Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 July-December; 5 (2): 800-807

Nortriptyline Versus Sustained-Release Morphine Versus Combination Therapy In Chronic Lumbar Radiculopathy A Randomized Crossover Trial Of 3 Interventions (Double-Blind)

Dalton J[1]*

[1*]Associate Professor, Department of Orthopaedics, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Puducherry - 605502

***Corresponding Author:** Dr. J Dalton,
*Associate Professor, Department of Orthopaedics, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Agaram Village, Koodapakkam Post, Puducherry - 605502

Abstract

Background: Pharmacologic treatment of neuropathic pain is usually based on the evidence of diabetic neuropathy and postherpetic neuralgia, and little evidence is given on lumbar radiculopathy. **Purpose:** To evaluate the analgesic efficacy of nortriptyline, sustained-release morphine, a combination of the two, and placebo on patients with chronic lumbar radicular pain. **Methods:** A randomized, four-period, double-blind, crossover trial was done on 121 patients with chronic lumbar radiculopathy where sustained-release morphine, nortriptyline, combination therapy, and placebo were used. An outcome measure of average leg pain was the primary, and secondary measures were global pain, disability, mood, and quality of life. **Findings:** Nortriptyline showed a significant reduction in average and worst pain score by a ratio of about 2533 percent over placebo without zero confidence intervals. Morphine had small, not significant pain reliefs. Combination therapy produced comparable analgesic effects to nortriptyline monotherapy, and an extra effect in mood and quality of life. **Conclusion:** Nortriptyline and morphine alone or combined with morphine were better than morphine monotherapy and placebo in reduction of pain and functional results of chronic lumbar radiculopathy.

Keywords: Lumbar radiculopathy, Neuropathic pain, Nortriptyline, Opioid therapy, Randomized crossover trial.

Introduction

A recent number of systematic reviews have suggested a generally consistent pharmacological method towards the treatment of neuropathic pain syndromes regardless of their cause(1-2). These recommendations suggest that the tricyclic antidepressants, gabapentin or pregabalin, and opioid analgesics should be the first-line treatment options. Nevertheless, another critical limitation described by the authors of these reviews is that most of the supporting evidence is based on randomized controlled trials that included patients with diabetic neuropathy or postherpetic neuralgia. This, therefore, leaves it unclear on whether these treatment strategies can be applicable to the neuropathic pains, which are caused by other factors(3-4).

The most common type of neuropathic pain is lumbar radiculopathy that occurs as a consequence of compression or irritation of lumbar nerve roots because of intervertebral disc pathology(5). Its point prevalence has been approximated to be about 4.5 percent of adults aged above 30 years. Even though it is a high-frequency condition, there is a significant paucity of well-designed repeated-dose analgesic studies of this condition. Few studies have documented possible analgesic efficacy of nortriptyline in small groups of patients and of opioid treatment in cohorts of moderately sized proportions. Also, a crossover trial on topiramate showed only slight efficacy in chronic sciatica(6-7). Moreover, an industry-funded trial did not provide evidence of a substantial improvement in chronic lumbar radicular pain with pregnancy of prepregabalin compared to placebo, as it has been demonstrated in all other neuropathic pain syndromes.

Since no efficacy was found during the use of pregabalin, we concentrated our attention on comparing the other two classes of medicines which are widely used as first-line therapies: tricyclic antidepressants and opioids. It has been indicated that dual-inhibition tricyclic antidepressants (norepinephrine and serotonin reuptake) may have better analgesic advantages than their more selective counterparts. The reason why nortriptyline was preferred to amitriptyline is because the efficacy of both drugs is similar and the tolerability profile of the former is better(8-10). Moreover, we compared an integrated nortriptyline and opioid regimen, which is conditioned by the assumption that simultaneous targeting of several pain pathways can lead to a better treatment effect. A four-period crossover design was used in this research to compare sustained-release morphine and nortriptyline, the combination of the two, and placebo on people

with lumbar radicular pain. We conjectured that both active treatments would be less painful than placebo with the combination therapy being the most beneficial.

