Hysterosalpingo-Foam Sonography, Less Painful and More Instructive as Compared with Hysterosalpingography: A Prospective Study

Abstract

Background: Hysterosalpingography (HSG) is a vital part of fertility evaluation, and can be painful and cause moderate to severe pain as reported by women. Hysterosalpingo-Foam Sonography (HyFoSy) is a quick, well-tolerated and less painful procedure than HSG for tubal patency testing. Moreover, HyFoSy is safe, non-invasive procedure, economic, and time efficient.

Objective: To assess whether HyFoSy is a less painful procedure for tubal patency and highly efficient compared to HSG.

Methods:

a) Design: A single-center, prospective, interventional clinical study.
b) Study setting: Reproductive Endocrine and Infertility Medicine Department, Ultrasound Unit of Women Specialized Hospital and Radiology Department of King Fahad Medical City Hospital (KFMC) between the period November 2015 and June 2016.
c) Intervention: Tubal patency testing by HyFoSy versus HSG.
d) Outcome measures: Mean pain scores during tubal patency testing.

Results: The mean pain score perception during the HyFoSy procedure was 2.44±1.71 compared with 5.03±2.26 during HSG, with a statistically significant difference (p=0.001). No statistical difference (p=0.597) was found between HyFoSy mean procedure time 125.01±35.21 compared to HSG mean time 128.15±37.18. Differences in pain perceived after HyFoSy can be explained mainly by the indication (p=0.001), history of ectopic pregnancy (p=0.002) and OTB (p=0.007).

Conclusion: The HyFoSy procedure is a less painful and less time-consuming tubal patency test compared with HSG.

Keywords: Hysterosalpingography; Hysterosalpingo-Foam Sonography; Hysterosalpingo-Contrast Sonography; Fallopian tube patency

Introduction

Subfertility is a disease of the reproductive system and defined as the failure to achieve pregnancy after 12 months of unprotected sexual intercourse [1]. Subfertility is a distressing condition for couples who are trying to achieve pregnancy and childbirth. Approximately 15% of couples are affected with subfertility, of which up to 20% remain unexplained. Female factors are identified in about 50% of couples [2]. The pelvic causes of female subfertility are varied and range from tubal and peri-tubal abnormalities to uterine, cervical, and ovarian disorders [2,3]. Tube abnormalities account for up to 40% of female subfertility [3,4]. Assessment of tubal patency is one of the first steps in infertility workup [5]. Various tests nowadays are available for the purpose of patent test; of these tests are hysterosalpingography (HSG), Salpingography, diagnostic laparoscopy with dye hydrotubation test and Hysterosalpingo-Contrast Sonography (HyCoSy) [6]. HSG is the most common first-line and widely available diagnostic test [5-7]. Although HSG assesses tubal status and provides an image of the outline of the uterine cavity, the intracavitary abnormalities are not visualized clearly due to the opacity of the dye used for the procedure [8-10]. Besides, the other main disadvantages are patients’ exposure to ionizing radiation that is significantly greater than that of a usual chest X-ray, the unpleasant pain experienced during the procedure and the risk of pelvic infection (1-3%) [7]. Moreover, laparoscopy with a dye test combined with hysteroscopy is...
considered the gold standard in diagnosing uterine abnormalities and tubal patency in infertile women. Its use is limited because it is expensive, time-consuming, needs general anesthesia and has risks of complications [3,11].

HyCoSy was introduced in 2006 to determine tubal patency, and different methods have been tried since then. It offered a quick method of assessing tubal patency obviating the need for ionizing radiation or general anesthesia [5,6]. Though pooled data from literature reported acceptable pain tolerance during the HyCoSy examination, the tolerance varies according to the used installation volume and contrast material [12-14]. Furthermore, the dyes were declared unsafe for gynecological use and could only be used for Doppler microvasculature. In 2007, HyFoSy was introduced as a safe procedure in which an inert material (hydroxymethyl cellulose), which has no reaction with the human body, was used as a contrast agent for sonohysterography, offering a more stable filling of the uterine cavity and fallopian tubes [15]. While HSG is a vital part of fertility evaluation, it can be painful and cause moderate to severe pain as reported by women. Pain and discomfort reach it peaks at the time of contrast installation. Cervical Instrumentation and uterine distention as well, may release local prostaglandins and thus induce uterine cramps [16,17]. On the other hand, literature has reported many advantages of HyFoSy. It is quick and well tolerated and less painful procedure than HSG for tubal patency testing. Moreover, HyFoSy is safe, non-invasive procedure, economic, and time efficient [11,18,19]. Experienced pain during HSG might have a negative influence on women cooperation, thus restraining the utility of the procedure, decrease their satisfaction and loss of confidence in clinicians. Therefore, women should have realistic prospects about the procedure [20,21].

