ORIGINAL RESEARCH

Randomized controlled trial comparing the effects of methoxyflurane and local anesthesia combination to local anesthesia alone in scrotal surgery

Jainik Shah[1], David Chung[2], Maximilian Fidel[1], Avinash Sarcar[3], Harliv Dhillon[3], Connor Roque[1], Yool Ko[1], Kayla Reynolds[1], Kulvir Badh[3], Robert Bard[3], Jasmir G. Nayak[2,3], Premal Patel[2,3]

[1]Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada; [2]Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; [3]Men's Health Clinic Manitoba, Winnipeg, MB, Canada

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ABSTRACT

INTRODUCTION: Outpatient scrotal surgery under local anesthesia (LA) has been associated with excellent safety, tolerability, and efficacy; however, needle phobia and periprocedural anxiety remain areas for improvement. This study evaluated the efficacy of methoxyflurane as an adjunct to LA in alleviating pain and anxiety during local anesthesia-based scrotal urologic surgeries.

METHODS: A non-blinded, randomized controlled trial was conducted at Men's Health Clinic Manitoba for patients undergoing scrotal surgery under LA. A power calculation determined a required sample size of 40. Patients were randomized to receive either LA alone or LA with inhaled methoxyflurane. Pain and anxiety were assessed pre- and postoperatively using a visual analog scale (VAS) and the State-Trait Anxiety Index (STAI). Comparisons of VAS pain scores and anxiety measures between groups were performed using the Mann-Whitney U-test.

RESULTS: Forty patients underwent scrotal procedures under LA without intraoperative or postoperative adverse events. Patients in the methoxyflurane group reported similar intraoperative pain levels compared to the LA group (1.35 vs. 1.85, p=0.3); however, intraoperative anxiety in the methoxyflurane group was significantly less than the control group (0.4 vs. 1.65, p=0.01). Patients receiving methoxyflurane also reported significantly higher procedural tolerability compared to controls (9.6 vs. 7.4, p=0.01).

CONCLUSIONS: Scrotal surgery under LA is well tolerated; however, inhaled methoxyflurane as an adjunct to LA is an effective means of reducing anxiety and further improving patient-reported experiences during scrotal urologic procedures.

INTRODUCTION

Various urologic procedures have undergone a paradigm shift toward ambulatory/outpatient surgery as a natural result of improvements in technique, coupled with increasing population demands and limited operating room resources. Peno-scrotal urologic procedures have been well-suited for the transition from standard anesthetic techniques to outpatient local anesthetic approaches due to the ability to deliver effective analgesia using simple and efficient regional nerve blocks (dorsal nerve or spermatic cord blocks).

Systematic reviews indicate that local anesthesia (LA) outcomes are at least comparable, if not superior, to general anesthesia (GA) across various surgical specialties.[1]

Our previous study further supports this, showing that 93.1% of patients preferred LA for penoscrotal surgery and would choose it again for a future procedure.[2] Despite the many potential benefits of transitioning to an LA technique for penoscrotal surgeries, there remain areas for improvement. Anxiety, needle phobia, and the need for repeated anesthetic administration in cases of incomplete analgesia remain key challenges in enhancing the tolerability of surgery under local anesthesia.[3,4]

While many patients in our previous studies expressed a preference for LA over traditional anesthesia, common concerns included heightened awareness during the procedure and a desire for reduced anxiety levels.[2] To address these limi-

tations, various adjunctive methods aimed at reducing anxiety and alleviating needle phobia are under investigation;[5] however, an optimal approach for effectively minimizing anxiety and enhancing tolerability has yet to be identified.

Inhaled self-administered anesthetics have been used for many years across healthcare specialties for their favorable properties to quickly induce an analgesic and anxiolytic effect for a short duration.[6,7] Entonox®, a mixture of 50% nitrogen and 50% oxygen (N_2O_2), has been previously shown to decrease pain associated with transrectal ultrasound-guided prostate biopsy and flexible cystoscopy.[8] A similar compound, methoxyflurane, is a volatile anesthetic that was largely used in the 20th century to manage acute and procedural pain. Currently, the use of methoxyflurane is limited to 6 mL/24 hours, with a maximum of 15 mL/week. This produces a level of sedation on par with that of nitrous oxide (albeit with a faster time to peak analgesia), provides ease of self-administration, and has analgesic effects that last longer into the post-procedure period, making it a suitable choice for ambulatory surgery.[9-11]

With these benefits in mind, our group sought to assess whether methoxyflurane as an adjunct to LA can produce greater pain management and reduction in anxiety than LA alone. We hypothesized that there would be a reduction in the pain associated with the administration of the LA, as well as perioperative pain and anxiety, with the effects lasting shortly into the postoperative period. Our secondary objective was to establish whether patients would opt in for this method of anesthesia if there were to be a hypothetical repeat procedure, demonstrating tolerability, as well as patient preference for methoxyflurane.

