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Therapeutic benefit of palmitoylethanolamide in the management of neuropathic pain

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Abstract: *Background*: Neuropathic pain is defined by International Association for the Study of Pain (IASP) as "Pain caused by a lesion or disease of the somatosensory nervous system". Elderly patients generally have high incidence of chronic neuropathic pain. The safe and effective treatment for chronic pain is a large public health concern. Palmitoylethanolamide (PEA) is an endogenously produced amide cannabimimetic compound with tissue protection and anti-inflammatory activity. *Objectives*: The aim & objective of this study is to evaluate the effectiveness and safety of Palmitoylethanolamide (PEA) in patients suffering from Neuropathic/Chronic Pain. *Study Designed*: Prospective Study. *Materials and Methods*: The Study was conducted in the Neurosurgery unit of Surgery Department in Gandhi Medical College & Associated Hamidia Hospital, Bhopal. A total no. of 150 patients aged 20-78 years were included in the study and divided into two groups, group I (Study group) and the group II (Control group) PEA was given to group I to evaluate the effect of PEA in neuropathic pain. *Result*: We studied 150 patients with PEA for 60 days in a dose of 354 mg orally three times (TDS) a day for first 10 days and then two times (BID) a day for 50 days. It is available in India by the name of Palmiges. PEA was associated with greater pain reduction in the study group compared to the placebo controlled group. The primary outcome measured was the mean pain reduction evaluated by VAS scale. *Conclusion*: PEA seems to be useful in the treatment of neuropathic / chronic pain and it is well tolerated in patients in study group. Palmiges PEA reduces the inflammation in neuropathic pain, which results in lowering/reduction of neuropathic pain. Controlled trials are further needed to prove efficacy and reliability and also to find out the adverse reaction associated with the drug.

Key words: PEA, Palmitoylethanolamide, Neuropathic Pain, Analgesics, VAS (Visual Analogue Score)

Introduction

Neuropathic Pain is a complex condition that has its origin in a primary lesion or dysfunction of any part of the nervous system from the peripheral receptor to the brain. Persistent neuropathic pain often interferes with sleep, work, recreational activities and the

emotional state of the individual who suffers from it, thus affecting quality of life [1]. Neuropathic pain is usually described as the perception of strange or unusual painful sensations like burning, stabbing or lancing pains experienced as electrical discharges or other painful sensations [2,3] . Neuropathic pain may be evoked by mechanical, thermal or chemical stimuli.

The Global Prevalence: reported in the literature

•A review of the epidemiology of chronic pain found that there is still no accurate estimate available for the population prevalence of neuropathic pain (Smith et al.2012). [4]

•Overall, neuropathic pain affects 7-10% of the general population.

•In the primary care setting, the prevalence has been reported to be between 2 to 11%.

•By Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) criteria, the prevalence of DPN was 29.2%.

•In cancer patients the prevalence is 19%.

In Indian Scenario: -

•The prevalence of Neuropathic pain in Indian scenario is difficult to establish, as there are many confounding factors that may lead to under reporting of neuropathic pain.

•The prevalence in males is around 26.1% and females is 33.8%, whereas prevalence of neuropathic pain in cancer patients is 19%.

•About 1% to 37% of chronic lower back pain patients may have a neuropathic component related to it.

•Prevalence of neuropathic pain in low backache-related leg pain (LBLP) patients varies from 19% to 80%.

•A study done by Ind INEP study group in Indian patients in the year 2008 suggests that painful diabetic neuropathy is the most common cause of neuropathic pain (72%).

•Ind INep study group also suggests that, about 50% of patients reported co-morbid mood disorders, while 67% reported medication-related adverse event in the preceding week.

Inflammation:

Inflammation is the response of living tissue to injury. It involves a well-organized cascade of fluid and cellular changes within living tissue. The inflammatory process is of great significance in the development of Neuropathic Pain (NP) [5]. PEA, an endogenously produced amide has been established to work on the inflammatory pathways acting as a pacifier against inflammation. In neuropathic pain, the amount of the amide reduces drastically in the body resulting in aggravated inflammation and furtherance of diseased condition [6] . The endogenously produced FAAH (Fatty Acid Amide Hydrolase) enzyme further degrades the available amide, further reducing its quantity and effectiveness. Palmiges (PEA) is an endogenously produced amide. PEA, Genistein and Daidzein function to counter the action of FAAH enzyme, thereby improving the condition of aggravated inflammation, which is the root cause of neuropathic pain [7].

