Original Article

Efficacy of inhalation of a nitrous oxide and oxygen mixture for pain management during rigid cystoscopy: a randomized controlled trial

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Keywords:
Entonox, nitrous oxide, cystoscopy, pain

Abstract

Objective: To evaluate the efficacy of pain management using inhalation of a nitrous oxide and oxygen mixture during rigid cystoscopy.

Materials and Methods: A total of 55 patients were prospectively selected and randomized to receive oxygen (27) or Entonox (28). Both groups were given the respective gas for 3 minutes via breath-activated facemask before cystoscopy and continued to breathe the gas until the end of the procedure. The oxygen and Entonox groups received 20 ml 2% lidocaine gel intraurethral 15 minutes before the procedure. Heart rate, and numeric pain rating scales were recorded before, during, and after the cystoscopy.

Results: Fifty-five patients were randomized into two groups, 27 were given oxygen and 28 Entonox. There were no statistically significant differences between the groups in terms of baseline patient characteristics. Intraoperative rigid cystoscopy pain scores were significantly lower in the Entonox group than in the oxygen group (2.4 vs 4.2, p = 0.009). There were no significant differences between the two groups as regards postoperative pain, intraoperative and post-operative heart rates, and side effects.

Conclusion: Entonox significantly reduces intraoperative cystoscopy-related pain, without significant complications.

Insight Urol 2023;44(2):62-7. doi: 10.52786/isu.a.73

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Manuscript received: March 20, 2023 **Revision received:** October 13, 2023

Accepted after revision: October 25, 2023

Introduction

Cystoscopy is the most commonly used urologic procedure for both diagnostic and therapeutic purposes such as bladder cancer detection or surveillance, bladder biopsy or ureteral catheterization. Even though many procedures can be performed with a flexible cystoscope to reduce intraoperative pain and discomfort, several procedures still require rigid cystoscopy, which is more painful than flexible cystoscopy.

Studies have demonstrated that insertion of intraurethral lidocaine gel before cystoscopy can reduce pain, but the efficacy of pain management is still subject to debate.[1,2] Current best practice is intraurethral instillation of 20 ml of 2% lidocaine gel 15 minutes before cystoscopy.[3] The most painful part of any urethral procedure occurs when the instrument passes through the external urethral sphincter, which is controlled by the pudendal nerve.[4]

Nitrous oxide, or laughing gas, is a colorless and odorless gas that has analgesic, sedative, anxiolytic, euphoric, and amnesiac effects. It is extremely soluble in blood and eliminated quickly via the lungs. The analgesic effect starts within 20 seconds of inhalation and reaches the maximum effect within 3-5 minutes. These features make nitrous oxide an attractive analgesic option for day-case procedures, including urological interventions.[5]

Entonox® (Linde (Thailand) Public company limited) is a commercial gas product that is composed of 50% nitrous oxide and 50% oxygen. It is a safe and rapidly effective agent used for anesthesia, analgesia and anxiolysis. Entonox is used for pain management in urologic situations in the emergency department such as renal colic pain[6], and also for flexible cystoscopy[7], transrectal ultrasound-guided biopsy for prostate cancer[8,9], or extracorporeal shock wave lithotripsy.[10] Rigid cystoscopy causes more pain than flexible cystoscopy, but it is widely used, and to date no previous studies into the efficacy of Entonox in rigid cystoscopy procedures have been published.

Therefore, we conducted a randomized controlled trail (RCT) to compare the levels of efficacy between Entonox® and a placebo (oxygen) inhalation for pain management during rigid cystoscopy. A secondary outcome was change of heart rate because heart rate normally increases with pain severity.

Materials and Methods

This RCT was conducted from November 2021 to November 2022. The study was approved by the Ethics committee of Thammasat university (Protocol Number: MTU-EC-SU-1-044/64) and the Thai Clinical Trail Registry (TCTR) Committee on November 6, 2021. The TCTR identification number is TCTR20211106001.

Participants

Inclusion criteria were all patients at least 18 years old who needed to undergo rigid cystoscopy with 22 Fr diameter sheath instruments, and who were willing to give their informed consent to participate in the study.

