was applied to broaden the search volume. The articles referenced in the retrieved publications were then reviewed to identify further relevant studies for potential inclusion. All abstracts that were identified by the above-mentioned search string were screened for eligibility. For all abstracts that were eligible, a full-text review was performed to determine whether the obtained information matched the inclusion criteria defined in the eligibility criteria. Exclusion criteria for full-text reviews were defined as follows: (1) conditions different from chronic anal fissure, (2) double publications, (3) non-randomized clinical trials, (4) fewer than two interventional arms receiving one of the above-mentioned treatments, (5) no data for the defined endpoints and (6) special patient characteristics (e.g. research on children, secondary anal fissures).

Geometry of the network

Network graphs were used to display the evidence base for the meta-analysis for each outcome. The network was laid out in the plane such that the nodes in the graph corresponded to the treatments and the edges displayed the observed treatment comparisons. In short, thicker lines represented more profound evidence [15].

Risk of bias within individual studies

The quality of the studies was assessed by one validated score, the Jadad score [16, 17].

Randomization, description/quality of randomization, blinding, description/quality of blinding and description/number of withdrawal and dropouts were assessed. The score was not used to determine whether the trials would be included in the analysis.

Summary measures

The main outcome measures were the healing and incontinence rates. The no-success rate was a secondary endpoint. In frequentist and Bayesian network meta-analysis rankings of the treatments were estimated.

Assessment of inconsistency

Details on the assessment of inconsistency are provided in Electronic Supplementary Material (ESM) Text S1.

Statistical analysis

Details on the statistical analysis are provided in ESM Text S2.

Results

Study selection and data extraction

Figure 1 describes the process of data inclusion. Initially, 2304 citations were identified, 1724 of which were published in the previously determined time period between January 1975 and October 2015. After screening the titles and abstracts, 188 studies proved to be RCTs comparing treatments of chronic anal fissures, and a full text review of those studies was performed. We then excluded 144 studies according to the above-mentioned exclusion criteria; the outcomes data of the 44 studies which remained were then extracted. These 44 studies, which involved a total of 3268 patients, were included in the meta-analysis reported here (Table 1).

Study characteristics and study quality

Table 1 summarizes the characteristics and Jadad scores [16] of all the studies included in the meta-analysis. In summary, the quality of the studies and implementation of the respective treatments and definitions of endpoints varied over all studies.

The time-point for assessment of healing ranged from 0.5 to 17.4 (median 2) months, and the duration of the follow-up ranged from 3 to 60 (median 12) months. The process of randomization was not always described properly. Some studies had high dropout and lost-to-follow-up rates. Blinding was often not described properly or not performed at all (especially if surgical procedures were involved), resulting in an overall median Jadad score of 3.

The definition of "chronic anal fissure" was predominantly described as the existence of both morphologic changes and the duration of clinical symptoms for more than 6–8 weeks. However, some studies only referred to either one of the criteria, whereas others [18] only included patients after failed conservative treatment.

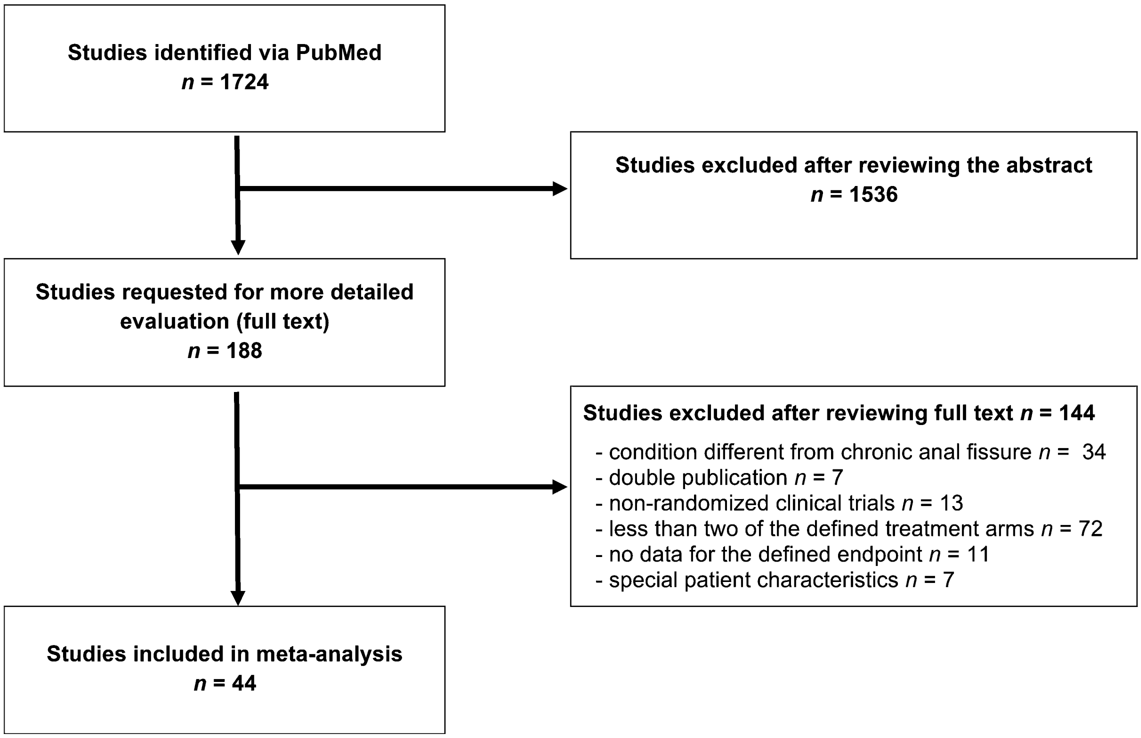

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart for data inclusion

The definition of "healing" differed throughout the studies; however, the majority of studies defined it as "painlessness" together with evidence of epithelialization of the fissure on rectoscopy. As a further expression of potential clinical heterogeneity, the definition of incontinence varied, as did its grading and the timing of evaluation.

In terms of treatments, procedures were standardized within each study but they differed among studies, especially after treatment group clustering.

Risk of bias and results of individual studies

The results for the endpoints of the individual RCTs are listed in Table 1.

Healing rate

Regarding the primary endpoint healing rate, in 31 studies there was one therapy arm with patients undergoing LIS, in 24 studies patients received conservative treatment and/or placebo, in 16 studies patients received BT injections, in eight studies patients underwent anal dilatation and in five studies patients underwent anoplasty and/or fissurectomy.

The healing rate after LIS varied from 37.8 [19] to 100% [20–29]. Healing in all patients was reported in ten of the 31 studies with LIS as the therapy arm. The study by Marby et al. [19] demonstrated a comparatively low healing rate after LIS, which might be explained by several potential sources of bias in the study: first, the dropout rate was as high at 24%; second, sphincterotomy, in contrast to dilatation, was performed under local anesthesia; third, 22 of the 78 patients who underwent LIS did not have pain as a presenting symptom before the operation, thus making the definition of "chronic anal fissure" somewhat doubtful.

