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Is Glyceryl Trinitrate an Effective Treatment for Reducing Visibility of Anal Fissures in Patients Without Heart Disease Compared to Placebo?

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Is glyceryl trinitrate an effective treatment for reducing visibility of anal fissures in patients without heart disease compared to placebo?

Christopher Deneault PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

December 18, 2015
Abstract

Objective: The objective of this systematic review is to determine whether or not topical glyceryl trinitrate is an effective treatment for reducing visibility of anal fissures in patients without heart disease compared to placebo.


Data Source: Three randomized controlled trials each evaluating the effectiveness of topical glyceryl trinitrate in the treatment of anal fissure, published in the English language, and containing exclusion criteria disqualifying participants with a history of heart disease.

Outcome(s) Measured: Healing was measured via visibility of fissure through examination and structured patient interview. The outcomes were measured by medical professionals, blinded consultants, or medical investigative interviewers.

Results: Average healing rate is 71% for the GTN group and 43% for placebo/lignocaine group.

Conclusions: Based on the combined evidence this systematic review finds that topical glyceryl trinitrate is an effective treatment for reducing visibility of anal fissures in patients without heart disease compared to placebo.

Key Works: anal fissure, glyceryl trinitrate, heart disease
Introduction

Anal fissure is a somatic condition consistently seen in many patient populations.\textsuperscript{1} An anal fissure is a linear tear or ulceration in the anal mucosa often extending from below the dentate line to the exterior of the anus.\textsuperscript{1,2} The tear or ulcer is known to cause extreme pain during defecation due to its location below the dentate line.\textsuperscript{1} The condition is often prolonged due to decreased blood flow from the associated spasm of the internal anal sphincter.\textsuperscript{1} The smooth muscle spasm associated with the anal fissure is in theory caused by the lack of nitric oxide synthesis, a known inhibitory neurotransmitter.\textsuperscript{2} The spasm of the internal sphincter additionally causes an increase in the maximum resting anal pressure (MRP); as a result, the increased MRP causes increased pain and discomfort upon defecation.\textsuperscript{3} The rise in MRP will also influence healing time due to its impact on localized ischemia and unremitting opening of the fissure during stooling.\textsuperscript{4} Ninety percent of anal fissures occur at the posterior commissure, leaving the remaining 10% to present at the anterior commissure.\textsuperscript{4,5} Anal fissures are deemed chronic if they present for over six weeks.\textsuperscript{5} Most anal fissures are visible on physical exam with minor patient straining; however, if physical exam fails to uncover the lesion in the setting of elevated clinical suspicion, then anoscopy may be required for visualization and diagnosis of fissures.\textsuperscript{5}

Patients often described the sharp pain associated with anal fissures as the feeling of defecating broken glass then enduring burning pain at their anus for hours after.\textsuperscript{2} While anal fissures invoke a certain embarrassing context in layman conversation, the condition has taken its place as one of the most common gastrointestinal complaints, and therefore, requires significant effort in both research and treatment.\textsuperscript{1,2} During the lifetime of a patient there is a 7.8-11\% chance they will develop an anal fissure.\textsuperscript{1,2} Although males still have a high occurrence rate, females have the most cases with 58\% of the predicted population based on cohort presentation.\textsuperscript{1} From superimposing the cohort results to the 2010 US census population it is predicted that
342,000 new diagnoses of anal fissure present in exam rooms across the United States each year.¹

The etiology of anal fissures is unclear; however, the condition is largely attributed to direct trauma on the anus.¹ In the past it has been believed that it is formed by hard stools or bouts of diarrhea; on the other hand, a recent study showed that only 25% of newly diagnosed anal fissures are preceded by constipation.¹ According to cohort data 15% of postpartum mothers have anal fissures.¹ Crohn’s disease, ulcerative colitis, HIV infection, neoplasia, syphilis, and tuberculosis have shown to be prevalent in new diagnoses of rare lateral positioned anal fissures.¹

