Short-term efficacy of a fixed association of Palmitoylethanolamide and other phytochemicals as add-on therapy in the management of chronic pain in elderly patients: a real-world retrospective study

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Abstract

Phytochemicals are promising adjuvant agents for the treatment of pain. This study aimed to explore the short-term efficacy and safety of a fixed-dose combined therapy with Palmitoylethanolamide and other phytochemicals as add-on therapy in elderly patients. Data on 47 elderly patients with non-oncologic chronic pain of mild-moderate degree were analyzed in a retrospective, descriptive, no-profit, double-center real-world study. Patients were administered the combined phytochemical therapy for 6 weeks, in addition to analgesics administered when needed. Patients showed a reduction in pain intensity both in mixed noninflammatory and in neuropathic pain and improvements in functional abilities, quality of life, and in the subjective belief about the efficacy of treatment. These results were also observed in the small subgroup of patients in monotherapy with phytochemicals (n=13). No adverse event led to treatment withdrawal. This exploratory study suggests that phytochemicals may represent an effective source of analgesics to be added to chemically synthesized drugs, therefore reducing the need of their up-titration and the risk of toxicity. These data must be considered as preliminary and need to be tested in randomized trials.

Introduction

Persistent pain is a common condition that particularly affects older patients.1,2 Pain is associated with substantial disability, reduced mobility, falls and emotional disturbances such as depression, anxiety, sleeping disorders and social withdrawal, which further impair patient’s quality of life.2,3 Also, chronic pain represents a huge economic burden for the healthcare systems, affecting up to 50% of community-dwelling elderly people, and up to 83% of long-term care residence people.4,5 Its incidence more than doubles once individuals pass the age of 60 and increases with each decade.6 Due to the growing aging of population, a further increase in chronic pain prevalence is expected.7,8 In addition, the real prevalence of pain in the elderly is probably underestimated due to difficulties in the assessment.7 In fact, elderly patients tend to minimize symptoms5 and to consider pain as a physiologic consequence of aging or of a given pathology.9 Management of pain in the elderly is complicated by the presence of comorbidities and consequent polypharmacy in this population.10 As a consequence, pain is often undertreated and/or treated with as-needed analgesics, mainly paracetamol and NSAIDs, a common clinical practice in the management of pain. Unfortunately, this pharmacological approach considers only mild degrees of pain and presents risks of interactions, adverse effects and toxicity over time. Similarly, the use of antidepressants, antiepileptics and opioids, although associated to a reduction of pain, may lead to pharmacologic interactions and adverse effects.11,12 Therefore, it would be interesting to explore analgesic-sparing approaches with increased efficacy and decreased toxicity in the management of pain in the elderly. To this aim, phytochemicals have received growing attention as add-on therapy. They have been defined as bioactive nonnutrient plant compounds in fruits, vegetables, grains, and other plant foods that have been linked to reducing the risk of major chronic diseases.13 Medicinal plants comprise sterols, flavonoids, terpenes, diterpenes, sesquiterpenes, and polyphenolics.14

In particular, four phytochemicals have received growing attention as adjuvant agents for the treatment of pain: Palmitoylethanolamide (PEA), Rosemary, Commiphora molmol (myrrh), β-Caryophyllene.15-17 In particular, the role of PEA on endocannabinoid system activation and its anti-inflammatory properties are well known.18,19 These agents are currently marketed in EU as nutraceuticals in humans. The combination of PEA with three special standardized extracts from Rosmarinus Officinalis, Commiphora Mirrha and Piper Nigrum, formulated in IdroOilMatrixTM that increases the bioavailability of lipophilic active ingredients, is available in Italy as a dietary supplement (Noxiall®) and is administered as tablet via oral route (Italian Registry of Supplements code 88326).

Taking into account these issues, we have conducted a descriptive, retrospective, real-world study in order to evaluate the short-term efficacy and safety of fixed-dose combined therapy with Noxiall® as add-on therapy in elderly patients with non-oncologic chronic pain of mild-moderate degree.