Exclusion criteria were patients who had history of lidocaine or nitrous oxide and oxygen mixture inhalation allergy, neurological disease impairing pain perception, could not communicate in the Thai language, had a history of pneumothorax, had facial injury or maxillofacial bone fracture, or who had a contraindication for use of Entonox.

Randomization

Randomization was performed using permuted blocks of 4 to 6 with assignment by an independent statistician using STATA version 12.0. Gas tank and valve mask appearance were similar for both Entonox and oxygen. Only the nurse in-charge knew which gas tanks were oxygen or Entonox. The in-charge nurse was the same person throughout the study and was the person who prepared the gas tanks for procedures however, never participated in procedures or recorded information. After patients were informed and had given their consent to join this research, they were randomly allocated gas assignment labels in sealed opaque envelopes, which were opened by the in-charge nurse before cystoscopy as shown in Figure 1.

Blinding

Patients and attending physicians, including the endoscopist, scrub nurse, and practical nurse, were blinded to the type of gas.

Pain scores and subjective outcomes, including adverse events, were assessed by the scrub nurse using a numeric rating scale. Heart rates were monitored by practical nurses who were also blinded to the type of gas.

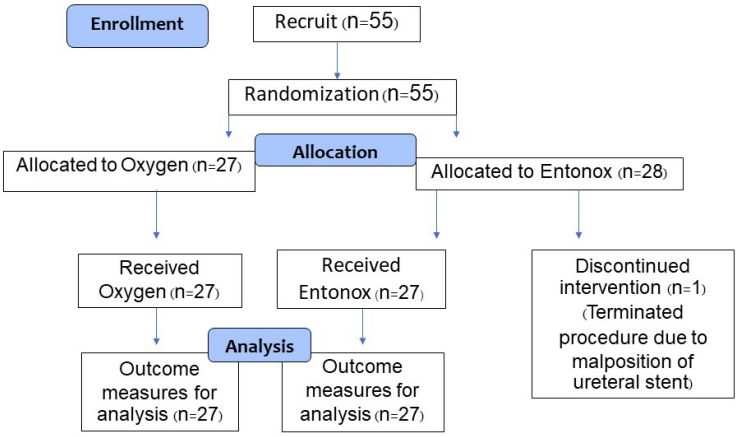

Figure 1. Flow diagram of the RCT.

Interventions

All patients, in both the Entonox® group and the placebo group, received 20 ml 2% lidocaine gel (AstraZeneca®) intraurethrally 15 minutes before cystoscopy. Then, via a breath activated demand valve mask, patients in the Entonox group inhaled Entonox and patients in the placebo group inhaled oxygen, from 3 minutes before cystoscopy until the procedure was completed.

Heart rate and pain score were evaluated before starting the procedure, 15 minutes after starting the procedure, every 15 minutes during the procedure, and immediately after completion of the cystoscopy. Pain perception was recorded using a numeric rating scale.

Statistical analysis was performed using STATA version 12.0. Significance was assumed at a p-value of less than 0.05.

Sample size

Based on a pilot study of 10 cases at Thammasat University Hospital, we compared pain scores between patients who used Entonox and patients who used oxygen during rigid cystoscopy. We found that patients who used oxygen had a numeric pain rating scale of 4.5±2.5 SD but patients who used Entonox had a numeric pain rating scale of 2.5±2.5 SD.

Our sample size was estimated and tested using a two-sided test based on type 1 error 5% and power 80%, suggesting a total of 52 patients (26 per group) were needed. Taking into account a potential loss of data and incomplete procedure of 5%, 54 patients were set as the target (27 per group).

Results

A total of 55 patients were recruited in this study. Twenty-eight patients out of the 55 were randomized to the Entonox group and 27 patients to the oxygen group. One patient from the Entonox group was later withdrawn from the study. (The endoscopist changed that patient's operation to ureterorenoscopy (URS) because a double J stent was malpositioned.) Therefore, 27 patients in each group were analyzed in this study. There were no statistically significantly differences between the groups in terms of sex, age, previous cystoscopy, indication for cystoscopy, additional procedures and timing of the operation as shown in Table 1.

