

Use of Flurbiprofen Ester in 4-Dimensional Hysterosalpingography: Does Flurbiprofen Ester Relieve Pain During an Infertility Evaluation?

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Abstract

Objective: The purpose of this study was to determine the analgesic effect of a flurbiprofen ester injection via continuous intravenous drip during transvaginal 4-dimensional hysterosalpingography (TVS 4D-HyCoSy).

Methods: Two hundred thirty patients who underwent TVS 4D-HyCoSy for infertility from May 2018 to August 2021 at our hospital were selected. The participants were grouped based on tubal patency, flurbiprofen ester use, and uterine cannula diameter, as follows: bilateral tubal patency group; non-bilateral tubal patency group; atropine group; atropine + flurbiprofen ester group; coarse tube group; and fine tube group. The analgesic effect during TVS 4D-HyCoSy and pain relief were compared between groups using visual analog scoring (NRS). Additionally, the incidence of adverse effects was recorded and factors related to the influence of pain were analyzed.

Results: 1. Tubal patency reduced pain during ultrasound tubal examination, flurbiprofenate provided significant analgesia after ultrasound tubalography and reduced adverse effects ($P < 0.001$). 2. The tube diameter thickness had no effect on tubal ultrasonography procedure-related pain. 3. Multivariable analysis of pain relief during imaging suggested that the use of flurbiprofen for bilateral tubal patency had a significant positive effect on pain relief within 30 min after the examination with an AUC of 0.732 (95% CI: 0.665–0.798).

Conclusion: A flurbiprofen ester continuous intravenous drip had a good analgesic effect in patients with TVS 4D-HyCoSy. Specifically, the pain relief effect after examination was significant and reduced the incidence of adverse reactions during the contrast examination. Flurbiprofen ester can be administered independently and is worthy of clinical promotion and application.

Keywords

Analgesia, atropine, flurbiprofen ester, uterine tubal ultrasonography.

In recent years, the declining fertility rate has become a widespread concern in Chinese society and the infertility rate among women of childbearing age in China is increasing year-after-year. Indeed, tubal factors are the primary cause of female infertility, accounting for 30%–35% of all cases [1, 2]. Transvaginal hysterosalpingo-contrast sonography (TVS 4D-HyCoSy), which can dynamically display the size and shape of the uterine cavity, and demonstrate fallopian tube patency in real time, has been widely used for fertility assessment in infertile women. Our team began to study the clinical application of HyCoSy since 2010 and found that HyCoSy has high specificity (86.3%) and sensitivity (93.5%) for verifying tubal patency [3]. Domestic and international studies have confirmed the high specificity and sensitivity of HyCoSy for tubal and uterine cavity assessment [4–10]. However, during

TVS 4D-HyCoSy intubation and contrast administration, patients often experience pain and discomfort, and even have adverse reactions, such as dizziness, nausea, vomiting, blurred vision, and shock. Moreover, it has been reported that pain during tubal imaging can cause tubal spasm, resulting in a higher false-positive rate and lower diagnostic accuracy [11]. Atropine is the currently used anti-spasmodic drug during HyCoSy and is often used by intramuscular injection 30 min before imaging, but studies have found that the effect of atropine in dilating the cervical canal is weak and the analgesic effect is not apparent [12]. Flurbiprofen ester belongs to a new type of NSAID that mainly consists of flurbiprofen and its encapsulated lipid microspheres, which is targeted compared to other NSAIDs and has been widely used for postsurgical analgesia [13], but no studies have been published related to the use

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of flurbiprofen ester during TVS 4D-HyCoSy. Therefore, this study was proposed to determine the analgesic effect of flurbiprofen ester injection via continuous drip during TVS 4D-HyCoSy.