For "conservative treatment and/or placebo", the healing rate ranged from 13.3 [30] to 88.9% [20]. In one study with a high healing rate (85%), the definition of "chronic" was not given [31], so it is possible that some patients with acute fissures were included in the patient population. In another trial with similarly good results, more than 90% of the patients were female. This gender disproportion may have induced some bias toward a better outcome [20].

For BT, the healing rates ranged from 25 [32] to 96% [33]. Brisinda et al. [33] demonstrated the highest rate in 1999. These authors used a total of 20 U of BT, half of which was injected into the internal anal sphincter on each side of the anterior midline. Festen et al. [32] had the lowest healing rate but reported using the exact same approach. The latter study was terminated prematurely due to stagnant recruitment and showed a high dropout-rate; both of these factors could have increased the risk of bias. In contrast to the former study, the latter was double blinded.

In the FIAP group the healing rates ranged from 68 [34] to 100% [21]. Magdy et al. 2012 [34] applied a V–Y anocutaneous skin flap and achieved the lowest healing rate

Table 1 Study characteristics and quality assessment

First author of reference	Year	Sample size (*n*)	Follow-up (months)		Jadad score [16] (0–5)	Treatment arm	Outcome		
			Healing	Longtime follow-up‡			Healing rate	No-success rate	Incontinence rate
Fischer [35]	1978	66	6	27	2	LIS	31/32, 97%		0/32, 0%
						DILA	30/33, 91%		6/31, 19%
Marby [19]	1979	156	4	12	2	LIS	17/45, 38%		
						DILA	25/41, 61%		
Jensen [23]	1984	58	2	18	2	LIS	30/30, 100%	1/30, 3%	1/30, 3%
						DILA	27/28, 96%	9/28, 32%	11/28, 39%
Hiltunen [24]	1986	41	2		2	LIS	14/14, 100%		
						DILA	15/19, 79%		
Olsen [49]	1987	20		12	2	LIS			2/10, 20%
						DILA			2/10, 20%
Weaver [38]	1987	111	17.4	17.4	3	LIS	29/39, 74%		2/39, 5%
						DILA	43/59, 73%		3/59, 5%
Saad [42]	1992	57	3	3	2	LIS	19/20, 95%		1/20, 5%
						DILA	35/37, 95%		9/37, 24%
Leong [22]	1995	40	3		3	FIAP	18/20, 90%		0/20, 0%
						LIS	20/20, 100%		0/20, 0%
Oettle [25]	1997	24	0.5	22	3	LIS	12/12, 100%	0/12, 0%	0/12, 0%
						NIT	10/12, 83%	2/12, 17%	0/12, 0%
Maria [30]	1998	30	2	16	5	BT	11/15, 73%	4/15, 27%	
						NIT	2/15, 13%	13/15, 87%	
Brisinda [33]	1999	50	2	15	4	BT	24/25, 96%		0/25, 0%
						NIT	15/25, 60%		0/25, 0%
Richard [50]	2000	82	1.5	6	3	LIS	34/38, 89%	3/38, 8%	
						NIT	13/42, 31%	32/42, 76%	
Evans [51]	2001	65	2	5	3	LIS	26/27, 96%		2/27, 7%
						NIT	20/33, 61%		0/33, 0%
Colak [52]	2002	62	2		3	BT	24/34, 71%		
						NIT	6/28, 21%		
Libertiny [26]	2002	70	2	24	3	LIS	35/35, 100%	1/35, 3%	1/35, 3%
						NIT	19/35, 54%	19/35, 54%	0/35, 0%
Hancke [43]	2003	60	3		3	FIAP	22/30, 73%		3/27, 11%
						LIS	24/30, 80%		6/30, 20%
Mentes [53]	2003	111	6	12	4	LIS	49/50, 98%	3/50, 6%	8/50, 16%
						BT	53/61, 87%	15/61, 25%	0/61, 0%
Siproudhis [54]	2003	45	2	3	5	BT	7/20, 35%		
						NIT	7/20, 35%		
Boschetto [41]	2004	36	1		2	DILA	17/18, 94%		
						NIT	7/18, 39%		
Parellada [20]	2004	63	2.5	3	3	LIS	27/27, 100%	0/27, 0%	12/27, 44%
						NIT	24/27, 89%	6/27, 22%	0/27, 0%
Arroyo [55]	2005	80	12	12	3	LIS	37/40, 92%		2/40, 5%
						BT	18/40, 45%		0/40, 0%
Ho [56]	2005	136	4	4	3	LIS	88/91, 97%		
						NIT	7/41, 17%		
Iswariah [18]	2005	38	6.5		3	LIS	19/21, 90%		0/21, 0%
						BT	7/17, 41%		0/17, 0%

