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ORIGINAL ARTICLE *Gynaecology*

Tramadol versus Celecoxib for reducing pain associated with outpatient hysteroscopy: a randomized double-blind placebo-controlled trial

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STUDY QUESTION: Which is better, Tramadol or Celecoxib, in reducing pain associated with outpatient hysteroscopy?

SUMMARY ANSWER: Both Tramadol and Celecoxib are effective in reducing pain associated with outpatient hysteroscopy but Celecoxib may be better tolerated.

WHAT IS KNOWN ALREADY: Pain is the most common cause of failure of outpatient hysteroscopy. A systematic review and meta-analysis showed that local anaesthetics were effective in reducing pain associated with hysteroscopy but there was insufficient evidence to support the use of oral analgesics, opioids and non-steroidal anti-inflammatory drugs, to reduce hysteroscopy-associated pain and further studies were recommended.

STUDY DESIGN, SIZE, DURATION: This was a randomized double-blind placebo-controlled trial with balanced randomization (allocation ratio 1:1:1) conducted in a university hospital from May 2014 to November 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Two hundred and ten women who had diagnostic outpatient hysteroscopy were randomly divided into three equal groups: Group 1 received oral Tramadol 100 mg, group 2 received Celecoxib 200 mg and group 3 received an oral placebo. All the drugs were given 1 h before the procedure**.** A patient's perception of pain was assessed during the procedure, immediately afterwards and 30 min after the procedure with the use of a visual analogue scale (VAS).

MAIN RESULTS AND THE ROLE OF CHANCE: There was a significant difference in the pain scores among the groups during the procedure, immediately afterwards and 30 min after the procedure ($P < 0.001$, 0.001, <0.001 respectively). Tramadol had significantly lower pain scores when compared with the placebo during the procedure (mean difference = 1.54, 95% confidence interval (CI) (0.86, 2.22), $P < 0.001$), immediately after the procedure (mean difference = 1.09; 95% CI (0.5, 1.68), $P < 0.001$) and 30 min later (mean difference = 0.95, 95% CI (0.48, 1.41), $P < 0.001$). Celecoxib administration also led to significantly lower pain scores than the placebo during the procedure (mean difference = 1.28, 95% CI (0.62, 1.94), $P < 0.001$), immediately after the procedure (mean difference = 0.72; 95% CI (0.13, 1.32), $P = 0.016$) and 30 min later (mean difference = 0.77, 95% CI (0.3, 1.24), $P = 0.001$). There were no significant differences in pain scores between Tramadol and Celecoxib at any time. Time until no pain differed significantly among the groups ($P = 0.01$); it was shorter with both Tramadol and Celecoxib groups when compared with placebo ($P = 0.002$ and 0.046, respectively). The procedure failed to be completed in one patient in the placebo group but no failure to complete the procedure occurred in Tramadol and Celecoxib groups. Four women in the Tramadol group reported nausea but no side effects were reported with Celecoxib group and no complications were reported in any group of patients.

LIMITATIONS, REASONS FOR CAUTION: All results were based on the subjective perception of pain, which varies among individuals and is related to the individuals' previous pain experience and level of anxiety.

WIDER IMPLICATIONS OF THE FINDINGS: Tramadol and Celecoxib are effective in reducing pain in outpatient hysteroscopy. Celecoxib may be better tolerated as no side effects were reported in the study, however further research on a larger sample size is required before drawing firm conclusions about lack of side effects.

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TRIAL REGISTRATION NUMBER: www.clinicaltrials.gov – NCT02071303.

Key words: outpatient hysteroscopy / pain / Celecoxib / cyclo-oxygenase-2 inhibitors / Tramadol

Introduction

Hysteroscopy is currently the most informative investigation for patients with abnormal uterine bleeding and uterine factor of infertility (Sharma *et al.*, 2009). Outpatient hysteroscopy involves the use of miniaturized endoscopic equipment to directly visualize the endometrial cavity, without the need of formal theatre facilities or anaesthesia (Van dongen *et al.*, 2007). However, the main limitation to the widespread use of outpatient hysteroscopy is the occurrence of pain (Campo *et al.*, 2005).

