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Analgesic Effects of Inhalation of Nitric Oxide (Entonox) and Parenteral Morphine Sulfate in Patients with Renal Colic; A Randomized Clinical Trial

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ABSTRACT

Objective: To compare the analgesiceffects of Nitrous oxide and morphine sulfate in patients with acute renal colic due to urolithiasis.
Methods: This was randomized clinical trial being performed in Imam Hossein hospital affiliated with Shahid Beheshti University of Medical Sciences during a 1-year period from May2013 to May2014. A total of number of 100 patients, with an age range of 20-50 years, who presented with renal colic secondary to urolithiasis confirmed by ultrasonography were randomly assigned to receive morphine sulfate injection (0.1 mg/kg) with 100 mg diclofenac suppository (n=50) or Entonox exhalation (50% nitric oxide and 50% oxygen)for 30-minutes with 100 mg diclofenac suppository (n=50). Quantitative measurement was of pain was performed according to a visual analogue scale (VAS), before, 3, 5, 10 and 30-minute after the intervention. The pain severity and side effects were measured between two study groups.
Results: The baseline characteristics of the patients in two study groups were comparable. The frequencies of pain persistence (at least 50%) at 3-, 5-, 10- and 30-minute intervals in morphine sulfategroup were 96%, 80%, 50% and 8%, respectively; these frequencies in Entonex were 82%, 42%, 12% and 2%, respectively (p<0.001). Cox regression modeling showed that use of Entonox was the only effective agent in the success of treatment, compared to the use of morphine, i.e. use of Entonox increased the success of treatment up to 2.1 folds compared to the use of morphine (HR=2.1; 95% CI: 1.2-3.6; p=0.006).
Conclusion: The results of the present study demonstrate that inhalation of Entonox is an effective and safe analgesic regimen for acute renal colic. It acts more rapidly and is more potent in relieving renal colic when compared to morphine sulfate.Entonox can be regarded as an appropriate alternative to analgesics like opioids in this ground.
Clinical Trial Registry: The current study is registered with Iranian Registry for Clinical Trials (www.irct.ir; IRCT2014120215620N4)

Keywords: Renal colic; Urolithiasis; Pain relief; Morphine; Entonox; Visual analogue scale (VAS).

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Introduction

Renal colic is one of the most common and painful medical emergencies. The incidence and prevalence of renal colic secondary to urolithiasis isincreasing all over the world, affecting almost 10% of the world population at present [1]. Prevalence rate in men is 3-4 times more than women [2]. The recurrence rate of nephrolithiasis after the first episode as high as 50% [3,4]. This condition bring an annual financial toll of $2.1 billion on the health systems some due to lostworking days and decreased productivity in the United States[5]. Renal colic, an intolerable pain, requires immediate intervention in order to relieve pain [6]. Non-steroidal anti-inflammatory drugs (NSAIDs) are first-line agents. Opioids are other effective analgesic, effectfaster than NSAIDs although with higher side effects [6,7]. The combination of NSAIDS and opiates is an acceptable approach for reducing the pain intensityand shortening the length of hospital stay in patients with acute renal colic due to urolithiasis [8]. NSAIDs are associated with several side effects and opioids may cause tolerance and dependence. Thus the optimum regimen for pain control in patients with renal colic is yet to be identified [9,10].

Entonox (mixture of 50% oxygen and 50% nitrous oxide) as an analgesic agent has been widely used for many years in different clinical contextssuch as colonoscopy, urologic procedures and labor pain [11]. Entonox is a relatively safe and effective drug with no serious side effects ifused intermittently [12]. Entonox mechanism is centrally which act rapidly and reaches an effective concentration and clears from the circulation by exhalation with minimum effect on the respiratory system [13,14]. The efficacy of Entonex in pain control has been tested and proved in several clinical conditions [11]. However data regarding its efficacy in acute renal colic is scarce. Thus, we performed the current clinical trial in order to determine the analgesic effects of Entonox when compared to parenteral morphine sulfate in patients with acute renal colicsecondary to urolithiasis.