The majority of anal fissures can heal rapidly without medical professional involvement; however, the high prevalence of anal fissures in population creates a significant amount patients requiring intervention.¹ Topical glyceryl trinitrate (GTN) is the non-operative treatment of choice.² GTN is effective both in clinical trials and in pathological theory.²⁻⁴ The replacement of the inhibitory neurotransmitter, nitric oxide, would in theory restore control of spasm to the internal sphincter smooth muscle.² Many studies have exclaimed the effectiveness and usage of GTN on anal fissures in the standard population.¹⁻⁵ However, with the equal efficacy and development of other non-operative treatments, it is crucial to evaluate and the true efficacy of GTN based upon ideal patient conditions.⁵ Systemic absorption of glyceryl trinitrate would induce symptoms that can replicate or exacerbate various heart diseases, such as, headache and theoretically hypotension.⁵,⁶ The headaches are reported in as many as 40% of the patients in cohort and have proven to be a reason for patient imposed treatment discontinuation.⁶ With the currently equal efficacy and different side effect profile of other non-surgical treatments, it is important to study the effectiveness of GTN in those patients that have less risk of experiencing
the side effects, patients without heart disease.\textsuperscript{5} Reviewing random controlled trials with the criteria for cohort selection to exclude participants with heart disease would give an accurate assessment of the effectiveness of GTN and possibly propel it to be the undisputed first line treatment for years to come.

There are many treatment options for anal fissure other than GTN. Conservative treatments target sphincter opening and stool softening include hydration, increased fiber intake, and stool softeners.\textsuperscript{2} Calcium channel blockers, botulinum toxin, clove oil, and sildenafil are non-operative treatments available.\textsuperscript{2} Surgical intervention is most commonly administered to recurrent or complicated cases; the gold standard surgical treatment is lateral internal anal sphincterotomy.\textsuperscript{2} Surgical intervention has the highest healing rate, but comes with the risk of permanent stool incontinence.\textsuperscript{2}

The cost of treating anal fissures differs depending on the modality and healthcare system. The 2005 United States healthcare system cost of a prescription filling of topical glyceryl trinitrate treatment is approximately $10, while outpatient surgical intervention for anal fissure is approximately $1119.\textsuperscript{7} The British model of medicine estimates the cost of treatment from check-in to resolution for glyceryl trinitrate is 615.92 pounds ($930.75) and surgical intervention is 840.62 pounds ($1270.30).\textsuperscript{8} The current cost of GTN in the United States is $566.\textsuperscript{9}

**Objective**

The objective of this selective evidence based medicine review is to determine whether or not topical glyceryl trinitrate is an effective treatment for visible resolution of anal fissures in patients without heart disease compared to placebo.

**Methods**
This systematic review looked into 3 randomized controlled trials. The studies each included participants with active anal fissures and various ages. The studies attempted to determine the efficacy of GTN when treating anal fissure. Each study compared GTN to placebo or a topical ointment only treating the perception of pain. The primary outcome measured was the visibility of the fissure to determine the level of healing; however, each study also evaluated the current level of pain and/or presence of pain upon defecation. Ahmad et al used 2 interventions separately on 2 participant groups consisting of: 0.2% GTN ointment BID x 8 weeks and 5% lignocaine ointment BID x 8 weeks. To measure outcomes Ahmad et al implemented a visual analog scale (VAS) for pain plus a clinical exam with digital rectal exam (DRE) and anoscopy; a blinded clinical consultant was used to assess the clinical signs of healing. Kenny et al used 2 interventions separately on 2 participant groups including: 0.2% GTN ointment BID x 6 weeks and Placebo paste BID x 6 weeks. To measure outcomes Kenny et al implemented the use of Smiley analogue pain scores and investigator completed clinical assessments of symptoms and signs of anal fissure in an outpatient clinic. Carapeti et al used 3 interventions separately on 3 participant groups including: 0.2% GTN ointment TID x 8 weeks, 0.2% GTN ointment weekly titrated 0.1% until 0.6% TID x 8 weeks, and placebo TID x 8 weeks. To measure outcomes Carapeti et al implemented clinical examination of the fissure, anal manometry, laser Doppler flowmetry, and linear analogue pain charts. The participants involved in the studies had to meet specific criteria including: presence of anal fissure, the ability to tolerate and administer treatment, and the ability to give consent via self or guardian. Further demographic and study characteristics can be found in TABLE 1.

This systematic review evaluated each article and compared the treatment times as outlined by visibility of fissure to determine the efficacy of GTN treatment on patients with anal
fissures and without heart disease. Each article was published in academic journals and released in the English language. The author researched the articles via PubMed through the PCOM Library website using the key words: glyceryl trinitrate, anal fissure, and heart disease. Articles were selected based upon their relevance to the desired topic, date of publication, language, and exclusion criteria. Statistics reported or used include: p-values, absolute benefit increase (ABI), numbers needed to treat (NNT), and numbers needed to harm (NNH).

