Efficacy and safety of tramadol in pain relief during diagnostic outpatient hysteroscopy: systematic review and meta-analysis of randomized controlled trials

Article *in* Fertility and Sterility · January 2019

DOI: 10.1016/j.fertnstert.2018.10.026

CITATIONS
12

READS
158

10 authors, including:

Omar Matter
Cairo University
28 PUBLICATIONS **482** CITATIONS
SEE PROFILE

Ahmed Ramadan Abdalla
Mansoura University
15 PUBLICATIONS **121** CITATIONS
SEE PROFILE

Mohamed Shehata
Zagazig University
27 PUBLICATIONS **306** CITATIONS
SEE PROFILE

Mohammad Sunoqrot
Cairo University
7 PUBLICATIONS **26** CITATIONS
SEE PROFILE

Efficacy and safety of tramadol in pain relief during diagnostic outpatient hysteroscopy: systematic review and meta-analysis of randomized controlled trials

Omar M. Mattar, M.B., B.S., M.Ch.,[a,b] Ahmed R. Abdalla, M.B., B.S., M.Ch.,[b,c] Mohamed S. A. Shehata, M.B., B.S., M.Ch.,[b,d] Ahmed Said Ali, M.B., B.S., M.Ch.,[b,e] Muhammed Sinokrot, M.B., B.S., M.Ch.,[a,b] Bassant A. Abdelazeim, M.B., B.S., M.Ch.,[a] Ayman Taher, M.D.,[f] Ahmed Samy, M.D.,[f] Mostafa Mahmoud, M.D.,[f] and Ahmed M. Abbas, M.D.[g]

[a] Kasr Al-Ainy Faculty of Medicine and [f] Department of Obstetrics and Gynaecology, Cairo University, [b] Medical Research Education and Practice Association (MREP), [e] Faculty of Medicine, Al-Azhar University, Cairo; [c] Faculty of Medicine, Mansoura University, Mansoura; [d] Faculty of Medicine, Zagazig University, Zagazig; and [g] Department of Obstetrics and Gynaecology, Faculty of Medicine, Assiut University, Assiut, Egypt

Objective: To evaluate the evidence about the safety and efficacy of tramadol in pain relief during diagnostic outpatient hysteroscopy (OH).
Design: Systematic review and meta-analysis of randomized controlled trials.
Setting: Not applicable.
Patient(s): Patients undergoing diagnostic OH received tramadol versus those who were administered placebo.
Intervention(s): Electronic databases were searched using the following MeSH terms (tramadol OR opioids OR opioid OR narcotic OR narcotics) AND (hysteroscopy OR hysteroscopic).
Main Outcome Measure(s): Pain assessed by visual analogue scale (VAS) during OH, immediately and 30 minutes after the procedure.
Result(s): One hundred thirteen studies were identified of which four randomized clinical trials were deemed eligible for this review (tramadol: n = 209; placebo: n = 209). The pooled estimate showed that tramadol significantly reduced VAS during procedure than placebo (weighted mean difference [WMD] = −1.33; 95% confidence interval [CI] −1.78 to −0.88, I^2 = 3%, P = .36). In addition, tramadol significantly reduced VAS immediately after the procedure (WMD = −1.05; 95% CI −1.49 to −0.61, I^2= 0, P = .84) and 30 minutes after (WMD = −0.98; 95% CI −1.30 to −0.65, I^2 = 0, P = .88).
Conclusion(s): This meta-analysis suggests that tramadol is safe, effective, and gives favorable results in reducing pain during diagnostic OH. (Fertil Steril® 2019;111:547–52. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Outpatient hysteroscopy, tramadol, narcotics, pain relief

Hysteroscopy is currently the most informative investigation for women with abnormal uterine bleeding and infertility (1). Outpatient hysteroscopy (OH) involves the use of miniaturized endoscopic equipment to directly visualize the endometrial cavity without the need of formal theatre facilities or anesthesia (2). This procedure offers some advantages, such as the avoidance of general anesthesia and the reduction of costs for the Public Health Service because of hospitalization. Compared with blind procedures, hysteroscopy provides a detailed description of uterine and endometrial abnormalities (3).

