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THE STUDY OF SAFETY AND EFFICACY FOR THE COMBINATION OF AMITRIPTYLINE AND MECOBALAMIN IN NEUROPATHIC PAIN

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Conflicts of Interest: Nil

ABSTRACT:

Objective: Study was done to evaluate the efficacy as well as safety for the combination of amitriptyline and mecobalamin.

Methods: Study was conducted at 72 centres all over India. The patients who met with the inclusion and exclusion criteria were enrolled in the study and treated with the combination of amitriptyline and mecobalamin, taken once a day at night before sleep. Patients were evaluated for the efficacy by visual analogue scale (VAS). Safety was evaluated through the noted adverse events occurring during the clinical trial. Patients VAS score were noted on baseline, visit 2 at day 30 and visit 3 at day 45 and also asked for any adverse events and accordingly case report forms were filled by the investigators. Then from the collected data change in mean VAS score and percent decrease in pain intensity from baseline to visit 2 and visit 3 and percentage of patients achieving ≥50% reduction in pain from the baseline were collected.

Results: The mean VAS score at baseline was 7.39 decreased to 5.6 at visit 2 and further decreased to 3.99 at visit 3. The percent decrease in mean VAS score was found to be 24.22% at visit 2 and 46% at visit 3**.** 63.99% and 82.44% patients at visit 2 and visit 3 had ≥50% reduction in neuropathic pain. No serious side effects were observed.

Conclusion: The combination of amitriptyline and mecobalamin was found to be safe and efficacious in the treatment of neuropathic pain.

Keywords: AmNurite, Amitriptyline, Methylcobalamin, safety, efficacy.

Introduction

The International Association for the Study of Pain (IASP) defined Neupathic pain as "pain resulting from damage or disease of the central or peripheral nervous systems, and from dysfunction of the nervous system".[1]

In neuropathic pain, the nerve fibres may be damaged, injured or dysfunctional. These damaged nerve fibres don't send correct signals to other pain centers. The effect of nerve fibre injury includes a change in nerve function both at the areas around the injury and area at the site of injury.[2]

The pathophysiological properties that are responsible for neuropathic pain can be broadly categorised into five groups: fibre interactions, ectopic impulse generation in damaged primary afferent fibres, central sensitisation, plasticity (degenerateve and regenerative changes associated with altered connectivity) and disinhibition (failure or reduction of normal inhibitory mechanisms).[1]

There are so many causes for the development of neuropathic pain including Diabetes, Alcoholism, Autoimmune diseases, poststroke pain ('thalamic pain syndrome'), pain related to multiple sclerosis and pain due to spinal cord

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injury. Post herpetic neuralgia and radicular pain due to nerve root fibrosis following failed back surgery.[1,3]

In India diabetes is rapidly gaining the status of a potential epidemic with more than 62 million patients of diabetes currently diagnosed. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India.[4]

Diabetic peripheral neuropathy (DPN) is an important & advancing microvascular complication of diabetes mellitus.[4] According to an estimate; two thirds of diabetic patients have clinical or subclinical neuropathy. Neuropathies are among the most common chronic complications of diabetes, affecting up to 50% of patients.[5]

Diabetes is the major cause for the development of Neuropathic pain. There are mainly 3 mechanisms for the development of neuropathic pain because of diabetes including microvascular damage, metabolic disorders and changes in the interactions between neuronal and immunological systems in parallel with glial cell activation. First we are discussing the mechanism of microvascular damage for the development of diabetic neuropathy. In microvascular damage there is change in the blood vessels supplying the peripheral nerves. These changes are based on increase in the wall thickness with the hyalinization of the vessel wall and basal lamina of the arterioles and capillaries which leads to nerve ischemia. Through revised primary capillary membrane to the endoneurium penetrates the plasma protein, causing swelling and increased interstitial pressure in the nerves and capillary pressure, fibrin deposition as well as thrombus formation. Proximal and distal segments of the nerve shows multifocal fibre loss along the length of the nerves which leads to the diabetic neuropathic pain. The second mechanism for the diabetic neuropathy is metabolic disorders. Hyperglycemic state in the type 1 diabetes which is responsible for the enhanced activation of polylol pathway (Fig. 1). In the hyperglycemic state, the affinity of aldose reductase for glucose is increased which leads to the increased production of sorbitol. Sorbitol doesn't cross cell membranes and gets intracellularly accumulated in the nervous tissue, thus generates osmotic stress. Osmotic stress increases the intracellular water influx and fluid molarity, nerve fibre degeneration and Schwann cell damage. Furthermore, upregulation of the NADPH oxidase complex results in oxidative stress through reduced glutathione production, decreased nitric oxide concentrations and increased reactive oxygen species concentrations (Fig. 1). Free radicals, oxidants, and some unidentified metabolic factors activate the nuclear enzyme poly (ADP-ribose) polymerase (PARP), which is a fundamental mechanism in the development of diabetic neuropathy.[6]