**TABLE 1 – Demographics & Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age in Years</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W / D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad J, 2007</td>
<td>RCT</td>
<td>50</td>
<td>9-59</td>
<td>Patients with an anal fissure that consent to the study and can apply a pea sized amount of ointment to the area as directed.</td>
<td>Patients with perianal fistula, perianal abscess, inflammatory bowel disease, ischemic heart disease, migraine, and pregnancy.</td>
<td>5</td>
<td>0.2% GTN BID x 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% lignocaine BID x 8 weeks</td>
</tr>
<tr>
<td>Kenny SE, 2001</td>
<td>RCT</td>
<td>40</td>
<td>0.7-15.9</td>
<td>Positive diagnosis of anal fissure with visibility and pain with defecation.</td>
<td>History of recurrent fissure, congenital heart disease, or severe headaches.</td>
<td>9</td>
<td>0.2% GTN BID x 6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo paste BID x 6 weeks</td>
</tr>
<tr>
<td>Carapeti EA, 1999</td>
<td>RCT</td>
<td>70</td>
<td>21-72</td>
<td>Patients with anal fissure for three months duration or longer, with clinical features of chronicity such as fibrosis of the base of the ulcer or associated sentinel pile.</td>
<td>Pregnant women, patients already on nitrate treatment for ischemic heart disease, patients with fissures attributed to an underlying identifiable pathology such as Crohn’s disease or HIV, and patients with a history of migraine.</td>
<td>2</td>
<td>0.2% GTN TID x 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2% GTN weekly titrated up to 0.6% TID x 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo x 8 weeks</td>
</tr>
</tbody>
</table>

**Outcomes Measured**
GTN, lignocaine, and placebo supplemented healing was measured via visibility of fissure and pain through physical examination and structured patient interview. The outcomes were measured by medical professionals, blinded consultants, or investigative clinicians. Tools used to measure outcomes included clinical expertise, anoscopy, anal manometry, laser Doppler flowmetry, linear analogue pain charts, Smiley analogue pain scores, and DREs.

Results

Ahmad et al used 50 participants and randomly divided them into 2 groups. The first group of 25 participants received GTN and the second lignocaine. See TABLE 1 for dosage and criteria. There were 18 females and 32 males divided at random. The average age was 31.28 with a low of 9 and a high of 58 years old. There were no participant drop outs or disqualifications from the study. Healing was determined based on defecation pain score, clinical exam, and disappearance of fissure. After 8 weeks of treatment the GTN group experienced fissure healing in 80% of the patients compared to the 32% in the lignocaine group with a p-value of less than 0.002. Headaches occurred in 68% of the GTN group compared to 32% in the lignocaine group with a p-value of 0.01. Pruritis ani and postural hypotension occurred in a minority but was deem not statistically significant. The NNT for the GTN is 3 to illicit significant clinical benefit. The NNH for GTN headaches is 2 and postural hypotension is 12. See TABLE 2 for healing and side effects data.

TABLE 2 – Healing and side effects data for Ahmad et al

<table>
<thead>
<tr>
<th></th>
<th>GTN Group (n=25)</th>
<th>Lignocaine Group (n=25)</th>
<th>p-value</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing at 8 weeks</td>
<td>20 (80%)</td>
<td>8 (32%)</td>
<td>$P &lt; 0.002$</td>
<td>NNT = 3</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (68%)</td>
<td>7 (28%)</td>
<td>$P = 0.01$</td>
<td>NNH = 2</td>
</tr>
<tr>
<td>Pruritis ani</td>
<td>2 (8%)</td>
<td>4 (16%)</td>
<td>Not significant</td>
<td>*</td>
</tr>
</tbody>
</table>
Deneault, GTN, 7

<table>
<thead>
<tr>
<th>Postural hypotension</th>
<th>1 (4%)</th>
<th>0</th>
<th>Not significant</th>
<th>NNH = 12</th>
</tr>
</thead>
</table>

* lignocaine group cannot be used as control due to its potential for causing pruritis ani

Carapeti et al used 70 patients ranging from 21-72 years old with a mean age of 35. The participants were randomly divided into 3 groups. Two groups of 24 participants underwent GTN treatment at various titrations (see TABLE 1) and the placebo group consisted of 22. One person in each of the GTN groups dropped out due to one not having a fissure and the other becoming uncontactable. One person in the placebo group did not finish the study due to needing a lateral sphincterotomy and was considered to be treatment failure. Healing was determined based on clinical examination of fissure, anal manometry, and laser Doppler flowmetry. After treatment and a 2 week waiting period 32% of the placebo group, 65% of the 0.2% GTN, and 70% of the titrated GTN were found to have healed with a p-value of 0.008. The p-value was calculated based on placebo versus combined GTN healing rate. Headaches were experienced in 72% of the combined GTN groups and 27% of the placebo with a p-value of <0.001. The NNT for GTN is 3 to illicit significant clinical benefit. The NNH in the form of headaches by GTN 2. See TABLE 3 for healing and side effects data.