The emergence of pain is usually a two-step process involving the cervical dilatation and the dilation of the uterine cavity by advancing through the

Received August 23, 2018; revised and accepted October 25, 2018; published online January 30, 2019.
O.M.M. has nothing to disclose. A.R.A. has nothing to disclose. M.S.A.S. has nothing to disclose. A.S.A. has nothing to disclose. M.S. has nothing to disclose. B.A.A. has nothing to disclose. A.T. has nothing to disclose. A.S. has nothing to disclose. M.M. has nothing to disclose. A.M.A. has nothing to disclose.
Reprint requests: Ahmed M. Abbas, M.D., Department of Obstetrics and Gynaecology, Assiut University, Women Health Hospital, Assiut, Egypt (E-mail: bmr90@hotmail.com).

Fertility and Sterility® Vol. 111, No. 3, March 2019 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.10.026

isthmus and placing the hysteroscopy device. Due to these factors, many centers prefer to administer general anesthesia to their patients undergoing OH. Several approaches, such as analgesia or local anesthesia, have been used in an attempt to reduce the discomfort associated with hysteroscopy.

Among these, orally administered mefenamic acid or dexketoprofen and celecoxib reduce the pain after hysteroscopy, although they fail to eliminate the discomfort occurring during the procedure (4). Also, topical anesthesia before hysteroscopy provided only limited benefits.

Tramadol is an opioid analgesic with a central mechanism of action thought to be produced by the release of serotonin and inhibition of the neural uptake of noradrenalin. Its analgesic effects usually start 1 hour after administration, reaching a peak at 2 hours, and lasting nearly 4–8 hours (5).

Tramadol shows some effectiveness in OH, as discussed in our article. The aim of this systematic review and meta-analysis is to synthesize evidence from published randomized clinical trials about the safety and efficacy of tramadol in pain reduction during diagnostic OH.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (6). Because this study was a systematic review and meta-analysis, formal ethical approval was not required.

Search Strategy

A detailed search was conducted using several electronic databases included MEDLINE, EMBASE, Dynamed Plus, ScienceDirect, TRIP database, ClinicalTrials.gov, and the Cochrane Library. Combinations of the following MeSH terms were used: (tramadol OR opioids OR opioid OR narcotic OR narcotics) AND (hysteroscopy OR hysteroscopic). We conducted a manual search of the references of included studies and previously published systematic reviews to retrieve studies that were not identified by database searching.

The title and abstract searches were also done. Research articles and conference abstracts were limited to English language. One investigator (O.M.M.) performed the searches and all identified articles were retrieved, and their reference lists were checked manually for further relevant studies.

Eligible Criteria

We included all published randomized clinical trials that compared the efficacy and safety of tramadol versus placebo or any other active drug in pain relief during diagnostic OH. There was no restriction regarding age, ethnicity, location, and publication date.

We excluded studies for the following reasons: [1] non-English studies, [2] conferences, books, review articles, posters, thesis, editorial, notes, letters, case series, and case reports, [3] unreliable extracted data, overlapped data sets, and only abstract available, and [4] animal studies.

Study Selection

Title and abstract of all identified articles were screened independently by four reviewers to assess relevance to this meta-analysis. In case of disagreement, the full text was retrieved and reviewed independently by a senior author (A.M.A.) for a final decision.

All identified articles were evaluated according to a standardized format including study design, methods, participant characteristics, intervention, and results. Two investigators (B.A.A., M.S.) scored the studies and collected the information independently. In case of discrepancies in scoring, a consensus was reached after discussion.

