Nitrous Oxide Inhalation to Improve Patient Acceptance and Reduce Procedure Related Pain of Flexible Cystoscopy for Men Younger Than 55 Years

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Purpose: Flexible cystoscopy in men younger than 55 years is painful despite the current best standard anesthesia (20 ml 2% lidocaine gel 15 minutes before endoscopy). The anesthetic value of lidocaine gel is debated and led us to seek an alternative. Nitrous oxide is a well established analgesic and anxiolytic agent, and it significantly reduces pain associated with transrectal ultrasound guided prostate biopsy. We studied its use in flexible cystoscopy in men younger than 55 years.
Materials and Methods: A total of 61 patients were prospectively randomized to receive air (31) or Entonox® (30). Both groups had 3 minutes of gas via a breath activated facemask (either Entonox or air) before endoscopy. The gel control group was comprised of 8 patients who underwent cystoscopy after instillation of lidocaine gel. The air and Entonox groups had lidocaine gel as per best standard. Vital signs were recorded before, during and after cystoscopy. Patients completed a visual analog score for gel insertion and cystoscopy.
Results: There were no statistically significant differences between the groups in terms of baseline characteristics. Pain scores for cystoscopy ($p < 0.001$) and intraoperative pulse rate ($p = 0.008$) were significantly less with Entonox. Side effects were transient and seen more often with Entonox ($p < 0.05$). More of the air group would require more analgesia ($p = 0.001$) or a general anesthetic ($p = 0.011$) if undergoing repeat cystoscopy.
Conclusions: Nitrous oxide inhalation significantly reduces cystoscopy related pain without significant complications. We propose that Entonox should be the anesthetic agent of choice for men younger than 55 years.

Key Words: nitrous oxide, lidocaine, pain measurement, cystoscopy

Flexible cystoscopy is an integral part of the evaluation of hematuria. In addition to its diagnostic role, it is also required for followup in transitional cell carcinoma of the bladder. Given a quoted prevalence of microscopic hematuria in a United States male population of between 1% and 16% this translates into a potentially large number of procedures.[1] There is an increasing body of literature showing that diagnostic procedures in urology (eg transrectal ultrasound guided prostate biopsy) are painful and require more analgesia than previously administered.[2] We believe flexible cystoscopy in younger men to be one of these procedures. Despite the optimal use of periurethral lidocaine, flexible cystoscopy in males is a painful procedure.[3–5] This seems to be especially true for males younger than 55 years. The current best evidence practice is for 20 ml 2% lidocaine gel instilled 15 minutes before cystoscopy.[3] However, recent work suggests lidocaine gel to be no better than lubricating gel.[5,6]

The most painful part of urethral instrumentation is said to occur when the instrument passes through the external urethral (ie striated) sphincter. Anatomically, the Pudendal nerve supplies the striated sphincter and indirect evidence for the urethral sphincter being the most painful point of urethral instrumentation comes from George and Dixon who have shown that the sensation of pain associated with urethral catheterization is inhibited by bilateral pudendal nerve block.[7] The implication of these observations is that an alternative to lidocaine, and possibly a nontopical agent, is required for optimal anesthesia in flexible cystoscopy.

Entonox (50% nitrous oxide and oxygen) is a safe and rapidly effective agent used for anesthesia/analgesia and anxiolysis in obstetrics,[8] emergency departments[9] and in dental practice throughout the world.[10] It has been shown to be effective for the relief of pain associated with transrectal ultrasound guided prostatic biopsies.[2] Therefore, we performed this randomized blinded controlled trial to assess its efficacy in relieving pain in flexible cystoscopy for men younger than 55 years.

PATIENTS AND METHODS

Following approval for the study from the regional ethics committee, the records of all men 55 years old or younger listed for flexible cystoscopy were screened for exclusion criteria. These were lidocaine allergy, concurrent use of anti-inflammatory medications, neurological disease impairing pain perception, requirement for a secondary procedure or a history of significant cardiac or cardiopulmonary disease. Those without exclusion criteria were invited by mail to

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Study received regional ethics committee approval.
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participate in the study. On the day of the procedure fully informed consent was obtained.

Those who consented were prospectively randomized to an air or Entonox treatment group. Randomization was performed by the prepared card in envelope method and it was not possible to see the card through the envelope. The remaining 8 men formed a control group for gel insertion and cystoscopy was performed immediately after instillation of lidocaine gel.

