The Impact of Ulipristal Acetate (UPA) *versus* Dienogest on Pain Related to Endometriomas Evaluated with Visual Analogue Scale (VAS)

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Visual analogue scale (VAS) is a psychometric scale applied to measure subjective characteristics. The purpose of our study was to evaluate the efficiency of Ulipristal acetate (UPA) compared with Dienogest for endometriomas related pain using VAS. We performed a randomized study on women with symptomatic endometriomas. The study was realized between January 2016–December 2018. The patients were randomized in two groups: Group A- that received UPA in doses of 5 mg daily for 12–13 weeks and Group B that received 2 mg Dienogest for 12–13 weeks. Each group received de VAS (Visual Analogue Scale) questionnaire before and after treatment. 70 women wereincluded in the study with 35 patients for each group. The age the mean age was 30.20 years. For Numeric Rating Scale before treatment in the group with UPA the median value was 6 (CI= 5.26, 6.51) and for group B the median was 5 (CI= 5.13, 5.66). After treatment for group A the median value was 4 (CI= 3.58, 4.29) and for group B the median value 4 (CI= 4.23, 4.6). For FRS before treatment in the group with UPA median value was 6 (CI= 5.87, 6.58) and for the group B median was 6 (CI= 6.16, 6.57). After treatment for group A the median value was 4 (CI= 4.12, 4.73) and for group B the median value 5 (CI= 4.9, 5.06). The pain significantly improved for group A. ($p < 0.05$) VAS represent a good method to evaluate the quality of pain for patients with endometriomas. The UPA and Dienogest treatment improve the VAS parameters with better results for UPA in the present study.

Keywords: endometriosis, VAS, dienogest, ulipristal, pain

Endometriosis is represented by ectopic implants of endometrial cells that cause local inflammatory response[1]. The pathogenesis is controversial but it includes altered immunity, aberrant endocrine signalling or genetic factors with six genomic regions affected[2]. Endometriosis treatment is medical or surgical. The medical classes used for endometriosis treatment are: nonsteroidal analgesics, gonadotropin-releasing hormone (GnRH), agonists hormonal contraceptives and aromatase inhibitors. There is a lack of data to prove that one treatment or combination is better than another. The treatment is guided by symptom severity, treatment efficacy, medication side effects, contraceptive needs, costs, patient preferences and availability[3].

It was observed that for women with pelvic pain caused by endometriosis or for the ones who have contraindications for combined estrogen-progestin contraceptives, progestin-only represents a good treatment option. The most used progestins administered for the treatment of endometriosis-related pain are medroxy-progesteroneacetate norethindrone acetate and Dienogest[4]. In recent systematic reviews about progestin therapy for endometriosis Dienogest was superior to placebo[5].

Progesterone receptors antagonists were used in the early 1990 by Philibert *et al* as contraceptive drugs and nowadays there is produced a wide spectrum of similar drugs with PR (progesterone receptor) agonist and antagonist effects[6]. Ulipristal acetate (UPA) is introduced and approved since 2009 for leiomyomas treatment and contraceptive reasons by the EMA (European Medicines Agency) and in 2010 by FDA (U.S. Food and Drug Administration). UPA is a dose dependent PR antagonist and agonist with impact on endometrium and myometrium. It acts as PR antagonist with contraceptive effect, also inunique administration (emergency contraception)[7]. Lately the therapeutic indication of UPA wereextended to endometriosis as well.

The therapeutic response for endometriosis use is related to symptoms reduction and quality of life improvement. For quality of life and evaluation there are many standard questionnaires. Among those visual

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analogue scales (VAS) are psychometric scales applied to measure subjective characteristics. At the beginning they were used for different types of disorders, and for research and social investigationspurpose[8]. We performed a randomized study about the efficiency of UPA compared with dienogest for endometriomas related pain using VAS.

Experimental part

A randomized study was conducted on women with symptomatic endometriomas. The study is multicentre centre study, extended between January 2016–December 2018. Ethical approval and patient's informed consent for treatment and study were obtained.

The study included women with symptomatic endometriomas that received conservative management. Transvaginal ultrasound was performed by two experienced sonographists and the endometriomas were measured and mapped. It was considered only the largest diameter of the endometrioma and in order to reduce biasses the same doctor evaluated the same patient at the beginning and at the end of the treatment.