METHODS

A non-blinded, randomized controlled trial with a 1:1 allocation ratio was conducted among patients undergoing scrotal urologic procedures at a single ambulatory surgical center (ASC), Men's Health Clinic Manitoba, to evaluate the efficacy of using methoxyflurane as an adjunct to LA (Figure 1). These procedures included hydrocelectomy, spermatocelectomy, or epididymectomy. This study was approved by the University of Manitoba's Health and Research Ethics Board (HS26348).

Study population and data collection

All scrotal urologic procedures were performed at a single urologic outpatient ASC from April 2024 to October 2024 by three senior authors (PP, JN, RB). Patients were included according to the following criteria: at least 18 years of age, undergoing a hydrocelectomy, spermatocelectomy, or epididymectomy under LA. Patients were excluded if there was a history of substance use disorder, history of renal impairment, history of liver dysfunction, previous hypersensitivity to methoxyflurane or related compounds, or personal or family history of malignant hypothermia.

Patient demographics, including age, history of scrotal procedures, prior experience with conscious sedation and GA, alcohol and substance use, and the Charlson comorbidity index (CCI), were collected preoperatively by a research team member. Baseline pain (1: no pain, 10: excruciating pain) and anxiety levels were assessed using a six-question short form of the State-Trait Anxiety Index (STAI). Immediately post-procedure, patients rated their pain and anxiety levels again using the same scales. Finally, patients were asked whether they would recommend this sedation method to others and if they would choose it again for a hypothetical repeat procedure.

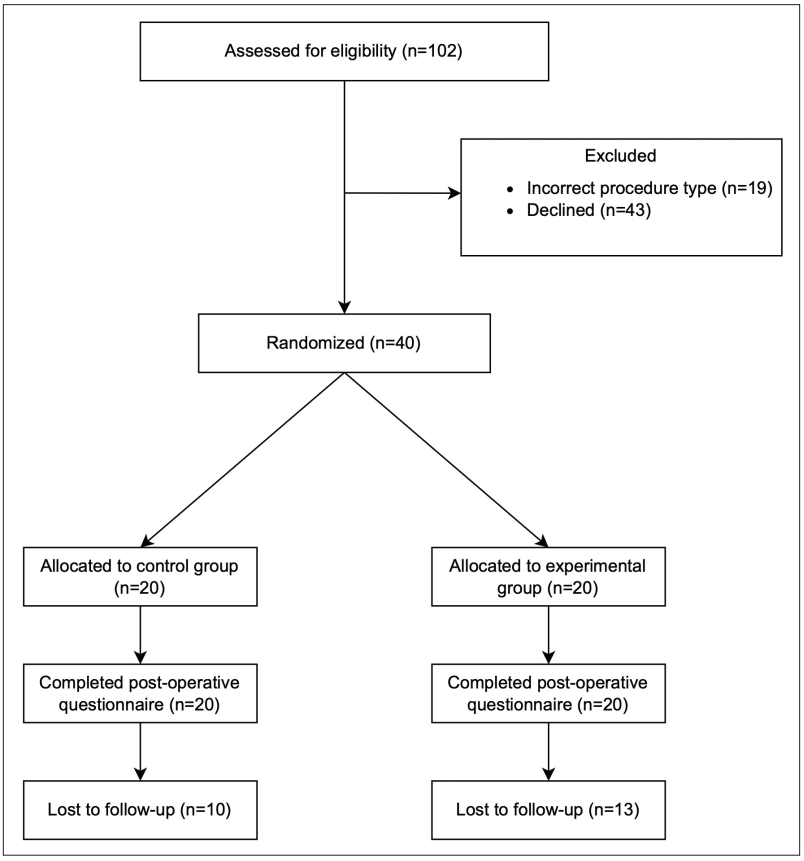

Figure 1. CONSORT diagram depicting the flow of patients throughout the study period.

