Investigating the Analgesic Effect of Sublingual Glycerol Trinitrate (GTN) Spray as an Alternative Treatment in Renal Colic Pain: A Triple-Blinded Randomized Controlled Trial

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Abstract- Renal colic, a severe pain caused by renal and urethral calculi, causes millions of patients to visit the emergency department (ED) worldwide each year. Based on international guidelines, NSAIDs are the first-line analgesics of choice for renal colic management. The second most preferred analgesic is opioids. NSAIDs and opioids have several complications and contraindications that limit their administration and necessitate the search for alternative treatments for renal colic pain. The present study aimed to assess the effect of sublingual Glycerol Trinitrate (GTN) spray, a smooth muscle-relaxing agent, on renal colic pain as an alternative treatment. In this triple-blinded randomized controlled trial, 94 patients with renal colic who visited the emergency department (ED) were included. The drug group included 48 patients who were administered sublingual GTN spray, and the placebo group consisted of 46 patients. After diagnosis, the patients' pain was assessed based on the Numeric Rating Scale (NRS), a 30-milligram dose of ketorolac was administered to all patients, and sublingual GTN/placebo spray was administrated. The pain was also recorded 5 min after spray administration. Again, 30 min after spray administration, the NRS was reassessed. 94 patients enrolled in this study, the mean age of the participants was 39.22±11.72, and 82 (87.23%) of them were male. Five minutes after GTN/placebo administration, The NRS in both groups decreased significantly compared with the NRS upon arrival (P<0.01). Furthermore, in both groups, the NRS measured at 30 minutes also decreased significantly from the NRS measured at 5 minutes (P<0.01). Nevertheless, the reduction in the NRS score between the drug and placebo groups was not significantly different (P=0.365). Our results showed no significant pain reduction with sublingual GTN spray in comparison with placebo; thus, sublingual GTN spray might not have considerable analgesic effects in patients with renal colic referred to the ED.

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Introduction

Renal colic, a severe pain syndrome, presents an excruciating acute flank pain as a result of obstructed urinary tract caused by renal calculi. This pain can radiate toward the hypogastric region, groin, or genitals. It can be among the most severe types of pain to be experienced (1-5). Colicky spasms of the smooth muscles in the wall of the urinary tract are caused by locally released arachidonic acid metabolites and prostaglandins which result from the stretched renal pelvis (6). Millions of emergency department (ED) visits globally are attributed to this disorder, which is the leading cause of ED visits and a common reason for admission (4,7,8).

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Thus quick and efficient pain management techniques are required to alleviate excruciating pain (9). Several medications are available to relieve the discomfort caused by acute renal colic (9). Although medications such magnesium sulfate, alpha-blockers, calcium channel blockers, corticosteroids, paracetamol, vasopressin analogs, lidocaine, and ketamine have demonstrated varying degrees of pain relief in various studies, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the main analgesics used to manage renal colic (9-15).

International guidelines recommend that the first-line analgesics of choice in renal colic management are NSAIDs (10,16,17). NSAIDs, such as ketorolac, are inhibitors of cyclooxygenase (COX) isoenzymes that can suppress prostaglandin-mediated pain pathways, which leads to pain relief (2,3,18). There are limitations in the use of NSAIDs due to their renal and gastrointestinal complications and the specific restrictions on certain patient populations with diseases such as Chronic Obstructive Pulmonary Disease (COPD), coronary artery disease, and asthma (3,19-22).

Opioids, such as morphine sulfate (23), can be considered the second preferred analgesic in this patient population, especially in cases where NSAID use is not recommended or does not adequately relieve pain (3,17). These compounds remain a popular treatment option because they can be adjusted depending on the degree of pain and are highly effective (17,23,24). However, administration of these drugs should be limited due to complications such as respiratory depression and nausea/vomiting and the risk of abuse or misuse opiates (5,17,25,26). Alternative pain-relieving treatments could reduce opioid usage in patients presenting with renal colic.

For more than a century, glycerol trinitrate (GTN) has been used as a medication. GTN is considered a nitric oxide (NO) donor, but its actions result in nitrite production rather than the NO production seen in authentic NO donors (27,28). NO synthesis causes the activation of guanylate, resulting in an elevation in the cellular concentration of cyclic guanosine monophosphate (cGMP) (28-30). Consequently, myosin light chain phosphatases are activated by cGMP-dependent protein kinase, resulting in smooth muscle relaxation (28,31). Although GTN is also believed to cause guanylate cyclase to be activated, studies indicate a separation between GTN-induced vasodilation and NO production (28,32-34).

