

## The effectiveness of tibial nerve stimulation in managing chronic anal fissures: Systematic review and meta-analysis

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**Abstract:** Surgical sphincterotomy, such as lateral internal sphincterotomy (LIS), and chemical sphincterotomy, such as Glyceryl Trinitrate (GTN) or Botulinum Toxin (BT), have been the main options for treating chronic anal fissures for many years. However, in recent years, tibial nerve stimulation (TNS) has emerged as a non-invasive alternative for managing this condition. This systematic review and meta-analysis aim to gather evidence on the effectiveness of TNS in treating chronic anal fissures. The authors conducted a comprehensive search across PubMed, Google Scholar, and Web of Science databases, covering publications from January 2000 to January 2024. The search keywords included tibial nerve stimulation, percutaneous tibial nerve stimulation, transcutaneous tibial nerve stimulation, sacral neuromodulation, and anal fissure. A total of 282 studies were identified; after removing duplicates and irrelevant studies based on inclusion and exclusion criteria, six studies were included in the analysis. The healing rates for LIS, TNS, and GTN are 92.2%, 63.1%, and 67.5%, respectively. The healing rate for LIS is statistically significantly higher than that for TNS, while there is no statistically significant difference between the healing rates of TNS and GTN. The complication rates for GTN, LIS, and TNS are 7.5%, 1.3%, and 0%, respectively. The rate of complications is higher in GTN and LIS compared to TNS; however, this difference is not statistically significant. The recurrence rates for TNS, GTN, and LIS are 21.3%, 9.3%, and 2.8%, respectively. The recurrence rate for TNS is statistically significantly higher than that for LIS, while there is no statistically significant difference between the recurrence rates of TNS and GTN. Although LIS remains the gold standard procedure for chronic anal fissures due to its high success rate and low recurrence rate, TNS has emerged as a promising non-invasive treatment option with a favorable success rate and no reported complications.

**Keywords:** Anal fissure, Neuromodulation, Percutaneous tibial nerve stimulation, Tibial nerve stimulation, Transcutaneous tibial nerve stimulation.

### 1. Introduction

Anal fissures are linear or oval ulcers that develop below the dentate line in the squamous epithelium of the anal (anoderm). This benign anorectal condition usually affects both sexes in middle age [1] but it can also affect the elderly and children less frequently. Ninety percent of patients develop a posterior anal fissure, while ten percent develop an anterior fissure, with the latter being more common among women [2]. There are two types of anal fissures: acute and chronic. Acute anal fissures cause severe pain, often likened to passing broken glass, along with anal bleeding, they typically respond well to sitz baths and stool softeners. On the other hand, chronic anal fissures last for more than 6 weeks, they are characterized by raised fissure edges, visible internal sphincter muscle fibers, and sentinel skin tags. The exact cause of anal fissures remains uncertain, but various factors such as hard stool passage, anal canal stretching, or trauma are believed to play a role, additionally, hypertonia of the

sphincter and relative ischemia in the posterior part of the anal canal can hinder the healing process of the fissures [3-5].

Acute anal fissures typically respond well to conservative treatments, such as sitz baths and a high-fiber diet, however, chronic anal fissures may require more advanced management. For chronic anal fissures, GTN is usually used as a chemical sphincterotomy. GTN can heal anal fissures more effectively than a placebo, with a healing rate of 49% compared to 37%. However, successful treatment can still result in recurrence rates as high as 50% [6]. One significant drawback of GTN is that around 20% of patients experience headaches, leading them to stop receiving treatment [7-9].

Another method of chemical sphincterotomy for anal fissures is the use of BT. Studies have shown that this approach has a healing rate of up to 80% and a recurrence rate of up to 42% [10, 11]. LIS is considered the gold standard procedure for treating chronic anal fissures, with healing rates approaching 90% and incontinence rates around 15% [12].

