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CLINICAL ARTICLE

A randomized, placebo-controlled, double-blind study of hysteroscopic-guided pertubal diluted bupivacaine infusion for endometriosis-associated chronic pelvic pain

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ABSTRACT

Objective: To assess the effectiveness of hysteroscopic-guided pertubal diluted bupivacaine infusion for endometriosis-associated chronic pelvic pain (CPP). *Methods:* Between June 2010 and July 2013, a randomized, placebo-controlled, double-blind study was undertaken at Mansoura University Hospital, Mansoura, Egypt. Patients meeting inclusion criteria (laparoscopically confirmed endometriosis, patent fallopian tubes, ≥6 months CPP, pain score on visual analogue scale [VAS] >5) were randomly assigned using a computer-generated randomization sequence to receive either office hysteroscopic-guided pertubal diluted bupivacaine infusion (0.25%) or placebo. Response to treatment was assessed using subjective data for scores on VAS and a monthly verbal rating scale ($VRS_{monthly}$) at baseline and at 1, 2, and 3 months of follow-up. Additionally, women completed a questionnaire to evaluate the overall satisfaction at 3 months. *Results:* Thirty patients were assigned to each group. In the bupivacaine group, VAS and $VRS_{monthly}$ scores were significantly lower at 1, 2, and 3 months than at baseline ($P < 0.05$ for all). Additionally, scores were significantly lower in the bupivacaine group than in the placebo group at 1, 2, and 3 months ($P < 0.05$ for all). At 3 months, 22 (73%) women in the bupivacaine group expressed satisfaction, compared with 2 (7%) in the placebo group ($P = 0.18$). *Conclusion:* Office pertubal hysteroscopic-guided diluted bupivacaine infusion could be used to manage endometriosis-associated CPP for at least 3 months.
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1. Introduction

The successful treatment of endometriosis-associated chronic pelvic pain (CPP) typically requires surgical and medical interventions. Some pharmacologic treatments inhibit the growth and activity of endometrial implants, such as combination oral contraceptives, danazol (an androgenic agent), gonadotropin-releasing hormone analogues, progestins, aromatase inhibitors, selective estrogen receptor modulators, and selective progesterone receptor modulators [1–4]. Locally long-acting pharmacologic agents that can specifically target the endometrial implants rather than systemically reducing estrogen levels have not yet been assessed fully in clinical practice. However, pertubation with lignocaine has been shown to be an effective non-hormonal treatment option for women with dysmenorrhea and pelvic endometriosis [5–7].

In an open-label preliminary observational pilot study at Mansoura University Hospital, Mansoura, Egypt, office hysteroscopic-guided pertubal bupivacaine infusion (0.25%) was shown to reduce CPP intensity in women with stage I–IV pelvic endometriosis (unpublished data). Bupivacaine is more cardiotoxic than are other local anesthetics [4]. Most of its adverse effects are caused by accelerated absorption from the injection site, unintentional intravascular injection, or slow metabolic degradation. However, several clinical trials have confirmed the safety of this local anesthetic drug [8–10].

Notably, the effectiveness of pertubal diluted bupivacaine infusion (0.25%) has not been tested against placebo. The aim of the present study was to assess the short-term effectiveness of the office hysteroscopic-guided pertubal diluted bupivacaine infusion (0.25%) for endometriosis-associated CPP in a randomized, placebo-controlled trial.

2. Materials and methods

Between June 1, 2010, and July 30, 2013, a randomized, placebo-controlled, double-blind study was conducted at Mansoura University Hospital. Women were eligible when they had experienced CPP for at least 6 months, had a pain score on the visual analogue scale (VAS) of more than 5 (0–10 scale), had laparoscopically confirmed stage I–IV

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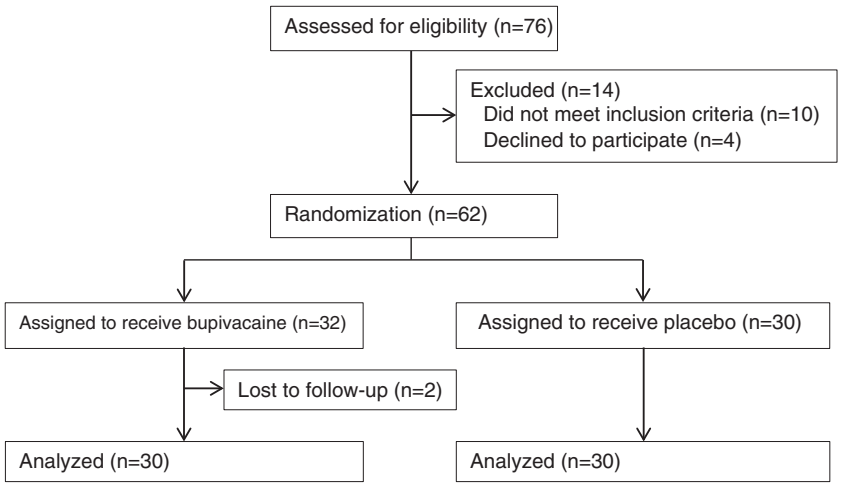

Fig. 1. Study profile.

pelvic endometriosis, and had patent fallopian tubes. Exclusion criteria were age younger than 18 years, any hormonal therapy in the previous 3 months, a desire to conceive within 1 year, occluded fallopian tubes with or without pelvic adhesions, non-gynecologic causes of CPP (intestinal, urinary, or musculoskeletal), and known hypersensitivity or contraindications to bupivacaine or any amide local anesthetic agent. The institutional ethics committee approved the study. All participants provided written informed consent.