The inclusion criteria were: women with symptomatic endometriomas, that involved one or both ovaries, the endometriomas dimension under 5 cm and patients that agreed with the study. Exclusion criteria were: patients who didn't accept the study, other types of endometriosis such as deep infiltrative endometriosis, endometriomas with diameters over 5 cm that had indication for surgical approach.

A randomized controlled study was designed. The patients were randomized from the beginning in two groups: Group A- that received UPA in doses of 5 mg daily starting with the first or second menstrual day for 12-13 weeks and Group B that received 2 mg Dienogest starting with the first or second menstrual day for 12-13 weeks. Each group received de VAS (Visual Analogue Scale) questionnaire before and after treatment.

The randomization was made according to seal envelope method. The patient signed the inform and then the patient selected a sealed envelope from a pile opened it in front of the person that was in charge for recruiting patients for the trial. Then the patient was distributed in one of the categories. The physicianshow performed the ultrasound scan were blinded. Patients were informed about their treatment and signed the informed consent. The statistician was informed that there were 2 groups: A and B. He did not have any information regarding the patient treatment. At the end of the treatment courses the patients were examined by ultrasound and filled VAS questionnaire.

Statistical analysis was carried out with Statistical Package for Social Sciences (SPSS)Software 25.0. The differences between the treatment groups were evaluated by One Way ANOVA and t-test. Data were expressed as mean ± standard deviation (std dev). Pearson's correlation was used as appropriate and two-sided *p*-values of <0.05 were considered to indicate statistical significance.

Results and discussions

A group of 70 women was randomized in our study with 35 patients for each group. The main group characteristics for the entire study group are illustrated in Table 1. The age of the patients included in the study group varied between 18 and 42 years, the mean age being 30.20 years. Clincial symptoms severity, timing and all other significant information related to endometriosis were obtained. History of each patient was obtained and it revealed that 54.3% of the patients from the whole study group had previous surgical interventions for endometriosis. The main complains were dyspareunia, dysmenorrhea as reported in Table 1. Overall the patients described an altered quality of life dueto endometriosis symptoms but it improved in 74.3 % cases after treatment. For UPA group 80% patients admitted that quality of life improved whereas 68.6% patients from Dienogest group described such association.

All the patients underwent ultrasound examination. Regarding endometriomas distribution it was observed that 37.1 % involved the right ovary, 42.9 % affected the left ovary and 20% were bilateral. It was identified that before treatment the mean endometrioma dimension was 3.63 cm and decreased to the mean dimension of 3.49 cm ($p< 0.001$) for the entire study groups. Endometriomas dimensions diminutionafter UPA and Dienogest treatment ($p< 0.001$) isdetailed in table 2.

Group characteristics		
Age [years]	30,20 years (mean)	(min:18 years, max 42 years, std dev:5.78)
Endometrioma dimension before treatment [mm]	3.63 cm (mean)	(min:2 cm, max 4.7 cm, std dev:0.66)
Endometrioma dimension after treatment [mm]	3.49 cm (mean)	(min:1.8 cm, max 4.5 cm, std dev:0.67)
Dyspareunia	Yes 72.9%	No 27.1%
Dysmenorrhea	Yes 71.4%	No 28.6%
Previous operations	Yes 54.3%	No 45.7 %
Quality of life improvement	Yes 74.3%	No 25.7%

Table 1
THE STUDY GROUP CHARACTERISTICS

group		t	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
UPA	dimension1	28.194	.000	3.31143	3.0727	3.5501
	dimension2	27.292	.000	3.15143	2.9168	3.3861
dienogest	dimension1	51.990	.000	3.96000	3.8052	4.1148
	dimension2	49.574	.000	3.83429	3.6771	3.9915

Table 2
THE DIMENSION OF ENDOMETRIOMAS BEFORE AND AFTER TREATMENT

The main purpose of the present study was to characterize the pain associated to endometriomas. To the first point of the scale (Option 1) with 10 points for *no paint* and 0 points for worst pain ever it is observed from images 1 (a and b) the characteristics of pain before and after treatment. Before treatmentin the group with UPA the median value was 4 (CI= 3.75, 4.64) and for the group B the median was 5 (CI= 4.22, 4.97). After treatment for group A the median value was 6 (CI= 5.33, 6.28) and for group B the median value 6 (CI= 5.38, 5.93). The pain significantly improved for group A($p < 0.001$) (fig. 1 a, b).

