Comparison of the Analgesic Effects of Inhalation of Entonox and Injection of Morphine Sulfate in Patients with Renal Colic

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Abstract: Analgesics used to relieve patients' pain have their specific efficacy and side effects. Therefore, it is important to administer drugs with the maximum efficacy and minimum side effects. The present clinical trial was undertaken to compare analgesia induced by Entonox (nitrous oxide gas) and that brought about by injection of morphine sulfate in patients with renal colic. A total of 100 patients, with an age range of 20–50 years, who had presented with renal colic, were randomly divided into two groups: one group received Entonox with diclofenac suppository and the other group received morphine sulfate injection with diclofenac suppository. Two-way ANOVA, post hoc Tukey test, Kaplan-Meier curves and Cox regression analysis were used for data analysis. Statistical significance was defined at $P<0.05$. The frequencies of pain persistence (at least 50%) at 3-, 5-, 10- and 30-minute intervals in the morphine group were 96%, 80%, 50% and 8%, respectively; these frequencies in the Entonox group were 82%, 42%, 12% and 2%, respectively ($P<0.0001$). 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 (P=0.006; 95% CI:1.2–3.6; HR=2.1). The results of the present study showed that, compared to morphine, Entonox is an effective drug in relieving pain in patients with renal colic. It acts more rapidly and is more potent in relieving renal colic.
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Introduction

Renal colic is one of the most common and painful medical emergencies. Its prevalence and incidence are on the rise all over the world, affecting almost 10% of the world population at present (1). Men are afflicted with this condition 3-4 times more than women (2). Based on estimates available, the recurrence of this condition after the first episode is up to 50% (3,4). This high rate of prevalence and recurrence of the condition inflicts an annual financial toll of $2.1 billion on the health and treatment systems, not considering the indirect costs of lost working days and decreased productivity in the work environment (5). Renal colic requires immediate intervention in order to relieve pain. In this context, use of drugs with maximum efficacy and minimum side effect is of utmost importance (6,7). Various medicines, including opioid analgesics (8), non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, aminophylline, tramadol and nitrous oxide gas (Entonox), have been used to this end so far. The efficacy of Entonox in relieving pain in various clinical situations, including pain due to colonoscopy, urologic procedures, labor pain and some other clinical situations, have been shown (15).

Entonox is used easily because it has very few contraindications, is inexpensive and has very few side effects; in addition, it rapidly reaches its effective concentration and is rapidly removed from the bloodstream (9). Entonox exerts minimum effect on the respiratory system and mainly exhibits its effects centrally (10). Therefore, it appears Entonox is a suitable alternative for a large number of analgesic drugs. Therefore, the present clinical trial was undertaken to evaluate and compare analgesia induced by inhalation of Entonox with that of morphine sulfate injection in patients with renal colic.

Materials and Methods

The present randomized single-blind clinical trial was carried out on one hundred 20–50 year-old patients with renal colic, referring to the Emergency

Wards of Imam Hussein Hospital and Shohadaye-Tajrish Hospital, which are third-level hospitals in Tehran, Iran. Affliction with renal colic was confirmed based on patient history and description, clinical examination and CT scan results. The inclusion criteria consisted of an age range of 20–50 years, a stable hemodynamic condition (pulse rate=60–120 beat/min; systolic blood pressure >90 mmHg; SPO_2 ≥90%; respiratory rate=8–22 per min) and patients' consent to take part in the study. Exclusion criteria consisted of pregnancy, a history of asthma, chronic pulmonary obstruction, intestinal obstruction, hypertension, cardiac failure, a history of surgery on kidneys and the urinary tract, peptic ulcers and gastrointestinal hemorrhage, a history of allergy to aspirin, NSAIDs and morphine, a decrease in consciousness level, trauma to the head and the thoracic cavity, pneumocephaly, 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 during the previous 24 hours and at entry into the emergency ward.

