

The analgesic effect of inhalational Entonox for extracorporeal shock wave lithotripsy

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Abstract Extracorporeal shock wave lithotripsy (ESWL) is a non-invasive procedure that allows urinary stones to be fragmented using acoustic shock waves. The impact of the shock waves causes transient stinging pain at the entry site as well as deep visceral discomfort, requiring analgesia during the procedure. The objective of this study was to compare the clinical efficacy of Entonox and pethidine for pain relief during outpatient ESWL. We randomized 150 outpatients undergoing elective ESWL into three groups of 50 patients, each group receiving inhalational Entonox, intravenous pethidine, or inhalational compressed air during ESWL. Quantitative evaluation of pain was performed according to a visual analogue scale (VAS), before and after the intervention. Analysis of variance (ANOVA) and paired *t* tests were used to compare VAS scores in the three groups, before and after the intervention. Entonox and pethidine decreased the pain score significantly, while compressed air did not. There was no significant difference between pain relief by Entonox and pethidine. This study demonstrates for the first time that inhalational Entonox is an effective analgesic regimen for ESWL. Entonox can be regarded as an appropriate alternative to analgesics like opioids in relieving pain during ESWL.

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Introduction

Since 1980, extracorporeal shock wave lithotripsy (ESWL) has become the first-line treatment for most urinary stones in adults and children [1]. However, the vast majority of patients do not tolerate the procedure without analgesia or sedation. Several monitored anesthesia care techniques have been used to provide sedation and analgesia [2–5]. Some of the analgesic drugs administered for ESWL, however, carry the risk of respiratory depression, delayed discharge, and/or unplanned hospital admission [6].

Entonox is a mixture of 50% nitrous oxide and 50% oxygen. Inhalation produces analgesia without loss of consciousness [7]. Self-administration of Entonox as an analgesic has been widely used for many years, particularly in obstetric practice [8], and by paramedics for prehospital care [9]. Entonox has a good safety record, with no serious side effects recorded for intermittent use [7], and is rapidly cleared from the circulation by exhalation [10].

The aim of this study was to compare the clinical efficacy of inhalational Entonox and pethidine for pain relief during outpatient ESWL.

Methods

A total of 150 patients (97 men and 53 women) with stones located in the renal pelvicalyceal system were prospectively randomized to receive Entonox (prefixed equimolar nitrous oxide and oxygen mixture), pethidine, or compressed air for sedoanalgesia during lithotripsy with a third

generation electromagnetic lithotripter (Dornier Compact Delta magneto lithotripter).

After institutional review board approval, written informed consent was obtained during the anesthesia consultation, which was performed at least 48 h before ESWL. During this consultation, the method of pain assessment was explained to the patients. Patients were asked to rate their pain on a scale from 0 (no pain) to 10 (worst possible pain).

Patients were included in the study if they were older than 15 years of age, had pelvicalyceal stones, and understood the pain scoring. Patients were excluded from the trial if they had any of the following: (1) serum creatinine > 200 $\mu\text{mol/l}$; (2) history of chronic use of analgesics and/or sedatives; (3) allergy to any of the study medications; or (4) history of middle ear surgery within the previous month.

Just before entering the lithotripsy room, the patients were randomly assigned to one of the three treatment groups (Entonox, pethidine, 1 mg/kg intravenously over 10 min, or compressed air, each to be provided if the patient asked for pain relief during ESWL) by opening a sealed envelope. All patients were assessed by a single physician who was blinded to the patient group assignment. All patients received no premedication and they were told not to eat or drink for at least 4 h prior to the procedure.

The control group received compressed air, followed by Entonox gas if pain relief was considered inadequate by the patient.

Pain was assessed before and 2 min after receiving pain medication by using a visual analogue scale (VAS) with two anchor points, zero denoting no pain and ten for the worst pain the patient had ever experienced.

Statistical analysis

Data are expressed as mean (\pm SD) and numbers (percentages). The paired *t* test was used to analyze VAS score before and after medication. Comparison of means (VAS decrease) in the three groups was performed using one-way ANOVA. Comparison of percentages was performed using Chi-square analysis.

All statistical analyses were performed using SPSS® software, version 9.0, for Windows. Results throughout the text and tables are presented as mean \pm SD unless otherwise specified, and statistical significance was defined as $P < 0.05$.

