Original Article

Role of oral tramadol 50 mg in reducing pain associated with outpatient hysteroscopy: A randomised double-blind placebo-controlled trial

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Background: Several drugs have been used to reduce hysteroscopy-associated pain. Although the Royal College of Obstetricians and Gynaecologists has recommended against the use of opiates in outpatient hysteroscopy, we wished to investigate if opioids can be used if the appropriate opioid was given in the appropriate dose.
Aim: To study the effectiveness of tramadol 50 mg in reducing pain associated with outpatient hysteroscopy.
Materials and Methods: A prospective randomised double-blind placebo-controlled trial conducted in the outpatient hysteroscopy clinic at Cairo University Hospital. Main outcome measures were the severity of pain during the procedure, immediately after the procedure and 30 minutes later assessed by a visual analogue scale (VAS). VAS of 0 indicates no pain and VAS of 10 indicates the worst possible pain.
Results: A total of 140 women who had diagnostic outpatient hysteroscopy were randomised to receive oral tramadol 50 mg or placebo one h before performing outpatient hysteroscopy. There was no difference between the groups in the age, parity, duration of the procedures or indications of hysteroscopy. The median pain score was significantly lower in the tramadol group during the procedure (5 vs 6; $P = 0.013$), immediately after the procedure (3 vs 4; $P < 0.036$), and 30 minute later (1 vs 2; $P = 0.034$). Two women in the tramadol group reported nausea, but this was mild and did not warrant cancelling the procedure.
Conclusions: Oral administration of tramadol 50 mg before hysteroscopy reduces the pain evoked by the procedure and the drug was well tolerated by women.

Key words: hysteroscopy, pain, tramadol.

Introduction

Hysteroscopy is currently the most informative investigation for women with abnormal uterine bleeding and infertility.[1] Office hysteroscopy is comparable with surgical inpatient hysteroscopy but offers reduced anaesthesia risks and decreased overall costs.[2] Outpatient hysteroscopy involves the use of miniaturised endoscopic equipment to directly visualise the endometrial cavity, without the need of formal theatre facilities or anaesthesia.[3] However, the main limitation to the widespread use of outpatient hysteroscopy is the occurrence of pain.[4,5]

In an attempt to reduce the outpatient hysteroscopy-associated pain, a lower uterine filling pressure was recommended.[6] Flexible hysteroscopy was also found to reduce hysteroscopy-associated pain when compared with rigid hysteroscopy.[7]

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Several drugs have been used to reduce pain during the procedure, including the use of topical anaesthetics, opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Tramadol hydrochloride is an orally active centrally acting synthetic opioid. It is an atypical analgesic with a dual mechanism of action: serotonin and norepinephrine reuptake inhibition and modest μ-opioid agonist. It has a lower incidence of respiratory depression, cardiac depression, side effects on smooth muscle and abuse potential as compared to typical opioid agents.[8,9] Intravenous and intramuscular tramadol given before hysteroscopy were shown to reduce pain associated with hysteroscopy, but no data were available on the effectiveness of oral tramadol.[10,11]

The study objective was to evaluate the effectiveness and side effects of oral tramadol 50 mg in reducing pain associated with outpatient hysteroscopy.

Materials and Methods

This was a single-centre, prospective, randomised, with balanced randomisation (allocation ratio 1:1), double-blind and placebo-controlled study. The study was approved by the research ethics committee of Cairo University Hospital

and was registered with www.clinicaltrials.gov, registration number NCT02068209. It was conducted in the outpatient hysteroscopy clinic at Cairo University Hospital from May 2014 to March 2015. The sample size was calculated to detect a mean difference of one unit between tramadol and placebo pain scores during the procedure using VAS assuming that the within group standard deviation would be 2. We would need to study 64 cases in each group to be able to reject the null hypothesis that the population means of the tramadol and placebo groups are equal with probability (power) 0.8. We added six cases to each arm accounting for any missing data ending in 70 cases in each group. The Type I error probability associated with this test of the null hypothesis is 0.05. Sample size calculation was performed using Stats Direct statistical software version 2.7.2 for MS Windows, Stats Direct Ltd., Cheshire, UK.

