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A Multi-Centered Study to Evaluate the Efficacy and Safety of Amitriptyline and Mecobalamine in the Management of Low Back Pain and Lumbar Radiculopathy

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Abstract
Introduction: *Low Back Pain (LBP) is a pain and disability comfort localized below costal margins and above the inferior gluteal folds with or without referred pain in legs. Lumbar Radiculopathy (LR) is a term used to describe pain caused by compression or irritation of nerve root in the low back. An FDC of Amitriptyline a neuroanalgesia and Mecobalamine (Vitamin B_{12}) a damage nerve rejuvenator have an important role in management of LBP and LR caused by Neuropathic pain.*
Methodology: *Of 400 registered, 339 patients completed the study. Efficacy assessment was made by reduction in mean VAS score and percentage of patients with ≥50% reduction in LBP and LR was calculated at conclusion visit and used to determine the corresponding NNT. Safety assessment was made by investigating the adverse events during the study.*
Results: *Reduction in mean VAS score, in LBP patients was from 8.01 (baseline) to 4.18 (day 30) and 1.74 (day 45) and in LR patients reduction was from 7.24 (baseline) to 4.80 (day 30) and 3.20 (day 45). Nearly all the patients had experience ≥50% reduction in LBP and LR. NNT score was calculated by using risk reduction parameter at conclusion visit. Overall 116 patients experience adverse events and were of mild to moderate intensity.*
Conclusion: *The combination of Amitriptyline and Mecobalamine was safe, efficacious and well-tolerated in management of Low back pain (LBP) and Lumbar Radiculopathy (LR).*
Keywords: *Low back pain, Lumbar radiculopathy, Neuropathic pain, Amitriptyline, Mecobalamine, VAS score and NNT score.*

Introduction

Neuropathic Pain (NP) is a medical condition develops after a lesion or disease affecting the somatosensory nervous system either at peripheral or central level.[1],[2] Diabetic neuropathy, trigeminal neuralgia, post-spinal cord injury pain, and post-herpetic neuralgia are characteristic examples of NP. NP serves a significant role in

the pathogenesis of numerous diseases related to the spine. However, and is based on a characteristic symptom profile and diagnostic tests, the diagnosis of NP remains clinical.[3]

Low Back Pain (LBP) is defined as pain and disability comfort localized below costal margins and above the inferior gluteal folds with or without referred pain in legs.[4],[5] LBP is the most common musculoskeletal pain and one of the most widespread public health related problem worldwide. The differential for LBP is broad and amongst other diagnoses, should include Lumbar LR (LR). LR is a term used to describe pain caused by compression or irritation of nerve root in the low back. It can be caused by degeneration of the spinal vertebra, lumbar disc herniation and narrowing of the foramen from which the nerves exit the spinal canal. However, any process that stimulates the irritation of the spinal nerve can cause radicular symptoms.[6]

Multiple studies have yielded variable results on the prevalence of LBP and thus the epidemiology of LR is unclear. This is likely because the conditions that cause lower extremity Back Pain are often poorly defined. However, the incidence of LBP is estimated between 13 to 31%. Moreover, the incidence of radicular symptoms in patients with LBP ranges from 12 to 40%. Patients with chronic LBP account for 80% to 90% of all health care expenditures.[6]

Despite the introduction of new treatments, the management of patients with NP remains a challenge. In clinical practice, patients with NP include those with spinal pain, often receive suboptimal treatment. [7] One of the treatment option available for LBP and LR caused by NP is Drug Therapy. Anti-depressants are commonly prescribed drug and their use is increasing for the treatment for LBP and LR. [5] The two main groups used as Drug Therapy is Tricyclic anti-depressants (TCAs) and Selective Serotonin Re-uptake Inhibitors (SSRIs).[5],[8] However, there is evidence to indicate that the TCAs and SSRIs have an effect on endogenous opioid and peripheral system.[5],[9] Anti-depressants at significantly lower doses are used to treat NP than those which are used for depression.[5], [10] A high quality trial by Atkinson, which performed a head to head comparison of TCAs and SSRIs, reported a greater reduction in pain intensity with low doses of TCAs than with all doses SSRIs. Therefore Low dose anti-depressants are a common treatment for LBP and LR.[5], [11]

