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Fibroset™ and neuromuscular pain: a multicentric, real world, observational, post-marketing surveillance study in Indian patients suffering from neuromuscular pain

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ABSTRACT

Background: Neuromuscular disease (NMD) is a condition due to abnormality or damage to muscles and nerves causing painful symptoms. Symptomatic management involves use of conventional painkillers, but desirable relief is not achieved due to multimodal pathophysiology of disease. This study evaluated the efficacy and safety of Fibroset™ tablets in subjects with neuromuscular pain.
Methods: Subjects with neuromuscular pain, previously unsatisfied with standard therapies, were enrolled. Subjects were advised to take Fibroset™ one tablet BID for 2 weeks with their standard therapy. Efficacy was evaluated on pain, stiffness, swelling, weakness, tenderness, and difficulty in activity of daily living (ADL) as per the visit schedule. Tolerability of therapy was also evaluated.
Results: 59 patients were enrolled in study and 46 patients were included in the final analysis. Fibroset™ supplementation significantly reduced all evaluated parameters ($p<0.05$ vs baseline). The mean pain score from 2.50 to 0.89, while mean stiffness score was reduced to 0.55 from 1.87 at end of study. The mean swelling score was reduced to 0.81 from 2.04, while the mean weakness score was reduced to 0.64 from baseline score of 1.79. The mean tenderness score was reduced from baseline score of 1.90 to 0.65 and the mean ADL score was reduced to 0.63 from baseline score of 2.00. No treatment related side effects were observed.
Conclusions: Fibroset™ is a potentially effective and safe therapy for subjects with neuromuscular pain. It can be used to reduce symptoms in patients with unsatisfactory results with conventionally standard care therapy.

Keywords: Fibroset™, Boscurin®, Palmitoylethanolamide, Acetyl-L-carnitine, Pain, Safety

INTRODUCTION

The neuromuscular system is a complex and critical system for the normal functioning of body. It is mainly comprised of motor neurons, muscle fibres and the junction between them (termed as neuromuscular junction).[1] Neuromuscular disease (NMD) is characterized by impaired neuromuscular system leading to abnormal neuromuscular functioning.[1] Chronic neuromuscular pain, muscle weakness, fatigue, reduced locomotion are the common symptoms of neuromuscular diseases that can have a negative impact on the overall quality of life (QoL) of patients.

Neuropathy is a chronic painful condition characterized by complex pathways involving multiple pathological changes like reduced Peroxisome proliferator-activated receptor α (PPAR-α) activation, increased mast cell activity leading to increased inflammatory mediators release, reduced endocannabinoid system activation, increased NMDA activity and abnormal neuronal firing, and reduced mitochondrial functioning resulting in reduced muscle functioning and output.[2-6] These can further lead to either prolong activation of nociceptive pathway or reduced nociceptive threshold or both. This is known as central and peripheral sensitization, a major reason for uncontrolled pain generation.[7]

The current treatment strategy involves the use of conventional NSAIDs, muscle relaxants, opioid analgesics, tricyclic antidepressants, physical therapy, nerve blocking agents (both topical and injectable), acupuncture, counselling and psychotherapy, calcium channel blockers and other analgesics that primarily suppress only pain. Standard therapies are effective in reducing acute pain but have modest or no effect on chronic pain.[8] This may be due to the multiple pathophysiological and idiopathic pathways involved in the development of neuropathy. Additionally, chronic use of standard therapies have high risk of side effects like the gastric and kidney related complications observed due to chronic consumption of NSAIDs.[8] Also, a recent retrospective study conducted involving more than 2 lakh patients diagnosed with diabetic neuropathy and treated with standard neuropathic medications concluded that the patients consuming Gabapentin and Pregabalin have significant higher risk of developing cardiovascular related adverse events including heart failure, myocardial infarction, peripheral vascular disease, deep venous thrombosis, and pulmonary embolism within 3 months of short duration.[9] This lead to high relapse rate with poor satisfaction amongst the patients.[10]

Therapies working on novel molecular targets or pathways can overcome the above-mentioned limitations of standard therapies. Use of such therapies have been increased in recent decades for the management of chronic pain due to their efficacy and long-term safety profile. Palmitoylethanolamide, *Boswellia serrata*, *Curcuma longa* and acetyl-l-carnitine are very well known for their efficacy and safety in various chronic painful conditions.