Patients were asked to stop any analgesic medications before enrollment into the study. Potential participants underwent a complete pelvic examination and high-resolution transvaginal ultrasonography. Basic work-up investigations were done whenever indicated to exclude concomitant non-gynecologic causes of CPP, including mid-stream urine analysis, stool analysis, intravenous urography, and full blood count.

At the time of office recruitment, participants were randomly assigned to receive bupivacaine or placebo in a 1:1 ratio according to a computer-generated randomization sequence using numbered, sealed envelopes. All patients and investigators were masked to group allocation, including during data analysis.

Procedures were undertaken as a day-case in an endoscopic suite. One treatment was to be given before ovulation on day 7–12 of their cycle. Under paracervical block and using Ringer solution as a uterine distending medium (Hysteromat, Karl Storz, Tuttlingen, Germany), an office hysteroscope (2.7 mm; Karl Storz, Tuttlingen, Germany) was passed and one tubal orifice was identified. Under hysteroscopic guidance, a 3-Fr ureteric catheter was introduced, cannulated through the tubal ostium, and passed proximally for 2–3 cm. After successful cannulation, participants assigned to the bupivacaine group received 10 mL diluted bupivacaine (0.25%; Marcaine, AstraZenica, Istanbul, Turkey) plus 100 mL Ringer solution, which was infused through the catheter over 15–20 minutes. Participants assigned to the placebo group received a 10-mL placebo infusion (sterile water) plus 100 mL Ringer solution. The allocated study solution was provided to the surgeon intraoperatively by senior nursing staff. Solutions were indistinguishable and were preloaded into identical unlabeled Ringer solution bottles.

None of the patients used any adjunctive measures or analgesics following the original treatment. Follow-up visits were arranged after 1, 2, and 3 months. Patients were advised to stop any analgesic medications and to use barrier contraception for these 3 months. All patients completed a daily diary about pain during the month preceding the procedure and follow-up visits. These diaries were collected at each visit; new ones for the next month were provided.

As part of the diary, participants were asked to provide a subjective assessment of the severity of pelvic pain on a VAS, on which 0 indicated no pain and 10 indicated severe pain. It was recorded daily on a 10-cm ruler in the diary. Mean VAS scores for the month were calculated for each patient. At monthly follow-up appointments, participants were asked to provide a monthly pain score on a verbal rating scale ($VRS_{monthly}$), on which a score of 0 indicated no pain and 100 indicated the maximum pain.

After 3 months, participants were asked to complete a multiple-choice questionnaire that assessed overall patient satisfaction independent of age, duration or severity of the symptoms.

Sample size was calculated using Epi Info version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA), setting the type I error (α) at 0.05 and the power ($1-\beta$) at 0.8. Using data from previous studies [5–7] and a 95% confidence interval, a minimum sample size of 60 patients was established.

Epi Info version 6.0 was used to record and analyze the data. Only women who completed 3 months of follow-up were included in analyses. The paired *t* test, Mann–Whitney *U* test, and Wilcoxon and Friedman two-way ANOVA tests were used as appropriate. $P < 0.05$ was deemed significant.

3. Results

A total of 76 patients were enrolled. Data from 60 were included in analyses (Fig. 1). After identification, the baseline clinical characteristics for both groups were comparable in terms of age, parity, body mass index, and laparoscopic endometriosis staging (Table 1).

In the bupivacaine group, VAS and $VRS_{monthly}$ scores were significantly lower at 1, 2, and 3 months than at baseline (Table 2). Additionally, the scores on both scales were significantly lower in the bupivacaine group than in the placebo group at 1, 2, and 3 months

Table 1
Baseline characteristics.[a]

Measure	Bupivacaine group (n = 30)	Placebo group (n = 30)	*P* value[b]
Age, y	32.8 ± 5.0	33.0 ± 2.6	0.63
Parity	2.7 ± 1.2	3.0 ± 1.1	0.39
Body mass index[c]	27.2 ± 2.1	29 ± 1.0	0.65
Laparoscopic staging			0.90
Stage I	14 (47)	16 (53)	
Stage II	10 (33)	8 (27)	
Stage III	4 (13)	4 (13)	
Stage IV	2 (7)	2 (7)	

[a] Values are given as mean ± SD or number (percentage), unless indicated otherwise.
[b] Continuous data analyzed using *t* test when normally distributed and Wilcoxon rank-sum test when not normally distributed. Categorical data analyzed using Fisher exact test.
[c] Calculated as weight in kilograms divided by the square of the height in meters.