

Original Article

DOI: 10.22114/ajem.v0i0.3

Pain Relieving Effect of Sublingual Glycerol Trinitrate in Renal Colic: a Randomized Placebo-Controlled Trial

Leyla Nasehi¹, Reza Taslimi², Ahmadreza Dehpour³, Javad Seyedhosseini^{4*}

1. Department of Radiology, Cleveland Clinic Foundation; OH, USA.

2. Department of Gastroenterology, Imam-Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

3. Department of Pharmacology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

4. Department of Emergency Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

*Corresponding author: Javad Seyedhosseini; Email: jshosseini@gmail.com

Abstract

Introduction: Renal colic is caused by colicky spasms of ureters. As has been shown in previous experiments, glycerol trinitrate (TNG) can inhibit these muscular spasms.

Objective: This study was performed to assess the pain relieving effect of TNG among patients referred due to renal colic pain to the emergency department (ED).

Methods: This study is a randomized, placebo-controlled study on 60 patients with renal colic who were referred to the ED, who were diagnosed clinically to have renal colic, and their pain was more than 5 based on a visual analogue scale (VAS). The patient's pain was recorded at the moment of clinical diagnosis, and each one received one capsule, either 0.4 mg TNG or placebo, plus a 100 mg indomethacin suppository. The pain score was re-assessed after 5 and 30 min. The values were recorded and compared using SPSS-16 software.

Results: Sixty patients with a mean age of 35.75 ± 11.99 years were enrolled (73.3% male). Patients in the two groups were matched for age ($p = 0.290$), sex ($p = 0.559$), and the presence of microscopic hematuria ($p = 0.292$). Pain relief from the start point until the end of the intervention was statistical different in all studied patients ($p < 0.05$); but the comparison between the two groups showed no significant difference in this regard ($p = 0.440$).

Conclusion: It is likely that adding TNG to an indomethacin suppository had no significant effects on better pain management of patients referred with renal colic to the ED.

Key words: Emergency service, hospital; Nitroglycerin; Pain management; Renal colic

Cite this article as: Nasehi L, Taslimi R, Dehpour A, Seyedhosseini J. Pain Relieving Effect of Sublingual Glycerol Trinitrate in Renal Colic: a Randomized Placebo-Controlled Trial. *Adv J Emerg Med.* 2018;2(1): e2.

INTRODUCTION

Renal colic is one of the most disturbing pains people ever experience; it is categorized comparable to or even more severe than labor pain. The average global prevalence was reported to be about 3.25% in the 1980s and 5.64% in the 1990s (1, 2). Colicky spasms of the urethra, resulting in ureteric colic, has been proven to be the main pathophysiology of inducing pain in these patients. During the stone passage, the resultant obstruction of urine increases tension on the walls of the ureteral and produces severe pain (3).

Non-steroidal anti-inflammatory drugs (NSAIDs) and morphine sulfate are most commonly considered as the mainstay of therapy at the present time. These drugs can have various side effects, which may limit their administration in some instances (4-6). As an example, NSAIDs, although quite safe, can cause gastrointestinal and renal side effects (7). On the other hand, opioid

analgesics can cause dizziness, respiratory depression, hypotension, and bradycardia, and also might be abused (8). Considering what has been mentioned above, a significant number of patients would benefit from finding a safer pain killer agent. Glycerol trinitrate (TNG) releases nitric oxide that stimulates guvanilate cyclase, causing smooth muscle relaxation. It has been shown to have minimal side effects (9, 10). A number of researchers have studied the efficacy of TNG in relaxing smooth muscles (10-13). It seems that TNG effectively dilates the smooth muscles of blood vessels, the gastrointestinal tract, and biliary tracts which are the most comparable both anatomically and physiologically to urethral tract muscles. Thus, it could be possibly be used for the treatment of renal colic. Although some studies are available on the efficacy of this drug in renal colic management, all have only been performed on a small number of

patients and are still non-conclusive. Therefore, this study was conducted to assess the pain-relieving effect of TNG in patients referred due to renal colic to the ED.

METHODS

Study design

This study was a triple blind, randomized, placebo-controlled trial, conducted in the ED of Shariati Hospital, Tehran, Iran. The study protocol was approved by the institutional review board and the code of 30847 was assigned. The patients entered the study after they signed the informed consent form. The researchers were adherent to the Declaration of Helsinki Principles throughout the study.