Pain scores during intraoperative cystoscopy in the Entonox group were statistically significantly lower than in the oxygen group (2.4 vs 4.2, p = 0.009) but there were no significant differences in the pre-operative period (0.3 vs 0.4, p = 0.765) or the immediate post-operative period (0.6 vs 1.1, p = 0.177) (Table 2).

There were also no significant differences in heart rate including preoperative cystoscopy (80.9 vs 78.1, p = 0.451), intraoperative cystoscopy (80.9 vs 76.3, p = 0.195) and post-operative cystoscopy (80.9 vs 78.1, p = 0.451) as shown in Table 3.

The main side effects noted by patients were nausea (1 patient (3.7%)), dizziness (4 patients (14.8%)) and euphoria (1 patient (3.7%)). All of these were transient without serious adverse events and were resolved before discharge. There were no significant differences in side effects between the Entonox group and the oxygen group (p = 0.5) (Table 4).

Table 1. Demographic data of the two groups (N=55)

Patient characteristic	Group placebo (n=27)	Group intervention (n=27)
Sex, n (%)		
Male	13 (48.15)	17 (62.96)
Female	14 (51.85)	10 (37.04)
Age (year), mean (SD)	58.7 (11.8)	59.5 (13.1)
Previous cystoscopy, n (%)	12 (44.44)	16 (59.26)
Indication for cystoscopy, n (%)		
Hematuria	4 (14.81)	6 (22.22)
Bladder cancer	3 (11.11)	8 (29.63)
LUTS	3 (11.11)	2 (7.41)
Ureteric calculi	10 (37.04)	3 (11.11)
Vesical calculi	7 (25.93)	6 (22.22)
UTI	0	2 (7.41)
Additional procedures, n (%)		
Biopsy	1 (3.70)	1 (3.70)
Ureteric catheter insertion	13 (48.15)	9 (33.33)
Timing of operation, mean (SD)	23.1 (11.1)	20.7 (9.9)

SD = standard deviation, n = number, LUTS = lower urinary tract symptoms, UTI = urinary tract infection.

Table 2. Comparing of pain scores using the pain rating scale at pre-cystoscopy, during cystoscopy and post-cystoscopy in both groups.

Pain score	Group placebo (n=27)	Group intervention (n=27)	P-value
0 min, (SD)	0.4 (1.6)	0.3 (1.1)	0.765
15 mins, (SD)	4.2 (2.7)	2.4 (2.2)	0.009
Post-op 0 min, (SD)	1.1 (1.7)	0.6 (1.0)	0.177

SD = standard deviation, n = number, min = minute, mins = minutes.

Table 3. Demonstrated comparing the changing of the heart rate at pre-cystoscopy, during cystoscopy and post-cystoscopy of both groups.

Heart rate	Group placebo (n=27)	Group intervention (n=27)	P-value
Baseline bpm, (SD)	78.1 (13.0)	80.9 (13.2)	0.451
HR at 15 min bpm, (SD)	76.3 (12.9)	80.9 (12.7)	0.195
Post op HR bpm, (SD)	78.1 (13.0)	80.9 (13.2)	0.451

SD = standard deviation, n = number, bpm = beats per minute, HR = heart rate, min = minute.

Table 4. Comparison of adverse events between the groups.

Adverse event, n (%)	Group placebo (n=27)	Group intervention (n=27)	P-value
Nausea	0	1 (3.7)	0.5
Dizziness	3 (11.11)	4 (14.81)	0.5
Euphoria	0	1 (3.70)	0.5

Discussion

Nitrous oxide is an interesting inhalation agent because of its analgesic, anxiolytic and amnesic properties. It can be used as a pain medication. Both the anxiolysis and analgesic effect are probably responsible for the lower pain levels seen in the Entonox group in this study. Nitrous oxide effects are dependent on the concentration

inhaled, and at 50% concentration, N_2O will cause mainly analgesia and anxiolysis, A 50% concentration inhaled for 3 minutes can cause complete or partial relief of pain in 75% to 80% of patients, without affecting the cardiovascular system.[7] The effect dissipates within 4 minutes as the gas is excreted from the lungs.[11]

