



Effect of intramuscular hyoscine-n-butyl bromide on fallopian tube spasm and pain perception during and after hysterosalpingography in infertile women: A randomized single-blind controlled clinical trial

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Abstract

Background: Hysterosalpingography plays an important role in diagnostic work-up and treatment planning for infertile women. This procedure is usually uncomfortable and painful. The present study plans to investigate the effect of intramuscular Hyoscine-N-Butyl Bromide (HBB) on fallopian tube spasm and pain perception during and after hysterosalpingography (HSG) in infertile women.

Methods: This randomized single-blind controlled clinical trial (IRCT2017021132455N2) was conducted on infertile women scheduled for HSG in one radiology clinic affiliated to Arak University of Medical Sciences between July and August 2017. Patients were selected by convenience sampling and were randomly assigned to HBB (n=50) and a control group (n=50). Women received 20 mg/1cc HBB intramuscularly in the intervention group, 30 minutes before the procedure. Women in the control group did not receive any medication. The patients were requested to complete the Numeric Pain Rating Scale after injection of the dye, and also 30 minutes following the end of the HSG. Presence or absence of tubal spasm was determined after checking the radiographic images. For the data analysis using SPSS version 18, descriptive statistics, and analytical tests such as independent sample t-test, Mann-Whitney test, chi-square or Fisher's exact tests and logistic regression and ANCOVA were used.

Results: Statistically significant differences were not observed in pain scores between the HBB and the control groups at the point of dye injection and 30 minutes after ending the HSG ($p>0.05$). Also, tubal spasm in the HBB group was lower than in the control group, but the differences were not statistically significant between the two groups ($p=0.37$).

Conclusion: The use of intramuscular HBB before HSG has no advantage in reducing tubal spasm and the induced pain during dye injection and 30 minutes after the HSG procedure. Thus, we don't recommend HBB use before the HSG in order to relief from pain and spasm.

Keywords: Pain, Spasm, Fallopian tubes, Hysterosalpingography, Infertility

Conflicts of Interest: None declared

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Introduction

Infertility is one of the most prevalent chronic health problems affecting young adults (1). It is defined as the

failure of a couple to conceive during one year of regular unprotected intercourse (2). The incidence of infertility

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↑What is "already known" in this topic:

Hysterosalpingography (HSG) is an invasive procedure that is usually uncomfortable and painful. Many different interventions have been applied for pain relief during and after HSG including oral, intravenous, intrauterine and topical analgesics.

→What this article adds:

This study indicated that use of intramuscular Hyoscine-N-Butyl Bromide (HBB), 30 minutes before (HSG), has no effect on pain relief and tubal spasm during and 30 minute after the HSG procedure.

among women between the ages of 15 and 44 has increased slightly in the last three years (3). Of all infertile couples, 40-50% is attributed to female infertility (4). It is caused by many factors, and fallopian tube abnormalities cause about 30-35% of cases of female infertility (5).

Imaging techniques, such as hysterosalpingography (HSG), play an important role in diagnostic work-up and treatment planning for infertile women (5). HSG provides an optimal depiction of the fallopian tubes, and is used to assess tubal patency because it has a sensitivity of 85% to 100% in identifying tubal occlusion (3, 6). In this procedure, the uterine and tubal cavities are visualized radiographically through the transcervical injection of radiocontrast dye (3). This invasive procedure is usually uncomfortable and painful because cervical instrumentation, uterine distension with injection of the dye or peritoneal irritation secondary to contrast material spill, can lead to pain and discomfort during the procedure (1, 2). The main cause of pain experienced during HSG is secondary to the uterine distension with the dye resulting in the release of local prostaglandins, which stimulate uterine cramps. The pain is conducted through the pelvic splanchnic nerves from the cervix and lower part of the uterus, whereas pain from the fundus and body of the uterus is transmitted by the hypogastric nerves (7).

Many different interventions have been evaluated for pain relief during and after HSG including oral, intravenous, intrauterine and topical analgesics (3, 8-10). However, there is no agreement in regard to the optimal method for pain relief or timing of its administration. Also, it seems that there is no evidence about methods that relieve fallopian tubes spasm during HSG.