Study population

Patients older than 16, who were diagnosed clinically by an emergency medicine specialist to have renal colic and their pain score was higher than 5 based on a visual analogue scale (VAS) were eligible. Those patients who had self-treated themselves or had any medical co-morbidity such as gastrointestinal, cardiac, renal or liver disease were not included. The items below were considered as exclusion criteria: signs of peritoneal irritation; pregnancy and lactation; presence of fever or hypotension; drug history of using sildenafil, tadalafil, vardenafil, anti-hypertensives, aspirin, anti-muscarinic, alcohol, ergotamine, haloperidol, or phenothiazine during the last 4 weeks; history of allergic reaction to TNG; severe clinical anemia; recent head trauma or any central nervous system insults; malnutrition; hypothyroidism; hypothermia; and illicit drug abusers.

Randomization and blinding

The patients were randomly divided using computerized blocked randomization into two groups. Thirty drugs and 30 placebo capsules were randomly packed in similar packages and were numbered. TNG capsules contained 0.4 mg Tri-nitro-glycerin, while placebo capsules contained glycerin oil, flavored with mint concentrate in order to have a similar flavor for the patients



Figure 1: In this photo you can see the placebo capsule in the right side and the TNG capsule at the left. No visible difference exists in order to ensure the study is blinded.

receiving them. They had absolutely similar appearances (Figure 1). We registered the number related to each package and the content as placebo or TNG capsule; the document was saved until the time of data analysis. Each eligible patient was assigned to one of these packages. Neither patients nor the physicians and analyzers knew which patients received TNG or placebo.

Intervention

All patients were also asked about demographic data such as age, sex, the history of previous attacks, and urinalysis data were registered, if available. Patient's pain was recorded using VAS on arrival, at the moment of clinical diagnosis, and each one received one capsule plus a 100 mg indomethacin suppository and was hydrated using 10 cc per minute normal saline.

As the study of P.W. Armstrong demonstrates, after sublingual administration, TNG appeared in the blood promptly and its level peaked within 2 min after dissolution of the tablet. Its concentration fell rapidly to levels that were barely detectable at 20 min (14). Therefore, we planned to measure the pain score of patients at 5 and 30 min after treatment with TNG or placebo capsules.

Pain relief was defined as a declining VAS pain score to less than 5; hence, pain in patients was measured again after 5 min and if the pain was still more than 5 VAS, the patient received another 100 mg indomethacin suppository. The pain was estimated 30 min after arrival again, and if the patient had a VAS pain score above 5, he/she was admitted and received morphine sulfate. Response to treatment was defined as having a VAS of less than 5.

