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The adjuvant use of N-palmitoylethanolamine and transpolydatin in the treatment of endometriotic pain

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ABSTRACT

Objective: To test the adjuvant use of the combination of N-palmitoylethanolamine and transpolydatin in the medical treatment of endometriotic pain.

Study design: We enrolled 47 patients admitted to the Outpatient Endometriosis Care Unit of Ferrara University from January 2011 to December 2011. They were divided into two groups according to the endometriosis site (group A: recto-vaginal septum; group B: ovary). One tablet, containing 400 mg of micronized N-palmitoylethanolamine plus 40 mg transpolydatin, was administered twice daily on a full stomach for 90 days. Each patient was requested to grade the severity of dysmenorrhea, chronic pelvic pain, dyspareunia and dyschezia using a 0–10 cm visual analogic scale prior to beginning treatment (T0), after 30 days (T1), 60 days (T2) and 90 days (T3). The continuous and categorical variables were compared, respectively, using Student's *t*-test and the chi-square test. Analysis of variance for repeated measures was used to verify the reduction of endometriotic pain.

Results: The intensity of endometriotic pain decreased significantly for both groups ($p < 0.0001$). The efficacy of drug treatment was significant after 30 days. Pain intensity decreased equally in the two groups except for dysmenorrhea, which was reduced more rapidly in group B.

Conclusions: The combination of N-palmitoylethanolamine and transpolydatin reduced pain related to endometriosis irrespective of lesion site. It had a marked effect on chronic pelvic pain determined by deep endometriosis and on dysmenorrhea correlated to ovarian endometriosis.

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1. Introduction

Chronic pelvic pain affects upward of 15% of women [1] and is a frustrating condition for both patient and physician. It is a complex interaction between neurologic, musculoskeletal, and endocrine systems that is further influenced by behavioural and psychological factors. A major cause of pelvic pain is endometriosis, one of the common gynaecological diseases in premenopausal women [2]. It is a chronic inflammatory condition defined by the presence of glands and stroma outside the uterine cavity. The intensity and type of endometriotic pain is quite diverse, and includes dysmenorrhea, dyspareunia, chronic pelvic pain and dyschezia according to the lesion site [3–5]. It can be effectively cured by definitive surgery [6], an option generally not accepted by patients wishing to preserve fertility. As conservative surgery

is often associated with only partial relief or recurrence of symptoms [7,8], prolonged medical therapies may be needed for endometriosis. Therefore, this disease should be viewed as a chronic pathology that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures. Several medical treatments have been tested over the years, but effective targeting of the pathogenic mechanism has yet to be achieved [9]. For this reason, research is now focused on testing drugs that act on the inflammatory process. Among these, the combination of N-palmitoylethanolamine (PEA) and transpolydatin in the management of the pain related to endometriosis is very promising [10]. Our aim was to evaluate the efficacy of PEA and transpolydatin as adjuvant medical therapy for endometriotic pain according to the lesion site.

2. Materials and methods

We conducted a prospective study to evaluate the effects of the combination of PEA and transpolydatin on pain related to endometriosis. We enrolled 47 patients admitted to the

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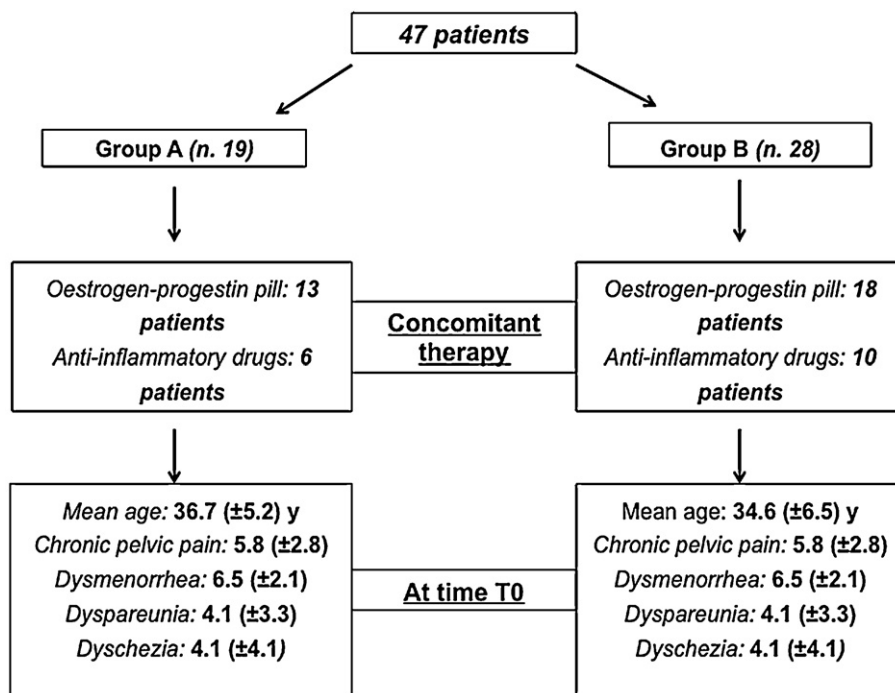