**TABLE 3 – Healing and side effects data for Carapeti et al**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>GTN (n=23)</th>
<th>GTN titrated (n=23)</th>
<th>Placebo (n=22)</th>
<th>p-value</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing at 10 weeks</td>
<td>15 (65%)</td>
<td>16 (70%)</td>
<td>7 (32%)</td>
<td>P = 0.008</td>
<td>NNT = 3</td>
</tr>
<tr>
<td>Headache</td>
<td>33 (72%)</td>
<td>combined GTN groups</td>
<td>6 (27%)</td>
<td>P &lt; 0.001</td>
<td>NNH = 2</td>
</tr>
</tbody>
</table>

Kenny et al used 40 participants ranging from 0.7 to 15.9 years old with a mean age of 3.83. The participants were randomly divided into 2 groups. The GTN group received 20 participants and the placebo received 20. The 2 groups received treatment base on their group
(see TABLE 1) and a daily dose of oral senna and lactulose. For various reasons outside of
know GTN side effects, the GTN group had 7 participants drop out compared to the placebo
group’s 2 (see TABLE 4). Two of the GTN group’s participants were present for the 6-week
evaluation and included in this systematic review as participants. Healing was determined via an
outpatient physical exam by medical investigators blind to treatment group allocation. At week 6
visible fissure was resolved in 54.4% of the GTN group compared to 75% in the placebo group
with no p-value given (see TABLE 5). The ABI is -26.5% for treatment with GTN. Due to the
significant difference in fissure visibility in the placebo and GTN groups at 6 weeks, the NNH
for GTN by way of prolonging visibility of fissure is 4 (see TABLE 5). None of the participants
reported headache.

**TABLE 4 – Participant withdrawal profile**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (year)</th>
<th>Sex</th>
<th>When withdrew (week)</th>
<th>Pain score on withdrawal</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTN</td>
<td>2.4</td>
<td>F</td>
<td>7</td>
<td>0</td>
<td>Lost contact</td>
</tr>
<tr>
<td>GTN</td>
<td>2.7</td>
<td>F</td>
<td>11</td>
<td>8</td>
<td>Persistent high pain scores; no fissure when examined under anesthetic</td>
</tr>
<tr>
<td>GTN</td>
<td>1.3</td>
<td>F</td>
<td>5</td>
<td>8</td>
<td>Persistent high pain scores; coryzal symptoms thought by parents to be due to GTN</td>
</tr>
<tr>
<td>GTN</td>
<td>0.7</td>
<td>M</td>
<td>1</td>
<td>10</td>
<td>No reason given</td>
</tr>
<tr>
<td>GTN</td>
<td>1.2</td>
<td>F</td>
<td>4</td>
<td>8</td>
<td>Perineal rash; examination under anesthetic at week 4: fissure healed, pain free at 8 weeks and oV laxatives</td>
</tr>
<tr>
<td>GTN</td>
<td>1.2</td>
<td>M</td>
<td>1</td>
<td>8</td>
<td>Gastrointestinal upset (colicky pains and vomiting)</td>
</tr>
<tr>
<td>GTN</td>
<td>3.6</td>
<td>F</td>
<td>14</td>
<td>2</td>
<td>Parental dissatisfaction with improvement; underwent fissurectomy</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.8</td>
<td>F</td>
<td>8</td>
<td>9</td>
<td>Persistent high pain scores; underwent fissurectomy</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.6</td>
<td>M</td>
<td>8</td>
<td>7</td>
<td>Persistent high pain scores; underwent fissurectomy</td>
</tr>
</tbody>
</table>
Combining the data from all studies involved in this review produces a healing rate of 71% for the GTN group and 43% for placebo/lignocaine group (see TABLE 6).

