Section: Neurology

Original Research Article

NON-RESPONDERS UNDER STANDARD GABAPENTINOIDS THERAPY SUBJECTED TO ADD ON JUVIANA® PLUS PROTOCOL IN PERSISTENT RADICULOPATHY (NUCLEUS TRIAL)

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ABSTRACT

Background: Lumbar radiculopathy is affecting a significant number of populations (up to 30%) with continuous experience of persistent pain for one year or more and there is an unmet medical need for the development of treatments that are both safer and more efficacious in addressing chronic neuropathic conditions and associated pain. The aim of the study was to evaluate efficacy and safety of Juviana® Plus as adjunctive therapy for chronic pain.

Materials and Methods: This was an open label study conducted across multiple centers in patients with persistent lumbar radiculopathy indication. Patients underwent three visits at day 0, day 30 and day 90. Pain intensity was assessed using VAS and NRS scale at each visit. In addition of quality-of-life assessment as impacted by pain over QoL scale. Adverse events were recorded throughout the study duration.

Results: Baseline characteristics such as demographic, BMI, obesity, pain duration, herniation level, herniation type, pain location and concurrent medications, were recorded for participants baseline profile. After three-month treatment, patients experienced a statistically significant reduction is pain. Mean VAS and NRS scores respectively reduced from 5.53 and 5.41 to 0.53 and 0.48 at end of the study compared to baseline visit. Quality of life improved significantly.

Conclusions: Juviana® Plus significantly reduced pain in lumbar radiculopathy patients who are partial or non-responders to first-line treatments and found to be safe and tolerable as no AE reported with any possible relation with study drug. However, further research is needed to confirm its long-term efficacy and safety.

Keywords: Lumbar radiculopathy, Juviana® Plus, VAS, NRS, Quality of life.

INTRODUCTION

The term "lumbar radiculopathy" (LR) refers to low back discomfort that spreads to either or both lower limbs. In the general population, lumbar disc herniation accounts for 60-80% of the lifetime incidence of low back pain.[1,2] The incidence of lumbar radiculopathy is 5 to 10%, affecting both men and women.[3,4] A significant number of patients (up to 30%) experience persistent pain for one or more year, despite taking clinical course associated with acute lumbar radiculopathy (LR). In the majority of

cases, the initial pain and concurrent functional impairment tend to subside within a relatively short timeframe, typically around two weeks.[5,6,7] Numerous strategies have been investigated for the amelioration of chronic neuropathic pain attributed to lumbar radiculopathy such as Gabapentin, Amitriptyline, Pregabalin and combinations etc. However, it is evident that none of these approaches has demonstrated a pronounced degree of effectiveness. It is clear that there is an unmet medical need for the development of treatments that are safer and more efficacious both in addressing chronic neuropathic conditions and associated pain.

Agmatine has emerged as a promising compound with notable neuroprotective effects, and works through diverse mechanisms within the central nervous system (CNS). It exerts its influence by modulating various receptors and ion channels that play pivotal roles in both, the progression and resolution of CNS injuries. One of its primary mechanisms involves the modulation of neurotransmitter receptors such as N-methyl-D-aspartate (NMDA), α-2 adrenoreceptors, imidazoline, and serotonin receptors. Additionally, Agmatine can impact ion channels, including ATP-sensitive potassium and Voltage-gated calcium (Ca^{2+}) channels.[8]

Furthermore, its neuroprotective properties extend to inhibiting inducible nitric oxide synthase (iNOS) signaling and suppressing the activity of matrix metalloproteinases 2,9 (MMP-2 and MMP-9) in astrocytes. Specific modulation of N-methyl-D-aspartate (NMDA) receptors and nitric oxide (NO) signaling is implicated in its analgesic effects. Agmatine also plays a role in regulating microgliosis and astrogliosis through the modulation of bone morphogenetic proteins (BMP-2 and BMP-7) expressions, with BMP-7 particularly noted for its neuroprotective effect and ability to regulate glial cell differentiation. Moreover, agmatine contributes to the enhancement of remyelination following CNS injury and upregulates neurotrophic factors like Brain-derived neurotrophic factor (BDNF), Nerve growth factor (NGF), Insulin-like growth factor (IGF), and Neurotrophin-3 (NTF-3).[8,9,10]