Results

The three study groups were comparable with respect to demographic data, history of urinary calculi and ESWL,

and location of calculi. There were no statistically significant differences between the three groups (Table 1). All patients in the three groups required analgesia. Rescue medication in the form of pethidine was administered in only one case in the Entonox group after recording VAS scores because the analgesia was inadequate.

No ESWL procedure had to be prematurely terminated because of inadequate analgesia. A patient in the Entonox group had mild nausea that subsided spontaneously. The other patients did not develop any complications.

Mean \pm SD of VAS scores before and after intervention are shown in Table 2. Statistical analysis showed significant decrease (Table 2) in pain severity in patients receiving Entonox or pethidine. In contrast, patients receiving compressed air had no such change.

While VAS scores after receiving either Entonox or pethidine were significantly different from those in the control group ($P = 0.001$) after receiving compressed air, statistical comparison showed no significant difference between post-Entonox or post-pethidine VAS scores ($P = 0.5$), suggesting that inhalational Entonox may be as effective as intravenous pethidine in alleviating ESWL-associated pain.

No significant difference was found in VAS scores of male and female patients in each group (Fig. 1).

Discussion

Extracorporeal shock wave lithotripsy (ESWL) has become a valuable asset to the urologist and greatly benefits stone

Table 1 Demographic data and ESWL variables in three different groups

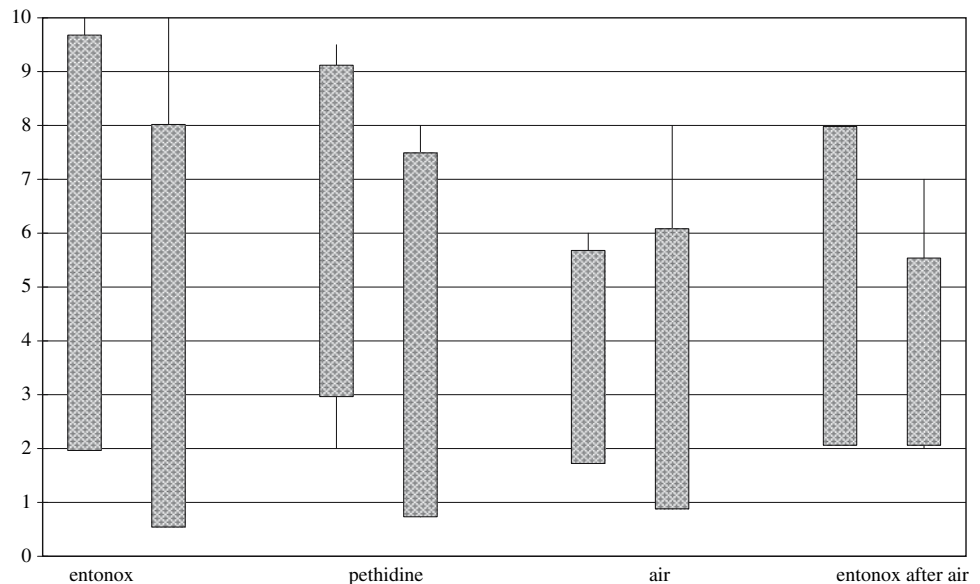
Groups	Entonox	Pethidine	Control
Age (years)	43.76 \pm 11.89	45 \pm 13.46	43.9 \pm 14.21
Weight (kg)	75 \pm 2	78 \pm 3	79 \pm 2
Height (cm)	165 \pm 10	167 \pm 12	164 \pm 8
Gender (M/F) (<i>n</i>)	30/20	34/16	33/17
Stone location (%)			
Renal	80	78	84
Ureteral	20	20	15
Both	0	2	1
Number of shocks delivered	2,010 \pm 320	2,000 \pm 560	2,500 \pm 450
Maximum voltage (kV) used	4.04 \pm 1.15	4.14 \pm 0.75	4.51 \pm 1.00
Past history of urinary calculi (%)	70	72	76
Past history of ESWL (%)	42	46	36

Data are expressed as mean \pm SD, numbers (*n*), or percentages (%)