Recruited women were randomly divided into two equal groups; Group 1 received an oral tramadol 50 mg (Tramal®, Memphis, Giza, Egypt) tablet and Group 2 received an oral placebo tablet similar in size, structure and colour to tramadol. All women were of reproductive age, and all procedures were scheduled to be done in the postmenstrual period. Exclusion criteria included women with known cardiac disease, known allergy to tramadol, pelvic infections, pregnancy, suspected cervical cancer and women with heavy bleeding. A registrar generated the allocation sequence using computer-generated random numbers and enclosed tramadol and placebo in sequentially numbered sealed envelopes kept with the attending nurse. The attending nurse allocated patients to the groups. The nurse, the patient and the physician were unaware of the drug used until the end of the study when the codes were broken. All women received the enclosed medication 1 h before the procedure.

The procedure was done in the lithotomy position. We used a 30° angle 2.9 mm rigid hysteroscope with 3.8 mm diagnostic sheath [Karl Storz, Germany]. Vaginoscopic approach was used for insertion of the hysteroscope in all cases (no use of speculum or tenaculum). The hysteroscope was gently introduced into the uterine cavity after visualisation of the cervix and identification of the external os. We used saline as the distension medium and the maximum pressure was set at 100 mm Hg. The uterine cavity and tubal ostia were systematically visualised. All the procedures were done by the same operator using the same equipment.

The woman's perception of pain was assessed for each group in three occasions: During the procedure, after the hysteroscope was introduced in the uterine cavity and a panoramic view of the uterine was obtained, immediately after the procedure when the hysteroscope was withdrawn from the uterus, and 30 minutes after completing the procedure. Pain was assessed with the use of a visual analogue scale (VAS). VAS of 0 indicates no pain and VAS of 10 indicates the worst possible pain. Women were also asked to report any side effects. The primary outcome was pain score during the procedure; secondary outcomes included pain immediately after the procedure, 30 minutes after the procedure and drug side effects.

Data were statistically described in terms of mean ± standard deviation (±SD), frequencies (number of cases) and percentages, medians and ranges when appropriate. Comparison of numerical variables between the study groups was done using Student *t*-test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency was <5. Median test was used to analyse the pain scores data. *P* values <0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

We approached 212 women referred to the outpatient hysteroscopy clinic at Cairo University Hospital to undergo diagnostic hysteroscopy. Women were invited to participate in the study after providing clear explanation of the study and its expected values. Forty six women declined to participate and 26 women were excluded: 19 had pelvic infections, four had cardiac diseases, two had an allergy to tramadol and one woman had a suspicious cervical lesion. The remaining 140 women were enrolled in the study after giving written consent (Fig. 1).

The baseline characteristics and indications of hysteroscopy in the study groups are summarised in Table 1. There was no significant difference between the groups in the age, parity, body mass index and indications for hysteroscopy. There was no difference in the duration of the procedure between the study groups.

The median pain score was significantly lower in the tramadol group during the procedure, immediately after the procedure and 30 minutes after the procedure (Table 2). Two women in the tramadol group reported nausea but this was mild and did not warrant cancellation of the procedure. No hysteroscopy complications were encountered. The procedure could not be completed in one woman in the placebo group because of intolerable pain, intention to treat analysis was adopted and the woman was considered to have pain score of 10 in the three assessment occasions. No procedures were cancelled because of uncooperative patients or failure of hysteroscope introduction. All women were fully oriented and conscious after the procedures.

Discussion

Our results showed that oral administration of tramadol 50 mg before outpatient hysteroscopy significantly reduced pain scores during the procedure, immediately after the procedure, and 30 minutes after the procedure when compared with a placebo. The main strength of the study is the investigation of the role of a small dose of a weak opioid to reduce pain in outpatient hysteroscopy and