Entonox is used to control pain in a wide range of medical situations, especially during labor. Many randomized controlled trials (RCT) have found Entonox more satisfactory than pethidine or oxygen. It can reduce the use of pethidine during labor pain without significant increase in maternal and neonatal complications.[12-15] Another study found that colonoscopy patients using Entonox felt no more discomfort than those sedated intravenously. Entonox was not associated with a reduction in colonoscopy quality, and patients who received Entonox recovered more rapidly than patients who received intravenous sedation.[16,17]

Interest in the use of Entonox for diverse urological procedures has been increasing recently. In one study, Entonox plus fentanyl was found to decrease pain severity in renal colic patients to a greater extent than oxygen plus fentanyl, and it became effective significantly faster (1.23 vs 1.71 min, $p < 0.0001$).[6] Another RCT demonstrated that Entonox was more rapid and more potent in reducing pain in renal colic patients than morphine sulfate.[18] Several studies have investigated using Entonox to reduce pain during transrectal ultrasound-guided prostate biopsy. Patients who receive Entonox during the operation had significantly less intraoperative pain than patients who received placebo, with only mild side effects such as drowsiness.[8,9,19]

A study comparing Entonox, pethidine and air in extracorporeal shockwave lithotripsy (ESWL) found no significant difference between Entonox and pethidine in reducing pain; therefore, Entonox is another potential analgesic option for ESWL.[10] Another study compared the efficacy of pain management in male patients less than 55 years old who underwent flexible cystoscopy. Patients in the Entonox inhalation group had significantly lower pain score and pulse rate than the patients in the air group, with only minor side effects, , including light-headedness, and tingling sensation. None of patients had serious complications.[7]

This study is the first RCT to compare the efficacy of Entonox and oxygen inhalation for pain control management during rigid cystoscopy. Our primary results show that pain during intraoperative cystoscopy was significantly lower in the Entonox group, with no significant differences observed in postoperative pain, heart rate, and side effects. Our results confirmed the findings of previous studies, which demonstrated similarly lower pain in Entonox group than in oxygen groups during various urological procedures.

The mechanism of action of nitrous oxide which produces analgesic and antinociceptive effect has been clearly identified. It induces opioid peptide release in the periaqueductal gray, which activates descending inhibitory pathways, resulting in modulation of nociceptive processes in the spinal cord.[20]

A limitation of our study is that in this instance no record of the number of bladder tissue biopsies or the number of attempts at ureteric catheterization. Nor did it record any long-term side effects of Entonox. Nitrous oxide can cause cardiac depression. Therefore, it should be used with caution in patients who have cardiac failure.[7] Contraindications of Entonox are the presence of head injury or elevated intracranial pressure, drug intoxication, hemodynamic instability, pneumothorax, bowel obstruction, or any other condition with a pathological, air filled body cavity.[5]

One particular concern is exposure of staff to Entonox as they work with patients frequently and for extended periods. The effect is dependent on the dose and exposure time. Excessive dose or duration of exposure to Entonox could result in reduction in fertility, development of cancer, or hematopoietic changes.[7] Information from this study can improve the quality of healthcare. It is useful for physicians and urologists who perform rigid cystoscopy under local anesthesia as an office-based procedure or in day cases. It can reduce the discomfort of patients undergoing a range of procedures or surgical interventions without intravenous sedation, which may cause adverse events and increase cost of treatment.

In summary, Entonox has both anxiolytic and analgesic effects, which significantly reduce pain in many urological procedures, including rigid cystoscopy, without significant complications. Entonox is a potential option for pain management for rigid cystoscopy.

Acknowledgments

We would like to thank Dr. Teerayut Tangpaitoon for assistance with the statistical analysis.