Several agents have been used to reduce pain during the procedure including the use of topical anaesthesia, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Tramadol hydrochloride is an orally active, centrally acting synthetic opioid having a lower incidence of respiratory depression, cardiac depression, side effects on smooth muscle and abuse potential as compared with typical opioid agents (Modi *et al.*, 2013). Intravenous and i.m. Tramadol given before hysteroscopy were shown to reduce pain associated with hysteroscopy but no data were available on the effectiveness of oral Tramadol (Bellati *et al.*, 1998; Floris *et al.*, 2007).

Various NSAIDs have been studied to reduce pain associated with hysteroscopy, including studies on Diclofenac, Mefenamic acid, Ketorolac and Dexketoprofen (Caligiani *et al.*, 1994; Nagele *et al.*, 1997; Tam and Yuen, 2001; Mercorio *et al.*, 2002). All these agents are non-selective cyclo-oxygenase-1 (COX-1) and COX-2 inhibitors with common gastrointestinal adverse effects. To the best of our knowledge no studies have been carried out on selective COX-2 inhibitors in outpatient hysteroscopy.

Celecoxib is a relatively recent selective COX-2 inhibitor. COX-1 plays a role in the protection of the gastrointestinal mucosa, renal hemodynamics, and platelet thrombogenesis, while COX-2 produces prostaglandins which are induced by inflammation and cause pain. This selective inhibition of COX-2 by Celecoxib reduces pain while minimizing gastrointestinal adverse effects that are common with non-selective NSAIDs (Bhatt *et al.*, 2008).

The objective of the study was to compare the effectiveness and side effects of oral Tramadol versus oral Celecoxib in reducing pain associated with outpatient hysteroscopy in an attempt to find the most effective drug with the least possible side effects to be used before outpatient hysteroscopy.

Methods

This was a single centre, prospective, randomized (with a balanced randomization of 1:1:1), double blind and placebo controlled study. The study was conducted in the period from May 2014 to November 2014.

We approached 245 women referred to the outpatient hysteroscopy clinic at Cairo University Hospitals to undergo diagnostic hysteroscopy. Patients were invited to participate in the study after receiving a clear explanation of the study and its objective. Twenty-three women declined to participate and 12 women were excluded. The remaining 210 patients were enrolled in the study after giving written informed consent. Inclusion criteria were 20–45 years of age and a clear indication for outpatient hysteroscopy which included infertility, abnormal uterine bleeding, recurrent miscarriage and suspected intrauterine lesion by ultrasound. Exclusion criteria were patients with known cardiac disease, known gastritis or peptic ulcer, menopausal women and women with known allergy to Tramadol and Celecoxib or NSAIDs.

An independent person generated the allocation sequence using computer generated random numbers in a 3 block table and enclosed the drugs in sequentially numbered, sealed envelopes kept with the attending nurse. The clinic nurse handed the envelopes to the patients. Neither the patient nor the physician was aware of the drug used. All patients received the enclosed medication 1 h before procedure.

We divided the patients into three groups according to the medication received. Group I received Tramadol 100 mg (Trama®, Global Napi, Giza, Egypt) orally, group II received Celecoxib 200 mg (Celebrex® 200, Pfizer, USA), and group III received placebo acting as the control group (Fig. 1). Treatments and placebo were identical in form and packaging, without any identifying label.

The procedure was performed in the lithotomy position. We used a 30 degree angle 2.9 mm rigid hysteroscope with 3.8 mm diagnostic sheath [Karl Storz®, Germany]. The 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 visualization of the cervix and identification of the external os. We used saline as the distension medium and the maximum pressure was set at 100 mmHg. The uterine cavity and tubal ostia were systematically visualized**.** Patients were informed beforehand that if a uterine lesion was detected during the hysteroscopy, treatment would be scheduled for another session after proper counselling.

A patient's perception of pain was assessed for each group during, immediately after and 30 min after the procedure with the use of the score on a visual analogue scale (VAS). A VAS score of 0 indicates no pain and a score of 10 indicates the worst possible experienced pain. To assess the pain during the procedure, the attending nurse gave the patient the VAS and the patient marked the point she thought was corresponding to her pain on the graph. Time until no pain was estimated by asking patients to report the time when they think pain has completely gone. All patients stayed in the clinic for at least 30 min and for up to 2 h until the time no pain was reported, and all patients were pain free before leaving the clinic. Patients were also asked to report any side effects.