Table 1. Demographic characteristics of patients in the LA-only arm vs. those in the LA + methoxyflurane arm

Characteristic	Local infiltration only (n=20)	Local infiltration + methoxyflurane (n=20)	Significance (95% CI)
Average age (+ SD)	56.5 (18.3)	56.9 (15.3)	p=0.74
Charlson comorbidity score (range)	0.75 (0–6)	0.3 (0–4)	p=0.30
Procedures administered Epididymectomy Spermatocelectomy Hydrocelectomy	20 3 9 8	20 6 4 10	
Previous scrotal surgery	7	10	
Previous conscious sedation	3	4	
Previous general anesthesia	13	13	
Average baseline pain (range)	1.2 (0–5)	1.6 (0–9)	p=0.88
State-Trait Anxiety Index, mean (SD)	9.7	10.8	p=0.32

CI: confidence interval; LA: local anesthesia; SD: standard deviation.

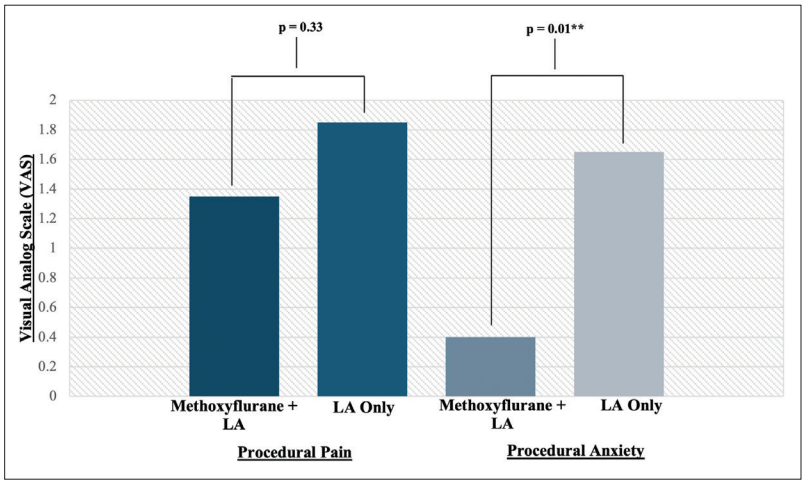

Figure 2. Procedural pain and anxiety differences in the methoxyflurane + local anesthesia (LA) arm vs. those in the LA-alone arm.

Sample size calculation

A power calculation was performed to detect a change in pain scores of 1.5. With a standard deviation of 1.75 in both groups (power 0.8, alpha error 5%, paired design), a sample size of 40 was required. Based on studies conducted by our group a priori, patients generally report mild pain with penoscrotal procedures under LA, with previous studies identifying a change in pain score of 1.1 to be clinically significant.[12]

Randomization and protocol

Randomization occurred on the day of the procedure, with participants randomly assigned in a 1:1 ratio to either methoxyflurane + LA or a control group of local infiltration alone. Patients in the methoxyflurane arm received an inhaler and were instructed by research personnel on self-administration and recognition of its effects. They were advised to begin inhalation 10 minutes before the procedure, considering its median onset time of five minutes.[12] In both study cohorts, LA was administered using 10–20 mL of 1% lidocaine and 0.25% bupivacaine along the median raphe of the scrotum and as a spermatic cord block. Additional LA was provided at the surgeon's discretion for deeper tissue anesthesia.

Statistical analysis

All captured information was stored and analyzed using REDCap electronic data capture tools hosted at the University of Manitoba.[13,14] Data was analyzed using the statistical software Graphpad Prism 10.4.1. Continuous variables were summarized as means and standard deviations, namely the demographic variables for the study. The analysis of changes in visual analog scale (VAS) pain scores and anxiety measures were compared between the groups using the Mann-Whitney U-test. Statistical analysis was completed with an alpha of 0.05 and with a p-value <0.05 considered statistically significant. Descriptive statistics were used to express categorical variables.

RESULTS

Forty patients participated in this study, with no patients lost to followup. Within the control arm (n=20), the distribution of procedures was as follows: three patients underwent an epididymectomy, nine patients underwent a spermatocelectomy, and eight patients underwent a hydrocelectomy. All these procedures were performed under LA, with no reported intraoperative complications. Within the experimental arm (n=20), six patients underwent an epididymectomy, four patients underwent a spermatocelectomy, and 10 patients underwent a hydrocelectomy. No intraoperative or perioperative complications were noted concerning the surgical procedure or anesthetic received.

Baseline demographics did not differ significantly, with no differences in age, CCI, average baseline pain, and pre-procedural anxiety as assessed by the STAI (Table 1). Intraoperative pain (mean, range) with the inhaled methoxyflurane group (1.35, 0–7) was lower than the control group (1.85, 0–6), although, this was not significantly different (p=0.33). Intraoperative anxiety in the experimental group (0.4, 0–4) was less than in the control group (1.65, 0–5), which was significantly different (p=0.01) (Figure 2).