Fig. 1. Graphical representation of endometriotic pain reduction. All values are means (S.E.M.).

Outpatient Endometriosis Care Unit of Ferrara University between January and December 2011. Inclusion criteria were: age between 20 and 45 years, pain related to endometriosis diagnosed on the basis of clinical and instrumental evaluations, endometriotic location on ovary (ovarian cyst < 4 cm) or recto-vaginal septum (RVS) (nodule < 2 cm), refusing or awaiting surgery. Exclusion criteria were: uncertain diagnosis of endometriosis, menopause, intolerable pain, oestrogen-progestin treatment started less than 6 months ago, and pregnancy. The patients provided written informed consent, and the study protocol was approved by the university's Ethics Committee. The study was in accordance with The Code of Ethics of the Declaration of Helsinki.

All patients received a first diagnosis of endometriosis made according to the ESHRE guideline [11]. They were then divided in two groups according to the endometriosis site (group A: RVS; group B: ovary). The patients had already received treatment for at least 6 months (31 by oestrogen-progestin pill, 16 by anti-inflammatory drugs as needed), which was continued for ethical reasons. Patients received twice daily a single tablet containing 400 mg micronized PEA plus 40 mg transpolydatin on a full stomach for 90 days. Each patient was requested to grade the severity of dysmenorrhea, chronic pelvic pain, dyspareunia and dyschezia using a 10.0 cm visual analogue scale (VAS) prior to beginning treatment (T0), and after 30 days (T1), 60 days (T2) and 90 days (T3). The patients were asked to indicate pain intensity on the scale from 0 = "no pain" to 10 = "the most painful sensation imaginable".

Data were analyzed by SPSS (20.0) software, and are expressed as the mean ± SD. The continuous and categorical variables were compared, respectively, using Student's *t*-test and the chi-square test. Analysis of variance for repeated measures was used to verify the reduction of endometriotic pain between the two groups. Tukey-Kramer test was used to compare the mean VAS score at different steps of the study. The level of statistical significance was set at $p < 0.05$.

3. Results

The study population comprised 47 patients. Mean age was 35.4 (±6.0) years (median 36 years, maximum 45 years, minimum 24 years). Pain intensity was evaluated by VAS prior to beginning treatment:

- Chronic pelvic pain: 5.11 (±2.65) points (median 6, maximum 10, minimum 0);
- Dysmenorrhea: 6.7 (±1.8) points (median 7, maximum 9, minimum 3);
- Dyspareunia: 3.85 (±3.04) points (median 4, maximum 9, minimum 0);
- Dyschezia: 2.57 (±2.91) points (median 2, maximum 9, minimum 0).

Groups A and B were composed of 19 and 28 patients, respectively. Mean age was not significantly different between groups ($p = 0.2$): 36.7 (±5.2) years in group A and 34.6 (±6.5) years in group B. Patients were receiving concomitant therapy as follows:

Table 1

ANOVA for repeated measures of pain intensity between the two groups prior and after treatment.

Group	T0 mean (S.D.)	T1 mean (S.D.)	T2 mean (S.D.)	T3 mean (S.D.)	<i>p</i> value
Chronic pelvic pain					
A	5.8 (2.8)	3.8 (2.4)	2.9 (1.7)	2.3 (1.9)	<0.0001
B	4.6 (2.4)	2.7 (1.7)	1.6 (1.6)	1.6 (1.3)	
Dysmenorrhea					
A	6.5 (2.1)	4.5 (1.1)	4.0 (1.1)	3.8 (1.3)	<0.0001
B	6.9 (1.6)	4.5 (1.5)	3.9 (1.8)	3.2 (1.5)	
Dyspareunia					
A	4.1 (3.3)	2.1 (1.6)	1.5 (1.4)	1.5 (1.5)	<0.0001
B	3.7 (2.9)	2.5 (1.1)	1.8 (1.5)	1.4 (1.3)	
Dyschezia					
A	4.1 (3.4)	3.3 (2.7)	2.7 (2.6)	2.9 (2.7)	<0.001
B	1.6 (2.1)	1.1 (1.4)	0.9 (0.9)	0.9 (1.1)	

