European Journal of Obstetrics & Gynecology and Reproductive Biology 195 (2015) 168–172

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

A comparison of hysterosalpingo-foam sonography (HyFoSy) and hysterosalpingo-contrast sonography with saline medium (HyCoSy) in the assessment of tubal patency

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ARTICLE INFO

Article history:
Received 23 March 2015
Received in revised form 2 October 2015
Accepted 15 October 2015

Keywords:
Hysterosalpingo-contrast sonography
Tubal patency testing
Infertility
Tubal occlusion

ABSTRACT

Objective: A randomized controlled selective cross-over trial was performed to compare the diagnostic yield and efficacy of ExEm foam (HyFoSy) with saline medium (HyCoSy) as a contrast agent for hysterosalping-contrast sonography in subfertile patients.
Study design: 40 patients were randomized into HyCoSy with saline medium and HyFoSy with ExEm foam. Tubal patency were assessed according to pre-determined objective criteria that classified tubes based on degree of certainty in tubal patency. Selective cross-over testing with the other medium was performed in patients who had at least one possibly occluded or unexaminable tube on the initial test.
Results: 80 tubes were evaluated. On initial testing, the proportion of tubes that were classified as patent was higher with HyFoSy compared to HyCoSy (70.0% vs 40.0%, $p = 0.01$). A higher proportion of patients in the HyCoSy group required crossover testing [80.0% (16/20) vs 45.0% (9/20), $p = 0.02$]. On cross-over testing, 41.7% (10/24) of possibly occluded or unexaminable tubes in the HyCoSy group were re-classified as patent when examined with Ex-Em foam, compared to 8.3% (1/12) of possibly occluded or unexaminable tubes in the HyFoSy group ($p = 0.03$).
Conclusion: ExEm foam medium (HyFoSy) might improve the diagnostic yield and efficacy over saline medium (HyCoSy) for hysterosalpingsonography.

Introduction

Evaluation of the fallopian tubes forms an essential part of the infertility investigation as tubal disorder accounts for 25–35% [1] of female infertility. Hysterosalpingo-contrast sonography (HyCoSy) has been validated for the first-line evaluation of tubal patency [2].

The diagnosis of occlusion in HyCoSy rests on the non-visualization of tubal patency. It is usually not possible to differentiate between true tubal occlusion and a 'false' occlusion. 'False' occlusions may be due to a mucous plug, blood clot, myometrial spasm, mucosal oedema or technical difficulty [3]. The fallopian tubes usually follow a multiplanar course. Sometimes it may only be possible to demonstrate proximal patency by visualizing paracornual flow of contrast. Tracing the flow of contrast through the entire tubal length increases confidence in the diagnosis of proximal and distal patency but is more technically demanding [4].

Saline [5,6] or a mixture of saline and air [7,8] have traditionally been used for HyCoSy [1]. Agents such as Echovist-200® (Schering AG, Berlin, Germany), Infoson® (MBI, San Diego, USA) and SonoVue® (Bracco, Milan, Italy) which produce more intense contrast effects were subsequently introduced. More hyperechogenic media [2] may enhance contrast visualization and enable clearer delineation of tubal anatomy. This may enhance confidence in the diagnosis of tubal patency, reduce 'false' occlusion results and improve the diagnostic yield of the test.

Most hyperechogenic contrast media are now no longer commercially available or not licensed for intrafallopian use. In 2007, a non-embryo toxic gel known as ExEm-gel® (GynaecologIQ, Delft, The Netherlands) containing hydroxyethylcellulose and glycerol was introduced [9]. The gel is mixed with water to create a hyperechogenic foam that is used as a contrast medium for hysterosalpingo-contrast sonography (HyFoSy).

We performed a randomized controlled selective cross-over trial to compare the diagnostic yield and efficacy of ExEm foam

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http://dx.doi.org/10.1016/j.ejogrb.2015.10.008
0301-2115/

(HyFoSy) with saline medium (HyCoSy) as a contrast agent for hysterosalpingo-contrast sonography in subfertile patients.

Materials and methods

All patients referred for tubal patency assessment at the Singapore General Hospital's Centre for Assisted Reproduction were invited to participate. Inclusion criteria were subfertile women who required office tubal patency evaluation after assessment by a consultant gynaecologist. Exclusion criteria were age below the legal limit for consent (21 years old), inability to give informed consent, active pelvic infection, active uterine bleeding (including menstruation) and refusal to undergo cross-over testing. The study protocol was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This included an explanation that selective cross-over would be offered if results fulfilled pre-determined criteria.

Patients were randomized using computer-generated block randomization into the two groups (HyCoSy with saline medium and HyFoSy) and were blinded to the outcome of the randomization. All tubal evaluation procedures were performed by two study investigators and a sonographer, using a GE Voluson E8 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with a 6–12 MHz 3D endovaginal probe.