Hyoscine N-Butyl Bromide (HBB) is an anti-spasmodic drug. It relieves spasms in the smooth muscle cells of the female genital tract, especially the cervico-uterine plexus (11). HBB blocks impulse transmission in parasympathetic ganglia with the onset of action taking 30 minutes from intake (12). It has been ordinarily utilized for the relief of abdominal cramps during many procedures such as endoscopy, renal colic, biliary colic etc. (13, 14). However, it seems that investigations of the potential benefit of HBB (20 mg I.M.) in HSG are scarce. Some studies were used with HBB administered orally in order to relieve the pain during HSG (2, 12) and intravenous HBB for relieving spasm during this procedure (15). There is no study that assesses the effect of intramuscular HBB on pain relief during and after HSG and tubal spasm during this procedure.

Since antispasmodic drugs are usually used for the relief of muscle spasms, our hypothesis was that an antispasmodic drug such as HBB could decrease pain and fallopian tube spasm during and after HSG by affecting uterine contractions.

The primary objectives of this study were to evaluate the efficacy of intramuscular HBB on decreasing pain during and after the performance of HSG and also to evaluate the relief of fallopian tube spasm during HSG. The secondary objective included evaluation of the side effects of HSG in HBB and control groups. To meet these objec-

tives, we administered intramuscular HBB prior to HSG in infertile women in a radiology setting, measuring the primary and secondary outcomes of patients.

Methods

Design

In this randomized single-blind controlled clinical trial, infertile women who referred to a radiology clinic affiliated to Arak University of Medical Sciences between July 2017 and August 2017, were invited to participate in this study.

According to a similar study (2), with an alpha error of 0.05 and a statistical power of 80%, a sample size of at least 43 women in each group was calculated. Considering a possible 15% sample attrition rate, the required sample size was calculated as 50 patients in each group.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\chi^1 - \chi^2)2}$$

Participants

Patients were selected by convenience sampling and then were randomly assigned to HBB and control groups according to predesigned blocks with a block size of 4. In this type of randomization, there are six possible permutations with balanced group allocation. At first, the list of blocks was specified, and numbers 1 to 6 were assigned to these blocks. Then numbers 1 to 6 were randomly selected from a table of random numbers, and a sequence of A and B were formed. Participants were assigned to intervention (A) and control (B) groups according to the randomly selected block.

One hundred women were assigned in the HBB group (n=50) and in the control group (n=50). They completed the HSG procedure and were evaluated for the outcome. Patients were blinded as to the assignments to intervention.

Women who had the inclusion criteria and were willing to be participants were included in this research. Inclusion criteria were infertile women, aged between 20-45 years old, who did not receive any analgesics in the 24 hour prior to HSG. Women who currently had anxiety and major depression, a sexually transmitted disease (STD), pelvic inflammatory disease (PID) or abnormal uterine bleeding, abnormal Pap smear, history of cervical surgery, uterus malignancies, hemodynamic instability during HSG, and contraindication or hypersensitivity to HBB were excluded. Before random allocation of the participants to HBB and control groups, sixteen women were excluded: three women had a history of cervical surgery, four women had irregular uterine bleeding and three women had received oral analgesics 24 hours prior to HSG. In addition, six women declined participation in the study (Fig. 1).

Since HSG is best scheduled for the period of 2-5 days immediately after the end of menses (3), all participants who were included in the study were appointed at this interval of their menstrual cycle.

