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Running title:

HyCoSy Tolerability. A systematic review and meta-analysis.

Title:

Severe pain during hysterosalpingo-contrast sonography (HyCoSy). A systematic review and meta-analysis.

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CAPSULE:

The objective is to assess the frequency of severe pain during HyCoSy in infertile women. Only 6% of the patients who underwent HyCoSy perceived severe pain during the procedure without finding significant differences between the different contrasts used.

ABSTRACT:

Purpose: To describe the frequency of severe pain perception during hysterosalpingo-contrast sonography (HyCoSy) in infertile patients. Secondary objective was to assess whether there are differences in the frequency of associated severe pain related to the procedure according to the contrast used.

Design: Systematic review and meta-analysis

Patients: Women undergoing HyCoSy as part of the study for a primary or secondary infertility.

Interventions: Searches were carried out in two databases (Pubmed and Web of Science). We included prospective or retrospective cohort observational studies that specified the type of contrast used during HyCoSy and report data regarding the number of patients who perceived severe pain during the procedure and the scale used for pain perception score.

Main Outcome Measures: Pooled frequency of severe pain perception during HyCoSy and the pooled frequency of severe pain perception based on the contrast used.

Results: Twenty-nine studies were included in this meta-analysis including a total of 7139 patients. In 10 studies, Saline solution with air was used as contrast (2103 patients), *EchoVist™* was used in ten studies (1353 patients); in five studies, *SonoVue™* was used (2014 patients) and in four studies *ExEm-Foam*™ was used as contrast (1369 patients). The pooled estimated frequency of severe pain perception during HyCoSy was 6% (95% CI: 4% – 9%). No statistically significant differences have been described regarding frequency of severe pain perception between the different contrasts used: Saline solution with air 7% (95% CI: 4% – 13%); *EchoVist™* 5% (95% CI: 2% – 10%); SonoVueTM 6% (95% CI: 4% – 9%); *ExEm-Foam*™ 5% (95% CI: 2% – 10%), respectively.

Conclusions: HyCoSy is a tolerable outpatient procedure. We did not find any evidence that one specific contrast was better tolerated than any other was.

KEYWORDS:

HyCoSy, HyFoSy, Tolerability, infertile women, tubal assessment

TEXT

INTRODUCTION

Approximately 35% of women with infertility present some tubal alteration, being the most frequent factor associated to female infertility[1]. Traditionally, fallopian tube evaluation has been investigated with laparoscopy and dye chromopertubation, but currently it is not recommended as routine due to its invasiveness[2]. X-ray hysterosalpingography (HSG) has been the alternative used for the assessment of tubal patency, but it involves pelvic ionizing irradiation and the use of iodinated contrast[2]. Hysterosalpingo-contrast-sonography (HyCoSy) was proposed as an alternative to HSG[3]

Saline solution (SS) mixed with air bubbles represents the most simple and economical ultrasound contrast medium used in clinical practice[4] but it requires some experience to appreciate the passage of the bubbles through the entire fallopian tube[5]. To solve this problem, the use of a hyperechoic contrast was advocated in early nineties. *Echovist™* is a galactose solution that highlights the fallopian tubes with a hyperechoic appearance on ultrasound when passing through them. Nevertheless, it has a short effect and may cause galactose allergies[6]. *SonoVue™* is a second-generation ultrasound contrast. It consists of a suspension of stabilized sulfur hexafluoride (SF6) microbubbles that provide high resistance and durability[6]. However, the safety of these contrasts been confirmed for intravenous use but its intrauterine and tubal use is off label[7]. In 2007, a non-embryotoxic gel was introduced as an intrauterine medium for HyCoSy as an alternative to previously mentioned contrasts. *ExEm-foam™* contains hydroxyethylcellulose and glycerol and its instillation offers a more stable filling of the uterine cavity[8].

Despite being a well-tolerated procedure, the most relevant side effect of the HyCoSY assessment of the uterine cavity and tubal patency is the pain associated with the procedure[9]. However, to the best of our knowledge, there is no systematic review analyzing and comparing the tolerability of the procedure regarding the type of contrast used.

The aim of this systematic review and meta-analysis is to describe the frequency of severe pain perception during HyCoSy in infertile patients. The secondary objective is to assess whether there are differences in the frequency of associated severe pain related to the procedure according to the contrast used.

MATERIAL AND METHODS

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (www.prisma-statement.org) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[10]. The inclusion and exclusion criteria for the selection of studies, as well as how data extraction and quality assessment, were defined before the start of the search. Institutional Review Board approval was waived because of study's nature and design. We did not register the protocol.