Materials and Methods

In this 6-week, retrospective, descriptive, no-profit, double-center real-world study we have enrolled 51 patients using the following inclusion criteria: age ≥65 years; duration of pain ≥3 months; mild-moderate degree of pain (4-5) as assessed by using the Numeric Pain Intensity Scale (NRS). Exclusion criterion was oncologic pain.

Specifically, primary outcomes were: reduction of pain intensity, changes in neuropsychiatric pain and patient’s referred positive subjective experience of the therapy. Secondary outcomes were: daily activities and quality of life improvements. Safety data were also recorded.

Patients were administered the combined therapy with Noxiall® (Noxiall®-FB Health S.p.A: PEA 600 mg, Commiphora Myrrha 50 mg, Piper Nigrum 13.4 mg (10 mg β-cariofillene) and Rosmarinus Officinalis 30.8 mg) for 6 weeks (2 tablets daily) but also analgesics when needed. Follow up evaluations were: after 3-7 days from baseline (by telephone) (T1), 10±2 days (T2), 30±2 days (T3) and 42±7 days (T4). Informed consent was obtained from each patient.
Instruments

The 0 to 10 NRS is a unidimensional measure of pain intensity in adults. Patients are asked to rate the intensity of their pain using any number between 0 and 10, where 0 is no pain and 10 is the strongest or worst pain you can imagine, on a segmented numeric version of the visual analog scale. The common format is a horizontal bar or line.

DN4 is a validated clinician-administered screening tool to assess neuropathic pain. The questionnaire contains 10 items, split across four questions. Patients are asked to provide a yes or no answer to each item. All yes responses are scored as 1, and no responses are scored as 0. The individual item scores are summed and a total score calculated. A score of 4 or greater indicates that the pain is likely to be of neuropathic origin.

PGIC is a 7-point, self-report measure to assess a patient’s belief about the efficacy of treatment. Patients are asked to rate efficacy on activity limitations, symptoms, emotions and overall quality of life related to their painful condition, from 1 (no change/or condition has got worse) to 7 (considerable improvement and efficacy).

ADL and IADL scales were used to assess functional abilities. The ADL scale is based on the level of independence in performing six daily actions: bathing with a sponge, bath or shower; dressing; toilet use; transferring in and out of a bed or chair; urine and bowel continence; and eating. The IADL scale is based on 7 criteria (use of the telephone, traveling via car or public transportation, food or clothes shopping, meal preparation, housework, medication use, and management of money) and there are two separate scores for males and females. Lower scores in ADL and IADL indicate worse autonomy.

To assess the impact of pain on quality of life (QoL), a non-validated, adapted version of the Brief pain inventory was used. Patients were asked to indicate a score from 0 (pain does not interfere) to 10 (pain completely interferes) for 7 items (sleep, appetite, walking, personal care, activities, mood, concentration).

DN4, PGIC, ADL, IADL and the QoL scale were administered at baseline, T2, T3, T4.

Safety

At each time point, any new adverse event that occurred or worsened in intensity and/or frequency was recorded; the potential correlation between the adverse events and the treatment was judged by the pain therapist.

Statistical analyses

For continuous variables, repeated measures factorial analysis of variance (ANOVA), followed by Fisher’s Protected Least Significant Difference (PLSD) post-hoc tests, were used to detect differences during time points. The nonparametric Friedman test was used to compare observations during time for ranked variables. Values are expressed, respectively, as mean ± standard deviation or median and range.

All analyses were conducted comparing baseline values with T1 (only for NRS), T2, T3 and T4 values to show the effects of treatment on the outcome measures at the mid- and end-term points of the study.

The level of statistical significance was defined as <0.05. Statistical analyses were performed by using the StatView statistical software package (SAS Institute INC., Cary, NC).

