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Efficacy of mefenamic acid and hyoscine for pain relief during saline infusion sonohysterography in infertile women: a double blind randomized controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy and level of satisfaction from mefenamic acid and hyoscine when used for pain relief during saline infusion sonohysterography.
Study design: In this double blind randomized controlled trial, 141 nulliparous women were allocated to receive 500 mg of mefenamic acid, 10 mg of hyoscine or a placebo, which was packed in the same outer capsule. Saline infusion sonohysterography (SIS) was performed 30 min later by one operator. Pain and satisfaction scores were evaluated using a 10 cm visual analog scale. Baseline characteristics, pain and satisfaction scores were compared among the three groups. Pain scores were recorded before, after catheter insertion, during, immediately after, and 30 min after the procedure.
Results: No statistically significant differences were found in baseline characteristics, pain and satisfaction scores among the three groups. Maximum pain during SIS was 4.40 ± 3.34, 4.67 ± 3.14 and 4.85 ± 3.19 in the mefenamic acid, hyoscine and placebo groups respectively. There was a 31.1% prevalence of intrauterine abnormality and the most frequent finding was endometrial polyp.
Conclusion: There is no benefit in using mefenamic acid and hyoscine in the prevention of pain occurring from SIS.

1. Introduction

The number of couples seeking infertility treatment has increased over the past years. Intrauterine abnormalities have not been diagnosed as the major cause of infertility but are considered to have an effect upon infertility treatments and pregnancy outcomes. The true prevalence of intrauterine lesions in infertile women is not known but some studies have reported an incidence of about 16–24% [1,2]. The most common findings were endometrial polyps and submucous myomas. The effect of endometrial polyps is uncertain but may be associated with interference with embryo implantation and resulting early pregnancy loss [3,4]. Therefore ongoing pregnancy rates significantly increase to 50% in women after hysteroscopic submucous myomectomy [5–7].

In order to diagnose intrauterine abnormalities, several investigative methods can be used, such as saline infusion sonohysterography (SIS), hysterosalpingography (HSG), and the gold standard, diagnostic hysteroscopy [8–10]. SIS has also been commonly used for screening for pathology in the uterine cavity. It provides 91% sensitivity, 83% specificity, 85% positive predictive value, and 90% negative predictive value [11,12]. There are several advantages of SIS over other methods, such as the simplicity of the technique, less time consuming, less expensive, less invasive, and no need for ionizing radiation or general anesthesia. Despite the fact that complications might be found after performing SIS, serious complications such as fever and peritonitis occurred less than 1% of the time, following SIS procedures [13].

Pain is one of the highest concerns when any procedure is to be performed, including SIS. The mechanism of pain is due to uterine distension with normal saline that may release local prostaglandins and lead to uterine cramps, and can be due to peritoneal irritation because of saline spills into the peritoneal cavity in patients with at least one patent fallopian tube. Other causes of pain may occur from the difficulties of the procedure, such as uterine cervix manipulation and grasping by a tenaculum [14].

To prevent or decrease pain during the performance of SIS, several types of SIS instruments and anesthetic drugs have been studied [15,16]. Guney et al. reported that women receiving intrauterine lidocaine infusion before SIS experienced statistically significant pain relief during the procedure [17]. The drawbacks of intrauterine lidocaine application for SIS, however, are the length of time for the drug to start acting and irritation. Oral medication should be beneficial over local intrauterine lidocaine use.

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Unfortunately, there has been no study evaluating the efficacy of oral analgesic drugs in terms of pain prevention or pain relief from SIS. Regarding the use oral painkillers and other gynecological procedures, there were some previous studies demonstrating the benefits of those drugs for the prevention of pain from hysteroscopy [18], fractional curettage [19], endometrial biopsy [20]. A recent study, however, showed that 50 mg of rofecoxib given preoperatively had no effect in reducing pain in patients who underwent uterine curettage [21].

Regarding anesthetic drugs, many types of them are commonly used to prevent pain from gynecological diseases, or from gynecological procedures including non-steroidal anti-inflammatory drugs (NSAIDs), hyoscine-N-butylbromide, and acetaminophen [22]. Mefenamic acid (Ponstan®), which is an NSAID and COX-1,2 inhibitor, inhibits prostaglandin synthesis by decreasing cyclo-oxygenase enzyme, with the onset of action at 30 min after oral administration. Hyoscine-N-butylbromide (Buscopan®), an antispasmodic drug, used to relieve genito-urinary spasm, was also of interest. The structure of the drug is similar to the neurotransmitter acetylcholine, and it blocks the parasympathetic pathway with the onset of action taking 30 min from oral administration. Previous studies attempted to use hyoscine to relieve abdominal cramping in many procedures such as endoscopy, renal colic and labour analgesia [23,24]. The benefits of its use are still controversial, but no study has investigated its benefit for pain relief in gynecological procedures.