Offering less invasive procedures with low cost is recommended by clinical guidelines, before going to more invasive with higher cost procedures [22,23]. Therefore, the aim of this clinical trial is to assess whether HyFoSy is a less painful procedure for tubal patency and if it is time efficient compared to HSG.

Materials and Methods

We conducted a prospective interventional study at the Reproductive Endocrinology Infertility Medicine Department and Ultrasound Unit of Women Specialized Hospital and Radiology Department of King Fahad Medical City Hospital (KFMC) between the period November 2015 and June 2016. 156 consecutive patients who were referred for tubal patency evaluation were invited to participate in the study. 75 patients out of the 156 were included in the study leaving the response at 48%. Excluded patients were those who did not meet the inclusion criteria and those who were unwilling and reluctant to participate and give informed consent. Ethical approval was obtained from the Institution Review Board at the study site. Informed consent was obtained before patient enrollment in the study.

Primary and secondary outcomes

The primary study outcome was the pain experienced by women after both procedures, as assessed by Visual Analogue Scale (VAS) with a scoring value (1-10). The secondary outcome was the procedure time, as measured in seconds.

Inclusion and exclusion criteria

The study included women aged between 18 and 40 years who were eligible for fallopian tube patency testing as part of their fertility evaluation. Women with chlamydia infection, pelvic pain or pelvic inflammation were excluded.

Clinical method

No premedication pain killers were given prior to both procedures. The procedures were performed after the cessation of menstrual bleeding and before day 14 in the ovulatory cycle. Women demographic and clinical characteristics (age, BMI, primary or secondary infertility, gravidity, parity, abortion, and comorbidity) were collected. Tubal patency was recorded in the data analysis as confirmed by HyFoSy.

The patients were sent to the ultrasound department where 2D/3DTVS is performed as an initial investigation by an automated sweep of a high-resolution transvaginal probe (7-9 MHz). The patients will be scheduled for HSG and subsequently to HyFoSy, after making sure they are not pregnant. The time difference between the two procedures was 4-5 days. HSG was performed in the radiology department. In lithotomy position, the radio-opaque dye was injected through the cervix and intermittently X-rays are taken, with the help of radiologist, uterine and tubal abnormalities are detected. In our hospital, HSG is performed on every sub-fertile woman as a standard initial investigation. The reading of HSG is not operator depended. It is easily and correctly reported by the consultant radiologist assigned to the radiology department. These radiologists were not aware of the ongoing study, and thus there was no observer bias on HSG reporting.