Patients receiving the methoxyflurane group reported less maximal pain during the procedure (2.14, 0–8) compared to the control group (4.0, 0–7), although this was not statistically significant (p=0.09). Patients receiving the inhaled methoxyflurane reported significantly (p=0.01) higher assessments of their procedure (9.6, 9–10) compared to the control group (7.4, 5–10) (Table 2). A total of 17 patients of the 40 were reachable for a phone followup for the study. Of those patients, none experienced any adverse events, including headaches, postoperative nausea, postoperative vomiting, or loss of consciousness.

To explore potential predictors of postoperative outcomes, a multiple linear regression analysis was performed, examining preoperative factors such as patient age, pack-year smoking history, cannabis use, baseline pain, and baseline anxiety, and their relationship with postoperative pain and anxiety within the experimental group. While none of the factors demonstrated statistically significant associations with postoperative outcomes, the analysis revealed no evidence of any preoperative variables exerting detrimental effects on postoperative anxiety (Tables 3, 4).

Table 2. Postoperative followup data

Characteristic	Local infiltration only (n=10)	Local infiltration + methoxyflurane (n=7)	Significance
Overall assessment of procedure under method of anesthetic, mean (SD)	7.4 (1.84)	9.6 (0.54)	p=0.01
Maximal pain during procedure, mean (range)	4.0 (0–7)	2.1 (0–8)	p=0.09
Pain 2 hours post-procedure	5.8 (2.8)	3.4 (2.6)	p=0.14
Would recommend method of anesthesia to others, %	100%	100%	

Bolded value indicate statistically significance. SD: standard deviation.

Table 3. Regression analysis of preoperative factors and postoperative pain in the experimental group

Factor	Regression coefficient (β)	Significance
Age	0.011	0.787
Pack-year smoking	-0.104	0.848
Cannabis use	2.609	0.432
Charlson comorbidity index	0.732	0.3305
Baseline pain	-0.044	0.075
Baseline anxiety	-0.132	0.516

Table 4. Regression analysis of preoperative factors and postoperative anxiety in the experimental group

Factor	Regression coefficient (β)	Significance
Age	-0.017	0.407
Pack-year smoking	0.052	0.842
Cannabis use	0.683	0.667
Charlson comorbidity index	0.083	0.815
Baseline pain	0.032	0.912
Baseline anxiety	-0.081	0.415

DISCUSSION

The shift of penoscrotal procedures to outpatient and ambulatory settings under LA represents an innovative approach to improving care delivery, reducing wait times, and lowering costs; however, ensuring effective pain control and anxiety management remains essential for optimizing procedural tolerability and patient satisfaction.

Methoxyflurane presents a promising adjunct for surgery under LA, offering effective analgesia and anxiolysis and a rapid-onset medication, with the advantage of preserving respiratory drive; however, its role in more complex urologic procedures requires further investigation to fully understand its efficacy and safety in these settings. Our randomized control trial demonstrated that 1) adjunctive use of methoxyflurane can significantly reduce anxiety outcomes compared to LA alone; 2) despite no significant reduction in pain, improved tolerability was seen with improved anxiolysis; and 3) methoxyflurane can safely be administered without extensive monitoring, with no adverse events seen.

The adjunctive use of inhaled methoxyflurane significantly reduced anxiety but did not have a notable impact on pain levels. Previous studies and anecdotal evidence remind surgeons that anxiety can often peak in the preoperative period, with quite high levels of stress seen before urologic procedures specifically.[15,16] There was no significant improvement in reported pain in the methoxyflurane group; despite this, penoscrotal surgery was well tolerated, with minimal pain reported in both groups.

Inhaled methoxyflurane has been primarily studied for pain control in trauma settings, with limited research on its use in urologic procedures; however, three randomized controlled trials have demonstrated significant pain reduction with nitrous oxide for cystoscopy, transrectal ultrasound-guided prostate biopsy, and extracorporeal shockwave lithotripsy (ESWL). It is important to note that significant pain reductions may have been seen with these procedures, as they often require sedation or general anesthesia (as in ESWL) or present challenges in achieving adequate local anesthe-

sia (as in cystoscopy). While TRUS biopsy is well suited for local anesthetic block, the trial showing significantly lower pain scores used a control group that did not receive any LA. Given that penoscrotal surgery under LA already results in low reported pain levels, the addition of inhaled methoxyflurane likely provided little to no additional pain relief.