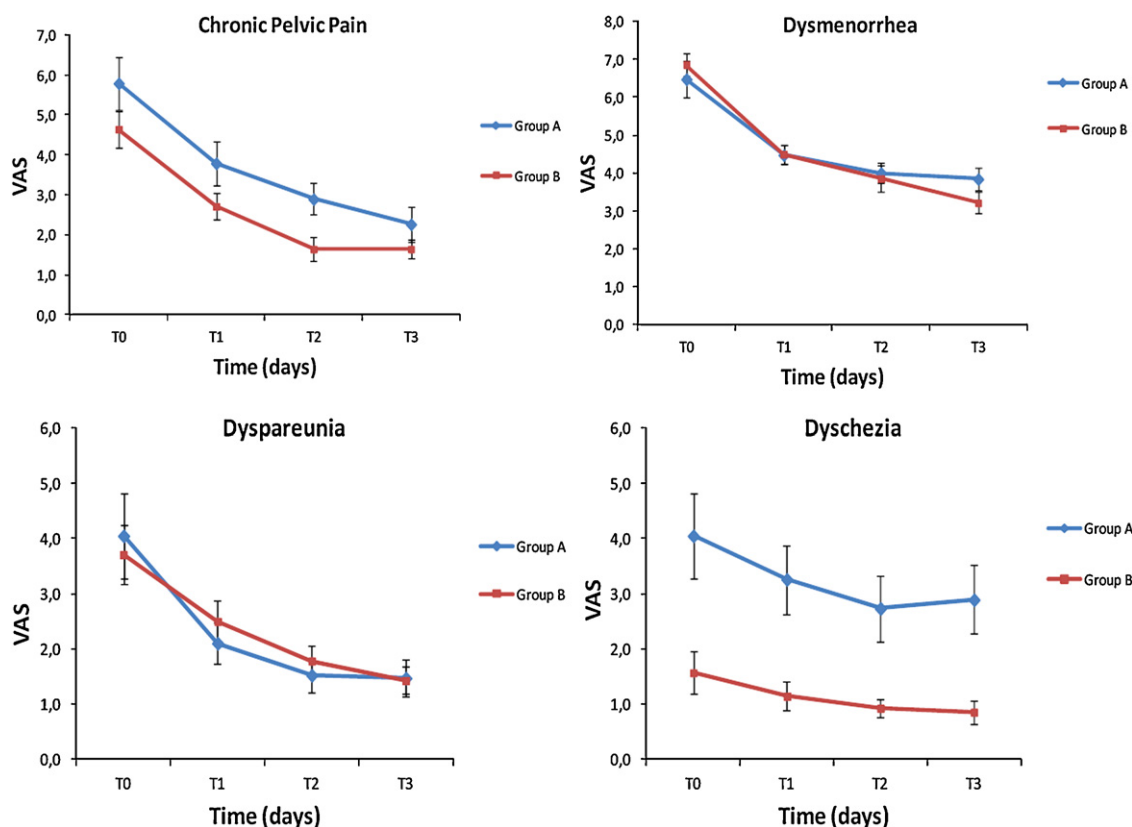


Fig. 2. Graphical representation of endometriotic pain reduction. All values are means (S.E.M.).

oestrogen-progestin pill – 13 in group A and 18 in group B; anti-inflammatory drugs according to need – 6 in group A and 10 in group B (Fig. 1). The difference between the two groups was not significant ($p < 0.08$).

The intensity of endometriotic pain decreased significantly over time for both groups (Table 1; Fig. 2). Analyzing specifically the different types of pain, we found that the reduction of VAS score for pelvic chronic pain and dyspareunia was influenced only by time. The reduction for dysmenorrhea, however, was influenced by age

(every 10 years there is a reduction of 0.75 points). Interestingly, dysmenorrhea tended to undergo reduction more rapidly in group B. For the other parameters, reduction occurred basically in parallel between the two groups.