Data Sources and searches

Two researchers searched in two databases (*PubMed* and *Web of Science*) for studies that reported the number of patients who perceived severe pain during HyCoSY. The terms used for the search included "tubal occlusion", "tubal patency" and "ultrasound". For example, for search in PubMed, we use the following Medical Subject Heading (MeSH) terms: (tubal occlusion [All fields] OR tubal patency [All fields] AND

ultrasound [All fields]). Language limit was set to English. No limit on the year of publication was included.

Study Selection

After searching both databases, two investigators screened the results to exclude duplicate articles. Reviews, letter-to-editors and studies not dealing with the investigated topic were excluded after reading the titles and abstract. Of the remaining articles, two investigators independently reviewed the full text. The criteria to identify potentially eligible studies were as follows: prospective or retrospective cohort observational studies that specified the type of contrast used during HyCoSy, made in the context of a study of primary or secondary infertility and report data from the number of patients who perceived severe pain during the procedure. Studies whose study population were not infertile patients, those that did not specify the contrast type used or studies that did not report data from the number of patients who perceived severe pain during the procedure were excluded. Studies that used painkillers or spasmolytics prior to the HyCoSy were not excluded.

Reference list of included studies were reviewed to identify any additional relevant study. The corresponding author for a given study was contacted in cases of missing data. However, no response was provided. These studies were also excluded.

Data extraction and quality assessment

Two investigators independently extracted data for each study definitely included. The extracted data were as follows: study's design, mean age and range, the use or not of painkillers before the procedure, type of contrast used, the use or not of tentaculum for insertion of the catheter into the cervix, the type of catheter used, the

scale used to assess pain, the number of patients included in the studies and the number of patients who perceived severe pain during HyCoSy. In case of discrepancy between these two investigators, a decision was made by consensus.

Two researchers made a qualitative assessment of the studies using the *Newcastle-Otawa Scale* (NOS) based on the domains of "Selection", "Comparability" and "Outcome"[11]. "Selection" domain includes four items (representativeness of the exposed cohort, whether the nonexposed is drawn from the same community that the exposed cohort, ascertainment of the exposure and demonstration that the outcome of interest was not present at the start of the study. It can sum up to six stars). "Comparability" domain includes one item (comparability according to control for confounders. It can sum up to two stars). "Outcome" domain includes three items (assessment of the outcome, enough follow-up time and adequacy of follow up. It can sum up to five stars). The NOS classifies studies as *good quality* (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain), *fair quality* (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain) and *poor quality* (0 or 1 star in selection domain, OR 0 stars in comparability domain, OR 0 or 1 stars in outcome domain). Disagreements were solved by discussion among all investigators.

Statistical analysis

Statistical analysis has been performed using the software R (Development Core Team, Vienna, Austria) and the pack "*meta*"[12]. The frequency of severe pain perception during the procedure in each of the included studies was calculated. To calculate de 95%

confidence intervals (CI) for individual studies it was used the Clopper-Pearson test. We use a continuity correction of 0.5 in studies in which no patient perceived severe pain.

Pooled estimates of the frequency of severe pain perception with the corresponding 95% CI were calculated using the random effects model. Then, patients were stratified into four groups according to contrast type used (SS with air, *Echovist™*, *SonoVue™* or *ExEm-foam™*) and we calculated the pooled estimates of the severe pain perception frequency in each group with the corresponding 95% CI using the random effects model.

Heterogeneity among included studies was studied using the I^2 statistic[13] and the maximum-likelihood estimator for Tau^2. I^2 values of 25%, 50% and 75% correspond to cut-off points for low, moderate, and high heterogeneity.

RESULTS

After the search we identified 1100 articles between both databases. 324 duplicated records were excluded after a first screening of the titles. On the remaining 776 articles, 615 articles were also excluded after reading the abstract for the following reasons: 588 studies were not related to the topic or their study population were not infertile women, 18 articles were reviews, meta-analysis or opinion articles and 9 were reported in non-English language. Full text of the 161 remaining articles was read. 132 studies were excluded because not reported enough data about severe pain perception during HyCoSy. Finally, we included a total of 29 studies published between 1996 and 2020 reporting on 7139 women undergoing HyCoSy as part of their infertility study[6,7,15-39]. Figure 1 reflect the search and selection flow-chart.

Of all 29 studies included, 26 were prospective studies and three studies were retrospective. In 10 of the included studies, SS with air was used as contrast. *EchoVist™* was the contrast used in other ten studies, while *SonoVue™* and *ExEm-Foam*™ were used in five and four studies, respectively. Only ten of the articles included specified whether some type of painkiller or spasmolytic was used before the procedure, using analgesia systematically in eight of them. The use or not of tentaculum for insertion of the catheter into the cervix was only specified in four studies. In five of the studies, the mean age of the patients was not available. Table 1 summarizes data from the studies included in this systematic review.

