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Comparative study of vaginal danazol vs diphereline (a synthetic GnRH agonist) in the control of bleeding during hysteroscopic myomectomy in women with abnormal uterine bleeding: a randomized controlled clinical trial

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ABSTRACT

Objective: To compare the usefulness of vaginal danazol and diphereline in the management of intra-operative bleeding during hysteroscopy.
Design: Randomized controlled clinical trial.
Setting: University hospital.
Patients: One hundred and ninety participants of reproductive age were enrolled for operative hysteroscopy. Thirty women were excluded from the study.
Interventions: One hundred and sixty participants with submucous myomas were allocated at random to receive either vaginal danazol (200 mg BID, 30 days before surgery) or intramuscular diphereline (twice with a 28-day interval).
Main outcome measures: Severity of intra-operative bleeding, clarity of the visual field, volume of media, operative time, success rate for completion of operation and postoperative complications.
Results: Overall, 145 patients completed the study. In the danazol group, 78.1% of patients experienced no intra-operative uterine bleeding, and 21.9% experienced mild bleeding. In the diphereline group, 19.4% of patients experienced no intra-operative uterine bleeding, but mild, moderate and severe bleeding was observed in 31.9%, 45.8% and 2.8% of patients, respectively. The difference between the groups was significant ($p < 0.001$). A clear visual field was reported more frequently in the danazol group compared with the diphereline group (98.6% vs 29.2%, $p < 0.001$). The mean operative time was 10.9 min and 10.6 min in the danazol and diphereline groups, respectively ($p = 0.79$). The mean volume of infused media was 2.0 L in both groups ($p = 0.99$). The success rate was 100% for both groups with no intra-operative complications.
Conclusion: Both vaginal danazol and diphereline were effective in controlling uterine bleeding during operative hysteroscopy. However, vaginal danazol provided a clearer visual field.

Introduction

Abnormal uterine bleeding is a significant issue, often caused by uterine fibroids [1]. Hysteroscopy can be used for visualizing and treating intra-uterine benign focal lesions. This operative technique is best performed with a flat and/or atrophic endometrium [2]. Complete myoma resection is one of the main determinants of treatment success. However, hysteroscopy may not be successful due to continuous uterine bleeding. Endometrial thickness or intra-uterine pathologies may further narrow the already-limited space, and obscure the vision in ways that are not safe and acceptable for the procedure. Any effort to enhance the feasibility of hysteroscopy will increase its success rate. Different pharmaceutical compositions are used before surgery to reduce the thickness of the endometrium in order to improve visibility during surgery, such as gonadotropin-releasing hormone (GnRH) agonists [3] and other anti-estrogenic compounds such as cabergoline [4], raloxifene plus progestins [5], ulipristal acetate [6] and gestrinone

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[7]. Although GnRH agonists have been used to reduce the size of uterine fibroids and to prepare the uterine cavity for hysteroscopic resection, the advantages of their use are still being questioned [8].

More recently, danazol has been administered for the treatment of endometrial hyperplasia with satisfactory results [9]. Danazol treatment, along with expression of hypoestrogenism through inhibition of the hypothalamic-pituitary axis, decreases aromatase expression with a direct, albeit dose-dependent, effect on the endometrium [10]. In cases of "minor" hysteroscopic surgery (e.g., removal of intracavitary fibroids), GnRH agonists may be considered too expensive and seen as "overtreatment". In such cases, danazol, which is less expensive with a shorter treatment course for pre-operative endometrial preparation, may be considered to be more suitable and sufficient to obtain satisfactory results and a better surgical environment. Danazol is also capable of reducing uterine volume, menorrhagia, endometrial thickness and length of surgery [10].

This randomized controlled clinical trial was designed to assess the short-term intra- and postoperative outcomes and consequent quality of treatment when using vaginal danazol before hysteroscopic surgery compared with GnRH agonists.