Table 1 continued

First author of reference	Year	Sample size (*n*)	Follow-up (months)		Jadad score [16] (0–5)	Treatment arm	Outcome		
			Healing	Longtime follow-up‡			Healing rate	No-success rate	Incontinence rate
Mishra [57]	2005	40	1.5		4	LIS	17/20, 85%		3/20, 15%
						NIT	18/20, 90%		0/20, 0%
Wang [36]	2005	100	1		2	FIAP	41/50, 82%	9/50, 18%	0/50, 0%
						LIS	49/50, 98%	1/50, 2%	0/50, 0%
De Nardi [58]	2006	30	3	36	2	BT	8/15, 53%	10/15, 67%	0/15, 0%
						NIT	10/15, 67%	9/15, 60%	0/15, 0%
Fruehauf [59]	2006	50	0.5		2	BT	6/24, 25%		0/23, 0%
						NIT	13/24, 54%		0/23, 0%
Katsinelos [27]	2006	64	2	20	3	LIS	32/32, 100%	0/32, 0%	4/32, 12%
						NIT	30/31, 97%	3/31, 10%	0/30, 0%
Brisinda [60]	2007	100	2	21	5	BT	46/50, 92%	4/50, 8%	
						NIT	35/50, 70%	27/50, 54%	
Ram [39]	2007	108		11.2	2	LIS			2/53, 4%
						DILA			8/55, 15%
Renzi [40]	2008	53	1.5	24	4	LIS	23/25, 92%	3/25, 12%	4/25, 16%
						DILA	20/24, 83%	4/24, 17%	3/24, 12%
Siddique [28]	2008	70	2.5		2	LIS	33/33, 100%		2/33, 6%
						NIT	21/31, 68%		0/31, 0%
Suknaic [61]	2008	60	3		1	LIS	21/28, 75%		5/28, 18%
						BT	19/27, 70%		3/27, 11%
Abd Elhady [31]	2009	160	2	60	3	LIS	38/40, 95%		2/40, 5%
						BT			0/40, 0%
						NIT	68/80, 85%		0/80, 0%
Festen [32]	2009	73	4	6.7	4	BT	7/28, 25%		1/21, 5%
						NIT	16/31, 52%		0/27, 0%
Mousavi [21]	2009	62	2	22	3	FIAP	30/30, 100%	1/30, 3%	2/30, 7%
						LIS	32/32, 100%	0/32, 0%	0/32, 0%
Nasr [62]	2010	80	6	6	3	LIS	36/40, 90%	8/40, 20%	6/40, 15%
						BT	25/40, 62%	31/40, 78%	0/40, 0%
Magdy [34]	2012	100	3	12	3	FIAP	34/50, 68%	26/50, 52%	0/50, 0%
						LIS	43/50, 86%	8/50, 16%	7/50, 14%
Samim [63]	2012	134	3	39	5	BT	26/52, 50%	33/52, 63%	0/52, 0%
						NIT	32/67, 48%	48/67, 72%	0/67, 0%
Valizadeh [64]	2012	50	3	12	3	LIS	23/25, 92%	2/25, 8%	4/25, 16%
						BT	20/25, 80%	13/25, 52%	0/25, 0%
Arslan [65]	2013	247	2	12	4	LIS	98/102, 96%	4/102, 4%	6/102, 6%
						NIT	81/105, 77%	29/105, 28%	0/105, 0%
Aslam [66]	2014	60	1.5		2	LIS	28/30, 93%		2/30, 7%
						NIT	15/30, 50%		0/30, 0%
Berkel [37]	2014	66	2.25	12	3	BT	18/27, 67%		5/27, 19%
						NIT	11/33, 33%		4/33, 12%
Giridhar [29]	2014	60	1	4.5	2	LIS	27/27, 100%		0/27, 0%
						NIT	23/26, 88%		0/26, 0%

FIAP Fissurectomy and/or anoplasty, *LIS* lateral internal sphincterotomy, *BT* botulinum toxin injection, *DILA* anal dilatation, *NIT* noninvasive treatment

‡ Longest follow up documented in the manuscript, normally time when no-success was documented

reported by the studies included in the meta-analysis. Interestingly, they excluded patients with a normal or low resting pressure before the operation. This approach was in contrast to that of Leoung et al. [22], who performed a rhomboid skin flap and achieved a much higher healing rate.

Incontinence rate

The rate of incontinence after LIS varied from 0 [18, 21, 22, 25, 29, 33, 35, 36] to 44.4% [20]. Parellada et al. [20] found the highest rate of minor incontinence, although the rate did decline to 15% after 24 months. Iswariah et al. [18] observed no newly emerged cases of incontinence at all based on calculations of a modified Wexner continence score before and after the operation.

Of the 17 studies with conservative treatment and/or placebo, 16 had an incontinence rate of 0%; the remaining one study [37] reported a rate of 12.1%, although the reported incontinence in patients using isosorbide dinitrate lasted only 1 week.

The incontinence rate after DILA ranged from 5.1 [38] to 39.3% [23]. In these studies, the lowest incontinence rate of 5.1% was reported after anal dilation with 4 fingers for 4 min [38], whereas another group applying this technique reported an incontinence rate of 14.5% [39]. More recently, there have been attempts to perform anal dilatation in a more controlled manner using pneumatic balloon dilatation (4 cm) [40, 41]. However, the incontinence rates in these studies using this modification still ranged up to 12.5% [40]. Doing a DILA to a much wider distance (7–8 cm) led to an even higher incontinence rate of 24.3% [42].

Incontinence after FIAP was examined in five studies. Three studies reported no incontinence at all. Moussavi et al. [21] reported a rate of 6.7%, and Hancke et al. reported a rate of 11.1% [43]. The latter used an anal retractor for fissurectomy, functionally performing a type of "dilatation," which might explain the higher rate of incontinence. However, this dilatation was only to a diameter of 2.4 × 1.3 cm, which can also be interpreted as the normal range of opening a retractor to perform any type of operation in the anal canal and not a dilatation per se [43].

Meta-analysis of healing rate

Network description

The evidence for this network is based on 2883 patients in 42 trials with 2190 events of healing. In the network for this analysis, LIS is associated with all other treatment modalities (Fig. 2). Therefore, for LIS, direct comparisons against all other treatments were available. For FIAP, direct comparisons were only conducted against LIS. Hence, the comparisons of FIAP against BT, DILA, and NIT are based on indirect comparisons only.

Meta-analysis of single event rates

A fixed effect and random effects meta-analysis for the healing rate for each intervention group revealed relevant heterogeneity in the visual examination of the forest plots. The test values for LIS ($I^2 = 75.6\%$, $Q = 123.1$, $p < 0.001$), DILA ($I^2 = 68.0\%$, $Q = 21.9$, $p = 0.003$) and BT ($I^2 = 81.6\%$, $Q = 81.5$, $p < 0.001$) represent substantial heterogeneity, while moderate heterogeneity was observed for FIAP ($I^2 = 55.9\%$, $Q = 9.1$, $p = 0.060$). The random effects model showed a significantly higher healing rate for anal fissures after LIS than for all other analysed treatment groups [93.1%, 95% confidence interval (CI) 88.9–95.7%]. DILA ranked second (84.4%, 95% CI 73.5–91.3%), followed by FIAP (79.8%, 95% CI 67.4–88.4%) and BT (62.6%, 95% CI: 50.6–73.2%). The healing rate for NIT reached 58.6% (95% CI 48.4–68.1%) (Fig. 3). These findings were confirmed by the fixed effect models.

Fixed and random effects network meta-analysis

For the network meta-analysis of the healing rate, significant heterogeneity and inconsistency were observed ($I^2 = 59.6\%$, $Q = 94.1$, $p < 0.001$). In the fixed effect heat plot substantial inconsistencies (i.e. differences between direct and indirect comparisons) for NIT and DILA and for LIS and DILA were detected. In contrast, in the random effects heat plot only moderate inconsistencies were observed. In the random effects network meta-analysis (main analysis), LIS had the highest OR of 9.93 (95% CI: 5.45–18.09), followed by DILA with an OR of 8.56 (95% CI: 3.05–24.02), FIAP with an OR of 3.51 (95% CI: 0.97–12.74) and BT with an OR of 1.95 (95% CI: 1.09–3.51). Fixed effect network meta-analysis yielded similar results for LIS (OR 9.30, 95% CI 6.37–13.57), DILA (OR 10.66, 95% CI: 5.76–19.75), FIAP (OR 3.59, 95% CI 1.67–7.71), and BT (OR 1.74, 95% CI: 1.26–2.41). Additionally, ranking the treatments equally substantiated these findings. LIS had the highest p score (with a p score of 0 meaning worst treatment and 1 meaning best treatment) with 0.898, followed by DILA (0.814), FIAP (0.483), BT (0.296) and NIT (0.010).