As stated above, 7139 infertile patients undergoing HyCoSy were finally been included in this meta-analysis. In 2103 patients, the contrast used was saline with air, in 1353 patients *EchoVist™* was used, and in 2014 and 1369 patients *SonoVue™* and *ExEm-Foam™* were used, respectively.

Using a random effect model, we estimated that pooled frequency of severe pain perception during HyCoSy was 6% (95% CI: 4% – 9%). The perception of severe pain during the procedure based on the contrast used for each study can be seen in figure 2. The percentage of patients who perceived severe pain during HyCoSy when SS+Air was used as ultrasound contrast was 7% (95% CI: 4% – 13%). This figure was 5% (95% CI: 2% – 10%) for the use of *EchoVist™* was used as contrast experienced severe pain during the procedure. In the group of women in which *SonoVue™* was used as a contrast, the percentage of patients who perceived severe pain was 6% (95% CI: 4% – 9%) while in the group of patients in which *ExEm-Foam*™ was used was 5% (95% CI: 2% – 10%). We observed a high heterogeneity of the included studies (I^2: 92.1%, 95% CI: 89.8%-93.9%, Tau^2 was 1.05, $p < 0.01$) (Figure 3). We did not observe significant differences in the

percentage of cases with severe pain according to the type of contrast used, using ExEm-foam as reference (p=0.6425)

The qualitative assessment of the studies included in this review based on the NOS criteria is shown in table 2. With regard to "Selection" domain, all of the included studies were considered to represent a selected group of the cohort under study (infertile women undergoing HyCoSy). All studies actually ascertained the exposure (all studies used defined pain scale). We considered that, only in the 26 prospective studies, the outcome of interest (severe pain perception during HyCoSy) was certainly not known at the start of the study.

Regarding the "Comparability" domain, we considered that the cohorts were comparable as seven studies controlled for the main confounders. It has been considered that in the two studies that specified the non-use of analgesia prior to the procedure, they have also controlled for other potential confounding factors.

Finally, with regard to the "Outcome" item, we considered that in all patients included follow-up has been a complete and adequate because the time between exposure (HyCoSy) and the outcome (Pain perception) was short. A correct assessment of the results has been considered in the 12 studies in which a validated pain scale has been used.

DISCUSSION

Main results.

In the present meta-analysis, we have assessed the tolerability of HyCoSy as an outpatient procedure. The pooled estimated frequency of severe pain perception during

HyCoSy was 6% (95% CI: 4% – 9%). We did not find any evidence that one specific contrast was better tolerated than any other was.

Interpretation of results

With the results obtained in this meta-analysis, we can conclude that HyCoSy is a tolerable procedure that can be performed in office for assessing tubal patency. However, since no statistically significant differences were found between the different contrasts, it seems that tolerability should not be the criterion to recommend the use of one of them specifically. Therefore, probably, diagnostic accuracy and cost should be the criteria to be used for recommending any of the contrasts.

To date, very few studies have been published comparing the diagnostic accuracy of the different contrasts. Currently, *EchoVist™* has been discontinued from the market. Therefore, it is clear that this contrast is no longer available and cannot be used. No prospective studies have been published comparing the diagnostic accuracy of *SonoVue™* and *ExEm-Foam™* and only three studies have been published comparing the diagnostic accuracy of *ExEm-Foam™* and SS with Air[40,41,42]. Despite being the SS with air a cheaper contrast and with greater availability, the common conclusion of these three prospective trials was a superior diagnostic accuracy of *ExEm-Foam™*.

Therefore, considering these data and our findings regarding tolerability, and the fact that *ExEm-Foam™* is the only one licensed for intrafallopian use[43], makes this contrast the most recommended ultrasound contrast for the assessment of tubal patency in infertile patients[44].

Limits and Strengths

The main strength of our study is that, as far as we know, this is the first meta-analysis reported addressing this issue. We think we provide some new data that could be relevant in clinical practice, as we observed that no statistically significant differences were found between the different ultrasound contrasts. Additionally, our results are based on data from 7139 infertile patients, which can be considered as a good sample size.

On the contrary, the main limitation of this meta-analysis is the great heterogeneity of the included studies. The use of different scales for the assessment of pain perceived by the patient and the use of painkillers prior to the procedure in some of the studies as well as the different caliber of the catheter used and other methodological differences during HyCoSy can explain this great heterogeneity between studies. It would be advisable to carry out randomized prospective studies comparing the tolerability of various contrasts.

CONCLUSION

HyCoSy is a tolerable outpatient procedure. Only the 6% of patients undergoing HyCoSy perceive severe pain during the procedure. No statistically significant differences have been described regarding tolerability between the different contrasts used. Nevertheless, there was significant heterogeneity in estimates across studies.

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Figures' legends

Figure 1. Flowchart showing studies selection process

Figure 2. Forest plot showing the rate of severe pain in each study

Figure 3. Forest plot showing the rate of severe pain according to the contrast used.