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Efficacy of A Mixture of Palmitoyl Ethonalamide, Acetyl L Carnitine and Vitamin E as A Nutraceutical In Decreasing the Intensity of Chronic Pain – A Randomized Double Blinded Trial

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Abstract

Chronic pain poses a significant challenge to individuals worldwide, prompting a search for innovative therapies beyond traditional methods. This randomized double-blinded trial was carried out in a multi-specialty hospital in South India which explores the potential efficacy of a novel nutraceutical combination—palmitoyl ethanolamide (PEA), acetyl-L-carnitine (ALC), and vitamin E—in alleviating chronic pain. Methods: The study involved 51 participants with chronic pain persisting for more than three months, randomly assigned to either the treatment group (Group N) or the control group (Group C). The nutraceutical intervention, known as Myofatige, demonstrated a substantial reduction in pain intensity, as evidenced by a significant decrease in both numerical rating scale (NRS) and Likert satisfaction scores. The VAS scores decreased from 6.76± 0.95 to 3.23± 0.99 in Group N (p value < 0.0001) while it was from 6.5 ±1.02 to 5.88± 1.07 in group C (p = 0.19). The pretreatment Likert scores of Group N decreased from 3.88± 0.65 to2.04 ± 0.84 while in Group C it was from 4.01 ±0.12 to 3.73± 1.00. The inter group difference was statistically significant (p value < 0.0001). Throughout the three-month trial, safety and compliance were meticulously monitored, with just two people in the treatment group experiencing temporary frequent stools. There were no major adverse events reported, which supports the safety profile of the nutraceutical combination. Conclusion: While acknowledging limitations such as a small sample size and a single-centre study, the findings suggest that the nutraceutical combination of PEA, ALC, and vitamin E as Myofatige holds promise as a therapeutic

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intervention for nociceptive pain. Further research is warranted to explore the specific contributions of each component and potential synergistic effects in a larger and more diverse population.

Introduction

Chronic pain is a significant and often devastating burden for people all over the world, affecting their quality of life and general well-being. As traditional therapy methods continue to fall short of giving complete relief, there is a growing interest in investigating alternative therapeutic alternatives. Osteoarthritis pain prompts varied self-treatments, with 63% of patients using non-drug methods, while others opt for over-the-counter (OTC) medications. Diclofenac is the most frequently used drug, followed by ibuprofen. Manual workers significantly favor non-steroidal anti-inflammatory drugs (NSAIDs) and topical analgesics. Most patients choose known pain relievers despite their side effects. They need holistic pain management plans[1] that incorporate educational and behavioral strategies, along with balanced use of medications, for effective pain relief and improved quality of life.

Nutraceuticals like glucosamine, chondroitin, collagen hydrolysates (CHs), and avocado-soybean unsaponifiables (ASUs) show variable efficacy in clinical trials. While some studies report improvements in pain and function, results are inconsistent. Nutraceuticals are safe, making them a suitable option for select patients, though not universally recommended.[2]

The current study intends to investigate the possible efficacy of a novel combination of palmitoyl ethanolamide (PEA), acetyl-L-carnitine (ALC), and vitamin E in reducing the intensity of chronic pain. Palmitoyl ethanolamide, an endogenous fatty acid amide with anti-inflammatory and analgesic properties, has garnered attention. It interacts with the endocannabinoid system, influencing neuroimmune responses related to chronic pain pathways. ALC, a mitochondrial modulator and antioxidant, is neuroprotective and has shown potential in the treatment of pain. Vitamin E, a potent antioxidant, is well known for its anti-inflammatory properties, which may aid with pain alleviation by lowering oxidative stress[3,4]

Despite their individual benefits, the synergistic effects of these drugs in combination remain scarcely studied in the setting of chronic pain. To fill this void, we have established a randomised double-blind experiment to systematically examine the safety and efficacy of this novel combination in a varied sample of chronic pain patients. Our study seeks to give useful insights into the potential of this new combination as a therapeutic intervention for chronic pain management by adopting a robust study design that includes objective pain evaluations and comprehensive outcome measures