Results

Fifty-one patients fulfilled the inclusion criteria and were consecutively enrolled. During the study period, 4 patients dropped out (3 for non-compliance, 1 for personal problems). Final sample was therefore composed by 47 patients. Demographic and clinical variables at baseline are shown in Table 1.

Regarding background therapy, n=13 patients (28%) remained free of analgesic treatment and therefore were administered Noxiall® in monotherapy for the whole study period.

Primary outcomes

Pain assessment

A repeated-measures ANOVA revealed that NRS values significantly changed over time (F-value= 128.121, P<0.0001). Specifically, mean values progressively decreased from baseline to each time point during the study period [7.5±1.8 (T0); 5.9±1.8 (T1); 4.8±1.5 (T2); 4.0±1.5 (T3); 3.2±1.5 (T4)] and each follow up value significantly differed from each other (data available upon request).

NRS values significantly changed over time also in the subgroup of patients in monotherapy with Noxiall® (n=13) (F-value= 47.644, P<0.0001). Specifically, mean values progressively decreased from baseline to the end of the treatment [7.6±1.6 (T0); 5.9±2.0 (T1); 4.5±1.5 (T2); 3.6±1.1 (T3); 3.1±1.3 (T4)] and follow up values significantly differed from baseline values (data available upon request).

Data on DN4 were available for 44 patients. A repeated-measures ANOVA revealed that DN4 values significantly changed over time (F-value= 54.957, P<0.0001). Specifically, mean values progressively decreased from baseline to each time point during the study period (5.2±2.7 (T0); 4.6±1.6 (T2); 3.8±1.5 (T3); 3.1±1.3 (T4)). Follow up values significantly differed from each other (data available upon request).

Patient’s belief about the efficacy of treatment

The non-parametric Friedman test was used to compare median values for PGIC. Data were available for 34 patients. PGIC values significantly changed over time (P=0.012) and median values progressively decreased from baseline to each time point during the study period (specifically, from no change/or condition has got worse to considerable improvement and efficacy at T2, T3 and T4). The percentage of patients rating the treatment as not effective ranged from 94% (n=32) at baseline to 47% (n=16) at T2 to 9% (n=3) at T3 and to 6% (n=2) at the end of the study period. At the end of the study period, 94% of the sample rated the treatment as effective or very effective (specifically, 71% effective, 23% very effective). In the subgroup of patients taking only Noxiall® for the whole study period, 100% rated the treatment as effective.

Secondary outcomes

Functional capacity

Data on ADL and IADL were available for 46 patients. A repeated-measures ANOVA revealed that ADL values significantly changed over time (F-value= 11.619, P=0.0012). Secondary outcomes on ADL and IADL values are presented in Table 1.

Table 1. Demographic and clinical characteristics of patients at baseline (n=47).

| Variable                        | Mean (± s.d.) or n (%) |
|--------------------------------|-----------------------|
| Age, years                     | 78±9                  |
| Female sex                     | 28 (60%)              |
| Pain, NRS                      | 7.5±1.8               |
| Pain duration:                 |                       |
| 3 months                       | 5 (11%)               |
| 4-6 months                     | 4 (8%)                |
| 7-12 months                    | 7 (15%)               |
| >12 months                     | 31 (60%)              |
| Painful condition or disorder: |                       |
| Arthrosis                      | 7 (36%)               |
| Fibromyalgia                   | 2 (4%)                |
| Fracture                       | 2 (4%)                |
| sLow back pain                 | 7 (15%)               |
| Diabetic neuropathy            | 6 (13%)               |
| Post-herpetic neuralgia        | 3 (6.5%)              |
| Radiculitis                    | 10 (21.5%)            |
| Analgesic treatment:           |                       |
| NSAIDs                         | 5 (11%)               |
| Aminoacetophenone alone        | 6 (13%)               |
| Aminoacetophenone and tramadol | 5 (11%)               |
| Aminoacetophenone and codeine  | 4 (8%)                |
| Dicyclomine/naloxone           | 2 (4%)                |
| Duloxetine                     | 2 (4%)                |
| Pregabalin                     | 8 (17%)               |
| Vit B12                        | 1 (2%)                |
| Lidoepaine patch               | 1 (2%)                |
| None                           | 13 (28%)              |

s.d., standard deviation; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs.
Discussion and Conclusions

This retrospective, descriptive, non-controlled, real-world study explored the effect of 6-week add-on therapy with a fixed combination of phytochemicals in elderly patients with chronic pain.