Data Extraction and Analysis

The extracted data included age, body mass index (BMI) in mean and SD, and parity (in number and percentage). Baseline data, such as duration and indication of the procedure, were also extracted. The extracted outcome was pain assessed by visual analogue scale (VAS) during three time periods (during the procedure, immediately after the procedure, and 30 minutes after the procedure). We used R software (package meta, version 4.9-2) for Windows during data synthesis.

The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous data. Relative risk and 95% CI were calculated for dichotomous data. Statistical heterogeneity among studies was assessed by I^2 statistics and values of $\geq 50\%$ were indicative of high heterogeneity (7). In case of significant heterogeneity, a random-effect model was used for meta-analysis. Otherwise, the fixed effect model was used. Subgroup analysis according to the tramadol dose was conducted.

Quality of Included Studies and Risk of Bias Assessment

The risk of bias was assessed according to the Cochrane risk of bias tool, which is described in Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. (8). The Cochrane Collaboration risk of bias tool includes six domains, namely random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The reviewers rated the quality of the included studies as low risk, high risk, or unclear risk of bias. The number of included studies in the analysis was >10, therefore we cannot assess the publication bias using Egger test (9).

RESULTS

Search Results Characteristics of Included Studies

The searching process returned 113 records. We removed the duplicates using Endnote software. Of the remaining 58 records screened by title/abstract 8 records were eligible. After reading the full-text of the eight studies we excluded four

studies, which were ineligible according to the criteria. We searched the references of the included studies manually, but no further records were added to the included studies. The four randomized clinical trials recruiting 488 patients who underwent hysteroscopy were included (Fig. 1). Tramadol was used to control pain resulting from the procedure in 209 patients. Similarly 209 patients took placebo (10–12). A total of 70 patients took celecoxib for pain control (13). The characteristics of the four studies are shown in Table 1.

Risk of Bias Assessment

We used the Cochrane Collaboration's tool to assess the risk of bias. The studies showed high quality in most criteria except for "allocation concealment." The results are represented in Supplemental Figure 1 (available online).

Outcomes

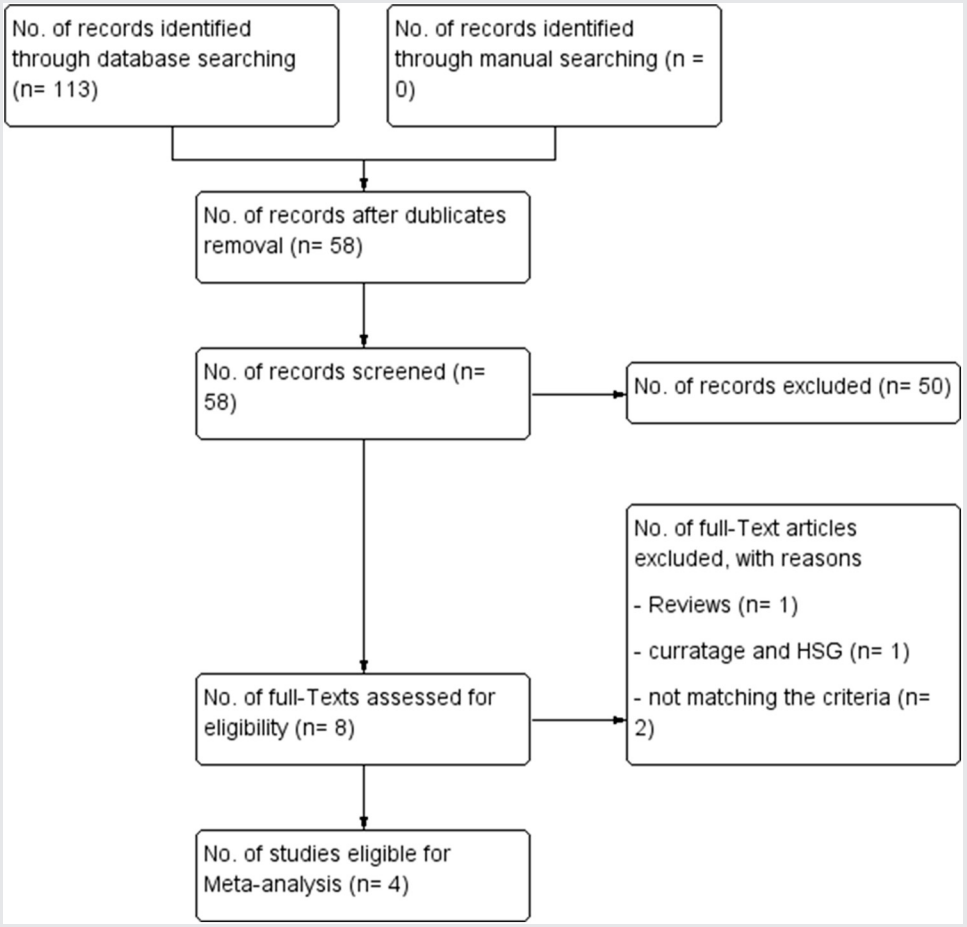
Primary outcome: VAS during procedure. The pooled estimate showed that tramadol significantly reduced VAS during the procedure more than in the placebo group (WMD = −1.33; 95% CI −1.78 to −0.88; Fig. 2). This translates to an average difference from placebo of about 1.33 cm on a 10-cm VAS scale. No significant heterogeneity was observed (I^2 = 3%, P = .36).

