Section: Neurology

Original Research Article

JUVIANA® IMPACT ON SMALL AND LARGE FIBER NEUROPATHY- INDIAN CLINICAL EXPERIENCE: JUSTICE TRIAL.

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Abstract

Background: Diabetic neuropathy pain presents significant challenges in management due to limited treatment options and associated side effects. Palmitoylethanolamide (PEA) and inorganic nitrate have potential as additional treatments for neuropathic pain. **Materials and Methods:** This open-label trial enrolled 150 participants with diabetic neuropathy pain across three centers. Participants received Palmitoylethanolamide and inorganic nitrate (Juviana®) for 90 days. Pain intensity was assessed using the Visual Analog Scale (VAS), and adverse events were monitored. **Results:** Both monotherapy and combination therapy with PEA and inorganic nitrate led to significant reductions in pain intensity over the 90-day period ($p < 0.001$). Adverse events were minimal, with occurrences of giddiness and tremors. **Conclusion:** Palmitoylethanolamide and inorganic nitrate (Juviana®) demonstrate promising efficacy in reducing diabetic neuropathy pain intensity with a favorable safety profile. Further research in larger clinical trials is needed to confirm these findings and establish their role in diabetic neuropathy management.

INTRODUCTION

The global rise of prediabetes and diabetes has led to an epidemic of complications associated with these conditions. Neuropathy is among the most common and debilitating consequences of diabetes mellitus, resulting in the highest morbidity and mortality rates. Diabetic neuropathy (DN) significantly impacts patients' quality of life and imposes a substantial financial burden.[1]

DN is characterized by the loss of sensory function, typically beginning distally in the lower limbs. This loss of sensation is often accompanied by discomfort, pain, and considerable morbidity. Nerve damage and pain due to inflammation can be debilitating, disrupting sleep and affecting patients quality of life The current management strategies primarily focus on controlling blood glucose levels to prevent further nerve damage and alleviating symptoms, particularly pain.[2]

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide and acts as a modulator of the endocannabinoid system, exerting anti-inflammatory and analgesic effects through multiple mechanisms. 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 (NF-κB) 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 and improvement in peripheral neuropathy.[3,4,5]

Inorganic nitrate/nitrite are naturally occurring compounds found in the human diet, predominantly sourced from vegetables and other plant-based foods. Vegetables contribute up to 90% of total dietary nitrate intake. Among these, green leafy vegetables such as lettuce, cabbage, red beetroot, and red spinach are particularly rich in nitrate concentrations.[6]

Inorganic nitrate is converted in the body to nitric oxide (NO), a molecule crucial for vascular health. This conversion process begins with the reduction of nitrate to nitrite by commensal oral bacteria, followed by the reduction of nitrite to NO in various tissues. Nitric oxide plays a crucial role in inhibiting the formation of advanced glycation end-products (AGEs), which are harmful compounds that contribute to the progression of diabetic complications, including neuropathy. By inhibiting AGE formation, NO helps to protect tissues from

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damage. Additionally, NO improves microcirculation by enhancing blood flow in small vessels, which is vital for delivering nutrients and oxygen to tissues. This improvement in microcirculation is further supported by the activation of endothelial nitric oxide synthase (eNOS), an enzyme that increases the production of NO. The resulting increase in NO levels leads to vasodilation, which reduces blood pressure and enhances blood flow. These combined effects of improved microcirculation and vasodilation help alleviate symptoms of peripheral neuropathy, such as pain, tingling, and numbness in the extremities. Overall, the intake of inorganic nitrate, through its conversion to NO, offers significant benefits in managing peripheral neuropathy by improving vascular health.[7]