In line with best evidence practice the Entonox and air groups received 20 ml 2% lidocaine gel (Instillagel®, Farco-Pharma GmbH, Cologne, Germany) 15 minutes before endoscopy. A penile clamp held the gel in the urethra during this time. All gel insertions took less than 5 seconds and were performed by nonendoscopy suite personnel before blinding.

The air group received air via a breath activated demand valve mask for 3 minutes before and during endoscopy. The treatment group received Entonox via an identical demand valve mask for the same time period. The gel control group did not use the mask. The endoscopist and assisting nurse were blinded as to the randomization.

For the purposes of the study pulse rate and oxygen saturation were measured before, during, immediately after and 15 minutes after completion of the cystoscopy. The intraoperative measurement coincided with intubation of the external sphincter. Blood pressure before, immediately after and 15 minutes after cystoscopy was also recorded.

During the 15-minute period after cystoscopy patients were asked to complete a questionnaire which included an assessment of pain response to gel insertion and cystoscopy. Pain perception was recorded using a standard visual analog score and verbal score.

A single operator performed all procedures using Olympus® instruments. Cystoscopy was performed to mimic standard United Kingdom practice as much as possible. Verbal contact between the patient, the endoscopist and/or the nurse during flexible cystoscopy was kept to a minimum in an effort to maintain the blinding. Statistical analysis was performed using SSPS®. Significance was assumed for a p value of less than 0.05.

RESULTS

In total 69 men were recruited into the study. A total of 30 were randomized to the Entonox group and 31 to the air group. There were no statistical differences between the groups in terms of age, diagnosis or pain scores for gel insertion (table 1 and fig. 1). The visual analog scores for cystoscopy ($p < 0.001$) were significantly decreased in the Entonox group (Anova $F = 15.145$). This was also the case with verbal score results ($p < 0.001$, Anova $F = 14.661$). Not unexpectedly, the mean pulse rates 15 minutes after cystoscopy, were reduced in all 3 groups, but not significantly so. There was a significant reduction in intraoperative pulse rate ($p = 0.008$, Anova $F = 5.346$) in the Entonox group compared to the air group. There were too few in the gel control group for subgroup analysis. Table 2 shows the pulse rates at the sampling times in the groups. The lack of an increase in pulse rate during cystoscopy in the Entonox group is indirect evidence of its analgesic/anxiolytic properties.

There were no significant differences in blood pressure readings or oxygen saturation readings between groups. The main side effects noted by this patient cohort were lightheadedness, pins and needles and mask related discomfort. All these were transient and resolved before discharge (table 3). They occurred more often in the Entonox group ($p < 0.05$). There were no serious adverse events associated with Entonox use. The study was not designed to assess any longer-term effects but our own experience and also that of others would suggest that for short exposure times, the risk

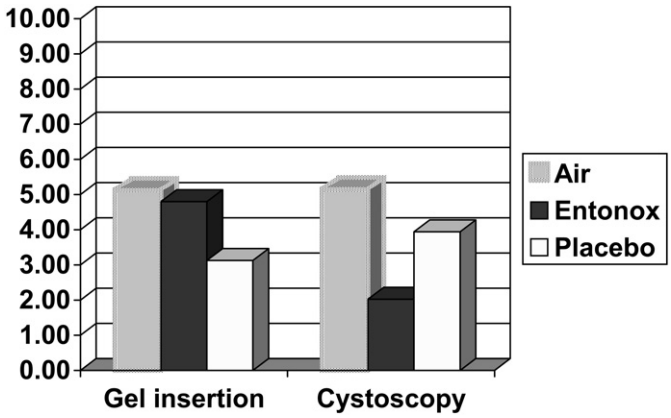

FIG. 1. Visual analog scores for gel insertion and cystoscopy. There was no significant difference between groups for gel insertion. Scores were significantly reduced in Entonox group (ANOVA $p < 0.0001$) compared to air and placebo groups. No significant difference between placebo and air groups (Tukey's test).