Palmitoylethanolamide (PEA) is naturally occurring, endogenous fatty acid amide produced by the mammalian cells "on-demand".[11] Its potent anti-inflammatory, anti-nociceptive, and neuroprotective activity protects mammalian cells from various pathological conditions.[12] In various disease condition, the level of PEA in body is increased and provides protective effect, but in neuropathic pain condition, the level of PEA is reduced in brain and spinal cord and can be attributed to the development of hyperalgesia in neuropathic condition.[11] Various clinical studies have demonstrated the safety and effectiveness of PEA in varied painful conditions including neuropathic pain, low back pain, radiculopathy, lumbosciatica, fibromyalgia, and in painful condition uncontrolled by conventional therapies.[13]

Carnitine is a conditionally essential nutrient which plays critical role in energy homeostasis of body. As maximum amount of body's carnitine (90-95%) is concentrated in muscles, deficiency of L-carnitine in muscles leads to muscle weakness and increased physical fatigue.[14] The clinical utility of acetyl-L-carnitine (ALC) in healthy as well as in various painful condition is evaluated in various clinical studies in which the use of ALC is associated with improved muscular parameters and reducing muscle fatigue leading to improved QoL of subjects.[15,16] Besides improving muscle energy, various clinical studies have demonstrated that carnitine supplementation increases endogenous total anti-oxidant capacity and reduces the rise of creatine kinase and lactate dehydrogenase and so can prevent muscle damage.[17]

Boscurin® is a standardized, proprietary combination of *B. serrata* gum resin and *C. longa* dried rhizome extracts in the ratio of 3:1 respectively. Boscurin® contains total boswellic acid (NLT 16%), Keto-boswellic acids/Acetyl-keto boswellic acids (NLT 2.5%) and total curcuminoids (NLT 14%). The active ingredients of Boscurin® act as dual COX-LOX inhibitor and can control peripheral sensitization by reducing the level of proinflammatory cytokines like TNF-α, IL-1ß, hs-CRP, IL-6, and PGE-2.[18]

Various clinical studies are conducted of PEA, ALC, *B. serrata* and *C. longa* in various painful conditions, but there is lack of clinical study in which the combination of these ingredients is evaluated in chronic painful condition. Hence, the current study was conducted to evaluate the efficacy and safety of Fibroset™ in Indian population suffering from neuromuscular pain and related functional disability.

METHODS

Study design, duration and setting

The current study is an open label, real world, multicentric, single arm, observational, post-marketing surveillance

study. The study was conducted between March 2022 and July 2022 in outpatient departments of discrete Indian centres.

Ethical consideration

The current study was conducted in accordance with the Declaration of Helsinki, 2013. The participants were described and explained about the study and after obtaining consent from the patients, they were enrolled in the study. The current study was a post-marketing, observational, surveillance study and hence prior registration and approval of the study was not mandatory.[19]

Study material

The investigational product is a nutraceutical composition (Fibroset™) which is a film coated tablet (manufactured by Sundyota Numandis Probioceuticals Pvt. Ltd., Ahmedabad, India). Each tablet is composed of Palmitoylethanolamide 300 mg, Acetyl-L-Carnitine 250 mg and Boscurin® (*Boswellia serrata* extract and *Curcuma longa* extract in 3:1 ratio) 150 mg.

Participants

The inclusion criteria were as follows: age ≥18 years; subjects suffering from neuromuscular pain including fibromyalgia, neuropathic pain, muscle pain; subjects previously treated with standard therapies for at least 2 weeks and had minimal symptomatic improvement; and subjects who attended the out-patient department with any of the complaints of pain, stiffness, swelling, weakness, tenderness, or difficulty in doing activities of daily living (ADL). The exclusion criteria were as follows: age <18 years; subjects with dementia, depression, schizophrenic disorder, or any other neurological complications; subjects with severe hepatic or renal disease; subjects with active cancer and under active chemotherapy or radiation therapy; pregnant females or women undergoing IVF or lactating women; any other medical condition that (in the view of investigator) prohibited the participation of subject in this study; history of substance abuse or any other factors that would limit the subject's ability to cooperate with study procedures; subjects with known hypersensitivity to any of the study material ingredients. Patients visiting the out-patient department of study centers were screened as per the inclusion and exclusion criteria. Informed consent was obtained from subjects fulfilling the criteria and were enrolled in the study.

Study methodology

The demographic profile, medical assessment, and evaluation parameters of eligible patients were recorded in a predesigned Case Report Form (CRF) that was maintained for each subject. Eligible patients were instructed to orally consume 1 Fibroset™ tablet twice daily for 14 days along with their standard medications and visit the study center at Day 0, 7, and 14 for safety and efficacy evaluation. Efficacy evaluation for the symptoms of pain, stiffness, swelling, weakness, tenderness, and difficulty in activity of daily living (ADL) was done by measuring the severity of symptoms with score of minimum 0 (no symptom) to maximum 3 (severe symptom). The change in symptoms severity score was measured on day 0, day 7, and day 14. Safety and tolerability evaluation was conducted by spontaneous reporting of adverse events after initiation of therapy till the end of study period. All subjects were advised to maintain their therapy regimen throughout the study period and information regarding any change in therapeutic regimen need to be informed to the study centre investigator.

