Original article

Micronized palmitoylethanolamide reduces bladder chronic pelvic pain due to different etiologies and improves bladder functions

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Abstract: Chronic pelvic pain (CPP) is a common condition among women of reproductive age. It frequently co-occurs with other pelvic and extra-pelvic pain conditions, including immunologic disorders. The co-occurrence of immunologic hyperstimulation and diffuse mast cell activation might have a negative impact on the progression of CPP diseases and also influence outcome of therapeutic treatment. The aim of this study is to assess the effect of micronized palmitoylethanolamide (m-PEA), an N-acylethanolamine known to modulate mast cell activity, on bladder pain and bladder functions in patients with CPP with and without concomitant allergy. Bladder pain was evaluated using the visual analog scale, while functional bladder capacity, daily frequency and nocturia were obtained from bladder diary and uroflometry. The presence of allergy did not change pain intensity mean scores. Average pain intensity score significantly decreased with m-PEA adjuvant therapy. The functional bladder capacity was lower while daily frequency and nocturia were higher in CPP patients with allergy. Functional bladder capacity increased while daily frequency and nocturia decreased after m-PEA adjuvant therapy in both CPP patients with and without allergy. The quality of life (12-item Short Form Health Survey) was not modified by allergy co-occurrence. m-PEA treatment improved the quality of life and physical and mental components in CPP patients with and without allergy. These results support the hypothesis of an important role of mast cell activation in symptomatology and organ functionality in CPP patients and confirm the ability of m-PEA to reduce CPP and limit pelvic disease progression by controlling mast cell activation.

Keywords: Chronic pelvic pain; Micronized palmitoylethanolamide; Mast cells; Allergy; Bladder dysfunctions.

INTRODUCTION

Chronic pelvic pain (CPP) involves up to 38% of all women ages from 15 and 73 years. In United Kingdom and United States up to 24% of all women of reproductive age are affected by CPP. Its incidence is higher than other common disorders such as headache, asthma and low back pain (incidence of 2.1%, 3.7% and 4.1%, respectively)[1-3]. CPP seems to have multifactorial etiology involving the urogynaecologic, gastroenteric, musculoskeletal, and nervous systems. Indeed, CPP in women is often related with different chronic pelvic painful conditions, such as interstitial, post-radiotherapy and recurrent cystitis, irritable bowel syndrome, gynaecologycal disorder and extra-pelvic painful conditions: fibromyalgia, headache, temporomandibular disorder, and chronic fatigue syndrome[4]. Moreover, there is strong evidence for the involvement of peripheral somatosensory alterations in pelvic structures that are sources of pelvic pain, including the sprouting of new fibers and peripheral sensitization[4]. Central sensitization pain mechanisms as well as other spinal and encephalic changes in areas devoted to pain transmission and elaboration have also be described, confirming the intricacies involved and suggesting these alterations might be connected with cognitive and emotional processes in pain processing in CPP disorders[5,6]. This central hypersensitivity explains the chronic pain in the absence of detectable peripheral pathology and the discrepancy between the magnitude of tissue damage and pain and disability in CPP syndrome[7].

It is also relevant that conditions associated with mast cell activation (allergies, asthma, atopy, food intolerances and autoimmune diseases) co-occur with high frequency in CPP[8]. On the other hand, all conditions associated with CPP are characterized by an altered density of mast cells in pelvic tissues as well as a their shift from quiescent to activated phenotype[9]. This evidence suggests that inappropriate mast cell activation may represent an underlying unifying mechanism in all these conditions, and proposed as the basis of modern epidemic noninfectious inflammatory disorders[8].

Since inappropriate mast cell activation may result in both local and/or central neuroimmune dysfunctions leading to peripheral and/or central sensitization, its pharmacological control could limit progression of inflammatory processes, reduce chronic pain and improve organ functions. In this regard, N-acylethanolamines are endogenous lipid mediators able to promote the resolution of inflammation and restore tissue homeostasis. Among N-acylethanolamines, palmitoylethanolamide (PEA), an endogenous fatty acid amide congener of the endocannabinoid anandamide, has been reported to reduce pain behaviors, and to inhibit somatosensory activation and correlated events in different models of pelvic inflammation[9,10]. Importantly, in a standardized rat model of viscerovisceral hyperalgesia obtained with induction of endometriosis plus ureteral calculosis (which closely mimics the clinical condition in comorbid women), prolonged oral treatment with ultramicronized PEA (um-PEA) significantly reduced the behavioral indices of uterine and ureteral pain, along with a reduction in cyst diameter. These effects were associated with a significantly lower mast cell number and the mast cell algogenic markers chymase and nerve growth factor in cysts and dorsal root ganglia, suggesting that um-PEA reduces viscerovisceral hyperalgesia by modulating mast cell activation. In a murine model, PEA protected against 2,4-dinitrofluorobenzene-induced keratinocyte inflammation, proposing its therapeutic use against contact allergic dermatitis[11].