Ethical committee approval

The study was approved by the research ethics committee at Cairo University.

Statistical analysis

To the best of our knowledge this is the first trial to investigate the role of oral Celecoxib and oral Tramadol in reducing outpatient hysteroscopy-associated pain, with no previous data to help calculate the required sample size**.** We did not use previous data on NSAIDs to calculate the sample size because we could not assume that different NSAIDs with

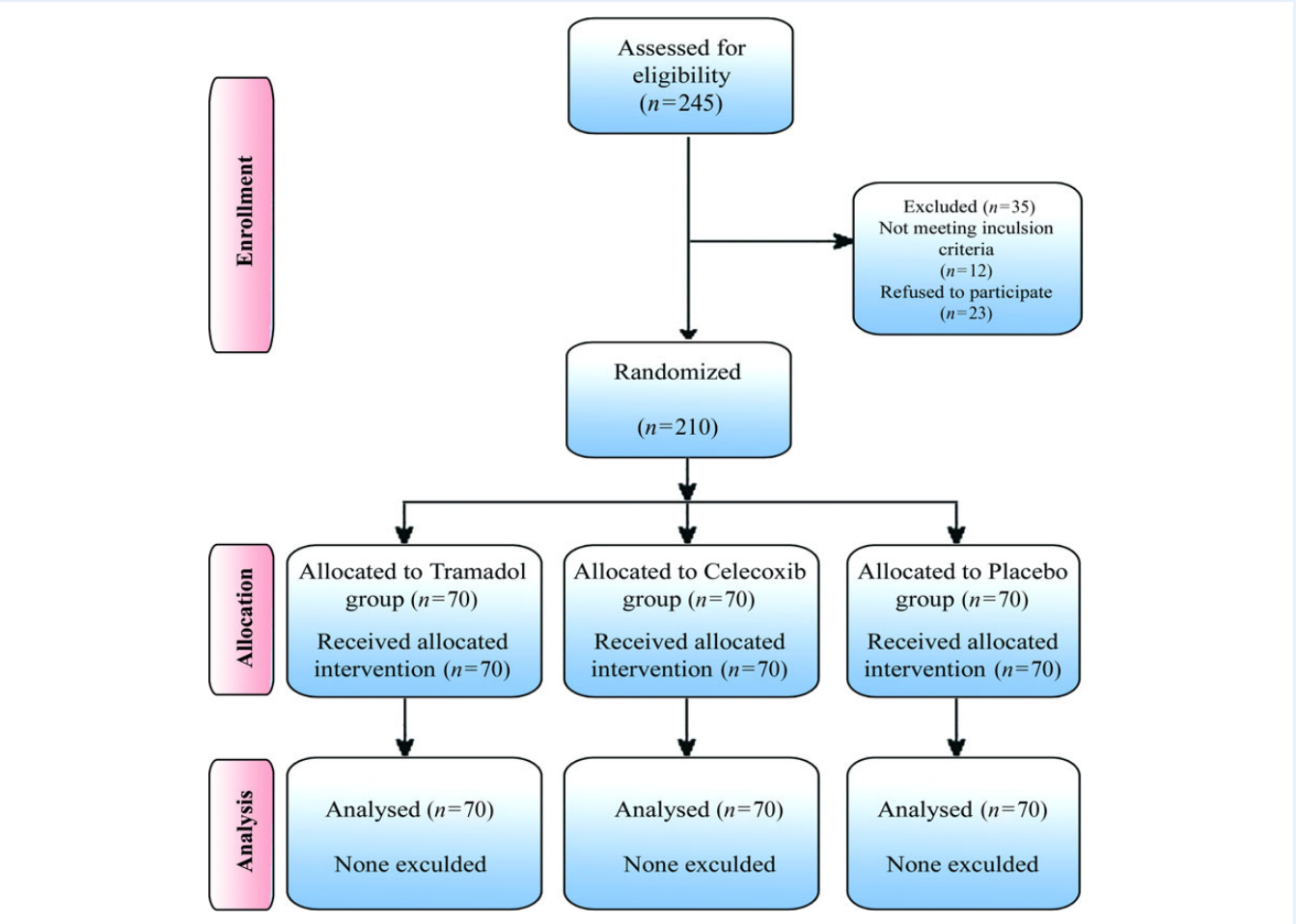

Figure 1 Consort flow diagram for the study of Tramadol versus Celecoxib for reducing pain associated with outpatient hysteroscopy.