Bayesian random effects network meta-analysis

To complete the statistical analysis in adherence to the actual PRISMA guidelines, a random effects Bayesian network meta-analysis was fitted (Fig. 3). This model confirmed significantly higher healing rates for LIS

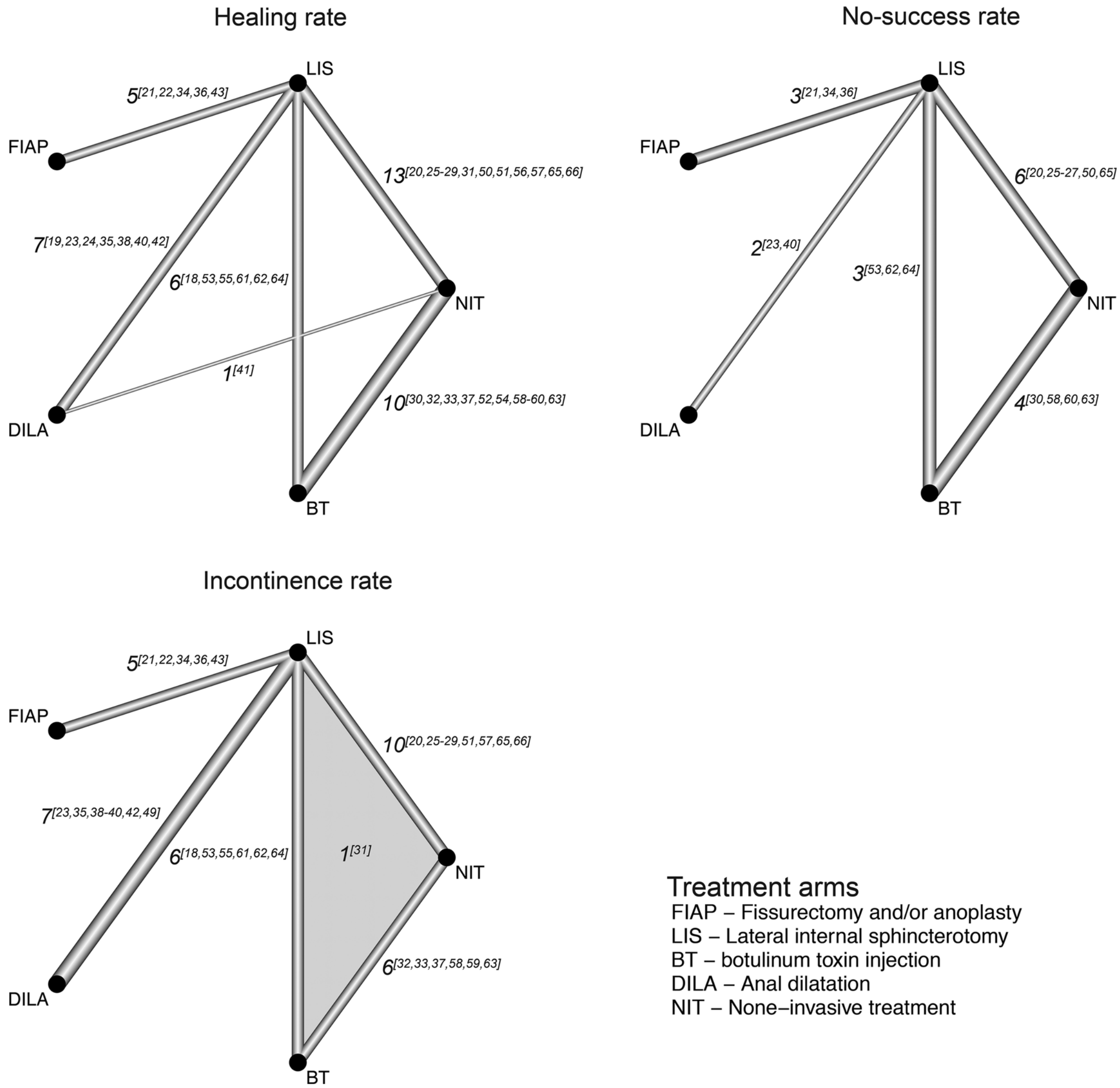

Fig. 2 Network graphs for healing rate, incontinence rate, no-success rate. *Thickness of the lines* corresponds to the amount of evidence in a single comparison. In the network for incontinence, the *plane in the trigon* represents the analysis in which LIS, NIT and BT are compared

compared with the other treatment groups (91.2, 95% CI 85.8−94.5%). DILA ranked second (85.0, 95% CI 73.9−92.0%), followed by FIAP with 80.6% (95% CI 62.6–91.4%) and BT (62.8, 95% CI 50.2−73.6%). The healing rate for NIT was 56.5% (95% CI 46.7−65.8%). Compared with NIT, LIS again had the highest OR of 7.92 (95% CI 4.31–14.27), followed by DILA with an OR of 4.39 (95% CI 1.98−9.65), FIAP with an OR of 3.20 (95% CI 1.21−8.73) and BT with an OR of 1.31 (95% CI 0.69−2.33) (Fig. 3). Ranking in the Bayesian analysis showed that LIS ranked first in 90.1% of models; DILA ranked second and third in 64.8 and 28.4% of the models, respectively, FIAP ranked second and third in 25.8 and 66.5% of the models, respectively, whereas BT ranked fourth in 76.3% of the models and NIT ranked last in 79.8% of the models.

Meta-analysis of post-interventional incontinence rate

Network description

The evidence for this network is based on 2393 patients in 35 trials with 144 events of incontinence. For FIAP and DILA, direct comparisons were only conducted with LIS. LIS is represented with comparisons to all other treatment groups (Fig. 2).