Methodology

Study Primer

The study was conducted in a multi-speciality hospital in South India according to the declaration of Helsinki. Chronic pain, persisting for more than three months without apparent treatable pathology, poses a formidable challenge to both individuals and healthcare providers. Traditional treatment modalities often fall short of providing comprehensive relief, prompting a quest for innovative approaches. In this pursuit, a randomized double-blinded trial has been designed to investigate the potential efficacy of a unique combination comprising palmitoyl ethanolamide, acetyl-L-carnitine, and vitamin E in reducing the intensity of chronic pain. The trial, involving 26 participants in each group, [Group N – nutraceutical & Group C – control] aims to contribute valuable insights into the realm of nutraceutical interventions for chronic pain management. The study was approved by the ethical committee (IRBSTH – 105/ 2023 dated 05- 02- 2023) and the study was conducted from March 2023 to December 2023.

Study Design

The randomized double-blinded trial employs a robust study design, where participants were randomly assigned to either the treatment group, receiving the novel mixture, (referred to as Myofatige of Fourrts India). or the control group, being administered a placebo. The double-blinded nature

of the study ensures that neither the participants nor the researchers involved in administering the treatment were aware of the group assignments, minimizing potential biases. A sealed envelope technique was used to achieve randomization. The study was double blinded with the patient and the observer being unaware of the group. The drugs were opened from the big named covers to ensure patient blinding.

Inclusion criteria specify individuals experiencing chronic pain of any area for over three months, with no apparent treatable pathology. Importantly, the existing treatment regimen for chronic pain remained unchanged throughout the study, allowing for a clear assessment of the additional impact of the nutraceutical intervention. Patients who were not willing and with other treatable illness with sepsis were excluded.

Intervention

Participants in the treatment group will be initiated on a nutraceutical intervention comprising palmitoyl ethanolamide, acetyl-L-carnitine, and vitamin E. This combination, (myofatige), recognized for its potential anti-inflammatory and analgesic properties, serves as the experimental arm of the study. The control group, on the other hand, will receive a sugar pill ensuring a rigorous comparison of the nutraceutical intervention against a placebo.

Outcome Measures

The major outcomes under consideration were pain (0- 10 eleven-point numerical rating scale (NRS) and Likert scale scores (1 – 5 Very satisfied, Satisfied, neither satisfied nor dissatisfied, Dissatisfied, and Very dissatisfied.), which were carefully measured before and after the intervention. 5Pain scores provide a quantifiable assessment of pain severity, whereas Likert scores provide a broader view on participants' general well-being and functional status. This comprehensive approach allows a nuanced assessment of the nutraceutical intervention's possible effects on both the degree of pain and its influence on everyday life.

Monitoring and Safety

Throughout the trial, participants will be closely monitored for any side effects arising from the nutraceutical intervention or the placebo. The follow up period was a period of three months of tablet daily after food. The compliance of 75 % was accepted.6 Noting and analysing these side effects are critical for comprehensively assessing the safety profile of the novel mixture. All the patients were on pregabalin in the night with paracetamol in the day which were asked to continue. The drug intake was also monitored. This meticulous attention to potential adverse events adds a layer of transparency to the study, ensuring that the overall well-being of participants remains a paramount consideration.

Statistics

Considering a significance level of 0.05, power of 0.8, margin of 1, drop out of 0, the value using Rao software was 20 in each group to get a difference of more than 20 % of reduction of VAS scores in the experimental group. We recruited 26 to avoid any drop outs. See figure 1. The mean and SD were analysed using the student t test. The rankings were done by Mann Whitney U test. The proportions were analysed by chi-square test, a p value of < 0.05 was considered significant.

Results

Fifty-one patients completed the study. Most cases on both groups were osteoarthritis of a single knee. Twenty five patients were administered placebo (Group C) while 26 were given a combination of palmitoyl ethonalamide, acetyl L carnitine and vitamin E (Group N). One patient was not considered as the compliance was less than 75 %. The mean age was 52.49 ± 5.24 in Group N and 54.68 ±5.9 years in Group C. The male: female ratio was similar between the groups. In the placebo group C, the reduction of pain and Likert scores were present but they were statistically insignificant. The pre-treatment VAS scores of both the groups were similar. The VAS scores decreased from 6.76± 0.95 to 3.23± 0.99 in Group N (p value < 0.0001) while it was from 6.5 ±1.02 to 5.88± 1.07 in group C ($p = 0.19$). The difference in reduction was clinically and statistically significant with pain reduction better in Group N. (p value < 0.0001) The Pretreatment Likert scores were similar in both the groups. ($p = 0.77$) The Likert scores decreased in Group N and C as described below. The pretreatment Likert scores of Group N decreased from 3.88± 0.65 to2.04 ± 0.84 while in Group C it was from 4.01 ±0.12 to 3.73± 1.00. The inter group difference was statistically significant (p value < 0.0001) Two