Amitriptyline, a Tricyclic antidepressants used as first- line treatment, also has analgesic properties and are effective in the treatment of neuropathic pain for many years. The mechanism of action lies on inhibiting sodium channels that allows the stabilization of neuronal peripheral level and modulation of neuronal hyperactivity at central level, also blocks the reuptake of norepinephrine and serotonin to pre-synaptic level, limiting the hyperalgesia induced by N-methyl-D-aspartate (NMDA) agonists, anti-histamine action on the H1 and H2 receptors, blockade of alpha receptors that can eliminate pain.[12], [13], [14]

Cobalamine has 4 analogues; cyanocobalamine, hydroxycobalamin, 5-deoxyadenosylcobalamin and mecobalamin, out of which mecobalamin accounts for 90% of total cobalamine, suggesting its close relationship with nervous system. Thus, it will be more be more appropriate to consider it in neuropathy rather than other analogues.[15] Mecobalamin is the neurologically active, most bioavailable and best utilization form of Vitamin B_{12}. [16] Mecobalamine helps in nerve rejuvenation by promoting myelination, restoring diminished neurotransmitter levels and axonal regeneration. It also offers protection against glutamate-induced neurotoxicity.[17]

As neuroanalgesia, Amitriptyline is of a particular value in the management of NP caused by LBP and LR. Mecobalamine is the physiologically most active from of Vitamin B_{12}. Mecobalamine restores diminished neurotransmitter levels, causes nerve rejuvenation by promoting myelination, and axonal regeneration. The combination of Amitriptyline and Mecobalamine can be valuable assets in the management of NP. However, due to paucity of available data on the

efficacy and safety of the combination of Amitriptyline and Mecobalamine this is the Indian clinical study (AMNEST) which evaluate the efficacy and safety of Amitriptyline and Mecobalamine combination in management of NP.

Methodology

Phase IV, multi-centered, clinical study was conducted in 250 centres all over India. Total 400 patients were recruited, out of which 339 patients completed the study and 61 patients lost to follow-up. From 339 patients, 213and 126 patients were of LBP and LR respectively.

Inclusion and Exclusion Criteria

The study includes patients of both the genders, age 18-65 years. Patients with confirmed diagnosis of Neuropathic pain caused by LBP and LR were included in the study. If the patient is diabetic, treatment with anti-diabetics drugs has been given. Patients with LBP and LRcaused by NP is not controlled by any other drug or treatment. Only patients who are participated and strictly adhere to protocol were mustered for this phase IV clinical study. Patients having hypersensitivity to any ingredient of the formulation were excluded from the study. Patients taking MAO-inhibitors were excluded or history of urinary retention due to benign prostatic hyperplasia were excluded from the study. Patients with renal/hepatic impairment or with any evidence of psychological disorder were also excluded from the study.

Study Intervention

Patients were instructed to take Study drug – A film coated bilayered tablet contains Amitriptyline 10 mg (Immediate release) and Mecobalamine 1500 mcg (Sustained release). The study drug was provided free of cost by the sponsor to recruited patients. Patients were instructed to the study drug (1 tablet) at night for study duration of 45 days.