Patients showed a reduction in pain intensity both in mixed/nociceptive and in neuropathic pain (NRS and DN4) as well as improvements in functional abilities (ADL in the whole sample and IADL for female patients). QoL in all the domains assessed, and in the subjective belief about the efficacy of treatment (PGIC). Despite these data must be considered as preliminary, and need to be tested in a larger scale study, interpretation of results may take into account the well-known advantages of a combined analgesic approach as well as the therapeutic properties of the phytochemicals.

Due to a synergistic effect, it is now recognized that the use of a combination therapy is associated with a better antinociceptive effect than monotherapy.16,27 Also, combination therapy has been shown to enhance the safety and tolerability of analgesic treatment,23 because it allows for lower doses of drugs to be used. Consistently, in our real-world study no clinically relevant adverse event (i.e. leading to treatment withdrawal) was observed. Another advantage is that combination therapy may result in better compliance,27 that is particular challenging in the elderly.2

In addition, the analgesic properties of the medicinal plants combined in Noxiall® are increasingly recognized. PEA (N-2-hydroxymethyl) hexadecamide, palmidrol belongs to the family of N-acylethanolamines and is an active anti-inflammatory agent.13 There is evidence that PEA has analgesic properties without side effects in humans.15 In an animal study, PEA was administered in combination with tramadol showing its enhanced analgesic efficacy also at low-doses.16

Rosemary, Rosmarinus (R.) officinalis L. has analgesic, anti-inflammatory and anti-neurodegenerative properties. It is used to alleviate rheumatic pain, stomachache and dysmenorrhoea.17,24

Myrrh is a resinous exudate (oleo-gum resin) obtained from the stem of Commiphora molmol, family bursaraceae, a small perennial tropical tree.24 Its analgesic properties have been shown by several studies.15,29-31 β-Caryophyllene is a member of sesquiterpene lactone found in large amounts in Piper Nigrum (black pepper) and other plants,32 with analgesic, antidia- betic, hepatoprotective and neuroprotective properties.33,34 Whilst myrrh has a Mu opioid effect, β-Caryophyllene is a selective cannabinoid receptor (CB) 2 receptor agonist, thus it does not have the psychotropic effects typical of other cannabinoids that

Table 2. Changes in quality of life domains during the study period (N=46).

| T0        | T2        | T3        | T4        | P-value | F-value |
|-----------|-----------|-----------|-----------|---------|---------|
| Sleep     | 6.8±2.2   | 4.9±2.1   | 3.7±2.0   | 2.8±1.5 | <0.0001 | 118.339 |
| Appetite  | 6.0±2.7   | 4.8±2.1   | 3.6±1.7   | 2.7±1.5 | <0.0001 | 59.576  |
| Walking   | 7.0±1.9   | 5.4±1.9   | 4.1±1.7   | 3.4±1.7 | <0.0001 | 122.372 |
| Personal care | 6.2±2.5   | 4.9±2.2   | 3.9±1.8   | 3.2±1.7 | <0.0001 | 96.181  |
| Activities | 6.3±1.8   | 5.5±1.8   | 4.4±1.6   | 3.5±1.6 | <0.0001 | 112.998 |
| Mood      | 7.0±1.9   | 5.5±1.9   | 4.2±1.7   | 2.9±1.6 | <0.0001 | 128.731 |
| Concentration | 6.8±1.8   | 5.3±1.7   | 4.1±1.6   | 3.0±1.6 | <0.0001 | 108.795 |

Data are expressed as mean ± standard deviations.

