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Ondansetron versus Amitriptyline in the Treatment of Peripheral Neuropathy: A Randomized Double Blind Prospective Clinical Study

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Authors' contributions

Author HS designed the study. Author BHP performed the statistical analysis. Author AM wrote the protocol and recorded the data, author AM also wrote the first draft of the manuscript. Authors DT, SS and PK managed the analyses of the study. Author VS managed the literature searches. This research work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Background and Objective: Clinical trials have shown the potential use of 5-HT3 receptor antagonists like Ondansetron, Tropisetron and Zacopride in a number of disorders of gastrointestinal tract and the central nervous system such as cancer chemotherapy induced vomiting, anxiety, depression, schizophrenia and migraine. Various experimental and clinical studies also point the usefulness of Ondansetron in neuropathic pain. Therefore, the present study was conducted to find out whether Ondansetron could be used as an alternative to a standard drug, Amitriptyline in the treatment of peripheral neuropathy.
Methodology: A randomized double blind prospective clinical study was conducted on

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thirty six patients of peripheral neuropathy divided into two groups of equal number of patients. Group 1 received Ondansetron 8 mg per day while Group 2 received Amitriptyline 25 mg per day. Patients were being evaluated on the basis of improvements (decrease) in LANSS (Leeds Assessment of Neuropathic Symptoms and Signs), VAS (Visual Analogue Scale) and NCV (Nerve Conduction Velocity) for six weeks. Student's t-test and/or repeated measure ANOVA followed by Bonferoni correlation was used to compare sets of paired observations. The Friedman test followed by multiple comparisons was used to compare the data which was not normally distributed.

Results: LANSS and VAS scores showed significant improvements in the 1st and 2nd visit in both the groups. NCV showed improvement in Ondansetron group with less number of adverse effects compared to that of Amitriptyline. NCV in Amitriptyline group demonstrated significant increase in one of the parameters, F-waves, indicating a worsening in left tibial nerve (p=0.036), whereas no such change was found in the group treated with Ondansetron.

Conclusion: Ondansetron has beneficial role in peripheral neuropathy by improving its sensory component as it significantly decreased LANSS and VAS scores. Our results also demonstrated that Ondansetron was at least as efficacious as Amitriptyline in the treatment of peripheral neuropathy with lesser adverse effects.

Keywords: 5-HT3 receptor antagonists; ondansetron; amitriptyline; peripheral neuropathy; LANSS (Leeds Assessment of Neuropathic Symptoms and Signs); VAS (Visual Analogue Scale); NCV (Nerve Conduction Velocity).

ABBREVIATIONS

LANSS: Leeds assessment of neuropathic symptoms and signs; VAS: Visual analogue scale; NCV: Nerve conduction velocity; SNCT: Sensory nerve conduction test.

1. INTRODUCTION

Peripheral neuropathy is a dysfunction of the axons or the myelin surrounding the peripheral nerves that causes pain, numbness, tingling and/or muscle weakness, usually in the lower extremities. It is seen in 50% diabetics [1] or may be a side effect of anticancer drugs [2,3], or due to physical injury, infection, toxic substances, disease (such as cancer, kidney failure, AIDS, Gullian-Bare Syndrome or malnutrition), or drugs (Amiodarone, Cisplatinum, Dapsone, Disulfiram, Isoniazid, Metronidazole) [4-8]. Nerve injury leads to enhanced descending excitatory drive from the RVM (rostral ventromedial medulla) to maintain the chronic pain states [9]. Disruption of ascending or descending pathways effectively blocks abnormal pain after neuropathy [10]. Motor and sensory nerve conduction studies are routinely performed to assess the peripheral neuropathy electro-physiologically.

Clinical trials had shown the potential use of 5-HT3 receptor antagonists such as Tropisetron, Zacopride, Ondansetron in a number of disorders of the gastrointestinal tract and central nervous system [11]. Various experimental [12] and clinical [13] studies also point to the usefulness of Ondansetron in neuropathic pain.

The present modality for the treatment of neuropathy is divided into two lines of therapy. First line of therapy includes tricyclic antidepressants (TCAs) like Amitriptyline, Imipramine, serotonin-norepinephrine reuptake inhibitors (SNRIs) like Duloxetine, Venlafaxine,

antiepileptics like Carbamazepine, Gabapentine, Lemotrigine. The second line therapy includes opioids (Morphine, Tramadol), antiarrhythmics (Mexiletine) and others like Clonidine, Memantine, Levodopa, Alpha lipoic acid (Thiotic acid), non-steroidal anti-inflammatory drugs (NSAIDs) like Acetaminophen, Aspirin and Ibuprofen [14].