Methods and materials

Patients

Two hundred thirty patients scheduled for TVS 4D-HyCoSy as part of an infertility evaluation from May 2018 to August 2021 at our hospital were selected and grouped according to tubal patency, use of flurbiprofen ester, and uterine cannula diameter, as follows: bilateral tubal patency group (**Figure 1**); non-bilateral tubal patency group (**Figure 2**); atropine group; atropine + flurbiprofen ester group; coarse tube group; and fine tube group. General statistics were based on tubal patency, i.e., bilateral ($n = 139$) and non-bilateral tubal patency ($n = 91$). General data, including age, years of infertility, history of dysmenorrhea, endometrial thickness at the time of examination, and tube diameter using a uterine cannula, were compared between the two groups. This study was approved by the Ethics Committee of the Medical

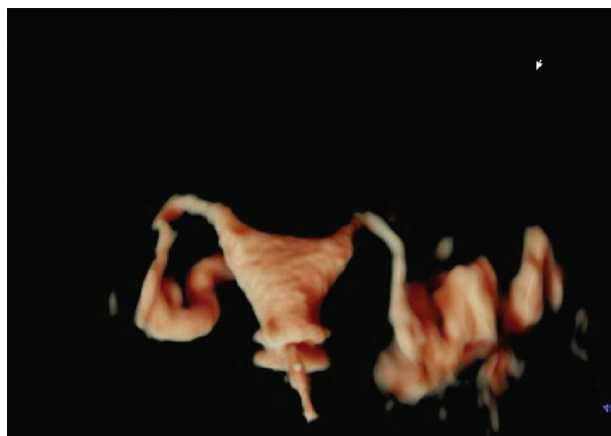


Figure 1 Bilateral tubal patency.

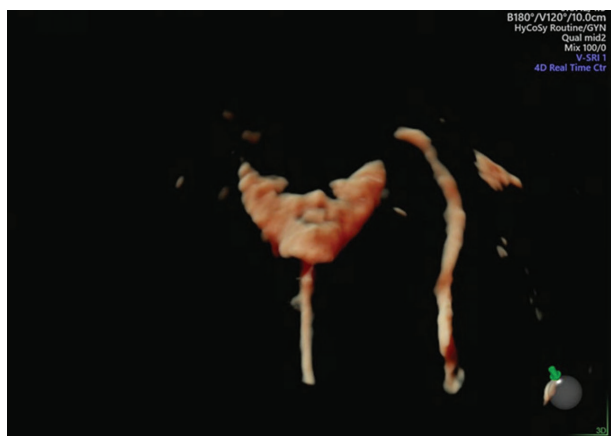


Figure 2 Non-bilateral tubal patency.

Ethics Committee of our hospital, and informed consent was obtained from the patients.

Inclusion and exclusion criteria

The inclusion criteria were as follows: ① healthy women who desire children without using contraception and are not pregnant; ② following treatment for tubal pregnancy; and ③ understood the study methodology and signed the informed consent form.

The exclusion criteria were as follows: ① peptic ulcers; ② severe hepatic, renal, and hematologic dysfunction; ③ severe heart failure and hypertension; ④ history of allergy to flurbiprofen ester, atropine, or contrast agent components; ⑤ aspirin-triggered asthma or a prior history of aspirin-triggered asthma; and ⑥ use of eloxacin, lomefloxacin, or norfloxacin.

Methodology

Preoperative preparation

Before undergoing TVS 4D-HyCoSy, a detailed medical history was obtained, a gynecologic examination was performed, and a routine white blood cell count and STD screening were performed. The patient was instructed to abstain from sexual intercourse after menstruation during the examination cycle. The examination was performed 5–10 d after menstruation or at the latest 20 d after menstruation if the patient has a long menstrual cycle. The bladder and rectum were emptied before the examination. In the atropine group, 0.5 mg of atropine sulfate (20180711; Henan Runhong Pharmaceutical Co., Ltd., Henan, China) was administered intramuscularly 30 min before TVS 4D-HyCoSy. In the combined atropine + flurbiprofen ester group, 0.5 mg of atropine sulfate (as above) was administered intramuscularly 30 min before TVS 4D-HyCoSy and a 20-mg flurbiprofen ester infusion was started 10 min before contrast cannulation. Flurbiprofen ester (3E171H; Hubei Noon Pharmaceutical Co., Ltd., Hubei, China) was added to 100 ml of saline for continuous intravenous infusion.

