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ORIGINAL SCIENTIFIC REPORT

Effect of Glyceryl Trinitrate Ointment on Pain Control After Hemorrhoidectomy: A Meta-analysis of Randomized Controlled Trials

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Abstract

Background Hemorrhoidectomy is associated with postoperative pain and prolonged wound healing. Glyceryl trinitrate has been shown to decrease muscle spasm and increase anodermal blood flow. A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy of topical glyceryl trinitrate application in pain relief after hemorrhoidectomy.

Methods PubMed, EMBASE, Cochrane Library, Scopus, and ClinicalTrials.gov registries were searched for studies published before August 2015. Individual effect sizes were standardized, and a meta-analysis was conducted to calculate a pooled effect size using random effects models. Pain was assessed using a visual analog scale on days 1, 3, 7, and 14 after operation. Secondary outcomes included time taken to resume routine activities, wound healing at 3 weeks after operation, complication, and headache incidence.

Results A total of 12 trials with 1095 patients were reviewed. Significant pain reduction was observed on days 1, 3, 7, and 14 after hemorrhoidectomy in the glyceryl trinitrate groups. Glyceryl trinitrate-treated patients appeared to resume routine activities earlier than those in the control group (weight mean difference −7.52; 95 % confidence interval: 16.13–1.08). The wound healing rates 3 weeks after operation were significant higher in the glyceryl trinitrate-treated groups than in the control group (risk ratio 1.79; 95 % confidence interval: 1.38–2.33). However, the incidence of headache significantly increased in the glyceryl trinitrate group (risk ratio 3.68; 95 % confidence interval: 1.62–8.34).

Conclusion Topical application of glyceryl trinitrate effectively relieves pain and promotes wound healing after hemorrhoidectomy; however, the substantial headache incidence may limit extensive application.

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Introduction

Hemorrhoidectomy is the most effective and the safest treatment for high-grade hemorrhoids. However, hemorrhoidectomy is associated with postoperative pain and prolonged wound healing, which may delay patients' resumption of routine activities [1]. Hemorrhoidectomy is treated through several surgical procedures, such as the Milligan–Morgan (open) hemorrhoidectomy or Ferguson techniques. In addition, stapled hemorrhoidectomy for prolapse and hemorrhoids reduces postoperative pain and enables early resumption of routine activities; however, these procedures are associated with a higher recurrence rate [2].

The cause of postoperative pain is multifactorial, spasm of anal sphincter, and puborectalis muscles have been implicated as one of various potential mechanisms [3]. Pain severity depends on various factors, including individual pain tolerance, anesthesia type, surgical technique, postoperative analgesia, and stool softener use [4]. Traditionally, postoperative pain has been reduced using narcotics or nonsteroid anti-inflammatory drugs; however, their use is confined to a short period and is associated with frequent side effects [5].

Glyceryl trinitrate (GTN), a nitric oxide donor, has been shown to decrease muscle spasm and increase anodermal blood flow [6, 7]. Topical application of GTN is commonly used to relieve pain and promote wound healing in patients with anal fissure [8, 9]. Two randomized controlled trials (RCTs) have investigated the topical use of GTN after hemorrhoidectomy; however, these studies could not provide conclusive results [10, 11]. A recent meta-analysis suggested that GTN ointment had a significant analgesic effect at days 3 and 7 after hemorrhoidectomy and significantly improved wound healing within 3 weeks [12]. However, this review did not clarify the heterogeneity of the pooled results, which is crucial in the random effects model [13]. Moreover, several RCTs evaluating GTN in pain control after hemorrhoidectomy have been published recently [14, 15]. Therefore, through a systematic review and meta-analysis of the evidence available to date, we investigated the outcome in patients using GTN topically after hemorrhoidectomy.

Materials and methods

Inclusion criteria

RCTs evaluating the outcome of topical application of GTN in open, closed, or stapled hemorrhoidectomy were included in this review. Studies were also required to clearly report the inclusion and exclusion criteria for patients, the anesthetic technique, the surgical technique, and the definition and evaluation of postoperative pain. We excluded trials that met at least one of the following criteria: (1) patients undergoing other surgical procedures concomitantly, such as transanal hemorrhoidal dearterialization; (2) patients had previously undergone nonhemorrhoid surgery, such as anal sphincterotomy or dilatation for anal fissure; or (3) patient cohorts reported in duplicates.

Search strategy and study selection

Relevant studies published before August 2015 were identified from the PubMed, Embase, Scopus, and Cochrane databases. The following Medical Subject Headings terms were used: *hemorrhoid, hemorrhoidectomy, glyceryl trinitrate* OR *nitroglycerin* OR *GTN, analgesia* OR *pain.* The "related articles" option in PubMed was used to broaden the search, and all abstracts, studies, and citations retrieved were reviewed. In addition, we identified other studies using the reference sections of relevant papers and by corresponding with subject experts. Finally, unpublished studies were collected from the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language restrictions were applied. The systematic review described herein has been accepted by PROSPERO, an online international prospective register of systematic reviews, curated by the National Institute for Health Research (CRD42015023274).