Palmitoylethanolamide (PEA) has been demonstrated to inhibit peroxisome proliferator-activated receptor alpha (PPAR-α), effectively controlling pain and inflammation. This is achieved by suppressing the nuclear factor-kappa B signaling cascade, leading to the downregulation of pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1b (IL-1b), and interleukin-6 (IL-6). It also upregulates neurotrophic factors and increasing synaptogenesis.[11,12,13] In a different context, Pyrimidine Nucleotides, uridine monophosphate (UMP), and cytidine monophosphate (CMP) have shown effectiveness in reducing pain intensity by stimulating nerve cell protein synthesis, facilitating the formation of nerve cell membranes, and aiding in the synthesis of myelin sheaths.[14]

As synergistic effect, these multifaceted mechanisms highlight the potential of Agmatine, Palmitoylethanolamide (PEA), Cytidine Monophosphate (CMP) and Uridine Monophosphate (UMP) as valuable players in neuroprotection and pain management within the CNS. The current study was planned to evaluate the efficacy and safety of a three-month oral fixed-dose combination of Juviana® Plus containing Agmatine 500 mg, PEA 300 mg, CMP 2.5 mg, and UMP 1.5 mg for patients with chronic neuropathic pain associated with lumbar radiculopathy, who have shown partial response or no response to conventional drug therapies.

MATERIAL AND METHODS

Study Design

An open-label study was undertaken to evaluate the effectiveness of a novel oral fixed-dose combination of Juviana® Plus containing agmatine (500 mg), palmitoylethanolamide (PEA 300 mg), cytidine monophosphate (CMP 2.5 mg), and uridine monophosphate (UMP 1.5 mg) as an adjunctive therapy for chronic pain. This study was conducted across multiple centers. Participants were recruited from the Neurology outpatient department (OPD) and were followed up until the end of the three-month study period. Ethical approval was obtained from the institutional ethics committee, and informed consent was obtained from all participants. The study included both male and female participants aged 18 years and older, all of whom had documented cases of chronic pain, as confirmed through medical history assessments and physical and neurological examinations.

Ethical Considerations

Ethical approval for the study was obtained from the institutional ethical committee, with the ethics approval code NUCLEUS/11/1/2023. Prior to their participation, all individuals involved in the study provided informed consent. This ensured that participants were fully aware of the study's objectives, procedures, potential risks, and benefits before agreeing to take part. Any concerns or queries raised by the participants were addressed promptly and appropriately by the research team.

Inclusion Criteria

The study included participants of both genders, aged 18 or older, who had clinically confirmed cases of chronic pain. Additionally, individuals with co-morbid conditions such as hypertension or diabetes were eligible for inclusion. Participants exhibited lumbosacral spine degenerative pathologies associated with radiculopathy and were partially responding or non-responding to combination treatment with traditional drugs such as gabapentin, pregabalin, amitriptyline, and duloxetine or combinations.

Exclusion Criteria

The study excluded participants with hypersensitivity, myelopathies, or serious chronic clinical conditions like cancer. Pregnant or lactating women were not eligible to participate. Additionally,

individuals who did not provide informed consent were excluded from the study. Patients suffering from substance abuse were also excluded to maintain the integrity and reliability of the study results.

Intervention

During the intervention phase of the study, participants were prescribed to take the fixed-dose combination (FDC) Juviana® Plus orally twice daily for a duration of three-month, equivalent to 90 days. This adjunctive treatment regimen was designed to assess the effectiveness and safety of Juviana® Plus in conjunction with their existing medication regimen for managing chronic pain related to lumbosacral spine degenerative pathologies associated with radiculopathy.

Assessment

During the study period, patients underwent three assessments: one at the initiation of the study phase, the second at follow-up (30 days), and another upon its completion (90 days). In the initial phase, patients were administered the Douleur Neuropathique 4 (DN4) diagnostic questionnaire to comprehensively evaluate neuropathic pain symptoms [15]. Pain intensity was assessed using both the visual analog scale (VAS) and the numerical rating scale (NRS), allowing for a comprehensive evaluation of pain severity. Additionally, a quality of life (QOL) scale ranging from 0 (not affecting) to 10 (completely affecting) was utilized to assess the impact of pain on QOL and the effectiveness of the treatment on patient's overall well-being. Records of treatment compliance and any adverse events experienced by the patients were meticulously documented throughout the study duration.[16,17]

Data Analysis

Study data was summarized using descriptive statistics. T-tests was used to determine the changes in VAS, NRS and QoL score at day 90 compared to the baseline. All statistical tests were performed at 5% level of significance.