Products based on micronized- (m-) and um-PEA have also been reported to reduce CPP in patients with different pelvic conditions such as endometriosis[12-14] primary dysmenorrhea[15] and vulvodynia[16,17]. This evidence prompted us to assess the efficacy m-PEA in patients with CPP due to different conditions with or without allergy.

MATERIAL AND METHODS

In our referral center (Urology Division, G. Fornaroli Hospital Magenta- Milan, Italy), from January 2011 to December 2012, 75 female patients affected by CPP due to interstitial cystitis/bladder pain syndrome (BPS/IC) and CPP due to other conditions, with or without allergic history, were enrolled in this study. All patients displayed long-lasting irritative bladder symptoms, including bladder pain, urgency, daytime frequency of six or more episodes, nocturia and pain in the perineum, lower abdomen, lower back or vagina for at least six months. Inclusion criteria were: age >18 years, ability to read, understand and fill a bladder diary, presence of pelvic chronic pain, and pain intensity score ≥4 evaluated using the visual analog scale (VAS). Exclusion criteria were: bacterial cystitis demonstrated by urinoculture, previous pelvic radiotherapy or chemotherapy, history or presence of cancer, neurologic bladder or neuro-psychiatric disorder, bladder or ureteral stones, post-voiding residual >150 cc.

According to inclusion and exclusion criteria, all patients received, beyond standard therapy according to good clinical practice and international guidelines, m-PEA treatment (Normast, Epitech Group SpA) at dose of 300 mg, 2 tablets daily for 1 month, followed by 1 table/day for 2 months.

Pain intensity score was assessed by VAS: a 10 cm long line, with the leftmost side representing 0 (no pain) and the rightmost side representing 10 (unbearable pain). The participants marked their current level of pain on the scale after normal daily activities. All patients had uroflow (UFM) with post voiding residual (PVR). All patients were evaluated 3 times. The pretreatment visit (baseline V0): for all patients comprised an anamnestic evaluation, clinical examination and metabolic features recorded in a data base. All patients received VAS evaluation, Short Form Health Survey (SF12) questionnaire to evaluate quality of life, UFM+PVR and voiding diary. After initiation of m-PEA treatment, patients underwent follow-ups at 30 (V1) and 90 (V2) days.

Visit at 30 (V1) and 90 (V2) days: All patients received VAS evaluation, SF12 questionnaire to evaluate quality of life, UFM+PVR and voiding diary. SF12 measures eight domains of health: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations and mental health. This yielded a total score regarding mental health and physical health. Higher scores indicate a better quality of life.

All patients were properly informed about the study. The study was carried out in accordance with Declaration of Helsinki and Good Clinical Practice Guidelines.

Statistical analysis

This study used the SAS system (SAS 9.2 System for Windows, SAS Institute, Cary, NC, USA) to conduct all statistical analyses. The results obtained by evaluating VAS pain intensity score, mental health and physical health total scores of SF12 questionnaire, bladder capacity, urinary frequency and nocturia were analyzed using the GLMM (Generalized Linear Mixed Model) in order to evaluate mean changes across m-PEA treatment time. m-PEA treatment time, presence of allergy, presence of concomitant disease were used as covariates. Data are expressed as mean ± standard error (SE), if not otherwise stated. Results are considered significant for p values less than 0.05.

RESULTS

All patients were compliant with treatment. The patient's age ranged from 18 to 75 years. The duration of CPP ranged from 2 to 20 years. Fifty-five of the 75 patients (73%) had one or more forms of allergy, including those of the respiratory tract and food-related. Among CPP allergic patients, 25 (45%) were affected by IC/PBS and 30 (54%) presented other forms of CPP derived from urethral syndrome, suprapubic pain, coccydynia, perineal pain, recto-ulcerative colitis, irritable bowel syndrome and vulvodynia. In addition to CPP and allergies, 24 patients (32%) displayed other painful pelvic or extra-pelvic conditions. Twenty CPP patients (27%) had no form of allergy; of these last group, 5 (25%) had other painful pelvic or extra-pelvic conditions.