Materials and Methods

Study Population

This was a prospective, single blind, randomized clinical trial being performed in emergency department of Imam Hossein hospital affiliated with Shahid Beheshti University of Medical Sciences during a 1-year period from May 2013 to May 2014. We included a total number of 100 adult patients (18-50 years of age) with acute renal colic secondary to urolithiasis presenting consecutively to emergency department of our center during the study period. All patients were hemodynamically stable (pulse rate=60-100 beat/min; systolic blood pressure ≥90 mmHg; SPO_2 ≥90%; respiratory rate=8-22 per min). We excluded pregnant women, those with a history of asthma, chronic pulmonary obstruction, intestinal obstruction, hypertension, cardiac failure, those who had undergone surgery on kidneys and the urinary tract, those with peptic ulcers and gastrointestinal hemorrhages and those with a history of allergy to aspirin, NSAIDs and morphine. A decrease in consciousness level, trauma to the head and the thoracic cavity, pneumocephalus, pneunothorax (or entrapment of air in any part of the body), drug abuse, tenderness and rebound tenderness, abdominal guarding, delayed menstruation and use of any analgesic within the previous 24-hourwere also excluded from the study. The study protocol was approved by medical Ethics Committee and institutional review board (IRB) of Shahid Beheshti University of Medical Sciences. All the patients provided their informed written consents before inclusion in the study. During the whole study period, the researchers were committed to observing all the ethical principles of Helsinki Declaration in a clinical trial study. The study protocol was registered by Iranian registry of clinical trial (IRCT2014120215620N4; www.irct.ir).

Study Protocol

The patients were diagnosed clinically by determining a detailed history and complete physical examination by single emergency medicine resident. The findings were recorded in a questionnaire which consisted of 3 sections. The first section consisted of demographic data and habits such as smoking. The second section included brief history of patient such as location of pain (flank, abdomen), prior history of renal stone, familial history of renal stone and physical examination and vital signs (blood pressure, pulse rate, respiratory rate, temperature, arterial oxygen saturation percentages). In the third section, stone, size, location and grading of hydronephrosis based on ultrasound or CT-scan and also laboratory findings such as hematuria were recorded. In this section, the severity of pain based on VAS scale at first visit, 3, 5, 10 and 30-minute after intervention was recorded. The validity of the questionnaire was confirmed by Cronbach's alpha coefficient of 0.88.

The urolithiasis and hydronephrosis was confirmed in all the patients with abdominopelvic ultrasonography or/and computerized tomography (CT) scan. The patients were randomly assigned to two study groups using a computer-based random digit generator. Those who were assigned to first group received intramuscularmorphine injection (0.1 mg/kg) along with 100 mg suppository of diclofenac. Those assigned to the second group received 30-minute of self-administered Entonox inhalation (containing 50% oxygen and 50% nitric oxide) via mask [15] along with100mg of suppository diclofenac.

Quantitative measurement of pain was performed according to visual analogue scale (VAS) [16], beforeand 3-, 5-, 10- and 30-minute after the

intervention. Pain scores were based on a standard 10-cm VAS. Treatment success was defined as achieving at least 50% of pain subsidence. The need for administration of rescue analgesics was evaluated for 2 hours. Any symptoms including nausea, vomiting, dizziness, unconsciousness and apnea, were evaluated and recorded in the data sheets. The length of hospitalization was also recorded.

Statistical Analysis

The sample size was estimated to be 49 patients in each group, considering the treatment success rate of 13% in the placebo and 43% in Entonox groups [15], by 90% power (β=0.1), 95% confidence interval (α=0.05), and 15% withdrawal rate.

All the statistical analyses were performed by statistical package for social sciences (SPSS Inc., Chicago, USA). The parametric data was compared with independent t-test. The pain scores were compared within groups by means of paired sample t-test. Non-parametric data was compared using chi-square test. Treatment success percentages were evaluated by Kaplan-Meier curves and log rank test was used to compare the curves. Cox regression model was used for data modeling and the consistency hypothesis of hazard ratios (HR) was confirmed by using the graphic method of the scatter diagram of Log (-log $_{(t)}$) on log $_{(t)}$ and observing the parallelism of the graphs. We report HR with 95% confidence interval (CI). A two sided p-value of less than 0.05 was considered statistically significant.

Results

Overall 117 patients were screened for the study out of whom 100 full filled the study criteria and were randomly assigned to two study groups each containing 50 patients. All the patients finished the study and thus the total number of patients included in the final analysis were 100 (Figure 1). Gender distribution of the patient were significantly different between two study groups (p=0.02). The demographic and baseline clinical characteristics of the patients are summarized in Table 1. The frequency of hematuria (p=0.62), hydronephrosis (p=0.070), stone size (p=0.17) and concomitant presence of multiple stones (p=0.488) were not differed between two groups. The location of pain was the flank region in 21 (43.8%) patients in morphine sulfate group and 27 (54.0%) patients in Entonox (p=0.23).