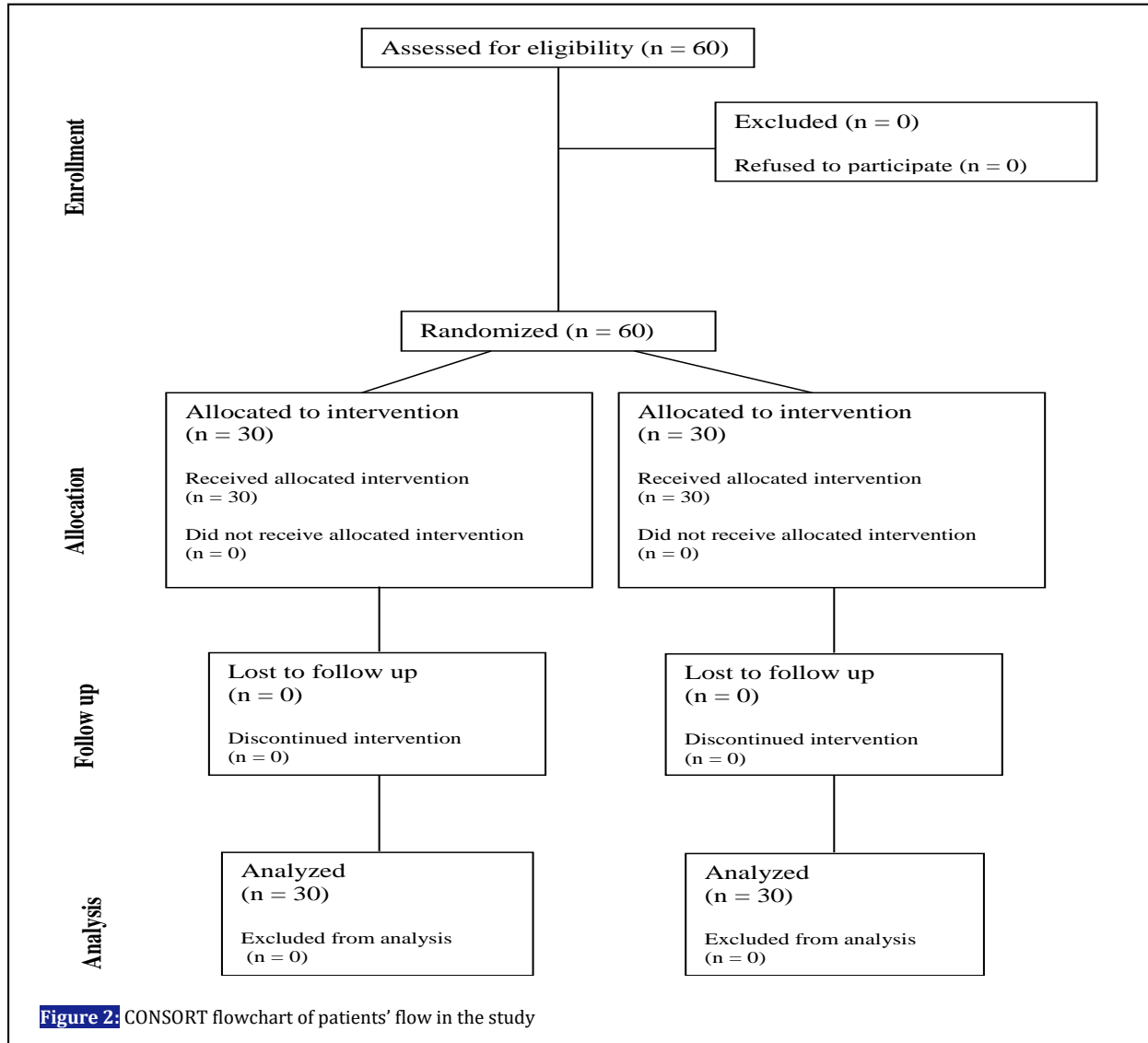
Statistical analysis

The collected data were analyzed by an analyst unaware of patient group assignment with SPSS-15 using paired T-tests, independent T-tests, and cross tab statistical tests. P-values less than 0.05 were considered to be significant.

RESULTS

Sixty patients with a mean age of 35.75 ± 11.99 years (range of 17 to 60 years) were enrolled in the trial of whom 44 cases (73.3%) were men. Thirty patients were assigned to the intervention group and the other 30 to the control group. The CONSORT flowchart of studied patients is shown in Figure 2. The baseline characteristics of studied patients are summarized in Table 1. Patients in the two groups were matched for age ($p = 0.290$), sex ($p = 0.559$), and presence of microscopic hematuria ($p = 0.292$).

Before any intervention, pain was scored and had a



mean of 8.7 ± 1.5 in the entire study population. Its mean was 8.7 ± 1.6 in the intervention group and 8.8 ± 1.4 in the control group ($p = 0.770$). Mean pain scores of the intervention and control group on arrival and at the follow-up times are illustrated in Table 2 and Figure 3. Pain scores 5 min after drug administration ($p = 0.613$) and 30 min after starting the intervention were not significantly different ($p = 0.384$). Pain score decreases from the arrival time until 5 min after drug administration ranged from 0 to 8.5, with a mean of 3.3 ± 2.7 in the intervention group (p -value < 0.05) and 2.9 ± 2.4 in the control group (p -value < 0.05). The mean changes of pain scores in the two groups during the first 5 min was not significantly different ($p = 0.669$). Pain score decreases from the arrival time until 30

min after starting the intervention ranged from 0 to 10 and had a mean of 4.4 ± 2.9 in the intervention group ($p < 0.05$) and 3.7 ± 2.8 in the control group ($p < 0.05$). The mean changes of pain scores in the two groups during the 30 min was not significantly different ($p = 0.368$). Pain score decreases from the 5 min after arrival till 30 min after arrival ranged from -7 to 8.5, had a mean of 1.1 ± 1.9 in the intervention group ($p < 0.05$) and 0.7 ± 2.9 in the control group ($p < 0.05$). The mean changes of pain score in the two groups during the elapsed 25 min was not significantly different ($p = 0.590$). Pain relief from the start point until the end of the intervention was statistical different in all studied patients ($p < 0.05$); but comparing the two groups shows no significant difference in this regard ($p =$

Table 1: Baseline characteristics of the studied patients

Variable	Intervention (n = 30)	Control (n = 30)	p
Age (years)	37.40 ± 11.99	34.10 ± 11.95	0.290
Female : male ratio	9:21	7:23	0.559
Microscopic hematuria	20	16	0.292

Table 2: Comparing mean pain scores between the intervention and control groups

Check point	Intervention (n = 30)	Control (n = 30)	p
	(mean ± SD)		
On arrival	8.7 ± 1.6	8.8 ± 1.4	0.770
5 th min after drug administration	5.4 ± 3.6	5.9 ± 2.9	0.613
30 th min after drug administration	4.3 ± 3.5	5.1 ± 3.4	0.384

0.440).

