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Original Article

Effect of oral hyoscine-N-butyl bromide on pain perception during hysterosalpingography: A randomized, double-blind, placebo controlled trial

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ABSTRACT

Objectives: The current study aims to investigate the analgesic effect of oral hyoscine-N-butyl bromide (HBB) for alleviating pain during hysterosalpingography (HSG).
Study design: Randomized, double-blind, placebo-controlled study.
Study setting: Assiut University Hospital, Egypt.
Materials and methods: The study was conducted between March and May 2016. Infertile women scheduled for HSG were randomized (1:1) to HBB or Placebo group. All women received oral 20 mg HBB or placebo tablets 30 min before the procedure. The primary outcome was the participant's self-rated pain perception utilizing a 10-cm Visual Analogue Scale (VAS) with 0 = no pain, and 10 = worst imaginable pain during the HSG procedure.
Results: Ninety-four women were enrolled (n = 47 in each group). No difference in the baseline characteristics. Oral HBB does not reduce the median VAS pain scores during injection of the dye (3.75 vs. 4.5, p = 0.195), immediately post-procedure (3 vs. 3, p = 0.102) and 30 min post-procedure (2 vs. 2.5, P = 0.745). No significant differences in women satisfaction score (p = 0.302). The rate of side effects was higher in the HBB group especially nausea (14.9%) and dizziness (10.6%) (p = 0.0001).
Conclusion: Utility of oral HBB 30 min before HSG has no benefit in alleviating the induced pain during and 30 min after the HSG procedure.

1. Introduction

Infertility, which is defined as the failure of couple to conceive during 12 months of regular unprotected intercourse [1], estimated to affect between 6.6 and 26.4% of reproductive-aged women in developed countries [2]. Out of the causes of female infertility, tubal abnormalities account for 30–40% of cases [3].

Hysterosalpingography (HSG) is considered the initial diagnostic tool for assessment of tubal patency. Additionally, it can be useful in the diagnosis of intrauterine pathology [4]. The procedure entails visualization of the uterine and tubal cavities radiographically through transcervical injection of radiocontrast dye [5]. However, cervical instrumentation, uterine distension with injection of the dye or peritoneal irritation as a result of its spill into the peritoneal cavity can lead to considerable pain that might affect women's cooperation during the procedure [6].

The main cause of pain experienced during HSG is thought to be related to the uterine distension with the dye resulting in release of local prostaglandins, which provoke uterine cramps [7]. The pain is transmitted through the pelvic splanchnic nerves (S2-S4) from the lower part of the uterus with the cervix and hypogastric nerves (T10-L1) from the uterine fundus and body of the uterus [8]. Many different modalities have been evaluated to prevent pain perception during HSG. These include oral, intravenous, intrauterine and topical analgesics [9]. However, there is no consensus in the literature regarding the optimal method for pain relief during the procedure.

Hyoscine n-butyl bromide (HBB) is an antispasmodic drug with peripheral anticholinergic effects on gastrointestinal, biliary and genitourinary system smooth muscle [10,11]. It has a similar structure to acetylcholine, so it blocks impulses transmission in parasympathetic ganglia with a rapid onset of action within 30 min from oral intake [12]. HBB has been commonly used for

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analgesic purposes in ureteral or renal colic, intestinal colic and labor analgesia [13–15].

Previous studies attempted to use HBB for pain relief during gynecological procedures reported no benefit from its use as analgesic during saline infusion sonohysterography (SIS) or hysterosalpingo-contrast sonography (HyCoSy) [12,16]. This could be attributed to the lower dose of oral HBB (10 mg) used in both studies. Since antispasmodic drugs are used for relief of muscle spasms, our hypothesis is that HBB, a muscarinic receptor antagonist with anticholinergic effects, can reduce HSG-associated pain through relief of uterine spasm.

To the best of our knowledge, no study has examined the efficacy of oral HBB on reducing HSG-associated pain. So, the aim of our study was to evaluate the efficacy of oral hyoscine-N-butyl bromide for pain relief during HSG.

2. Materials and methods

In this randomized, double-blind, placebo-controlled trial, all consecutive infertile women, attended the Infertility Clinic, Department of Obstetrics and Gynecology, Assiut University Hospital, Egypt between the 1st of March and the 31st of May 2016, were invited to participate in the study. This trial was registered at Clinical Trials.Gov (NCT02709603).

All eligible participants included in the study signed a written informed consent before participation after explaining the nature of the study. We included infertile women, aged 20–42 years old, and did not receive any analgesics or misoprostol in the 24 h prior to HSG. We excluded women with hypersensitivity or contraindication to hyoscine, abnormal uterine bleeding, acute cervicitis and suspected pregnancy. The Institutional Research Ethical Review Board approved the study.