TABLE 1. *Age and indication/diagnosis of the cohort*

	Air	Entonox	Placebo
Mean pt age (±SD)	43.84 (9)	45.1 (10.08)	47.38 (10.37)
No. indication/diagnosis:			
Hematuria	9	7	3
Obstruction	8	6	1
Lower urinary tract symptoms	10	13	2
Urinary tract infection	3	2	0
Transitional cell carcinoma followup	1	2	2
Total	31	30	8

TABLE 2. *Pulse rates in the 3 groups before, during and after the procedure*

	No. Pts	Mean	SD	SE	Min	Max
Preop:						
Air	31	82.29	17.207	3.090	46	139
Entonox	30	78.83	14.849	2.711	58	112
Placebo	2	85.00	18.385	13.000	72	98
Overall	63	80.73	15.981	2.013	46	139
Intraop:						
Air	28	88.32	15.804	2.987	51	120
Entonox	26	76.81	11.200	2.197	54	98
Placebo	1	67.00			67	67
Overall	55	82.49	14.852	2.003	51	120
Immediately postop:						
Air	31	82.13	16.225	2.914	51	128
Entonox	30	78.27	10.932	1.996	54	97
Placebo	2	78.50	14.849	10.500	68	89
Overall	63	80.17	13.806	1.739	51	128
15 Mins postop:						
Air	31	74.65	12.901	2.317	39	99
Entonox	30	72.03	11.944	2.181	56	100
Placebo	1	65.00			65	65
Overall	62	73.23	12.349	1.568	39	100

TABLE 3. *Patient reported sensations after cystoscopy*

	No. Air (%)	No. Entonox (%)	No. Gel Control (%)
None	27 (87)	17 (57)	2 (25)
Form not filled out	2 (6)	1 (3)	6 (75)
Urinary frequency	1	—	—
Mask discomfort	—	1	—
Light-headed	1	6 (20)	—
Tingling	—	4 (13)	—
Slight numbness	—	1	—
Dizziness	—	1	—
Very happy	—	1	—
Dissociated from world	—	1	—
Total	31	33*	8

* One patient had mask related discomfort and tingling, and commented on being "dissociated from the world" immediately after the procedure, but was feeling perfectly normal on leaving 20 minutes later. A second patient complained of light-headedness and tingling. All Entonox related side effects had ceased by discharge home.

of serious adverse events is minimal. Figure 2 illustrates the preferences for repetition of cystoscopy with 10 of the air group and 1 of the Entonox group saying they would not have the cystoscopy repeated under the same conditions (chi-square test p = 0.011). Figure 3 illustrates that 14 of the air group vs 4 of the Entonox group would have preferred more preoperative analgesia (chi-square test p = 0.001). A significantly greater proportion of the air group indicated a preference for a general anesthetic (chi-square test p = 0.011) for any subsequent cystoscopy.

DISCUSSION

There is an increasing body of evidence showing that periurethral lidocaine gel is at best of no benefit[5,6] and at worst, causes more pain when compared to plain lubricant.[11] Possible reasons for this lack of effect include difficulty in identifying the optimal regimen and conditions for use of topical lidocaine, the need to overcome patient anxiety and the need to adequately anesthetize the sphincter.

With regard to lidocaine administration, potential variables include the timing of cystoscopy post gel instillation (ie the dwell time), the rate of gel delivery or the temperature of the gel. A dwell time of at least 10 minutes, slow instillation and a gel temperature of 4C have all been suggested as ways of improving the analgesic effect of lidocaine. The work of Choong,[3] Holmes[4] and Brekkan et al[12] suggested minimum

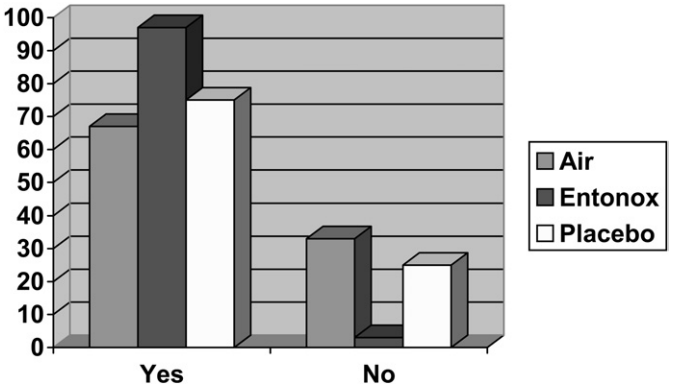

FIG. 2. Patient attitude (percentage of sample) to repeat cystoscopy in same manner. Using chi-square test there is significant difference between Entonox and other 2 groups (p = 0.011).