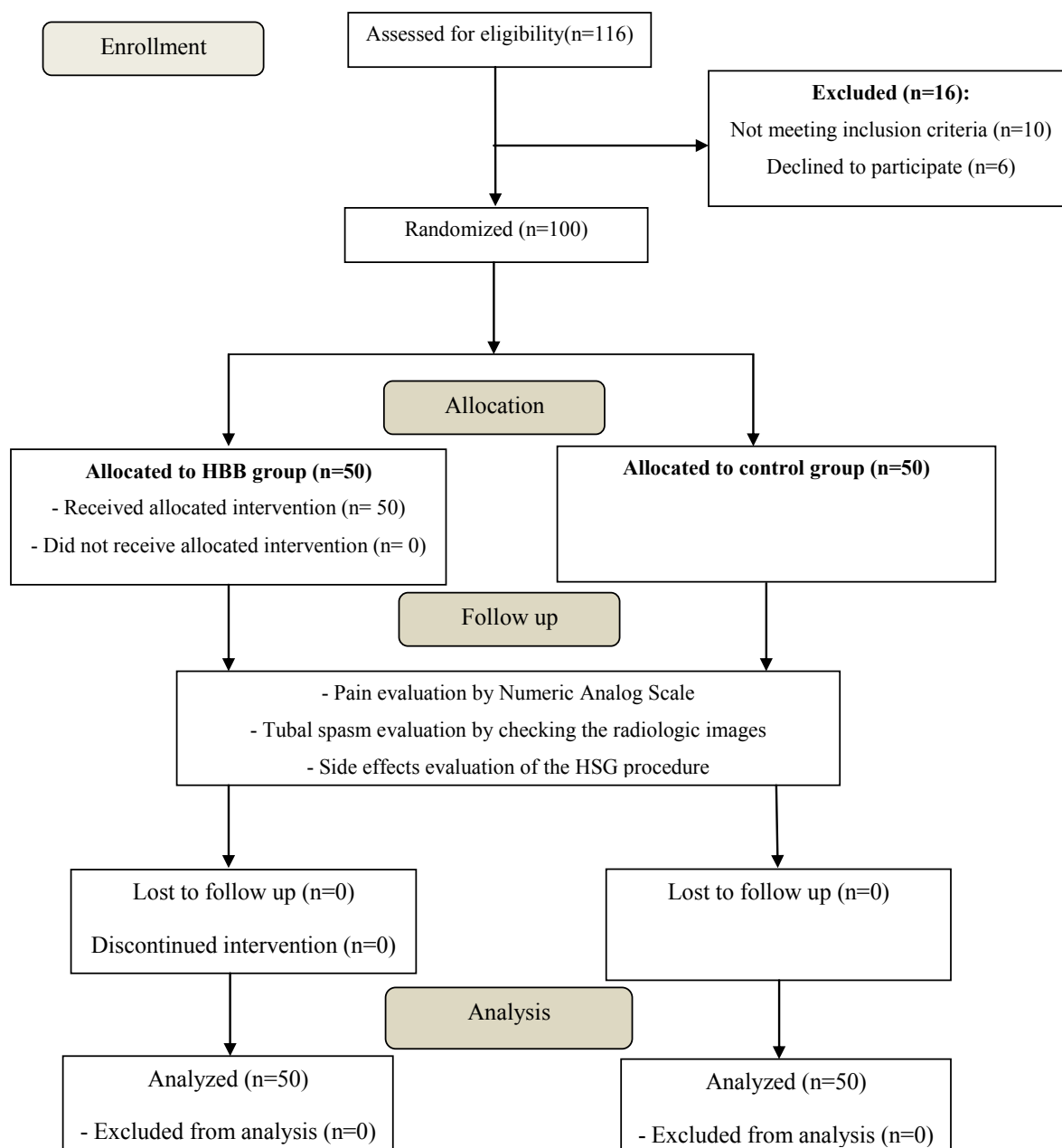


Fig. 1. CONSORT flow diagram of participant enrollment, allocation, follow up and data analysis

Intervention

Women in the HBB group received 20 mg/1cc HBB intramuscularly (Manufactured in Iran by OSVEH Pharma Co.) 30 minutes before the procedure. Women in the control group did not receive any medication.

All HSGs were performed by a single experienced radiologist (F.S.) and one assisting midwife. Women lay in the lithotomy position and then the radiologist placed a sterile speculum into the vagina and after visualization of the cervix, it was cleaned 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 5 ml water-soluble contrast dye (Iohexol; each ml contains: 518 mg Iohexol equivalent to 240 mg Iodine – Aburaihan Pharmaceutical Co; Tehran; Iran) was injected over 20 seconds into the uterine cavity.