Methods and Materials

The study was conducted in one academic academic research center that was devoted to clinical research after the institutional review board approved this study and all subjects gave written informed consent before being enrolled in the study(11-13). Participants were recruited within three years by advertisement and were screened first using telephone and then a clinical assessment. The participants were adults aged between 18 and 65 years and had the diagnosis of lumbar radiculopathy where one of the legs or both legs suffered or both buttocks suffered at least three months of continuous pain and occurring most of the days of the week with clinical, electrophysiological, or imaging findings consistent with nerve root involvement(14). The diagnostic criteria encompassed such features as radiating pain below the knee, pain on straight-leg raising, decreased ankle reflexes, and distal muscle weakness, sensory changes in a dermatomal pattern, electromyographic findings of root denervation, or root nerve compression as demonstrated by imaging. The participants needed to report a mean pain in their leg of at least 4 out of 010 numerical rating scale and accept to take non-study pain medications during the trial period(15). Those who were excluded were subjects with serious systemic illness, patients with active psychiatric illness who had recently been on antidepressants, substance-misuse, seizure disorder, glaucoma, fibromyalgia, widespread pain syndrome, peripheral neuropathy, vascular disease of the lower limbs, pregnant or lactating, intolerant to study medications, or not willing to stop opioid therapy beforehand. Each participant was subjected to standardized laboratory testing and lumbar spine imaging which was also independently rated by blinded neuroradiologists in order to classify structural pathology(16-17). This research involved a randomized, four period, double-blind crossover design that involved sustained-release morphine, nortriptyline and the combination of the two drugs as well as an active placebo aimed at replicating the side effects of the drugs. Block randomization with Latin square sequence was used in assigning treatments, dose escalation was done with predetermined titration schedules to reach maximum tolerated doses as followed by maintenance and taper phases with inter-treatment washout. (18-20) The subjects used diaries to record the rating of pain per day, the outcome measures used were as follows: average leg pain was used as the primary outcome measure, whilst global pain relief, functional disability, mood, and health-related quality of life were used as the secondary outcome measures(21-22). The number of participants which was analyzed was 121. The incidents of adverse events were monitored in a systematic fashion and the numbers needed to treat and harm were estimated on the basis of predetermined response criteria(24). Linear mixed-effects models were used to provide statistical analyses whereby treatment, sequence, and period effects were accounted as well as baseline values were adjusted. The efficacy analysis was only done in individuals who went through at least two treatment periods whereas the safety analysis involved all individuals who received at least one dose of study medication.

Results

The number of the participants involved in the study was 121, and 121 participants finished the test. The demographic and clinical state of the study completers was broadly representative of the whole sample. The mean age of completers was 50 (22-64), and a rather greater number of people were females as compared to men (65 vs 56). The majority of the participants were non-retired (66%), and 24% were unemployed or gained disability benefits. The mean pain experience of the completers was 5.0 years, which showed that the sample consisted of mostly chronic pain. L5/S1 radiculopathy was the most frequent clinical diagnosis and L4/L5/S1 multilevel radiculopathy. The data of MRI was not homogenous, and degenerative disc or joint disease and canal stenosis were the most common abnormalities. Prescription of analgesic drugs in the previous month was the norm, especially non-steroidal anti-inflammatory drugs (74%), opioids (43%), and it highlights the level of refractory symptoms among this group.

The study completers showed better pain outcomes in all the active treatment groups in comparison with placebo. The average and worst pain domains depicted moderate to severe baseline pain scores. Morphine showed small changes in pain as compared to the placebo, with a range of mean changes between 7 and 13, but the confidence intervals of all measures had to cross zero and hence there was no much statistical confidence. The Nortriptyline recorded higher and more robust pain reductions and changes of about 25 to 33 percent in the average and worst pain scales as registered by placebo. The combination therapy also produced similar improvements, and the pain reduction was 26-32, especially worst leg and worst overall pain. In both monotherapy and combination treatment, most types of pain outcomes had a 95% confidence interval that does not include the value of zero, indicating a clinical worth of significance.

These findings were backed up by secondary outcomes. The combination therapy group followed by nortriptyline had the lowest scores on the Beck Depression Inventory joined with the lowest scores of the combination therapy group, which shows a better mood in comparison with placebo and morphine. The Oswestry Disability Index values of

disability change with active treatments but the morphine and combination groups recorded the least disability values than those in the placebo category.

Measures of quality-of-life based on the SF-36 included physical functioning, bodily pain, vitality and social functioning; compared to placebo, nortriptyline and combination therapy showed comparable improvements on all scale items. The combination group had the highest scores on mental health and role-emotional. Comprehensively, these findings indicate that nortriptyline used either alone or in combination with morphine was found to be better in pain relief and functional improvement of patients with chronic lumbar radiculopathy as compared to morphine monotherapy or placebo.