In third mechanism, non-neuronal cells (microglia, astrocytes and immune cells) are activated under the hyperglycemic condition in the spinal cord, plays an important role in the spinal cord. Active glial cells, particularly microglia, which are resident macrophages of the central nervous system, are responsible for signalling between components of the nervous and immune systems. Microglia is responsible for the initiation of neuropathic pain.[6]

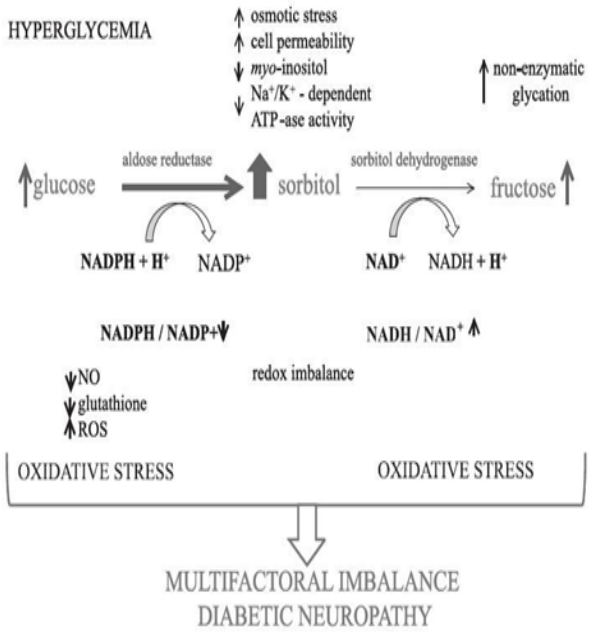

Figure 1: Multifactorial etiology of diabetic neuropathy. Hyperglycemia leads to enhanced

activation of the polyol pathway, oxidative stress and non-enzymatic glycation. These factors either interact or independently function toward the development of diabetic neuropathy, directly affecting nerve tissues or nutrient vascular tissues[6] The management of neuropathic pain goals in patients include glucose control and symptomatic pain relief. With regard to pain modulation, 50% reduction in pain, regardless of the baseline pain score, is considered a "meaningful" reduction in patients with neuropathic pain.[5]

National Institute for Health and Care Excellence (NICE)[7] and Canadian Pain Society (CPS)[8] have recommended Amitriptyline, a tricyclic antidepressant (TCA), as the first line drug for the neuropathic pain due to DPN; however titration to higher doses is limited by its anticholinergic adverse effects. Studies have demonstrated that the TCAs provide moderate to good relief of pain in patients with painful DPN. These drugs relieve pain independent of their antidepressant effects.[9] The starting dose of amitriptyline for DPN is 10–25 mg at night; increase by 10–25 mg every 7 nights, to a maximum dose of 150 mg at night.[10]

There are mainly 3 mechanism of actions of Tricyclic antidepressents which are useful in the treatment of neuropathic pain including 1)Sodium channel blockade is similar to the local anaesthetics, 2)Blockade of Serotonin receptors – 5-HT2A, 5-HT2C, 5-HT3, 5-HT6 and 5-HT7 and 3)Inhibition of Nicotinic Acetylcholine Receptors.[8]

The limitation of the conventional treatment (pregabalin, Duloxetine, amitriptyline etc.) is it does not address the underlying pathology of the disease or improve sensation, but only takes care of the pain. An alternative approach or some additional benefit is required to overcome the extensive magnitude of the problem and the insufficiency of treatment.[11] that's the reason that we have formulated the formulation as a bilayer tablet of amitriptyline as a conventional layer and mecobalamin as an sustained release layer. Because, many diabetic patients are vitamin B12 deficient which may manifest as a potential comorbidity.[12] This deficiency often goes unnoticed despite the fact many diabetic patients are at risk for this specific disorder. The most universally

& prominently used anti-hyperglycemic agent Metformin has a potential to lower serum vitamin B12 levels and is associated with vitamin B12 deficiency.[11]

Mecobalamin is used in the treatment of neuropathic pain because 1)It enhances the synthetic proteins in nerve cells 2)Promotes the myelinisation 3)Promotes Axonal regeneration and 4)Restore diminished neurotransmitter level.[13]

As per the prescription audit (SMSRC), combinations of mecobalamin and pregabalin are available in market and popular for neuropathic pain but very few combinations of amitriptyline and mecobalamin are available in market. As per the prescription audit (SMSRC), amitriptyline and mecobalamin are prescribed combinely hence we developed the combination of amitriptyline (10/25 mg) and mecobalamin (15000mcg SR).