Inspection method

After moderate filling of the bladder, the patient was placed in the cystotomy position, disinfected, and draped with sterile towels. A coarse-tube 12-gauge Foley catheter was placed and 2 ml of 0.9% sodium chloride solution was injected into the balloon to occlude the endocervical opening. The balloon size was adjusted according to the patient's height and uterine size to determine the passage tube to the endocervical opening without detachment or 1.5 ml of 0.9% sodium chloride solution with fine COOK hysterosalpingography tube parameters for those with no history of pregnancy and no history of hysterosalpingation. The contrast agent was selected from SonoVue (Bracco, Milan, Italy) and 5 ml of 0.9% NaCl solution was added

to form a suspension. Two milliliters of the suspension was removed and 18 ml of 0.9% NaCl solution was added to dilute the contrast agent. Bilateral fallopian tubes and pelvic contrast coating were observed dynamically to assess the patency of the fallopian tubes. If the initial imaging of the fallopian tubes was poor or suggested obstruction, a second tubal imaging was performed after lavage treatment. Adverse reactions, such as pain, dizziness, and allergy were also recorded in patients.

Observed indicators and assessment methods

- (1) To observe the patency of the uterine tubes in both groups Tubal patency was divided into bilateral and non-bilateral patency (obstruction of one or both tubes).
- (2) Pain level scoring criteria
The imaging procedure was divided into three stages: placement of the scrotal speculum and balloon catheter (T1); injection of contrast medium/throughput (T2); and within 30 min after extubation (T3). Pain was assessed, observed, and recorded, as perceived by the patients. ① The pain level was evaluated by visual analog scoring (NRS) with a score of 0 representing no pain, 1–3 representing mild pain, 4–6 representing moderate pain, and 7–10 representing severe pain. Pain relief was defined as pain level after the examination compared to the time of examination (T3→T2), e.g., severe or moderate pain reduced to mild or no pain. ② Adverse reactions during intubation and the examination were recorded, including allergies, dizziness, nausea, vomiting, limb numbness, palpitations, flush, and blurred vision.

Statistical methods

SPSS 26.0 statistical software was used for data analysis and the measurement data conforming to a normal distribution are expressed as the mean \pm standard deviation ($\bar{x} \pm s$). A t-test was used for comparisons between two groups. The counting data were expressed as percentage, and χ^2 test was used for comparisons between groups. The difference was considered statistically significant at a $P < 0.05$ and stepwise forward binary logistic regression analysis was used for multivariable analysis.

Results

Comparison of general information

There were 139 cases with an age range of 21–43 years and a mean age of 31.68 ± 4.60 years in the bilateral tubal patency group. The mean years of infertility was 2.08 ± 1.67 years. The mean endometrium thickness at the time of examination was 7.49 ± 1.89 mm. There were 91 cases with an age range of 23–43 years and a mean age of 32.99 ± 4.91 years in the non-bilateral tubal patency group. The mean

years of infertility was 2.94 ± 2.81 years, and the mean thickness of the endometrium at the time of examination was 7.82 ± 2.23 mm. A statistically significant difference in age and years of infertility between the two groups was detected ($P = 0.042$ and $P = 0.009$, respectively [t-test]), while no significant difference was detected with respect to endometrial thickness ($P = 0.221$). In the bilateral tubal patency group 65.5% (90/139) of patients had dysmenorrhea and 74.1% (103/139) used coarse tubes. In the non-bilateral tubal patency group 64.8% (59/91) had dysmenorrhea and 69.2% (63/91) used coarse tubes. No statistically significant difference was detected in the history of dysmenorrhea or the thickness of the intubated tube between the two groups ($P = 0.922$ and $P = 0.420$, respectively [χ^2]).

Comparison of adverse reaction incidence

Among the 78 patients in the atropine group there were 21 with nausea and dizziness, 12 with facial flushing, 3 with blurred vision, and 2 with limb numbness, for an adverse reaction rate of 48.71%. Among the 152 patients in the atropine + flurbiprofen ester group there were 6 with nausea, for an adverse reaction rate of 3.9%. The incidence of adverse reactions in the atropine + flurbiprofen ester group was lower than the atropine group and the difference was statistically significant ($P < 0.001$).

Comparison of analgesic effects during TVS 4D-HyCoSy

A comparison of pain levels during the tubal imaging procedure in the bilateral tubal patency versus non-bilateral tubal patency groups with atropine alone versus the combination of atropine + flurbiprofen ester is shown in **Table 1**. The results showed that pain was significant in the non-bilateral tubal patency group during inspection ($P < 0.0001$). After inspection, pain was not significant in the atropine + flurbiprofenate group ($P = 0.003$).