Meta-analysis of single event rates

A fixed effect and random effects meta-analysis for the post-interventional incontinence rate for each intervention group revealed heterogeneity in the visual examination of

Therapy	Studies	Patients	Events	Rate	95%CI	OR	95%CI
FIAP	5	180	145	79.8%	(67.4–88.4%)	**3.51**	(0.97–12.74)
				80.6%	(62.6–91.4%)	**3.20**	(1.21–8.73)
LIS	31	1105	1011	93.1%	(88.9–95.7%)	**9.93**	(5.45–18.09)
				91.2%	(85.8–94.5%)	**7.92**	(4.31–14.27)
BT	16	500	319	62.6%	(50.6–73.2%)	**1.95**	(1.09–3.51)
				62.8%	(50.2–73.6%)	**1.31**	(0.69–2.33)
DILA	8	259	212	84.4%	(73.5–91.3%)	**8.56**	(3.05–24.02)
				85.0%	(73.9–92.0%)	**4.39**	(1.98–9.65)
NIT	24	839	503	58.6%	(48.4–68.1%)	**1.00**	reference
				56.5%	(46.7–65.8%)	**1.00**	reference

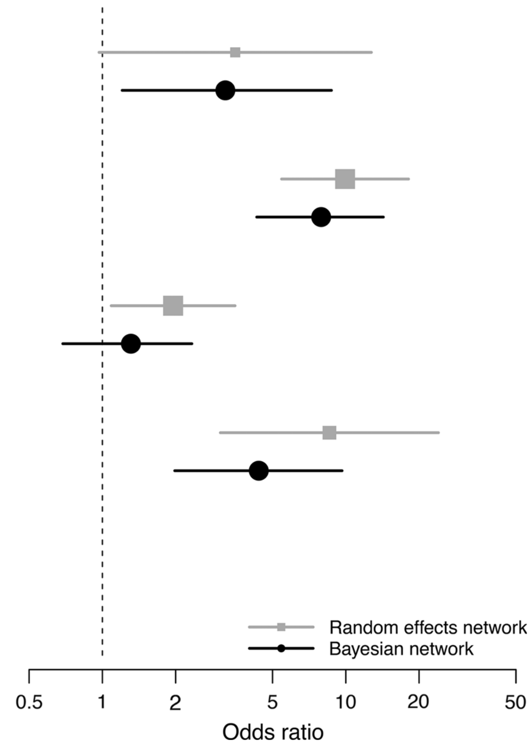

Fig. 3 Healing rate in random effects and Bayesian network meta-analysis. *OR* Odds ratio, *CI* confidence interval

the forest plots. The test of heterogeneity for LIS ($I^2 = 52.1\%$, $Q = 60.6$, $p = 0.001$) and DILA ($I^2 = 60.1\%$, $Q = 15.1$, $p = 0.020$) identified a moderate heterogeneity; however, only a low degree of heterogeneity was observed for NIT ($I^2 = 0\%$, $Q = 14.9$, $p = 0.600$), BT ($I^2 = 33.3\%$, $Q = 19.5$, $p = 0.108$) and FIAP ($I^2 = 21.6\%$, $Q = 5.1$, $p = 0.277$).

The random effects model revealed a significantly higher incontinence rate after DILA than after any other analysed treatment group (18.2%, 95% CI 11.2–28.2%). LIS ranked second (9.2%, 95% CI 6.7–12.7%), followed by FIAP (4.9%, 95% CI 1.9–12.0%), BT (4.1%, 95% CI 1.9–8.5%) and NIT (3.0%, 95% CI: 1.7–5.2%) (Fig. 4). These findings were confirmed by fixed effect models.

Fixed and random effects network meta-analysis

No significant heterogeneity or inconsistency was observed for the network meta-analysis of the incontinence rate ($I^2 = 0\%$, $Q = 24.1$, $p = 0.842$). No substantial inconsistencies were detected in either the fixed effect heat plot or the random effects heat plot.

In the random effects network meta-analysis, DILA yielded the highest risk for incontinence with an OR of 16.92 (95% CI 5.99–47.78), LIS ranked second with an OR of 6.81 (95% CI 3.08–15.06), followed by FIAP with an OR of 3.94 (95% CI 1.03–15.08) and BT with an OR of 1.63 (95% CI 0.71–3.74). NIT was the reference with an OR of 1.

The fixed effect network meta-analysis yielded similar results. Ranking of treatments in frequentist analysis further supported these results: NIT had the highest P score at 0.963, followed by BT (0.717), FIAP (0.487), LIS (0.289) and DILA (0.004).

Bayesian random effects network meta-analysis

This model confirmed significantly higher incontinence rates for DILA compared with the other treatment groups (20.4%, 95% CI 11.0–35.8%). LIS ranked second (9.5%, 95% CI: 6.4–14.2%), followed by FIAP (4.6%, 95% CI 0.8–22.4%) and BT (2.0%, 95% CI 0.4–7.4%). NIT reached 0.5% (95% CI 0–3.8%). Compared with NIT, DILA again had the highest OR of 50.96 (95% CI 5.70–880.95), followed by LIS with an OR of 20.72 (95% CI 2.53–334.96), FIAP with an OR of 9.70 (95% CI 0.64–228.15) and BT with an OR of 3.82 (95% CI 0.55–55.92) (Fig. 4). Ranking in Bayesian analysis showed that NIT ranked first in 87.4% of the models with the lowest risk for incontinence, BT ranked second in 70.7% and third in 20.0% of the models, FIAP ranked second in 18.1% and third in 58.3% of the models, LIS ranked fourth

Therapy	Studies	Patients	Events	Rate	95%CI	OR	95%CI
FIAP	5	177	5	4.9%	(1.9–12.0%)	**3.94**	(1.03–15.08)
				4.6%	(0.8–22.4%)	**9.70**	(0.64–228.15)
LIS	29	980	84	9.4%	(6.8–13.0%)	**6.81**	(3.08–15.06)
				9.5%	(6.3–14.2%)	**20.72**	(2.53–334.96)
BT	12	373	9	4.1%	(1.9–8.5%)	**1.63**	(0.71–3.74)
				2.0%	(0.4–7.4%)	**3.82**	(0.55–55.92)
DILA	7	244	42	18.2%	(11.2–28.2%)	**16.92**	(5.99–47.78)
				20.4%	(11.0–35.8%)	**50.96**	(5.70–880.95)
NIT	17	619	4	3.0%	(1.7–5.2%)	**1.00**	reference
				0.5%	(0.0–3.8%)	**1.00**	reference

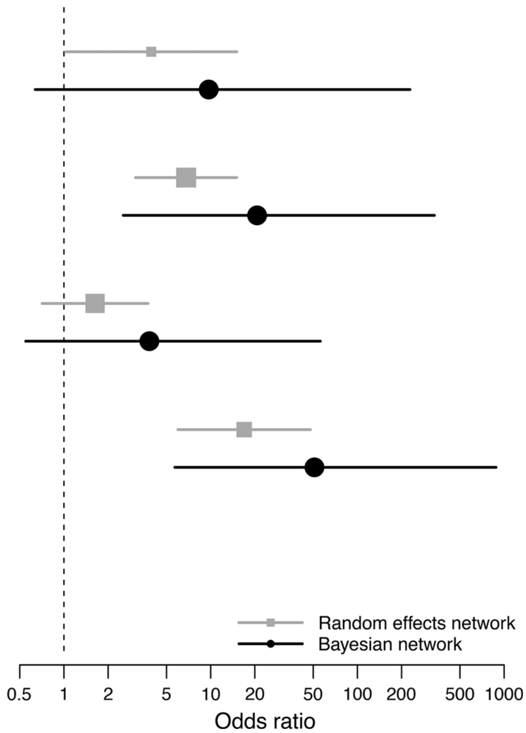

Fig. 4 Incontinence rate in random effects and Bayesian network meta-analysis

in 78.1% of the models and DILA ranked last in 93.8% of the models, indicating the highest risk for post-interventional incontinence.