The pain scores after the intervention is also demonstrated in Table 1. We found that the pain intensity significantly decreased in both study groups. Pain persistence frequencies (at least 50%) at 3-, 5-, 10- and 30-minute intervals in the morphine groupwere 96% (95% CI: 95.9-96.1%), 80% (95% CI: 79.8-80.2), 50% (95% CI: 49.9-50.1) and 8% (95% CI: 7.95-8.06). While in the Entonox group these values were82% (95% CI: 81.96-82.04), 42% (95% CI: 41.7-42.3), 12% (95% CI: 11.9-12.1) and 2% (95% CI: 1.8-2.2), respectively (p<0.001, based on long rank test) (Figure 2). There were no significant adverse effects during 2-hour of observation after

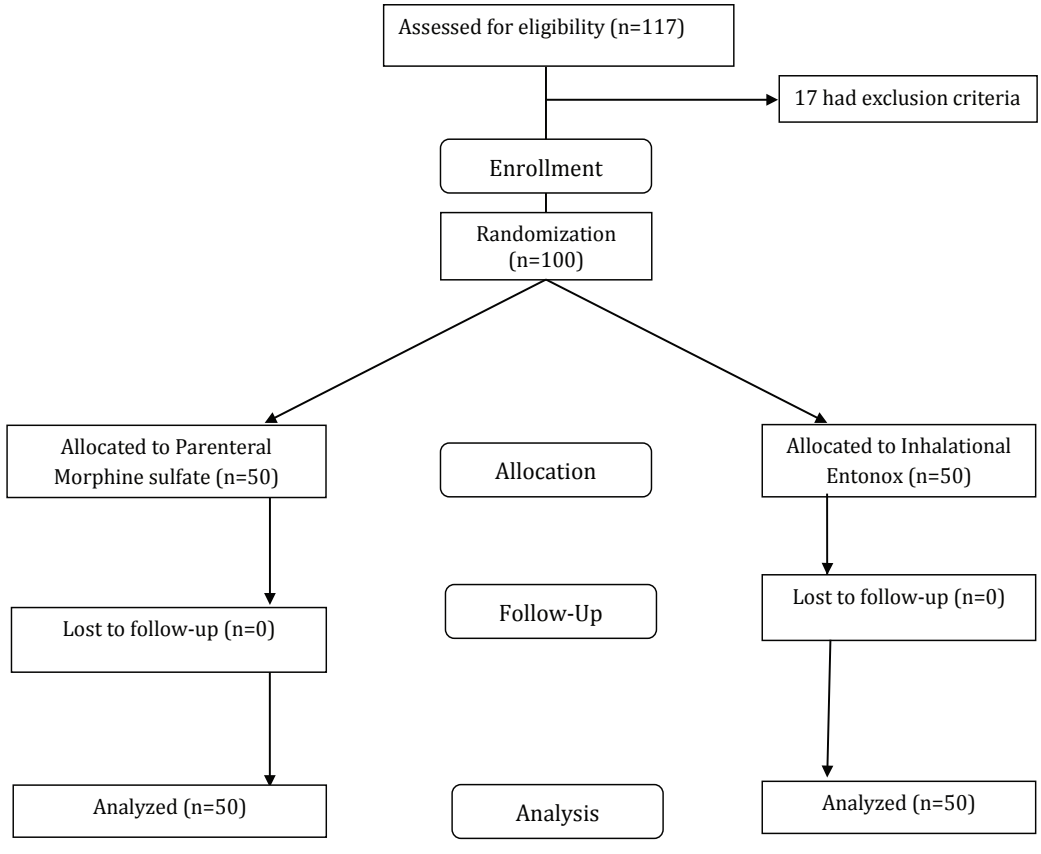

Fig. 1. CONSORT flow diagram of the study.

Table 1. The baseline characteristics and outcome of 100 patients with acute renal colic secondary to urolithiasis receiving morphine sulfate (n=50) or Entonox (n=50) as analgesia.

	Morphine (n=50)	Entonox (n=50)	*p* value
Age (years)	34.7±8.3	32.1±8.3	0.120
Gender			
Men (%)	39 (79.6%)	29 (58.0%)	0.021
Women (%)	10 (20.4%)	21 (42.0%)	
Smoking (%)	15 (30.6%)	21 (42.0%)	0.211
Multiple stone	14 (29.2%)	11 (22.0%)	0.488
Stone size (mm)	5.98±3.9	7.9±9.0	0.170
Hydronephrosis			
Mild (%)	34 (68.0%)	32 (61.5%)	0.070
Moderate (%)	13 (26.0%)	9 (17.3%)	
Severe (%)	3 (6.0%)	11 (21.2%)	
VAS[a] score			
On admission	9.6±0.8	9.6±0.7	0.94
3-minute after intervention	8.6±1.6	6.4±1.9	<0.001
5-minute after intervention	6.95±2.4	5.3±2.3	0.007
10-minute after intervention	5.0±2.5	3.6±1.8	0.002
30-minute after intervention	2.0±1.8	1.8±1.3	0.525