The positive impact of systemic nitrates in lowering the tone of vascular smooth muscles is commonly utilized in cardiovascular disease management (35-37). Additionally, studies have indicated a possible relaxing effect of GTN, topical or systemic, on other smooth muscles such as gastrointestinal smooth muscles (38), internal anal sphincter (39) sphincter of Oddi (40-44), non-vascular respiratory smooth muscles (45), and urethral smooth muscles (46).

Objectives

Thus, owing to these relaxing effects, GTN might have a pain-relieving effect on renal colic. There have been some studies on the pain-relieving effects of GTN, but the results of these studies have been non-conclusive (47-50). In our previous study, we assessed the effect of sublingual GTN on renal colic and found no significant effects (50). Therefore, this study aimed to further assess the effect of sublingual GTN spray on renal colic and opioid use reduction in emergency department.

Materials and Methods

Study design, setting, and participants

In this triple-blinded (patients, physicians, and data analysts) randomized controlled trial, 94 patients with renal colic who met all inclusion and exclusion criteria were included. of these, 48 were administered sublingual GTN spray as the drug group and 46 were given a placebo spray containing GTN's excipients as the placebo group (Figure 1).

The study was conducted in accordance with the Consort 2010 guidelines in the emergency department of the Shariati Hospital in Tehran, Iran, between January 2022 and February 2023.

All included participants were patients presenting with renal colic who, based on imaging modalities (abdominopelvic CT scan or Ultrasound of Kidney, ureters, and bladder), were diagnosed with kidney or ureter stones by an emergency medicine specialist, were above 16 years of age and their initial pain score upon hospital admission was higher than 5 out of 10 based on the Numeric rating scale (NRS). Also, the exclusion criteria were as follows: any prior history of taking medications that are contraindicated or have interactions with GTN including using sildenafil, vardenafil, tadalafil, phenothiazine, haloperidol, aspirin, Antimuscarinics, ergotamine, and alcohol during the last 24 hours; pregnancy and lactation; history of illicit drug abuse; history of allergic reaction to GTN; signs and symptoms of peritoneal irritation; fever; hypotension; and the history of self-treating the symptoms of their renal colic (50).