Meta-analysis of no-success rate

The random effects model of the no-success rate supported the findings of the meta-analysis for the healing rate in an inversely arranged ranking. Details on this analysis data are provided in ESM Text S3 and Fig. 5.

Discussion

This study is the first network meta-analysis of RCTs concerning both invasive and non-invasive treatments of chronic anal fissures.

In all of the effects models investigated, LIS was persistently the most efficacious treatment option, with a healing rate of 93.1%. However, 9.4% of the patients suffered from postoperative incontinence. Anal dilatation yielded the highest risk for postoperative incontinence (exceeding 18%) and should therefore be abandoned in clinical practice in accordance with actual guidelines [8]. Other treatment options were less efficacious but were more safe: FIAP had a healing rate of almost 80% with a risk for postoperative incontinence of 4.9%, BT had a healing rate of 62.6% with a risk for post-interventional incontinence of 4.1% and NIT achieved a healing rate of 58.6%.

In agreement with our findings, Nelson et al. also reported that LIS yielded the highest healing rate in their two separate pair-wise meta-analyses [10, 11]. The main differences between the our network meta-analysis and those of Nelson et al. [10, 11] are a significantly higher healing rate for BT in our analysis compared with conservative treatment and a significantly lower incontinence rate after both FIAP and BT compared with LIS. One reason for this inconsistency may be that there was only one study comparing fissurectomy and LIS head-to-head with respect to incontinence in the meta-analysis by Nelson et al. Another explanation might be the variety and heterogeneity of the studies and that in contrast to pairwise meta-analyses, network meta-analysis enables the measurement of relative efficacy between every intervention.

The high incontinence rate after LIS may even increase over the long term. A recent conventional meta-analysis [9] confirmed a high rate of incontinence after LIS. That review of 22 RCTs, which analysed long-term disturbance in continence after LIS (24–124 months), found an overall incontinence rate as high as 14%. Hasse et al. [44] demonstrated that the incontinence rate increases rather than decreases with time after LIS. In the cohort study of these authors 14.8% of the patients had continence

Therapy	Studies	Patients	Events	Rate	95%CI	OR	95%CI
FIAP	3	130	36	20.4%	(5.0–55.6%)	**0.31**	(0.08–1.25)
				26.0%	(9.3–53.8%)	**0.36**	(0.09–1.33)
LIS	14	548	34	6.9%	(4.3–11.0%)	**0.05**	(0.03–0.12)
				7.1%	(3.6–14.2%)	**0.08**	(0.03–0.19)
BT	7	258	110	43.5%	(23.9–65.3%)	**0.36**	(0.18–0.75)
				41.3%	(23.2–62.7%)	**0.69**	(0.28–2.14)
DILA	2	52	13	25.0%	(12.7–43.3%)	**0.18**	(0.03–0.93)
				27.9%	(8.5–61.1%)	**0.39**	(0.08–1.80)
NIT	10	399	188	47.3%	(31.2–63.9%)	**1.00**	reference
				49.7%	(35.0–64.7%)	**1.00**	reference

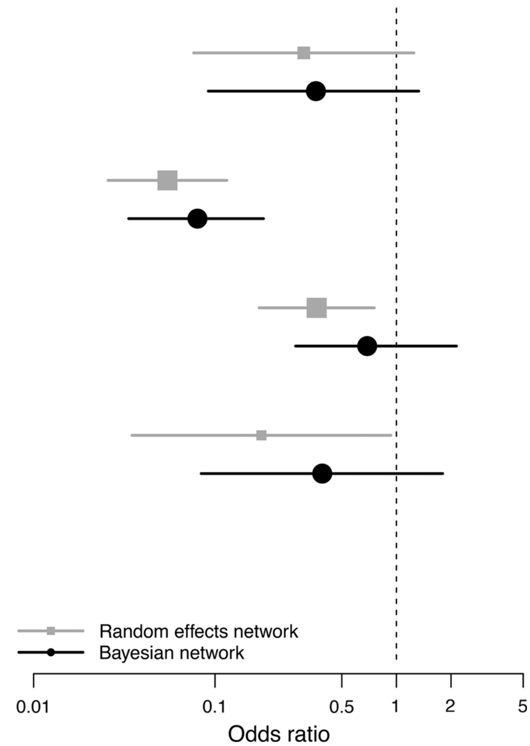

Fig. 5 No-success rate in random effects and Bayesian network meta-analysis

disturbance after 12 weeks, with an increase to 21% after a median follow-up of 124 months.

Although it was not possible to evaluate the proportion of transient and persistent incontinence rates after the respective procedures in this meta-analysis, it is barely conceivable that NIT as well as BT injection could, due to their mechanisms of action, cause persistent incontinence. This assumption is also supported by evidence from a prospective trial [45].

According to our results, FIAP might be both an efficient and safe treatment alternative to LIS on the one hand and to conservative treatment on the other. BT did indeed yield a significant, but only marginally, higher healing rate than conservative treatment, so its use as a first-line treatment might be questionable. Combined with fissurectomy however, BT injection could have an additional benefit in targeting both pathogenic factors of chronic anal fissures, i.e. sphincter hypertonicity and fibrotic ulceration. However, to date, no RCTs have examined this combination treatment. Lindsey et al. demonstrated in their prospective trial that 93% of the fissures were healed at a median of approximately 4 months and that 7% of the patients experienced transitory flatus incontinence [46].

It has to be mentioned that BT is, in most countries, not officially approved for the indication of anal fissures and is thus used "off-label."

The limitations of this investigation need to be acknowledged.

First, there was undoubtedly heterogeneity between and within the included studies. Clinical heterogeneity derived from diverging definitions of inclusion criteria, treatment and outcome parameters, lengths of follow-up and patient collectives. Methodological diversity comprised the variability in study design and risk of bias, such as from blinding or allocation concealment. Statistical heterogeneity is a consequence of the latter two factors and manifests itself in the observed treatment effects. Test values in the present network meta-analysis, e.g., I^2, showed that there may be moderate to substantial heterogeneity, which may reduce the degree of confidence in the treatment proposals. However, the fixed effects and Bayesian effects models showed virtually the same results as the random effects model and thus support the statistical significance of these models. Further, a certain heterogeneity in pooled reviews is inevitable and should not lead to the exclusion of studies according to the current recommendations of the Cochrane Collaboration [47, 48].