Study Procedure

The study duration to determine the safety and efficacy of study drug combination (Amitriptyline and Mecobalamine) in management of neuropathic pain caused by LBP and LR was kept 45 days. Neuropathic pain patients satisfying the inclusion/exclusion criteria were recruited for the study. Physical examination includes blood pressure plus, rate and respiratory rate was conducted and case history was taken by the investigators. Five blister packs (10 tablets each blister) was dispensed to patients and were advised to take a dose of one tablet at night. Determination of efficacy in patients were evaluated by using Visual Analogue Scale (VAS) score. The VAS score of patients was noted on Baseline visit (V1) on day 1, Re-evaluation visit (V2) on day 30 and Conclusion visit (V3) on day 45. As compared to the baseline, the change in VAS score at V2 and V3 was statistically evaluated. Any adverse event or adverse drug reaction occurred during the study stretch of 45 days was noted by patients as instructed by the investigators. Patients were requested to withdraw the study medication in case of any severe adverse event or drug reaction by the investigator. Number Needed to Treat (NNT) is a measure to rank the efficacy of the treatment including analgesics. NNT is use to relate the efficacy of treatment in chronic pain and is defined as the number of patients that need to treated for a given period of time to achieve beneficial outcome i.e. 50% pain relief. NNT close to 1 means treatment is 100% effective. Basically smaller the NNT, fewer the number of patients needed to treat to achieve a beneficial effect.

Concomitant Therapy

During the study duration patients were instructed not to use any other analgesics apart from the study medication. Any non-pharmacological therapy to attenuate pain was allowed during the study duration. Any use of concomitant medications was also noted.

Efficacy Assessment

The primitive assessment was done by determining the reduction in the VAS score on an eleven-point scale (0 to 10) where 0 means no pain and 10 means worst possible pain. The subsidiary assessment was done to evaluate

percentage of patients with ≥50% reduction in pain caused by LBP and LR from baseline were calculated at V3 i.e. day 45 and this value was used to access the corresponding NNT. Hence, the NNT was calculated using risk reduction.

Safety Assessment

Any adverse event or adverse drug reaction if occurred, patients were examined at each visit and was noted in the case report form (CRF) by the investigator. The adverse events are classified into serious and non- serious adverse events Naranjo's scale of probability was used to classify the adverse event as drug related or non-drug related. Investigator can be withdrawn from study if adverse event found to be serious and necessary follow-up and treatment was provided till the adverse events resolves.

Regulatory Matters

The study combination has been approved for manufacturing and marketing in 2005. The combination is available under various brands but is classified as schedule H drug in India, i.e. to be sold in presence of prescription of registered medical practitioners only. All the patients who participated in the study has read and signed the informed consent form voluntarily. The protocol, case record form (CRF), informed consent form (ICF), undertaking by investigators, CV and medical registration certificates (including post-graduation certificates) of investigators and ethics committee registration certificates were submitted to the office of Central Drugs Standard Control Organization (CDSCO).

Results

Total 339 patients were analysed based on inclusion and exclusion criteria, out of which 213 and 126 patients were diagnosed with LBP and LR respectively. The two main outcome of the study is change in mean VAS score from baseline visit (V1) at day 1 to conclusion visit (V3) at day 45 and percentage of patients observed with ≥50% reduction in pain responds to study medication.

In patients of LBP, the mean VAS score at baseline visit (V1) was found to be 8.01 which reduced to 4.18 (48%) at V2 and further reduced to 1.74 (78%) at V3 (Figure 1). Percentage of patients with ≥50% reduction in pain during visit V2 and V3 was found to be 76% and 92.30% respectively (Figure 2).

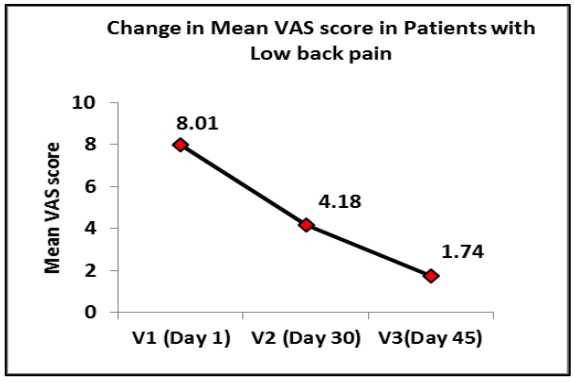

Figure 1: Change in Mean VAS score in LBP patients

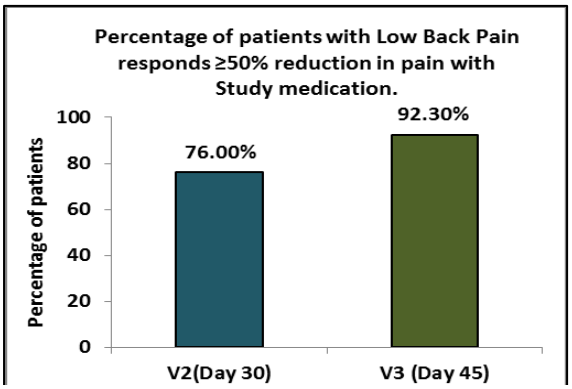

Figure 2: Percentage of LBP patients responds (≥50% reduction in pain) to Study medication