RESULTS

Total 60 participants enrolled in the study. Participants age ranged from 28 to 66 years with mean age as 42.33 ± 10.25 years. Study population distributed as 61.66% males and 38.33% females. Mean weight and height of the study participants was 64.9 ± 9.12 kg and 1.58 ± 0.11 m, respectively. BMI was calculated as per the demographic data, ranges from 17.27 to 39.00 kg/m2 with mean value as 26.18 ± 4.85 kg/m2. Out of 60 patients, 3 were underweight (BMI <18.5), 22 were at a healthy weight (BMI 18.5–24.9), 26 were overweight (BMI 25–29.9), and 10 were classified as obese (BMI ≥30). Participants suffering with pain from 1- 5 year of duration with either case of extrusion, protrusion or both. Enrolled participants were identified with herniation levels as L3-4 (n=22), L4-5 (n=12), L4-5+L5-S1 (n=4) and L5-S1 (n=22). 50 participants were experiencing pain in back and leg both while 10 in back only at baseline. Participants were permitted to administer Gabapentin (n=16), Gabapentin and Amitriptyline (n=21), Pregabalin (n=15) and Pregabalin and Duloxetine (n=8) as concurrent medication. Detailed results are described under below table 01. [Table 1]

Effects of Treatment on persistent radiculopathy pain

The primary objective of the study was to assess the efficacy of Juviana® Plus as an adjunctive treatment in reducing pain in persistent radiculopathy and to evaluate this reduction VAS and NRS scales were used. The visual analog scale (VAS) is a validated, subjective measure for pain assessment. VAS represented a 10 cm line with well-defined endpoints such as no pain (0)" and "worst pain (10)", on which participants were able to indicate their judgments or feelings. [18, 19] The 11-point numeric pain rating scale ranges from '0' representing no pain to '10' representing worst pain.

Mean VAS score was reduced from 5.53±0.98 at baseline to 0.53 ± 0.65 by day 90. While, baseline mean NRS score was 5.41±0.94 which decreased by 0.48±0.59 at Day 90 or end of study. This pain reduction, assessed over VAS and NRS scales, was statistically significant ($p<0.001$). At day 90, mean VAS and NRS score indicates towards no pain condition (see Figure 1(a) and 1(b)).

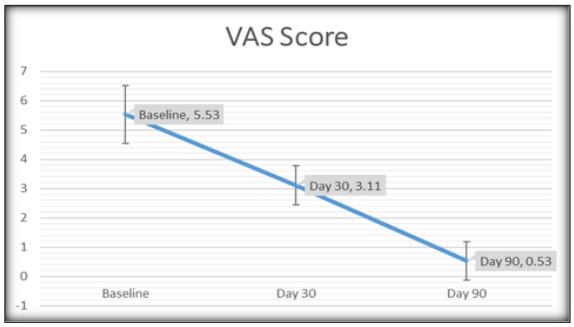

Figure 1 (a): Change in mean VAS score

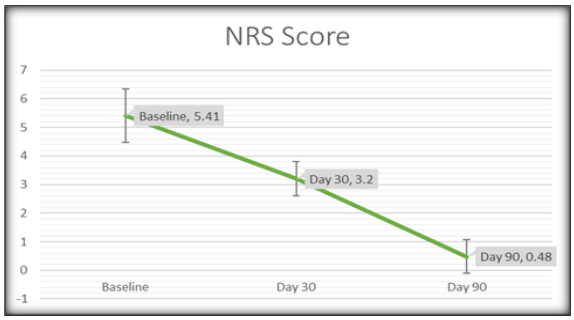

Figure 1 (b): Change in mean NRS score

Improvement in Quality of Life

Pain significantly affects various aspects of the quality of life of the participants including their mental and physical health status, routine activities, relationship with family, social interactions, sleep during the night, enjoyment, and fun experiences. Pain effect on these parameters ranged from 0 to 10, where 0 indicated no effect of pain and 10 indicated the complete effect of pain on quality of life.