Table 2 Mean \pm SD of VAS scores and *P*-value of comparing scores before and after Entonox, pethidine, and compressed air administration in different groups

VAS scores	Entonox	Pethidine	Compressed air	Entonox in the compressed air group
Before administration	5.76 \pm 1.92	6.04 \pm 1.54	3.6 \pm 1.1	4.96 \pm 1.42
After administration	3.73 \pm 2.13	4.11 \pm 1.69	3.48 \pm 1.3	3.8 \pm 1.74
<i>P</i> -value	0.001	0.001	0.426	0.001

In control group, after testing with compressed air, we used Entonox. As can be seen in this group, like Entonox group, VAS score decreased significantly

Fig. 1 VAS scores in different groups before and after administration of Entonox, pethidine, and compressed air

patients. In a short period of time, ESWL has completely changed the management of urinary stone disease and has almost entirely supplanted open surgical and most endourologic approaches [11]. Today, third-generation mobile electromagnetic lithotripters yield an average of 80% stone-free rate for kidney and ureteral calculi [12].

As ESWL is frequently carried out on an outpatient basis, it is crucial to provide adequate analgesia with minimal adverse effects [13].

Chaussy and Thuroff [14] demonstrated that analgesia requirements in ESWL depend on lithotripter, stone location, age, gender, and number of shock waves. The pathogenesis of pain in ESWL is still not clearly known. Whether it is due to cutaneous or deep visceral afferent stimulation is debatable [15]. The pain is presumably due to cavitation-mediated stimulation of nerve fibers. The intensity of pain perceived during ESWL depends on the energy level of shock waves passing through the tissues [16]. Although the development of new generation lithotripters has decreased pain during ESWL, some form of sedation and anesthesia may still be required to provide adequate patient comfort and effective treatment [15].

Any technique for alleviating ESWL-associated discomfort/anxiety should ideally be reliable in its effect, of rapid onset and short duration of action, free of adverse events, cost-effective, and easily administered [17].

Opioids are the most commonly used analgesics during ESWL [18]. Despite their effectiveness, their use may be complicated by central nervous system (CNS) or respiratory depression, circulatory failure, or gastrointestinal problems [19].

Several studies have compared different local and systemic analgesia regimens for pain relief during ESWL, but this, to our knowledge, is the first randomized clinical trial to evaluate the efficacy of Entonox in the treatment of ESWL-associated pain.

Nitrous oxide has been used for pain relief during childbirth since the 1930s and was initially delivered at a concentration of 50% in air, producing an effective analgesic mixture. In 1961, Mike Tunstall premixed 50% nitrous oxide with oxygen, and called it Entonox, which was stored as a compressed gas mixture in cylinders. Since then, the convenience of Entonox has made it a successful and popular analgesic for labour [20]. Entonox has also

proved effective in providing pain relief in other specialties [21, 22].

Our randomized clinical trial demonstrated that Entonox and pethidine were equally effective in providing analgesia during ESWL and that they were superior to compressed air. Entonox fulfills many of the criteria for an ideal analgesic during ESWL [17] and, compared to intravenously administered pethidine, provided comparable analgesia with less CNS, circulatory, and respiratory depression or nausea and vomiting.

Entonox provides rapid and effective analgesia without heavy sedation and leads to adequate patient relaxation and cooperation. The effect of Entonox was of short duration, allowing the patients to leave the ESWL unit without the need for a long recovery period [23]. Entonox appeared to be associated with few, minor, and short-lived adverse effects such as nausea and vomiting, dizziness, dry mouth (breathing dry gas), buzzing in the ears, and rarely, pins and needles or numbness, dreams or drowsiness, ranging from 0 to 30% [24]. Nitrous oxide–oxygen inhalation may thus provide a valuable alternative to conventional analgesia regimens during ESWL.

In addition to short-acting parenteral sedative narcotics, e.g., alfentanil, midazolam, and propofol, topical agents such as EMLA cream, lidocaine, prilocaine and piroxicam have been used to minimize pain during SWL [25]. Further studies are, therefore, warranted to compare the efficacy and safety of Entonox with those of other analgesic regimens.

Conclusions

Entonox can provide easy, rapid, and adequate pain relief for patients undergoing ESWL, and is associated with few and minimal side effects.

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