Kadiroğulları et al. (12) reported the median VAS score for tramadol and placebo group to be 3.6 and 5.9, respectively. There is a significant difference favoring the tramadol group.

Secondary outcomes: VAS immediately after procedure. The pooled estimate showed that tramadol significantly reduced VAS immediately after the procedure (WMD = −1.05; 95% CI −1.49 to −0.61; Supplemental Fig. 2, available online). This means that there is an average difference from placebo of about 1.05 cm. No significant heterogeneity was observed (I^2 = 0, P = .84).

Secondary outcomes: VAS after 30 minutes. The pooled effect size showed that the tramadol significantly reduced VAS after 30 minutes (WMD = −0.98; 95% CI −1.30 to −0.65; Supplemental Fig. 3, available online). This translates to an average difference from placebo of about 0.98 cm. No significant heterogeneity was observed (I^2 = 0, P = .88).

FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart of the study selection process.

Mattar. Tramadol as analgesic in hysteroscopy. Fertil Steril 2018.

TABLE 1

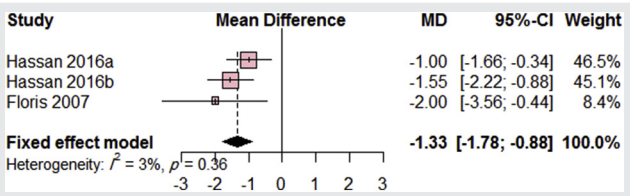
Baseline patient characteristics of included studies.

Study ID	Study groups	Age (y)	BMI	Number of parous women (%)	Duration of procedure (min)	Infertility	Indication of procedure		
							Recurrent miscarriage	Abnormal bleeding	Uterine lesion
Floris et al. 2007 (10)	IV tramadol (100 mg/2 mL)	47.2 ± 2.8	NA	25 (100)	1.64 ± 0.16	NA	NA	10 (40)	14 (56)
	Placebo	44.3 ± 2.5	NA	25 (100)	1.64 ± 0.19	NA	NA	8 (32)	17 (68)
Hassan and Haggag 2016 (11)	Oral tramadol (50 mg)	31.5 ± 7.4	29.1 ± 2.9	NA	2.4 ± 1.2	30 (43)	16 (23)	17 (24)	7 (10)
	Placebo	32.3 ± 8.1	28.8 ± 2.8	NA	2.1 ± 1.1	32 (46)	19 (27)	14 (20)	5 (7)
Hassan et al. 2016 (13)	Oral tramadol (100 mg)	29.25 ± 6.39	25.77 ± 4.37	25 (35.7)	1.92 ± 0.98	39 (55.8)	10 (14.2)	16 (22.9)	5 (7.1)
	Celecoxib (200 mg)	29.52 ± 6.44	26.18 ± 4.47	32 (45.7)	2.01 ± 0.97	36 (51.4)	6 (8.6)	22 (31.4)	6 (8.6)
	Placebo	30.8±6.0	25.84±4.46	34 (48.5)	2.02 ± 0.83	34 (48.6)	4 (5.7)	27 (38.6)	5 (7.1)
Kadiroğullari et al. 2016 (12)	Oral tramadol (100 mg)	45 ± 1.4	27 ± 2.8	NA	NA	NA	NA	15 (34.1)	29 (65.9)
	Placebo	44.08 ± 1.3	28.2 ± 1.9	NA	NA	NA	NA	19 (43.2)	25 (56.8)