The anxiety reduction, coupled with low reported pain with the LA surgical approach, has notable implications for patient tolerability as well. A previous study by our group demonstrated that although LA alone had favorable tolerability, many patients reported that they would like to have reduced memory of the procedure.[2] This is reflected in our current findings, as decreased perceived anxiety in the intervention arm, despite similar levels of pain, led to significantly improved tolerability in the postoperative setting. This demonstrates that anxiolysis was achieved effectively due to the sedative properties of patient-administered inhaled methoxyflurane at relatively low doses, helping patients achieve a self-administered level of sedation while optimizing the benefits of LA.[17] Anxiety is a common experience among patients undergoing procedures, making the use of adjuncts with anxiolytic properties, such as inhaled methoxyflurane, a valuable strategy to enhance the overall patient experience.

Finally, when considering an adjunct to an LA surgical approach, safety and the level of monitoring required are important considerations. Deep intravenous sedation has been previously explored with good efficacy; however, given the concern for respiratory depression, an anesthesiologist is required for the safe administration of the sedation.[18] The ability for patients to self-administer a rapid-onset medication, combined with the minimal effect on respiratory drive, allowed for all cases in our cohort to be performed without an anesthesiologist.

Furthermore, no adverse events were observed among patients who received methoxyflurane in addition to LA compared to those who received LA alone. These qualities make methoxyflurane a safe and effective adjunct for procedures performed under LA, as it does not require extensive monitoring or the presence of an anesthesiologist, who may not always be readily available.

Another advantage of methoxyflurane in an ambulatory setting is that while its analgesic effects extend into the early postoperative period, its sedative properties do not, enabling safe patient discharge without the need for prolonged monitoring or additional stay.

Strengths and limitations

Strengths of our study include its randomized controlled design, with full study recruitment to our calculated sample size (40/40). Additionally, we accounted for baseline anxiety and pain levels, controlling for these variables to ensure they did not influence our study outcomes. This study is among the few randomized controlled trials evaluating methoxyflurane as an adjunct to LA across any procedure type. We demonstrated a significant reduction in patient anxiety and improved perceived tolerability despite comparable low pain levels between groups. These findings may also apply to other surgical specialties seeking effective analgesic and anxiolytic adjuncts to local anesthesia.

While this study provides valuable insights into the efficacy of methoxyflurane as an adjunct to LA, our study is not without limitations. The non-blinded design may have introduced some degree of bias, as both patients and providers were aware of the intervention. Additionally, this study was not placebo-controlled, and the reduction in pain and anxiety could have been attributed to a placebo effect. The study's sample size of 40 patients, coupled with its single-center design, may limit its external validity, but can still serve as a foundation for future research.

Furthermore, this study relied on patient-reported measures of pain and anxiety, which may be limited by how patients interpret the question prompt; however, we aimed to mitigate this potential bias with the use of standardized questionnaires, such as the VAS pain scale and the STAI. Subsequently, there may have been some element of a recall bias for those patients who did respond to their followup questionnaire.

Finally, while significant improvements in anxiety and patient tolerability were observed in the inhaled methoxyflurane group, it is important to note that our power calculation was designed to detect differences in pain levels, not anxiety. Despite these limitations, the promising results support the need for larger, double-blinded, randomized controlled trials to further validate these findings and explore a broader range of objective measures.

CONCLUSIONS

This study provides compelling preliminary evidence supporting the efficacy of methoxyflurane as an adjunct to LA in scrotal urologic procedures. By significantly reducing both pain and anxiety, methoxyflurane enhances patient comfort and improves procedural outcomes compared to LA alone. These findings align with existing literature, positioning methoxyflurane as a valuable tool in pain management and anxiolysis during

outpatient procedures. Despite the study's limitations, including its non-blinded design and small sample size, the promising results warrant further research, particularly larger, double-blinded trials. Continued exploration of methoxyflurane's long-term effects and its potential side effects will be essential for its integration into routine clinical practice. Ultimately, methoxyflurane offers a significant advancement in enhancing patient care, optimizing surgical workflows, and improving procedural satisfaction in ambulatory surgical settings.

COMPETING INTERESTS: Dr. Patel has been a consultant for Boston Scientific. The remaining authors do not report any competing personal or financial interests related to this work.

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CORRESPONDENCE: Dr. Patel, Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; ppatel5@hsc.mb.ca