Data extraction

Baseline and outcome data were independently abstracted by 2 reviewers (JWL and KWT), and the study designs, study population characteristics, inclusion and exclusion criteria, surgical and anesthetic techniques, drug administration strategies, complications, and postoperative parameters were extracted. Decisions recorded individually by the reviewers were compared, and disagreements were resolved by the third reviewer (KTK). The authors of the studies were contacted for additional information.

Methodological quality appraisal

Two reviewers (JWL and KWT) independently assessed the methodological quality of each study using the risk of bias method recommended by the Cochrane Collaboration [16]. Several domains were assessed, including adequacy of the randomization, allocation concealment, blinding of the patients and outcome assessors, length of follow-up, information provided to the participants regarding study withdrawals, whether intention-to-treat analysis was performed, and freedom from other biases.

Outcomes

The primary outcome was the occurrence and severity of postoperative pain, which was measured on days 1, 3, 7, and 14 after the operation. The secondary outcomes included analgesia consumption, complication, incidence of headaches, wound healing rate, and work resumption date.

Statistical analyses

Data were entered and analyzed using the Review Manager, version 5.3 (The Cochrane Collaboration, Oxford, England). Meta-analysis was performed in line with the PRISMA guidelines [17]. Standard deviations were estimated from the provided confidence interval limits or standard error. Dichotomous outcomes were analyzed using risk ratios (RRs) as the summary statistic. Effect sizes of continuous outcomes were reported as the weighted mean difference (WMD). The precision of the effect sizes were reported as 95 % confidence intervals (CIs). A pooled estimate of the RR and WMD was computed using the DerSimonian and Laird random effect model [18].

To evaluate statistical heterogeneity and inconsistency of treatment effects across studies, Cochrane Q tests and I^2 statistics, respectively, were used. Statistical significance was set to $p < 0.10$ for Cochrane Q tests. Statistical heterogeneity across studies was assessed using the I^2 test, which quantified the proportion of the total outcome variability across the studies. Moreover, subgroups analyses were performed by pooling available estimates for similar subsets of patients across trials.

Results

Trial characteristics

Figure 1 is a flowchart describing the screening and selection of trials. The initial search strategy yielded 496 citations, and 348 among these were ineligible based on the criteria used for screening titles and abstracts. Thus, the full texts of 148 studies were retrieved. However, most were excluded from our final review because of the following reasons: 8 were retrospective studies or prospective articles; 118 included treatment for other diseases, such as anal fissure surgery; 5 evaluated the effects of local anesthesia using different interventions, such as botulinium toxin; and 5 discussed other topics concerned with hemorrhoid surgery. Thus, 12 studies were eligible for inclusion in this study [10, 11, 14, 15, 19–26] (Table 1).

These 12 trials were published between 2001 and 2014 and had sample sizes ranging from 20 to 210 patients.