The rationale for combining PEA and inorganic nitrate (Juviana®) lies in their complementary mechanisms of action. Palmitoylethanolamide's anti-inflammatory and neuroprotective effects can reduce pain and prevent further nerve damage,[8] while inorganic nitrate's ability to improve blood flow and reduce oxidative stress can enhance overall nerve health and function. This combination therapy could potentially offer a more comprehensive approach to managing diabetic neuropathy pain, addressing both symptomatic relief and the underlying causes of nerve damage.[7,9,10,11] This open-label trial aims to evaluate the efficacy and safety of palmitoylethanolamide and inorganic nitrate (Juviana®) as an adjunctive therapy for managing diabetic neuropathy pain. The study will assess the combined impact of these agents on pain reduction, nerve function, and overall patient well-being. The study aims to provide evidence for a novel therapeutic strategy that could significantly enhance and reduce diabetic neuropathic pain and the quality of life for patients suffering from diabetic neuropathy.

MATERIALS AND METHODS

A total of 150 participants were enrolled across three study centers for a multicenter, open-label trial. These participants were aged over 18 years and diagnosed with diabetic neuropathy pain. They received the investigational drug (Juviana®) either alone or as adjunctive/combination therapy for a duration of 90 days, at the discretion of the principal investigator. Pain intensity was assessed using the Visual Analog Scale (VAS), and adverse events were monitored throughout the study period. The study data were subsequently analyzed separately for the mono therapy group, combination therapy group, and the overall study population. Prior to enrollment, eligible participants provided informed consent, and the study was conducted in accordance with ethical principles and regulatory requirements.

RESULTS

The study enrolled 150 participants across three study centers, with a gender distribution of 52% females and 48% males, and a mean age of 54.3 years.(see Table 1) At baseline, participants reported chief complaints of numbness (52 patients), tingling (80 patients), burning pain (53 patients), pain (36 patients), and extreme sensitivity to touch (6 patients). [Figure 1]

Vital signs, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), were recorded without abnormalities. In the monotherapy group, mean SBP was 132.362 mmHg (SD 16.349) and mean DBP was 83.362 mmHg (SD 10.462), while in the combination therapy group, mean SBP was slightly lower at 131.402 mmHg (SD 14.099) and mean DBP was 78.174 mmHg (SD 9.026). Overall, the mean SBP for the entire study population was 131.727 mmHg (SD 14.845) and mean DBP was 79.928 mmHg (SD 9.812). [Table 2]

The reductions in diabetic neuropathy pain intensity over the 90-day study period, assessed by the Visual Analog Scale (VAS), were notable. In the monotherapy group, mean pain intensity decreased from 6.784 at baseline to 1.659 by day 90, with a significant mean change of -5.125 on the VAS scale. Similarly, in the combination therapy group, mean pain intensity decreased from 7.495 to 0.592, with a substantial mean change of -6.903. [Table 3] These reductions were statistically significant ($p < 0.001$) for both groups and the overall study population, indicating the efficacy of Palmitoylethanolamide and inorganic nitrate (Juviana®) in alleviating diabetic neuropathy pain. Adverse events were minimal, with occurrences of giddiness in the combination therapy group and tremor in one patient in the monotherapy therapy group.