Average pain intensity score decreased from 8.4 ± 0.3 at baseline to 2.9 ± 0.2 at 90 days, and from 8.7 ± 0.2 to 2.1 ± 0.2 with m-PEA adjuvant therapy in CPP patients without and with concomitant allergy, respectively. This reduction in mean score was highly significant (p=0.0001). The presence of allergy did not change pain intensity score at all times analyzed (p<0.6966). However, the time trend was influenced by allergy presence, i.e. a constant and progressive score reduction was observed in CPP + allergy patients while a slower reduction in CPP patients was observed after the first month of treatment (p<0.0010) (Figure 1).

Functional bladder capacity was evaluated by measuring the mean voided volume recorded on a bladder diary and UFM. Functional bladder capacity at baseline was 155.00 ± 17 ml in CPP patients without concomitant allergy and

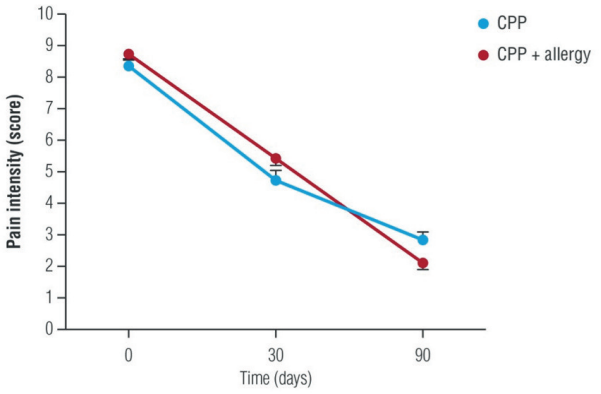

Figure 1. – Effect of m-PEA addition on pain intensity scores in CPP patients undergoing therapy, with or without concomitant allergy. Data are expressed as means ± SE; n = 20 for CPP and 55 for CPP + allergy. Note that in both groups pain intensity score decreases with m-PEA treatment over time: p<0.0001.

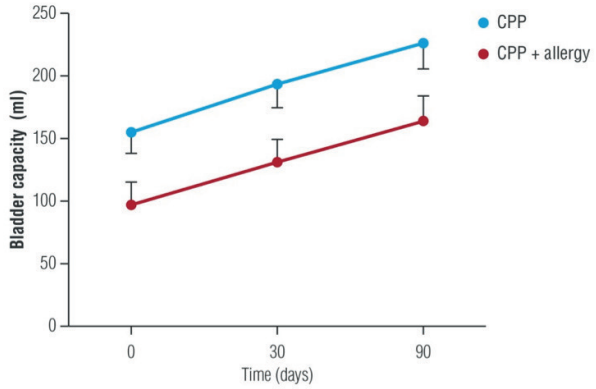

Figure 2. – Effect of m-PEA addition on bladder capacity in CPP patients undergoing therapy and with or without concomitant allergy. Data are expressed as means ± SE; n = 20 for CPP and 55 for CPP + allergy. Note that in both groups the bladder capacity increased with m-PEA treatment over time (p<0.0001) with the same time trend (p<0.7921).

TABLE 1. Effect of m-PEA addition on physical health (PCS12) and mental health (MCS12) in patients with CPP with or without concomitant allergy. Data are expressed as means +/- SE; n = 20 for CPP and 55 for CPP + allergy.

Time (days)		0	90	p
PCS12	CPP	41.1 ± 1.7	44.3 ± 1.5	< 0.0001
	CPP + allergy	42.1 ± 1.0	46.6 ± 0.5	
MCS12	CPP	39.1 ± 2.1	45.9 ± 1.9	< 0.0001
	CPP + allergy	37.1 ± 1.0	43.8± 0.89	

98.00 ± 6 in CPP patients with allergy (Figure 2). In both groups, functional bladder capacity increased at 30 and 90 days after m-PEA adjuvant therapy, rising from 155.00 ± 17 ml to 193.50 ± 19 and 226.00 ± 20, respectively, in CPP patients without allergy ($p<0.0001$), and from 98.00 ± 6 to 130.36 ± 9 and 163.45 ± 10 in CPP patients with allergy ($p<0.0001$). In CPP + allergy functional bladder capacity was lower at all times analyzed ($p<0.0006$) while the time trend after m-PEA therapy was not influenced ($p<0.7921$) (Figure 2).