Note: Data are presented as mean ± SD or n (%). BMI = body mass index; NA = not available.

Mattar. Tramadol as analgesic in hysteroscopy. Fertil Steril 2018.

FIGURE 2



Forest plot for visual analogue scale during procedure.

Mattar. Tramadol as analgesic in hysteroscopy. Fertil Steril 2018.

Subgroup Analysis According to the Tramadol Doses

The results of subgroup analysis according to the tramadol doses were consistent with the overall pooled estimate. Tramadol (100 mg) significantly reduced VAS during the procedure (WMD = −1.62; 95% CI −2.24 to −1.00), VAS immediately after procedure (WMD = −1.09; 95% CI −1.67 to −0.51), and VAS 30 minutes after the procedure (WMD = −0.95; 95% CI −1.41 to −0.49) compared with placebo. In addition, tramadol (50 mg) significantly reduced VAS during the procedure (WMD = −1.00; 95% CI −1.66 to −0.34), VAS immediately after procedure (WMD = −1.00; 95% CI −1.66 to −0.34), and VAS 30 minutes after the procedure (WMD = −1.00; 95% CI −1.46 to −0.54) compared with placebo.

Safety and Adverse Effects

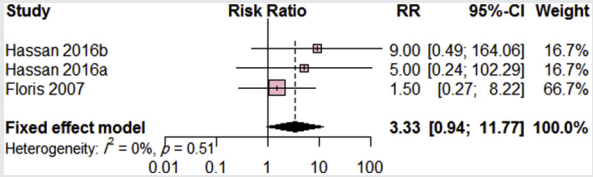
The pooled results of three studies reporting nausea showed no significant difference between the two groups (relative risk = 3.33; 95% CI 0.94 to 11.77; Fig. 3). Two patients in the placebo group were unable to continue the study (11, 13). Also, Floris et al. (10) reported vomiting and bradycardia in the tramadol and the placebo groups as 1 of 25 patients versus 0 of 25 patients and 4 of 25 patients versus 3 of 25 patients, respectively.

DISCUSSION

To our knowledge this is the first systematic review and meta-analysis to investigate the efficacy and safety of tramadol in pain relief during diagnostic OH. This was estimated by VAS score during and after the procedure.

Recently, OH is gaining popularity; however, the lack of appropriate analgesia is a major limitation. The current systematic review and meta-analysis proved the effectiveness of

FIGURE 3



Forest plot for adverse effects of tramadol.

Mattar. Tramadol as analgesic in hysteroscopy. Fertil Steril 2018.

tramadol (compared to placebo) in reducing pain during, immediately after, and ≤30 minutes after the procedure. This was held true whether tramadol was given orally or intravenously. Although not included in our review, Bellati et al. (14) proved the effectiveness of IM tramadol versus no treatment. Tramadol was statistically superior to placebo by around 1 cm on a 10-cm VAS scale during and ≤30 minutes after the procedure. However, the clinical relevance of such a value cannot be determined due to lack of studies defining the clinically important difference in gynecological procedures.