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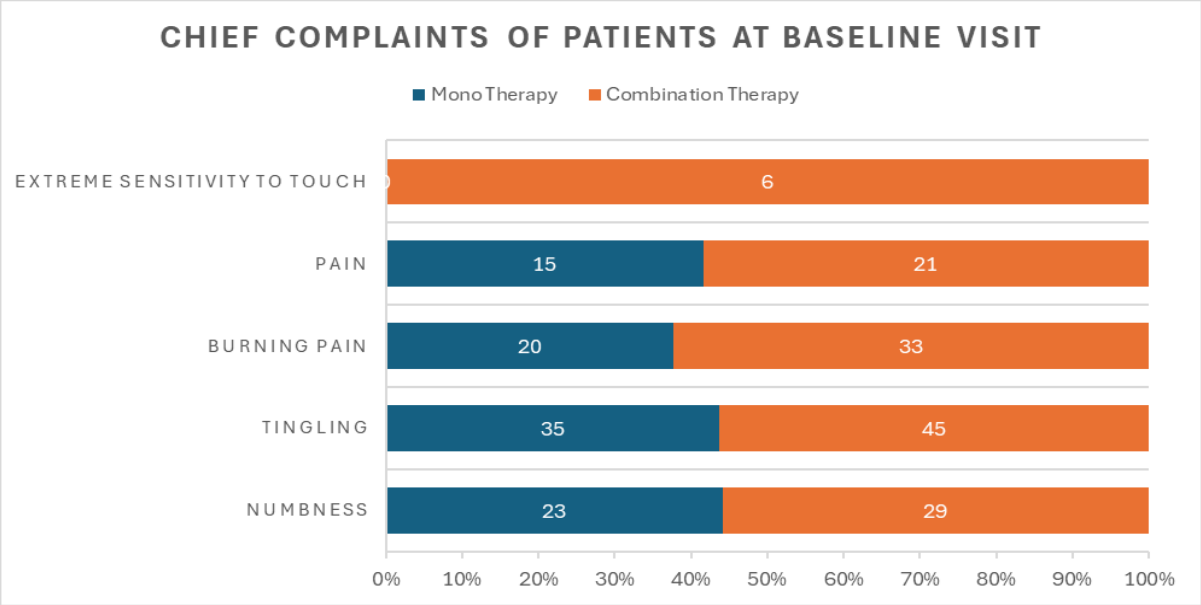

Figure 1: Showing chief complaints of patients at baseline visit

Table 1: Showing Sex distribution of participants

Gender	Mono Therapy n (%)	Combination Therapy n (%)	Overall n (%)
Male	19 (36.5%)	48 (54.5%)	67 (47.9%)
Female	33 (63.5%)	40 (45.5%)	73 (52.1%)
Total	52 (100%)	88 (100%)	140 (100%)

Table 2: Baseline Vital Signs of Study Participants

Statistics	Mono Therapy	Combination Therapy	Overall
Systolic Blood Pressure (mmHg)			
n	47	92	139
Mean	132.362	131.402	131.727
SD	16.349	14.099	14.845
Median	130	130	130
Min	103	100	100
Max	170	170	170
Diastolic Blood Pressure (mmHg)			
n	47	92	139
Mean	83.362	78.174	79.928
SD	10.462	9.026	9.812
Median	80	80	80
Min	70	60	60
Max	110	117	117
* Missing values were excluded from the analysis			

Table 3: Efficacy Assessment: Change in Diabetic Neuropathy Pain Intensity over Visual Analog Scale (VAS)

Statistics	Baseline	Day 30	Day 90	Change from Baseline to Day 90
Mono Therapy				
n	51	48	45	-
Mean (SD)	6.784 (2.003)	3.638 (3.046)	1.659 (1.778)	-5.125 (-0.225)
Median	7	3	1	-
Min, Max	2, 12	0, 11	0, 7	-2, -5
p Value	-	-	-	0.000
Combination Therapy				
n	98	98	98	-
Mean (SD)	7.495 (2.902)	1.959 (0.957)	0.592 (0.537)	-6.903 (-2.365)
Median	9	2	1	-
Min, Max	3, 12	1, 5	0, 2	-3, -10
p Value	-	-	-	0.000
Overall				
n	149	146	143	-
Mean (SD)	7.252 (2.644)	2.781 (2.381)	1.097 (1.384)	-6.155 (-1.260)
Median	7	2	1	-

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Min	2, 12	0, 11	0, 7	-2, -5
p Value	-	-	-	0.000
* Missing values were excluded from the analysis				

DISCUSSION

Prevalence of peripheral neuropathy among diabetic patients is 40.3%. It is more prevalent in patients with type 2 diabetes with 42.2% are compared to type 1 diabetes with 29.1%.