Similarly in patients of LR the mean VAS score at baseline visit (V1) was found to be 7.42 which reduced to 4.80 (35.3%) at V2 and further reduced to 3.20 (56.81%) at V3 (Figure 3). Percentage of patients with ≥50% reduction in pain during visit V2 and V3 was found to be 47.05% and 76.47% respectively (Figure 4).

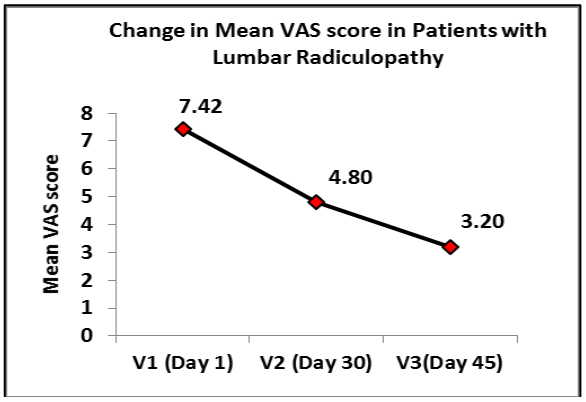

Figure 3: Change in Mean VAS score in LR patients

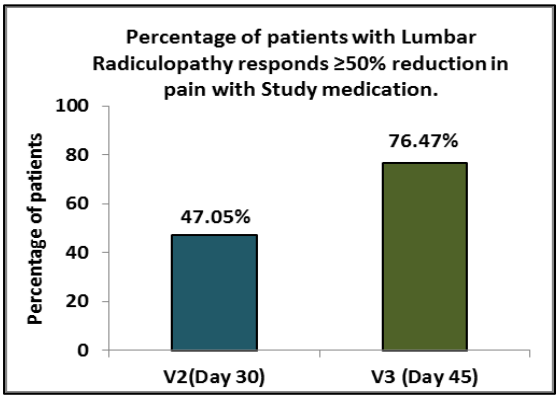

Figure 4: Percentage of LR patients responds (≥50% reduction in pain) to Study medication

NNT of study medication in patients with LBP and LR was calculated using percentage of patients observed with ≥50% reduction in pain at V3 (Table 1). NNT close to 1 means that a treatment is nearly 100% effective.

Table no. 1: NNT of Study medication in Patients of LBP and LR.

Sr.no	Type of Pain	Percentage of patients with ≥50% reduction in pain at Conclusion visit (V3)	Risk Reduction (RR)	Number needed to treat (NNT)
1.	LBP	92.30	0.923	1.08
2.	LR	74.47	0.764	1.30

No serious adverse events was observed during the study duration. The overall incidence of reported study drug related adverse effects were seen in 34.21% patients. The list of adverse events with the number of episodes is mentioned in Table 2.

Table no. 2: Adverse events, no. of episodes, no. of patients and percentage of patients experience from total population

Adverse event	No. of patient	Percentage of patients
Sedation and Drowsiness	81	23.89
Dizziness	15	4.42
Dry mouth	32	9.43
Constipation	17	5.01
GI irritation	28	8.25
Total	**116**	**34.21**

Discussion

Neuroanalgesics with neuron rejuvenator's combination are available in the market and are quite popular. "AMNEST" is the first Indian study determining the safety and efficacy of Amitriptyline and Mecobalamine combination in management of LBP and LR caused by NP in Indian patients. The strength of the study is both the parameters which leads to reduction in NP i.e. change in mean VAS score and NNT were clinically studied over the study duration of 45 days.