Regarding the safety of tramadol, there are no major concerns as all studies reported that adverse events (nausea, vomiting, and bradycardia) were not significantly different from placebo. There is no consensus on the best pain management protocol. Several factors affect the severity of pain perceived by the women undergoing OH (e.g., nulliparity, menopause, cervical synechiae, patient's anxiety level, using a speculum or a tenaculum and the hysteroscope diameter). All factors are associated with increased pain intensity (15, 16). Kadroğullari et al. (12) was the only study using a 5-mm-thick hysteroscope, which might explain the loss of efficacy 15 minutes after the procedure. The other factors were either heterogeneous or not reported in some studies, therefore we cannot judge whether they affected the pain score.

Several anesthetic and analgesic techniques have been studied, yet the ideal analgesic is still out of reach. These include oral or IV opioids, nonsteroidal anti-inflammatory drugs, and local anesthetics using intracervical injection, paracervical block, transcervical instillation, or topical anesthetic gel or cream. A recent Cochrane review and meta-analysis by Ahmad et al. (17) showed that local anesthetics were statistically superior to placebo or no treatment but the effect size was too small to be clinically important. Subgroup analysis was only significant in the intracervical injection group.

Another meta-analysis by Cooper et al. (18) showed that only paracervical and intracervical injections were significantly different from control, whereas topical anesthetics, misoprostol, and transcervical injections were not. A major drawback of local anesthetics is that their administration can be more painful than the procedure itself (19).

Regarding the effectiveness of tramadol, Ahmad et al. (17) only included two studies, Hassan and Haggag (11) and the other one is Hassan et al. (13). Both articles were not combined in a meta-analysis model, therefore our review should provide a better insight.

Compared with other analgesics, IM tramadol was superior to an intracervical injection of mepivacaine (14). On the other hand, oral tramadol was not significantly different from oral celecoxib, but the lack of adverse events might favor celecoxib (13).

The main limitations in this review are the small number of included studies and our inability to get all the data needed from the investigators. We did not identify any potential biases in the review process. High-quality, large-scale studies are needed to establish the best dose and route of administration and also to determine which group of patients is more likely to benefit from tramadol. In addition, studies comparing tramadol with other analgesics are also needed. In conclusion this systematic review and meta-analysis suggests that tramadol is an effective and safe option for pain relief during diagnostic OH.