Because of the failure of the existing painkillers to provide adequate relief, there is a constant search for newer options – for treating pain of diabetic neuropathy. Tricyclic antidepressants are now considered the first-line choice of treatment for chronic pain associated with diabetic neuropathy. They have no serious side effects even on prolonged usage. It is widely accepted that oral TCAs have an analgesic effect in neuropathic pain [15-17] with evidence of efficacy existing for Amitriptyline [15,18-23]. Accumulated evidences suggest that such efficacy may be due to block of voltage gated Na+ channels similar to local anaesthetics and antiarrhythmic agents [23,24]. These findings suggest that Amitriptyline could extend its clinical usefulness for peripheral nerve blockade [25].

The 5-HT3 receptor is a ligand-gated cation channel located in the central and peripheral nervous system. The 5HT3 receptors are predominantly localized in the superficial dorsal horn [26-28] on nerve terminals of small diameter afferents [26,29]. Blocking spinal 5HT3 receptors using the selective antagonist Ondansetron and related drugs has implicated a pronociceptive role of these receptors [26,30,31]. In the periphery, it is found on autonomic neurons and on the neurons of sensory and enteric nervous system. The 5-HT3 receptor antagonists restore normal behaviour in rodents and primates, disturbed by increasing limbic dopamine functions and aversive situations [32], and do not induce pronounced changes of physiological functions in healthy subjects [33]. Recent findings of efficacy of Ondansetron on mechanical punctate evoked responses following peripheral nerve injury favours the potential clinical use of this agent for the treatment of neuropathy, particularly in patients with tactile allodynia [26]. More recently, it was observed that Ondansetron exerts greater effectiveness after nerve injury compared to sham controls, particularly on mechanical punctate responses [26,34]. Various case reports suggest that analgesia can be achieved by the clinical use of oral Ondansetron in chronic neuropathic pain without much adverse effects [35].

In a randomized controlled double blinded study to see the effect of Ondansetron pre-treatment in alleviating the pain due to Propofol injection; it was found that Ondansetron (4 mg intravenously) pre-treatment was successful in relieving pain without any adverse effect in a significant number of patients [36].

Ondansetron does not modify any aspect of normal behaviour in animals or man. It is well tolerated over wide dose ranges, the most common side effects being headache or constipation [37] with lower incidence of sedation and only isolated case reports of extrapyramidal reactions [38].

Based on the available data on the effects of Ondansetron on animal models with neuropathy and clinical evidences of its beneficial effects in neuropathy in human subjects, the present study was planned to explore the efficacy of Ondansetron in neuropathy, in comparison to Amitriptyline.

2. MATERIALS AND METHODS

A randomized double blind prospective interventional study was carried out in the department of Clinical Pharmacology and Therapeutics, in collaboration with the

departments of Internal Medicine and Human Physiology, at B. P. Koirala Institute of Health Sciences, Dharan, Nepal. The study was conducted on thirty six patients (divided into two groups of eighteen each) from the out-patient department (OPD) of Internal Medicine, who had either diabetes or other causes of peripheral neuropathy, with sub-acute and/ or chronic neuropathy based on the inclusion and exclusion criteria. As the investigator gave codes to both patients and to drugs through computerized randomization, without telling the researcher which drug is being given by the investigator to be dispensed to patient, the researcher was blinded. The study was of one year or two follow-ups at four weeks and six weeks period. This clinical trial was approved by the Institute's Ethical Review Board. Diagnosis of neuropathy at baseline (Visit 0) was accepted when two or more of the cardinal symptoms (i.e., burning pain, paresthesia/dysesthesia, shooting/lancinating pain, numbness and allodynia10) were present.

2.1 Inclusion and Exclusion Criteria

2.1.1 Inclusion criteria

a) Patients of either sex with =18 years of age and body mass index (BMI) =18 kg/m^2 having neuropathy, irrespective of cause.
b) Patients with a Leeds Analysis of Neurological Symptoms and Signs (LANSS) scale score =12 and/or Visual Analogue Scale (VAS) score =7 and/or with sensory nerve conduction test (SNCT) abnormalities.

2.1.2 Exclusion criteria

a) Pregnancy and/or having arterial occlusive diseases and/or arrhythmia or any other severe disease
b) On medication (two weeks prior to the study) i.e. likely to have interactions with Amitriptyline or Ondansetron.
c) Being treated with any of the investigational drugs, 30 days prior to study and/or with known hypersensitivity to study drugs
d) Patients with abnormal electrocardiogram (requiring ECHO), liver function test or renal function test and/or mean arterial pressure (MAP) of <70mmHg or >120 mmHg on 3 different readings at half hourly interval.
e) Patients who came for follow-up beyond 28±3rd day, and 42±3rd day.