In recent years, non-invasive neuromodulation procedures such as sacral nerve stimulation and TNS have shown promise in managing pelvic floor conditions, and chronic anal fissures [13, 14]. These procedures are becoming increasingly popular as they offer patients a safe and effective alternative to invasive treatments [15-17].

Both sacral nerve stimulation and TNS target the same nerve (S2-S3), which transmits afferent fibers from the anal canal and pelvic floor. Stimulating this nerve can effectively reduce pain and enhance blood supply, which is essential for healing chronic anal fissures [18]. The gate theory is a well-accepted explanation for achieving pain relief through peripheral nerve stimulation, it suggests that stimulating large nerve fibers (Beta) can inhibit the transmission of pain signals carried by small nerve fibers (C) [19]. Another proposed mechanism is that peripheral nerve stimulation may trigger the release of endogenous opiates [20].

Tibial nerve stimulation has emerged as a favored alternative to the surgical implantation of a sacral neuromodulation unit in the management of chronic anal fissures, this stimulation can be administered either percutaneously (PTNS), employing a needle electrode, or transcutaneously (TTNS), utilizing an adhesive electrode.

The available literature on the efficacy of tibial nerve stimulation in the management of chronic anal fissures is limited, this systematic review and meta-analysis aim to gather the evidence in this domain.