Statistical analysis

Data was expressed as mean±standard deviation for the severity score of pain, stiffness, swelling, weakness, tenderness, and difficulty to perform ADL. Statistical analysis was performed using GraphPad Prism software version 9.0 (Graph Pad software, USA). The data of individual symptom severity score were analysed using one-way analysis of variance (ANOVA) followed by post-hoc analysis using Dunnett's multiple comparison test. A p value of <0.05 was considered as statistically significant.[5]

RESULTS

Patients' demographics

Total 59 subjects were initially enrolled in the study from 12 out-patient departments from all over India. At final visit, 13 patients were lost to follow-up and data of total 46 subjects were presented in the study. The detailed demographic profile of all subjects is presented in Table 1.

Efficacy on individual symptoms

The result of this study is presented in Figure 1, where the individual graphs represent the effectiveness of Palmitoylethanolamide, Boscurin® and Acetyl-L-Carnitine combination on individual symptoms. A progressively significant reduction in pain score was reported at 1st week of intervention. The pain severity score was reduced by 31.30% and 64.35% at 1st week and 2nd week respectively significantly ($p<0.0001$). Stiffness score was significantly reduced by 38.03% and 70.42% at 1st week and 2nd week respectively significantly ($p<0.0001$). Swelling score (n=26) was significantly reduced by 35.85% and 60.38% at 1st week and 2nd week respectively ($p<0.01$). Weakness score (n=28) was significantly reduced by 30% and 64% at 1st week and 2nd week respectively ($p<0.05$). Tenderness score was significantly reduced by 42.11% and 65.79% at 1st week and 2nd week respectively ($p < 0.01$). Chronic pain is one of the reasons for difficulty in performing the activities of daily living (ADL). Difficulties in performing the activities of daily living score (n=32) was significantly

reduced by 39.06% and 68.75% at 1st week and 2nd week respectively (p<0.001) (Figure 1).

Tolerability

An intervention composed of palmitoylethanolamide, Boscurin® and acetyl-L-carnitine combination was well tolerated by all the participants. No serious adverse events due to the treatment was reported throughout the study. Light dizziness (n=1), headache (n=1) and nausea (n=1) were reported in just 3 participants only. These side effects were very mild and did not result into treatment discontinuation. None of the dropout was related to tolerability issue.

Table 1: Demographic characteristics of included subjects.

Characteristics	Subjects enrolled in study (n=59)	Subjects completed the study (n=46)
Mean age±SD (in years)	49.24±10.65	48.61±10.23
Number of males/females	27/32	21/25
Males, mean age±SD (in years)	47.63±10.24	47.57±10.11
Females, mean age±SD (in years)	50.59±10.97	49.48±10.46