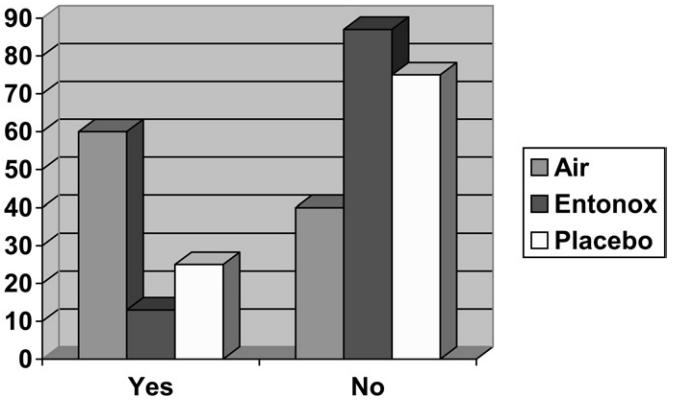

FIG. 3. Patient desire (percentage of sample) for greater analgesia before repeat procedure. Using chi-square test there is significant difference between Entonox and other 2 groups (p = 0.001).

dwell times of 15, 10 and 10 minutes, respectively, before cystoscopy. Such dwell times are not commonly used. The results of McFarlane et al suggest that dwell time is not important because they noted no difference with dwell times of 15 minutes.[5] In a group undergoing followup flexible cystoscopy, Herr and Schneider noted no difference between the lidocaine and lubricant gel groups with a dwell time of 10 to 15 minutes.[6] This lack of benefit may be due to the older age of this group or their reduced anxiety as they had all undergone flexible cystoscopy in the past. No consensus has been agreed concerning the effect of gel temperature on pain. There is only 1 article in the English language literature dealing with rate of gel delivery and it showed significantly greater pain scores in patients with a delivery time of 2 vs 10 seconds.[13]

Anxiety is also postulated as a major cause of pain felt during cystoscopy. Goldfischer et al demonstrated this for outpatient rigid cystoscopy.[14] Choong et al showed second procedures to be less painful than first, presumably due to a reduction in anxiety due to increased familiarity.[3] This may explain the low pain scores recorded by Herr and Schneider.[6] These were all older patients who underwent previous cystoscopy by the same operator and with whom dialogue was maintained throughout. Periurethral lidocaine does little for this component of urethral pain.

Pain in younger males has been demonstrated to be worse. Choong et al[3] and Brekkan et al[12] showed a significant increase in pain scores in those less than 55 years. Khan[13] and Holmes et al[4] disagree. Holmes et al found no link, although their study had few patients younger than 55. Khan et al looked at pain from gel insertion and found no difference between those older or younger than 60.[13] Our pain scores are higher than those of Choong et al (2.1 after dwell time of 25 minutes vs 5 after dwell time of 15 minutes) but our gel insertion pain scores are similar to those recorded by Khan et al for gel insertion in a population from the same geographic region. As far as we are aware, ours is the only study to exclusively examine pain in men younger than 55 years. Therefore, these pain scores may represent the actuality of the pain experienced in men younger than 55. They also reflect our attempt to mimic the clinical situation as much as possible and in part may relate to the attempt to keep the operator and nurse blinded to the randomization by the lack of verbal reassurance to the patient, which they would normally supply.

The ideal agent for flexible cystoscopy in younger men would overcome these 3 major problems. Nitrous oxide is such an agent because of its analgesic, anxiolytic and amnesic properties. The combination of anxiolysis and analgesia is probably responsible for the lower pain scores and lower intraoperative pulse rates seen in the Entonox group in this study. Nitrous oxide has been in clinical use for more than a hundred years. It is highly effective in reducing anxiety as has been shown in many dental publications[15] and is commonly used in pediatric[16] and emergency departments.[9] In all these applications it has been shown to be safe and effective. Its effects are dependant on the concentration inhaled and at the 50% concentration these are mainly analgesia and anxiolysis with a smaller degree of amnesia. Carbajal has demonstrated analgesia within 3 minutes of inhalation with complete or partial relief of pain in 75% to 80%. The effect wears off in less than 4 minutes by excretion from the lungs.[16]

The mechanisms behind the analgesic and antinociceptive effects of nitrous oxide are becoming clearer.[17] The evidence suggests that the trigger is release of opioid peptide from the periaqueductal gray matter leading to activation of descending inhibitory pathways, which are thought to be predominantly noradrenergic. Activation of the descending inhibitory pathways results in modulation of nociceptive impulses.

