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ORIGINAL ARTICLE

Role of a natural integrator based on lipoic acid, palmitoiletanolamide and myrrh in the treatment of chronic pelvic pain and endometriosis

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ABSTRACT

BACKGROUND: Dysmenorrhea and chronic pelvic pain occur in a significantly higher percentage in women with endometriosis; this benign condition has an incidence ranging from 5% to 10% in the general population, while 35% to 50% of infertile women are affected. Treatment of the symptoms demands integrated approaches with the use of anti-inflammatory substances or drugs and lifestyle changes, including attention to diet. The use of traditional anti-inflammatory drugs over the long term is not very successful because of the fear of side effects so they are almost always used with a short-term formula of 7-10 days when the woman's general condition becomes difficult to bear. In recent years, particular attention has been paid to natural substances with recognized anti-inflammatory activities that, associated with one another, are able to synergize individual actions. A nutraceutical containing substances capable of fighting chronic pelvic pain has recently been put on the market. The possible action mechanism derives from a synergy of action between alpha-lipoic acid, palmitoiletanolamide (PEA) and myrrh (Pelvinox, Laborest Italia srl, Nerviano, Milan, Italy), whose action is so effective that it is able to replace the use of anti-inflammatory drugs. The aim of the study was to evaluate the effect of these active ingredients in women with endometriosis and chronic pelvic pain.
METHODS: This multicenter study saw the recruitment of 60 women (divided between the three centers participating in the study, Siena, Bologna and Udine) aged between 20 and 39 suffering from endometriosis (ovarian) and chronic pelvic pain. All the women took one nutraceutical (Pelvinox) at a dose of two tablets per day for 6 months.
RESULTS: The results showed a significant reduction in pain symptoms as regards dyspareunia, dysmenorrhea and chronic pelvic pain, while there was no change in the mean diameter of the endometriosis cysts.
CONCLUSIONS: In light of the above, it is believed that substances such as alpha-lipoic acid, PEA and myrrh may play a very important role in this type of patient in the treatment of individual symptoms.

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KEY WORDS: Endometriosis; Dysmenorrhea; Pain.

Women with chronic pelvic pain (CPP) often turn up for imaging studies, lab tests or physical examinations without evident causes.[1] Women with CPP often present several apparently unrelated symptoms, but in some cases endometriosis, painful bladder syndrome, vulvodynia, myofascial pain, pelvic hypertension, irritable bowel syndrome and primary dysmenorrhea may coexist. Chronic pain is recognized as a systemic disease and as such

should be treated, using a multidisciplinary approach.[2]

Pelvic menstrual pain (dysmenorrhea) or pain outside menstruation also occurs in a significantly high proportion of women with endometriosis;[3] this chronic benign disease is characterized by the presence of endometrial tissue outside the uterine cavity. Its incidence varies between 5 and 10% in the general population,[4] while 35% to 50% of infertile women[5] are affected. This disease represents one of the most frequent gynecological disorders during a woman's reproductive life.

The clinical impact of this symptom may be negative for the reproductive and systemic health of a woman.[6] Neglecting the pain symptom may, over the years, lead to the emergence of unrecognized diseases that could be countered with a preventive approach.

CPP treatment involves integrated approaches and the use of anti-inflammatory substances or drugs and lifestyle changes, including attention to the type of diet.

The use of traditional anti-inflammatory drugs over a long period is not very successful[7] because of the fear of side effects and they are almost always used with a short-term formula of 7-10 days when the patient's general condition becomes difficult to sustain. In recent years, particular attention has been paid to natural substances with recognized anti-inflammatory activity that, in association with one another, are able to synergize individual actions.

On the basis of these considerations, more and more attention is being paid to new therapeutic perspectives in the use of long-term non-pharmacological products in the treatment of certain gynecological pathologies which, like endometriosis, cause chronic pelvic pain and affect the quality of life of young women of childbearing age.

Alpha-lipoic acid is a powerful natural antioxidant and enzymatic cofactor of the mitochondrial respiratory chain;[8] it has been shown to be a substance capable of improving blood sugar control in patients with type II diabetes, presumably due to its ability to reduce oxidative stress and insulin resistance.[9] In addition, this active ingredient is able to significantly reduce body weight in obese patients by reducing the accumulation of triglycerides in non-adipose peripheral tissues.[10]

Palmitoilethanolamide, or PEA, is the amide of an endogenous fatty acid and belongs to the class of nuclear factor agonists.[11] PEA binds to specific nuclear receptors and performs a wide variety of biological functions related to chronic pain and inflammation. This amide is considered a potent anti-inflammatory and pain-reliever. Since the 1970s, it has come under broad attention as an anti-inflammatory and analgesic drug in over 30 international clinical studies, in a total of about 6000 patients, demonstrating powerful anti-inflammatory action in chronic pain, particularly neuropathic pain.[12]

Myrrh is an aromatic gum-resin extracted from a tree or shrub of the genus Commiphora, of the Burseraceae family;[13] there are more than two hundred species of Commiphora,[14] growing on the banks of the Red Sea, in Senegal, Madagascar and India. In ancient times it was used by the Egyptians as embalming oil and, in general, as oil for anointing or as perfume; nowadays, by contrast, important antibacterial, antifungal and anesthetic properties are recognized, as it belongs to the family of the sesquiterpenes, molecules with the same action mechanism as the cannabinoids.

