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Comparative study between calcium dobesilate and proteolytic enzymes in treatment of simple ovarian cyst

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Abstract

Introduction: Functional ovarian (FU) cysts represent the most common type of ovarian cysts in women in the reproductive age group. They are mostly asymptomatic and may disappear without treatment within three months. The appropriate management of functional ovarian cysts is the most controversial problems facing gynecologists today despite the different treatment modalities.

Aim of the study: The study aimed to assess the efficacy of Doxium versus chymotrypsin on the resolution of simple ovarian cysts.

Subjects and Methods: 100 patients with functional ovarian cysts were included in this randomized controlled study without previous ovarian cysts management before. The patients were divided into two equal groups, each with 50 women. Group A included women treated with Doxium, where group B had the women treated with Alphintern. All patients attended the outpatient clinic after the end of menstruation for three consecutive months for a transvaginal ultrasound.

Results: Both lines of treatment resulted in the management of FOC, with persistence percentage in doxium and alphintern (20% and 5%, respectively), but doxium has better results in a patient with normal BMI than obese and overweight than alphintern.

Conclusion: Doxium and Alphintern proved their effectiveness in FOC management (new novel), but we need to increase the dose of doxium in overweight and obese patients. Moreover, alphintern is more efficient in the improvement of functional ovarian cyst in overweight and obese patient.

Keywords: Functional ovarian cyst; calcium dobesilate; alphintern; vascular endothelial growth factor.

1. Introduction

Follicular and corpus luteal cysts are considered functional or physiologic cysts, where both occur during the normal menstrual cycle. Follicular cysts arise when follicles fail to rupture during ovulation and appear smooth, thin-walled, and unilocular. In the follicular phase, follicular cysts may form because of a lack of ovum

physiological release due to excessive FSH stimulation or absence of the usual LH surge at mid-cycle just before ovulation. These cysts continue to grow because of hormonal stimulation. Follicular cysts are usually larger than 2.5 cm in diameter. Granulosa cells lead to excess estradiol production,

which lead to decrease frequency of menstruation [1].

Functional ovarian cysts have variable clinical manifestations. Most of them are discovered during the ultrasound examination. Most cysts are safely left with no interference and are monitored with follow-up by pelvic examination and ultrasound. Some functional cysts can regress rapidly with the intake of combined contraceptive pills [2].

CaD belongs to the 2,5-dihydroxyphenylic ac-ids, a newly described family of molecules that interfere with

growth factor signaling. CaD binds to the heparin-binding domain of FGF-1, thus reducing FGF-1 activity. CaD could act as a new VEGF antagonist without adverse side effects [3].

Chymotrypsin has potent anti-inflammatory properties that accelerate the reabsorption of inflammatory edema and postoperative and post-traumatic hematomas and edema. Moreover, chymotrypsin has a proteolytic activity, which enables the destruction of the fibrinous formations. That results from subacute or chronic inflammatory processes [4].

2. Subjects and methods

2.1. Subjects

The study started from March 2020 to December 2020. A hundred patients with functional ovarian cysts were recruited. All participants attend the single outpatients' clinic, Department of Obstetrics and Gynecology, Fayoum University Hospital, Fayoum, Egypt. The participated women represented a homogenous group of the community. None of those women were treated for ovarian cysts before. A full assessment of the medical history was performed for all women. That included age, occupation, address, marital status, chronic pelvic pain, backache, dyspareunia, leukorrhea, abnormal uterine bleeding, amenorrhea, infertility, mid-menstrual pain, obstetric history, menstrual history, and history of contraception.

Patients attended the outpatient clinic after the end of menstruation. A transvaginal

ultrasound was performed for the selection of cases. The patients were divided into two equal groups. Each group included 50 women as follows: Group A included women treated by Doxium. Group B included women administered Alphintern. Women managed by either of the two modalities were followed up by transvaginal ultrasound (Philips) monthly for three successive months postmenstrual.

Each tablet of alphintern (Amoun Pharmaceutical Co., Al Obour, Al Qalyubia, Egypt) contains: Chymotrypsin 300 E.A.U. (14 micro Katal), Trypsin 300 E.A.U. (5 micro Katal). The dose was one swallowed tablet at three times/day. Doxium 500 mg capsules (Minapharm Pharmaceutical Co., 10th of Rammadan, Cairo, Egypt) was administered orally at a daily dose of 0.5-2 g (equivalent to 1-4 tablets).