Second, the present meta-analysis did concentrate on the two outcome parameters "healing rate" and "incontinence." Because the data to calculate the "no-success rate" were missing in many trials, it could only be a secondary endpoint. The meta-analysis did not examine complications other than incontinence. In the literature, there are other reported complications, such as postoperative wound pain or bleeding/hematoma, after both LIS and fissurectomy to different degrees. Another factor is that quality of life was not assessed. It is unknown to what extent minor incontinence affected the patients and to what degree they were still satisfied with their respective operative treatments.

We conclude that treatment of chronic anal fissures should account for the trade-offs between risks and benefits. In our network meta-analysis, LIS was clearly the most efficacious treatment option. It had the highest healing rate and the lowest no-success rate. However, patients had to face a comparatively high risk of postoperative incontinence that was over 9%. In clinical practice, we therefore recommend a gradual approach and a treatment algorithm. As a first step, medical treatment is safe with few side effects. In persistent fissures, fissurectomy and/or BT injection may be performed to approach both fissure scarring and sphincter hypertonicity. In patients with treatment failure, LIS can be discussed. However, patients should be carefully selected, especially with respect to preoperative sphincter dysfunction and risk factors for postoperative incontinence [9].

Additional RCTs are needed, especially concerning the long-term incontinence rates after fissurectomy and/or BT and the combined effect of these two treatments.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval Being a metaanalysis, no direct patients data analysis was done in the present analysis. Still the principles of good clinical practice and the current version of the Deklaration of Helsinki were followed, as applicabel.

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References

1. Pascual M, Pera M, Courtier R, et al. Endosonographic and manometric evaluation of internal anal sphincter in patients with chronic anal fissure and its correlation with clinical outcome after topical glyceryl trinitrate therapy. Int J Colorectal Dis. 2007;22:963–7.
2. Herzig DO, Lu KC. Anal fissure. Surg Clin North Am. 2010;90:33–44.
3. Ayantunde AA, Debrah SA. Current concepts in anal fissures. World J Surg. 2006;30:2246–60.
4. Schouten WR, Briel JW, Auwerda JJ, et al. Ischaemic nature of anal fissure. Br J Surg. 1996;83:63–5.
5. Cross KL, Massey EJ, Fowler AL, et al. The management of anal fissure: ACPGBI position statement. Colorectal Dis. 2008;10[Suppl 3]:1–7.
6. Griffin N, Acheson AG, Tung P, et al. Quality of life in patients with chronic anal fissure. Colorectal Dis. 2004;6:39–44.
7. Ortiz H, Marzo J, Armendariz P, et al. Quality of life assessment in patients with chronic anal fissure after lateral internal sphincterotomy. Br J Surg. 2005;92:881–5.
8. Perry WB, Dykes SL, Buie WD, et al. Practice parameters for the management of anal fissures (3rd revision). Dis Colon Rectum. 2010;53:1110–5.
9. Garg P, Garg M, Menon GR. Long-term continence disturbance after lateral internal sphincterotomy for chronic anal fissure: a systematic review and meta-analysis. Colorectal Dis. 2013;15:e104–17.
10. Nelson RL, Thomas K, Morgan J, et al. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. 2012;15(2):CD003431.
11. Nelson RL, Chattopadhyay A, Brooks W, et al. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2011:CD002199.
12. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med. 2013;11:159.
13. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ. 2013;346:f2914.
14. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777–84.
15. Rucker G, Schwarzer G. Automated drawing of network plots in network meta-analysis. Res Synth Methods. 2016;7:94–107.
16. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
17. Berger VW, Alperson SY. A general framework for the evaluation of clinical trial quality. Rev Recent Clin Trials. 2009;4:79–88.
18. Iswariah H, Stephens J, Rieger N, et al. Randomized prospective controlled trial of lateral internal sphincterotomy versus injection of botulinum toxin for the treatment of idiopathic fissure in ano. ANZ J Surg. 2005;75:553–5.
19. Marby M, Alexander-Williams J, Buchmann P, et al. A randomized controlled trial to compare anal dilatation with lateral subcutaneous sphincterotomy for anal fissure. Dis Colon Rectum. 1979;22:308–11.
20. Parellada C. Randomized, prospective trial comparing 0.2 percent isosorbide dinitrate ointment with sphincterotomy in treatment of chronic anal fissure: a two-year follow-up. Dis Colon Rectum. 2004;47:437–43.
21. Mousavi SR, Sharifi M, Mehdikhah Z. A comparison between the results of fissurectomy and lateral internal sphincterotomy in the surgical management of chronic anal fissure. J Gastrointest Surg. 2009;13:1279–82.
22. Leong AF, Seow-Choen F. Lateral sphincterotomy compared with anal advancement flap for chronic anal fissure. Dis Colon Rectum. 1995;38:69–71.
23. Jensen SL, Lund F, Nielsen OV, et al. Lateral subcutaneous sphincterotomy versus anal dilatation in the treatment of fissure in ano in outpatients: a prospective randomised study. Br Med J (Clin Res Ed). 1984;289:528–30.
24. Hiltunen KM, Matikainen M. Anal manometric evaluation in anal fissure. Effect of anal dilation and lateral subcutaneous sphincterotomy. Acta Chir Scand. 1986;152:65–8.
25. Oettle GJ. Glyceryl trinitrate vs. sphincterotomy for treatment of chronic fissure-in-ano: a randomized, controlled trial. Dis Colon Rectum. 1997;40:1318–20.
26. Libertiny G, Knight JS, Farouk R. Randomised trial of topical 0.2% glyceryl trinitrate and lateral internal sphincterotomy for the