Nitrous oxide is a colorless and odorless gas although to some it has a faint sweet smell. Its major adverse effect of light-headedness is transient and said to be not unpleasant. Its use as an analgesic in concentrations up to 50% is associated with no significant cardiovascular changes. Nitrous oxide may cause some slight cardiac depression but this is of little clinical concern in the majority of patients but for this reason it should be used with care in those with significant cardiac failure and in those with chronic obstructive pulmonary disease.[2] These conditions are not commonly seen in males younger than 55 years.

There have been some concerns regarding the use of nitrous oxide in relation to prolonged administration to patients or chronic exposure of staff. Symptoms from exposure to nitrous oxide are time and dose related. According to Weimann there is little evidence to support the earlier reported reduction in fertility or the development of cancer.[18] Early hematopoietic changes require 6 hours of continuous exposure to sedative concentrations of nitrous oxide while measurable change in granulocytes needed 2 or more weeks of continuous exposure. The mechanism relates to the interference of the action of vitamin B_{12}.[18] These risks are mainly associated with the use of continuous flow nitrous oxide rather than the demand valve system and are significantly reduced by gas scavenging systems. In dental practice there are guidelines for minimizing exposure to nitrous oxide which when implemented reduce staff exposure to accepted levels.[10] The low exposure from use in flexible cystoscopy would not be expected to cause any adverse hematological effects.

Flexible cystoscopy is a day case office procedure. One of the questions raised about the use of nitrous oxide whether patients could drive themselves home. We did not address this particular issue but can comment on it with studies by Martin et al.[19] Martin et al performed complex psychomotor testing on a group of 40 men and women undergoing flexible sigmoidoscopy with either Entonox or air as the analgesic agent. These psychomotor tests are designed to detect drug induced impairment of driving ability. Their results show no significant difference between scores of those who did or did not receive Entonox. Based on this study they concluded that the use of Entonox would not impair driving skills. We monitored vital signs and oxygen saturations during the study but the guidelines issued by the American Society of Anesthesiologists Task Force indicate that less than 50% nitrous oxide and oxygen mixture constitutes minimal sedation and thus minimal risk.[20] This implies little monitoring is required. Clinical evidence for this is provided by Frampton et al who demonstrated that little added care was required using Entonox in a pediatric emergency setting.[9]

CONCLUSIONS

This study and others have shown flexible cystoscopy in men younger than 55 years to be painful. The increased pulse rate in the air group as the endoscope passed through the external sphincter suggests that this is the most painful part of the procedure and, thus, should be the target of analgesic agents. Therefore, the place of periurethral lidocaine as sole anesthesia for flexible cystoscopy in younger males must be questioned. In our cohort Entonox with its anxiolytic and analgesic effects significantly improved the pain experience for younger males. The increased analgesia was achieved at no cost to the patient and avoided the use of a general anesthetic, which would otherwise have been necessary for these men. With the application of well established standards of care this reduction in pain as a consequence of Entonox is achieved without increased risk to endoscopy suite staff. Therefore, we propose that Entonox is the agent of choice for flexible cystoscopy in men younger than 55 years.

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EDITORIAL COMMENT

Intravenous nitrous oxide is a sedative-analgesic that may relieve anxiety and discomfort during diagnostic procedures. Inhaled N_2O has shown promise in providing sedation for atrial flutter ablation[1,2] and flexible bronchoscopy.[3] Its sedative properties and ability to reduce anxiety may be beneficial for patients who undergo diagnostic cystoscopy, and the authors have clearly shown that in this article. However, side effects can limit efficacy. Effects such as dizziness, headache and light-headedness suggest the need for postoperative monitoring. Administration by mask may not only induce anxiety for patients but may also increase procedure related costs. Finally, it would be interesting to learn whether second procedures appear to be less painful than first procedures as a result of a reduction in patient anxiety. This may also decrease N_2O requirements in future procedures, as would be the case for patients who need periodic surveillance cystoscopy.

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