The procedure was scheduled during the immediate post-menstrual phase (days 6–12 of the menstrual cycle). Antibiotic prophylaxis was given at the referring consultant's own discretion, if there was a history of pelvic infection, or if tubal occlusion or a hydrosalpinx was demonstrated. Analgesia was given after the procedure if required.

A routine non-contrast vaginal ultrasound assessment of the pelvic organs was performed before tubal evaluation. The procedure for HyCoSy using saline medium was as follows: The cervix was visualized with a Cussco speculum and cleaned with an antiseptic. A No. 5 paediatric Foley catheter was introduced into the cervical os, using a tenaculum if necessary. The balloon was positioned in the lower uterine cavity and inflated with 2 ml of saline to prevent backflow of contrast medium through the cervix. The speculum was removed and the vaginal transducer was reintroduced in the longitudinal plane to confirm correct placement of the catheter. Sterile normal saline (0.9% NaCl) in a 20-ml syringe was introduced into the endometrial cavity while observing the uterine cornua at the transverse plane using B-mode and colour Doppler in the 2D and 3D modes. After tubal evaluation is completed, the balloon is deflated and up to 5 ml of normal saline instilled to look for intracavitary lesions.

The procedure for HyFoSy was as follows: The cervix was visualized and cleansed in the same manner as with HyCoSy. The pre-packaged balloon-less cervical catheter was introduced into the cervical os, using a tenaculum if necessary. The speculum was removed and the vaginal transducer was reintroduced in the longitudinal plane. Up to 5 ml of sterile water was instilled to confirm correct placement of the catheter and look for intracavitary lesions then re-aspirated before proceeding to tubal evaluation. 20 ml of foam contrast was reconstituted from ExEm-gel and water according to the manufacturer's instructions and introduced into the endometrial cavity while observing the uterine cornua at the transverse plane using B-mode. 3D volume acquisition was performed during injection.

With both media, tubal patency and quality of visualization were classified according the following parameters:

(1) Flow over the whole length of the tube, fimbrial outflow or peritoneal spillage of contrast provided definite evidence of complete (i.e. proximal and distal) tubal patency.
(2) Paracornual flow only without visualization of fimbrial outflow or peritoneal spillage suggested at least proximal patency.
(3) Contrast filling of the endometrial cavity without cornual flow suggested possible tubal occlusion.
(4) Technical difficulty making tubal evaluation impossible e.g. absent filling of the endometrial cavity due to backflow of contrast, inability to introduce the catheter into the cervical os or maintain the catheter in the correct position preventing instillation of contrast into the endometrial cavity.

Selective cross-over testing was performed immediately after the initial tubal evaluation in patients who had at least one possibly occluded (parameter 3) or unexaminable tube (parameter 4). Participant blinding was maintained for the medium used for the cross-over test. A tube was considered patent when there was definite evidence of complete tubal patency (parameter 1) or suggestion of at least proximal patency (parameter 2). Cross-over testing was not performed when both tubes were patent.

Maximal pain scores assessed according to a visual analogue scale were recorded immediately after the procedure. All patients were given a 24-h contact number for emergencies and contacted by telephone two weeks later to screen for late post-procedural complications. They were also given a follow-up appointment within a month of the procedure.

Analysis

The following outcome measures were used to assess diagnostic yield:

- Proportion of patent tubes detected with the initial tubal patency test.
- Proportion of possibly occluded or unexaminable tubes that were re-classified as patent on cross-over testing.

Efficacy was defined as the proportion of patients who required cross-over testing (i.e. had at least one possibly occluded or unexaminable tube on the initial tubal patency test).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc, Chicago, IL, USA). Analysis was by intention-to-treat. Differences in outcomes of quantitative data were tested for statistical significance using the Mann–Whitney *U* test. Differences in outcomes of qualitative data were tested for statistical significance using the Fisher's exact test or Chi-square test. All variables with a *p*-value of less than 0.05 were significant.

Results

51 women were referred for sonographic tubal evaluation at the Singapore General Hospital Centre for Assisted Reproduction over a 9-month period from April 2014, of which 40 participants were recruited, giving a response rate of 78.4%. There were no significant differences in baseline characteristics between the two groups (Table 1).

80 tubes were evaluated (Table 2). A higher proportion of tubes in the HyFoSy group demonstrated complete tubal patency (60.0% vs 35.0%, $p = 0.04$). A higher proportion of tubes in the HyCoSy group demonstrated possible tubal occlusion (55.0% vs 25.0%, $p = 0.01$). Overall, the proportion of tubes that were classified as patent was higher with HyFoSy compared to HyCoSy (70.0% vs 40.0%, $p = 0.01$).

There was no significant difference in median maximal pain scores between the two groups ($p = 0.17$).

Technical difficulty was encountered in the initial evaluation of two patients with 4 tubes. There was significant backflow