Current treatment modalities and their Drawbacks:

•Current treatment drugs such as gabapentin, pregabalin and duloxetine etc. have annoying side effects such as drowsiness, dizziness, blurred vision, somnolence, peripheral edema etc. Moreover, using these drugs in the long term causes desensitization

of neuron receptors. Therefore, the dose of these drugs has to be increased to elicit the desired response and that leads to more number of side effects. In addition, some drugs require dose adjustment in renal impairment. Hence, the current treatment paradigms have some gaps and require some new arsenal to fight against neuropathic pain. Thus, what is needed at this critical juncture is a solution which corroborates to the core of neuropathic pain with no side effects.

PALMIGES contains the following components:

A. Palmitoylethanolamide (PEA):

•PEA is considered an endogenous Peroxisome Proliferator Activated Receptors (PPAR) agonist or activator, interacting with this receptor to inhibit inflammatory pathways & oxidative stress.

•During neuropathic pain, PEA can modulate the PPAR pathway that is able to attenuate Nuclear Factor Kappa B cells (NFKB) induced inflammatory factors or tumor necrosis factor (IL-1 or TNF), inhibit infiltration and activation of MC, reduce mesangial matrix proliferation induced by reactive oxidative stress (ROS) which then resulted in albuminuria [8] .

B. Genistein:

•Genistein is a FAAH inhibitor that not only prevents the degradation of PEA from FAAH enzyme in the body but also exerts synergistic effect with PEA to reduce oxidative stress in the over- inflamed neuronal cells.

C. Daidzein:

•Daidzein belongs to the class of isoflavones and serves as a potent FAAH inhibitor in conjunction with Genistein. It works as a competitive binder to FAAH disallowing it to degrade the externally supplemented PEA.

D. MPFAITECH: A technology to ensure the proprietary blend is presented in a form that could be easily absorbed in the human body.

Palmitoylethanolamide (PEA) is a cannabimimetic compound which reduces neuropathic pain. It is a special food for medical purpose in the treatment of chronic pain.

Material and Methods

The study includes patients with neuropathic pain and pain due to various causes like chemo-therapy induced neuropathic pain, chronic pain, trigeminal neuralgia, lower back pain and cervical spondylosis pain etc. These patients reported in the outpatient department (OPD) of Neurosurgery of Hamidia Hospital Bhopal. In a period of four months total 150 patients with neuropathic pain between age group of 20-78 years were studied. Male patients were 94 and female patients were 56. They were divided into two groups each consisting of 75 patients. The control group received usual conventional treatment like NSAID's, antiepileptics (Carbamazepine, Gabapentein or Pregabalin etc.), SNRIs (Duloxetine), Opioids (Acetaminophen, tramadol, tapendol etc.) or TCAS (Amitriptolene, Nortreptolene). The study group patients received PEA (Palmiges) daily, three times a day for 10 days (TDS), and then two times a day (BID) for 50 days. Patients were allowed to continue with their usual treatment if they had other comorbidities. Pain reduction was more evident in group I (study group) treated with

PEA as compared to controlled group.

Source of data: 150 patients were examined and treated on OPD basis in the Neurosurgery OPD of Hamidia Hospital Bhopal from Oct 2017 to Feb 2018 and 14 Patients were admitted in the Neurosurgery Unit of Surgery Department.

Discussion

Neuropathic Pain can be treated with neuroepileptics, antidepressants and opioids whereas musculoskeletal pain can be treated with acetaminophen and non-steroidal anti-inflammatory (NSAID) drugs. Chronic use of analgesics is often limited by side effect, toxicity and diminished patient compliance and is a problem, especially in older patients.

Neuropathic pain results from damage or disease affecting the somatosensory system. Up to 7-8% of the western population is affected and in 5%, it may be severe also. Treatment of neuropathic pain is challenging because about 50% of patients with neuropathic pain get partial relief from treatment which currently comprises of opioids, NSAIDS, and antiepileptics etc. So the choice of treatment for neuropathic pain should always be taken into consideration, besides efficacy, safety and tolerability of the treatment and interaction with other concomitant treatments.

The draw backs of current drugs in neuropathic pain and need of new solution: Current treatment options for neuropathic pain are mainly focused on neuronal system suppressing GABA or other inhibitory receptors. Most of the drugs used for neuropathic pain cause drowsiness, dizziness, blurred vision, somnolence, peripheral edema, psychomotor slowing and paresthesia and many more. Moreover, using these drugs on long term basis causes desensitization of receptors. Therefore, there is an increase in the dose of these drugs to elicit the desired response and that leads to more number of side effects. In conclusion, the current treatment paradigms have some gaps and require some new arsenal to fight against neuropathic pain.