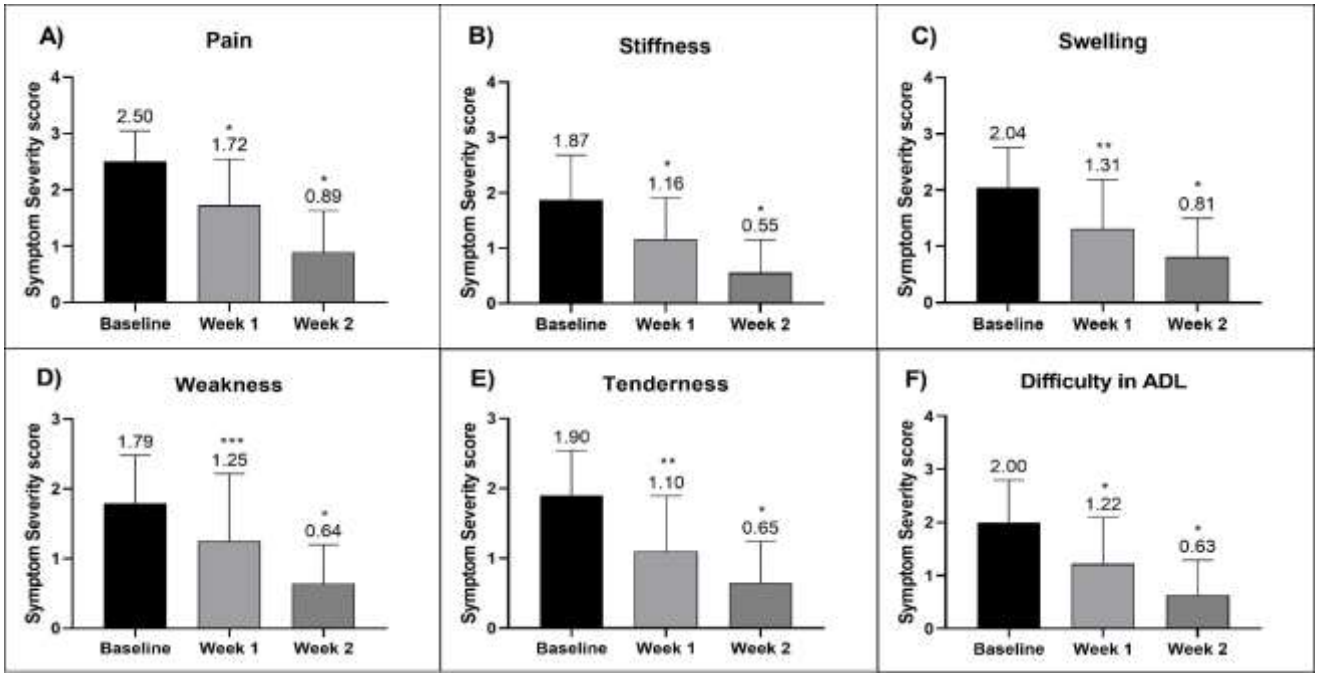

Figure 1: Effect of Fibroset™ treatment on the severity of symptoms of (A) pain (B) stiffness (C) swelling (D) weakness (E) tenderness and (F) difficulty in ADL. Values are expressed as mean±SD. Statistical analysis was performed using one-way ANOVA, followed by Dunnett's multiple comparison test as a post-hoc analysis to identify significant differences among week 1 and week 2 visit values compared to respective baseline value. *p<0.001; **p<0.005; ***p<0.05 compared to respective baseline values.

DISCUSSION

Palmitoylethanolamide, Boscurin® and acetyl-L-carnitine combination showed significant reduction in neuromuscular pain when added with standard treatment in patients who were not satisfied with standard treatment. PEA is an endogenous fatty acid amide with well researched safety and efficacy profile for over 50 years.[20] PEA showed significant reduction in pain when added with gabapentin, pregabalin, oxycodone, hydromorphone, transdermal fentanyl, transdermal buprenorphine, tramadol and paracetamol in patients with radiculopathy, osteoarthrosis, herpes zoster infection, diabetic neuropathy and failed back surgery syndrome who were unsatisfied with results or discontinued due to side effects of standard therapy.[21] PEA is reported to augment the outcome of duloxetine and pregabalin therapy.[22] PEA demonstrated its safety and efficacy in reducing pain and QoL improvement in more than 6000 patients suffering from chronic painful conditions.[23] PEA exerts analgesic, anti-inflammatory, and neuroprotective effect due to its multitargeted mechanism of action in both central and peripheral nervous systems. PEA's major action is due to activation of Peroxisome proliferator-activated receptor α (PPAR- α).[24] PPAR- α is found to be expressed in dorsal root ganglion and plays important role in pain signalling pathway. Activation of PPAR- α results into suppression or silencing of nociceptive fiber firing leading analgesia.[25] Mast cells are immune cells with their presence in various central and peripheral locations. Glial cells (especially microglia) are

non-neuronal cells resident in central and peripheral nervous system. PEA modulates mast cell – glial cell hyperactivity leading to reduced neuroinflammation and hence providing analgesic and anti-inflammatory action.[24] In chronic neuropathic pain, the hyperactivity of mast cell and glial cells causes extensive release of various inflammatory mediators, leading to prolonged activation of nociceptive pathway.[24]