Before taking any samples, the protocol of the study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences and during the whole study period the researchers were committed to observing all the ethical principles of Helsinki Declaration. Sampling was carried out by simple random sampling technique and after renal colic was confirmed the patients were randomly divided into two groups; one group received nitrous oxide gas (Entonox) along with diclofenac suppository and one group received morphine sulfate injection along with diclofenac suppository. Finally, 50 patients were included in each group. Based on the treatment protocol of the present study, before administration of drugs, pain scores of the patients were determined based on a standard 10-cm visual analog scale (VAS) and recorded (11). Then the patients underwent treatment with morphine (0.1 mg/kg; single dose) along with diclofenac suppository (100 mg) or Entonox with a mask for 30 minutes along with diclofenac suppository (single dose), based on inclusion and exclusion criteria. Subsequently, the patients' pain severity was re-evaluated at 3-, 5-, 10- and 30-minute intervals. Finally, the need for re-administration of analgesics and hospitalization of the patients were evaluated. Furthermore, during the follow-up and during the presence of the patient in the emergency ward the side effects of Entonox, including nausea, vomiting etc, and morphine, including apnea etc, were evaluated and recorded in the data sheets. The first section of this sheet consisted of questions on demographic data and smoking. In the second section presence of macroscopic hematuria, vital signs and arterial oxygen saturation percentages were recorded. In the third section, the results of CT scan evaluations, including the renal stone, size, its location and severity of hydronephrosis and also laboratory findings such as hematuria were recorded. In this section, the perceived severity of pain based on VAS, was recorded at baseline and at 3-, 5-, 10- and 30-minute intervals. In the fourth section, the drug side effects and the need for re-administration of analgesic were recorded. The data sheet was designed under the supervision of an emergency medicine specialist, a urologist and an epidemiologist and Cronbach's alpha coefficient (0.88) was used to confirm its reliability and reproducibility.

Statistical analysis

Data were entered into SPSS 11.5 statistical software program and then into STATA 11.0 software program for data analysis. T-test was used to analyze quantitative data and chi-squared test was used to analyze qualitative variables. Treatment success percentages were evaluated by Kaplan-Meier curves and log rank test was used to compare the curves. To this end, treatment success was defined as achieving at least 50% of pain subsidence. Cox regression model was used for data modeling and the consistency hypothesis of risk ratios 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. Statistical significance was defined at $P<0.05$.

Results

Fifty patients were evaluated in each group. The means and standard deviations of patient ages in groups under treatment with morphine and Entonox were 34.7±8.3 and 32.1±8.3 years, respectively. Males comprised 79.6% and 58% of the patients in the morphine and Entonox groups, respectively (P=0.02). A history of renal culculi was observed in 28.6% (14) of the patients in the morphine group and in 17.8% (9) of the patients in the Entonox group (P=0.25). In addition, the means of pain scores at baseline were 9.6 (0.8) and 9.6 (0.7) in the morphine and Entonox groups, respectively (P=0.94). It should be pointed out that there were no significant differences between the two groups in smoking (P=0.12), hematuria (P=0.62), hydronephrosis (P=0.25), stone size (P=0.18) and concomitant presence of multiple stones (P=0.24). The location of pain was the flank region in 21 (43.8%) and 27 (54.0%) patients in the morphine and Entonox groups, respectively. After the flank region, the right lower quadrant (RLQ) in the morphine group (29.2%) and left lower quadrant (LLQ) in the Entonox group (30%) were the most common locations of pain (P=0.02). There was no significant difference between the two groups in CVAT location (P=0.23).

As Figure 1 shows use of Kaplan-Meier technique showed the following pain persistence frequencies (at least 50%) at 3-, 5-, 10- and 30-minute intervals in the morphine group, respectively: 96% (95.9–96.1%), 80% (79.8–80.2%), 50% (49.9–50.1%) and 8% (7.95–8.06%). The percentages in the Entonox group were 82% (81.96–82.04%), 42% (41.7–42.3%), 12% (11.9–12.1%) and 2% (1.8–2.2%), respectively (P<0.0001, based on long rank test). The results, therefore, showed that Entonox was more efficacious in relieving pain at all the intervals evaluated compared to morphine.