different doses have the same effect, especially when the available data were conflicting (Caligiani *et al.*, 1994; Nagele *et al.*, 1997; Tam and Yuen, 2001; Mercorio *et al.*, 2002). Assuming that the response would be normally distributed, the sample size was calculated to detect a mean difference of 1 unit between Tramadol and Celecoxib pain scores during the procedure (a lower difference was not considered clinically relevant) using the 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 Celecoxib are equal, with a probability (power) of 0.8. We added 6 cases to each arm accounting for any missing data, giving 70 cases in each group. The Type I error probability associated with this test of this null hypothesis is 0.05 using the Student's *t*-test for independent samples. Sample size calculation was carried out using Stats Direct statistical software version 2.7.2 for MS Windows (Stats Direct Ltd., Cheshire, UK).

We conducted intention to treat analysis. Data were described in terms of mean $\pm$ SD, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was by one-way analysis of variance. For comparing categorical data, a Chi square (χ^2) test was performed. An exact test was used instead when the expected frequency is less than 5. A *P*-value less than 0.05 was considered statistically significant. A Kaplan–Meier plot was used to display data for the time until no pain among the groups; the logrank test was used to distinguish lines from one another on the plot. All statistical calculations were carried out using the Statistical Package for the Social Science program (SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

The baseline characteristics of the three study groups were similar, with no significant differences. The indications for hysteroscopy included infertility, recurrent miscarriages, abnormal uterine bleeding, and suspected uterine lesion and these did not differ between groups. Baseline characteristics and indications for hysteroscopy are summarized in Table I. There was no significant difference in the mean duration of the procedure among all groups.

There was a significant difference in the pain scores among the groups during the procedure, immediately after and 30 min after the procedure ($P < 0.001, 0.001, <0.001$ respectively; Table II). Tramadol had significantly lower pain scores when compared with the placebo during the procedure [mean difference = 1.54, 95% confidence interval (CI) (0.86, 2.22), $P < 0.001$]; immediately after the procedure [mean difference = 1.09; 95% CI (0.5, 1.68), $P < 0.001$]; and 30 min later [mean difference = 0.95, 95% CI (0.48, 1.41), $P < 0.001$]. Celecoxib also had significantly lower pain scores than the placebo during the procedure [mean difference = 1.28, 95% CI (0.62, 1.94), $P < 0.001$]; immediately after the procedure

Table I Baseline characteristics of patients and indications of hysteroscopy.

	Tramadol ($n = 70$)	Celecoxib ($n = 70$)	Placebo ($n = 70$)
Baseline characteristics:			
Age (years)	29.25 ± 6.39	29.52 ± 6.44	30.8 (6.0%)
Parity (proportion of parous women)	25 (35.7%)	32 (45.7%)	34 (48.5%)
BMI (kg/m^2)	25.77 ± 4.37	26.18 ± 4.47	25.84 (4.46%)
Duration of the procedure	1.92 ± 0.98	2.01 ± 0.97	2.02 (0.83%)
Indications of hysteroscopy			
Infertility	39 (55.8%)	36 (51.4%)	34 (48.6%)
Recurrent miscarriage	10 (14.2%)	6 (8.6%)	4 (5.7%)
Abnormal bleeding	16 (22.9%)	22 (31.4%)	27 (38.6%)
Suspected uterine lesion	5 (7.1%)	6 (8.6%)	5 (7.1%)

Data are presented as mean ± SD or *n* (%).

Table II Comparison between pain scores on the visual analogue scale (VAS) in the study groups.

	Tramadol ($n = 70$)	Celecoxib ($n = 70$)	Placebo ($n = 70$)	*P*-value
Pain during the procedure	4.37 ± 1.77	4.63 ± 1.63	5.92 ± 2.26	<0.001
Pain immediately after the procedure	2.18 ± 1.46	2.55 ± 1.46	3.27 ± 2.02	0.001
Pain 30 minutes after the procedure	0.6 ± 0.95	0.77 ± 1	1.55 ± 1.71	<0.001
Time until no pain (minutes)	24.15 ± 14.88.2	27.46 ± 15.36	34 ± 13.92	0.01

Data are presented as mean ± SD.
One-way analysis of variance test was used to compare the pain scores and Kaplan–Meier plot was used to compare time until no pain in the study groups.