When the uterine cavity was fully filled with the dye, radiographic images were taken in the anteroposterior view. After checking the radiographic images, it was determined whether another image should be prepared or not. The presence or absence of tubal spasm was determined in this stage according to the radiologic images.

At the end of the procedure, all instruments were removed and women were under observation in the radiology clinic for 30 minutes. Women were offered mefenamic acid (250 mg), as an additional analgesic if needed, at 30 minutes post-procedure.

Measurements

Baseline characteristics of these women were collected through a questionnaire (age, type, and duration of infertility, history relating to dysmenorrhea, dyspareunia, pel-

vic inflammatory disease, and previous delivery type) before the procedure.

One of the primary outcomes was the patients' self-reported pain on a 10-point Numeric Pain Rating Scale (NPRS) ranging from 0= no pain to 10= maximum pain. Women were asked to rate the intensity of pain experienced twice: immediately after injection of the dye, and 30 minutes following the end of the procedure. The NPRS is a valid and reliable scale to measure pain intensity (16). High test-retest reliability has been observed for this scale ($r=0.96$) (17). For construct validity, the NPRS was shown to be highly correlated to the Visual Analog Scale (VAS) range from 0.86 to 0.95 (16).

Another primary outcome was the patients' tubal spasm that was determined according to the radiologic images. When the uterine cavity was filled with the dye, and radiographic images were taken, presence or absence of tubal spasm was determined by a radiologist (F.S) in the clinic.

In addition, secondary outcomes included patients' response to questions about side effects of HSG. Nausea, vomiting, sweating, dizziness, bradycardia, and hypotension associated with the HSG were assessed after the procedure.

Data Analysis

Statistical analysis was performed using SPSS version 18 (PASW Statistics 18, SPSS Inc, Chicago, IL). Descriptive statistics are presented as mean and standard deviation for quantitative variables and as frequency distribution for categorical variables. To ensure that the data were normally distributed, a Kolmogorov-Smirnov test (K-S test) was carried out. An independent sample t-test, chi-square or Fisher's exact tests were used to determine statistically significant differences when comparing the characteristics of HBB and control groups. Because the pain score variable was not normally distributed, it was presented as median (p10, p90) and compared between two groups using Mann-Whitney test. Logistic regression

analysis and ANCOVA were carried out to identify the effect of group on the tubal spasm (yes/no) and pain in the presence of demographic and clinical variables. $p<0.05$ was considered as statistically significant.

Ethical considerations

This study received the registration number IRCT 2017021132455N2 in the Iranian Registry of clinical trials. The study was approved by the Ethics Committee of Vice Chancellor for Research, Arak University of Medical Sciences with the code of IR.ARAKMU.REC.1395.37. Information about this study was provided to all participants, and they signed the informed consent form.

Results

Mean age of the sample in the intervention group was (31.46 ± 5.54) years and in the control group was (29.40 ± 5.25) years. Also, mean duration of infertility in the intervention and control groups were (25.32 ± 30.19) and (27.26 ± 32.84) years, respectively. There was no statistically significant difference between the two groups related to the age ($p=0.06$, $t=1.90$) and duration of the infertility ($p=0.44$, $t=1.47$) at the beginning of the study. Also,

there was no significant difference in baseline characteristics between the two groups according to the type of infertility, history of dysmenorrhea, dyspareunia, pelvic inflammatory disease, and previous delivery type ($p>0.05$) (Table 1).

Although the women who received HBB recorded a slightly lower pain score both immediately after dye injection ($p=0.29$) and 30 minutes after the procedure ($p=0.26$), statistically significant differences were not observed between the HBB and the control groups. In comparing the pain score at the point of dye injection, the pain score is dramatically decreased 30 minutes after ending the HSG procedure in both groups (Table 2).

