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# Is Transdermal Glyceryl Trinitrate a Safe and Effective Treatment for Primary Dysmenorrhea?

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# **Is transdermal glyceryl trinitrate a safe and effective treatment for primary dysmenorrhea?**

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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

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## ABSTRACT

Objective: The objective of this selective evidence based medicine review is to determine whether or not transdermal glyceryl trinitrate is a safe and effective treatment for primary dysmenorrhea.

Study Design: Review of two English language randomized control trials (RCTs) published in 1996 and 1999 and one English language pilot study in 1997.

Data Sources: Two double-blind, randomized, placebo-controlled cross-over studies and one pilot study comparing transdermal glyceryl trinitrate to placebo were found using PubMed, Medline and OVID.

Outcome Measured: Outcomes measured were based on pain intensity scores (PID) assessed on a visual analog scale and the time-weighted sum of pain intensity differences (SPID) in the Ali et al and Moya et al studies. Ali et al converted the SPID into percentages of pain relief, while Moya et al analyzed the PID and SPID using an analysis of variance (ANOVA) model. Pittrof et al used a visual analogue self-assessment form to evaluate efficiency, and results were reported as mean scores.

Results: Pain relief from primary dysmenorrhea was considerably improved with glyceryl trinitrate therapy as seen in the randomized control trial by Moya et al. The remaining two studies in this systematic review were limited by study design and didn't provide a definitive answer. The pilot study conducted by Ali et al failed to provide clinical significance because there was no control group for comparison, participants weren't blinded and two different doses of the intervention were used at random. Pitroff et al did show improvement in patient symptoms, but had more than 20% of the participants lost to follow-up. The most common adverse effect of glyceryl trinitrate therapy was headache when compared to placebo.

Conclusion: The results of this selective EBM review are inconclusive, however do suggest that glyceryl trinitrate may be a safe and effective treatment for primary dysmenorrhea. Due to limitations within these studies, this topic does warrant additional research.

Key Words: Primary dysmenorrhea, Transdermal glyceryl trinitrate

## INTRODUCTION

Primary dysmenorrhea is defined as lower abdominal pain in women with normal pelvic anatomy that interferes with daily activities<sup>5</sup> and occurs at the beginning of menses. It is described as cramping, wave-like pain that may radiate to the back and gradually decreases over the next 12-72 hours after onset<sup>4</sup>. In addition to the abdominal pain, women can experience nausea, diarrhea, fatigue and headaches<sup>8</sup>. There is no current cure for primary dysmenorrhea, however there are many drugs that are generally helpful for symptom reduction. This paper evaluates two double blind, randomized cross-over control trials and one pilot study comparing the efficacy of glyceryl trinitrate as a transdermal medication for primary dysmenorrhea relief.

Dysmenorrhea is one of the most commonly reported menstrual disorder worldwide<sup>2</sup> and is the leading cause of lost time from school and work among women in their teens and twenties<sup>9</sup>. The understanding of primary dysmenorrhea is important to the physician assistant and fellow physician in order to provide the best point of care to patients, as well as to focus on decreasing morbidity and increasing quality of life for those women who are suffering. In the United States, the annual economic loss has been estimated at 600 million work hours and 2 billion dollars<sup>9</sup>. Although an exact number of healthcare visits associated with primary dysmenorrhea is unknown, it's estimated that 60-93% of women who menstruate complain of pain for 1-2 days/month<sup>2,8</sup>.

The etiology of primary dysmenorrhea is not exactly understood, however it's thought to be caused by the release of prostaglandins from the endometrium at the time of menstruation<sup>8</sup>. The pain is produced as a result of uterine vasoconstriction, anoxia and sustained contractions<sup>3</sup>. Currently the recommended treatment for dysmenorrhea is pain relievers, such as NSAIDs, or hormonal medications, such as birth control pills in conjunction with heat<sup>2</sup>. In addition, some

lifestyle changes may be indicated, such as exercise, getting adequate sleep and relaxation techniques<sup>3</sup>. Transdermal glyceryl trinitrate may provide a superior alternative for the relief of primary dysmenorrhea by providing localized relaxation of myometrium contractions.

## OBJECTIVE

The objective of this systematic evidence based medicine review is to determine whether or not transdermal glyceryl trinitrate is a safe and effective treatment for primary dysmenorrhea.

