

Pilot study to assess the feasibility of self-administered, low-dose methoxyflurane for cystoscopic procedures

Jennifer A. Locke¹, Sarah Neu², Joanne Lawrence², Sender Herschorn²

¹Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; ²Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Cite as: Locke JA, Neu S, Lawrence J, et al. Pilot study to assess the feasibility of self-administered, low-dose methoxyflurane for cystoscopic procedures. *Can Urol Assoc J* 2024;18(8):251-4. <http://dx.doi.org/10.5489/cuaj.8676>

Published online April 2, 2024

ABSTRACT

INTRODUCTION: Methoxyflurane (MEOF) (Penthrox™) is an inhaled, self-administered, non-opioid analgesic approved by Health Canada for the short-term relief of moderate to severe acute pain associated with trauma or interventional medical procedures. In this pilot study, we evaluated the feasibility of using MEOF as an anesthetic agent in 11 patients undergoing outpatient cystoscopic procedures.

METHODS: The average duration of the procedure was 24 (range 20–35) minutes and this included 10 minutes of administration time of the drug and five minutes of wait time before the procedure. The average monitoring time from start to end of the procedure was 23 (range 20–35) minutes and this included 15 minutes of monitoring post-procedure. On a scale of 0–10, patients on average rated the pain 4/10 (standard deviation [SD] 2.6).

RESULTS: Global performance was on average 3/4 (SD 1.3) for the patients and 3/4 (SD 1.1) for the operator. Of the 11 patients, four reported adverse events; two experienced euphoria, one experienced dizziness, and one was unable to tolerate the medication. Two patients noted their adverse events to be of moderate intensity, while the other two were of mild intensity. None of the adverse events was deemed serious.

CONCLUSIONS: Our findings in this pilot study provide proof of principle for the design of a randomized control trial to evaluate MEOF as an anesthetic in an outpatient cystoscopic procedural setting. As more urologic procedures are being performed in an outpatient setting, this may offer significant clinical benefit.

INTRODUCTION

Methoxyflurane (MEOF) (Penthrox™) is an inhaled, self-administered non-opioid analgesic approved by Health Canada for the short-term relief of moderate to severe acute pain associated with trauma or interventional medical procedures.^{1,2} Many patients with chronic urological conditions require multiple and sometimes painful procedures.³ These procedures would ideally be done in the cystoscopy suite without general anesthetic.

Currently, intravesical lidocaine is used for bladder procedures, but this anesthetic requires catheterization by a nurse, a dwelling time of approximately 20 minutes, and post-procedural monitoring.⁴ Furthermore, intravesical lidocaine has been associated with adverse events from systemic absorption.^{5,6} Compared to other anesthetic agents such as intravesical lidocaine, MEOF has the additional benefits of being self-administered, having a short onset of action (less than five minutes), allowing for avoidance of intravenous access, and maintaining consciousness so that airway manipulation is seldom required.¹

To date, there are two other studies reporting the use of MEOF in urology in transrectal prostate biopsies and water vapor thermal therapy for benign prostatic enlargement.^{7,8}

Given these properties of MEOF and its potential usefulness in an ambulatory procedural setting, we performed a pilot study to assess the feasibility of using MEOF for cystoscopic procedures. We utilized a patient and study physician

questionnaire to assess the efficacy and adverse events associated with the medication.

METHODS

This study was approved by the Sunnybrook Health Sciences Ethics committee (431-2019). Patients undergoing outpatient cystoscopic procedures at the site were approached by a research coordinator to determine eligibility for the study. Inclusion criteria were conscious adult patients ≥ 18 years of age, who were scheduled for cystoscopy and onabotulinumtoxinA injections for overactive bladder or neurogenic detrusor overactivity, diagnostic hydrodistension for painful bladder syndrome, biopsy or cauterization of bladder tumors, biopsy, cauterization and/or injection of Hunner's lesions, visual urethrotomy/bladder neck incision with or without injection of stricture, or evaluation of complex urinary tract problems. They were required to understand the nature of the study and provide written informed consent, follow study requirements and procedures, and complete the required questionnaire. Exclusion criteria included inability to communicate in English. Patients deemed potential candidates for the study were asked to participate, and the alternatives, risks and benefits were discussed. Those interested provided informed consent.