The main objective of this study was to evaluate the safety and efficacy of the combination of amitriptyline (10/25 mg) and mecobalamin (15000mcg SR) in the patients with the neuropathic pain.

Materials and Methods

To evaluate the efficacy and safety, a six week study was conducted on 786 patients on adults of either sex or age with Neuropathic pain in 72 trial centers. Patients satisfying the inclusion and exclusion criteria were been enrolled in the study. Inclusion criteria were that a volunteer should be over 18 years of age; should have neuropathic pain due to neuritis, diabetic neuropathy, spondylitis, chronic low back pain, padiculopathy, trigeminal neuralgia; patients with neuropathic pain not controlled on other drugs and if the patient is Diabetic, specific treatment for Diabetes with Anti-diabetics should be continued. Subjects were excluded if the patients were taking MAO inhibiting drugs, history of urinary retention – BPH, hepatic or renal impairment, Pregnant or Breast Feeding women

or any evidence of Psychological disorder. For the study Drs having speciality in neurology, diabetology and internal medicine were selected. The entries were recorded in the case record form by the investigator. The accuracy of all data on the CRF was attested by the signature of the investigator.

Patients were screened during Visit 1 and who satisfied with the inclusion and exclusion criteria were enrolled in the study. Patients were treated with the study medication of AmNurite (combination of amitriptyline 10/25 mg and mecobalamin 1500 mcg). The efficacy and safety was assessed in two visits at Visit 2 on day 30 and Visit 3 on day 45. Pain was assessed by a 10 point Numerical Pain Intensity Scale or the visual analogue scale (VAS), the patients were asked to rate their pain and the corresponding visual analogue score was recorded by the investigator. The pain assessed during the first visit before treating any medication was served as the baseline score. The nature and severity of the adverse events reported were assessed at the end of the study.

The primary outcome measure was the change in the pain level by the VAS score in Visit 2 (day 30) and Visit 3 (day 45) as compared to the baseline (visit 1). Secondary outcome measures included reporting of the adverse events that were either spontaneously reported by the patient or noticed by the physician during the trial and safety was recorded.

Change in mean VAS score, percent decrease in pain intensity, and percentage of patients who had ≥50% reduction in neuropathic pain from baseline to visit 2 to visit

3 were calculated. And additionally risk reduction and number needed to treat for the patients who had ≥50% reduction in pain at visit 3 was also calculated.

Result:

Change in VAS score from baseline to visit 2 to visit 3 is depicted in figure 2.

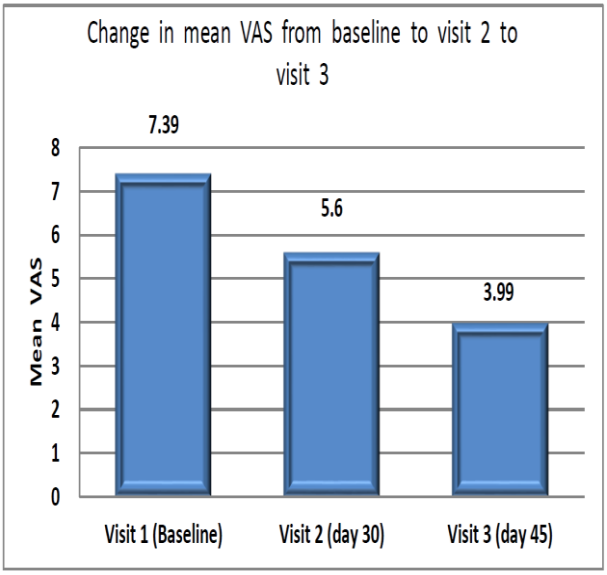

Figure 2: Change in mean VAS score from baseline at visit 1 to visit 2 on day 30 and visit 3 on day 45

Percentage decrease in the pain intensity at visit 2 was -24.22% compared to baseline and at visit 3 (day 45) was 46% =compared to baseline as shown in figure 3.

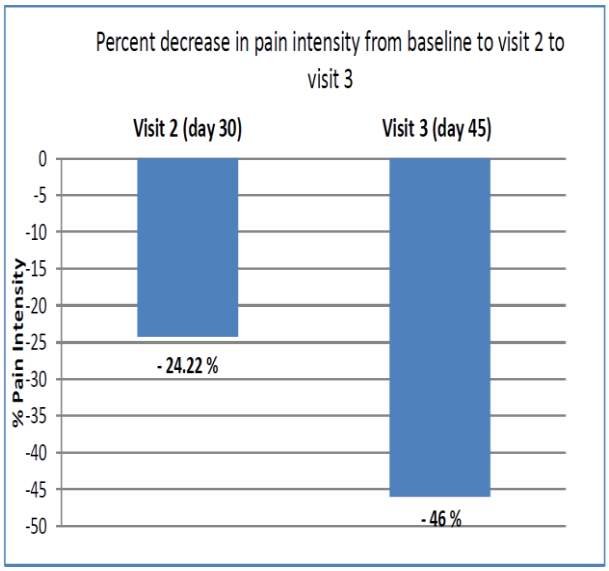

Figure 3: Percentage decrease in the pain intensity from baseline to visit 2 to visit 3