[mean difference = 0.72; 95% CI (0.13, 1.32), $P = 0.016$]; and 30 min later [mean difference = 0.77, 95% CI (0.3, 1.24), $P = 0.001$]. There were no significant differences in pain scores between Tramadol and Celecoxib during the procedure [mean difference = −0.25, 95% CI (−0.82, 0.31), $P = 0.374$]; immediately after the procedure [mean difference = −0.36, 95% CI (−0.85, 0.12), $P = 0.144$]; and 30 min after the procedure [mean difference = −0.17, 95% CI (−0.49, 0.15), $P = 0.303$]. Time until no pain was significantly different among the groups ($P = 0.01$); it was shorter with both Tramadol and Celecoxib compared with the placebo ($P = 0.002$ and 0.046, respectively). A Kaplan–Meier plot was used to display the time until no pain data among the groups (Fig. 2).

Five women in the Tramadol group, seven women in the Celecoxib group and eight women in the placebo group had uterine lesions confirmed by hysteroscopy. They were evenly distributed among the groups ($P = 0.679$). Subgroup analysis between women with confirmed intrauterine lesions and those without revealed no significant difference in the baseline characteristics and the duration of the procedures. There were no significant differences in the pain scores during the procedure, immediately after the procedure, and 30 min after the procedure between the subgroups (Table III).

None of the procedures had to be stopped in the Tramadol and Celecoxib group but the procedure failed to be completed in one patient in the placebo group because of severe intolerable pain (VAS of 10). We included the pain scores of this patient during, immediately after and 30 min after the procedure as well as time until no pain.

Four women in the Tramadol group reported nausea but no side effects were reported in the Celecoxib group. No complications were reported from the procedure in the three groups of patients.

Discussion

Outpatient hysteroscopy is increasingly being used as a cost-effective alternative to in-patient hysteroscopy under general anaesthesia. The use of miniature hysteroscopes and the vaginoscopic approach have made outpatient hysteroscopy more feasible, more convenient and less painful for many patients. However, some patients still experience pain during the procedure, which has been reported as a common cause of failure to complete the procedure (Critchley *et al.*, 2004; Jivraj *et al.*, 2004).

Several RCTs studied the use of various analgesics before hysteroscopy to reduce pain associated with the procedure. Three trials studied the use of opioids (Bellati *et al.*, 1998; Lin *et al.*, 2005; Floris *et al.*, 2007) and four others studied the use of NSAIDs (Caligiani *et al.*, 1994; Nagele *et al*, 1997; Tam and Yuen, 2001; Mercorio *et al.*, 2002) before outpatient hysteroscopy, all of which were non-selective COX inhibitors. Two of the opioid studies examined the use of Tramadol (100 mg), 50 min before outpatient hysteroscopy, given i.m. in one study (Bellati *et al.*, 1998) and by i.v. infusion in the second study (Floris *et al.*, 2007). The first study found that the women in the Tramadol group ($n = 40$) had significantly less pain at the end of the procedure when compared with women in the intracervical block group ($n = 40$)

and women who received no medication ($n = 40$) (Bellati et al., 1998). These results were supported by those from the second study which reported significantly lower pain scores in the Tramadol group ($n = 25$) compared with placebo ($n = 25$) during and 15 min after the procedure (Floris et al., 2007). The third opiate trial studied the use of sublingual Buprenorphine (0.2 mg) ($n = 80$) 40 min before the procedure compared with placebo ($n = 84$) and found no significant reduction in pain with Buprenorphine (Lin et al., 2005). However, a 3.1 mm flexible hysteroscopy was used in this non-blinded study. Flexible hysteroscopy is associated with less pain than rigid hysteroscopy (Unfried et al., 2001), which we believe might have contributed to the lack of significant difference between Buprenorphine and placebo.