patients in the Group N developed frequent stools which normalized in a day. (see Table 1) The same cannot be attributed to the drug. There were no major side effects otherwise.

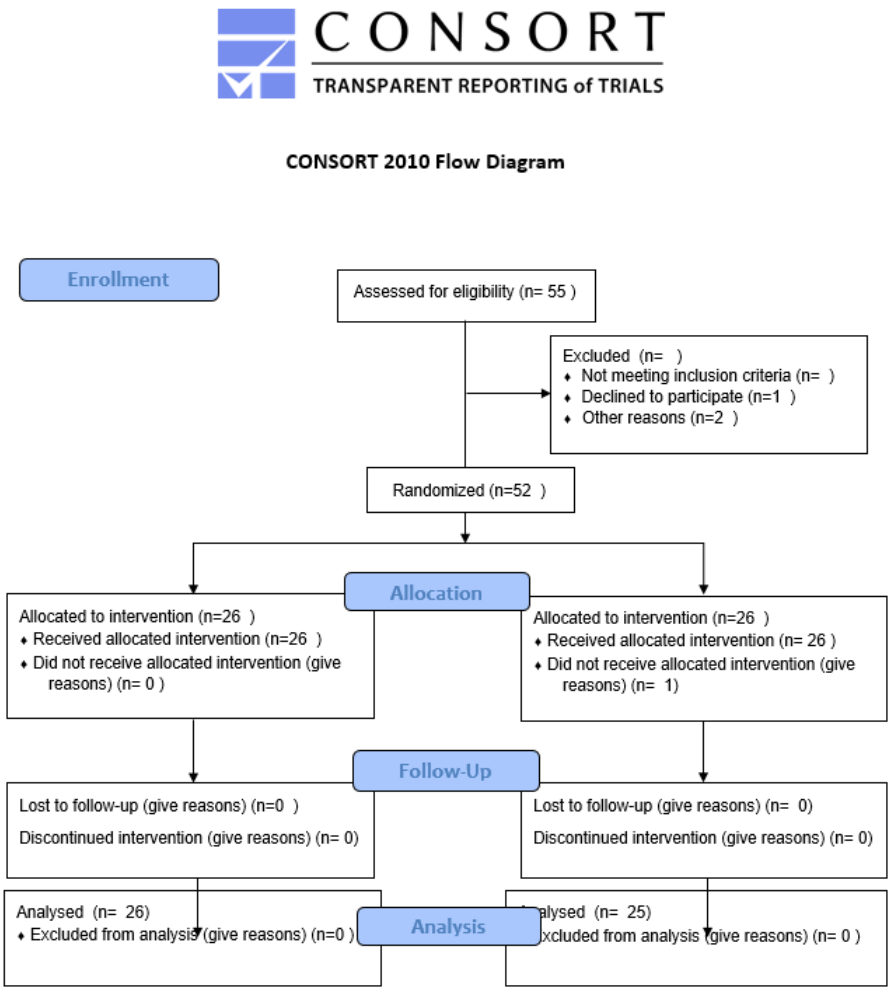

Fig. 1: consort flow diagram

Table 1: showing the mean values with tests and p values

	Group N	Group C	P value Within group N	P value Within group C	P value Between groups
Mean /SD AGE	52.49 ± 5.24	54.68 ±5.9			P = 0.55
Male: female	11: 14	13:12			Chi square P = 0.67
Pre VAS	6.76± 0.95	6.5 ±1.02			P = 0.68
Post VAS	3.23± 0.99	5.88± 1.07	**P < 0.0001**	p = 0.19	**P < 0.0001 Post – VAS**
Pre Likert	3.88± 0.65	4 ±0.12			P = 0.77
Post Likert	2.04 ± 0.84	3.73± 1.00	**P < 0.0001**	P = 0.45	**P = 0.001 Post – likert**