On the same patients, HyFoSy was performed in the Reproductive Endocrinology Infertility Medicine Department. The patient was placed in a lithotomy position; the cervix was visualized with the help of a speculum. A balloon catheter was introduced into the uterine cavity and the balloon filled with 1-1.5 ml of saline solution to fix the catheter and prevent foam backflow. First, 3-5 ml of saline was injected gradually into the uterus to distend and outlines the cavity, revealing any abnormalities (Mullerian anomaly and endometrial lesions). Then the prepared foam was injected slowly which passed through the fallopian tubes, causing their distension and finally spilling into the pelvis through the fimbrial ends. This foam is easily visible by the ultrasound and is thus its flow could be traced into the uterine cavity and tubes to check for any abnormalities (Mullerian anomaly and endometrial lesions). Then the prepared foam was injected slowly which passed through the fallopian tubes, causing their distension and finally spilling into the pelvis through the fimbrial ends. This foam is easily visible by the ultrasound and is thus its flow could be traced into the uterine cavity and tubes to check for any abnormalities (Mullerian anomaly and endometrial lesions). Then the prepared foam was introduced into the uterine cavity and the balloon filled with 1-1.5 ml of saline solution to fix the catheter and prevent foam backflow. First, 3-5 ml of saline was injected gradually into the uterus to distend and outlines the cavity, revealing any abnormalities (Mullerian anomaly and endometrial lesions). Then the prepared foam was injected slowly which passed through the fallopian tubes, causing their distension and finally spilling into the pelvis through the fimbrial ends. This foam is easily visible by the ultrasound and is thus its flow could be traced into the uterine cavity and tubes to check for any abnormalities (Mullerian anomaly and endometrial lesions). Then the prepared foam was injected slowly which passed through the fallopian tubes, causing their distension and finally spilling into the pelvis through the fimbrial ends. This foam is easily visible by the ultrasound and is thus its flow could be traced into the uterine cavity and tubes to check for any abnormalities (Mullerian anomaly and endometrial lesions). Then the prepared foam was injected slowly which passed through the fallopian tubes, causing their distension and finally spilling into the pelvis through the fimbrial ends. This foam is easily visible by the ultrasound and is thus its flow could be traced into the uterine cavity and tubes to check for any abnormalities (Mullerian anomaly and endometrial lesions).

Statistical analysis

Data were analyzed using SPSS version 22.0 (SPSS, Chicago, IL, USA). A descriptive analysis (mean, frequency and percentages) was used to describe women characteristics. Paired sample t-test was used to assess the significant difference in the mean pain scores for both procedures. Booker’s test was used to...
determine the level of concordance between HSG and HyFoSy in the levels of pain scores. Independent t-test was used to evaluate difference and compare the mean between HSG and HyFoSy mean pain score and patients variable. One-way ANOVA was used to assess difference and compare the mean pain score of HyFoSy and the three categories of tubal patency (Both Tubes Patent [BTP], One Tube Blocked [OTB] and Both Tubes Blocked [BTB]). A univariate analysis model was established to assess which of the patients' characteristics is a predictor for higher pain perception.

Results and Discussion

Utilizing a consecutive sampling method, 75 patients were involved in the study and underwent HSG procedure and subsequent HyFoSy. The mean age score of the participants was 30.53±5.34 (range: 19-40 year), and the Body Mass Index (BMI) was 28.41±5.61 (range: 18-49) (Table 1). Merely 48 (64%) of the patients they have primary infertility impending 27 (36%) with secondary infertility. The majority were nulliparous 63 (84%) and nulligravida 62 (82.7%). Among the patients, 11 (14.7%) they have a history of one abortion and 7 (9.3%) have a history of more than one abortion. The majority of patients had no comorbidity (84%); however, 7 (9.3%) had hyperthyroidism, 4 (5.3%) had diabetes and only 1 (1.3%) had hypothyroidism. With regards to tubal patency, 10 (13.3%) were found to have unilateral tubal blockage, and 3 (4%) had bilateral tubal blockage (Table 1).

Table 1: Patients Characteristics.

| Patients Characteristics | HyFoSy | HSG | p-value |
|--------------------------|--------|-----|---------|
| Age                      | 30.53±5.34 | 30.53±5.34 | 0.001* |
| Body Mass Index          | 28.41±5.61 | 28.41±5.61 | <0.001* |
| Subfertility Type        | n (n%) | n (n%) | <0.001* |
| Primary Infertility      | 48 (64%) | 48 (64%) | |
| Secondary Infertility    | 27 (36%) | 27 (36%) | |
| Gravidity                | n (n%) | n (n%) | <0.001* |
| Nulligravida             | 47 (62.7%) | 47 (62.7%) | |
| Primigravida             | 9 (12%) | 9 (12%) | |
| Multigravida             | 19 (25.3%) | 19 (25.3%) | |
| Parity                   | n (n%) | n (n%) | <0.001* |
| Nulliparous              | 63 (84%) | 63 (84%) | |
| Primiparous              | 6 (8%) | 6 (8%) | |
| Multiparous              | 6 (8%) | 6 (8%) | |
| Abortion                 | n (n%) | n (n%) | <0.001* |
| No abortion              | 57 (76%) | 57 (76%) | |
| ≤2                       | 11 (14.7%) | 11 (14.7%) | |
| ≥3                       | 7 (9.3%) | 7 (9.3%) | |
| Comorbidity              | n (n%) | n (n%) | <0.001* |
| NO                       | 63 (84%) | 63 (84%) | |
| Diabetes Mellitus        | 4 (5.3%) | 4 (5.3%) | |
| Hyperparathyroidism      | 1 (1.3%) | 1 (1.3%) | |
| Hypothyroidism           | 7 (9.3%) | 7 (9.3%) | |
| Tubal Patency            | n (n%) | n (n%) | <0.001* |
| Both Tubes patent        | 62 (82.7%) | 62 (82.7%) | |
| One Tube Blocked         | 10 (13.3%) | 10 (13.3%) | |
| Both Tubes blocked       | 3 (4%) | 3 (4%) | |