Comparison of pain relief between groups

- (1) Pain relief in the atropine versus atropine + flurbiprofen ester groups are compared in **Table 2**. Atropine + flurbiprofenate relieved pain during tubal imaging in the bilateral and non-bilateral tubal groups ($P = 0.001$ and $P = 0.001$, respectively)
- (2) Flurbiprofen ester use was compared in the thick tube group with pain relief in the thin tube group among patients with bilateral patent fallopian tubes (**Table 3**). The data suggested that atropine + flurbiprofenate relieved pain during tubalography in the bilateral tubal patency group in whom fine tubes were used ($P = 0.001$).
- (3) Flurbiprofen use was compared with pain relief in the thick versus thin tube group among patients in the non-bilateral tubal patency group, as shown in **Table 4**.

Table 1 Comparison of Pain Levels During Tubal Imaging

Pain Assessment Period	Pain Grading	Grouping	Percentage of Moderate-to-Severe Pain (%)	P
During intubation	II-III degree	Bilateral patency of the fallopian tubes	54.7 (76/139)	0.303
		Non-bilateral patent fallopian tubes	61.5 (56/91)	
		Atropine	56.4 (44/78)	0.829
		Atropine + flurbiprofen ester	57.9 (88/152)	
During inspection	II-III degree	Bilateral patency of the fallopian tubes	39.6 (55/139)	0.000
		Non-bilateral patency of the fallopian tubes	68.1 (62/91)	
		Atropine	50.0 (39/78)	1.000
		Atropine + flurbiprofen ester	50.0 (76/152)	
After inspection	II-III degree	Bilateral patency of the fallopian tubes	12.9 (18/139)	0.847
		Non-bilateral patency of the fallopian tubes	12.1 (11/91)	
		Atropine	21.8 (17/78)	0.003
		Atropine + flurbiprofen ester	7.9 (12/152)	

Table 2 Comparison of Pain Relief Between Atropine and Atropine + Flurbiprofen Ester in Tubal Imaging

Projects	Grouping	Number of Cases	Relief	No Relief	P
Bilateral tubal patency group (N1 = 139 cases)	Atropine	29	17	12	0.001
	Atropine + flurbiprofen ester	62	58	4	
Non-bilateral tubal patency group (N2 = 91 cases)	Atropine	49	22	29	0.001
	Atropine + flurbiprofen ester	90	63	27	

Table 3 Comparison of Pain Relief Between the Thick and Thin Tube Groups in Bilaterally Patent Fallopian Tubes

Grouping	Coarse Tube		Fine Tube	
	No Relief	Relief	No Relief	Relief
Atropine	25	15	2	7
Atropine + flurbiprofen ester	21	42	6	21
P	0.278		0.001	

Table 4 Comparison of Pain Relief in Thick and Thin Tubes in the Non-bilateral Tubal Patency Group

Grouping	Coarse Tube		Fine Tube	
	No Relief	Relief	No Relief	Relief
Atropine	8	14	4	3
Atropine + flurbiprofen ester	4	37	0	21
P	0.000		0.000	

The results indicated that in the non-bilateral tubal patency group, atropine + flurbiprofenate relieved pain during tubalography whether fine or coarse tubes were used ($P < 0.001$ and $P < 0.001$, respectively).

Multifactor logistic regression analysis for pain relief during tubal angiography

Patient age, years of infertility, history of dysmenorrhea, endometrial thickness, tube diameter at the site of

insertion, tubal patency, and flurbiprofen continuous drip were analyzed for pain relief correlations. The statistically significant ($P < 0.05$) univariate indicators, including flurbiprofen continuous drip, thick tube, and bilateral tubal patency as independent variables and pain relief as the dependent variable were analyzed by binary logistic regression. The results suggested that flurbiprofen continuous drip and bilateral tubal patency had a significant positive relationship with pain relief, while tube diameter did not significantly affect pain relief (Table 5) and the ROC curve AUC of this model was 0.732 (95% CI: 0.665–0.798; Figure 3).