Discussion

The role of palmitoylethanolamide (PEA) in addressing chronic pain, particularly in conditions like inflammation, neuropathic pain, and joint disorders are well known. PEA's mechanisms involve interactions with various receptors and modulation of non-neuronal cells, leading to anti-inflammatory and analgesic effects. The use extends to PEA's potential in managing primary headaches, menstrual pain, joint health, exercise recovery, and sleep. Notably, PEA's positive impact on joint health, exercise recovery, and sleep quality is established. The challenges in PEA's bioavailability and introduction of LipiSperse® technology as a promising approach to enhance PEA absorption is a breakthrough invention. Hence the pain reduction with the individual PEA is well known and evidence based. Endogenous acetyl-L-carnitine (ALC) not only aids in energy metabolism but also acts as an antioxidant, protecting against oxidative stress. It regulates neurotransmitters such as acetylcholine, serotonin, and dopamine, in addition to neurotrophic factors like nerve growth factor and metabotropic glutamate receptors, via epigenetic pathways. ALC increases the expression of mGlu2, which provides analgesic effects while limiting spinal sensitization. It demonstrates for a long time demonstrable neurotrophic and analgesic properties in persistent pain of experimental animals.[7-9]

Lu *et al*[10] have found antinociceptive effects of a combination of vitamin E and C and described that serum concentrations and dietary consumption of -tocopherol and lycopene were found to have a significant negative relationship with functional impairment in patients with osteoarthritis knee.[11] This goes along with our findings of combination of two other nutraceutical with Vitamin E in being effective in producing analgesia in patients predominantly with pain knee. In the analgesic treatment of chronic pain, a meta-analysis[12] of double-blind randomised controlled studies found a cumulative effect favouring PEA over placebo or active comparators. In numerous studies, PEA was related with increased functional status and quality of life, whereas reported adverse effects were practically non-existent. While their study promoted the potential of a role for PEA in clinical analgesia, it also raised some critical unsolved concerns. Yet the results go along with our studies which had minimal side effects.[13] Salaffi *et al* [14] have described a combination of PEA and ALC act synergistically with routine drugs like pregabalin in fibromyalgia to improve pain which matched with our findings. Anders *et al*[15] have found ALC to be effective in neuropathic pain but our cases were mainly of nociceptive variety. Palmitoyl ethanolamide (PEA), a naturally occurring lipid, has showed promise in the treatment of chronic pain due to its anti-inflammatory and neuroprotective effects. According to clinical research, PEA can help relieve pain and enhance quality of life in individuals with chronic pain syndromes like neuropathy and fibromyalgia. PEA is a beneficial adjuvant in the treatment of chronic pain due to its efficacy and excellent safety profile.[16,17] Acetyl L-carnitine (ALC) has been studied for its potential benefits in chronic pain management, particularly in neuropathic pain conditions. Research indicates ALC may improve nerve function and reduce pain by modulating neurotransmitter activity and promoting nerve regeneration. Its neuroprotective properties make ALC a promising adjunct treatment for chronic pain.[18,19] Vitamin E has been explored for its potential in managing chronic pain, primarily due to its antioxidant properties which can reduce oxidative stress and inflammation. Studies suggest that Vitamin E supplementation may help alleviate pain in conditions like osteoarthritis and neuropathy.[20] Its ability to neutralize free radicals makes it a supportive option in chronic pain management. The future research can orient towards comparison of each component and conducting trials.

Limitations

The small sample size and unicentric study are the key constraints. The study did not include a comparison between individual components with their combination.

Conclusion

The study concludes that co administration of nutraceutical combination of palmitoyl ethonalamide, acetyl L carnitine and vitamin E decreased pain scores and improved satisfaction among patients with predominant chronic nociceptive pain.

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Conflict of interest
Nil for all the authors

Ethical approval
Yes

Patient consent
Yes

The data is in the excel sheet and only in case of absolute necessity, and on request, the corresponding author may share. We state that both the authors have contributed significantly in design, data collection and manuscript preparation.
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