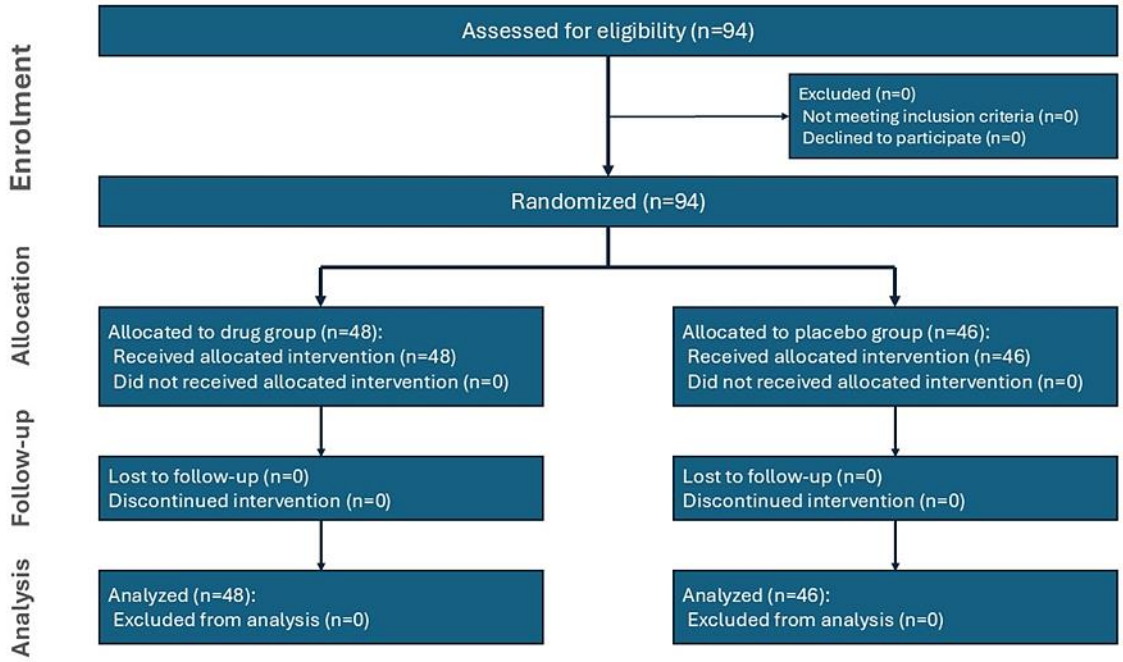

Figure 1. Consort chart for the study

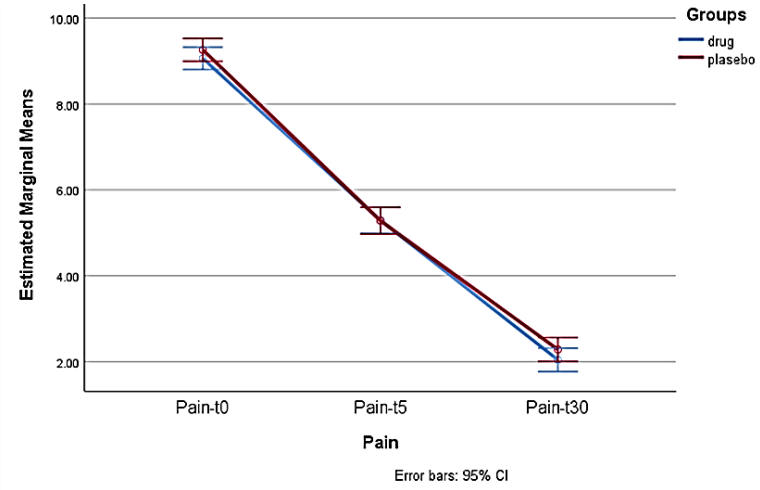

Figure 2. Comparison of pain scores (NRS) over time between drug and placebo groups with 95% confidence intervals

Randomization and blinding

Participants were divided into two groups using computer-generated block randomization. 48 GTN and 46 placebo sprays were randomly packed into identical packages and numbered. GTN sprays contained 0.4 mg Glycerol Trinitrate, while placebo sprays contained excipients accounting for similar appearances and Oduor to GTN. Patients, physicians, and data analysts were not informed of whether each patient received GTN or placebo.

The numeric rating scale (NRS)

In this study, we measured pain using a numeric rating scale for pain score (NRS). Scores are derived from self-reported symptom assessments, indicated by a score between 0 and 10 along a numerically marked line from 0 to 10, in which the left endpoint of the scale (0) represents “no pain” and the right endpoint (10)

represents "worst pain". The pain score was determined by measuring the interval between the left endpoint (starting point) and the mark placed by the patient in centimeters.

Interventions

Demographic data, including sex, age, history of previous episodes, and urinalysis results if available, were collected from All Participants. The pain score of each patient was documented using NRS upon arrival when the clinical diagnosis was made.

Following the NRS measurement, each patient received an intravenous dose of 30 mg of ketorolac and was hydrated with intravenous normal saline, followed by treatment with GTN or placebo sprays. Studies have shown that after sublingual administration, GTN quickly appears in the blood and reaches its highest level within 2 min of administration (43,51). Moreover, its concentration rapidly decreased to barely detectable levels after 20 min (52). Thus, the pain score was measured at 5 and 30 minutes following the treatment with GTN or placebo sprays. Furthermore, a decrease in NRS pain score of less than 5 was considered pain alleviation, if the measured pain score after 5 min of administration was equal or higher than 5 out of 10, then the patient received 3 mg of morphine sulfate per dose. The use of the narcotic agents has also been documented.

Statistical analysis

Statistical analyses of the collected data were performed using SPSS version 25 (Armonk, NY: IBM Corp); t-test, independent t-test and cross tab statistical tests were used and probability values (*P*) less than 0.05 were considered to be statistically significant.

Results

Of the 94 patients enrolled in this triple-blinded randomized controlled trial, 48 were allocated to the drug group and 46 to the placebo group. All Patients included in this trial had a mean age of 39.22±11.72 years, with the oldest patient being 69 years old and the youngest being 18 years old. In our study, 82 (87.23%) patients of the included participants were male, and 12 (12.77%) were female. Also, 91.49% of patients had no prior medical history, as shown in more detail in Table 1. Furthermore, non-contrast computed tomography was used in 88.29% of patients diagnosed the disease.

Table 1. patients' previous medical history

previous medical condition	Number (percentage)
No prior medical history	86 (91.49%)
Asthma	1 (1.06%)
Diabetes mellitus (DM)	2 (2.13%)
Systolic hypertension	3 (3.20%)
DM + Systolic hypertension	1 (1.06%)
Systolic hypertension + Diastolic hypertension	1 (1.06%)

In both placebo and drug groups, the mean±standard deviation (STD) of the NRS score, upon arrival and before any intervention, was 9.26±0.88 and 9.06±0.93, respectively, which was not significantly different between the two groups ($P>0.05$).