Drugs used for trial were Ondansetron (8mg per day; Group 1) and Amitriptyline (25mg per day; Group 2). After the informed written consent of subjects, they were randomized into two groups for all tests. Each patient was assigned a code (patient code number, issued by the hospital) and was given drugs with separate drug code, different from patient code. After being purchased from the market as tablets, it was crushed to powdered form and then dispensed in the form of similar looking capsules. At Visit 0, patients were supplied drugs to suffice for four weeks, and at the first follow up they received drugs to suffice for two weeks (total duration for drug supply was six weeks). Each patient was instructed to take one capsule a day at a fixed time.

Patients were followed up twice (at four and two weeks intervals), i.e. 28th, and 42nd day (Visit 1 and 2, respectively). At each visit, clinical examination, LANSS and VAS were assessed. At Visit 0 and 2, nerve conduction test was performed. Patients were enquired about any adverse effects and they were withdrawn from further study if they developed intolerable adverse effects.

2.2 Parameters Recorded

1. Patients' symptom score
2. Motor and sensory nerve conduction test: Latency, amplitude, conduction velocity, and F-waves latency of bilateral common peroneal nerves. Similarly, same parameters except F-waves latency were recorded for bilateral sural nerves.
3. The Leeds assessment of neuropathic symptoms and signs (LANSS) scale: This scale consisted of five symptom and two examination items. It assessed whether the pain, if experienced, was predominantly due to nerve damage or not. It also helped in assessment of other components of neuropathy. Scored out of 24, a score of = 12 was strongly suggestive of neuropathic pain.
4. Visual Analogue (VAS) Scale: it assessed the type of origin of pain. Scored out of 10; a score of = 7 was suggestive of neuropathic origin of pain. For analyzing the data, normally distributed data sets of paired observations were compared using student's t-test and/or repeated measure ANOVA followed by Bonferoni correction (e.g. LANSS). For analyzing the differences within and between the groups in electrophysiological variables student's t-test was used. For observations not normally distributed (skewed), e.g. VAS1 at visit 1, non-parametric (Friedman) test was used, Hence, all the data involving VAS were analyzed by the non-parametric test.

3. RESULTS AND DISCUSSION

LANSS scores on Visit 2 (LANSS2) was much less than that of Visit 0 (11.18±1.13 vs 13.41±1.93, p=000). Further, the effect on Visit 2 (LANSS2), was more intense than on Visit 1 (p=002), implying that Ondansetron had persistent effect (Table 1). Amitriptyline also exhibited further decrease in the LANSS score on Visit 2 (LANSS2) compared with score on Visit 0, which was statistically significant (Table 1).

Table 1. Effect of drugs on pain and neuropathy (LANSS) score

Groups	LANSS						p-value			
	0		1		2		Overall	LANSS0 vs. LANSS1	LANSS0 vs. LANSS2	LANSS1 vs. LANSS2
	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD				
ODS	17	13.41±1.93	17	11.94±1.56	17	11.18±1.13	<0.001	<0.001	<0.001	0.005
AMIT	15	13.80±1.85	15	11.73±1.58	15	10.73±1.28	<0.001	<0.001	<0.001	<0.001

Abbreviations: ODS: Ondansetron; AMIT: Amitriptyline; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; LANSS0: LANSS score at Visit 0; LANSS1: LANSS score at Visit 1; LANSS2 = LANSS score at Visit 2

Compared to the VAS scores at baseline i.e. on Visit 0 (VAS0), Ondansetron demonstrated significant lowering of VAS scores on Visit 1 (VAS1), 7(2) and 5(1) respectively, p=0.000. Similarly it exhibited significant decrease in VAS score at Visit 2 i.e. VAS2, compared to VAS0 with values of 5(2) vs 7(2), p=0.000. Similar results were also seen with Amitriptyline. It significantly decreased the VAS scores on Visit 1 and Visit 2 (VAS1 and VAS2 respectively, both p=0.000) compared with Visit 0 (VAS0) (Table 2).

Both Ondansetron and Amitriptyline were comparable in terms of their effects on the NCV. As shown in (Table 3) below, they produced similar effects on all the electrophysiological variables of the motor nerves (left & right common peroneal nerves), indicating that Ondansetron is at least as effective as Amitriptyline in its effect on NCV (nerve conduction

velocity) parameters. They were also comparable in terms of their effects on the electrophysiological variables of the sensory nerves (left & right sural nerves) (Table 4).