Discussion

The main clinical methods to determine tubal patency include laparoscopic fluid staining, X-HSG, and TVS 4D-HyCoSy, each with advantages and disadvantages. Laparoscopic fluid staining, which is the “gold standard,” technique is invasive [14] and has disadvantages, such as high invasiveness, high cost, and anesthesia risk, so laparoscopic fluid staining is usually used as a second-line verification or treatment after confirming obstruction by HSG. During X-HSG the patient is subjected to x-ray exposure, prolonged time to conception, and may be at risk for iodine allergy. HyCoSy is an ultrasound examination of the uterus and fallopian tubes to assess tubal patency with a transcervical contrast agent (air saline or microbubble contrast) [15]. HyCoSy has been shown to have a therapeutic role in addition to showing high accuracy in evaluating tubal patency [16, 17]. However, patients often exhibit varying degrees of pain and discomfort during the

Table 5 Multi-factor Logistic Regression Analysis of Pain Relief During 4-Dimensional Hysterosalpingography

Variables	B	Standard Error	Wald	P	OR (95% CI)
Coarse tube (vs. fine tube)	-0.703	0.381	3.395	0.065	0.495 (0.235-1.046)
Bilateral tubal patency (vs. non-bilateral tubal patency)	1.134	0.345	10.824	0.001	3.107 (1.581-6.103)
Flurbiprofen esters (vs. flurbiprofen-free)	1.356	0.317	18.277	0.000	3.881 (2.084-7.226)

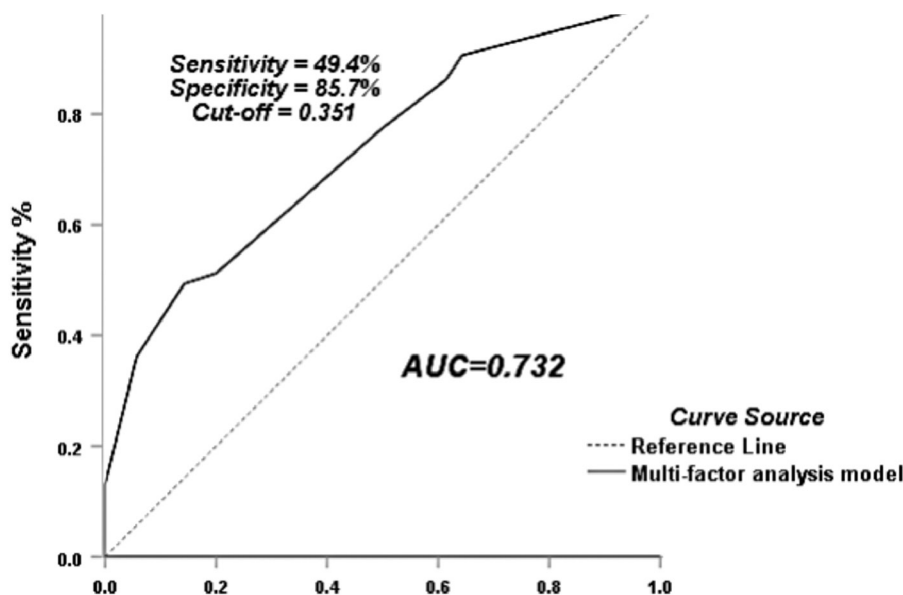


Figure 3 Flurbiprofen to relieve 4-dimensional hysterosalpingography pain ROC curve.

series of maneuvers during the HyCoSy examination which affects the accuracy of the results. Therefore, how to alleviate pain during and after the examination has become a focus of concern for clinicians and patients. Possible causes of pain from HyCoSy include psychological tension, excessive speed of contrast injection, size of the contrast catheter balloon, and the patient’s own diseases, such as uterine adhesions, cervical stenosis, and inflammation [18]. The pain level in most patients occurs from a combination of these factors. It has been suggested that HyCoSy triggers the most intense pain with cervical dilation [19]. In contrast, Guzel et al. [20] concluded that the most intense pain was caused by increased pressure in the uterine cavity during contrast injection.