The urinary daily frequency and nocturia in CPP patients with and without allergy at baseline and after m-PEA therapy are reported in Figure 3. Daily frequency was 8.4 ± 0.3 at baseline in CPP patients and was reduced to 7.0 ± 0.3 following 90 days of m-PEA therapy ($p<0.0001$). A similar reduction in daily frequency was observed in CPP + allergy patients: mean value at baseline of 11.3 ± 0.5 decreased to 8.7 at 90 days after m-PEA therapy ($p<0.0001$). Daily frequency was higher at all times analyzed in CPP + allergy patients ($p<0.0011$). The presence of allergy modified the time trend after m-PEA therapy ($p<0.0142$). Nocturia was 2.9 ± 0.4 at baseline in CPP patients and decreased to 1.8 ± 0.3 after 90 days of m-PEA therapy ($p<0.0001$). A similar reduction in nocturia was observed in CPP + allergy patients: baseline mean value of 4.5 ± 0.2 decreased to 3.1 ± 0.2 at 90 days after m-PEA therapy ($p<0.0001$). Nocturia was higher at all times analyzed in CPP + allergy patients ($p<0.0002$). The presence of allergy did not modify the time trend after m-PEA therapy ($p<0.2265$) (Figure 3).

The impact of CPP on quality of life was not modified by allergy co-occurrence, as demonstrated by $p<0.2613$ for physical health (PCS12) and $p<0.2236$ for mental health (MCS12). An improvement of quality of life was observed in both CPP patients with and without allergy ($p<0.0001$ for both groups) (Table 1).

DISCUSSION

CPP is frequently associated with diseases characterized by mast cell activation such as allergies, asthma, atopy, food intolerances and autoimmune diseases[5]. The concomitant occurrence of allergy or syndromes characterized by mast cell activation may have a negative impact on the progression of diseases associated with CPP and may also influence the outcome of therapeutic treatment. The present clearly shows that the bladder functional parameters, e. g. daily frequency and nocturia as well as bladder capacity, are compromised by the presence of allergy. In fact, at all times analyzed bladder capacity was lower and daily frequency and nocturia higher in CPP with concomitant allergy compared to patients with CPP alone. This result might in part be due to the presence of a high number of patients affected by IC/PBS in the CPP + allergy (25/55) group. However, the differences remained also when IC/PBS patients were excluded from the analysis, suggesting that the occurrence of allergy might directly affect bladder functions. In support of this hypothesis, bladder symptoms of frequency, urgency and pelvic pain in a patient with asthma and allergic rhinitis was subsided after anti-IgE therapy and specific immunotherapy with omalizumab[18,19]. These findings further support the involvement of mast cell activation in CPP conditions, particularly those associated with bladder dysfunctions. There is general agreement that mast cells play an important role in pain syndromes and, in particular, in BPS/IC, as they participate early in disease development in nociceptive pain, e.g., by sensitization of nerve fibers. Yet, little is known about mast cell activation and organ function where mast cell activation is dysfunctional. Our findings suggest that mast cell activation might significantly worsened organ function while continuing to perpetuate both acute and chronic pain.

In the present analysis, pain intensity did not seem to be worse in CPP patients with allergy. However, at baseline in both groups pain intensity was near the maximal value, suggestive of severe pain. Also the quality of life, both in physical and mental health terms, was not affected by the co-occurrence of allergy.

Notably, addition of m-PEA evoked a significant reduction of pain intensity and improved bladder functional parameters as well as quality of life in CPP patients with and without concomitant allergy. The m-PEA-induced reduction in pain intensity and improvement of daily frequency was similar in patients with and without allergy, although different response trends could lead one to hypothesize that subjects with allergy achieve more benefit.