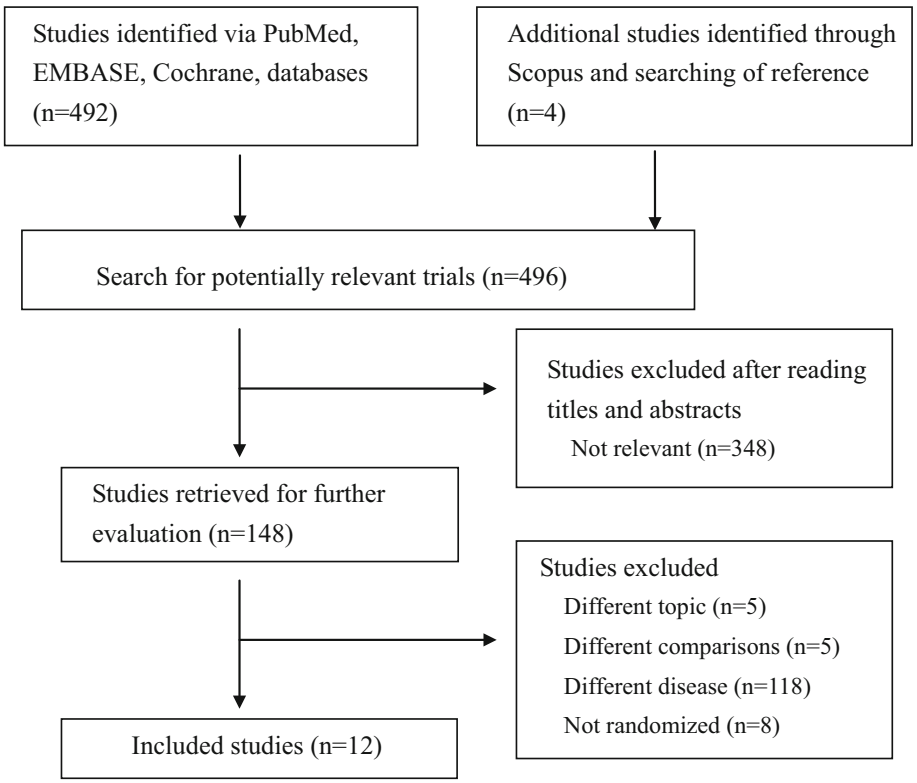

Fig. 1 Flowchart describing the inclusion of studies

Table 1 Characteristics of the selected randomized controlled trials

Study	Inclusion criteria	Setting	No. of patients (% male)	Age, years	Intervention
Cross [14]	Third- and fourth-degree hemorrhoids	GA; stapled hemorrhoidectomy	G: 100 (57) C: 110 (67)	G: 49.8 (22–79)[a] C: 50.6 (22–79)	G: 0.2 % GTN ointment 3 times daily × 2 weeks C: control
Di Vita [10]	Third- and fourth-degree hemorrhoids	GA; 1 surgeon; Milligan–Morgan hemorrhoidectomy	G: 15 (60) P: 15 (53)	G: 35 ± 20 P: 40.6 ± 18	G: Lactulose 20 ml × 2 days before + 2 weeks after surgery; metronadizole IV 400 mg before + 400 mg tid × 7 days after surgery; 0.2 % GTN ointment 3 times daily × 2 weeks P: placebo
Elton [11]	Third- degree hemorrhoids	GA; 2 surgeons; Milligan–Morgan hemorrhoidectomy	G: 10 (80) P: 10 (40)	G: 53.9 P: 52.6	G: 0.2 % GTN ointment twice daily × 42 days P: placebo ointment twice daily × 42 days
Franceschilli [15]	Third- and fourth-degree hemorrhoids	LA; Milligan–Morgan hemorrhoidectomy with Ligasure	G: 103 (58.3) C: 100 (65)	G: 45.6 ± 10 C: 51.5 ± 12	G: 0.4 % GTN ointment twice daily × 42 days C: control
Hwang [19]	Third- and fourth-degree hemorrhoids	SA; 1 surgeon; Milligan–Morgan hemorrhoidectomy	G: 55 (76.4) P: 55 (71.1)	G: 41.8 ± 12.1 P: 41.7 ± 10.1	G: 0.2 % GTN ointment 3 times a day × 3 weeks P: placebo
Karanlik [20]	Third- and fourth-degree hemorrhoids	GA; Ferguson hemorrhoidectomy	G: 30 (50) P: 30 (53)	G: 34.4 ± 10.8 P: 36.6 ± 10.4	G: 0.2 % GTN ointment twice daily × 2 weeks P: placebo
Khan [26]	Third- and fourth-degree hemorrhoids	GA or SA; Milligan–Morgan hemorrhoidectomy	G: 70 L: 70 G + L: 70	G: 41.7 ± 9.3 L: 43.4 ± 8.5 G + L: 41.2 ± 10.1	G: 0.2 % GTN ointment twice daily L: 2 % lidocaine ointment twice daily G + L: 0.2 % GTN + 2 % lidocaine ointment twice daily
Mari [21]	Second- and third-degree hemorrhoids	GA or SA; stapled hemorrhoidectomy	G: 21 (71) L: 20 (65)	G: 48.7 ± 9.0 L: 48.3 ± 8.6	G: 0.4 % GTN ointment twice daily × 2 weeks L: 2.5 % lidocaine chlorohydrate gel twice daily × 2 weeks
Patti [22]	Third- and fourth-degree hemorrhoids	GA; Milligan–Morgan hemorrhoidectomy	G: 30 (30) P: 30 (26)	G: 33 ± 15 P: 36 ± 18	G: 0.2 % GTN ointment 3 times daily × 15 days P: placebo
Patti [23]	Third- and fourth-degree hemorrhoids	GA; 1 surgeon; Milligan–Morgan hemorrhoidectomy	G: 15 (46) B: 15 (53)	G: 38 ± 16 B: 40 ± 15	G: 0.2 % GTN ointment 3 times daily × 30 days B: 0.4 ml of 20 IU botulinum toxin
Tan [24]	Third- and fourth-degree hemorrhoids	GA; open diathermy hemorrhoidectomy	G: 40 (72.5) P: 42 (76.2)	G: 45.8 ± 11.6 P: 39.9 ± 9.6	G: 0.2 % GTN ointment 3 times daily × 2 weeks P: placebo
Wasvary [25]	Patients for hemorrhoidectomy	SA; Ferguson hemorrhoidectomy	G: 19 (42.1) P: 20 (60)	G: 54 P: 49	G: 0.2 % GTN ointment 3 times daily × 7 days P: placebo