Our study showed that preoperative injection of atropine was not effective in relieving patient pain, which is consistent with the literature [21]. Flurbiprofen ester has been widely used in surgical procedures, such as brain, upper abdominal, and gynecologic surgery, and significant analgesic effects have been achieved [13, 22, 23]. In the present study we attempted to introduce flurbiprofen ester during uterine tubal ultrasonography. Flurbiprofen ester is a non-steroidal analgesic with significant effects for various types of pain and targeted effects on inflammation and surgical sites [21, 23]. After entering the site of action through the carrier lipid microspheres, flurbiprofen ester was released by the carrier and rapidly hydrolyzed by the action of carboxyl lipase to produce flurbiprofen, which has a significant inhibitory effect on prostaglandin synthesis and in turn produces

analgesic effects. The drug has a high safety factor, rapid onset of action, and long-lasting analgesic effect [21, 24].

In this study we showed that the addition of a flurbiprofen ester continuous intravenous drip to the routine preoperative injection of atropine had an effect on analgesia during ultrasound tubography, which was mainly reflected after the examination ($P = 0.003$). The flurbiprofen ester continuous intravenous drip was not significant for analgesia during intubation and examination, likely for the following reasons: 1. the greatest pain occurred during intubation and the TVS 4D-HyCoSy examination; 2. There was a high level of patient tension during intubation and the TVS 4D-HyCoSy examination, as well as pain-inducing factors, such as cervical dilation and increased pressure in the uterine cavity during contrast injection; and 3. after the examination the catheter was removed, the patient’s tension was relaxed, and flurbiprofen ester was more likely to have an objective role. We also found that at the time of examination, patency of the fallopian tube had a significant positive significance for analgesia ($P = 0.000$), and at the time of catheterization and after the examination, patency of the fallopian tube had no significant effect on analgesia, which suggests that patency of the fallopian tube may be one of the main causes of pain during HyCoSy. Flurbiprofen ester under continuous intravenous drip conditions was effective in relieving pain within 30 min after imaging, regardless of the patency of the fallopian tube. In conclusion, the patency of the fallopian tube affects pain during the examination and a flurbiprofen ester continuous intravenous infusion is effective in relieving pain.

During HyCoSy a flurbiprofen ester continuous intravenous infusion had a significant positive effect on pain relief during ultrasound tubography. With the use of thick tubes, flurbiprofen ester provided insignificant pain relief in those with bilateral tubal patency and significant pain relief in those with non-bilateral tubal patency, suggesting that tubal patency correlates with pain relief during the imaging procedure. With the use of fine tubes, flurbiprofen ester is effective in relieving pain regardless of the patency of the tubes. One possible reason to explain this phenomenon is that women with thick tubes, all of whom had been pregnant or delivered and had a history of hysterectomy, may be less nervous and more tolerant of pain. Second, those with bilateral patent fallopian tubes and with thin tubes who had no history of pregnancy and had not undergone a hysterectomy may be more nervous and less tolerant of pain. In order to further verify the relationship between pain relief during tubal imaging and the patency of the tubes, the effect of flurbiprofenac, and the diameter of the cannula, we performed a multivariable logistic regression analysis of pain relief during tubal imaging. The results showed that the patency of the tubes and the effect of flurbiprofenac were associated with pain relief during tubal imaging and were not related to the diameter of the cannula.

Moreover, our study also showed that the incidence of adverse reactions (excluding pain and dry mouth) was significantly lower in the flurbiprofen ester group than the atropine alone group. In addition, the psychological burden of the patients was relieved during the imaging process.

This study had several limitations. First, this study was single-center data and the sample size was not large enough. Second, this study was a retrospective study. This study needs to be validated by more center samples at a later stage.

Conclusion

A flurbiprofen ester continuous drip has a good analgesic effect in patients undergoing TVS 4D-HyCoSy. Specifically, the pain relief effect was significant after the examination and reduced the incidence of adverse reactions. A flurbiprofen

ester continuous drip can be administered independently during a contrast examination and is worthy of clinical promotion and application.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Sun Yat-sen Memorial Hospital of Sun Yat-sen University (SYSKY-2022-479-01).

Conflict of interest

The authors have no potential conflicts of interest to declare.

Author contributions

All authors contributed to the design and implementation of the study. LT and SJW: writing—original draft, collected, and analyzed data; ALM and SML: writing—review and editing, collected, and analyzed data; SLZ: writing—review and editing; SZ and PXC: supervision, writing—review and editing; ND and BML: conceptualization, supervision, writing—review and editing. All authors read and approved the final manuscript.

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