Percentage of patients who had experienced ≥50% reduction in neuropathic pain is shown in the following diagram

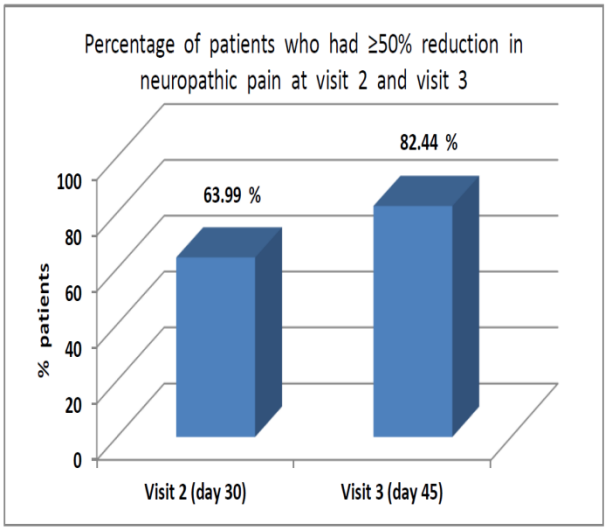

Figure 4: Percentage of patients who had ≥50% reduction in neuropathic pain in visit 2 (day 30) and visit 3 (day 45)

Interim data showed that treatment with AmNurite was well tolerated. Adverse events were observed in only 5% of the patients including dry mouth, constipation, sedation and dizziness which were most common adverse events.
Risk reduction (RR) and number needed to treat (NNT) for the patients who had ≥50% reduction in neuropathic pain at visit 3 is mentioned in the table below

Table 1: Risk reduction (RR) and number needed to treat (NNT) for the patients who had ≥50% reduction in neuropathic pain at visit 3

Patients who had ≥50% reduction in neuropathic pain at visit 3	**RR**	**NNT**
82.44 %	0.824	1.21

Discussion

AmNurite has demonstrated good efficacy in the management of the neuropathic pain as monotherapy. In the randomized study comparing amitriptyline, desipramine and fluoxetine among patients with painful DPN, amitriptyline improved pain in the 74% of study participants, which was more than 61% of the patients who had received Desipramine the 48% of patients who improved with fluoxetiene.[14] Which concludes that amitriptyline was more efficacious than the amitriptyline, desipramine and fluoxetine.

So because of that we have developed the dosage form containing amitriptyline (10/25 mg) and mecobalamin (1500mcg SR). We have done the phase 4 clinical studies at 72 different trial centers on 786 patients. And the data we got was analysed statistically.

Pain intensity was measured by the VAS. Mean VAS at the baseline was 7.39 which was decreased to 5.6 at visit 2 on day 30 and further decreased to 3.99 at visit 3 on day 45. Which states that after taking AmNurite tablet (combination of amitriptyline 10/25 mg and mecobalamin 1500 mcg) mean VAS score was constantly decreased in visit 2 and visit 3. Which means AmNurite is having efficacy in reducing the neuropathic pain.

In second statistical analysis we have measured the decrease in the percent pain intensity by considering that the mean VAS score at baseline was 100%. Then as per the statistical analysis at visit 2 on day 30 it was decreased by 24.22% and at visit

3 on day 45 it was decreased by 46%. Which also states that after taking AmNurite tablet (combination of amitriptyline 10/25 mg and mecobalamin 1500 mcg) percent pain intensity was constantly decreased at visit 2 and visit 3. Which means AmNurite is having efficacy in reducing the neuropathic pain.

In third statistical analysis, we found that 63.99% patients in visit 2 and 82.44% patients in visit 3 had experienced more than ≥50% reduction in neuropathic pain.

As per the above 3 statistical analysis regarding efficacy, combination of amitriptyline and mecobalamin is having good efficacy in reducing neuropathic pain. And good percentage of patients had experienced ≥50% reduction in pain. Which states that the AmNurite was having the good efficacy in reducing neuropathic pain intensity of more than 50%.

No serious side effects were observed in any patient. Adverse effects were observed in only 5% of the patients. Dry mouth, constipation, sedation

and dizziness were the most common adverse effects those observed during the study.

Conclusion

The AmNurite (combination of amitriptyline 10/25 mg and mecobalamin 1500 mcg) was found to be safe as well as efficacious in the treatment of neuropathic pain.

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