**TABLE 5 – Healing data for Kenny et al**

<table>
<thead>
<tr>
<th>Healing at 6 weeks</th>
<th>GTN (n=15)</th>
<th>Placebo (n=16)</th>
<th>ABI of GTN</th>
<th>NNH for GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing</td>
<td>8 (54.4%)</td>
<td>12 (75%)</td>
<td>-21.66%</td>
<td>4</td>
</tr>
</tbody>
</table>

**TABLE 6 – Combined Healing data**

<table>
<thead>
<tr>
<th>Healing at 6-8 weeks</th>
<th>GTN (n=86)</th>
<th>Placebo/lignocaine (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing</td>
<td>61 (71%)</td>
<td>27 (43%)</td>
</tr>
</tbody>
</table>

**Discussion**

This systematic review is comprised of studies that both support and reject the efficacy of using GTN for treating anal fissures in patients without heart disease. There are a few important points that need to be discussed before a conclusion can be constructed.

GTN is labeled for use in angina/coronary artery disease and anal fissure. The off label uses include esophageal spastic disorders, gastroesophageal variceal hemorrhage, sympathomimetic vasopressor extravasation injury, uterine relaxation, and short-term management of pulmonary hypertension. Contraindications to GTN include hypersensitivity to organic nitrates, concurrent use of phosphodiesterase-5 inhibitors or riociguat, increased intracranial pressure, and severe anemia. Systemic absorption is known to have adverse drug reactions in some cases including but not limited to: bradycardia, flushing, hypotension, orthostatic hypotension, peripheral edema, syncope, tachycardia, headache, dizziness, lightheadedness, nausea, vomiting, and diaphoresis. The adverse drug reactions are the primary reason this study chose to reject random controlled trials that failed to add heart disease to their
exclusion criteria. The adverse drug reactions have the potential to simulate symptoms of heart disease. Excluding people with heart disease reduced the risk of GTN group dropout and maladaptive administration; therefore, the exclusion criteria requirement gave a better estimate on how GTN works on anal fissures without the confounding of variable from comorbid conditions.

The age gap between the studies may have had an effect on the results. Ahmad et al and Carapeti et al had participant age averages of 31.28 and 35 years old. Kenny et al had an average participant age of 3.83 years old. While the pathology and treatment remains the same, the younger patient population was less successful with GTN treatment. Kenny et al self-identified as an outlier compared to other similar studies in the discussion section of their study and attempted to explain why their results were different. A lower age group has been hypothesized to change voiding habits in response to pain, for example less frequent voiding, which can increase the maximum resting anal pressure and reduce the efficacy of treatment. Kenny et al also had the highest withdrawal rate associated with the GTN group. While the age difference is cause for further investigation regarding its impact on GTN efficacy, age was not a specified exclusion parameter in this systematic review and likely introduced confounding variables.

Ahmad et al and Carapeti et al displayed adverse events associated with GTN. Both studies had headaches in a significant number of their GTN patients. With a NNH of 2, the headache prevalence is an important side effect to communicate to patients. One patient reported postural hypotension in the GTN group of Ahmad et al, producing a NNH of 12. Both of the studies did not lose any participants to side effect related symptoms in the GTN group; therefore, when educating patients on GTN side effects it is important to highlight the likely mild severity.
With all of the differences aside, two of the three articles, Ahmad et al and Carapeti et al, conclude GTN is an effective treatment and found success rates much higher than expected. Ahmad et al and Carapeti et al both produced data that establishes a NNT of 3 for GTN from their EER values of 80% and 72% respectively. Kenny et al found that GTN was an ineffective treatment. Furthermore, if prolonged healing were to be considered an adverse drug reaction, then the data from Kenny et al could conclude that GTN in fact has a NNH of 4. While the studies greatly differed in many areas, they fit the parameters of this systematic review and thereby must all be given equal strength in the evaluation and fulfilment of this systematic review’s objective. Even though the majority supported the use of GTN, Kenny et al produced results that without question rejects the use of GTN.

**Conclusion**

Based on the combined evidence this systematic review finds that topical glyceryl trinitrate is an effective treatment for reducing visibility of anal fissures in patients without heart disease compared to placebo. A secondary finding is the adverse drug reactions of GTN are not significant enough to cause patients without heart disease to discontinue treatment. Age and confounding variables may have played a role in reducing the overall efficacy of GTN in this review; however, the evidence supporting GTN treatment is convincing enough to overcome one random controlled trial reporting the contrary. The inclusion of a study with a low average participant age, Kenny et al, was a flaw in the methods of this systematic review. To reduce risk of confounding variables and better evaluate the efficacy of GTN in ideal patients, future reviews should target studies that require patients developed enough to properly administer their own treatment and provide supportive care for their fissure.
References


4. Carapeti EA, Kamm MA, McDonald PJ, Chadwick SJ, Melville D, Phillips RK. Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut.* 1999;44(5):727-730.