B botulinum group, *C* control group, *G* glyceryl trinitrate group, *GA* general anesthesia, *GTN* glyceryl trinitrate, *L* lidocaine group, *LA* local anesthesia, *NTG* nitroglycerin, *P* placebo group, *SA* spinal anesthesia

[a] Data are presented as mean ± SD except mean (range)

Nine trials recruited patients with third- and fourth-degree hemorrhoid [10, 14, 15, 19, 20, 22–26]. Milligan–Morgan hemorrhoidectomy was performed in the majority of the included trials; Ferguson-closed hemorrhoidectomy was performed in 2 studies [20, 25], and stapled hemorrhoidectomy was performed in 2 trials [14, 21]. Nine trials compared the effects of GTN topical application and a control or placebo [10, 11, 14, 15, 19, 20, 22, 24, 25].

Table 2 Assessment of methodological quality of included studies

Study [year]	Country	Allocation generation	Allocation concealment	Blinding of patients and assessors	Data analysis	Loss to follow-up (%)	Selective reporting	Other bias
Cross [14]	Australia	Computer generated	Unclear	Assessor blinded	ITT	2.9	Low risk	Lack of clinical supervision in application of GTN ointment
Di Vita [10]	Italy	Unclear	Unclear	Unclear	ITT	0	Complication not evaluated	–
Elton [11]	London	Random numbers	Adequate	Double blinded	ITT	0	Low risk	Male is predominant in GTN group
Franceschilli [15]	Italy	Shuffling method	Adequate	Unclear	ITT	0	Low risk	–
Hwang [19]	Korea	Computer generated	Adequate	Double blinded	PP	7.3	Low risk	–
Karanlik [20]	Turkey	Computer generated	Unclear	Double blinded	PP	13	Low risk	–
Khan [26]	Pakinstan	Computer generated	Unclear	Double blinded	PP	8.6	Low risk	Duration of experimental drugs used was not provided
Mari [21]	Italy	Computer generated	Unclear	Patient blinded	ITT	0	Low risk	–
Patti [22]	Italy	Unclear	Unclear	Unclear	ITT	0	Low risk	–
Patti [23]	Italy	Computer generated	Unclear	Assessor blinded	ITT	0	Low risk	–
Tan [24]	Singapore	Sealed envelopes	Adequate	Double blinded	PP	17.2	Low risk	–
Wasvary [25]	Michigan	Unclear	Adequate	Double blinded	ITT	0	Low risk	–

Risk of bias was assessed according to the method recommended by the Cochrane collaboration

ITT intention-to-treat, *PP* per-protocol

GTN outcomes combined with the use of lactulose and metronidazole were investigated in one of these 9 trials [10]. Two studies evaluated the results between topical application of GTN and lidocaine chlorohydrate gel [21, 26], and one trial assessed the anesthetic effects of botulinum toxin [23]. GTN and placebo dosages were adjusted according to various protocols. Baseline characteristics in the treatment groups of the 12 included RCTs were balanced.

The methodological quality of the included trials is summarized in Table 2. Nine studies reported acceptable methods of randomization [11, 14, 15, 19–21, 23, 24, 26]. Three studies did not describe the blinding of patients and outcome assessors [10, 15, 22]. Eight studies used intention-to-treat analysis [10, 11, 14, 15, 21–23, 25]. The number of patients lost to follow-up was acceptable (<20 %) in all studies. Biases in the selected studies included a lack of clinical supervision in the application of GTN ointment [14]; males were predominant in the GTN groups [11]; and no mention on the duration of experimental drugs used [26].

Pain score

Postoperative pain had been assessed in 10 studies through a 10-point visual analog scale (0 = no pain, 10 = severe pain) [10, 14, 15, 19–25], whereas two studies used a 0–100 scale [11, 26]. The 12 studies were converted to a 10-point scale to compare the outcome measures. These measured outcomes on days 1, 3, 7, and 14 after the operation were compared because of variation in pain assessment time among the studies. Data obtained from 7 RCTs were included; data from 5 were excluded because the studies reported only median and range [14] or mean visual analog scores without standard deviation [11, 23, 25, 26]. The pooled mean difference in degree of pain score were −1.24 (95 % CI −2.42 to −0.06) on day 1, −1.77 (−2.82 to −0.71) on day 3, −2.21 (−3.08 to −1.33) on day 7, and −1.15 (−1.72 to −0.59) on day 14 after operation. The GTN group showed significantly reduced postoperative pain when compared with the control group (Fig. 2). The value of I^2 was 0–96 % at different time points after the operation, indicating low to severe heterogeneity across the