Analyzing mean VAS score at different time points of the study revealed a significant reduction in pain after only 30 days of treatment (T1) except for dyschezia (Table 2). Analyzing mean VAS score at T2 in group A, there was still a highly significant reduction for chronic pelvic pain. In group B mean VAS score difference at T1

Table 2
Patient evaluation parameters at the indicated time intervals.

Group	T0 mean (S.E.M.)	T1 mean (S.E.M.)	T2 mean (S.E.M.)	T3 mean (S.E.M.)
Chronic pelvic pain				
A	5.6 (0.6)	3.7 (0.5)	2.9 (0.4)	2.2 (0.4)
Comparison with previous time	***	***	***	
B	4.4 (0.5)	2.6 (0.4)	1.6 (0.3)	1.5 (0.3)
Comparison with previous time	***	***	n.s.	
Dysmenorrhea				
A	6.8 (0.4)	4.7 (0.3)	4.2 (0.3)	4.1 (0.3)
Comparison with previous time	***	n.s.	n.s.	
B	6.9 (0.4)	4.5 (0.2)	3.8 (0.3)	3.2 (0.2)
Comparison with previous time	***	n.s.	*	
Dyspareunia				
A	3.8 (0.7)	2.0 (0.4)	1.5 (0.4)	1.4 (0.3)
Comparison with previous time	**	n.s.	n.s.	
B	3.5 (0.6)	2.4 (0.4)	1.8 (0.3)	1.4 (0.3)
Comparison with previous time	*	*	n.s.	
Dyschezia				
A	3.8 (0.6)	3.1 (0.5)	2.6 (0.4)	2.8 (0.5)
Comparison with previous time	n.s.	n.s.	n.s.	
B	1.3 (0.5)	1.0 (0.4)	0.7 (0.3)	0.7 (0.4)
Comparison with previous time	n.s.	n.s.	n.s.	

Values are adjusted means (net of other effects). Tukey–Kramer test.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.0001$.

and T2 was significant for chronic pelvic pain and dyspareunia. Analyzing the differences at T2 and T3, we found a further significant reduction only for chronic pelvic pain in group A and for dysmenorrhea in group B (Table 2).

4. Comment

Endometriosis is increasingly being recognized as an inflammatory condition, as ectopic lesions secrete chemotactic molecules that recruit immune cells to the peritoneal fluid [12]. Oestrogens have a crucial role in this process, as supported by the observation of an apparent resolution of symptoms during pregnancy. Pain can therefore be controlled by treatments designed to reduce oestrogen activity (anti-oestrogen therapy, aromatase inhibitors, gonadotropin-releasing hormone, hormonal contraceptive therapy, progestins) and by those that reduce inflammation (non-steroidal anti-inflammatory drugs [12]). Recent studies reported an increased presence of activated and degranulating mast cells in deep infiltrating endometriosis and a close relationship between mast cells and nerves. These observations led to the proposal that mast cells may contribute to the development of pain and hyperalgesia in endometriosis, possibly by exerting a direct effect on nerve structures [13,14]. Mast cells produce and release a variety of degranulation products, such as nerve growth factor, which may interact with nociceptive neurons causing their activation or sensitization [15,16]. Mast cells may therefore be an innovative target for therapeutic strategies [17] due to their role in inflammation and in the consequent hyperalgesia and allodynia.

The discovery of anandamide as an endogenous ligand for cannabinoid receptors led to a resurgence of interest in the fatty acid amides. PEA, a shorter and fully saturated analogue of anandamide, is a member of the N-acylethanolamines and found in most mammalian tissues. PEA accumulates during inflammation and possesses a number of anti-inflammatory actions observed in clinically relevant animal models of inflammatory pain [18]. It is a fatty acid amide, which through the autacoid local injury antagonism (ALIA) mechanism controls tissue inflammation, thereby reducing mast cell degranulation [19]. Under experimental conditions characterized by inflammation and pain, PEA has been reported to exert anti-inflammatory and analgesic effects [20,21] in both acute and neuropathic pain conditions [22]. In particular, PEA, acting as ligand of peroxisome-proliferator activated receptor (PPAR)- α , might regulate neurosteroidogenesis in astrocytes and decrease in nitric oxide production, neutrophil influx, and expression of proinflammatory proteins such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [23].