Conflict of Interest

The authors declare no conflict of interest. The funding for this study was provided by the Faculty of Medicine, Thammasat University. The funding source had no role in the design, practice or analysis of this study

References

1. McFarlane N, Denstedt J, Ganapathy S, Razvi H. Randomized trial of 10 mL and 20 mL of 2% intraurethral lidocaine gel and placebo in men undergoing flexible cystoscopy. J Endourol 2001;15:541-4.
2. Herr HW, Schneider M. Outpatient flexible cystoscopy in men: a randomized study of patient tolerance. J Urol 2001;165:1971-2.
3. Choong S, Whitfield HN, Meganathan V, Nathan MS, Razack A, Gleeson M. A prospective, randomized, double-blind study comparing lignocaine gel and plain lubricating gel in relieving pain during flexible cystoscopy. Br J Urol 1997;80:69-71.
4. George NJR, Dixon JS. Normal Sensation of the Lower Urinary Tract. In: George NJR, Gosling JA, editors. Sensory Disorders of the Bladder and Urethra. London: Springer London; 1986. p. 7-16.
5. Young A, Ismail M, Papatsoris AG, Barua JM, Calleary JG, Masood J. Entonox® inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence. Ann R Coll Surg Engl 2012;94:8-11.
6. Ahmadi O, Dehkordi AS, Heydari F, Esfahani MN, Mahaki B. The effect of nitrous oxide in comparison to oxygen combined with fentanyl on the hospitalization time and pain reduction in renal colic patients at emergency department. J Res Med Sci 2018;23:18.
7. Calleary JG, Masood J, Van-Mallaerts R, Barua JM. Nitrous oxide inhalation to improve patient acceptance and reduce procedure related pain of flexible cystoscopy for men younger than 55 years. J Urol 2007;178:184-8; discussion 8.
8. Manikandan R, Srirangam SJ, Brown SC, O'Reilly PH, Collins GN. Nitrous oxide vs periprostatic nerve block with 1% lidocaine during transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, controlled trial. J Urol 2003;170:1881-3; discussion 3.
9. Masood J, Shah N, Lane T, Andrews H, Simpson P, Barua JM. Nitrous oxide (Entonox) inhalation and tolerance of transrectal ultrasound guided prostate biopsy: a double-blind randomized controlled study. J Urol 2002;168:116-20; discussion 20.
10. Mazdak H, Abazari P, Ghassami F, Najafipour S. The analgesic effect of inhalational Entonox for extracorporeal shock wave lithotripsy. Urol Res 2007;35:331-4.
11. Carbajal R. [Analgesia using a (50/50) mixture of nitrous oxide/oxygen in children]. Arch Pediatr 1999;6:578-85.
12. Chantrasiri R, Wanapirak C, Tongsong T. Entonox(®) versus pethidine in labor pain relief: a randomized controlled trial. Int J Environ Res Public Health 2021;18:12571.
13. Parsa P, Saeedzadeh N, Roshanaei G, Shobeiri F, Hakemzadeh F. The effect of entonox on labour pain relief among nulliparous women: a randomized controlled trial. J Clin Diagn Res 2017;11: Qc08-11.
14. Attar AS, Feizabadi AS, Jarahi L, Feizabadi LS, Sheybani S. Effect of entonox on reducing the need for pethidine and the relevant fetal and maternal complications for painless labor. Electron Physician 2016;8:3325-32.
15. Sheyklo SG, Hajebrahimi S, Moosavi A, Pournaghi-Azar F, Azami-Aghdash S, Ghojazadeh M. Effect of entonox for pain management in labor: A systematic review and meta-analysis of randomized controlled trials. Electron Physician 2017;9:6002-9.
16. Robertson AR, Kennedy NA, Robertson JA, Church NI, Noble CL. Colonoscopy quality with Entonox(®) vs intravenous conscious sedation: 18608 colonoscopy retrospective study. World J Gastrointest Endosc 2017;9:471-9.
17. Forbes GM, Collins BJ. Nitrous oxide for colonoscopy: a randomized controlled study. Gastrointest Endosc 2000;51:271-7.
18. Kariman H, Majidi A, Taheri S, Shahrami A, Hatamabadi HR. Analgesic effects of inhalation of nitric oxide (Entonox) and parenteral morphine sulfate in patients with renal colic; a randomized clinical trial. Bull Emerg Trauma 2015;3:46-52.
19. McIntyre IG, Dixon A, Pantelides ML. Entonox analgesia for prostatic biopsy. Prostate Cancer Prostatic Dis 2003;6:235-8.
20. Fujinaga M, Maze M. Neurobiology of nitrous oxide-induced antinociceptive effects. Mol Neurobiol 2002;25:167-89.