## METHODS

Specific selection criteria of two randomized control trials and one pilot study were used for this review. The population of interest included adolescent females and adult women who complained of persistent primary dysmenorrhea. The interventions utilized in each study were transdermal patches, each delivering glyceryl trinitrate at a dose of 0.1 mg/h, 0.2 mg/h or 10 mg/24 hours<sup>1,6,7</sup>. Comparisons were made between the experimental group receiving transdermal glyceryl trinitrate patches to the control group who received a visually matched placebo patch. Outcomes in each study were based on patient oriented evidence that matters (POEMs) and measurements of the efficacy and tolerability of transdermal glyceryl trinitrate for the treatment of primary dysmenorrhea.

Key words used in the searches were “transdermal glyceryl trinitrate” and “primary dysmenorrhea”. All articles searched were published in peer-review journals and in the English language. The author researched the studies through PubMed, Medline and OVID. Articles were chosen based on the application to the research practicum and if the outcomes measured POEMs. Inclusion criteria consisted of primary research studies that were published in 1996 or later with participants over the age of 12 years old. Exclusion criteria included articles with disease oriented evidence (DOE), published before 1996, with participants under the age of 12 years old

or patients who experienced painful menses for reasons other than primary dysmenorrhea. The statistics used in the studies were ANOVA model<sup>6</sup>, PID, SPID, RRR, ARR, NNT, and p-values.

## OUTCOMES MEASURED

Outcomes measured were based on pain intensity scores (PID) assessed on a visual analog scale and the time-weighted sum of pain intensity differences (SPID) in the Ali et al and Moya et al studies. Ali et al converted the SPID into percentages of pain relief, while Moya et al analyzed the PID and SPID using an analysis of variance (ANOVA) model. Pittrof et al used a visual analogue self-assessment form to evaluate efficiency, and results were reported as mean scores with 95% confidence intervals. Overall assessment of efficacy and the incidence of adverse events were analyzed by the Stuart-Maxwell or the McNemar test as appropriate in the Moya et al study. Safety and tolerability of transdermal glyceryl trinitrate were both measured on actual reports of patients in the studies.

## RESULTS

The demographics of the studies included in this review are outlined in **Table 1**. One of the studies was conducted for two consecutive menstrual cycles (Pittrof et al) and two of the studies were conducted for three consecutive menstrual cycles (Ali et al, Moya et al). All participants were females who suffer from primary dysmenorrhea. The results were presented in dichotomous form for studies conducted by Moya et al and Pittrof et al, while results for Ali et al were reported in a continuous form.

**Table 1:** Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ali, 1997 <sup>1</sup>	Pilot study	65	18-33	Moderate to severe pain associated with menses	History of severe bleeding during menses,	0	Transdermal nitroglycerine 0.2mg/hr or 0.1 mg/hr

					concomitant genitourinary infections, concomitant neoplasia or history of arterial hypotension		
Moya, 1999 <sup>6</sup>	Multi-national, double blind, randomized, crossover	88	Mean= 22.6	Primary dysmenorrhea	Secondary dysmenorrhea	14	Transdermal glyceryl trinitrate 0.1 mg/h
Pittrof, 1996 <sup>7</sup>	Double blind, randomized, placebo controlled, two period crossover	14	17-36, mean =27	Persistent and regular severe dysmenorrhea which interfered with social and professional lives	Evidence of gynecological pathology via transvaginal ultrasound	3	Transdermal glyceryl trinitrate 2.5 mg/24 hrs

Ali et al conducted a pilot study that involved 65 women with primary dysmenorrhea over the course of three consecutive menstrual cycles. This study did not have a control group; instead all participants used a form of the active medicated patch. The participants were not blinded to the intervention. The participants were instructed to use transdermal nitroglycerine patches that delivered either 0.2 mg/h (“Minitran”) or 0.1 mg/h with the onset of primary dysmenorrhea<sup>1</sup>. If the pain persisted for 4 hours after the first patch, patients were instructed to apply a second patch. Eight patients used a patch that delivered 0.2 mg/h of transdermal nitroglycerine, while the remaining 57 used patches that delivered 0.1mg/h. It is unknown if the assignment of patients to treatment was randomized or not. Patches were to be applied as necessary for pain for days 1-3 of the women’s cycles. Pain intensity was measured by the patients at baseline and then again at 0.5, 1, 2, and 4 hours after patch application. The pain scale used was: 3 (severe), 2 (moderate) 1 (mild) and 0 (no pain)<sup>1</sup>. The pain intensity differences

versus baseline values were calculated and the sum of pain intensity differences (SPIDs) were then converted into percentages of pain relief. Pain relief was defined into three categories: excellent, satisfactory and unsatisfactory (**Table 2**).