Table 2 shows the primary and secondary outcomes, the pain score and procedure time. A statistically significant difference (p<0.001) in the mean pain score was found between HSG procedure (5.03±2.26); with pain score range (VAS: 0-6), and HyFoSy (2.44±1.71) with pain score range (VAS: 1-10). With regards to procedure time (sec), no significant difference (p=0.697) was observed between HSG (125.01±37.18) and HyFoSy (125.01±35.21).

Table 2: Primary and Secondary outcomes.

This study found that patients with primary infertility had a statistically significant (p<0.002) lower mean pain scores (1.98±1.56) after HyFoSy procedure compared to patients with secondary infertility. Patients with a history of ectopic pregnancy had a statistically significant difference (p=0.013) higher mean pain score (5±1.160) compared with those without previous experience of ectopic pregnancy (2.3±1.63).

There was a significant difference (P=0.023; One-way ANOVA test) in patients’ pain perception according to tubal patency after HyFoSy. Our finding revealed that patients after HyFoSy with OTB (3.81±1.99) and BTP (2.24±1.58) had a higher mean pain score compared to patients with BTB (2±2). On the other hand, among these subgroups, no significant difference was found in the mean pain score after HSG. Looking at the mean pain scores for all independent patients’ variables, we found that the mean pain scores were higher among patients after HSG compared to those after HyFoSy (Table 4). Nevertheless, no statistical difference (p<0.597) was observed in the procedure time for HyFoSy and HSG (125.01 and 128.15 respectively) (Table 1).

Univariate linear regression analysis showed that differences in pain perceived after HyFoSy could be explained mainly by the indication (p=0.001), history of ectopic pregnancy (p=0.002) and OTB (p=0.007) (Table 5).
Table 3: Comparing reported pain levels scores between HyFoSy and HSG.

| HSG       | No Pain | Mild Pain | Moderate Pain | Severe Pain | Total |
|-----------|---------|-----------|---------------|-------------|-------|
| No Pain   | 0       | 0         | 0             | 0           | 0     |
| Mild Pain | 8 (57.1%) | 6 (15.8%) | 2 (8.7%)       | 0           | 16 (21.3%) |
| Moderate Pain | 6 (42.9%) | 23 (60.5%) | 12 (52.2%) | 0 | 41 (54.7%) |
| Severe Pain | 0       | 9 (23.7%) | 9 (39.1%)     | 0           | 18 (24%)  |
| Total     | 14 (18.7%) | 38 (50.7%) | 23 (30.6%) | 0 | 75     |

1HyFoSy: Hysterosalpingo-Foam Sonography
2HSG: Hysterosalpingography

Table 4: T-test and One-way ANOVA analysis of patient mean pain after HyFoSy and HSG.