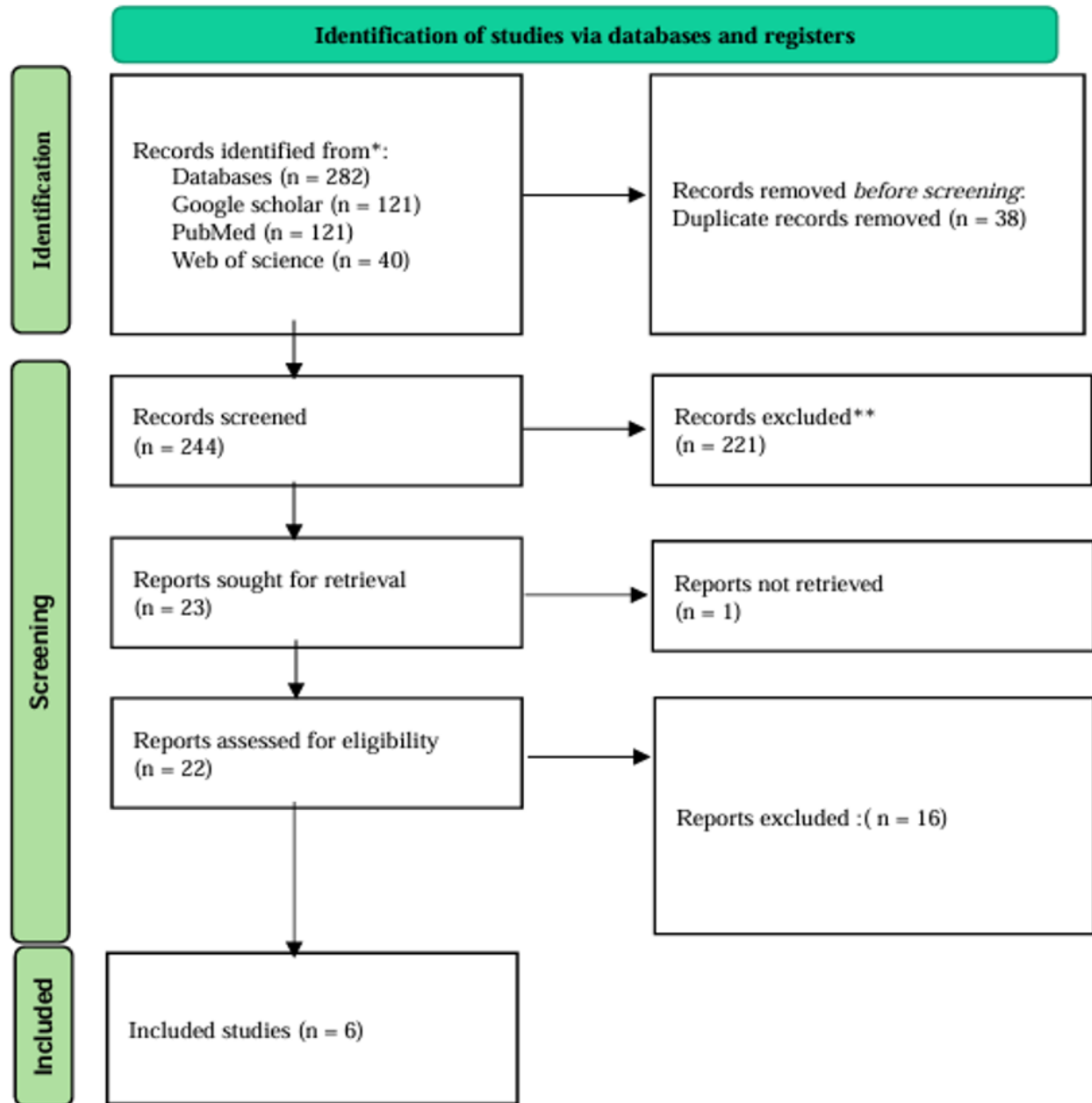
## 2. Measure of Outcome

The outcomes were measured in terms of the healing rate, complications rate, and recurrence rate of chronic anal fissures among TNS, GTN, and LIS

Healing of chronic anal fissures is defined as complete relief from symptoms and mucosal healing. Recurrence is defined as the reappearance of symptoms or clinical evidence of an anal fissure during a clinical examination after complete healing.

## 3. Materials and Methods

The authors conducted a comprehensive search across Pubmed, Google Scholar, and Web of Science, encompassing retrospective and prospective cohorts, cross-sectional studies, case reports, case series, and clinical trials published from January 2000 to January 2024. The search keywords consist of tibial nerve stimulation, percutaneous tibial nerve stimulation, transcutaneous tibial nerve stimulation, neuromodulation, AND anal fissure. The studies considered for this review must meet the following criteria: they must be, published in English, involve human subjects, and pertain to the treatment of anal fissures through tibial nerve stimulation, whether percutaneously or transcutaneously. Studies involving sacral nerve stimulation were excluded, as well as those not published in English due to potential translation challenges. The authors conducted reviews of the titles, abstracts, and references of the retrieved articles, based on predetermined inclusion and exclusion criteria. Adherence to the PRISMA guidelines [21] was maintained during the selection of studies for the systematic review and meta-analysis (Figure 1).



**Figure 1.**  
The PRISMA flow diagram illustrating the study selection Process for the systematic review and meta analysis.  
Note: \* PRISMA guidelines [21].

A datasheet was utilized to document the author's name, publication year, country of origin, study type, patient enrollment count, and outcomes related to healing rates, complications, and recurrence rates (Table 1).

**Table 1.**  
The details and outcome of the included studies.

Author	Year	Country	Study type	NO Patients	Nerve stimulation Procedure	Outcome
Altunrende, et al. [22]	2013	Turkey	Case series	10	TTNS	Out of 10 patients, 6 healed, no complications, and 1 recurrence.
Moya, et al. [23]	2016	Spain	Case series	6	PTNS	Out of 6 patients, 6 healed, no complications, 3 recurrences
Aho Fält, et al. [24]	2019	Sweden	Case series	9	PTNS	Out of 9 patients, 5 healed, no complications, and 0 recurrence.
Youssef, et al. [25]	2015	Egypt	Randomized Control clinical trial	36 in TTNS group, 37 in LIS group	TTNS	Out of 36 patients in TTNS group, 26 healed, no complications, and 11 recurrences. Out of 37 patients in LIS group, 33 healed, 1 complication, and 1 recurrence.
Ruiz-Tovar and Llavero [26]	2017	Spain	Randomized control clinical trial	40 in PTNS group, and 40 in GTN group	PTNS	Out of 40 patients in PTNS group, 35 healed no complications, and 2 recurrences. Out of 40 patients in GTN group, 26 healed, 6 complications, and 3 recurrences
Shehata, et al. [27]	2022	Egypt	Randomized clinical trial	40 in PTNS group, and 40 GTN group 40 LIS group	PTNS	Out of 40 patients in PTNS group, 11 healed, no complication, and 2 recurrences. Out of 40 patients in GTN group, 28 healed, no complications, and 2 recurrences. Out of 40 patients in LIS group, 38 healed, no complications, and 1 recurrence.