Table 3. Occurrence and intensity of adverse events during the study period [n (%)] (N=47).

| Type of AE | T1 Mild | Moderate | Severe | Total | T2 Mild | Moderate | Severe | Total | T3 Mild | Moderate | Severe | Total | T4 Mild | Moderate | Severe | Total |
|-----------|--------|----------|--------|-------|--------|----------|--------|-------|--------|--------|----------|--------|-------|--------|----------|--------|-------|
| Nausea    | 4 (8.5%) | 3 (6%)   | 1 (2%) | 8 (17%) | 17 (5%) | 0 (0%)   | 0 (0%) | 0 (0%) | 7 (15%) | 1 (2%) | 0 (0%)   | 1 (2%) | 0 (0%) | 1 (2%) | 0 (0%)   | 0 (0%) | 0 (0%) | 1 (2%) |
| Vomiting  | 1 (2%)   | 0 (0%)   | 1 (2%) | 2 (4%) | 1 (2%) | 0 (0%)   | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) |
| Dizziness | 9 (19%)  | 1 (2%)   | 1 (2%) | 8 (17%) | 17 (5%) | 0 (0%)   | 0 (0%) | 0 (0%) | 8 (17%) | 5 (11%) | 0 (0%)   | 0 (0%) | 5 (11%) | 4 (8.5%) | 0 (0%)   | 0 (0%) | 4 (8.5%) |
| Drowsiness| 4 (8.5%) | 2 (4%)   | 1 (2%) | 7 (15%) | 15 (5%) | 1 (2%)   | 0 (0%) | 6 (13%) | 3 (6%) | 0 (0%) | 0 (0%)   | 3 (6%) | 1 (2%) | 0 (0%) | 0 (0%)   | 1 (2%) | 0 (0%) | 1 (2%) |
| Dry mouth | 4 (8.5%) | 2 (4%)   | 1 (2%) | 7 (15%) | 15 (5%) | 1 (2%)   | 0 (0%) | 5 (11%) | 3 (6%) | 2 (4%) | 0 (0%)   | 5 (11%) | 3 (6%) | 0 (0%) | 0 (0%)   | 3 (6%) |
| Itch      | 6 (13%)  | 0 (0%)   | 1 (2%) | 7 (15%) | 14 (5%) | 1 (2%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) |
| Other     | 0 (0%)   | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%)   | 0 (0%) | 0 (0%) | 0 (0%) |

AE, adverse event.
bound to CB1. These receptors are expressed on the microglia and modulate their action, and under pain conditions they are exposed on the cell surface.18-37

Our data preliminarily suggest that phytochemicals as add-on therapy may represent an effective source of analgesics to be added to chemically synthesized drugs. As observed in this study, a combined therapeutic approach may result in decreased suffering and a general increase in QoL in elderly people.

Thus, our data shows a significant effect on pain relief and improvement in the QoL during the follow-up in our sample. However, the main limitation of this study is the retrospective, non-controlled design. These results may be potentially affected by biases linked to the study design. In particular, the lack of control group and the administration of other drugs do not allow drawing conclusions on the effectiveness of the phytochemicals as adjunct treatment of persistent pain, so far. Another possible confounding factor is the potential inclusion in the study of patients well-educated, motivated, with higher income, socially active and empowered. In addition, the exact mechanisms of action of phytochemicals remain to be elucidated.

Despite these limitations, our study may provide preliminary data that deserve to be tested in larger, ongoing, placebo-controlled studies. As implication for clinical practice, increasing our knowledge on the efficacy of add-on therapy with phytochemicals in elderly patients with pain may potentially reduce the need of up-titrate chemically synthesized drugs, and, possibly, the risk of toxicity.

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