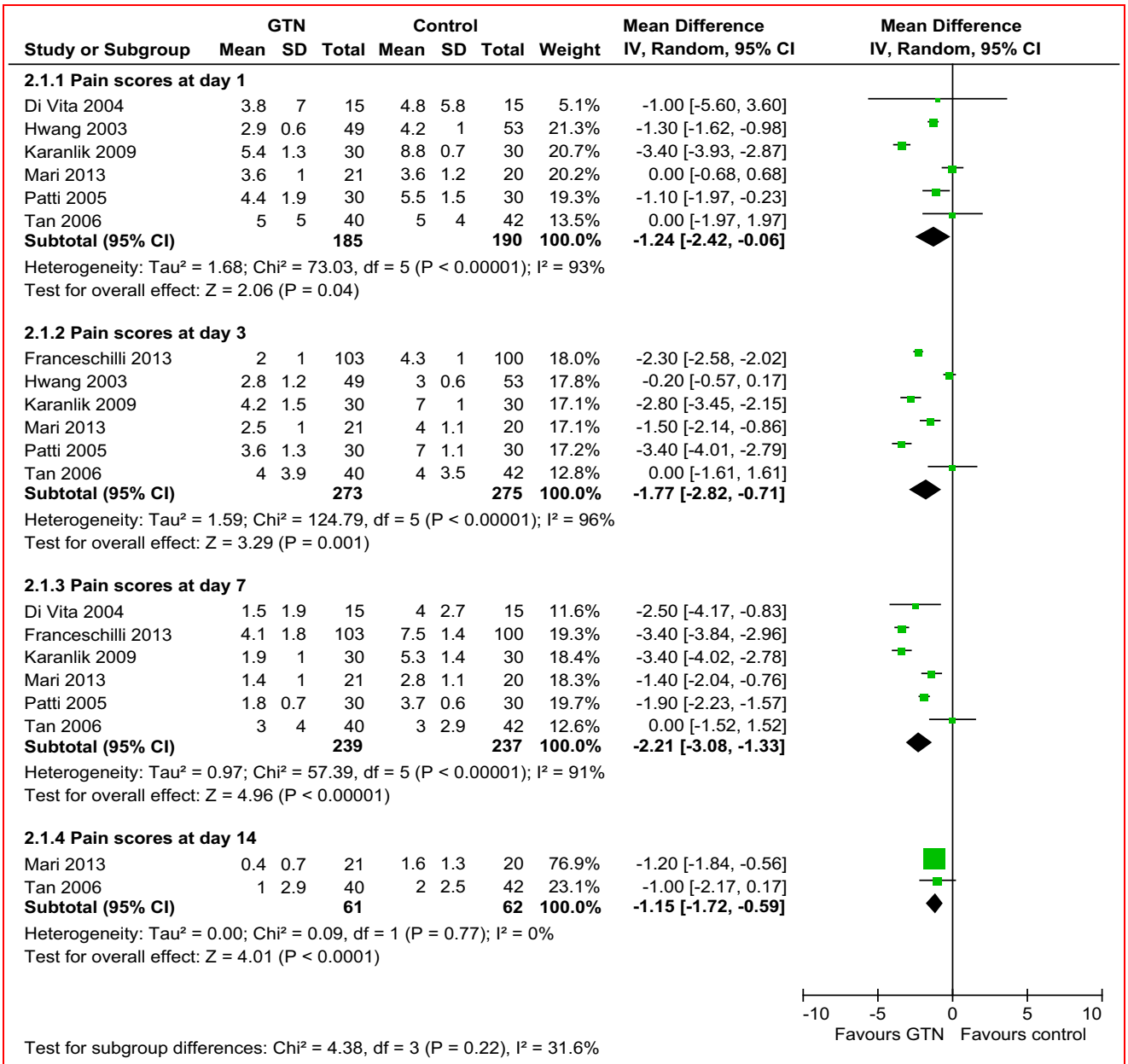

Fig. 2 Forest plot of comparison: GTN ointment application versus control; outcome: incidence of postoperative pain on days 1, 3, 7, and 14

studies (Fig. 2). Subgroup analysis according to surgical types was performed. In patients who had undergone Milligan–Morgan, Ferguson, or stapled hemorrhoidectomy, our analysis revealed that GTN application in the treated groups significantly reduced pain compared with the control group.

The studies excluded from the meta-analysis reported varied results. Patti et al. compared with the effect of topical application of GTN and the injection of botulinum toxin on pain relief after hemorrhoidectomy and reported that a single intrasphincter injection of botulinum toxin was more effective than repeated applications of GTN in reducing early postoperative pain during rest but not during defecation [23]. Khan et al. reported that statistically significant reductions in pain scores from day 1 to 4 after operation in GTN and lidocaine combination group [26]. Three studies also revealed less pain in the GTN group but with nonsignificant differences compared with the control group [11, 14, 25].