Table 2. Effect of ondansetron and amitriptyline on VAS scores

Groups	VAS						p-value			
	0		1		2		Overall	VAS 0 vs. VAS 1	VAS 0 vs. VAS 2	VAS 1 vs. VAS 2
	No.	Median (Range)	No.	Median (Range)	No.	Median (Range)				
ODS	17	7 (2)	17	5 (1)	17	5 (2)	<0.001	<0.001	<0.001	0.002
AMIT	15	8 (3)	15	5 (2)	15	5 (3)	<0.001	<0.001	<0.001	<0.001

Abbreviations: ODS: Ondansetron; AMIT: Amitriptyline; VAS: Visual analogue scale; VAS0: VAS score at Visit 0; VAS 1: VAS score at Visit 1; VAS 2 = VAS score at Visit 2

Table 3. Comparison of the effects of drugs on electrophysiological variables (NCV) of common peroneal nerves (motor nerves)

Electrophysiological parameters	Ondansetron			Amitriptyline			p value
	No.	Mean±SD	SEM	No.	Mean±SD	SEM	
Latency (RCP)	15	3.79±1.08	0.28	12	4.23±0.99	0.28	0.28
Amplitude (RCP)	17	2.77±1.91	0.46	16	2.77±3.26	0.81	0.99
Conduction velocity (RCP)	14	41.09±7.81	2.08	11	39.94±6.64	2.00	0.70
F-waves (RCP)	9	55.44±12.09	4.03	10	51.75±4.36	1.38	0.37
Latency (LCP)	13	3.14±0.55	0.15	12	3.55±0.71	0.20	0.12
Amplitude (LCP)	17	2.73±2.01	0.48	16	3.29±3.12	0.78	0.54
Conduction velocity (LCP)	13	41.54±7.68	2.13	12	41.73±5.50	1.58	0.94
F-waves (LCP)	10	50.00±7.74	2.45	10	51.49±5.55	1.75	0.62

Abbreviations: RCP: Right common peroneal nerve; LCP= Left common peroneal nerve

Table 4. Comparison of the effects of drugs on electrophysiological variables (nerve conduction velocity) of sural nerves (sensory nerves)

Electrophysiological parameters	Ondansetron			Amitriptyline			p value
	No.	Mean±SD	SEM	No.	Mean±SD	SEM	
Latency (RS)	14	2.26±0.44	0.13	11	2.50±0.64	0.19	0.28
Amplitude (RS)	18	9.40±7.92	1.86	17	8.24±9.38	2.27	0.69
Conduction velocity (RS)	14	50.69±6.97	1.86	11	49.16±9.37	2.82	0.64
Latency (LS)	14	2.26±0.27	0.07	11	2.62±0.84	0.25	0.14
Amplitude (LS)	18	9.09±8.36	1.97	17	8.48±10.48	2.54	0.84
Conduction velocity (LS)	14	50.39±7.55	2.01	11	47.75±7.35	2.21	0.39

Abbreviations: RS: Right sural nerve; LS: Left sural nerve

Amitriptyline demonstrated significant increase in one of the parameters i.e. F-waves in NCV (nerve conduction velocity), indicating the worsening in left tibial nerve, (p=0.036). Some worsening was also seen in the F-waves of right tibial nerve, which was however, not statistically significant (Table 5). Ondansetron did not produce any such effect in any of the NCV parameters.

Table 5. Effect of amitriptyline on electrophysiological parameters of right and left common peroneal nerves and left tibial nerves

Electrophysiological parameters	Amitriptyline group			p value
	No.	Mean±SD	SEM	
F-WAVES0 (RT)	13	51.00±6.01	1.66	
F-WAVES2 (RT)	13	52.71±6.56	1.82	0.054
F-WAVES0 (LT)	13	51.30±4.43	1.22	
F-WAVES2 (LT)	13	52.04±4.52	1.25	0.036

Abbreviations: RT: Right tibial nerve; LT = Left tibial nerve

3.1 Adverse Effect Profiles of Drugs

Three out of thirty six patients reported adverse effects. One patient each from the two groups complained of constipation only. One patient from Amitriptyline group reported headache and constipation, whereas such constellation of adverse effects was not observed in the Ondansetron group.

Our results showed that baseline characteristics were comparable between the two groups. The two groups were similar in terms of age, body mass index (BMI), and mean arterial pressure (MAP), and LANSS and VAS scores. LANSS and VAS scores were measured on the basis of verbal answers given by the patients, in response to the questions asked. NCV test was carried out on the basis of symptoms (numbness, tingling, loss of sensation etc.).