The trials included in the review and meta-analysis were evaluated for bias risk using Cochrane's "Risk of Bias" tool [28] (Figure 2).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ruiz-Tovar J et al 2017							
Shehata MA et al 2022							
Youssef T et al 2015							

**Figure 2.**  
 Risk of bias for included randomized clinical trials.  
**Note:** \* Youssef, et al. [25] \* Ruiz-Tovar and Llavero [26] \* Shehata, et al. [27].  
 \* Cochrane's "Risk of Bias" tool [28].

#### 4. Statistical Analysis

Data was inputted manually into RevMan version 5.4. at 95% CI a P-value of <0.05 was deemed significant. Furthermore, a heterogeneity exceeding 50% was considered high. Descriptive statistics, in

the form of percentages, were employed in the pooled data to reflect healing, complications, and recurrence rates.

**5. Results**

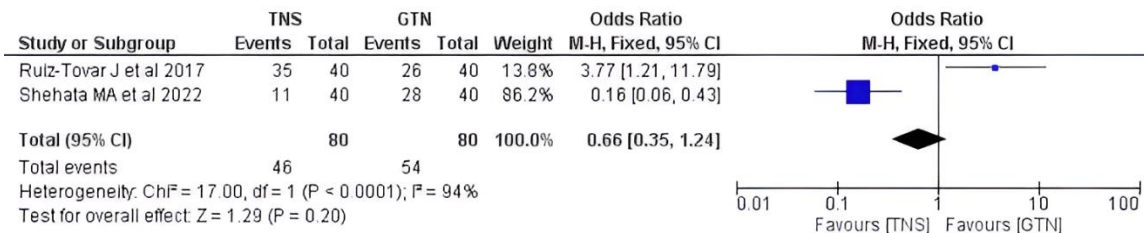
In our systematic literature review, We identified a total of 282 studies (Google Scholar (121), PubMed (121), and Web of Science (40)). After removing duplicate and irrelevant articles, We were left with 6 studies that met the inclusion criteria, comprising 3 case series and 3 randomized control trials.

*5.1. Results of Pooled Data Analysis*

In the pooled data analysis, 141 patients underwent TNS (67.5% undergoing PTNS and 32.5% undergoing TTNS), the overall healing rate was 63.1%, with a complication rate of 0% and a recurrence rate of 21.3%. Additionally, in the pooled data analysis, 80 patients were part of the GTN control group in two randomized clinical trials; the overall healing rate for this group was 67.5%, with a complication rate of 7.5% and a recurrence rate of 9.3%. Furthermore, in the pooled data analysis, 77 patients were part of the LIS control group in two randomized clinical trials, this group exhibited an overall healing rate of 92.2%, a complication rate of 1.3%, and a recurrence rate of 2.8%.

