



The effect of preemptive intravenous ibuprofen for pain relief during hysterosalpingography in women with infertility: A randomized, double-blind controlled study

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Abstract

Aim: HSG is an invasive diagnostic procedure that involves the radiographic evaluation of the genital system after the injection of a radiopaque substance from the cervical canal in infertile women. Preemptive intravenous ibuprofen is commonly used for postoperative pain management. However, only a limited number of studies have reported the intravenous use of ibuprofen for short-term painful procedures. This study aimed to investigate the effectiveness of intravenous ibuprofen for pain management during HSG.

Materials and Methods: A total of 91 patients planned to undergo HSG due to infertility were included in the prospective, randomized, double-blind study. Patients were assigned into two groups: the ibuprofen group (group I, n = 43) and the control group (group C, n = 48). About 30 min before the procedure, 800 mg ibuprofen in 100 ml saline infusion was administered to the ibuprofen group, whereas 100 ml saline infusion was administered to the control group 30 min before the starting the procedure. Pain scores using a visual analog scale (VAS) during the procedure were evaluated at four-stage; (1) insertion of the speculum (2) holding and traction (3) administration of contrast matter; and (4) 30 min after the procedure. Besides, the patients were evaluated according to a scale with a range of 1–4 in terms of satisfaction.

Results: There was no statistically significant difference in terms of demographic data ($p > 0.05$). VAS pain scores in the median (25%–75%) during the administration of contrast agent were lower in group ibuprofen (median, 1; range 1–2) than in group control (median, 5.5; range 5–6) ($p < 0.001$). There was no statistically significant difference between groups in terms of pain scores other stages of HSG ($p > 0.05$). Patient satisfaction was significantly higher in group ibuprofen than in group control ($p < 0.001$).

Conclusion: Intravenous ibuprofen can be administered as an alternative approach to decrease pain and increase patient satisfaction in the HSG procedure performed under outpatient conditions. In conclusion; to the best of our knowledge, this is the first study that administered intravenous ibuprofen in the HSG procedure. However, further studies are needed to compare its effectiveness.



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Introduction

Today, an average of 6.6–26.4% of women living in developed countries are affected by infertility [1]. Tubal factors are considered to be responsible for 14%–40% of these cases of infertility, defined as the absence of pregnancy despite one year of unprotected intercourse [2]. Therefore,

HSG is the golden standard in evaluating infertile couples as well as detecting tubal passage and abnormalities of the uterus [3].

HSG is an invasive diagnostic method that involves radiographic examination of the genital tract after the administration of a radiopaque fluid from the cervix. Although the procedure has a short duration and is performed in the outpatient clinics, the pain that occurs during its execution constitutes its most prominent limitation. Approximately 70% of patients experience pain during the procedure [4].

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Contact of the contrast drug with the pelvic and abdominal peritoneum causes pain due to peritoneal irritation and uterine distention [5]. Nonsteroidal anti-inflammatory drugs (NSAIDs), oral paracetamol, intravenous opioid injections and topical analgesics may be given to patients to combat the severity of pain that occurs [6]. However, based on literature data, there is no clear opinion regarding the optimal timing and administration method of the analgesic to be applied [2]. The growing demand for HSG due to the latest developments in reproductive medicine has led to the need for painless and more comfortable execution of the procedure.

Ibuprofen is a propionic acid-like molecule with analgesic, anti-inflammatory and antipyretic properties [7]. Its oral use is safe and is the preferred route of administration. The intravenous (IV) form of ibuprofen has been used in pain treatment since 2009. Although there are limited studies on IV ibuprofen, its effectiveness, safety, and side effect profile in orthopedic, particularly abdominal, cases for the postoperative treatment of pain have been reported [8]. However, in light of the present data, its effectiveness in a short duration procedure such as HSG, which is performed in a brief period in outpatient clinics, has not been demonstrated.

Our main goal in this study is to investigate the advantages of intravenous ibuprofen in reducing pain during the HSG procedure.

Materials and Methods

This prospective, randomized, double-blind study was performed in the infertility department of our gynecology and obstetrics clinic. Ethics committee approval was received for this study from the ethics committee of Ataturk University Local Ethic Committee. Patients with an indication for HSG were included after the necessary information was provided, and their consent was obtained. Patients who were undergoing acute pelvic inflammatory disease or acute cervicitis, those who had positive human β -chorionic gonadotropin (β -hCG) test before the operation, those aged <18 years, and those allergic to nonsteroidal anti-inflammatory medication were excluded. The demographic data of the patients were recorded. The procedure was performed using a single-use speculum in the dorsal lithotomy position and a tenaculum for uterine traction. During the HSG scan, the Rubin cannula was pressed against the cervix, and the speculum was extracted. After that, 15 ml radiopaque matter was injected via the cannula, and a series of radiological images were taken.