| Variables               | HyFoSy1 (n=75) | HSG2 (n=75) |
|-------------------------|----------------|-------------|
|                         | Mean ± SD      | p-value     | Mean ± SD    | p-value     |
| Indication              |                |             |              |             |
| Primary Infertility     | 1.98±1.56      | 0.002*      | 4.75±2.11    | 0.18        |
| Secondary Infertility   | 3.26±1.68      |             | 5.52±2.47    |             |
| Parity                  |                |             |              |             |
| Nulliparous Parous      | 2.38±1.80      | 0.365       | 4.97±2.23    | 0.644       |
| 2.75±1.14               |               |             | 5.33±2.50    |             |
| Gravidity               |                |             |              |             |
| Nulligravida Multigravida | 2.23±1.67    | 0.185       | 4.91±2.10    | 0.601       |
| 2.79±1.75               |               |             | 5.21±2.53    |             |
| History of Ectopic Pregnancy |          |             |              |             |
| No                      | 2.3±1.63      | 0.013*      | 4.89±2.21    | 0.051       |
| Yes                     | 5±1.160       |             | 7.5±1.73     |             |
| Tubal Patency           |                |             |              |             |
| Both Tubes Patent       | 2.24±1.58     | 0.023*      | 4.85±2.17    | 0.356       |
| One Tube Blocked        | 3.8±1.99      |             | 5.9±2.73     |             |
| Both Tubes blocked      | 2±2           |             | 5.67±        |             |

*a: Independent T-test analysis, b: One-way ANOVA analysis
1HyFoSy - Hysterosalpingo-Foam Sonography
2HSG - Hysterosalpingography

Table 5: Univariate linear regression model: Predictors of the patients’ characteristics one reported pain score after HyFoSy1.

| Variables          | Un-standardized Coefficients | Standardized Coefficients | t   | p-value |
|--------------------|------------------------------|---------------------------|-----|---------|
|                    | B                             | Std. Error                | Beta|         |
| Indication         | 1.280                         | 0.386                     | 0.362| 3.314   | 0.001*|
| Parous             | 0.369                         | 0.541                     | 0.080| 0.683   | 0.497 |
| Gravidity          | 0.552                         | 0.406                     | 0.157| 1.359   | 0.178 |
| Ectopic Pregnancy  | 2.704                         | 0.826                     | 0.358| 3.272   | 0.002*|
| One Tube Blocked   | 1.558                         | 0.561                     | 0.312| 2.778   | 0.007*|
| Both Tubes blocked | -0.242                        | 0.973                     | -0.028| 0.028   | 0.804 |

*a: Dependent Variable: HyFoSy Pain Score
1HyFoSy: Hysterosalpingo-Foam Sonography
In our study, we evaluated the experienced pain after HSG and HyFoSy procedure and the duration of the procedure. HyFoSy is a safe, nontoxic and a less expensive alternative procedure to Hycosy [6]. Our findings are in concordance with the results of other studies in supporting the evidence of the lower pain experienced after HyFoSy compared to HSG [11,24]. The study showed about 50% difference in favor of HyFoSy in the mean pain score in comparison to HSG. Remarkably, the difference (0.98:1; HyFoSy and HSG, respectively) in the procedure time between HyFoSy and HSG was not significant, about 2 minutes for each, which is contrasting previous published data in the literature [11,24]. However, the average time for HyFoSy is in other studies was about 5 minutes.

Our results added new value to the current knowledge of pain with HyFoSy in evaluating the effect of the clinical characteristics on pain perception among patients. Among these variables is the type of patients’ infertility (Primary vs. Secondary). The results indicated a significant difference in patients’ perception of pain (nearly 40% lower) after HyFoSy between the two types of infertility in favor of primary infertility. We found that the history of ectopic pregnancy had its effect in the perception of pain; patients with history of one or more ectopic pregnancy experienced higher pain perception (about 50% more) after HyFoSy. Regarding tubal patency, our results are in line with a previous study, in which the mean pain score after HyFoSy for patients with BTP was less than the mean of patients with OTB [21].

Van Schoubroeck et al. [21] reported parity as a predictor for explaining the difference in the perception of pain [21]; however, our finding revealed that parity was not a predictor for pain perception. Our observation showed that the patients’ type of infertility (indication), history of ectopic pregnancy and tubal patency (OTB) variables that have an association with pain perception. The main limitation of this study is we did not assess the mean pain score according to the installed volume of contrast medium.

Conclusion

The experienced pain after HyFoSy procedure is well-tolerated. Patients’ clinical characteristics could predict the anticipated pain; hence, considering these characteristics help in physicians’ decision to give pain killer before HyFoSy procedure. Future research is required for large number of patients and should focus on assessing the pain during the stages of HyFoSy procedure.

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