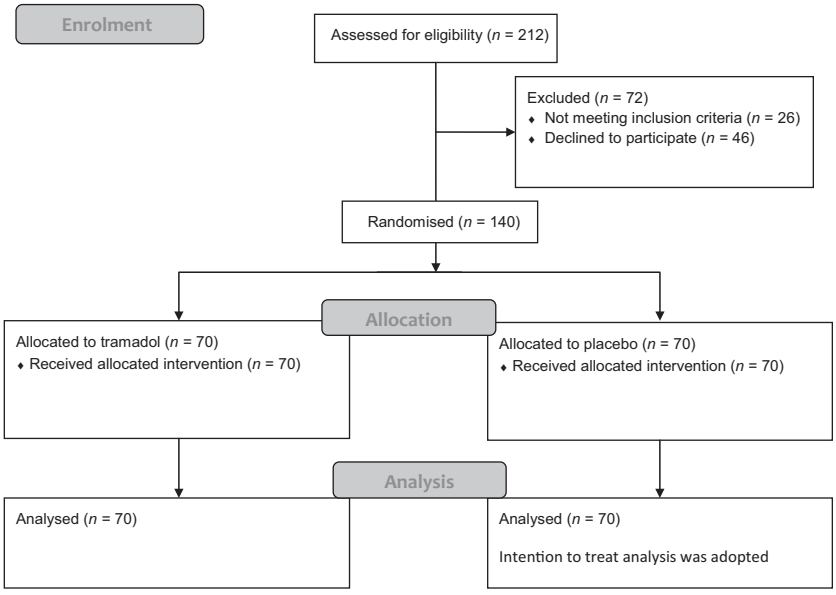

Figure 1 Consort flow diagram of the study.

Table 1 Baseline characteristics and hysteroscopy indications of the groups†

	Tramadol (n = 70)	Placebo (n = 70)	P value
Age (years)	31.5 ± 7.4	32.3 ± 8.1	0.524
Parity	1.2 ± 1.2	1.3 ± 1	0.504
Body mass index (kg/m^2)	29.1 ± 2.9	28.8 ± 2.8	0.627
Duration of the procedure (minutes)	2.4 ± 1.2	2.1 ± 1.1	0.256
Ease of the procedure‡	64 (91.4%)	63 (90%)	0.771
Saline volume used in the procedure (mL)	539.2 ± 117.6	572.1 ± 140.5	0.136
Indications for the procedure:			
Infertility	30 (43%)	32 (46%)	0.734
Recurrent miscarriage	16 (23%)	19 (27%)	0.558
Abnormal bleeding	17 (24%)	14 (20%)	0.541
Suspected uterine lesion	7 (10%)	5 (7%)	0.546

†Data are presented as means and standard deviations. Ease of the procedure and Indications are presented as frequencies and percentages.
‡Ease of the procedure was subjectively assessed by the operator.

Table 2 Comparison between pain scores in the Tramadol and Placebo groups†

	Tramadol n = 70	Placebo n = 70	P value
Pain during the procedure	5 (8)	6 (8)	0.013
Pain immediately after the procedure	3 (8)	4 (8)	0.036
Pain 30 minutes after the procedure	1 (5)	2 (6)	0.034

†Data are presented as medians (ranges).

is tolerated by patients. This may result in changing the practice of avoiding all opioids before outpatient hysteroscopy. The main limitation of the study is that all results were based on the subjective perception of pain. This varies among individuals and is related to the individuals' previous pain experience and level of anxiety.

Several randomised controlled trials studied the use of various analgesics to reduce hysteroscopy-associated pain. Our results agreed with some of these studies that demonstrated a beneficial effect of analgesics before outpatient hysteroscopy. Bellati *et al.* randomised 120 women undergoing outpatient hysteroscopy to receive intramuscular tramadol 100 mg (n = 40) 50 minutes before the procedure, intracervical block (n = 40) or no medications (n = 40). Women in the tramadol group had significantly less pain at the end of the procedure when compared with those in the intracervical block group and those who received no medication. Side effects were not reported in this study.[10]

In addition, Floris *et al.* randomised 50 women undergoing outpatient hysteroscopy to receive tramadol 100 mg (n = 25) IV infusion 50 minutes before the procedure or a placebo (n = 25). Women in the tramadol group reported lower pain scores immediately after the procedure and 15 minutes later. There was no significant

difference between the groups in the incidence of nausea, vomiting or bradycardia.[11] Our results concur with those of Bellati *et al.* and Floris *et al.*, but the oral route of tramadol administration had the advantage of ease of administration and convenience to the women.