Patient groups were randomized into two separate groups using computer software. Patients and clinicians do not know which group-specific medication is being given.

The patients were randomized into two groups using a computer program. The ibuprofen group (group I, n = 45) had 800 mg ibuprofen in 100 ml saline infusion administered 30 min prior to the procedure, whereas the control group (group C, n = 50) had 100 ml saline infusion administered 30 min before the procedure.

Each patient was informed about the VAS scoring (0, no pain; 10, the worst pain imaginable) prior to the procedure and was asked to score the four stages of the procedure

from 0 to 10. The first step was defined as the insertion of the speculum in the patient; the second step as holding and traction of the cervix with the tenaculum; the third step as the administration of contrast matter; and the fourth step as 30 min after the procedure. The patients were observed in the gynecology service for 60 min after the procedure. Moreover, the patients were evaluated according to a scale with a range of 1–4 in terms of patient and operator satisfaction (measured as a score of 1 to 4: poor, moderate, good, and excellent, respectively).

Statistical analysis

Statistical analyses were performed using the IBM SPSS 20 statistical analysis software. The data are presented as mean, standard deviation, median, minimum, maximum, percentage, and numbers. Shapiro–Wilk’s test was used to verify the normal distribution of continuous variables. In the comparison between two independent groups, the independent sample t-test was used when normal distribution condition was met, whereas Mann–Whitney’s U test was used when the normal distribution condition was not met. In the 2 × 2 comparisons between categorical variables, the Pearson chi-square test was used when the expected value was >5; the chi-square Yates test was used when the expected value was between 3 and 5, and the Fisher’s exact test was used when the expected value was <3. A p-value of <0.05 was considered to be statistically significant. Post-hoc power analysis was done using the ClinCalc calculator (clincalc.com/stats/Power.aspx) for inactivation time.

Results

A total of 95 patients were included. Two patients were excluded due to the routine β -hCG test giving a positive result, one was excluded due to acute pelvic inflammatory disease, and one was excluded due to inadequate compliance with VAS scoring. The data of 43 and 48 patients in the ibuprofen and control groups were examined, respectively (Figure 1). No allergic reactions toward NSAIDs or

Table 1. Demographic data of study.

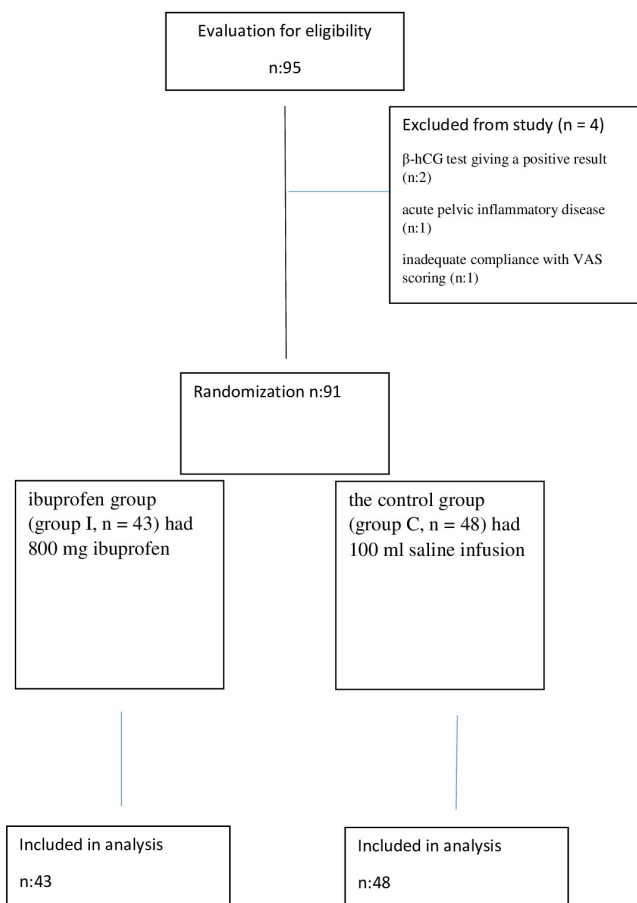
		Group Ibuprofen (n=43)	Group Control (n=48)	P
Age (year)	(mean ± SD)	29.30 ± 6.18	30.19 ± 5.77	0.482 ^a
Weight (kg)	(mean ± SD)	64.72 ± 10.06	63.44 ± 10.33	0.658 ^b
Height (cm)	(mean ± SD)	161.00 ± 6.05	161.29 ± 6.98	0.539 ^b
		(n=43) %	(n=48) %	
Infertility	Primary	30 (70%)	30 (62.5%)	0.465 ^c
	Secondary	13 (30%)	18 (37.5%)	
Abnormal findings	Yes	14 (32.5%)	10 (20.8%)	0.205 ^c
	No	29 (67.5%)	38 (79.2%)	