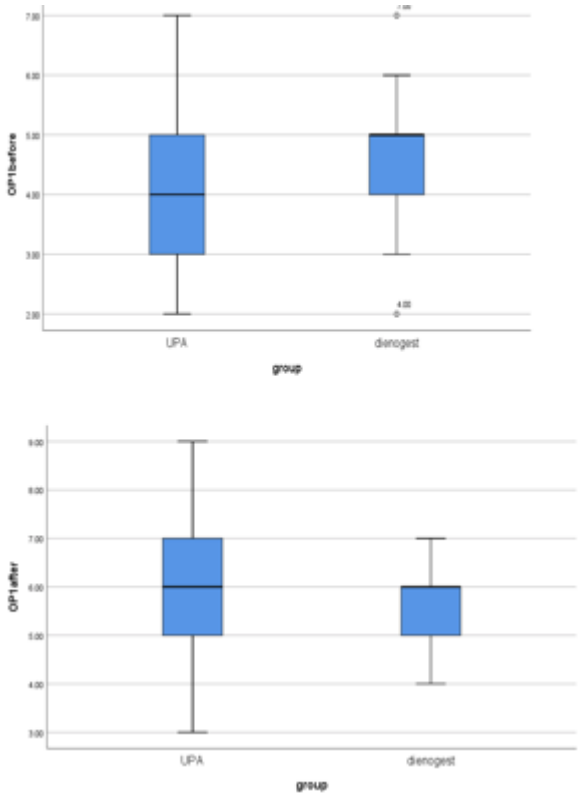

Fig. 1 (a, b): Option 1 before and after treatment

For the second point of the scale (Option 2) with 10 points for *worst pain ever* and 0 points for *no paint* it is observed from images 2 (a and b) the characteristics of pain before and after treatment. Before treatment in the group with UPA the median value was 6 (CI= 5.29, 6.18) and for group B the median was 6 (CI= 5.11, 5.85). After treatment for group A the median value was 4 (CI= 3.6, 4.39) and for group B the median value 5 (CI= 4.26, 4.93). The pain significantly improved for group A ($p < 0.001$)(fig. 2 a, b).

For the third point of the scale (NRS-Numeric Rating Scale) with 10 points for *worst possible pain* and 0 points for *no pain* it is observed from images 3 (a and b) the characteristics of pain before and after treatment. Before treatment in the group with UPA the median value was 6 (CI= 5.26, 6.51) and for group B the median was 5 (CI= 5.13, 5.66). After treatment for group A the median value was 4 (CI= 3.58, 4.29) and for group B the median value 4 (CI= 4.23, 4.6). The pain significantly improved for group A ($p < 0.001$) (fig. 3 a,b).

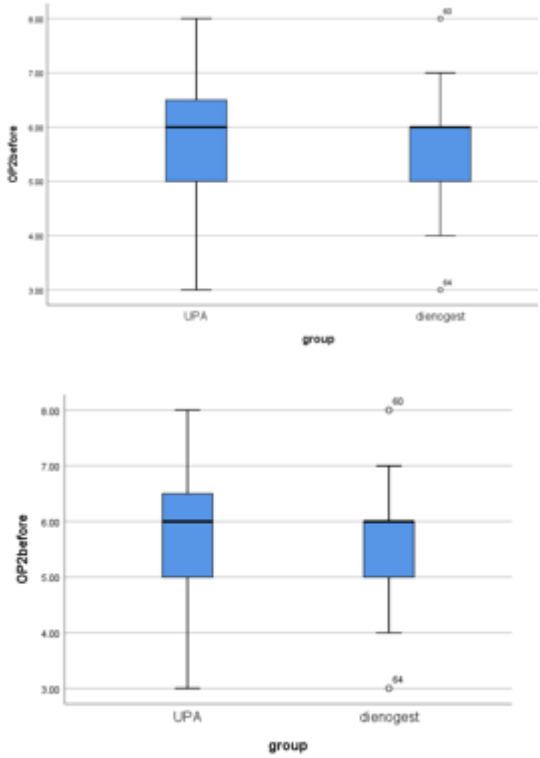

Fig. 2 (a, b): Option 2 before and after treatment

For the fourth point of the scale (FRS-Face Rating Scale) with 10 points for *hurts* and 0 points for *no hurt* it is observed from images 4 (a and b) the characteristics of pain before and after treatment. Before treatment in the group with UPA median value was 6 (CI= 5.87, 6.58) and for the group B median was 6 (CI= 6.16, 6.57). After treatment forgroup A the median value was 4 (CI= 4.12, 4.73) and for group B the median value 5 (CI= 4.9, 5.06). The pain significantly improved for group A ($p < 0.001$)(fig. 4 a,b).