On the other hand, some studies failed to show a significant reduction in pain scores when using analgesics before outpatient hysteroscopy. Lin *et al.* randomised 164 women undergoing outpatient hysteroscopy to receive sublingual buprenorphine (0.2 mg) ($n = 80$), 40 minutes before the procedure or a placebo ($n = 84$) and found no significant reduction in pain with the use of buprenorphine.[12] However, a 3.1 mm flexible hysteroscope was used in this nonblinded study. Flexible hysteroscopy is associated with less pain than rigid hysteroscopy[7] which we believe may have contributed to the lack of significant difference between buprenorphine and placebo in this study. There was a high incidence of side effects in the form of nausea, vomiting and drowsiness in the intervention group (38.8%) compared to none in the control group. Based on these data the Royal College of Obstetricians and Gynaecologists has recommended against the use of opiates before outpatient hysteroscopy.[13] However, we found that tramadol 50 mg was tolerated by women, two (4%) reported nausea but this did not warrant cancellation of the procedure. Our results have shown that opioids can be used before outpatient hysteroscopy if the appropriate opioid was given in the appropriate dose.

Some studies have investigated the role of NSAIDs in reducing the outpatient hysteroscopy-associated pain. Issat *et al.* randomised 150 women undergoing outpatient hysteroscopy. Women were randomised to receive vaginal misoprostol, 400 μg, with 100 mL of 5% intravenous glucose (misoprostol arm); intravenous ketoprofen, 50 mg/mL, in 100 mL 5% glucose with intravaginal placebo (ketoprofen arm); or vaginal placebo tablets, 100 mL 5% intravenous glucose (placebo arm) before outpatient hysteroscopy. Pain scores were significantly lower in the misoprostol group than in the ketoprofen ($P = 0.02$) or placebo ($P = 0.006$) groups. There were no statistical differences between the three arms in the pain scores assessed at 15 minutes after the procedure ($P = 0.16$).[14]

Caligiani *et al.*[15] found that combined ketrolac 30 mg IM and cervical block was superior to cervical block alone in reducing pain associated with outpatient hysteroscopy. This was not reproduced by Mercorio *et al.*[16] who found that oral dexketoprofen 25 mg was not superior to cervical block in reducing pain in postmenopausal women undergoing outpatient hysteroscopy. Oral diclofenac 50 mg was not found to reduce hysteroscopy-associated pain[17] and oral mefenamic acid 500 mg was not found to reduce the pain during the procedure but significantly reduced pain 30 minutes and 60 minutes after the procedure.[18]

Teran-Alonso *et al.* conducted a randomised study on 200 women undergoing outpatient hysteroscopy. One hundred women received paracetamol 1 g and ibuprofen 600 mg one h before the procedure and 100 women did not receive any medication. The pain scores were not significantly different between the groups, but the occurrence of nausea, vomiting and hypotension were significantly lower in women who received paracetamol and ibuprofen.[19] In the absence of a placebo control, the reduction in side effects in this study may be attributed to the placebo effect rather than the pharmacological effect of the paracetamol and ibuprofen.

Local anaesthetic sprays are also described. Esin *et al.* studied 82 women undergoing outpatient hysteroscopy. Women were randomised to receive either sublingual misoprostol and placebo of lidocaine or lidocaine pump spray applied to the cervix and placebo of misoprostol. When compared with the lidocaine group, women in the misoprostol group reported less pain scores immediately after the procedure, whereas pain scores at 10 minutes were similar between groups.[20]

It is to be noted that most of the studies that disagreed with our results were studying NSAID rather than opioids. Further research is needed to compare the roles of opioids and NSAIDs before outpatient hysteroscopy. Pain during hysteroscopy can be attributed to cervical manipulations, uterine distension, touching the endometrium which may cause contractions. Delayed pain is caused by prostaglandins release secondary to uterine distension and uterine manipulations.[5] Whereas tramadol acts centrally as a μ-opioid agonist making it effective in reducing pain during and after the procedure, NSAIDs act mainly through reducing prostaglandins level, making them more effective in reducing pain after the procedure.

We conclude that the use of oral tramadol 50 mg before hysteroscopy reduces the pain evoked by the procedure and is well tolerated by women.

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