Values are presented as mean ± standard deviation or number (%), p values <0.05 were considered to be statistically significant. ^a Independent Sample t test, ^b Mann–Whitney-U test, ^c Chi-square test.

Table 2. Pain scores and patient satisfaction.

		Group Ibuprofen (n=43)	Group Control (n=48)	P
		Median (min-max)	Median (min-max)	
VAS (0-10)	Insertion of the speculum	1 (1-1)	1 (1-1)	0.203 ^a
	Holding and traction	3 (2-3)	3 (2-3.5)	0.757 ^a
	Administration of contrast	1 (1-2)	5.5 (5-6)	<0.001^a
	After the procedure (30 min)	0 (0-0)	0 (0-0)	1.000 ^a
		(n=43)	(n=48)	
		%	%	
Patient Satisfaction	Poor	0	20	<0.001^b
	Moderate	5	22	
	Good	23	6	
	Excellent	15	0	

Values are presented as median (percentage 25-75) or number (percentage), VAS: Visual Analogue Pain Scale, p values <0.05 were considered to be statistically significant. ^a Mann Whitney-U test, ^b Chi-square test.

**Figure 1.** CONSORT flow diagram, group I (ibuprofen) and group C (saline infusion).

contrast matter were observed in any patients. The mean ages of the ibuprofen and control groups were 29.3 ± 6.18 and 30.19 ± 5.77 years, respectively. The demographic data of the patients are presented in Table 1. No significant differences were detected between the two groups in terms of age, height, weight, infertility type, and abnormal HSG findings ($p > 0.05$).

Abnormal HSG findings such as intrauterine abnormalities, blockage in fallopian tubes, and hydrosalpinx were reported in 14 and 10 patients (33% and 21%) in the ibuprofen and control groups, respectively.

When the pain scores were separately evaluated for the four-stage of the procedure, no significant difference was observed between the two groups in stages 1, 2, and 4 ($p > 0.05$). However, in the third stage, a statistically lower pain score was found in the ibuprofen group than that in the control group ($p < 0.001$; Table 2). Patient satisfaction was significantly higher in the ibuprofen group than that in the control group ($p < 0.001$; Table 2).

Discussion

The results of this study showed that IV ibuprofen can be used for decreasing pain increase patient satisfaction in the HSG procedure. For women, the inability to give birth and the failure to satisfy the maternal instinct leads to several biological, psychological, economic, and even cultural problems. Women generally feel more stress than men [9]. HSG, a golden standard diagnosis procedure for infertility, may appear as a simple interventional procedure; however, it can cause a moderate level of pain in patients.

The HSG procedure is an easy to perform, highly reliable, and low-cost method to evaluate tubal opening; however, the fact that it is not accepted by certain patients due to pain has led researchers to address this issue [10]. There are several studies conducted researching for both technical and therapeutic methods. A previous study has tried different oral, intrauterine, intravenous, and topical methods for patients [2]. In a 2007 Cochrane analysis of 12 randomized trials, Ahmad et al. showed that eight studies found no differences in pain-related parameters between the group receiving placebo and the group receiving analgesics [11]. However, in their study, updated later in 2015, only topical anesthetics and intravenous opioids were evaluated as effective in reducing pain levels during HSG [5]. The effects of oral or intravenous NSAIDs in decreasing pain during HSG have been demonstrated [12]. In their study comparing NSAID (diclofenac) and misoprostol, Hassa et al. showed that diclofenac is superior in de-

creasing pain in comparison to misoprostol [13]. The study showed by Karaman et al. revealed that one-time rectal indomethesis showed a statistically significant reduction in pain [14]. In a study evaluating 88 patients, Elson et al. found paracetamol to be ineffective and NSAIDs to be effective [6]. In agreement with the previous studies, our study found that the most painful step for the control group was the third stage, which involved uterine filling and contrast matter transfer. It was shown that ibuprofen significantly decreased pain especially at this stage.