Boscurin® is a novel, proprietary botanical blend of *B. serrata* gum extracts and *C. longa* dried rhizome extracts. Prostaglandins and leukotrienes synthesized by COX and LOX enzymes respectively are well known for their role in neuropathy.[26] *B. serrata* and *C. longa* have inhibitory effect against 5-LOX and COX respectively due to their active constituents boswellic acids and curcuminoids respectively.[18] Besides the anti-inflammatory spectrum, the beneficial effects of *B. serrata* and *C. longa* on nerve health is well reported.[27,28] Boswellia extract is reported to increase the nerve regeneration rate at low, medium, and high dose in sciatic nerve crush injury model. This may be due to its ability of stimulating the Schwann cells proliferation.[27] Curcumin is reported to attenuate thermal hyperalgesia and hot plate latency by inhibiting nitric oxide and tumour necrosis factor-α (TNF-α) release in streptozotocin-induced diabetic neuropathic mice.[28] Curcumin attenuates thermal hyperalgesia and mechanical allodynia by acting on descending monoamine system of nociceptive pathway in chronic constriction injury induced neuropathy mice model.[29] Curcumin dose-dependently reduces mechanical & cold allodynia by reducing spinal mature IL-1β and also reduces pain hypersensitivity by reducing JAK2-STAT3 pathway and inflammasome accumulation in astrocytes in spared nerve induced injury model.[30] Curcumin significantly increases the thermal and mechanical withdrawal threshold by reducing the expression of nuclear factor-κβ (NF-κβ) and CX3C-chemokine receptor 1 in dorsal root ganglion in chronic sciatic nerve constriction injury model of neuropathic pain.[31] Curcumin reduces glial cells action, astrocytic hypertrophy and extracellular signal-regulated kinase (ERK) pathway in spinal cord to reduce thermal and mechanical hyperalgesia in chronic nerve constriction induced neuropathic pain model of rats.[32]

L-carnitine is a conditionally essential nutrient with its maximum concentration (90-95%) found in cardiac and skeletal muscle.[14] Carnitines have essential role in transfer of long and medium chain fatty acids in mitochondria for subsequent β-oxidation and production of ATP molecules. Hence, carnitine have critical role in maintaining energy balance across cellular membranes, energy metabolism, carbohydrate utilization, and acting as buffering system.[14] Acetyl-L-carnitine (ALC) is the Acetyl- ester form of L-carnitine and is endogenously produced by human brain, liver, and kidney. Besides its role in energy metabolism, ALC has shown to promote nerve regeneration, provide neuro-protective effect, anti-apoptotic effect in neuropathy, reduce sensory neuronal loss, and improve peripheral nerves functioning by increasing nerve conduction velocity.[33,34] In various pre-clinical models of neuropathy, including diabetic neuropathy, chronic constriction-induced neuropathy, and chemotherapy-induced neuropathy, it was observed that prophylactic administration of ALC prevented neuropathic pain development and also ALC supplementation produces strong anti-nociceptive action when given after neuropathic pain development.[34]

The effectiveness of ALC was evaluated in a 1-year duration clinical study in which ALC supplementation was associated with improved neurophysiological parameters and reduced pain in patients with diabetic neuropathy.[35] In another study involving data from two 52-week duration randomized clinical trials, ALC treatment was effective in reducing pain and improving nerve fiber regeneration and vibration perception in patients with diabetic neuropathy.[36] Similar observations were found in another clinical setting involving patients with chemotherapy-induced neuropathy, where ALC supplementation resulted in significant reduction of peripheral sensory neuropathy, improved nerve electrophysiological parameters, and reduced cancer-associated fatigue and improved physical conditions of patients.[37]

The current study has certain strengths. Firstly, the current study is the first study that evaluated the efficacy of Palmitoylethanolamide, Boscurin® and acetyl-L-carnitine combination in subjects with neuromuscular diseases. The results of provides rigid evidence regarding the synergistic effectiveness of this nutraceutical combination in reducing pain and improving overall physical functionality in subjects with chronic painful conditions. The current study has certain limitations too. Firstly, the current study is an open-label study without any comparison (placebo or control) arm. As various previous traditional methodology clinical studies have evaluated and confirmed the efficacy of the individual components present in Fibroset™ and the current study being a real-world study, the use of open label, non-comparative study design might be justifiable. Secondly, the smaller number of subjects enrolled in the study needs to be addressed by conducting further clinical studies with randomized, blinded, parallel-arm design is recommended. The current study can be considered as a pilot study to design and conduct future clinical studies with similar patient population.

Overall, this study has shown that a combination of Palmitoylethanolamide, Boscurin® and acetyl-L-carnitine is effective in reducing the symptoms of neuromuscular diseases like pain, stiffness, swelling, weakness, tenderness, and difficulties in performing the activities of daily living in patients who were unsatisfied with existing standard therapies of neuropathy management.

CONCLUSION

Neuromuscular pain is a deliberating condition having negative impact on the quality of life of patients. The current study concludes that Fibroset™ is a potentially

effective and safe therapy for pain reduction in patients suffering from neuromuscular pain and related complications. This study being the first combination study provides the clinical strength but also being an open label study warrants more randomised, controlled trials to further explore and strengthen the results of the current study.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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