Five minutes after GTN/placebo administration, the mean±STD of the NRS score in the placebo group was 5.28±0.95, which was significantly reduced from the NRS score upon arrival ($P<0.01$). In the drug group, the mean±STD of NRS score 5 minutes after GTN/placebo administration was 5.29±1.14, which was significantly decreased than the NRS score upon arrival ($P<0.01$). The NRS scores in each group on these three different times and their comparisons are shown in Table 2 and Figure 2.

Table 2. Comparing mean NRS scores between the drug and placebo groups

All participants n=94 (100%)	The NRS score			*P*
	On arrival	5 minutes after GTN/placebo administration	30 minutes after GTN/placebo administration	
	Mean±STD			
drug group n=48(51.06%)	9.06 ± 0.93	5.29 ± 1.14	2.04 ± 1.01	*P*<0.01
placebo group n=46 (48.94%)	9.26 ± 0.88	5.28 ± 0.95	2.28 ± 0.88	*P*<0.01

thirty minutes after GTN/placebo administration, in the drug group, the mean±STD of the NRS score was 2.04±1.01, which is lower than the NRS score 5 minutes after GTN/placebo administration which was a significant reduction in the NRS score (P<0.01). As for the placebo group, after 30 minutes from GTN/placebo administration, the mean±STD of NRS score significantly reduced to 2.28±0.88 than the NRS score measured 5 minutes after GTN/placebo administration (P<0.01) (Table 2 and Figure 2).

However, the reduction of the NRS score between the placebo and the drug group was not significantly different (P=0.365) (Table 2). Since all patients of this study received morphine sulfate, comparison between the two groups was not performed. It should be noted that no complications were observed in this study.

Discussion

Many studies have suggested that NO, GTN, and other NO donors can have relaxing effects on smooth muscles (28,31,33,34,36,38,39,42,45,46). Interestingly, Iversen *et al*., observed that NO, sodium nitroprusside (SNP), and GTN suppressed smooth muscles activity in the in vitro human upper urinary tract (53). Thus, this study aimed to evaluate the pain-relieving effect of a sublingual GTN spray in patients with renal colic.

In the present study, 5 min after the administration of the spray, the NRS scores of both placebo and drug groups were significantly reduced compared to the NRS score upon arrival; Furthermore, both groups had further significant reduction at 30 minutes after drug/placebo administration than 5 minutes from administration of the spray, therefore suggesting that in our study, renal colic in both placebo and drug groups was significantly reduced after the administration of the spray. However, at 5 min and 30 min after the administration of the spray, there were no significant differences in the reduction of the NRS score between placebo and drug group, implying that in our study, sublingual GTN spray did not have a considerable pain-relieving effect in renal colic patients. Additionally, our results indicated that sublingual GTN spray administration did not reduce narcotic agent administration in patients with renal colic.

Few studies have evaluated the analgesic efficacy of TNG for colicky renal pain. In our previous randomized, triple-blind placebo-controlled trial on 60 patients with renal colic visiting the ED of Shariati Hospital, Tehran, Iran, on the analgesic effect of sublingual GTN capsules, using the NRS as the measuring tool for pain, we showed that treatment of 100 mg indomethacin suppository and hydration with 10 cc/minnormal saline with sublingual GTN or placebo capsules did reduce pain significantly in both groups from drug administration until the intervention was over (50). However, our previous results, consistent with results of current study, showed no significant differences in the reduction of pain between the GTN and placebo group and failed to support the hypothesis that GTN could reduce pain in patients with renal colic (50). In another prospective, randomized, double-blinded, and placebo-controlled clinical trial on 100 outpatients, Lee *et al*., studied the effect of GTN on renal and ureteral colic pain using a 4-grade pain assessment method. (54), Razi *et al*., showed that GTN administration, followed by two more doses as required at 5-minute intervals, was ineffective in alleviating renal colic pain (0.05<P<0.07) (47). This study is in line with the result of our study, as GTN showed no significant pain-relieving effects in this patient population in either study. However, their pain assessment methods differed from ours. Additionally, in a similar study on 50 patients with a single, less than 10 mm stone in their ureter, Hussain *et al*., administered a GTN/placebo patch every day for a six-week treatment period (49). They observed that Although GTN caused fewer pain episodes in the drug group than in the placebo group, the difference was not significant (49). They also observed that the number of patients who passed stones in the six-week period, the median duration of stone passage, and the patients who needed interventions in both groups were similar (49). Although they assessed the pain episodes in six weeks, the results of this study could be interpreted as similar to the results of the current study, as they showed that GTN did not cause any significant changes in pain and stone passage in participants in comparison with placebo.