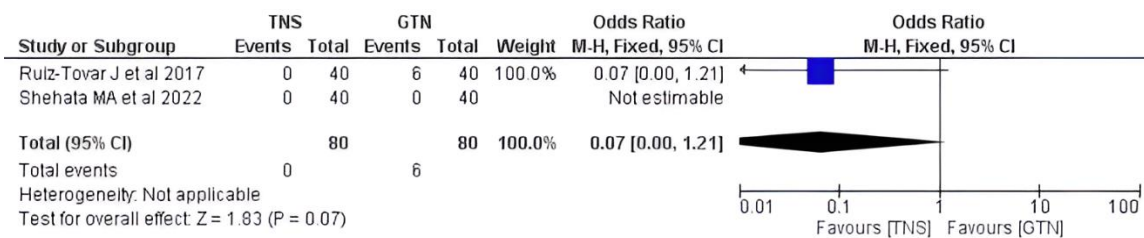
*5.2. Results of a Meta-Analysis of Two Clinical Randomized Trials Comparing TNS and GTN Are as Follows*

The healing rate is slightly higher in GTN than in TNS (54 patients in the GTN compared to 46 patients in the TNS). However, the difference is not statistically significant (OR = 0.66, 95% CI 0.35 to 1.24; p = 0.20). There was also very high heterogeneity observed, with Chi<sup>2</sup> = 17.00, df = 1 (p ≤ 0.0001), and I<sup>2</sup> = 94%.(Figure 3).



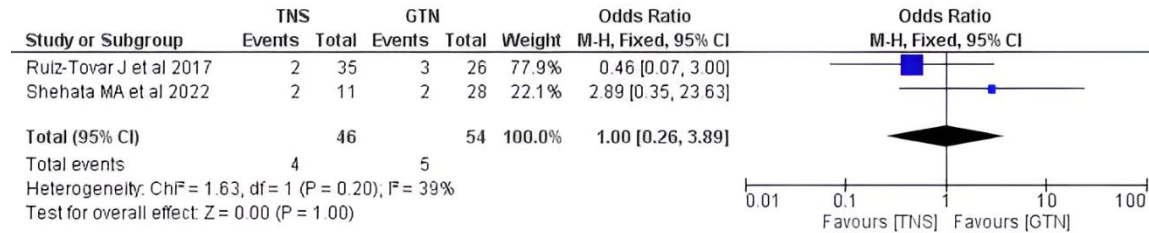
**Figure 3.**  
Comparison of healing rates between TNS and GTN.  
**Note:** \* Ruiz-Tovar and Llaverro [26] \* Shehata, et al. [27].

The complications rate is higher in GTN than in TNS (six patients in the GTN compared to 0 patient in the TNS), without a statistically significant difference (OR = 0.07, 95% CI 0.00 to 1.21; p = 0.07). Heterogeneity is not applicable. (Figure 4).



**Figure 4.**  
Comparison of complications rates between TNS and GTN.  
**Note:** \* Ruiz-Tovar and Llaverro [26] \* Shehata, et al. [27].

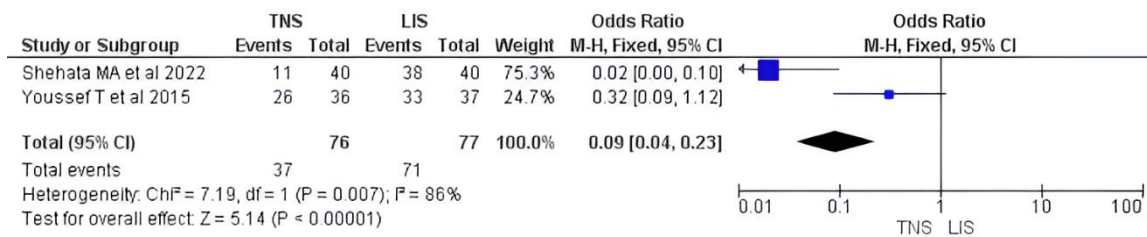
The recurrence rate was slightly higher in GTN than in TNS (Five patients in the GTN compared to 4 patients in the TNS). However, there was no statistically significant difference found (OR = 0.26, 95% CI 0.26 to 3.89; p = 1.00), with low heterogeneity observed (Chi<sup>2</sup> = 1.63, df = 1, p = 0.20; I<sup>2</sup> = 39%). (Figure 5).



**Figure 5.**  
Comparison of recurrence rates between TNS and GTN.  
**Note:** \* Ruiz-Tovar and Llavero [26] \* Shehata, et al. [27].