To date, only two clinical studies [10,24] have been performed to evaluate the ability of PEA/transpolydatin to relieve pain associated with endometriosis. The first one [24], although based on only four patients, reported encouraging results: PEA appeared to reduce chronic pelvic pain and deep dyspareunia. The second one [10] evaluated treatment effectiveness in the management of chronic pelvic pain related to endometriosis after laparoscopic assessment, in which PEA/transpolydatin was more effective than placebo. The characteristics of endometriosis pain vary, however, as a function of lesion site, with intensity and type of pain depending on closeness of the endometriotic lesions to nervous fibres [25]. In particular RVS lesions, having a deep localization, result in a pain of greater intensity characterized mainly by chronic pelvic pain, dyspareunia and dyschezia. In view of this, we tested the effectiveness of PEA plus transpolydatin by selecting patients according to location of the disease.

The evaluation of pain characteristics reported by patients in both groups confirmed the results described above. Indeed, patients with deep endometriosis of the posterior pelvic compartment reported mostly chronic pelvic pain, dyspareunia and dyschezia

(Table 1; Fig. 1). Dyschezia can be explained by the possible bowel involvement typical in this kind of lesion [26], while chronic pelvic pain and dyspareunia are likely driven by the action of a greater number of nerve fibres in deep endometriosis [3,25]. In contrast, patients with ovarian endometriosis reported mostly dysmenorrhea explained by peritoneal irritation triggered during each menses with overflow of a small amount of blood in the abdomen [5]. The effect of association between PEA and transpolydatin was evident, with a gradual and significant decline of mean VAS score for all types of pain (Table 1; Fig. 2). Indeed, one sees the characteristic VAS score relating to dysmenorrhea decreasing more and with greater rapidity in group B. Considering variables such as age and concomitant therapy, the first had a significant influence on reduction of VAS score for dysmenorrhea in both groups ($p = 0.0002$), while the second variable had no influence.

These observations show the importance of early treatment of dysmenorrhea caused by ovarian endometriosis. While exclusion of “concomitant therapy” as a factor is fundamental to avoid bias (but not wanting to suspend current treatment for ethical reasons), we selected only patients treated for at least 6 months to avoid confusing the effect of PEA with that of oestrogen-progestin therapy [26]. The effectiveness of PEA/transpolydatin was already evident after 30 days (T1) with a significant reduction in both groups; efficacy was not dependent on disease site (Table 2). Treatment efficacy was less evident for mean VAS score of dyschezia, which decreased significantly (albeit more gradually) during therapy. Because the mean VAS score for dyschezia was not high at T0, one would not expect a meaningful decrease of already low values. At T2 these differences remained statistically significant only for chronic pelvic pain between the two groups and for dyspareunia in group B (Table 2). In group A, treatment effectiveness was still significant but only for chronic pelvic pain at T3, while a further significant decrease of VAS score for dysmenorrhea was observed in group B (Table 2). In group A, this can be explained by considering the pathophysiological mechanism of PEA action, which reduces mast cell degranulation [13] responsible for chronic pelvic pain and dysmenorrhea in endometriosis. This mechanism is unable to further decrease the VAS score for dyspareunia and dyschezia, as these types of pain in the deep endometriosis are determined not only by inflammation but also by a “mass effect” [27]. The findings obtained in group B, on the other hand, can be explained by the ability of PEA to reduce the peritoneal inflammation directly responsible for dysmenorrhea in the endometriotic ovarian cyst [28].

In conclusion, the combination of PEA and transpolydatin demonstrated an ability to reduce pain related to endometriosis independent of lesion site. In particular, efficacy was already evident after 30 days and reached its maximum after 60 days. Confirming its pharmacodynamic characteristics, it has a great effect on chronic pelvic pain determined by deep endometriosis and on dysmenorrhea correlated to ovarian endometriosis. The adjuvant use of PEA/transpolydatin in association with classical treatments (in particular the oestrogen-progestin pill) has a scientific rationale: on the one hand the hormonal therapy works on the disease progression through an oestrogen-dependent mechanism, while on the other hand the PEA/transpolydatin combination works on the symptoms exerting a neuroprotective and antinociceptive effect. We have to emphasize, however, that the pain reported by patients prior to adjuvant therapy was of a medium degree. At the moment, we do not know the actual efficacy of the compound in severe endometriosis pain; therefore this may be an interesting field of research. Although based on a relatively small sample size, the combination of PEA and transpolydatin shows promise as a valid adjuvant therapy in the medical treatment of endometriosis.

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