However, some studies have reported different results in comparison to our studies, suggesting a pain-relieving effect for NO, GTN, and other NO donors in renal colic pain; In a randomized, open clinical trial on 80 patients with pain due to acute ureteral colic, assessing the pain-relieving effect of GTN (in three forms of capsule, atomizer spray and intravenous infusion) versus intravenous butylscopolamine bromide (BSB), using a three-grade scale for pain assessment (requirement for alternative treatment, moderate and good), Hofstetter *et al*., showed that GTN showed efficient pain reduction in 40% of patients (48). A moderate effect was observed in 46.7% of patients, while no reaction occurred in 13.3% (48). Although these results are not in comparison with a placebo, they show a relative effect for GTN, which is not

entirely contrary to our results, where GTN administration reduced pain; however, in our study, it did not significantly reduce pain in comparison to the sublingual placebo spray. Furthermore, in 1997, in a double-blinded randomized study of 12 patients with renal colic who were divided into two groups: Group A was administered intravenous normal saline solution and sublingual GTN spray and Group B was administered intravenous morphine and sublingual placebo spray, Dubinsky *et al*., using the visual analogue scale (VAS) and a two-grade scale (no different/worse or better), showed that GTN was less effective at 5 minutes of drug administration (55). However, after 20 minutes, the pain relief was similar in both groups (55). These results are inconsistent with our findings, which might be due to different pain assessment methods, sample sizes, demographics, and ethnic populations. In another study conducted in 2000, Kekeç *et al*., assessed the effectiveness of intravenous tenoxicam, an NSAID, in comparison with intravenous tenoxicam in combination with sublingual isosorbide dinitrate, which is an agent that can release NO in vascular smooth muscle, in renal colic pain using VAS score (56). They found that both interventions significantly reduced pain, although isosorbide dinitrate plus tenoxicam had a more significant pain-relieving effect than tenoxicam alone (56). Although their results were inconsistent with our result, the difference in the NO-releasing agent may, in part, explain the difference observed in the pain-relieving effect; this difference could also be clarified considering different study designs and different studied populations. Furthermore, In a single-blinded, prospective, randomized clinical trial, Kariman *et al*., using the VAS score, examined the analgesic properties between morphine sulfate and NO in patients suffering from acute renal colic in two groups consisting of 50 patients (57). They observed that although pain reduction was significant in both interventions, 30-minutes of Entonox (50% oxygen and 50% NO) exhalation with diclofenac suppository reduced VAS significantly at 3-, 5- and 10-minute intervals after intervention initiation versus diclofenac suppository plus morphine sulfate; however, the differences in VAS between the two groups at 30-minute intervals after intervention initiation were not significant (57). They concluded that NO has potent analgesic effects in comparison with morphine sulfate (57). As we did not find a significant pain-relieving effect of GTN in renal colic, the inconsistencies between their and our results could partly be due to different properties of GTN and NO, different study designs, and drug administration duration.

Although it is difficult to sort out inconsistencies in the results of these different studies, these differences may also, in part, be due to the different ethnic populations, study designs, sample sizes, and socioeconomic factors.

In the present study, as the excruciating pain was caused by renal colic, patients were treated with a combination of ketorolac, morphine and sublingual GTN/placebo spray, which is due to ethical reasons, fails to examine the exact sole effect of GTN with regard to renal colic; this problem needs to be addressed in future studies. Additionally, the population that was studied was only from patients referring to Shariati Hospital, Tehran, Iran, which, along with a limited sample size of 94 patients; further studies in different renal colic pain populations as multi-center studies and larger sample sizes are needed. Furthermore, the present study only assessed the acute effect of GTN on acute pain; this pain-relieving effect needs to be assessed in patients with more chronic symptoms. Lastly, the effectiveness of NO and other NO doners like GTN in renal colic pain needs to be assessed more in future studies.

In conclusion, the result of this study indicates that sublingual GTN spray, in comparison with sublingual placebo spray, might not be able to reduce the pain induced by renal colic. Thus, based on the results of our study, GTN may not have pain-relieving effects on renal colic. Furthermore, the results of the present study were not conclusive, and further studies on the probable pain-relieving effects of GTN are needed. However, it should be noted that based on our study, the administration of sublingual GTN spray might not be able to reduce opioid use in the emergency department.

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