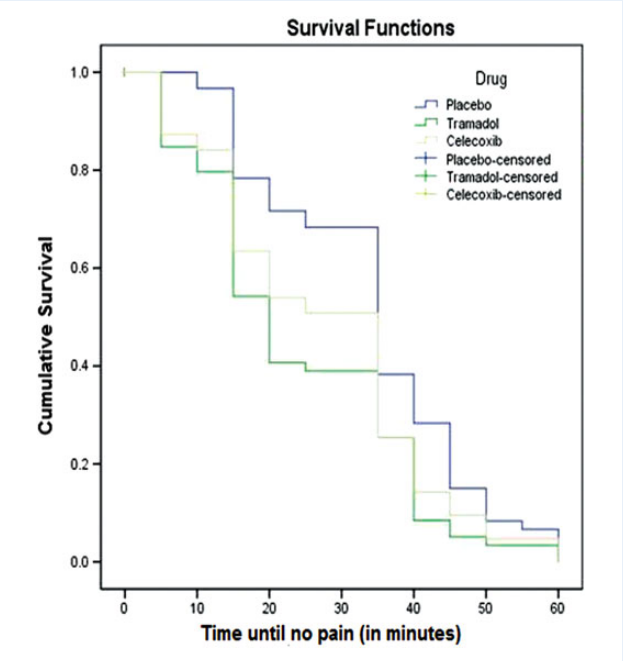

Figure 2 Time until no pain in the study groups.

Adverse effects were reported in the i.v. Tramadol study and the study on Buprenorphine (Lin et al., 2005; Floris et al., 2007). The i.v. Tramadol study found no significant difference between the groups in terms of incidence of nausea, vomiting or bradycardia (Floris et al., 2007), while in the Buprenorphine study, there was a high incidence of side effects in the form of nausea, vomiting and drowsiness in the intervention group (38.8%) compared with none in the control group (Lin et al., 2005).

On the other hand, four trials studied the use of various NSAIDs before outpatient hysteroscopy (Caligiani et al., 1994; Nagele et al, 1997; Tam and Yuen, 2001; Mercorio et al., 2002). NSAIDs were compared to local anaesthetic in two studies (Caligiani et al., 1994; Mercorio et al., 2002) and to a placebo in two other studies (Nagele et al., 1997; Tam and Yuen, 2001).

One of the two studies that compared NSAIDs to local anesthesic, examined the use of Ketorolac (30 mg) i.m. given with an intracervical block 45 min before the procedure, and compared it with cervical block alone (Caligiani et al., 1994). This study reported a significant reduction in pain with the addition of Ketorolac; however, it did not report *P*-values and there were only 12 women in each arm of the study, making it difficult to draw strong conclusions from the results (Caligiani et al., 1994). The other study (Mercorio et al., 2002) compared oral Dexketoprofen (25 mg) ($n = 148$) in post-menopausal women with intracervical injection of 5 ml Mepivacaine 2% ($n = 150$) and found that Dexketoprofen was not superior to Mepivacaine in reducing the discomfort of the procedure but significantly reduced post-operative pain.

Two other studies compared NSAIDs to placebo. One study, evaluated the use of oral Diclofenac (50 mg) ($n = 92$) 1–2 h before the procedure and found that it did not significantly reduce the pain experienced compared with placebo ($n = 89$) (Tam and Yuen, 2001). Adverse effects occurred in the Diclofenac group (one woman had drug rash and one complained of epigastric pain). The other study compared the use of oral Mefenamic acid (500 mg) 1 h before the procedure ($n = 49$) with placebo ($n = 46$) (Nagele et al., 1997), showing that Mefenamic acid did not significantly reduce the pain of the hysteroscopy, however, it significantly reduced the pain experienced at 30 and 60 min. There was no report on adverse effects in this study.

A Cochrane review by Ahmad et al. (2010) evaluated the role of analgesics in reducing pain associated with outpatient hysteroscopy. It concluded that there was no significant reduction in the mean pain

Table III Base line characteristics and VAS pain scores in women with diagnosed intrauterine lesions and women with no intrauterine lesions.