Twenty-three patients (38.3%) received 1 indomethacin suppository, 12 in the intervention group and 11 in the control group, while 37 patients (61.7%) received two, and 18 patients who received a TNG capsule needed two indomethacin suppositories compared with 19 of those who received a placebo (p = 0.791).

Figure 4 shows the timing of the response to treatment in both the intervention and control groups. The pain of 28 patients was relieved within 5 min after admission, 16 of whom were from the intervention group, while 3 patients of the intervention group and 6 of the control group responded within 30 min after admission (p = 0.446).

None of the enrollees experienced any complications from the drugs, either TNG or indomethacin.

DISCUSSION

Based on the findings, while the pain management in both groups was successful, there was no significant difference between the two groups. Therefore, adding TNG to an indomethacin suppository had no significant effects on better pain management of patients referred with renal colic to the ED.

Very few studies are available assessing the pain relieving effect of TNG on colicky renal pain. In a randomized clinical trial study conducted by Dubinsky et al. on only 12 patients, one group received a sublingual nitroglycerin spray and normal saline solution as an intravenous push; the other group received a sublingual placebo spray and morphine as an intravenous push. They reported that “TNG offered less pain relief at 5th min than did morphine, but pain relief was comparable at 20th min. Neither treatment had complete pain relief at 20 min; however, the reduction in pain was similar in the two treatment groups” (15). In contrast to the results of our study, patients who received TNG in this study did not have better pain relief. In our study, the pain of 16 and 12 patients from the intervention and control group was relieved 5 min after admission, respectively, while 3 patients in the intervention group and 6 in the control group responded 30 min after admission.

In another randomized clinical trial, the efficacy of 2.4 mg TNG in comparison to 20 mg of intravenous butyl-scopolamine-bromide in 80 patients suffering from acute urethral colic was assessed. TNG was effective in 40% of the cases, and butyl-scopolamine-bromide in 26.3% (16). This is comparable to our results in which 53.3% of patients who received TNG capsules reported pain relief within 5 min after treatment and an addition 10 responded after 30 min.

Razi A. and Zargushi J. in their study on 100 patients with renal colic scored patients' pains

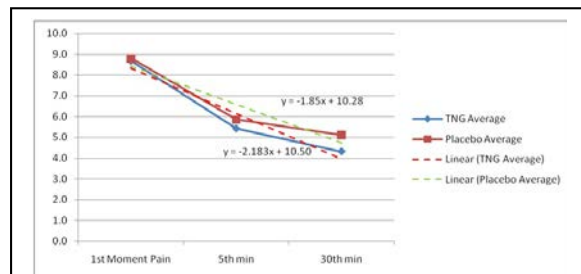


Figure 3: Comparing mean pain scores between the intervention and control groups

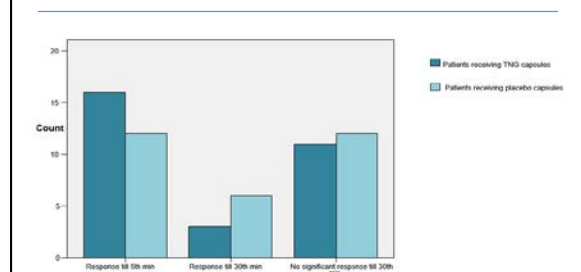


Figure 4: Timing of response to treatment in both the intervention and control groups

from 1 to 4, every 5 min for 15 min. Patients were then randomly allocated into two groups of intervention and control. A 0.4 mg TNG capsule was given to the patients in the intervention group at the moment of arrival and it could be repeated up to 3 times. The authors concluded that based on the 95% confidence interval no significant difference was seen between the two groups, but if the statistical accuracy was decreased to 92%, patients who received TNG significantly experienced one degree of additional pain relief compared with those who received nothing. In their study, pain was not measured by a standard VAS or NPS (numerical pain scaling system) and patients in the intervention group received different amounts of TNG (ranged from 0.4 to 1.2 mg), and this might have affected the study results (17).