Analgesic consumption

Analgesic consumption was reported in 10 trials [10, 11, 19–26]. Data pooling for analgesia consumption could not be performed because the clinical parameters among the selected trials were not uniformly reported. No significant difference was reported in the requirements for postoperative analgesia between the study groups in 5 of the selected trials [10, 11, 19, 22, 24]. Khan et al. reported that no significant difference in the use of analgesics between lidocaine and GTN groups [26]. However, Karanlik et al. and Wasvary et al. have shown that patients in the GTN group consumed significantly lower amounts of analgesics than those in the placebo group [20, 25]. Mari et al. reported that all 20 patients took analgesics in the lidocaine gel group, whereas only 5 patients took analgesics in the GTN group ($p < 0.0001$) [21].

Time to resume routine activity

The time necessary to resume routine activities was reported in 3 trials [15, 20, 22]. Although the difference is nonsignificant, GTN-treated patients appeared to resume routine activities earlier than the untreated patients did (WMD −7.52; 95 % CI −16.13 to 1.08) (Fig. 3). Moreover, Di Vita et al. reported that the time for patients in the GTN group to resume routine activities was significantly earlier than for those in the control group ($p < 0.05$) [10].

Wound healing rate

Wound healing 3 weeks after operation was reported in 3 trials [19, 20, 24]. Patients treated with GTN exhibited significantly more wound healing compared with the control group (RR 1.79; 95 % CI 1.38–2.33) (Fig. 4). Moreover, Patti et al. reported that the GTN group showed significantly faster epithelial healing rate than did the control group (22.7 ± 4.3 vs. 32.1 ± 7.2 days, $p < 0.05$) [22]; and Khan et al. indicated that patients in the GTN group had a mean healing time of 4.48 weeks as compared to 5.07 weeks for lidocaine group [26].

Complications

Among the included studies, no significant differences was observed in the GTN and control groups' bleeding-

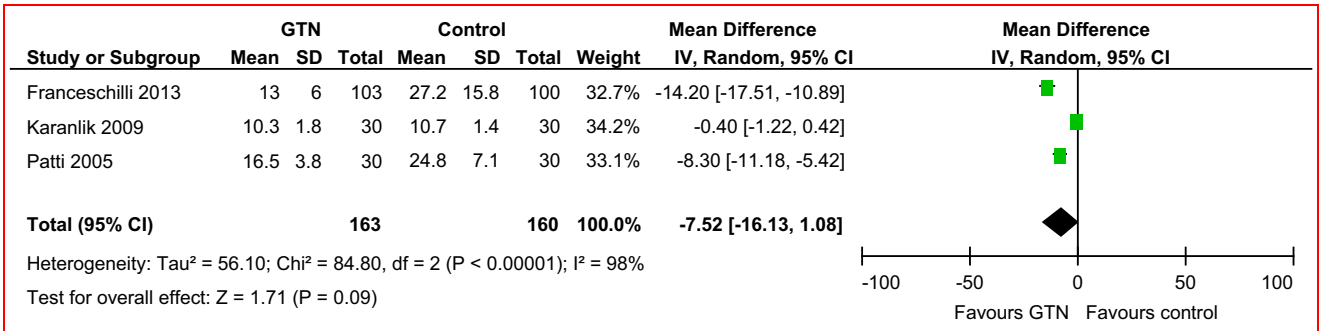

Fig. 3 Forest plot of comparison: GTN ointment application versus control; outcome: time to resume normal activities

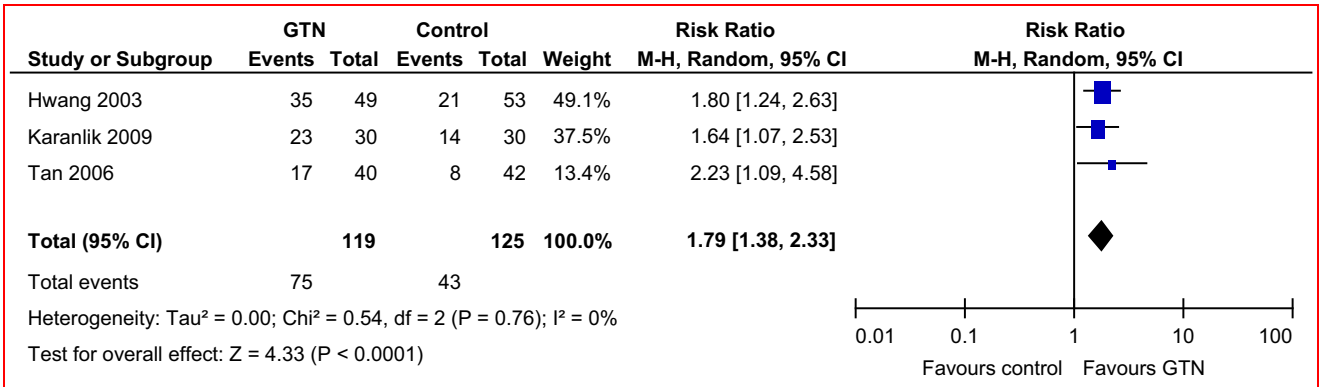

Fig. 4 Forest plot of comparison: GTN ointment application versus control; outcome: wound healing rate within 3 weeks after operation

associated postoperative complications [14, 15, 19, 20, 24], urinary retention [14, 19, 20, 22, 24], fecal impaction [14, 24], itching [15, 19, 20, 24], and residual skin tags [19, 24] (RR 0.92; 95 % CI 0.63–1.34) (Fig. 5).