REFERENCES

1. Gimpelson RJ, Rappold HO. A comparative study between panoramic hysteroscopy with direct ed biopsies and dilatation and curettage: a review of 276 cases. Am J Obstet Gynecol 1988;158:489–92.
2. Mercorio F, de Simone R, Landi P, Sarchianaki A, Tessitore G, Nappi C. Oral dexketoprofen for pain treatment during diagnostic hysteroscopy in postmenopausal women. Maturitas 2002;43:277–81.
3. Sharma JB, Aruna J, Kumar P, Roy KK, Malhotra N, Kumar S. Comparison of efficacy of oral drotaverine plus mefenamic acid with paracervical block and with intravenous sedation for pain relief during hysteroscopy and endometrial biopsy. Ind J Med Sci 2009;63.
4. Van Dongen H, de Kroon CD, Jacobi CE, Trimbos JB, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG 2007;114:664–75.
5. Lewis KS, Han NH. Tramadol: a new centrally acting analgesic. Am J Health Syst Pharm 1997;54:643–52.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;18:W65–94.
7. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
8. Green S, Higgins P, TJ, Alderson P, et al. Assessing risk of bias in included studies, Ch 8. In: Cochrane Handbook for Systematic Reviews of Interventions; 2011:3–10.
9. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
10. Floris S, Piras B, Orrù M, Silvetti E, Tusconi A, Melis F, et al. Efficacy of intravenous tramadol treatment for reducing pain during office diagnostic hysteroscopy. Fertil Steril 2007;87:147–51.
11. Hassan A, Haggag H. Role of oral tramadol 50 mg in reducing pain associated with outpatient hysteroscopy: a randomised double-blind placebo-controlled trial. ANZ J Obstet Gynaecol 2016;56:102–6.
12. Kadiroğulları P, Seçkin KD, Yücel B, Çetin BA, Barut SA, Yıldırım G. Analgesic efficiency of tramadol administered prior to hysteroscopy procedure. Gynecol Obstet Reprod Med 2016;22:152–5.
13. Hassan A, Wahba A, Haggag H. Tramadol versus celecoxib for reducing pain associated with outpatient hysteroscopy: a randomized double-blind placebo-controlled trial. Hum Reprod 2016;31:60–6.
14. Bellati U, Bonaventura A, Costanza L, Zulli S, Gentile C. Tramadol hydrochloride versus mepivacaine hydrochloride: comparison between two analgesic procedures in hysteroscopy. Giornale Italiano di Ostetricia e Ginecologia 1998;20:469–72.
15. De Freitas Fonseca M, Sessa FV, Resende JA Jr, Guerra CG, Andrade CM Jr, Crispi CP. Identifying predictors of unacceptable pain at office hysteroscopy. J Minim Invasive Gynecol 2014;21:586–91.
16. Carta G, Palermo P, Marinangeli F, et al. Waiting time and pain during office hysteroscopy. J Minim Invasive Gynecol 2012;19:360–4.
17. Ahmad G, O'Flynn H, Duffy JM, Attarbashi S, Pickersgill A, Watson A. Pain relief for office gynaecological procedures. Cochrane Database Syst Rev 2009;2.
18. Cooper NA, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis. BMJ 2010;340:c1130.
19. Keyhan S, Munro MG. Office diagnostic and operative hysteroscopy using local anesthesia only: an analysis of patient reported pain and other procedural outcomes. J Minim Invasive Gynecol 2014;21:791–8.

Eficacia y seguridad del tramadol en el alivio del dolor durante la histeroscopia diagnóstica ambulatoria: revisión sistemática y metaanálisis de ensayos controlados aleatorizados

Objetivo: Evaluar la evidencia sobre la seguridad y la eficacia de tramadol en el alivio del dolor durante la histeroscopia diagnóstica ambulatoria (HSC).

Diseño: Revisión sistemática y metaanálisis de ensayos controlados aleatorizados.

Configuración: No aplicable.

Pacientes (s): Pacientes sometidos a una HSC diagnóstica que recibieron tramadol frente a los que recibieron placebo.

Intervención (es): Se realizaron búsquedas en las bases de datos electrónicas utilizando los siguientes términos de MeSH (tramadol O opioides O opioides O narcóticos) E (histeroscopia O histeroscópico).

Principales variables de resultado: El dolor evaluado por la escala analógica visual (VAS) durante la HSC, inmediatamente y 30 minutos después del procedimiento.

Resultado (s): Se identificaron ciento trece estudios, de los cuales cuatro ensayos clínicos aleatorizados se consideraron elegibles para esta revisión (tramadol: n = 209; placebo: n = 209). La estimación combinada mostró que el tramadol redujo significativamente el VAS durante el procedimiento comparado con el placebo (diferencia de medias ponderada [DMP] = -1.33; intervalo de confianza del 95% [IC] 1.78 a -0.88, $I^2 = 3\%$, P = 0.36). Además, el tramadol redujo significativamente el VAS inmediatamente después del procedimiento (DMP = - 1,05; IC del 95%: -1,49 a - 0,61, $I^2 = 0$, P = 0.84) y 30 minutos después (WMD = - 0,98; IC del 95%: -1,30 a -0,65, $I^2 = 0$, P = 0.88).

Conclusión(s): Este metanálisis sugiere que el tramadol es seguro, eficaz y brinda resultados favorables para reducir el dolor durante la HSC diagnóstica.