At baseline visit (V1) o day 1, the mean VAS score for LBP and LR was found to be 8.01 and 7.42 which reduced to 4.18 and 4.80 at re-evaluation visit (V2) on day 30 and further reduced to 1.74 and 3.20 at conclusion visit (V3) on day 45 respectively. LBP and LR patients with ≥50% reduction in pain was found to be 76% and 47.05% at re-evaluation visit (V2) on day 30 and 92.30% and 76.47% at conclusion visit (V3) on day 45 respectively. Patients were also demonstrated on NNT for study medication and was calculated by using percentage of patients

with ≥50% reduction in pain at V3. The Risk reduction for LBP and LR was found out to be 0.923 and 0.747 respectively. NNT is inverse of risk reduction value and close to 1 means treatment is 100% effective. Hence with study medication NNT was found out to be 1.08 and 1.30 for LBP and LR respectively. In 116 patients, study drug related adverse events were reported. Sedation and Drowsiness (23.89%), Dizziness (4.42%), Dry mouth (9.43%), Constipation (5.01%) and GI irritation (8.25%) was the documented adverse event in this study and were of mild intensity affecting 34.21 % of the study population.

Kalita, J., et al.[18] has conducted an open-labeled, singled center, investigators initiated randomised controlled trial to report the safety and efficacy of Pregabalin (PG) and Amitriptyline (AT) in chronic low backache (CLBA). Patients with CLBA, age 15-65 years without specific cause and significant neurological deficit were included. Severity of pain was measured by Visual Analogue Scale (VAS) and disability by Oswestry Disability Index (ODI). Patients were followed up at 6 and 14 weeks respectively and their VAS score, ODI and side effect were noted. The main outcome of the study was pain relief i.e. patients response >50% improvement in VAS score at 14 weeks and ODI reduction (>20%) and side effects. Total 200 patients with CLBA were randomized in to two groups PG (n=97) and AT (n=103) by using random numbers. The VAS score and ODI improved significantly following PG and AT at 6 and 14 weeks compared to baseline. The improvement in pain (PG=39.2% Vs AT=57.3%; P=0.01) and disability (PG=49.5% Vs AT=65%; P=0.03) however was more in AT group. The composite side effects were noted and found to be similar in both groups. AT and PG are effective, but AT reduced pain and disability significantly compared to PG in CLBA.

Dongre Yasmin U., et al[19] as conducted open-labeled, multicentre, single-arm, prospective, observational clinical study for the duration of 14 days in Indian patients. Patients received fixed dose combination of sustained-release pregabalin combined with immediate release methylcobalamin. Data was collected for reduction in pain and other positive and negative symptoms associated with NP, including numbness or tingling, hyperesthesia, paresthesia, muscle weakness, burning sensation, impairment of movement, and sleep disturbances. Pain intensity was measured on a 0-10 point Visual Analogue Scale (VAS) (0 =no pain and 10 =worst pain ever). The drug safety was also evaluated throughout the study duration of 14 days. The data was analyzed using suitable statistical methods. The overall 72.3% reduction was observed in mean VAS score over 14 days. The reduction in mean VAS score was significant as early as the first week. Both positive and negative symptoms of peripheral NP were significantly improved in >50% patients within the 2 weeks. Giddiness (4.7%), sedation (3.6%), dizziness (2.9%), drowsiness (2.3%), and nausea (2.3%) were the most commonly observed adverse effects noted during the study. The overall efficacy and tolerability was rated as good to excellent by >95% of the investigators and patients. Therefore FDC of sustained-release pregabalin and methylcobalamin significantly reduced NP, with significant improvement in both the positive and negative symptoms associated with NP, in Indian patients and was well tolerated.

Conclusion

The drug combination of Amitriptyline and Mecobalamine was safe, efficacious and well-tolerated in management of Low back pain (LBP) and Lumbar radiculopathy (LR) due to Neuropathic pain (NP).

Acknowledgements and Disclosures

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