Headache incidence

All studies provided data on headache incidence. An analysis revealed that 10.5 % (50/478) of the patients in the GTN group experienced headaches. GTN application in the treated groups was significantly associated with more headache compared with the control, (RR 3.68; 95 % CI 1.62–8.34) (Fig. 6).

Discussion

Postoperative pain and difficulties in defecation are major clinical problems following hemorrhoidectomy. This meta-analysis indicated that topical GTN application following hemorrhoid surgery shows a significant pain reduction on days 1, 3, 7, and 14 after operation. GTN-treated patients had faster wound healing rate 3 weeks after operation and were able to resume routine activities earlier compared with the control group. However, application of GTN was associated with an increased headache incidence.

GTN topical application for acute and chronic fissure treatment has been evaluated for approximately 20 years

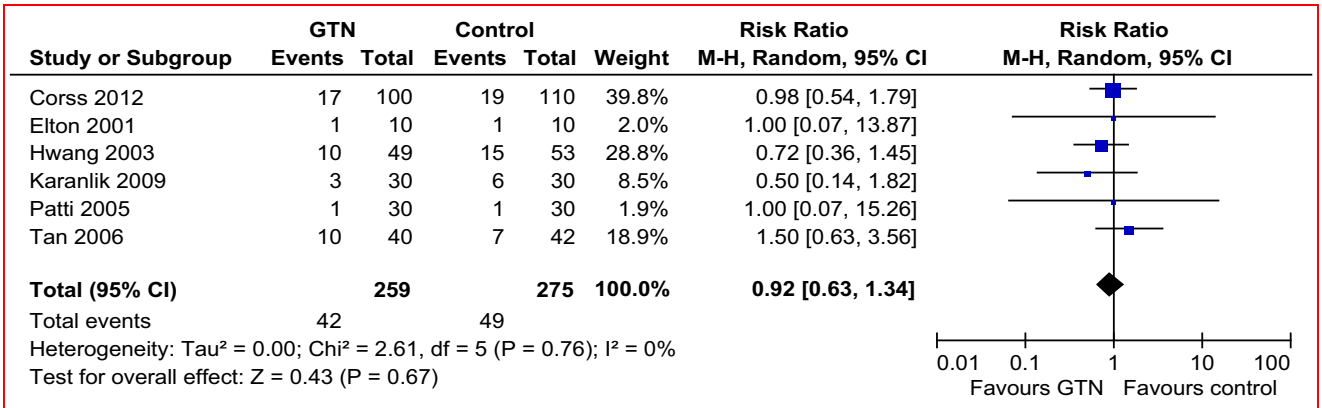

Fig. 5 Forest plot of comparison: GTN ointment application versus control; outcome: incidence of postoperative complications