From the uterine parts, the cervix and lower segment provide nerve conduction through the parasympathetic pathways of S2 and S4 and have blood vessels entering the cervix from the 3 o'clock and 9 o'clock directions [15]. Due to the visceral nerve distribution of the cervix, similar anesthesia applications are considered to be ineffective [16]. In our study, there was no statistical difference between the groups in which holding the cervix and traction with the tenaculum. Previous studies have demonstrated that pathological HSG findings are more related to Pain thought to come from obstruction or peritoneal adhesions in the tubes [17]. Karaman et al. stated that patients with tubal pathology in HSG felt more pain during contrast medium passage than patients with normal tubal anatomy in HSG [16]. However, Liberty et al. stated that there was no difference between abnormal and normal HSG images in terms of feeling pain [17]. Similarly there is no significant difference in our study findings in terms of pain between the normal and pathological HSG findings at any stage of the procedure. We believe that the reason for the absence of a difference during contrast matter transfer in our study, contrary to Karaman et al., was the decrease in pain caused by ibuprofen, especially during the filling stage and the peritoneal irritation point.

Ibuprofen is in a family of NSAIDs with analgesic, anti-inflammatory and antipyretic properties, which are used very often. The analgesic effect of ibuprofen is related to the inhibition of the cyclooxygenase enzyme (COX-1 and COX-2 isoenzymes). Inhibition of COX-1 has undesirable side effects. The COX-1 to COX-2 inhibition ratio of ibuprofen is 2.5:1, whereas, in other NSAIDs, this ratio can increase up to 330:1 [18]. The 800-mg IV-ibuprofen form has been used to decrease postoperative pain in various surgeries such as orthopedic surgery, abdominal hysterectomy, and laparoscopic cholecystectomy [8]. Particularly, when compared with placebo, it has been shown to decrease postoperative morphine consumption severely. Ahıskaloğlu et al. showed that even the use a single dose of 400 mg IV ibuprofen ensures postoperative analgesia and decreases morphine use by 45% [19]. Kroll et al. demonstrated in their patients with an abdominal hysterectomy that the postoperative morphine requirement in the group receiving IV ibuprofen decreased by 19% [20]. In our study, IV ibuprofen was used for the first time in a procedure that causes a moderate level of pain and severe anxiety such as HSG, and it significantly decreased pain in step 3 compared to the control group. IV ibuprofen, which is quickly absorbed and reaches peak plasma concentration in approximately 30 min, has a 60-min elimination half-life and 100% bioavailability [7]. The present study had some limitations. First, according to the results of our

study, although IV ibuprofen ensured analgesia in stage 3, no difference was detected in the other stages in terms of pain. In the study conducted by Canday et al., there was no statistically significant difference between the primary or secondary infertility of the patients during HSG application and the presence of abnormalities in HSG and VAS scores [21].

We think that the administration of a combined topical anesthetic with ibuprofen before performing an HSG reduces pain. The effectiveness of topical analgesics applied together with IV ibuprofen can be shown in further studies. Secondly, we preferred using the 800 mg dose independently of weight. Our reason and purpose for this preference was to ensure effective analgesia. The effectiveness of doses <800 mg can be studied as well. Finally, opioid consumption could have been used for a more objective evaluation of pain. However, we did not evaluate opioid consumption to avoid the side-effects of opioid use under outpatient conditions.

Conclusion

As a result, when we look at the general literature, intravenous ibuprofen administration in HSG applications is the first study. Intravenous administration of ibuprofen without the use of unnecessary anesthetic agents during the HSG procedure reduces the pain of peritoneal irritation and is positive in terms of patient satisfaction. Of course, further studies are needed to investigate the efficacy and success of ibuprofen.

Declaration of interests

The authors have no conflicts of interest to declare.

Informed consent

Written informed consent was obtained from individuals who agreed to participate in this study.

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Ethical approval

The protocol of this study was approved by the Ataturk University Clinical Research Ethics Committee. (Date: 16.01.2020, Decision No: B.30.2.ATA.0.01.00/136).

Author Contributions

Concept – EPTY, OEY, MEA, GNCS, EOA; Design – EPTY, OEY, GNCS; Supervision – EPTY, OEY, MEA, GNCS, IA, EOA; Resources - EPTY, OEY, MEA, GNCS, EOA; Materials – EPTY; Data Collection and/or Processing – OEY; Analysis and/or Interpretation – MEA; Literature Search – YET, GNCS, SKT, IA, EOA; Writing Manuscript – EPTY, GNCS; Critical Review – EPTY, YET, OEY, MEA, GNCS, SKT, IA, EOA.

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