**Table 2:** Relief of pain associated with primary dysmenorrhea in patients treated with transdermal nitroglycerin<sup>1</sup>

Pain relief	% Pain relief	% of Patients
Excellent	>75	47
Satisfactory	40-74	43
Unsatisfactory	<39	10

In order to evaluate the data as dichotomous, it was necessary to define a dichotomous “cut-off.” Since this research practicum is evaluating the use of transdermal nitroglycerin as a safe and effective pain reliever, the cut-off was defined at satisfactory. Thus, the unsatisfactory group represents the control event rate (CER), while the satisfactory and excellent groups represent the experimental event rate (EER). The CER was calculated to be 7% and the EER was 59% (**Table 5**). The relative benefit increase (RBI) was calculated to be 742% and the absolute benefit increase (ABI) was 52%. The number needed to treat (NNT) was calculated as 2 (**Table 5**), meaning 2 people need to be treated with transdermal nitroglycerin in order to prevent one person from experiencing menstrual pain from primary dysmenorrhea.

The only clinically significant side effect reported was a headache, which was reported by 20% of the patients<sup>1</sup>. All of these patients used a second patch due to continued pain after 4 hours of the first patch application.

In the study conducted by Moya et al 88 healthy volunteers participated<sup>6</sup>. Patients were evaluated during three menstrual cycles. During two of the cycles the patients were receiving the transdermal glyceryl trinitrate 0.1 mg/h active medicated patch (“Minitran-F patch”), while the



remaining cycle the patients were receiving a visually matched placebo patch. Patients were blinded as to which patch they were using. The women were instructed to place the patch on the lower abdomen on days 1-3 of their menstrual cycles. Each patient ranked her own pain intensity on a 0-100 visual analog scale, '0' meaning no pain and '100' meaning severe pain. These observations were recorded at 0.5, 1, 2, 4 and 6 hours after patch application. The study enrolled 88 participants but not all participants were represented in the efficacy results (N=74)<sup>6</sup>. There was no mention in either the methods or results section that addressed any participants who dropped out. **Table 3** provides the difference in pain intensity (PID) by hour after patch application and the sum of the pain intensity difference (SPID). This data is statistically significant, with a p-value of <0.01.

**Table 3:** Differences in SPID in those who received Transdermal glyceryl trinitrate vs. Placebo<sup>6</sup>

N=74	Transdermal glyceryl trinitrate Patch	Placebo Patch
Pain before patch application	76.01	75.6
Differences in pain intensity by hour after patch application		
0.5 hour	12.0	8.0
1 hour	22.8	15.1
2 hours	32.4	20.1
4 hours	37.2	24.4
6 hours	40.3	28.3
SPID	186.3	122.6

The CER was calculated to be 43% and the EER was 85%. The relative benefit increase (RBI) was calculated to be 98% and the absolute benefit increase (ABI) was 42%. The numbers needed to treat was calculated as 3 (**Table 5**), meaning a physician assistant would have to treat 3 people with transdermal nitroglycerin in order to attain one beneficial outcome for treatment of menstrual pain from primary dysmenorrhea.

Additionally, patients proved to use analgesic medication less during the active drug treatment (20.3%) than during the placebo group (39.2%), with a p-value of being statistically significant at  $p < 0.05^1$ .

The most common adverse event was a headache. Out of the 74 patients who participated, 26% reported a headache while on the active patch, compared to 6% reported the same symptom during the one placebo cycle ( $p < 0.001$ )<sup>6</sup> **Table 4.**

**Table 4:** Harms from headache of those treated with 0.1 mg/h of transdermal glyceryl trinitrate compared to a visually matched placebo<sup>6</sup>

CER	EER	RRI	ARI	NNH	P-value
6%	26%	333%	20%	5	<0.01

The numbers needed to harm was calculated as 5, meaning 5 patients have to be treated with glyceryl trinitrate to prevent one additional bad outcome, like a headache.