Patients consented to the study were taught how to self-administer MEOF by the study nurse. During the procedure each patient self-administered the MEOF, was monitored by the study nurse for signs of distress, and completed a questionnaire afterwards. After the procedure, the study physician also completed the questionnaire. In summary, the questionnaires were administered as follows: assessment 1 at end of urologic procedure; assessment 2 after monitoring time of 23 minutes (range 20–35 minutes) just prior to discharge; and assessment 3 24 hours later.

Patient demographics including age, gender, medical history, medications, allergies, and procedure type were recorded. Efficacy outcomes including procedure duration, monitoring time post procedure, and questionnaire responses (pain during procedure, global performance, fulfillment as per patient and whether the patient would use it again) were recorded. Adverse events were captured including severity, type, duration, intensity, whether anticipated or not, outcome, and if the study needed to be discontinued.

The goal of the questionnaires was to assess patients' overall pain, subjective relief of pain, willingness to use MEOF again, and whether study physicians' expectations regarding pain control were met. The questionnaires

consisted of the Numeric Rating Scale (NRS), the Global Medication Performance Scale, and the Fulfillment of Expectations Scale. The Numeric Rating Scale (NRS) was used to assess patient pain intensity (0–10, where 0 is no pain and 10 is the worst pain ever experienced). The Global Medication Performance Scale was used to rate patient pain relief given by MEOF in the last 24 hours (0–4, where 0 is poor and 4 is excellent) and patient willingness to use MEOF for future painful incidences (0–2, where 0 is no, 1 is yes, and 2 is not sure). The Operator Global Medication Performance Scale was used to rate pain relief given by the MEOF inhaler as per the operator (0–4, where 0 is poor and 4 is excellent). Lastly, the Fulfillment of Expectations Scale was used to measure the extent that the patient and healthcare professional's expectations regarding pain control were met with MEOF administration (0–4, where 0 is poor and 4 is excellent).

All data were summarized descriptively with averages, interquartile ranges, and standard deviations.

RESULTS

Demographics

Demographic variables for the 11 patients included in this study are summarized in Table 1. Median age was 63 (IQR 51–84). Twenty-seven percent were male and 73% were female. Table 1 also summarizes the patients' medical history, medications and allergies.

Procedural type included cystoscopy with injection ($n=5$ onabotulinumtoxinA, $n=2$ triamcinolone), cystoscopy with difficult catheterization ($n=2$), cystoscopy with ileal conduit stoma revision ($n=1$), and cystoscopy with visual internal urethrotomy ($n=1$).

Efficacy

Average duration of the procedure was 24 minutes (range 20–35 minutes) and this included 10 minutes of administration time of the drug and 5 minutes of wait time before the procedure (Table 2). Average monitoring time from start to end of the procedure was 23 minutes (range 20–35 minutes) and this included 15 minutes of monitoring post procedure. Nine of 11 patients finished quickly while two remained and required more time for monitoring (30 and 40 minutes for an adverse event and unknown reason).

On a scale of 0–10, patients on average rated the pain 4/10 (SD 2.6). Global performance was on average 3/4 (SD 1.3) for the patients and 3/4 (SD 1.1) for the operator. The patients rated fulfillment of pain expectations an average of 3/4 (SD 1.0). No patients required

rescue medication and 9/11 (82%) said they would use MEOF again. The two patients who declined using MEOF again included one undergoing cystoscopy with triamcinolone injections into Hunner's lesions and one undergoing cystoscopy with a difficult catheter change. Both had a history of chronic pain related to their underlying urologic condition.

Adverse events

Of the 11 patients, four reported adverse events. Two experienced euphoria, one experienced dizziness, and one was unable to tolerate the medication. Two patients noted their adverse events to be of moderate intensity while the other two were of mild intensity. None of the adverse events was deemed serious. All patients recovered from the adverse events and required no further intervention.