Functional Activity Score (FAS) was also evaluated before and after treatment. It can be observed from Table 3 that there was significant improvement of activity because of endometriosis treatment. The group A had mild limitation of activity in 88.6% cases and 11.4% cases before UPA administration. For group B the limitation of activity was severe for 85.7% cases and mild for 14.3% cases and after Dienogest administration the limitation was severe

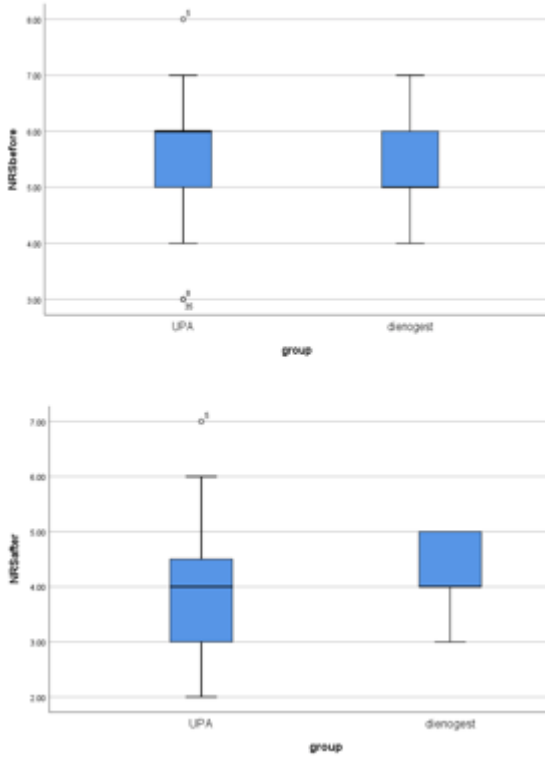

Fig. 3 (a, b): NRS before and after treatment

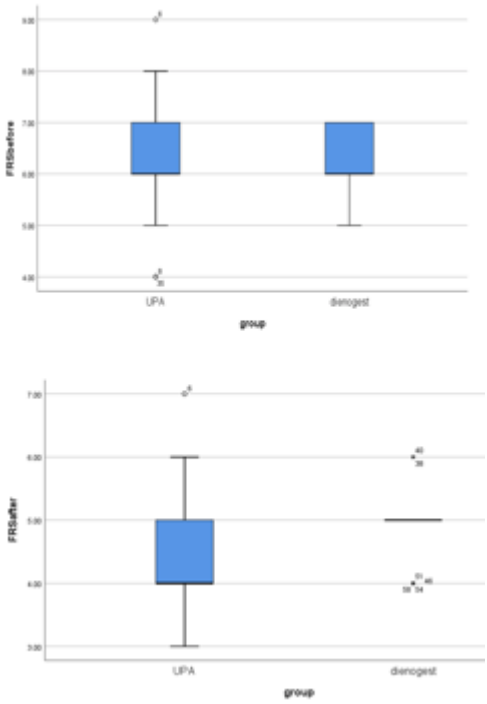

Fig. 4 (a, b): FRS before and after treatment

for 68.6% and remained severe for 31.4% cases. Overall the treatment improved the activity for patients with endometriosis but UPA was more efficient in this study (table 3).