In the Pittrof et al study, one participant was lost to follow up, one withdrew due to presumed side effects and one did not complete her self-assessment form<sup>7</sup>. The remaining eleven women (78.5%) participated in a randomized, double-blind placebo controlled, two period crossover trail for two consecutive menstrual cycles. The women were provided with adhesive patches that were either placebo or released 10 mg of glyceryl trinitrate transdermally over 24 hours. The women were instructed to apply one-quarter (2.5 mg) of the patch to their lower abdomen when menstrual pain began<sup>7</sup>. The participants recorded their symptoms on a visual analog self-assessment form. The data was collected and recorded as mean scores for the outcome measured as a total pain score and as a pain score on the worst day. No statistical significance was found with the total pain score ( $p = 0.059$ )<sup>7</sup>; however, there was statistical significance found with the improvement of pain scores on the worst day ( $p = 0.048$ ) with a 95%

CI<sup>7</sup>. The score on the worst day was lower with active treatment than with placebo. The reduction in the active group was 10.2% of the maximum possible score, while in the placebo group it was 11.6%. The relative benefit increase (RBI) was calculated to be 7%, while the absolute benefit increase (ABI) was 4% (**Table 5**). The number needed to treat was 25 people, meaning 25 people need to be treated with transdermal glyceryl trinitrate in order to prevent one person from experiencing menstrual pain from primary dysmenorrhea.

**Table 5:** Comparison of Dichotomous Data (in percentages)

	CER	EER	RBI	ABI	NNT	Treatment effect precision value
Ali et al	7%	59%	742%	52%	2	Not provided
Moya et al	43%	85%	98%	42%	3	p <0.01
Pittrof et al	56%	60%	7%	4%	25	95% CI

## DISCUSSION

This systematic review investigated three primary studies, two of which were randomized control trials, for the safety and effectiveness of transdermal glyceryl trinitrate as a treatment for primary dysmenorrhea. The study by Moya et al demonstrated this drug as a safe and effective treatment. However, the outcome strength of the study conducted by Ali et al did not reach any statistical significance due to the lack of validity. This study did not randomize or blind the participants. In addition, the study didn't provide a p-value or confidence interval. Finally, although the ABI is 52%, the RBI of 742% indicates that a relative change caused a large over estimation of benefit. The Pittrof et al provided statistical significance (CI of 95%) that transdermal glyceryl trinitrates is safe and effective for primary dysmenorrhea, however, the study only involved 11 participants. More than 20% of participants were not accounted for at the conclusion of the study, resulting in a wider confidence interval.

Primary dysmenorrhea can affect the quality of life of females who suffer from this condition and can lead to lost time at school or work, so treatment to improve the lives of these women is imperative<sup>9</sup>. The thought that exogenous nitroglycerin could relieve the pain associated with uterine myometrial contractions is further supported by current use of nitroglycerin for angina. Nitroglycerin patches have been FDA approved for the prevention of episodic angina in patients who suffer from coronary artery disease. Exogenous nitrogen causes vasodilation, which decreases pain. The most common adverse event is a headache. Hypotension and syncope occur infrequently.

## CONCLUSION

There were various limitations to the studies included in this systematic review, thus the evidence as to whether transdermal glyceryl trinitrate as a safe and effective treatment for improving the quality of life for patients with primary dysmenorrhea is inconclusive. The pilot study (by Ali et al) lacked clinical significance because the patients weren't blinded and there was no control group. In addition, two doses of glyceryl trinitrate were used, however, the results were interrupted as one in the same. As mentioned in this study, there is currently a randomized, double-blind, placebo-controlled study underway to confirm the pilot study results. The results of this ongoing study may provide more of a definitive clinical answer. Pittrof et al conducted a well designed study, however, more than 20% of the participants were lost to follow-up. Similarly, Moya et al provided valid data but lost validity when only 74 out of 88 participants were account for at the end of the study. In order to authenticate the benefits of transdermal glyceryl trinitrate as a safe and effective treatment for primary dysmenorrhea, future study is warranted. In addition, perhaps future research could address lowering the adverse side effect of headaches associated with the intervention.

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