Pain was affecting the quality of life of the patients, with a mean QoL score of 7.18 before the study drug administration. After three months of treatment, this effect decreased, and quality of life improved, with a score of 0.61 (Table 02, Figure 02). This improvement was statistically significant ($p<0.001$). Two adverse events were reported during the study course. However, it was found that two patients had +2 [moderate pitting (3-4 millimeters depth) with no visible deformation that returns in 15 seconds or less] pedal edema while taking the previous first-line combo drug (gabapentin and amitriptyline). Further, it was discovered that gabapentin and amitriptyline (300 mg + 10 mg) might have contributed to the pedal edema, and may have been the cause of the frequency, the dose was reduced from twice daily to once daily [Table 3]. No adverse events were observed for the FDC Juviana® Plus as an adjunctive treatment in any of the patients.

This investigation indicated no relation of AE with study drug [Table 3].

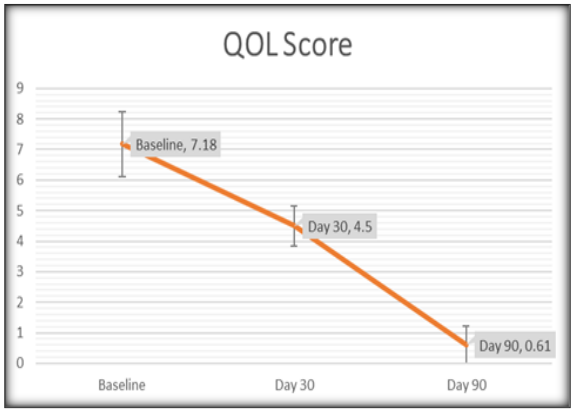

Figure 2: Change in mean QoL score

Table 1: Patient baseline demographic characteristics, clinical findings, general health status, and symptom severity

Category		Juviana® plus adjunctive with concurrent medication (n=60)
Age (Years)		42.33 ± 10.25
Range		28-66
Gender		
Male		37 (61.66%)
Female		23 (38.33%)
Weight (kg)		64.9 ± 9.12
Range		49-88
Height (m)		1.58 ± 0.11
Range		1.21- 1.79
BMI (kg/m2)		26.18 ± 4.85
Range		17.27- 39.00
Obese (as per BMI)		
Underweight		3 (5%)
Healthy Weight		22 (36.66%)
Overweight		25 (41.66%)
Obesity		10 (16.66%)
Pain Duration (years)		2.50 ± 1.07
Range		1-5
Herniation Level		
L3-4		22 (36.66%)
L4-5		12 (20%)
L4-5 + L5-S1		4 (6.66)
L5-S1		22 (36.66%)
Herniation Type		
Extrusion		33 (55%)
Protrusion		21 (35%)
Protrusion + Extrusion		6 (10%)
Pain Location		
Back + Leg		50 (83.33%)
Back only		10 (16.66%)
Concurrent medication		
Gabapentin		16 (26.66%)
Gabapentin+ Amitriptyline		21 (35%)
Pregabalin		15 (25%)
Pregabalin + Duloxetine		8 (13.33%)

Table 2: Change in QoL scale from baseline to day 90

Parameters	Baseline	Day 30	Day 90
QOL Scale			
Mean ± SD	7.18 ± 1.06	4.5 ± 0.65	0.61 ± 0.61
P-Value	-	-	<0.001

Table 3: Suspected adverse drug reaction details due to concurrent medications and intervention adopted

SN	Past Medications (Generic Names)	Dose (mg)	Frequency	AE noted in a patient during past medications	Change in dose/frequency of past medications due to AE
01	Gabapentin + Amitriptyline	300+10	BD	Pedal edema	Once Daily
02	Gabapentin + Amitriptyline	300 +10	BD	Pedal edema	Once Daily

DISCUSSION

The most common origin of lumbar radiculopathy is nerve root compression. It commonly results in disc herniation. A disc herniation can be either due to an acute injury or secondary to chronic degeneration of the spine. In lumbar radiculopathy, 63-72% of patients experience paresthesia, 35% experience radiation of pain in the lower limb, and 27% of patients endorse numbness. Muscle weakness is reported in up to 37%, absent ankle reflexes in up to 40%, and absent knee reflexes in 18% of patients.[20] Lumbar radiculopathy, being neuropathic, significantly impairs biopsychosocial functioning compared to nociceptive low back pain or other musculoskeletal conditions. Patients with lumbar radiculopathy exhibit higher pain severity and first line treatment includes medications (i.e. Gabapentin, Amitriptyline, Pregabalin and combinations etc) and physical therapy etc. Pain reduction and management are necessary to improve quality of life and fulfillment of routine activities. [21,22]