The m-PEA-induced pain intensity reduction confirms the ability of the micronized PEA formulation to exert pain-reducing effects in chronic conditions affecting pelvic organs. This action of m-PEA has been reported in patients with chronic pain associated to endometriosis[12-14], perineal pain[20], vulvodynia[17], and irritable bowel syndrome. However, here we provide the first evidence specifically for chronic bladder pain. This finding is particularly relevant for patients affected by IC/PBS, since this group represents one-third of all patients analyzed in the current observational study. Importantly, in addition to providing pain relief m-PEA treatment led to an improvement in bladder functions. Worsening of bladder capacity along with daily frequency and nocturia in CPP patients greatly contribute to the progressive decline in quality of life. The ability ofm-PEA to reduce pain and bladder dysfunctions throughout

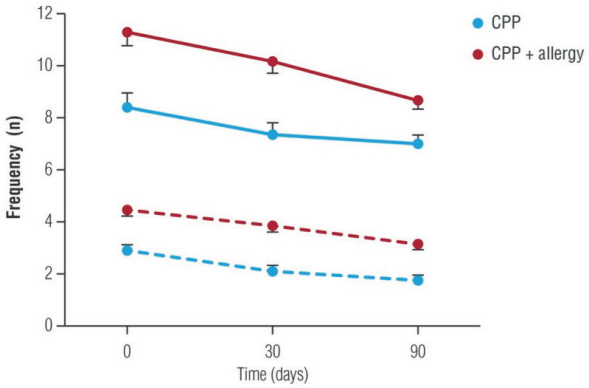

Figure 3. – Effect of m-PEA addition on daily frequency (solid line) and nocturia (dashed line) in CPP patients undergoing therapy and with or without concomitant allergy. Data are expressed as means ± SE; n = 20 for CPP and 55 for CPP + allergy. Note that in both groups the daily frequency and nocturia decreased with m-PEA treatment over time ($p<0.0001$, both groups). The time trend after m-PEA therapy was modified by allergy co-occurrence in the case of daily frequency ($p<0.0142$) but not for nocturia ($p<0.2265$).

the treatment period supports a disease-modifying action of the NAE, as observed in other conditions associated to chronic pain[21]. In chronic models of pain, PEA not only prevents pain threshold alterations, but also preserves nerve morphology spares from nerve degeneration[22,23]. In these studies, the neuroprotective effect of PEA was associated with a limited recruitment and activation of immune cells in the nerve as well as a reduced activation of spinal cord glia. Conceivably, in CPP associated with bladder dysfunctions, m-PEA might promote recovery of damaged tissues by facilitating resolution of inflammatory processes and allowing for improved organ functions. This view is supported by evidence showing that um-PEA attenuated pain behavior, voids and gross bladder damage in an experimental model of cystitis[24].

m-PEA was efficacious in CPP patients with and without concomitant allergy. However, the m-PEA-induced reduction of pain intensity and improvement of daily frequency was slight but significantly higher in CPP patients with allergy. This finding might be related to ability of m-PEA to directly act both on mast cell activation-mediated pelvic organ dysfunctions and mast cell activation mediated-allergic processes. The current study is one of the very few in this area, at the same time, caveats include the non-homogeneity of patients at baseline and absence of a control group.

In conclusion, the results obtained underscore the potential benefit of m-PEA in patients with CPP, especially in subjects with allergy - thus supporting the proposed importance of mast cell activation in modern epidemic non-infectious inflammatory disorders. Clearly, the present data need to be confirmed in a placebo-controlled, double-blind clinical study. Even so, these results suggest that the control of mast cell activation with m-PEA might represent a novel opportunity to reduce CPP and limit the progression of pelvic diseases.

DISCLOSURES

No financial support has been received by the authors.

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Comment

The theme of this chronic pelvic pain (CPP) issue is largely anatomical, the role of loose uterosacral ligaments unable to support the Frankenhauser nerve plexus and treatment thereof by some thype of ligament repair operation. Sekiguchi et al. (this issue) achieved a 79% cure/improvement rate with TFS cardinal/uterosacral repair. This is historically a fairly optimal result for this type of surgery. All of which raises the question, 'what about the other 21% of patients? Was there some other cause? How many of these patients had the 'other etiologies' referenced by Somamriva et al.? Sommariva et al give statistically valid evidence of significant improvement in CPP. Average pain intensity score decreased from 8.4 ± 0.3 at baseline to 2.9 ± 0.2 at 90 days, and from 8.7 ± 0.2 to 2.1 ± 0.2 with m-PEA adjuvant therapy in CPP patients without and with concomitant allergy, respectively.

These results need to be seen in the context of symptom variation. There is a wide variation in how patients experience pain symptoms, from fairly minor to very severe requiring emergency hospital admission[1,2].

So it is not so much that the palmitoylethanolamide treatment more than halves the pain intensity. It can reduce it to a tolerable level, perhaps reducing or even preventing the hospital admissions required with severe episodes of pain.

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