DPN prevalence increases with age and diabetes duration. Major DPN risk factors are "older age" and loss of consciousness due to severe hypoglycemia episodes among patients with type 1 diabetes as well as "older age" and an adverse cardiovascular-metabolic profile (obesity, hypertension, low HDL-c levels, elevated triglycerides, low physical activity and limited range of motion) among patients with type 2 diabetes.

Diabetes micro- and macrovascular co-morbidities (diabetic nephropathy, retinopathy and peripheral artery disease) are strongly associated with the incidence of neuropathy.

Several treatments are available for chronic neuropathic pain attributed to diabetic radiculopathy such as Gabapentin, Amitriptyline, Pregabalin and combinations etc. Still there is an unmet medical need for the development of treatments that are safer and more efficacious in reducing pain generated by diabetic neuropathic condition.

Several studies have previously highlighted the beneficial effects of PEA in managing chronic pain, including neuropathic pain. Lang-Illievich et al. conducted a systematic review and meta-analysis of double-blind randomized controlled trials, concluding that PEA significantly reduces pain scores with a standard mean difference of 1.68 (95% CI 1.05 to 2.31, p = 0.00001) compared to placebos or active comparators.[13] This supports our findings, as participants in our study also experienced notable reductions in pain intensity.

Pickering et al. conducted a randomized controlled trial assessing the safety and efficacy of PEA for diabetic-related peripheral neuropathic pain. The study reported significant reductions in pain, inflammation, and improvements in mood and sleep, without major side effects.[14] These findings align with our study, where PEA, both as monotherapy and in combination with inorganic nitrate, significantly reduced pain with minimal adverse events.

Seol et al. demonstrated that PEA effectively relieves inflammatory and neuropathic pain in rats, particularly mechanical hyperalgesia, which aligns with our results showing significant pain reduction in diabetic neuropathy patients.[15] Similarly, Kamper's case study on the use of PEA for neuropathic pain from post-herpetic neuralgia found rapid pain relief, further supporting PEA's potential as an effective analgesic.[16]

Chiara et al. evaluated the effectiveness of micronized PEA (PEA-m) in diabetic patients with peripheral neuropathy, reporting significant reductions in pain severity and related symptoms.[17] Our study's findings are consistent with these results, as PEA monotherapy and combination therapy both resulted in substantial pain relief over the 90-day period.

Inorganic nitrate, on the other hand, has been studied for its potential benefits in type 2 diabetes and its complications. Bahadoran et al. reviewed the effects of nitrate/nitrite on glucose metabolism, vascular homeostasis, and insulin signaling, highlighting its anti-inflammatory and antioxidant properties.[7] These mechanisms are relevant in the context of diabetic neuropathy, as improved vascular function and reduced oxidative stress can enhance nerve health and function. Our study's results indicate that the inclusion of inorganic nitrate in the combination therapy may contribute to these beneficial effects.

Oghbaei et al. demonstrated that sodium nitrate preconditioning prevents the progression of neuropathic pain in a preclinical diabetic model.[18] which is consistent with our findings that inorganic nitrate, in combination with PEA, significantly reduces pain intensity in diabetic neuropathy patients. This suggests that the nitrate component of Juviana® may offer protective effects against nerve damage and improve overall nerve function.

The present open-label trial aimed to evaluate the efficacy and safety of palmitoylethanolamide (PEA) and inorganic nitrate (Juviana®) as adjunctive therapies for managing diabetic neuropathy pain. The results demonstrate significant reductions in pain intensity for both the monotherapy and combination therapy groups, with minimal adverse events, indicating the potential of this combination therapy to effectively manage diabetic neuropathy pain.

CONCLUSION

In conclusion, this study shows that combining palmitoylethanolamide and inorganic nitrate/nitrite (Juviana®) can effectively manage diabetic neuropathy pain, with minimal side effects. Our findings align with previous studies, highlighting the potential of this therapy. Future research with larger, randomized trials is needed to confirm these results and establish Juviana® as a add on treatment with standard treatment. This therapy could greatly improve the quality of life for patients with diabetic neuropathy.

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