[a]VAS: Visual analogous scale

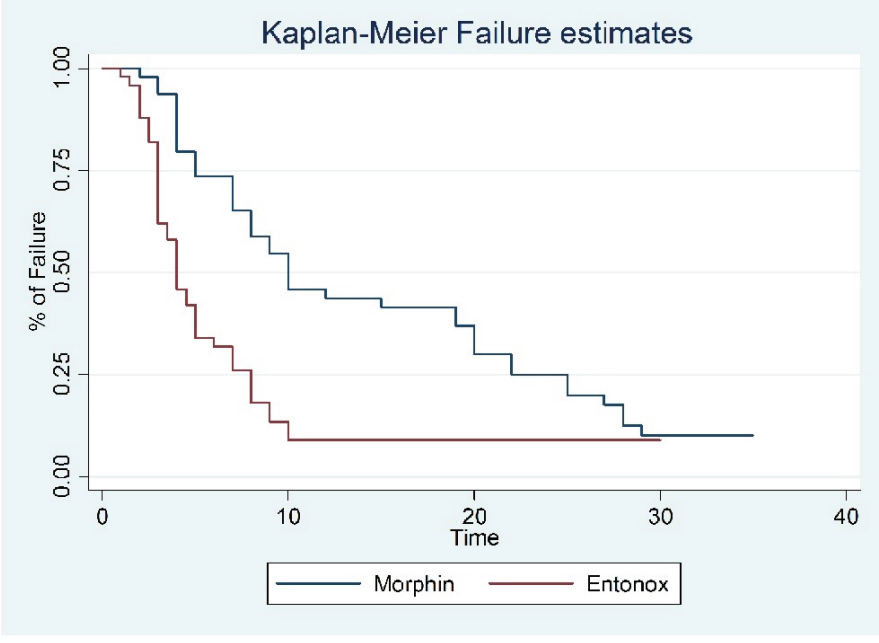

Fig. 2. A graph representing time intervals of pain relief in patients with renal colic. Treatment failure was defined as no decrease in pain severity to less than 50% or to 50%. Log rank analysis revealed significant differences between the two graphs (p<0.0001).

drug administration. Rescue dose was given in 6 patients (54.6%) in morphine sulfate group and 5 patients (45.4%) in Entonox group (p=0.72). In the final step, using Cox regression analysis we tried to determine whether any of the baseline characteristics could be responsible for the significant difference between the two groups. As seen in Table 2 and 3, the only factor found to be responsible for this difference was treatment type (HR=2.1; 95% CI: 1.2-3.6; p=0.006).

Discussion

Renal colic is one of the most common and painful medical emergencies affecting almost 10% of the world population [1]. With higher recurrence up to 50% after first episode [3,4]. The first priority in renal colic is providing pain control. Non-steroidal anti-inflammatory drugs (NSAIDs) are first-line agent. Opioids are also effective for pain killing faster than NSAIDs in spite of higher incidence of side effects. The combination of NSAIDS and opiates is an acceptable approach may reduce length of stay in the ED [8]. Entonox provides rapid and effective analgesia with less sedation [16]. Entonox may be associated with adverse effects in few patients such as nausea and vomiting, dizziness, dry mouth, buzzing in the ears ranging from 0 to 30 % [8].

Table 2. Hazard ratios of treatment failure according to the studied variables in 100 patients with acute renal colic secondary to urolithiasis receiving morphine (n=50) or Entonox (n=50) as analgesics based on univariate Cox regression.

Variable	Classification	Risk Ratio	Confidence Interval	*p*-value
Treatment type	Morphine	---	---	---
	Entonox	2.33	1.5-3.6	<0.0001
Age	20-29	---	---	---
	30-30	1.02	0.62-1.7	0.921
	40-50	1.01	0.59-1.7	0.950
Gender	Women	---	---	---
	Men	1.2	0.75-1.8	0.456
Smoking	No	---	---	---
	Yes	1.06	0.36-1.8	0.228
Location of pain		1.13	0.97-1.3	0.114
Size of stone	<4 mm	---	---	---
	4-9.9 mm	0.73	0.45-1.2	0.222
	≤10 mm	0.5	0.24-1.05	0.071
Hydronephrosis	Mild	---	---	---
	Moderate	0.6	0.34-1.02	0.071
	Severe	0.86	0.4-1.8	0.686
History of stone	No	---	---	---
	Yes	0.56	0.32-0.96	0.037
History of hospitalization	No	---	---	---
	Yes	0.61	0.34-1.09	0.098
Presence of multiple stones	No	---	---	---
	Yes	0.91	0.56-1.5	0.720
Family history of stone	No	---	---	---
	Yes	0.91	0.59-1.4	0.684