DISCUSSION

In this pilot study we evaluated the feasibility of using MEOF as an anesthetic agent in 11 patients undergoing outpatient cystoscopic procedures. In this population of 11 moderately co-morbid patients, all of them noted efficacy of MEOF and nine out of eleven patients would have used it again. Of the two who would not have used it again, the indications for MEOF were for Hunner's lesions in interstitial cystitis and difficult catheter change associated with chronic pain. The patient undergoing triamcinolone injections for Hunner's lesions noted that the MEOF had minimal efficacy. The patient undergoing a difficult catheter change did not like the taste of the MEOF and had difficulty following the administration instructions. In this case the physician performing the difficult catheterization had conducted these procedures on the patient in the past and noted that the patient appeared to have less discomfort with MEOF administration.

On average, the procedure time was short at 24 minutes with an average overall monitoring time of 23 minutes. No procedural time was longer than 20 minutes. For current bladder procedures intravesical lidocaine is utilized that requires nurse catheterization and a dwelling time of 20 minutes with post-procedural monitoring; thus, MEOF has a theoretically shorter overall time than intravesical lidocaine.

Furthermore, in our study, four patients experienced mild adverse events, mainly dizziness and euphoria, but these were self-limited. In the literature there is concern regarding dose-dependent nephrotoxicity presenting as diuresis.⁹ Urologic conditions may require multiple procedures over time, but this does not occur daily.

Table 1. Demographic variables

Patient ID	Age	Gender	Past medical history	Medications	Allergies
1	45	F	Hypothyroidism, endometriosis, hysterectomy, restless leg syndrome, bipolar disorder	Sertraline, oxycodone, acetaminophen, codeine phosphate, ferrous gluconate, fesoterodin	NKDA
2	45	F	Spinal cord tumor removal, neurogenic bladder, lumpectomy	Cephalexin	NKDA
3	74	F	Osteopenia, Graves' disease, radical cystectomy and ileal conduit, tubal ligation, cervical stenosis, breast cancer, depression, sciatica, leukopenia	Levothyroxine, atorvastatin, fluoxetine	NKDA
4	84	F	Elbow surgery	Metoprolol, folic acid, digoxin, rivaroxaban, rosuvastatin, nitrofurantoin	Norfloracin
5	67	M	Migraines, prostate cancer, radiation cystitis, transurethral resection of the prostate	Mirabegron	Sulfa
6	53	F	Uterovaginal agenesis reconstruction, urethrovaginal fistula repair, incontinence	Estrogel, mirabegron	NKDA
7	48	F	TVT-O, mesh erosion, pubovaginal sling, lung disease, reflux, interstitial cystitis	Phenazopyridine, famotidine, ibuprofen	NKDA
8	67	F	Multiple sclerosis, neurogenic bladder, tubal ligation	Fampridine, rosuvastatin, naproxen, sulfasalazine	NKDA
9	60	F	Lupus, myocarditis, vulvectomy, flap, colostomy, ARP, Mitrofanoff stenosis	Prednisone, epoetin, phenytoin, furosemide, phenobarbital, hydrochloroquine, bisoprolol mycophenolic acid, sacubitril/valsartan	NKDA
10	63	M	Diabetes, renal impairment, obstructive sleep apnea, Greenlight prostatic procedure, patella repair, post-traumatic stress disorder	Amlodipine, fesoterodine, oxycodone, acetaminophen, trazodone	NKDA
11	64	M	Coronary artery disease with stent, urinary retention, urethral stricture, reflux, ankle surgery	Esomeprazole, atorvastatin, ASA, desvenlafaxine	NKDA

ARP: acute recurrent pancreatitis; ASA: acetylsalicylic acid; F: female; M: male; NKDA: no known drug allergies; TVT-O: tension-free vaginal transobturator tape (TVT-O).

Therefore, the risk of dose-dependent nephrotoxicity is quite low given the infrequent need for MEOF.