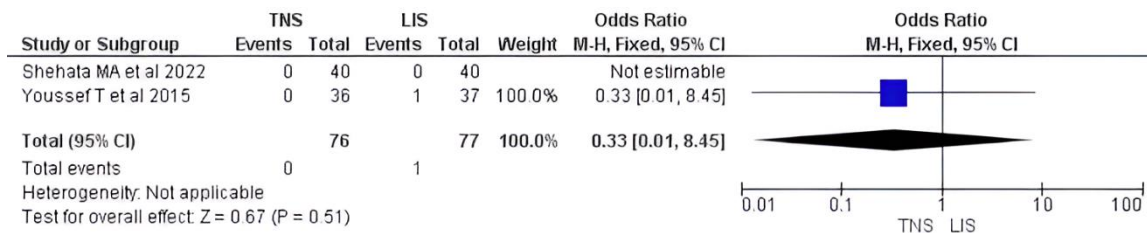
**5.3. Results of a Meta-Analysis of Two Clinical Randomized Trials Comparing TNS and LIS Are as Follows:**

The healing rate was higher in LIS (71 patients) than in TNS (37 patients) with a statistically significant difference (OR = 0.09, 95% CI 0.04 to 0.23; p ≤ 0.00001). High heterogeneity was observed (Chi<sup>2</sup> = 7.19, df = 1, p = 0.007; I<sup>2</sup> = 86%).(Figure 6).



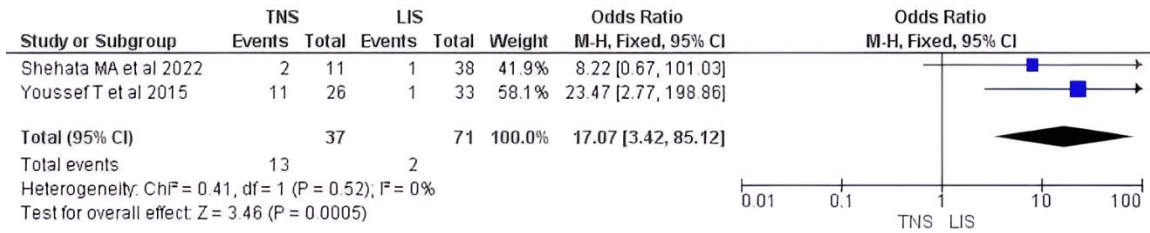
**Figure 6.**  
Comparison of healing rates between TNS and LIS.  
**Note:** \* Youssef, et al. [25] \*\* Shehata, et al. [27].

The rate of complications was slightly higher in LIS (one patient) compared to TNS (zero patient), without a statistically significant difference (OR = 0.33, 95% CI 0.01 to 8.45; p=0.51). Heterogeneity was not applicable. (Figure 7).



**Figure 7.**  
Comparison of complications rates between TNS and LIS.  
**Note:** \* Youssef, et al. [25] \*\* Shehata, et al. [27].

Recurrence was higher in TNS (13 patients) compared to LIS (2 patients), with a statistically significant difference (OR = 17.07, 95% CI 3.42 to 85.12; p=0.0005). Low heterogeneity was observed (Chi<sup>2</sup> = 0.41, df = 1, p = 0.52 ; I<sup>2</sup> = 0%). (Figure 8).



**Figure 8.**  
Comparison of recurrence rates between TNS and LIS.  
**Note:** \* Youssef, et al. [25] \*\* Shehata, et al. [27].

#### 5.4. Results in Summary

The healing rate is statistically significantly higher in LIS compared to TNS, while there is no statistically significance difference between healing rates in TNS compared to GTN.

The rate of complications is higher in GTN and LIS than in TNS; however, this difference is not statistically significant.

The recurrence rate is statistically significantly higher in TNS compared to LIS, while there is no statistically significance difference between recurrence rates in TNS compared to GTN.