Participants were randomized in a 1:1 ratio to receive active or placebo treatment. A statistician, not otherwise involved in the study, prepared a computer generated randomization tables and placed the allocation data in a serially numbered sealed envelopes. Each envelope had a card noting the intervention type inside. The envelopes opened only by a study researcher according to the order of attendance of women. Once allocation had been done, it could not be changed.

We randomly assigned all women into one of two groups: **(hyoscine-N-butylbromide, group):** received two tablets of 10 mg HBB (Buscopan®; Boehringer ingelheim International GmbH, Germany), and **(Placebo group):** received two placebo tablets of the same size, color and shape of HBB. The placebo tablets were manufactured by a pharmacist in the department of Pharmaceuticals, Faculty of Pharmacy. All study medications were packed by the same pharmacist into unlabeled sterile boxes, so neither the clinicians nor the women knew the type of the preparation (double-blind study).

One of the study researchers approached all included women and collected their baseline characteristics: age, parity, residence, educational level, previous miscarriages, vaginal or cesarean delivery, type and duration of infertility, history of dysmenorrhea or chronic pelvic pain, and history of previous HSG. Then, he explained the standard 10-cm visual analog scale (VAS) to the participants for pain scoring [17]. The severity of pain was assessed with VAS (with 0 = no pain and 10 = worst imaginable pain). Finally, he instructed the women to take the tablet 30 min before HSG.

All women were scheduled for HSG between day 6 and 10 of their menstrual cycle. A single experienced radiologist performed the HSG. Women were placed in the lithotomy position on a fluoroscopic table. The radiologist placed a sterile speculum into the vagina and cleansed the cervix with povidone-iodine. Then, the anterior lip of the cervix was grasped with a tenaculum and a sterile Rubin's cannula was inserted into the cervical canal. A 15 ml water-soluble contrast dye (Sodium amidotrizoate and meglumine at 76% Urografin® Bayer Hispania SL; Barcelona; Spain) was injected over 20 s into the uterine cavity. Radiographic images were taken in the anteroposterior view when the uterine cavity was fully filled with the dye. Finally, all instruments were removed, and women were observed in the clinic for 30 min.

Participants were asked to rate the intensity of pain experienced during HSG six times; before starting the procedure (anticipated pain), after speculum placement, after tenaculum placement, after injection of the dye, immediately and 30 min following the end of the procedure using the same 10-point VAS. Also, all women expressed their level of satisfaction with HSG at 30 min post procedure by completing a 10-cm VAS (with 0 = no satisfaction and 10 = maximum satisfaction). This score was used before in many studies [18,19]. All women were asked about the need for any additional analgesics at 30 min post-procedure. Women were offered diclofenac potassium 50 mg as an additional analgesic if needed as it was readily available in our clinic. All women were asked to report any side effects occurred during and within 30 min after HSG like; syncope, dizziness, nausea or vomiting. The duration and the results of HSG were also included in the final analysis.

The primary outcome was the difference in mean pain score during the procedure. The secondary outcomes included the difference in mean pain scores immediately and 30 min after HSG, the difference in women's satisfaction score, the number of women who need additional analgesics, and the side effects of the study medications

Sample size calculation was based on the VAS score during the most painful step of the HSG procedure. In the most recent RCT by Karaman et al. [20] for pain relief during HSG, the most painful mean VAS score was 5.3 with standard deviation (SD = 1.1) in the placebo group during injection of the dye. We considered a 15% reduction to an overall VAS score of 4.5 (SD = 0.9) in the active treatment group as significant. With an alpha error of 0.05, a statistical power of 95%, a sample size of at least 47 women in each group would be required.

Statistical analysis was performed using SPSS software Chicago, IL, USA, version 21. Comparison between categorical variables in both groups was done by Chi-square test and continuous variables were compared using Student T-test. For statistical analysis, we tested the different pain scores for normality by Kolmogorov-Smirnov test and they were not normally distributed, so they are presented as median scores and compared using the Mann-Whitney test. Multivariate linear regression analysis was done to determine the independent predictors of HSG pain. We considered P value < 0.05 as a significant value.

3. Results

One-hundred and three women were approached to participate in the study. Nine women have been excluded: two women had irregular uterine bleeding and four women had already received intravenous analgesics prior to HSG. Moreover, three women declined participation in the study. We randomly assigned the remaining 94 women into both groups (Fig. 1, the study flowchart).

There was no difference in the baseline characteristics between both groups (Table 1). Table 2 shows the median pain scores for both groups. The pain scores at all steps of HSG were not statistically significantly different between groups. The highest median pain score was during injection of the dye (3.75 [3–5] vs 4.5 [3–6]) in those who received HBB or placebo respectively.

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