There are limitations to this study. Firstly, it is a single-center single-arm study of only 11 patients who had a variation of different urologic procedures. Secondly, we did not compare intravesical lidocaine to MEOF in a randomized controlled trial setting. Thirdly, we did not evaluate the use of MEOF over several

Outcome	Measure
Procedure time	24 minutes (range 20–35)
Overall monitoring time	23 minutes (range 20–35)
Pain rating (0–10) (mean)	4 (SD 2.6)
Global performance (0–4) (mean)	
Patient	3 (SD 1.3)
Operator	3 (SD 1.1)
Fulfilment of pain expectation (0–4) (mean)	3 (SD 1.0)
Rescue medication required	
Yes	0
No	11 (100%)
Would use MEOF again, n (%)	
Yes	9 (82%)
No	2 (18%)

MEOF: methoxyflurane; SD: standard deviation.

procedures in the same patients. Fourthly, we did not evaluate for the possibility of malignant hyperthermia that can occur with general anesthetic agents including methoxyflurane. These concerns may be addressed in future studies.

In a report on the use of MEOF for transrectal ultrasound-guided prostate biopsy, Huang et al compared MEOF alone in 42 patients vs. MEOF plus periprostatic infiltration of 2% lidocaine in 30 patients. They found that patients in the MEOF plus lidocaine group reported significantly lower median pain intensity than those in the MEOF alone group, although all patients indicated that they would be happy to have another prostate biopsy in the future.⁷ In a report on the use of MEOF for water vapor thermal therapy for benign prostatic enlargement, Elterman et al evaluated the safety and efficacy in 10 patients. They found that MEOF was low-cost, rapid, feasible, and easy to administer as a pain management strategy for this procedure.⁸

The goal of this first pilot study was to assess the feasibility of MEOF for cystoscopic local anaesthesia procedures. We demonstrate appropriate perceived efficacy with minimal adverse events.

CONCLUSIONS

Our findings in this pilot study provide proof of principle for the design of a randomized control trial to evaluate MEOF as an anesthetic in an outpatient cystoscopic procedural setting. As more urological procedures are being performed in an outpatient setting, this may offer significant clinical benefit.

COMPETING INTERESTS: Dr. Herschorn was a principal investigator on a Pentrox study supported by Purdue. The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer reviewed.

REFERENCES

- Ikeda S. The reincarnation of methoxyflurane. *J Anesth Hist* 2020;6:79-83. <https://doi.org/10.1016/j.janh.2019.07.001>
- Health Canada Pentrox Approval. 2018.
- Pode D, Zylber-Katz E, Shapiro A. Intravesical lidocaine: Topical anesthesia for bladder mucosal biopsies. *J Urol* 1992;148:795-6. [https://doi.org/10.1016/S0022-5347\(17\)36722-8](https://doi.org/10.1016/S0022-5347(17)36722-8)
- Masic D, Liang E, Long C, et al. Intravenous lidocaine for acute pain: A systematic review. *Pharmacotherapy* 2018;38:1250-9. <https://doi.org/10.1002/phar.2189>
- Birch BR, Miller RA. Absorption characteristics of lignocaine following intravesical instillation. *Scand J Urol Nephrol* 1994;28:359-64. <https://doi.org/10.3109/00365599409180513>
- Clapp CR, Pass WB, Gilento BG. Lidocaine toxicity secondary to postoperative bladder instillation in a pediatric patient. *Urology* 1999;53:1228. [https://doi.org/10.1016/S0090-4295\(98\)00485-3](https://doi.org/10.1016/S0090-4295(98)00485-3)
- Huang S, Pepdjonovic L, Konstantatos A, et al. Pentrox alone vs. Pentrox plus periprostatic infiltration of local analgesia for analgesia in transrectal ultrasound-guided prostate biopsy. *ANZ J Surg* 2016;86:139-42. <https://doi.org/10.1111/ans.12974>
- Elterman D, Zorn KC, Bhojani N, et al. Efficacy and safety of methoxyflurane (Pentrox) for pain control during water vapor thermal therapy (Rezüm) for benign prostatic enlargement. *Can J Urol* 2022;29:11355-60.
- Crandell WB, Pappas SG, Macdonald A. Nephrotoxicity associated with methoxyflurane anesthesia. *Anesthesiology* 1966;27:591-607. <https://doi.org/10.1097/0000542-196609000-00010>

CORRESPONDENCE: Dr. Jennifer A. Locke, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; jennlocke@gmail.com