The second described treatment is PEA. PEA has high affinity to the nuclear peroxisome proliferator activated receptors α (PPAR-α) and PEA has indeed analgesic and anti- inflammatory effects in clinical trials. Biosynthesis of PEA in tissues, live neurons and glial cells occurs in inflammatory and chronic pain states [9]. When given orally, PEA has almost no side effect, though it has clear pain reducing properties in various pain states [10].

It seems that PEA reduces pain via the natural modulation pathway and besides modulation of the central nervous system, through the release of endorphins, serotonin, norepinephrine and dopamine. Pain reducing effects of acupuncture can also be explained by suppression of activated glial cell [11]. PEA may have a synergistic effect in modulating glial cells, mast cells and neurons [12s]. We often observe pain reduction when we add PEA to our treatment. PEA also enhances the analgesic effect of compounds such as pregabalin and amitriptyline.

In 1986, the famous neuroscientist professor Erminio Costa delivered a key note lecture in Washington, bearing the title “To follow where nature leads”. In this speech Costa talked with great vision about how

nature itself can become our tutor in developing new drugs. PEA is one of these molecules entering clinical use and developed according to Costa's vision. That is why PEA seems such a good compound to combine with other treatment modalities.

Result

PEA (palmitoylethanolamide) generally provided better pain relief than placebo in a comparison that includes three different chronic neuropathic pain conditions (trigeminal neuralgia, diabetic neuropathy and cervical pain). There was some indication of pain improvement, mainly over the short term, but with poorly defined outcome. The mean decrease on the VAS was largest in the study group: a reduction from 7.1 to 2.1 which is more than 50% pain reduction. In the control group, the VAS score decreased from 6.6 to 4.6.

PEA resulted in a significant reduction in pain symptoms in neuropathic pain after 7 weeks (49 days). The median values obtained from TSS (Total Symptom Score) and NSPI (Neuropathic Pain Symptoms Inventory) were compared to base level at many observation points until the end of treatment at 60 days confirming a significant attenuation ($P<0.001$) in the intensity and presence of symptoms. After completion of treatment i.e. after 60 days the same significant reduction ($P<0.001$) was seen in relation to the frequency and intensity of symptoms like pain, burning, numbness and paresthesia.

What we have is an indication that PEA can produce good level of pain relief for some patients with distressing chronic painful conditions.