## 6. Discussion

This systematic review and meta-analysis revealed that LIS has a superior healing rate compared to GTN and TNS, with rates of 92.2%, 67.5%, and 63.1%, respectively. This finding aligns with existing literature indicating a 90% healing rate for chronic anal fissures with LIS [29-32]. The healing rate using GTN is consistent with the findings of a prospective, randomized, double-blind, placebo-controlled study where 0.2% GTN was applied twice daily. After 8 weeks, healing was observed in 68% of patients treated with GTN, compared to only 8% of those in the control group [33]. TNS is considered promising management of chronic anal fissures because the healing rate is approaching the healing rate of GTN without statistically significant difference, with minimal complications compared to GTN, and according to Ruiz-Tovar and Llaveró [26] TNS is a dependable and secure substitute for GTN in treating chronic anal fissures [26]. In their series, Moya P and his colleagues utilized PTNS to treat patients with refractory chronic anal fissures unresponsive to other therapies. Their study concluded that PTNS is a non-invasive procedure without complications, providing a therapeutic alternative for patients with chronic anal fissures resistant to conventional treatments [23].

Compared to GTN and LIS, TNS has a lower rate of complications (7.5% vs 1.3% and 0%, respectively). A significant advantage of this procedure is its non-invasive nature, and according to Moya, et al. [23] PTNS is a safe procedure without complications, it can be considered for patients who have not responded to other treatments and may serve as an alternative for individuals who are not suitable for surgery or prefer non-surgical interventions [23]. GTN has several major drawbacks, including causing intractable headaches, which lead to 15-20% of patients discontinuing treatment, and orthostatic hypotension, as reported in the literature [34, 35]. In a study by Carapeti, et al. [36] comparing GTN to a placebo for the management of anal fissures, it was observed that 72% of patients reported experiencing headaches as a side effect. Carapeti, et al. [36] even though the LIS is widely acknowledged as the gold standard procedure for managing chronic anal fissures due to its high success rate and low recurrence rate, there is a significant concern regarding the reported incidence of fecal incontinence, which has been documented to be as high as 30% in some literature [37, 38]. Due to fear of fecal incontinence, some studies advocate that chemical sphincterotomy should be tried first, and surgical sphincterotomy should be offered if pharmacological therapy fails [39].

Based on this systematic review and meta-analysis, the TNS had a higher recurrence rate (21.3%) compared to GTN (9.3%) and LIS (2.8%). Perivoliotis, et al. [40] also highlighted the high recurrence rate of TNS; they conducted a systematic review to evaluate the recurrence rate of chronic anal fissures



treated with PTNS, which was determined to be 19%. [40]. In their study, Carapeti, et al. [36] and colleagues reported a 33% recurrence rate of anal fissures with GTN, which is higher than our systematic review [32]. A low recurrence rate of anal fissure when using LIS has also been confirmed by Littlejohn and Newstead [41] in their study, which demonstrated a 1.4% recurrence rate [41].

## 7. Limitations

The limitations of this systematic review and meta-analysis are the variations in follow-up duration among the studies; this variability could potentially affect the assessment of healing, complications, and recurrence rates. Another limitation is the authors' inability to effectively manage the high heterogeneity by conducting sub-group analyses, due to the limited number of clinical trials on TNS as a management strategy for anal fissures. In addition, the clinical trials included in the meta-analysis were not blinded, meaning that the placebo effects cannot be ruled out.

While studies highlight the advantages of outpatient TNS sessions, there is a lack of comparison regarding the financial cost and patient satisfaction of TNS for anal fissure management.

## 8. Conclusion

Although LIS remains the gold standard procedure for chronic anal fissures due to its high success rate and low recurrence rate, the TNS has emerged as a noninvasive treatment for chronic anal fissures with a promising success rate and no complications. TNS offers hope for individuals who prefer non-invasive treatments or those who have not responded well to other therapies.

### Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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