	Diagnosed intrauterine lesion ($n = 20$)	No intrauterine lesions ($n = 190$)	*P*-value
Age (years)	31.7 ± 6.73	29.96 ± 6.25	0.176
Parity (proportion of parous women)	8 (40%)	83(43.6%)	0.273
BMI (kg/m^2)	26.05 ± 4.44	25.92 ± 4.43	0.902
Duration of the procedure (minutes)	1.9 ± 1.07	21 ± 0.91	0.648
Pain during the procedure	4.7 ± 2.29	5 ± 1.99	0.518
Pain immediately after the procedure	2.25 ± 1.64	2.71 ± 1.73	0.252
Pain 30 min after the procedure	0.675 ± 0.94	1.01 ± 1.36	0.282
Time until no pain (minutes)	29.06 ± 14.28	28.49 ± 15.34	0.998

Data are presented as mean ± SD or *n* (%).
Data were compared using the student *t*-test, Chi square test was used to compare parity and Kaplan–Meier plot was used to compare time until no pain.

score with the use of NSAIDS or opioid analgesics compared with placebo during or within 30 min after the procedure and recommended further studies to provide the necessary data on the efficacy of oral analgesics. The meta-analysis included only the study by Lin *et al.* (2005), to evaluate role of opioid analgesic and only the study by Tam and Yuen (2001) to evaluate role of NSAIDs. Both studies did not show significant reduction in mean pain score during or within 30 min of the procedure. However, this systematic review did not include the studies of Floris *et al.* (2007) and Bellati *et al.* (1998) which showed a significant reduction in pain with Tramadol. Also, in this systematic review (Ahmad *et al.*, 2010), no RCTs were identified comparing the use of oral opioid analgesics with placebo or no treatment. There was no report on the use of Celecoxib or any other non-selective COX 2 inhibitor.

To the best of our knowledge, this is the first trial to study oral Tramadol and oral Celecoxib (a selective COX-2 inhibitor) to reduce pain associated with hysteroscopy. Our results have shown that oral Tramadol (100 mg) and oral Celecoxib (100 mg) significantly reduced the pain during, immediately after and 30 min after the hysteroscopy compared with placebo. No significant difference in the mean pain scores was observed between Tramadol and Celecoxib whether during, immediately after or 30 min after the procedure. Time until no pain was significantly shorter with Tramadol and Celecoxib compared with placebo. No significant difference in time until no pain was observed between Tramadol and Celecoxib.

The peak plasma level of Tramadol is achieved at 1–3 h and that of Celecoxib at 2–3 h (Medsafe – New Zealand Medicines and Medical Devices Safety Authority, 2015a,b). We were guided by the time of administration used in similar studies in addition to convenience to the patient. Also, we have chosen the same time of administration for all medications to ensure equal treatment of all groups of patients to avoid bias. With the double blinding, it would not have been possible to administer medication with consideration of peak plasma level.

Four patients in the Tramadol group experienced nausea while no side effects were reported in the Celecoxib group, however a larger sample size is required before drawing firm conclusions about the lack of side effects. The data on time until no pain demonstrated the effectiveness of treatment compared with placebo, although it might be argued that it is of little clinical significance as the mean difference of 4 min might not be clinically valuable. A proper answer to that would require a patient questionnaire. We believe that the results of this study could have significant clinical implications as the lower pain scores in the treatment group with shorter time until no pain may have a positive impact on improving patient satisfaction and minimizing the rate of procedure failure due to pain. This is more true in the Celecoxib group who did not report side effects from treatment, further improving patient satisfaction by avoiding intolerable side effects.

Celecoxib, as a selective COX-2 inhibitor, has the advantage of avoiding the side effects of other non-selective NSAIDs as well as avoiding the side effects of opioids. Although there has been concern over the risk of major cardiovascular events (non-fatal myocardial infarction and stroke) with the use of selective COX-2 inhibitors, this risk was found to be dose dependent and similar to most non-selective NSAIDs (Bhala *et al.*, 2013).

Limitations of the study include the fact 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. Also, it was not possible to test different times of administration to coincide with peak plasma levels, as this would have affected blinding. Further studies are needed to test efficacy of Celecoxib with different times of administration before hysteroscopy to see if this will affect the perception of pain.

We conclude that the use of Tramadol and Celecoxib before hysteroscopy reduces the pain evoked by the procedure. Celecoxib is better tolerated with no reported side effects in the sample tested but further research on a larger sample size is needed to confirm these findings.

Authors' roles

All authors contributed in designing the study, conducting the study, collecting the data and revising the paper. A.H. performed the data and statistical analysis. A.W. wrote the main manuscript.

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Conflict of interest

None declared.

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