This study aims to evaluate the efficacy of mefenamic acid and hyoscine in pain relief during SIS when compared to a placebo, and also to evaluate the satisfaction score after SIS between women who receive mefenamic acid, hyoscine and a placebo before the procedure in infertile women who attended Siriraj Infertility Unit.

2. Materials and methods

In this double blind randomized controlled trial, consecutive infertile women, who firstly attended Siriraj Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University from March 2009 to December 2009, were invited to participate in the project by their physician. From the patients, those who met the inclusion criteria and were willing to be participants were included in the study. Inclusion criteria were nulliparous women, age over 18 years who had never had HSG or hysteroscopy performed. Women who currently had a sexually transmitted disease (STD) or pelvic inflammatory disease (PID), abnormal Pap smear, or contraindication or hypersensitivity to mefenamic and hyoscine were excluded. Contraindications for mefenamic acid are a history of upper gastrointestinal disease or ulceration, bleeding disorder, asthma, renal disease, and warfarin, aspirin or lithium use. Contraindication for hyoscine is myasthenia gravis.

The study was conducted in accordance with the ethical principles stated in the recent version of the Declaration of Helsinki. The study protocol was approved by the Siriraj Institutional Review Board (SiRB), Faculty of Medicine Siriraj Hospital, Mahidol University. The protocol number is 615/2551(EC1).

All participants who were included into the study were given an appointment on day 6 (or up to 10) of their menstrual cycle. After informed consent forms were signed, baseline characteristics were noted in the case record form, under the following categories; age, time married and time of no contraception use, level of education, history of abortion, day of menstrual period, and gynecological history relating to dysmenorrhea, dyspareunia, chronic pelvic pain, sexually transmitted diseases and uterine curettage.

Participants were divided into three study groups and each group received medication as follows: two tablets of mefenamic acid (250 mg), one tablet of hyoscine (10 mg) and one placebo or two placebo tablets. All medications were packed into the same outer capsule by a single Siriraj pharmacist and then the drugs were arranged into envelopes following computerized randomization numbering, blocks of 9, by other nurses who were not involved in the study. Blinding was continued until analysis. All participants had to take the drug 30 min before the start of the SIS.

SIS was performed in the same way with all participants, by the same operator (R.J.) and one assisting nurse at Siriraj Infertility Unit. Participants lay in the lithotomy position and a small Pederson speculum was inserted using sterile technique. A non-balloon catheter with 6.6 Fr outer diameter was used. Normal saline was infused by syringe (50 ml) and the same total volume (200 ml) was used for each participant, with the objective of controlling a variable which could affect the pain score, except in the case that there was not enough volume to successfully evaluate the intrauterine abnormality. Transvaginal ultrasound was performed using ALOKA SSD-3500SX.

Pain and satisfaction scores were self-evaluated using a 10 cm visual analog scale (VAS). Pain scores were evaluated at five points in time (before starting the procedure, after catheter insertion, maximum pain during SIS, immediately after SIS had finished, and 30 min after SIS had finished). Satisfaction scores were also evaluated using a 10 cm visual analog scale at 30 min after the procedure. Details and findings from the procedure were recorded in the case record form.

Statistical analysis was performed using the Statistics Package for Social Sciences (SPSS) for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). Descriptive data were presented in N (%) for qualitative data and in the mean ± SD and median [range] for quantitative data. A chi-square test was used to compare qualitative variables. One-way ANOVA and Kruskal–Wallis test were used to compare normal and non-normal distribution quantitative variables respectively. Distribution was tested using the Kolmogorov–Smirnov test.

3. Results

Overall 141 infertile women were included in the study. Intervention failed in six cases because of inability to pass the catheter through the cervical os, two in the mefenamic acid group, three in the hyoscine group and one in the placebo group. Finally there were 44, 44 and 47 participants who completed the procedure in the mefenamic, hyoscine and placebo groups respectively (Fig. 1). There was no difference in baseline characteristics between the three groups according to age, body mass index, education, and time of non-use of contraception, experience of abortion or abnormal gynecological history (Table 1).

The pain scores at every point in time were not statistically significantly different between groups (Table 2). The highest mean pain was during SIS, with mean pain scores of 4.40 ± 3.33, 4.67 ± 3.14 and 4.85 ± 3.18 in those who received mefenamic acid, hyoscine or placebo respectively. After categorization of the pain into mild (0–3), moderate (4–6) and severe (7–10), there was no statistical difference in the number of participants in each category of pain between the three groups. No statistically significant difference in satisfaction score between the study groups was found. The mean satisfaction scores were 8.99 ± 1.40, 9.13 ± 1.00 and 9.20 ± 1.31 in the mefenamic acid, hyoscine and placebo groups respectively. Moreover, the characteristics and findings of the procedure did not show any statistically significant difference (Table 3).

Subgroup analysis was performed to evaluate variables which may have had an effect upon the pain score. Nineteen women who had a history of uterine curettage had significantly higher pain scores after the insertion of catheters than those who had not (2.58 ± 1.88 versus 1.56 ± 1.87 respectively; $p = 0.010$). The maximum pain during SIS, however, was not statistically significantly