Subsequently, factors effective in the relief of the patients' pain were evaluated. Based on the univariate analyses presented in Table 1, use of Entonox increased the odds of pain relief compared to the use of morphine (HR=2.33; 95% CI: 1.5–3.6; P<0.0001). However, a history of renal stone delayed pain relief (HR=0.56; 95% CI: 0.32–0.96; P=0.037). After the hypothesis of the consistency of risk ratios was confirmed an attempt was made to model Cox regression. Therefore, all the variables in univariate analyses with P<0.2 were entered into the model. Based on the results of this analysis, use of Entonox, compared to the use of morphine, was the only agent effective in treatment success, i.e. Entonox increased the success rate up to 2.1 times, compared to the use of morphine (HR=2.1; 95% CI: 1.2–3.6; P=0.006).

It is noteworthy that no complications, such as respiratory problems or circulatory insufficiencies etc were noted. In the morphine group, 21 patients (52.5%) and in the Entonox group, 19 patients (47.5%) needed hospitalization (P=0.62). Meanwhile, 3 patients (1 patient receiving morphine and 2 patients receiving Entonox) needed TUL and 3 other patients (all in the Entonox group) needed percutaneous nephrostolithotomy (PCNL). Eleven patients needed re-administration of an analgesic, 6 of which (54.6%) were in the morphine group and 5 patients (45.4%) were in the morphine group (P=0.72).

Discussion

The results of the present study showed that Entonox is an effective drug in relieving pain in patients with renal colic. Compared to morphine, Entonox acts more rapidly and is more potent in relieving renal colic in patients. Although during the first 30 minutes after administration of both drugs there is a similar decrease in pain perceived by patients, Cox egression model showed that treatment success with Entonox was up to 2.1 times higher than that with morphine. In addition, since Entonox has fewer side effects compared to morphine and results in no drug dependence it might be used as an alternative medicine in relieving pain in patients with renal colic.

Entonox is a safe and effective drug which can be easily used in pre-hospital conditions and emergency units. It activates mechanisms to relieve pain, which guarantee its safety. Similar to other anesthetic gases, it results in unspecific suppression of the central nervous system. Nitrous oxide (the effective agent in Entonox) is related to the opioid system, i.e. it mainly affects those parts of the brain and spinal cord that have a lot of cells sensitive to morphine (12), as evidenced by the antagonistic effect of naloxone on N_2O. It is a partial agonist of μ, κ and possibility some other opioid receptors (13–15). Imaging studies have shown that the main activity of N_2O is in the medial thalamic area (10). The effect of Entonox in relieving pain due to colonoscopy (16–19), urologic procedures including transrectal ultrasonography-guided prostate biopsy (20,21), flexible cystoscopy (22) and extracorporeal shock wave lithotripsy (ESWL) (23,24), labor pain (25) and some other clinical procedures has been proved. In addition, different derivatives of this gas effectively relieve pain in fractures, joint dislocations, musculo-skeletal injuries, ulcers and wounds, ureteral colic, acute abdominal pains, myocardial pain and migraine headaches (12). All the conditions discussed above show moderate-to-high efficacy of Entonox in relieving pain. However, to the best of our knowledge, there is no study available on the effect of this gas on relieving renal colic and its comparison with morphine and other analgesics. Therefore, it is not possible to made comparisons in this respect. Only in one study Mazdak et al showed that Entonox, as an inhalational drug, significantly decreases pain severity in patients undergoing treatment with ESWL (24). In addition, Ozil et al reported some findings in relation to the efficacy of Entonox and morphine in relieving pain due to burns (26). However, a low efficacy has been reported for morphine and Entonox in relieving pain due to the removal of a chest tube (27).

Morphine has long been used as an effective analgesic to relieve pain in various clinical situations, including renal colic. However, due to its various side effects, researchers are trying to find safe drugs with efficacy similar to that of morphine. For example, a double-blind clinical trial by Bektas et al showed that intravenous injection of paracetamol (Apotel) is effective in relieving renal colic, similar to intravenous injection of morphine (28). Serinken et al, too, showed that intravenous administration of paracetamol not only is an effective intervention in relieving renal colic in the emergency ward but also it has fewer side effects (29). O'Conner et al compared the efficacy of petidine and morphine in relieving renal colic and reported similar efficacy for these two drugs. They also reported that morphine is a better drug for pain relief in such patients due to the established side

effects of petidine (30). A study by Engeler et al showed that use of diclofenac and rofecoxib to relieve pain due to the renal colic has low efficacy compared to morphine (31).