VAS was first introduced in 1921 and it was initiated as a *graphic rating method* [9]. It is considered that the main advantage of this method is that it offers the possibility to evaluate detailed subtypes of judgement of the patient. It also requires the patient hand-eye coordination and visual ability[10]. The most important disadvantage is that it can be used in written (or digital) format and not for oral interviews and considerable effort for data entry and statistical analysis [11].This is the first study that compare the therapeutic effect of UPA and Dienogest in endometriosis related symptoms evaluated using VAS. In the present study we observed that overall both UPA and Dienogest ameliorate the pain for patients with endometriomas. There are significant changes regarding dysmenorrhea (from 72.9 to 27.1%), dyspareunia (from 71.4 to 28.6%) and quality of life improvement dyspareunia (from 74.3 to 25.7%). The parameters of VAS suffered significant changes after treatment. It was identified that UPA and Dienogest improved pain with impact on numeric rating scale and face rating scale, but UPA results were superior to Dienogest results. The pain significantly improved for group A. ($p < 0.05$)

The purposes of endometriomas treatment are to removethe symptoms as pain, to reduce the tumor dimensions, to improve subfertility or to avoid and prevent complications such as the cyst rupture or torsion. It was observed that medical therapy did not resolve endometriomascompletely[12]. Symptomatic or rapidly increasing endometriomas are treated laparoscopically. It was proved that laparoscopy improves the quality of life and sexual function after different procedures in pelvic area such myomectomy[13] and for all types of endometriosis with laparoscopic approach [14,15]. The most important disadvantage of endometriomas surgical removal is that the ovarian reserve diminish with each procedure. For ovarian protection reserve, asymptomatic and small ovarian endometriomas (≤ 5 cm) can benefit from medical approach [16].

Estrogen expresion suppression and progesterone receptors activation represent the essential target for current drugs, and also for research and new drugs development. The most used and studied agents for

group			Frequency after	Percent after	Frequency before	Percent before
UPA	Valid	no limitation	1	2.9	0	0
		mild limitation	25	71.4	31	11.4
		severe limitation	9	25.7	35	88.6
		Total	35	100.0	5	100.0
Dienogest	Valid	mild limitation	24	68.6	4	14.3
		severe limitation	11	31.4	31	85.7
		Total	35	100.0	100.0	100.0

Table 3
FAS SCORE BEFORE AND AFTER TREATMENT

endometriosis treatment are oral GnRH antagonists, aromatase inhibitors SERMs (Selective Estrogen Receptors Modulators) and SPRMs [17-19]. UPA is generally prescribed for conservative treatment of fibroids to preserve fertility. UPA was approved treatment for uterine fibroids since 2012. The action on the myometrium are antiproliferative, antifibrotic and proapoptotic with reduction a fibroid volume reduction to up 45%[20]. UPA effect is safe for endometrium[21].

The clinical effects of Dienogest for endometriosis treatment are reported in different studies and it was observed that it reduces the size of endometriomas and determine symptome relief for women with recurrent endometriosis [22]. Dienogest is efficient and safe for management of endometriosis associated pelvic pain[23] and avoidpain recurrence post surgery. Dienogest is well tolerated and side effects can be clinically managed [24]. Vaginal treatment with dienogest is innovative for symptomatic deeply infiltrating rectovaginal endometriosisand should receive further investigation in pharmacokinetic and clinical studies [25]. On the ovary, Duphaston and Dienogest are effective progestins that can be used as oral contraceptivewith different ovulation inhibitory effects [26,27]. The ovulation inhibitory effect induced by Dienogest could be reverse rapidly by stopping treatment [28,29]. Studies demonstrated the beneficial effect on pain generated by cyst endometrioma[30]. Side effects of progestin are represented by irregular uterine amenorrhea (dienogest), mood changes (depression) weight gain, and bone loss[31].

UPA and Dienogest are proved to be effective as anti-endometriosis drugs inducing apoptosis and reducing proliferation and adhesions. UPA and Dienogest are very well tolerable by the patient. For Dienogest use endometrial glandular hyperplasia was described and, follicle accumulation for UPA[32]. Ulipristal acetate can control irregular bleeding by inducing amenorrhea while Dienogest may cause irregular uterine bleeding[33,34].

This study is a pilot research that compares the effects of UPA versus Dienogest insymptomatic patients with endometriomas evaluated by VAS. The strength of our study is represented by the accuracy of the protocol with good applicability before and after treatment. The limitation of the study is the reduced number of patients.

Conclusions

VAS represent a good method to evaluate the quality of pain for patients with endometriomas. The UPA and Dienogest treatment improve the VAS parameters with better results for UPA in the present study. Further research is needed aiming also other administration ways (vaginal) and on larger patients cohorts to asses the benefits and the safety of UPA in endometriosis.

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