The nutraceutical of our study, based on 400 mg of alpha-lipoic acid, 300 mg of palmitoiletanolamide (PEA) and 100 mg of myrrh (Pelvinox, Laborest Italia srl, Nerviano, Milan, Italy), is able to induce a significant anti-inflammatory and pain-relieving effect. Both alpha-lipoic acid and PEA as well as myrrh are recognized as having important pain-relieving properties due to their action on the peripheral nerves, where they play an important role in the onset of pain. The hypothesis is that there is a synergy of action between these substances effective enough to be able to replace the use of anti-inflammatory drugs.

The aim of the study was to evaluate the effect of Pelvinox treatment in women with endometriosis and chronic pelvic pain.

Materials and methods

Multi-center study involving 60 women (divided between the three centers participating in the

study, Siena, Bologna and Udine) aged between 20 and 39 with endometriosis (ovarian) and chronic pelvic pain.

The diagnosis of endometriosis was based on the ultrasound presence of an endometriosis cyst (endometrioma) at ovarian level. The enrolment period lasted about one year (March 2017-February 2018); the treatment period for each individual patient was 6 months.

The size of the endometrioma before and after 3 and 6 months was evaluated by pelvic ultrasound. All women took a nutraceutical product based on 400 mg alpha-lipoic acid, 300 mg palmitoiletanolamide (PEA) and 100 mg myrrh, at a dose of two tablets per day. The total duration of treatment was 6 months.

The women before and after 3 and 6 months underwent transvaginal ultrasonography to determine the volume of the endometrial ovarian cyst.

In addition, all the women were asked to complete a questionnaire (time 0, 3 months, 6 months) for the subjective evaluation of pain symptoms.

Patients were included in the study according to the following inclusion criteria:

- presence of at least one of the following symptoms: dysmenorrhea, pelvic pain;
- 2D ultrasound, power Doppler diagnosis of ovarian endometrioma;
- fertile age (range 20-39 years);
- patients who had completed the 6-month period of medical treatment;
- willingness to give free and informed consent.

Oncological patients or patients treated with hormone therapies at the time of recruitment were excluded from the study.

The baseline data for patients in the study are summarized in Table I.

TABLE I.—*Baseline data of patients in the study.*

Patients (N.=60)	
Age (years)	30.6±5.02
Mean diameter endometriosis cyst (mm)	25.09±6.65
Dysmenorrhea (VAS)	7.68±1.55
Dyspareunia (VAS)	5.72±2.2
Chronic pelvic pain (VAS)	5±2.11

Values are expressed as mean (M)±standard deviation (SD).

Ultrasound assessment

The ultrasound investigation was conducted using an E6 ultrasound system (GE Healthcare, Zipf Austria). The transvaginal scan of the pelvic organs was performed using a 3D endovaginal probe (2.8-10 MHz). The evaluation of tissue vascularization was performed with the power Doppler technique (6-9 MHz; PRF 0.6 kHz, gain -4.0).

Specifically, the following associated ultrasound characteristics were evaluated: solid unilocular cystic formation with fine background granulation, clean, regular margins, little vascularized on power-Doppler examination.

Evaluation of symptomatology

At the time of enrolment, a questionnaire was completed with the patient to assess the extent of symptoms. This questionnaire was re-assessed 3 months and 6 months after treatment with nutraceutical products based on 400 mg of alpha-lipoic acid, 300 mg of palmitoilethalonamide (PEA) and 100 mg myrrh.

Dysmenorrhea and pelvic pain were evaluated using an Analog Pain Scale (VAS), specifying the duration (in days) of the symptoms present. In the field of pelvic pain, symptoms such as diffuse abdominal pain, dysuria, dyschezia, constipation, diarrhea, dyspareunia, lower back pain, lower limb pain were evaluated (Figure 1).

Statistical analysis

The total sample consisted of 60 patients divided among the three centers that took part in the study. The collected data were entered in an Excel spreadsheet with all the anamnestic, symp-

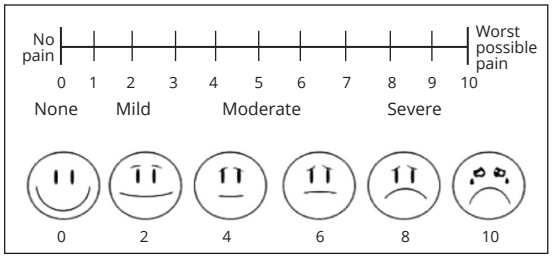

Figure 1.—Pain scale (VAS).

tomatological and ultrasound criteria considered in the study in order to statistically analyze them in the different stages of therapy.