2.2. Inclusion criteria

Age: 18y-45y, Size: 2.5-6 cm, simple ovarian cyst (Done post menstrual, Round or oval anechoic space with smooth thin walls, Posterior acoustic enhancement, No solid component or septation, No internal flow at color Doppler US).

2.3. Exclusion Criteria

Age: >45 and <18 years, size: <2.5 cm or >6 cm, any other ovarian lesion, hydrosalpinx/ pyosalpinx/ ovarian torsion, any other cyst (dermoid cyst-endometriotic cyst).

3. Results

The study revealed a statistically significant difference between doxium and alphintern regards Parity. While no statistically significant difference between

2.4. Statistical analysis

Sample size calculation was done using G power program for a power of 0.8. Statistical presentation and analysis of the present study were conducted, using SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA) statistics and using ANOVA with post hoc significance for continuous variables, chi-square test for qualitative data. P-value less than 0.05 was considered significant.

doxium and alphintern as regards the size of the cyst (cm), FU after one, two, and three months ($P>0.05$) (Table 1).

Table 1: Effect of Both treatments in both patent’s groups.

	Groups		Mann Whitney	P-value
	A	B		
Parity	1 (0-4)	3 (2-4)	888	0.011
Cyst size (cm)	3.3 (3-4.22)	3.9 (3.2-5)	977	0.059
FU one month.	3 (2.7-3.77)	3 (3-4.5)	1135	0.424
FU two months.	2.70 (0-3)	1 (0.07-3)	1164	0.546
FU three month.	1 (0-3)	0.5 (0-3)	1120	0.346

It revealed a statistically highly significant difference between FU after one, two, and three months regards the doxium group. There is a significant difference

between FU after 1month when compared with either FU after two and three months, ($P<0.001$) (Table 2).

Table 2: Effect of doxium on the Functional cysts' sizes.

	FU Age (Month)			Kruskal-Wallis	P-value
	1	2	3		
Size (Cm)	3 ^a (2.7-3.8)	2.7 ^b (0-3)	1 ^b (0-2.7)	21.519	<0.001

It revealed a statistically significant difference between FU after one, two, and three months regards the Alphintern group. There was a significant difference between FU after one month when compared with

either FU after two or three months ($P < 0.001$) (Figure 1).

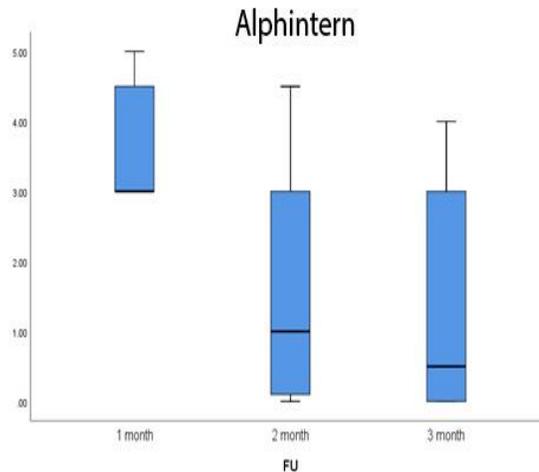


Figure 1: Effect of alphintern on the Functional cysts' sizes.

4. Discussion

Ovarian follicles and the corpus luteum (CL) produce several angiogenic factors. However, vascular endothelial growth factor (VEGF) was thought to play a paramount role to regulate the normal and abnormal angiogenesis in the ovary. The expression of VEGF in ovarian follicles depends on the follicular size. Inhibition of VEGF expression results in decreased follicle angiogenesis and the lack of mature antral follicles. The permeabilizing activity of VEGF was involved in follicle antrum

formation and the ovulatory process. In the CL, VEGF expression corresponds to different angiogenesis patterns during its lifespan [5].

Chymotrypsin possesses potent anti-inflammatory and anti-edematous properties that enable hasten the resorption of inflammatory edema and postoperative and post-traumatic hematomas and edema. Furthermore, chymotrypsin has proteolytic properties that facilitate destroying in situ the fibrinous formations resulting from

subacute or chronic inflammatory processes [4].

The current study aimed to assess the effect of two medical treatment on the resolution of simple ovarian cyst instead of the Conservative management, which represent a source of anxiety for patients and clinicians and the unnecessary burden of surgical intervention on resources. Treatments included Doxium (calcium dobesilate), by its VEGF antagonist action, versus chymotrypsin (proteolytic enzyme), by its anti-inflammatory and anti-edematous actions.