Materials and methods

This randomized controlled clinical trial was conducted from August 2013 to January 2015 at Alzahra Teaching Hospital, Tabriz University of Medical Sciences. One hundred and ninety participants of reproductive age with a history of persistent mild-to-moderate uterine bleeding that was resistant to treatment, and submucous myomas <4 cm in diameter as the underlying cause of bleeding were enrolled. One hundred and sixty of these women were eligible for hysteroscopic resection of the myoma. The researchers received ethical approval from the University Ethical Committee and the patients' informed consent was obtained. Pilot study data indicated that 29% of patients in the diphereline group experienced no intra-operative uterine bleeding, and 52% of patients experienced no intra-operative uterine bleeding in the danazol group. Thus, our study required 72 experimental subjects and 72 control subjects in order to reject the null hypothesis that the intra-operative uterine bleeding experience rates for experimental and control subjects are equal with a power of 0.8. The Type I error probability associated with the test of the null hypothesis is 0.05. In order to reject the null hypothesis, then, each group had a sample size of 80. Random sampling was used to assign the patients to groups. Randomization was performed using Rand List Version 2.1 (DatInf GmbH, Tübingen, Germany) with sequentially-numbered containers. Research coworkers introduced the eligible patients to the main researcher who generated the random allocation sequence, enrolled the participants and assigned participants to interventions. Pap smear, transabdominal and transvaginal sonography and official endometrial sampling were all undertaken to determine the pathology of the endometrium before pharmaceutical treatment. Patients with hypertension; liver problems; adnexal pathology; lung, renal, cardiovascular and metabolic diseases; cervical and uterine cancer; submucous myomas >4 cm in diameter; uterine septa; genital tract infections; pregnancy and recent history of anticoagulant consumption were excluded. Eligible patients were divided at random into two equal groups. One group received vaginal danazol (200 mg BID) (Cipla Ltd, Mumbai Central, Mumbai, India), which was placed into the posterior vaginal fornix every 12 h for 30 days prior to hysteroscopy (starting on the first day of menstrual bleeding), and the other group received diphereline (3.75 mg/im) (IPSEN Pharma Biotec, Paris, France) every 28 days for 2 months prior to hysteroscopy, starting on the 18th day of the menstrual cycle. The amount of bleeding during surgery was determined using an ordinal scale. During surgery, the amount of bleeding was classified from zero (no bleeding) to 5 (severe bleeding) by agreement between the surgeon and nurse. In addition to routine blood tests, sodium and potassium levels were measured before surgery and 6 h after surgery. Changes in blood pressure and heart rate during anaesthesia were documented. Dextrose 5% was used as a medium in both groups. Care providers and those assessing the outcomes were blinded after assigning the patients to the interventions. All patients underwent general anaesthesia in the same way, and the same surgeon performed all procedures.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) and frequency (%). Statistical Package for the Social Sciences Version 16 (SPSS Inc., Armonk, NY, USA) was used to analyze the data. Normally distributed quantitative data were studied using a Kolmogorov–Smirnov test and a q–q plot. A t-test was used for independent samples to compare quantitative variables. Qualitative data between the two groups were compared using Chi-squared test or Fisher's exact test, and $p < 0.05$ was considered to indicate statistical significance. In terms of length of disease, the standard error of the mean has been reported rather than the SD.

Results

One hundred and forty-five patients (73 patients in the danazol group and 72 patients in the diphereline group) completed the study. The CONSORT flow diagram is shown in Appendix A, and the characteristics of the patients are summarized in Table 1. Details of intra-operative bleeding and intra-uterine view in the two groups are shown in Table 2; the differences between the two groups were statistically significant ($p < 0.001$). The results of pre-operative partial thromboplastin time (PTT) in the danazol and diphereline groups were 30.5 ± 2.2 and 32.2 ± 3.2, respectively; this difference was significant ($p < 0.001$). The results show that postoperative serum haematocrit and haemoglobin levels were significantly lower in the diphereline group compared with the danazol group [2.5% vs 1.3% ($p = 0.01$) and 0.9 vs 0.3 mg/dl ($p < 0.001$), respectively]. The mean serum volume used during surgery in the danazol and diphereline groups was 2.0 ± 1.2 l and 2.0 ± 1.4 l, respectively

Table 1
The characteristics of the studied patients; group 1 (danazol) and group 2 (diphereline).

Variable	Group 1 ($n = 73$) Mean ± SD	Group 2 ($n = 72$) Mean ± SD	p-value*
Age	40.22 ± 5.12	39.50 ± 5.25	0.14
Gravidity	3.05 ± 1.54	4.14 ± 1.71	0.76
Parity	2.58 ± 1.33	2.72 ± 1.79	0.56
Length of disease (months)	32.04 ± 3.96	18.60 ± 2.52	0.01
Number of myomas	1.36 ± 0.59	1.25 ± 0.53	0.25

* Differences were considered statistically significant at $p < 0.05$.

Table 2
The percentage of intraoperative bleeding and view in group 1 (danazol) and group 2 (diphereline).

Variable	Group 1 % (N)	Group 2 % (N)	p-value*
No bleeding	78.1 (57)	19.4 (14)	<0.001
Mild bleeding	21.9 (16)	31.9 (23)	
Moderate bleeding	0.0	45.8 (33)	
Severe bleeding	0.0	2.8 (2)	
Light view	98.6 (72)	29.2 (21)	<0.001
Dark view	1.4 (1)	70.8 (51)	

* Differences were considered statistically significant at $p < 0.05$, N = number.