Almost all variables were normally distributed, and hence student's t-test and/or repeated measure ANOVA were used. However, the visual analogue scale (VAS) scores obtained at visit 1 (VAS1) of the total sample as well as the individual group were not normally distributed. This may be attributed to the dramatic improvement occurring in majority of the patients whose pain scores were decreased to a considerable extent by the treatments, while leaving some patients as non-responders whose scores were on the higher side, giving rise to the left skew in the distribution. Therefore, for the analysis involving VAS1, non-parametric test e.g. Friedman test was used.

This study was an attempt to compare the effect of Ondansetron in patients with peripheral neuropathy with the standard control Amitriptyline. Most of the patients that were included in the study had peripheral neuropathy due to diabetes mellitus. It is interesting to note that the effect of Ondansetron was persistent as evidenced by the further decrease of LANSS scores on Visit 2 compared to Visit 1 and Visit 0, suggesting that Ondansetron may sustain the decrease the pain and neuropathy scores in chronic neuropathic conditions. Amitriptyline also exhibited similar effects on LANSS scores. It was further observed that the two drugs were equally efficacious on their effects on LANSS scores. Likewise, the VAS scores showed similar trend, with the benefit further maintained at the last visit indicating its persistent effect on neuropathy. There are prior reports of the effects of Ondansetron on VAS scores on pain with the decrease in the scores [39,40]. Similar study was carried out to evaluate the effect of Amitriptyline in neuropathy using VAS as a variable [41] with significant effect on pain scores.

As in our study, earlier a few studies have used both LANSS and VAS scores to assess the analgesic activity of various other drugs [42,43] indicating that these tests are important instrument for the evaluation of effect of drugs in neuropathy.

Most patients that were included in the study had symptoms in the lower limbs, therefore, NCV test of different nerves of the lower limbs was carried out at visit 0 and Visit 2 and comparison between the two NCV tests (pre-and post-treatment) was performed to evaluate the effect of Ondansetron in peripheral neuropathy. Ondansetron tended to cause improvement in the variables, but the natural course (progressive) of the disease tended to worsen them. However, among 22 electrophysiological variables, majority of them were observed to follow improving trends.

It is interesting to note that patients in Amitriptyline group produced significant increase in F-wave of the left tibial (motor) nerve, indicating worsening of neuropathy. The same parameter of the right tibial nerve also exhibited increasing trend. Previous studies on Amitriptyline showed delayed latencies and smaller amplitudes of the autonomic nerves in comparison with the controls [44] indicating the autonomic side effects of the drug.

Earlier, a significant effect in neuropathy has been reported with Ondansetron. Our results are consistent with the results obtained in various other human and animal studies [45,46], which showed marked improvement in the pain scores (VAS etc). Previous study has also demonstrated that even a single intravenous injection of Ondansetron produced significant reduction of pain scores in humans with chronic neuropathic pain of more than 1 year duration of mixed etiology unresponsive to the currently available analgesics [37].

As this was a study of first of its kind and there were no previous study done in human beings using Ondansetron in peripheral neuropathy, so we included a small sample. The idea was to reduce the incidence of adverse effects in the population, and to see the efficacy of the test drug without compromising the treatment of the patient. There were few other limitations like as the most of the patients coming to medicine OPD with complaints of neuropathy were mostly diabetic, so we could not compare how much effective Ondansetron is in other types of neuropathy. We were not able to see adverse drug reactions if any, due to small sample size; the pain scale (LANSS, VAS) are a subjective type of tests making it a little difficult to accurately assess the improvement.

Our study is consistent with the previous studies and showed that Ondansetron produces significant improvement in neuropathy and neuropathic pain. It also demononstrated that Ondansetron was as efficacious as Amitriptyline.

In our study, nearly 10% of the patients (3 out of 36) reported adverse effects such as headache and constipation (Constipation in 1 case of Ondansetron, Constipation in 2 cases of Amitriptyline and 1 case with headache in Amitriptyline group. These adverse effects were mild and it is important to mention here that none of the patients had to withdraw from the study because of the adverse effects.

4. CONCLUSION

Ondansetron has beneficial role in peripheral neuropathy as it improves its sensory component. It decreases LANSS and VAS scores in patients with peripheral neuropathy. Ondansetron as such elicits these results at a dosage at or below the antiemetic dose range. In our study majority of the patients had diabetes mellitus and associated neuropathy and Ondansetron produced significant improvement in symptoms and test parameters of neuropathy in these patients. Our results also demonstrated that Ondansetron was at least as efficacious as Amitriptyline in the treatment of peripheral neuropathy with less adverse

effects. Weather it also reduces neuropathic complications in diabetic mellitus is yet to be seen.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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