Patients enrolled in the current study are those who were referred to Shariati Hospital. This hospital is a general, referral and well-known hospital placed in the middle of Tehran, Iran and patients with various socioeconomic backgrounds refer to it; so that the study can be generalized to a larger population. However, it is noteworthy that people living in Tehran as the capital of Iran have their own culture and life style; hence pain assessment may also be affected by these factors. The authors of this paper believe that the effect of TNG is not adequate and so cannot recommend its usage. However, the available data regarding the possible effect of TNG on patients suffering from renal colic is still non-conclusive and further studies with higher power and better methods are still needed.

Limitations

Although patients were asked about illicit drug usage before they entered the study, since it is

socially and legally unacceptable, there may have been some patients who had used them even though they denied it. This could have confounded the study results.

Pain as a qualitative symptom has its own limitations to be measured, although we used the VAS for this purpose, which is a standard method for pain measurement. Pain assessment might be affected by several factors, such as socioeconomic condition and life expectations. Therefore, the studied population might not be a representative sample of all Iranians.

CONCLUSIONS

It is likely that adding TNG to indomethacin suppository treatment had no significant effects for better pain management of patients referred with renal colic to the ED.

ACKNOWLEDGEMENTS

We would like to thank all of the ED staff whom participated in this study.

AUTHORS' CONTRIBUTION

All authors made an individual contribution to the writing of the article including: conception and design, acquisition of data or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version published.

CONFLICT OF INTEREST

None declared.

FUNDING

None declared.

REFERENCES

1. Romero V, Akpınar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol.* 2010;12(2-3):e86.
2. Bartoletti R, Cai T, Mondaini N, Melone F, Travaglini F, Carini M, et al. Epidemiology and risk factors in urolithiasis. *Urol Int.* 2007;79(Suppl. 1):3-7.
3. Masarani M, Dinneen M. Ureteric colic: new trends in diagnosis and treatment. *Postgrad Med J.* 2007;83(981):469-72.
4. York NE, Borofsky MS, Lingeman JE. Risks associated with drug treatments for kidney stones. *Expert Opin Drug Saf.* 2015;14(12):1865-77.
5. Miller NL, Lingeman JE. Management of kidney stones. *BMJ.* 2007;334(7591):468-72.
6. Arhami-Dolatabadi A, Mema E, Kariman H, Nasiri-Gigloo K, Baratloo A. Intranasal Desmopressin Compared with Intravenous Ketorolac for Pain Management of Patients with Renal Colic Referring to the Emergency Department: A Randomized Clinical Trial. *Anesth Pain Med.* 2017;7(2):e43595.
7. Sevinsky R, Stewart D, Harirforoosh S. Nonsteroidal anti-inflammatory drugs: Is there a link between cardiovascular and renal adverse effects? *J Integ Nephrol Androl.* 2017;4(1):1-2.

8. Berde C, Nurko S. Opioid Side Effects — Mechanism-Based Therapy. *N Engl J Med.* 2008;358(22):2400-2.
9. Connolly C, Tierney S, Grace P. Systemic glyceryl trinitrate reduces anal sphincter tone: is there a therapeutic indication? *Ir J Med Sci.* 2017:1-6.
10. Hill P-A, Panteleimonitis S, McKay G, Watson C, Prach A, Macdonald A. Sublingual glyceryl trinitrate during colonoscopy and terminal ileal intubation: a randomized controlled trial. *Scott Med J.* 2017;62(1):11-5.
11. Golzari S, Soleimanpour H, Rahmani F, Safari S, Heshmat Y. Therapeutic approaches for renal colic in the emergency department: a review article. *Anesth Pain Med.* 2014;4(1):e16222.
12. Kaffes AJ, Bourke MJ, Ding S, Alrubaie A, Kwan V, Williams SJ. A prospective, randomized, placebo-controlled trial of transdermal glyceryl trinitrate in ERCP: effects on technical success and post-ERCP pancreatitis. *Gastrointest Endosc.* 2006;64(3):351-7.
13. Talwar A, Dare C, Pain J. Does topical GTN on the sphincter of Oddi facilitate ERCP? A double-blind randomized control trial. *Surg Endosc.* 2005;19(7):902-4.
14. Armstrong P, Armstrong J, Marks G. Blood levels after sublingual nitroglycerin. *Circulation.* 1979;59(3):585-8.
15. Dubinsky I, Penciner R. Nitroglycerin and renal colic. *Ann Emerg Med.* 1997;29(6):824-5.
16. Hofstetter A, Kriegmair M. Treatment of ureteral colic with glycerol trinitrate. *Fortschr Med.* 1993;111(16):286-8.
17. Razi A, Zargoosh J. Effect of sublingual nitroglycerine on pain relief in renal and ureteral colic. *Med J IR Iran.* 1997;11(2):103-4.