The results revealed that doxium might be a successful choice in ovarian diseases, in which VEGF had a role in their pathogenesis. A previous study proven that Calcium dobesilate (CaD) treatment reduced OHSS to 12%, compared to complete recovery (62%) in the group received doxium in our study. Moreover, Calcium dobesilate (CaD) de-creased severe OHSS to 2% [6]. Another study tested the management of the ovarian cyst, but they used contraceptive pills as a line of treatment for functional ovarian cyst [7].

Although functional ovarian cyst may be present with different complaints, the most common complaints are pain and bleeding, and sometimes it may be accidentally discovered. Our results revealed that pain was present in about 32% of the doxium group and 48% in the alphintern group. A previous study has proven similar results (44.8%) [7].

In the current study, we compared the effect of both drugs after one, two, and three

months. We found that alphintern group patients improved earlier than the doxium group, however, both drugs had the same effect on the cyst size after three months of treatment (median =1 in doxium and 0.5 in alphintern with $P=0.346$). A previous study had used the contraceptive pills only for two months and found shared with us in the significant improve appeared after two months (P-value < 0.005 between pre-treatment and after two months cyst in the contraceptive study and alphintern group and doxium group) [7].

Regarding the ovarian cyst size, our results agreed with the study conducted by Ismael et al., (2020) regarding the ovarian cyst size (median =3.3 in the doxium group and 3.9 in the alphintern group) versus 4.452 ± 1.0603 for three months. At the end of the study, they found that the cyst was persistent in about 22 % of the patients versus 10 (20 %) patients and 8 (16 %) patients in doxium and alphintern groups, respectively [7].

5. Conclusion

Doxium and Alphintern are recommended as the line of FOC management (new novel). They also hasten the disappearance of functional ovarian cysts. They are associated with high success rates in patients with a functional ovarian cyst, but we need to increase the dose of doxium in overweight and obese patients. Moreover, alphintern is more efficient in improvement of FOC in overweight and obese patients.

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Ethical Approval Statement: The protocol was approved by the Ethical Committee of

Fayoum Faculty of Medicine, Fayoum, Egypt. The researcher informed the participants about the objectives of the study, the examination, investigations that were done, the confidentiality of their information, and their right not to participate in the study.

Informed Consent Statement: Written informed consents were obtained from all patients.

Conflicts of Interest: All authors declare no conflict of interest.

References

1. Bonde AA, Korngold EK, Foster BR, Fung AW, Sohaey R, Pettersson DR, Guimaraes AR, Coakley FV. Radiological appearances of corpus luteum cysts and their imaging mimics. *Abdom Radiol (NY)*. 2016 Nov;41(11):2270-82. doi: 10.1007/s00261-016-0780-1.
2. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. *Obstet Gynecol*. 2010 Jan;115(1):206-18. doi: 10.1097/AOG.0b013e3181cb50b5.
3. Njau F, Shushakova N, Schenk H, Wulfmeyer VC, Bollin R, Menne J, Haller H. Calcium dobesilate reduces VEGF signaling by interfering with heparan sulfate binding site and protects from vascular complications in diabetic mice. *PLoS One*. 2020 Jan 14;15(1):e0218494. doi: 10.1371/journal.pone.0218494.
4. Shaker H, Tawfik M, Gawad K, Albert G. Efficacy and safety assessment of α -chymotrypsin injection in postoperative and post-traumatic edema: a prospective, open-label, multicenter observational registry study in Egypt. *The Egyptian Journal of Surgery* 2017; 36(1), 88. doi: 10.4103/1110-1121.199896.
5. Kaczmarek MM, Schams D, Ziecik AJ. Role of vascular endothelial growth factor in ovarian physiology - an overview. *Reprod Biol*. 2005 Jul;5(2):111-36.
6. Saad AS, Khalid AM. Calcium Dobesilate versus Cabergoline for Prevention of Ovarian Hyper Stimulation Syndrome. *Reprod Syst Sex Disord*. 2017; 61, 1-5. doi: 10.4172/2161-038X.1000204.
7. Ismael N, Mohamed S, Atout M, Aga Q, Alk-hammas S. The Effect of Using Combined Oral Ethinyl Estradiol and Levonorgestrel in the Resolution of Menstrual Pattern Disorder and Functional Ovarian Cyst. *Annals of the College of Medicine, Mosul* 2020, 41(2),190-6. doi: 10.33899/mmed.2020.164163.