During the HSG, 24% of those in the HBB group had

Table 1. Characteristics of the HBB and control groups

Variable	Category	Hyoscine-N-butyl bromide group (n=50) n (%)	Control group (n=50) n (%)	X ²	p
Type of infertility	Primary	30 (60)	30 (60)	2.09 [†]	1
	Secondary	20 (40)	20 (40)		
History of dysmenorrhea	Yes	23 (46)	18 (36)	1.03 [†]	0.41
	No	27 (54)	32 (64)		
History of dyspareunia	Yes	18 (36)	13 (26)	1.18 [†]	0.38
	No	32 (64)	37 (74)		
History of PID	Yes	2 (4)	7 (14)	3.05 [†]	0.16
	No	48 (96)	43 (86)		
Previous delivery type	Previous NVD	8 (16)	11 (22)	0.90	0.63
	Previous CS	12 (24)	9 (18)		
	Nulliparous	30 (60)	30 (60)		

[†] Fisher exact test

Abbreviations: NVD: Normal Vaginal Delivery; CS: Cesarean Section

Table 2. Pain scores in HBB and the control groups

NPRS ^a score results ^b	Hyoscine-N-butyl bromide group (n=50)	Control group (n=50)	p [†]
Pain after dye injection	7 (4-10)	8 (3-10)	0.29
Pain 30 min after HSG	1 (0-5)	1.5 (0-7)	0.26

^a Numeric Pain Rating Scale

^b All results are presented as median [inter-percentile range]

[†] Mann-Whitney test

tubal spasm, while in the control group this was 34%. However, the difference was not statistically significant between the two groups ($p=0.37$) (Table 3).

Logistic regression analysis and ANCOVA showed that none of the demographic and clinical variables have any effect on the relationship between the treatment groups and spasm and pain during and after HSG. In other words, these variables were not predictors for spasm and pain

experienced during and after HSG (Tables 4, 5, 6).

The results revealed that there was no statistically significant difference between the HBB and the control groups in terms of reported side effects of the HSG procedure ($p=0.52$). Main reported side effects were nausea and dizziness that occurred in nineteen women in both of the two groups (Table 7). None of the women showed an allergic response to the contrasting agent. All women were

Table 3. Tubal spasm during HSG in the HBB and the control groups (n=100)

Tubal spasm during HSG	Hyoscine-N-butyl bromide group (n=50)	Control group (n=50)	p†
	n (%)	n (%)	
Yes	12 (24)	17 (34)	0.37
No	38 (76)	33 (66)	
Total	50 (100)	50 (100)	

† Fisher exact test

Table 4. Results of the logistic regression in investigating of the effect of HBB on tubal spasm in the presence of demographic and clinical variables

Predictor variables	OR (95% CI)	p
Constant	9.320	0.181
Study groups (base=without Hyoscine)	2.186 (0.802-5.957)	0.126
Age	0.976 (0.886-1.076)	0.627
Infertility time	0.991 (0.977-1.005)	0.215
PID history (base=no)	1.193 (0.233-6.099)	0.832
Dysparonia (base=no)	0.488 (0.171-1.390)	0.179
Dysmenorrhea (base=no)	0.591 (0.299-1.524)	0.277
Delivery type (base=none)		
NVD	0.282 (0.063-1.259)	0.097
C/S	1.035 (0.297-3.614)	0.957

Dependent Variable: Tubal spasm

Table 5. Results of the linear regression in investigating of the effect of HBB on pain during HSG in the presence of demographic and clinical variables

Parameters	B (95% CI)	p
Intercept	8.589 (5.598-11.579)	0.000
Study groups (base=without Hyoscine)	-0.073 (-1.160-1.014)	0.894
Age	-0.050 (-0.157-0.056)	0.350
Infertility time	0.006 (-0.011-0.024)	0.459
PID history (base=no)	0.899 (-0.937-2.736)	0.333
Dysparonia (base=no)	0.012 (-1.163-1.186)	0.984
Dysmenorrhea (base=no)	0.094 (-0.979-1.168)	0.862
Delivery type (base=none)		
NVD	-0.721 (-2.199-0.758)	0.336
C/S	0.118 (-1.499-1.264)	0.866

Dependent variable: Pain during

Table 6. Results of the linear regression in investigating of the effect of HBB on pain after HSG in the presence of demographic and clinical variables