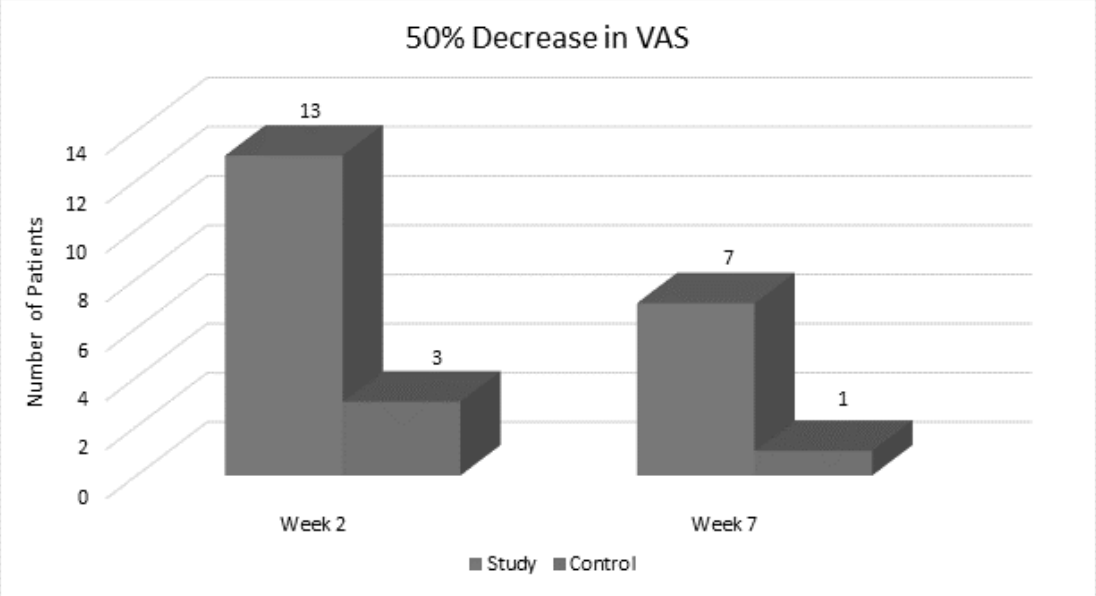

Figure 1 - 50% decrease in VAS in study and control groups

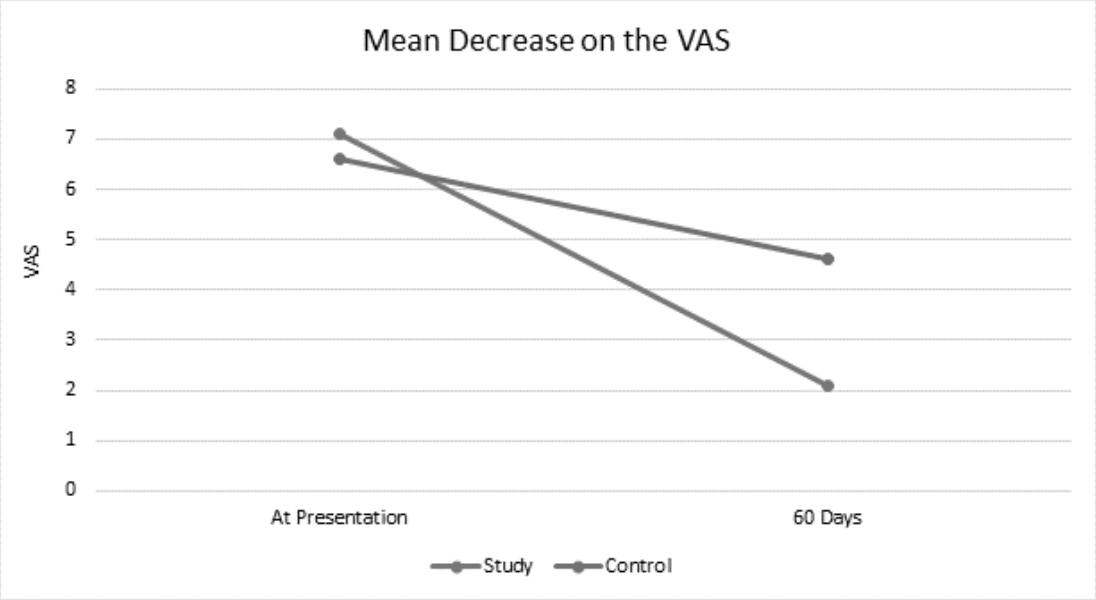

Figure 2 - The mean decrease on the VAS was largest in the study group: a reduction from 7.1 to 2.1 which is more than 50% pain reduction. In the control group the VAS score decreased from 6.6 to 4.6