Results

The administration of nutraceuticals in the study was well tolerated and none of the women abandoned it.

The ultrasound evaluation of the ovarian endometriosis cysts showed that they had not been reduced and their average diameter was almost unchanged from before the treatment, with an average diameter of 25.09±6.65 mm to 25.12±6.94 mm after 6 months of treatment.

With regard to pain symptoms and in particular chronic pelvic pain, patients reported a significant improvement at 3 months, and this was again significantly reduced after 6 months of treatment from VAS values of 5±2.11 at time 0 to 3.75±1.8 after 3 months to reach 3.28±1.37 after 6 months of therapy (Figure 2).

Dyspareunia improved significantly only after 6 months of treatment from 5.72±2.2 at time 0 to 4.38±1.62; in addition, dysmenorrhea was the symptom most affected in terms of less menstrual pain already after 3 months (from VAS values of 7.68±1.55 to 5.72±1.87 at three months) and this further improved after 6 months (with values of 4.52±1.77), with great relief to the patients.

Further data worth reporting concern the feeling of diminished abdominal swelling reported by most women during the postmenstrual period.

Discussion

The present study has shown the good tolerance and efficacy of the nutraceutical product used for the evaluation of chronic pelvic pain, dyspareunia and dysmenorrhea from which the women participating in the study were suffering.

With regard to action on the volume of ovarian endometriosis cysts, administration of the nutraceutical product did not alter the dimensions that remained unchanged during the various ultrasound checks, although the fact that they had not grown suggests a positive role *versus* swellings of this type that normally tend to grow over time.

The results were homogeneous among the groups of women participating in the study and this fact lends even more support to our observations.

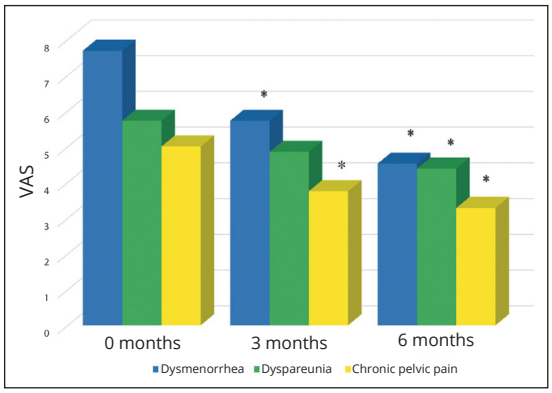

Figure 2.—VAS values for dysmenorrhea, dyspareunia and chronic pelvic pain in the group of patients under study (N.=60) after 0, 3 and 6 months of treatment; data are expressed as mean (M)±standard deviation (SD). Values are considered significant for *P<0.05.

The substances present in the product perform specific actions whose effectiveness and mechanism of action are well documented in the literature. The added value of this type of association is that of the synergistic action between the various substances contained in the product, which, in the case of the clinical situations for which it was used, have led to an action similar if not the same as that observed in the use of the normal NSAIDs employed in these pathologies.

In evaluating the results obtained with nutraceuticals, however, we must always take into account that a part of the therapeutic success may be due to the placebo effect linked to the personal conviction of the patient who uses it. The gold standard for identifying the placebo effect of a nutraceutical substance would be to employ a randomized double-blind study, but the intrinsic complexity of this means that it is not always feasible.

Even more relevant were the excellent tolerance, the absence of side-effects and the fact that patients did not abandon the study, demonstrating that the women enrolled felt more comfortable taking a nutraceutical than a pharmacological product.

Analyzing the course of individual symptoms, we can say that the reduction in chronic pelvic pain was homogeneous in most women and saw a

reduction in the pain scale of about 30-35%. The most annoying symptom for women with this condition is dyspareunia. All women reported a significant improvement that allowed a return to an almost normal sexual activity.

As for the dysmenorrhea symptom, a specific symptom related to the perimenstrual period, it too recorded significant improvement during the 6 months of treatment.

The main problem with these posology schemes is that they make patients affected by the symptom take formulations of any kind for long periods of time.

Therefore, a specific protocol of 7-10 days should be tested in order to evaluate its effectiveness or otherwise with short-term administration.

Conclusions

In light of the above, it is considered that products of this type and in particular substances such as lipoic acid, PEA and myrrh can play a very important role in this type of patient in the treatment of individual symptoms, but also in the control of the growth of endometriosis cysts.

A preventive role can also be hypothesized for this type of disease with the administration of natural products such as the one used in the present study to women at risk of developing endometriosis and related symptoms such as dyspareunia and chronic pelvic pain.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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