Parameters	B (95% CI)	p
Intercept	3.560 (0.508-6.611)	0.023
Study groups (base=without Hyoscine)	-0.437 (-1.546-0.672)	0.436
Age	-0.047 (-0.155-0.062)	0.396
Infertility time	0.000 (-0.018-0.017)	0.966
PID history (base=no)	1.042 (-0.832-2.916)	0.272
Dysparonia (base=no)	-0.190 (-1.389-1.008)	0.753
Dysmenorrhea (base=no)	0.670 (-0.426-1.765)	0.228
Delivery type (base=none)		
NVD	-0.638 (-2.147-0.871)	0.403
C/S	-0.134 (-1.544-1.276)	0.850

Dependent variable: Pain after

Table 7. The side effects of HSG in the HBB and the control groups

Side effects	Hyoscine-N-butyl bromide group (n=50)	Control group (n=50)	p †
	n (%)	n (%)	
Nausea	8 (16)	7 (14)	0.52
Vomiting	0 (0)	0 (0)	
Sweating	2 (4)	4 (8)	
Dizziness	11 (22)	12 (24)	
Bradycardia	0 (0)	0 (0)	
Hypotension	4 (8)	3 (6)	

† Chi-Square

discharged from the clinic 30-45 minutes after the procedure was completed.

Discussion

This study was designed to assess the efficacy of intramuscular HBB on decreasing pain during and after the performance of HSG and also to evaluate relief of fallopian tube spasm during HSG.

The results indicated that there is no significant difference in pain scores between two groups; therefore, there is no advantage in using intramuscular HBB in the relief of pain at the point of dye injection and 30 minutes after HSG. This technique is quite simple, less invasive and provides reliable information at less cost (3, 18). Pain is the most common side effect of HSG and the majority of women believe that this diagnostic tool is painful (19). Abbas et al. (2017) found that administration of 20 mg oral HBB 30 minutes before HSG has no advantage in reducing the pain during and 30 minutes after the procedure (2). Also, other studies showed that there is no benefit in administering 10 mg oral HBB for prevention of pain occurring from sonohysterography (12, 20).

Results of this study showed that the pain score at the point of dye injection is higher than 30 minutes after the procedure in both groups. Results of other studies also indicated that injection of the dye into the uterine cavity was the most painful part of the HSG procedure (2, 18, 19). The feeling of pain peaks at the time of uterine distension due to contrast media injection, especially if there is peritoneal irritation as a result of contrast spillage into the peritoneal cavity (18). Use of new methods for contrast injection may allow an injection of a smaller amount of contrast media, preventing spillage of the medium into the peritoneal cavity, and therefore probably decreasing the intensity of pain (21).

The findings of this study showed that there was no statistically significant difference in tubal spasm during HSG between the two groups; so there is no benefit in using intramuscular HBB in the prevention of spasm during HSG. Very few researches have been performed about the effect of HBB on Fallopian tube spasm during HSG. However, results of one study suggested that administration of 20 mg intravenous HBB appears to be a safe and effective drug for relief of tubal spasm (15). Therefore, it seems that the injection method of HBB influences its effect on fallopian tubes spasm.

In the present study, dizziness and nausea were the most reported side effects of HSG in both groups. Abbas et al. (2017) reported that nausea and dizziness are the most common side effects of HSG procedure in patients administered HBB (2).

This research had some limitations. Firstly, because there is currently no other objective parameter to evaluate pain, the basic limitation of this study is that reporting pain via Numeric Analog Scale is a subjective process. Second is that pain measurements are performed only at two points; immediately after the dye injection and 30 minutes after the procedure. Similar studies are needed to evaluate and compare the severity of pain during other stages of HSG. Also, another limitation of this research

was that no baseline (pre-HSG) pain scores were measured.

In the present study, administering 20 mg HBB intramuscularly did not significantly reduce pain in patients undergoing HSG. Therefore, intervention studies to test the efficacy of intravenous HBB in pain relief during the HSG procedure must be performed.

Conclusion

We found that the use of intramuscular HBB, 30 minutes before HSG, has no effect in alleviating tubal spasm and pain relief during and 30 minutes after the HSG. Therefore, we don't recommend intramuscular HBB usage before the HSG to reduce tubal spasm and to provide pain relief.

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Conflict of Interests

The authors declare that they have no competing interests.

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