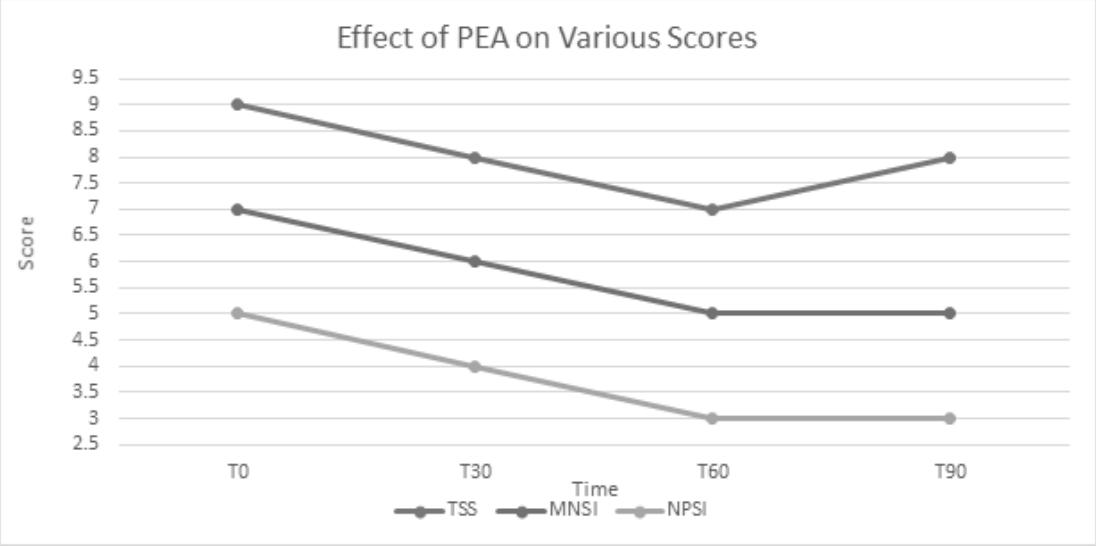

Figure 3 - Effect of PEA on painful neuropathy evaluated by Michigan Neuropathy Screening Instrument (MNSI), Neuropathic Pain Symptoms Inventory (NPSI) and Total Symptom Score (TSS),. Analysis of variance shows a significantly decreased pain intensity and symptom scores observed by MNSI, TNPSI and TSS ($P < 0.0001$) during the treatment period

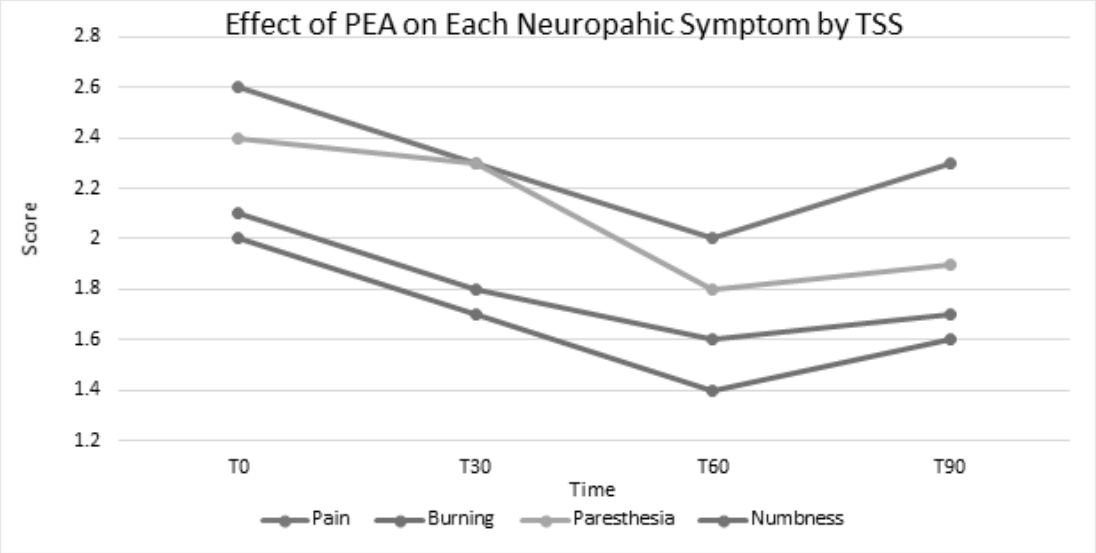

Figure 4 - Effect of micronized PEA on each neuropathic pain symptom assessed by Total Symptom Score (TSS). The intensity and frequency evaluated by TSS, show a significant mitigation ($P < 0.0001$) after 60 days of treatment compared to baseline. This effect was persistent even after one month of treatment discontinuation

In this study the important observation is that a clinical and statistical difference was found that after 7 weeks (49 days) and onset of pain reduction was at 2 weeks (14 days) but the pain reduction at 7th week was satisfactory. These observations support the recommendation to use PEA for at least 2 months before evaluating the result.

Overall completeness and applicability of evidence available include:

- Limited Size
- Short Duration
- Inadequate Outcome
- Incomplete Outcome Assessment

In order to be sure that PEA works in neuropathic/chronic pain and to be confident of the magnitude of the effect, the ideal would be several large randomized double blind studies comparing PEA at sensible doses with placebo over 8 to 12 weeks.

Conclusion

Chronic pain management remains a challenge for the clinician. PEA induced pain relief is progressive, age and gender independent and not related with the etiopathogenesis of chronic pain. PEA also controls the mechanism common to different conditions where neuropathic pain is associated e.g. neuro inflammation.

PEA is safe and well tolerated treatment for control/reduction of chronic neuropathic pain and can be combined with other standard/routinely used analgesic medications. PEA possesses intrinsic efficacy towards syndromes co-morbid with chronic pain e.g. depression and anxiety. PEA also lacks acute and chronic toxicity and is not associated with gastric mucosal lesions. That is why it has become possible to include PEA in

new class of therapeutic agent called food for special medical purposes "FSMP". PEA is safe and well tolerated treatment for the reduction of neuropathic pain and can easily be combined as well added to classical medication without fear of negative interactions.

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