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. However, similar to other drugs, Entonox has some contraindications. Its use is contraindicated in cases of increased pressure such as intracranial air, intestinal obstruction, diseases of the middle ear, decompression sickness or air embolus, a decrease in consciousness level, early stages of pregnancy, vitamin B_{12} or folate deficiency, compromised immune system and overt cardiac insufficiency (12). All the factors above were considered in the present study. Therefore, it is suggested that during the use of this drug attention be paid to such conditions. In addition, it should be pointed out that pregnant personnel should have no contact with this gas.

The present study had some limitations. One of the limitations was exclusion of patients who needed re-administration of drugs during the first 30 minutes of the study. In addition, the patients in the emergency ward were followed 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.

Conclusion

The present clinical trial showed 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.

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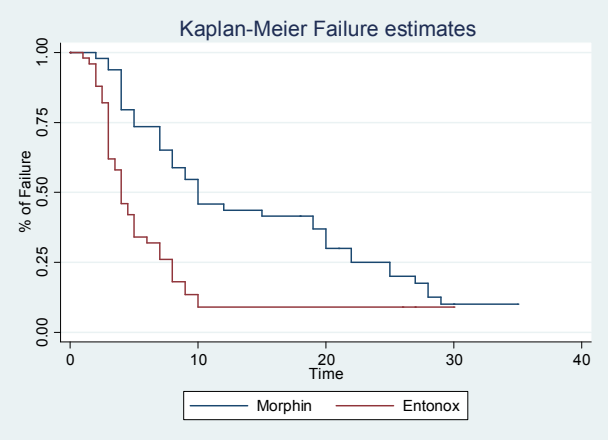

Figure 1. A graph representing time intervals of pain relief in patients with renal colic. Treatment failure was defined as no decrease in pain severity to less than 50% or to 50%. Log rank analysis revealed significant differences between the two graphs (P<0.0001).

Table 1. Risk ratios of treatment failure in terms of variables under study

Variable	Classification	Risk Ratio	Confidence Interval	P
Treatment intervention	morphine/diclofenac	---	---	---
	Entonox/diclofenac	2.33	1.5-3.6	<0.0001
Age	20-29	---	---	---
	30-30	1.02	0.62-1.7	0.92
	40-50	1.01	0.59-1.7	0.95
Gender	female	---	---	---
	Male	1.2	0.75-1.8	0.46
Smoking	no	---	---	---
	Yes	1.06	0.36-1.8	0.23
Location of stone		1.07	0.95-1.2	0.24
Location of pain		1.13	0.97-1.3	0.11
Size of stone	<4 mm	---	---	---
	4-9.9 mm	0.73	0.45-1.2	0.22
	≤10 mm	0.5	0.24-1.05	0.07

Variable	Classification	Risk Ratio	Confidence Interval	P
Hydronephrosis	mild	---	---	---
	moderate	0.6	0.34-1.02	0.07
	Severe	0.86	0.4-1.8	0.69
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	0.72
Family history of stone	no	---	---	---
	yes	0.91	0.59-1.4	0.68

Table 2. Modeling of factors involved in failure of treatment with analgesics with the use of Cox regression analysis

Variable	Classification	Risk Ratio	Confidence Interval	P
Treatment intervention	morphine/diclofenac	---	---	---
	Entonox/diclofenac	2.1	1.2-3.6	0.006
Location of pain	RLQ	---	---	---
	LLQ	1.8	0.89-3.6	0.1
	Flank	1.3	0.7-2.5	0.39
	LLQ/Flank	0.67	0.08-5.8	0.72
	R & L Flank	1.2	0.13-11.0	0.87
	LUQ/Flank	3.4	0.64-18.0	0.15
	LLQ/Flank	3.8	0.73-19.4	0.11
Size of stone	<4 mm	---	---	---
	4-9.9 mm	1.0	0.54-1.9	0.98
	≤10 mm	0.35	0.06-2.0	0.24
Hydronephrosis	mild	---	---	---
	moderate	0.94	0.47-1.9	0.86
	Severe	2.7	0.48-15.0	0.26
History of stone	no	---	---	---
	Yes	0.7	0.3-1.8	0.47
History of hospitalization	no	---	---	---
	yes	0.7	0.45-1.3	0.63

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