treatment of patients with chronic anal fissure: long-term follow-up. Eur J Surg. 2002;168:418–21.
27. Katsinelos P, Papaziogas B, Koutelidakis I, et al. Topical 0.5% nifedipine vs. lateral internal sphincterotomy for the treatment of chronic anal fissure: long-term follow-up. Int J Colorectal Dis. 2006;21:179–83.
28. Siddique MI, Murshed KM, Majid MA. Comparative study of lateral internal sphincterotomy versus local 0.2% glyceryl trinitrate ointment for the treatment of chronic anal fissure. Bangladesh Med Res Counc Bull. 2008;34:12–5.
29. Giridhar CM, Babu P, Rao KS. A comparative study of lateral sphincterotomy and 2% diltiazem gel local application in the treatment of chronic fissure in ANO. J Clin Diagn Res. 2014;8:NC01–2.
30. Maria G, Cassetta E, Gui D, et al. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. N Engl J Med. 1998;338:217–20.
31. Abd Elhady HM, Othman IH, Hablus MA, et al. Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. S Afr J Surg. 2009;47:112–4.
32. Festen S, Gisbertz SS, van Schaagen F, et al. Blinded randomized clinical trial of botulinum toxin versus isosorbide dinitrate ointment for treatment of anal fissure. Br J Surg. 2009;96:1393–9.
33. Brisinda G, Maria G, Bentivoglio AR, et al. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. N Engl J Med. 1999;341:65–9.
34. Magdy A, El Nakeeb A, el Fouda Y, et al. Comparative study of conventional lateral internal sphincterotomy, V-Y anoplasty, and tailored lateral internal sphincterotomy with V-Y anoplasty in the treatment of chronic anal fissure. J Gastrointest Surg. 2012;16:1955–62.
35. Fischer M. Hamelmann H. Dilatation or sphincterotomy as the treatment of primary-chronic fissure in ano. Results of a random, clinical study after 2–3 years. Chirurg. 1978;49:215–8.
36. Wang ZY, Sun JH, Chen XJ. Prospective randomized trial of optimum anal canal release treatment for chronic anal fissure. Zhong Xi Yi Jie He Xue Bao. 2005;3(190):206.
37. Berkel AE, Rosman C, Koop R, et al. Isosorbide dinitrate ointment vs botulinum toxin A (Dysport) as the primary treatment for chronic anal fissure: a randomized multicentre study. Colorectal Dis. 2014;16:O360–6.
38. Weaver RM, Ambrose NS, Alexander-Williams J, et al. Manual dilatation of the anus vs. lateral subcutaneous sphincterotomy in the treatment of chronic fissure-in-ano. Results of a prospective, randomized, clinical trial. Dis Colon Rectum. 1987;30:420–3.
39. Ram E, Vishne T, Lerner I, et al. Anal dilatation versus left lateral sphincterotomy for chronic anal fissure: a prospective randomized study. Tech Coloproctol. 2007. doi:10.1007/s10151-007-0373-7
40. Renzi A, Izzo D, Di Sarno G, et al. Clinical, manometric, and ultrasonographic results of pneumatic balloon dilatation vs. lateral internal sphincterotomy for chronic anal fissure: a prospective, randomized, controlled trial. Dis Colon Rectum. 2008;51:121–7.
41. Boschetto S, Giovannone M, Tosoni M, et al. Hydropneumatic anal dilation in conservative treatment of chronic anal fissure: clinical outcomes and randomized comparison with topical nitroglycerin. Tech Coloproctol. 2004;8:89–92 (discussion 92–3).
42. Saad AM, Omer A. Surgical treatment of chronic fissure-in-ano: a prospective randomised study. East Afr Med J. 1992;69:613–5.
43. Hancke E, Schwaner S. Chronic anal fissure-operativ treatement with analdialtation, fissurektomy vs. lateral sphinterotomy. Coloproctology. 2003;25:95–105.
44. Hasse C, Brune M, Bachmann S, et al. Lateral, partial sphincter myotomy as therapy of chronic anal fissue. Long-term outcome of an epidemiological cohort study. Chirurg. 2004;75:160–7.
45. Jost WH. One hundred cases of anal fissure treated with botulin toxin: early and long-term results. Dis Colon Rectum. 1997;40:1029–32.
46. Lindsey I, Cunningham C, Jones OM, et al. Fissurectomy-botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. Dis Colon Rectum. 2004;47:1947–52.
47. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.
48. Higgins JPT GSe. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration. Available from http://www.cochrane-handbook.org. 2011 (updated March 2011).
49. Olsen J, Mortensen PE, Krogh Petersen I, et al. Anal sphincter function after treatment of fissure-in-ano by lateral subcutaneous sphincterotomy versus anal dilatation. A randomized study. Int J Colorectal Dis. 1987;2:155–7.
50. Richard CS, Gregoire R, Plewes EA, et al. Internal sphincterotomy is superior to topical nitroglycerin in the treatment of chronic anal fissure: results of a randomized, controlled trial by the Canadian Colorectal Surgical Trials Group. Dis Colon Rectum. 2000;43:1048–57 (discussion 1057–8).
51. Evans J, Luck A, Hewett P. Glyceryl trinitrate vs. lateral sphincterotomy for chronic anal fissure: prospective, randomized trial. Dis Colon Rectum. 2001;44:93–7.
52. Colak T, Ipek T, Kanik A, et al. A randomized trial of botulinum toxin vs lidocain pomade for chronic anal fissure. Acta Gastroenterol Belg. 2002;65:187–90.
53. Mentes BB, Irkorucu O, Akin M, et al. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. Dis Colon Rectum. 2003;46:232–7.
54. Siproudhis L, Sebille V, Pigot F, et al. Lack of effficacy of botulinum toxin in chronic anal fissure. Aliment Pharmacol Ther. 2003;18:515–24.
55. Arroyo A, Perez F, Serrano P, et al. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. Am J Surg. 2005;189:429–34.
56. Ho KS, Ho YH. Randomized clinical trial comparing oral nifedipine with lateral anal sphincterotomy and tailored sphincterotomy in the treatment of chronic anal fissure. Br J Surg. 2005;92:403–8.
57. Mishra R, Thomas S, Maan MS, et al. Topical nitroglycerin versus lateral internal sphincterotomy for chronic anal fissure: prospective, randomized trial. ANZ J Surg. 2005;75:1032–5.
58. De Nardi P, Ortolano E, Radaelli G, et al. Comparison of glycerine trinitrate and botulinum toxin-a for the treatment of chronic anal fissure: long-term results. Dis Colon Rectum. 2006;49:427–32.
59. Fruehauf H, Fried M, Wegmueller B, et al. Efficacy and safety of botulinum toxin a injection compared with topical nitroglycerin ointment for the treatment of chronic anal fissure: a prospective randomized study. Am J Gastroenterol. 2006;101:2107–12.
60. Brisinda G, Cadeddu F, Brandara F, et al. Randomized clinical trial comparing botulinum toxin injections with 0.2 per cent nitroglycerin ointment for chronic anal fissure. Br J Surg. 2007;94:162–7.
61. Suknaic S, Patrlj L, Steresinic M, et al. Surgical or biologic sphincterotomy in the treatment of chronic anal fissure. Acta Med Croatica. 2008;62:73–80.
62. Nasr M, Ezzat H, Elsebae M. Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure: a randomized controlled trial. World J Surg. 2010;34:2730–4.

63. Samim M, Twigt B, Stoker L, et al. Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial. Ann Surg. 2012;255:18–22.
64. Valizadeh N, Jalaly NY, Hassanzadeh M, et al. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial. Langenbecks Arch Surg. 2012;397:1093–8.
65. Arslan K, Erenoglu B, Dogru O, et al. Lateral internal sphincterotomy versus 0.25% isosorbide dinitrate ointment for chronic anal fissures: a prospective randomized controlled trial. Surg Today. 2013;43:500–5.
66. Aslam MI, Pervaiz A, Figueiredo R. Internal sphincterotomy versus topical nitroglycerin ointment for chronic anal fissure. Asian J Surg. 2014;37:15–9.