This unique study is designed to explore the efficacy and safety of a combination fixed-dose combination (FDC), Juviana® Plus (Agmatine 500 mg + PEA 300 mg + CMP 2.5 mg + UMP 1.5 mg), in lumbar radiculopathy concurrently with traditional drugs such as pregabalin, gabapentin, amitriptyline, or combination. The findings of the present study indicate that a three-month adjunctive treatment with fixed-dose combination (FDC), Juviana® Plus, is beneficial in the reduction of neuropathic pain in patients with radiculopathy-related degenerative diseases of the lumbosacral spine. The results are similar to previous studies, indicating that biological metabolite agmatine sulphate treatment is efficacious, safe, and tolerable without reporting any notable adverse effects. [23,24]

Agmatine (500 mg) is a key ingredient of Juviana® Plus and has been recognized as a natural biological metabolite for more than a century. [25,26] Previous studies demonstrated protective effects of agmatine against various organ diseases, encompassing neuroprotection and glucoprotection. Numerous scientific studies have demonstrated that agmatine sulphate may influence several molecular targets associated with neuroprotection and neuropathic pain management including ADP-ribosylation of proteins, nitric oxide (NO) synthesis, polyamine metabolism, and extracellular protein modifications, such as the inhibition of matrix metalloproteinases and advanced glycation end (AGE)-product formation.[27] These mechanisms potentially underlie the positive effects of agmatine in patients with spinal stenosis and lumbar disc-associated radiculopathy.

In addition, Juviana® Plus second ingredient is bio-optimized palmitoylethanolamide (PEA), an endogenous compound, that plays a role in decreasing neuropathic pain. PEA efficiently inhibits the transcription factors PARP1 and NF-κB, which are involved in inflammation, and reduces neuroinflammation, which helps in the improvement of peripheral neuropathy.[28,29,30] A prospective single-blind study found that PEA treatment, given after acetaminophen/codeine at a low dosage, is able to reduce pain in all patients with nonsurgical lumbar radiculopathy (VAS scores 3-10); however, this treatment was unable to completely resolve disability in patients with severe pain (VAS scores >7), highlighting the need for additional research on pain management. In a clinical trial with peripheral neuropathies, nucleotides like uridine monophosphate (UMP) have been shown to be effective in treating the underlying cause of the myelin sheath lesion.[31]

This study's results marked a straight reduction in pain from baseline to end of treatment. As assessed over VAS and NRS scale, participants reported either no or minimal pain (0.53 VAS and 0.48 NRS score) after 03-month treatment. As pain was affecting quality of life of the participants, this pain reduction positively impacted their life. Participants reported no or minimal impact of pain on their mental and physical health status, routine activities, relationship with family, social interactions, sleep during night, enjoyment and fun experiences with a 0.61 QoL score. Clinical evaluations of the current study concluded no treatment-related abnormalities in individuals receiving Juviana® Plus as an adjunctive treatment. Despite the positive findings, it's important to acknowledge several significant limitations. The open-label study design may introduce biases and a randomized placebo-controlled study would better address the potential effects of concurrent therapies. Moreover, the modest sample size limits the ability to comprehensively assess disparities in gender, age, or BMI.

CONCLUSION

In conclusion, the findings from this study suggest that the fixed-dose combination (FDC) Juviana® Plus significantly reduces overall pain intensity in lumbar radiculopathy patients showing partial/nonresponder to first-line neuropathic pain-relieving agents. The study drug was found to be safe and tolerable as no AE was reported with possible relation with Juviana® Plus. The unique composition of this combination as a novel adjunctive treatment for neuropathies demonstrates promising results. However, further

research is crucial to explore the long-term effects and validate the efficacy and safety profile of FDC Juviana® Plus as a potential therapeutic intervention for persistent lumbar radiculopathy. This study's initial findings underscore the need for more extensive investigations to better inform clinical practice and enhance our understanding of its utility in managing neuropathic pain.

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