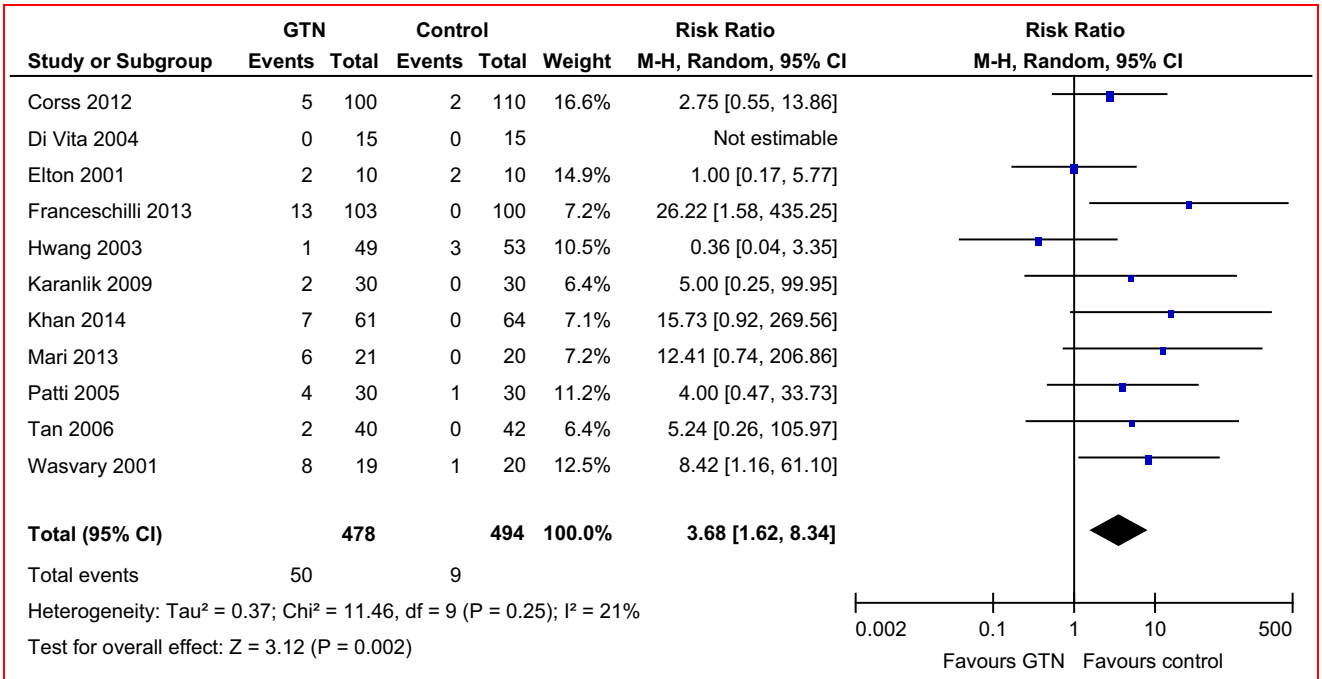

Fig. 6 Forest plot of comparison: GTN ointment application versus control; outcome: incidence of headache

[27–29]. Systematic reviews have indicated that medical therapy may cure chronic and acute anal fissures and fissures in children. Medical therapies for adults with chronic fissures are less effective than surgery is [30, 31]. However, a previous meta-analysis investigating the role of GTN after hemorrhoidectomy has reported that GTN has a significant analgesic effect and improves wound healing within 3 weeks [12]. In an updated review, 8 more RCTs were included in the analysis [10, 11, 14, 15, 21, 23, 26], and the analgesic efficacy of GTN in the early (day 1) and late (day 14) postoperative period was validated. Moreover, the current study reports that GTN application was significantly associated with more headaches, but this relationship was statistically nonsignificant in the previous meta-analysis [12].

The optimal topical GTN dosage is inconclusive. In the included trials, a high GTN dose (0.4 % twice daily) [15, 21] revealed lesser analgesic effects than did a low dose (0.2 % 2 or 3 times daily). No difference of GTN toxicity, such as postoperative complications, was observed, and headache incidences were reported in both low and high doses of experimental drugs.

Previous studies have shown that a third of the patients do not comply because of GTN-induced headache [12]. Our study revealed a 10.5 % incidence of headache in GTN-treated patients. In one of the included studies, Tan et al. documented a case of severe headaches requiring treatment cessation of simple analgesics [24]. The application of GTN was discontinued in 3.27–17 % of patients because of local discomfort and headaches in 3 trials [14, 15, 26]. Mari et al. reported 6 patients with headaches in the GTN group; 4 of them reduced the GTN dose by 50 % and reported cessation of headaches [21]. However, most included trials reported that headaches were not clinically significant to discontinue GTN ointment use in clinical practice and can be controlled using simple analgesics such as paracetamol.

Other RCTs had evaluated the effects of topical diltiazem or nifedipine, a calcium channel blocker, in reducing pain after hemorrhoidectomy [32–34]. These studies noticed no significant difference in morbidity between intervention and control groups. Therefore, diltiazem or nifedipine seems to be an effective alternative ointment of GTN to prevent headaches. However, the efficacy of these drugs in reducing pain and analgesic tablets consumption are still questionable [32, 34]. Further research focusing on these outcomes is warranted.

The studies included in our analysis displayed considerable heterogeneity because of various clinical factors. First, surgical techniques were not the same across all studies and included open, closed, and stapled hemorrhoidectomy. Second, some trials did not standardize the preoperative protocol [10]. Finally, the experimental drug dosage application differed across studies. Such diversities among studies resulted in heterogeneity.

The study has several limitations. First, some trials had a small sample size of 10 patients recruited per treatment group. Second, only 3 studies reported the measurements of postoperative anal pressure changes [21–23], a measure of reduced postoperative pain, and enhanced healing. Finally, several of the primary and secondary outcomes were variably reported; the wound healing was judged by a clinician and is therefore subjective, thereby potentially limiting the inference of our analysis.

In conclusion, our meta-analysis revealed that GTN application after hemorrhoidectomy significantly decreases pain and reduces the wound healing time compared with a placebo. However, an approximately 10 % headache incidence was found in the GTN group. Therefore, if patients want pain relief and early wound healing time, they may opt for GTN application after hemorrhoidectomy, and the resulting headaches can be dealt with simple analgesics.

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