Table 3. Modeling of risk factors of treatment failure in 100 patients with acute renal colic secondary to urolithiasis receiving morphine (n=50) or Entonox (n=50) as analgesics using multivariate Cox regression analysis.

Variable	Classification	Hazard Ratio	Confidence Interval	*p*-value
Treatment type	Morphine	---	---	---
	Entonox	2.1	1.2-3.6	0.006
Location of pain	RLQ[a]	---	---	---
	LLQ[b]	1.8	0.89-3.6	0.100
	Flank	1.3	0.7-2.5	0.392
	LLQ/Flank	0.67	0.08-5.8	0.721
	Rt, Lt Flank	1.2	0.13-11.0	0.875
	LUQ/Flank	3.4	0.64-18.0	0.149
	LLQ/Flank	3.8	0.73-19.4	0.112
Size of stone	<4 mm	---	---	---
	4-9.9 mm	1.0	0.54-1.9	0.981
	≤10 mm	0.35	0.06-2.0	0.238
Hydronephrosis	Mild	---	---	---
	Moderate	0.94	0.47-1.9	0.864
	Severe	2.7	0.48-15.0	0.263
History of stone	No	---	---	---
	Yes	0.7	0.3-1.8	0.470
History of hospitalization	No	---	---	---
	Yes	0.7	0.45-1.3	0.627

[a]RLQ: Right lower quadrant; [b]LLQ: Left lower quadrant

Entonox like as other anesthetic agents results in nonspecific suppression of the central nervous system. Nitrous oxide (the effective agent in Entonox) contributed to opioid system of the brain particularly medial thalamic area and spinal cord that have a lot of cells sensitive to morphine [13,17]. Entonox efficacy was proved in relieving pain due to colonoscopy, urologic procedures including transrectal ultrasonography-guided prostate biopsy [18-24], extracorporeal shock wave lithotripsy (ESWL), and labor pain [16,25].Some derivatives of this gas relieve pain in fractures, joint dislocations, musculo-skeletal injuries, ulcers and wounds, ureteral colic, acute abdominal pains, myocardial

pain and migraine headaches [17]. Entonox can be effective as much as Fentanyl in pain relievingwith similar rate of side effects [12]. There is limited evidence about Entonox efficacyfor renal colic managementin compare to morphine. Mazdak *et al*. showed inhaled Entonox, decreases pain severity in patients undergoing treatment with ESWL , significantly[16].

Opiod replacing by a safe and effective drug was tried by Bektas *et al*. which showed intravenous injection of paracetamol (Apotel) is as effective as intravenous injection of morphine for relieving of renal colic [26]. Serinken *et al*. used parenteral paracetamol not only is an effective and safe intervention for renal colic [27]. There are comparisons between NSAID and opiods which show lower efficacy of NSAID in compared to morphine[28].

The present study, as the first randomized clinical trial on the subject, showed that Entonox is a more effective drug compared to morphine. Although the pain relief score means were similar in the two groups at 30-minute interval, the rate of pain relief by Entonox was more than that by morphine. Since there were no significant differences in re-administration of the drugs and hospitalization between the two groups it can be concluded that similar to other clinical situations, use of Entonox in renal colic is safer, in addition to higher efficacy compared to morphine.

The present study had some limitations. The patients in the emergency ward were administered drugs for only 30 minutes and if they had been followed for a longer period of time, it was possible that different results would have been achieved. However, what is important in renal colic is rapid pain relief. Therefore, the researchers in the present study believe that evaluation of patients for 30 minutes is sufficient. Finally, due to ethical considerations it was not possible to design a control group. Therefore, the morphine group was in fact considered as the control group and the efficacy of Entonox was compared with that of morphine.

In conclusion,the present study demonstrated that Entonox, in comparison with morphine, is an effective drug in relieving pain in patients with renal colic. It is a fast-acting drug and is very potent in relieving renal colic. Since Entonox has fewer side effects compared to morphine and leads to no drug dependence, it might be used in relieving pain in patients with renal colic. However, further studies are necessary to substantiate the results of the present study.

Conflict of interest: None declared.

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