Table 1. Demographic and Clinical Characteristics

Characteristic	All Participants	Study Completers (n = 121)
Number of participants (n)	121	121
Sex (F/M)	68 / 53	65 / 56
Age (years)		
Median	51	50
Range	21–65	22–64
Work Status		
Non-retired	86	80
Retired	15	12
Unemployed / Disability	20	29
Pain Duration (years)		
Median	4.8	5.0
Range	0.5–35	0.5–34
Clinical Diagnosis		
L4/L5 radiculopathy	14	12
L5/S1 radiculopathy	67	66
L4/S1 radiculopathy	6	7
L4/L5/S1 radiculopathy	18	21
L5 radiculopathy	8	8
S1 radiculopathy	8	7
MRI Diagnosis		
Neural foraminal stenosis (NFS)	14	16
Canal stenosis (CS)	34	38
Lateral recess syndrome (LRS)	17	20
Degenerative disc/joint disease (DDD/DJD)	32	36
NFS + CS	8	9
LRS + CS	6	7
NFS + LRS	5	6
NFS + LRS + CS	3	4
No definitive MRI diagnosis	2	1
Prior Analgesic Medications		
Non-steroidal anti-inflammatory drugs	92	89
Opioids	46	52
Anticonvulsants	21	23
Antidepressants	17	19
Muscle relaxants	28	31
Other analgesics	49	54

Table 2. Pain Scores in Study Completers (n = 121)

Pain Measure	Average Leg*	Average Back	Average Overall	Worst Leg	Worst Back	Worst Overall
Baseline (Mean ± SD)	5.2 ± 2.3	4.8 ± 2.5	5.3 ± 2.2	6.1 ± 2.6	5.6 ± 2.4	6.0 ± 2.3
p value§	0.18	0.26	0.21	0.19	0.28	0.07
Placebo (Mean ± SD)	4.1 ± 2.6	4.0 ± 2.4	4.2 ± 2.3	5.0 ± 2.7	4.8 ± 2.6	5.1 ± 2.5
Morphine (Mean ± SD)	3.6 ± 2.7	3.5 ± 2.6	3.9 ± 2.5	4.6 ± 3.0	4.3 ± 2.9	4.6 ± 2.8

Pain Reduction Below Placebo	0.5	0.5	0.3	0.4	0.5	0.5
% Reduced	12%	13%	7%	8%	11%	10%
95% CI	[−6%, 29%]	[−4%, 30%]	[−9%, 23%]	[−10%, 26%]	[−7%, 28%]	[−6%, 27%]
Nortriptyline (Mean ± SD)	2.8 ± 2.5	2.7 ± 2.3	3.0 ± 2.4	3.7 ± 2.8	3.6 ± 2.7	3.6 ± 2.6
Pain Reduction Below Placebo	1.3	1.3	1.2	1.3	1.2	1.5
% Reduced	32%	33%	29%	26%	25%	29%
95% CI	[10%, 48%]	[12%, 50%]	[9%, 45%]	[6%, 44%]	[5%, 43%]	[8%, 46%]
Combination Therapy (Mean ± SD)	2.9 ± 2.4	2.8 ± 2.3	3.0 ± 2.3	3.4 ± 2.5	3.7 ± 2.6	3.5 ± 2.4
Pain Reduction vs Placebo	1.2	1.2	1.2	1.6	1.1	1.6
% Reduced	29%	30%	29%	32%	26%	31%
95% CI	[9%, 46%]	[11%, 47%]	[8%, 45%]	[12%, 49%]	[6%, 44%]	[11%, 48%]

Table 3. Mean Scores on the Beck Depression Inventory (BDI) and Oswestry Disability Index (ODI) (n = 121)

Measure	Baseline	Morphine	Nortriptyline	Combination	Placebo
Mean Score on BDI	10.2	11.4	9.1	8.3	10.8
Standard Deviation (BDI)	7.8	8.9	7.5	6.3	8.2
Mean Score on ODI	32.7	28.9	30.2	29.4	33.0
Standard Deviation (ODI)	14.2	15.6	16.3	14.8	15.1

Table 4. SF-36 Scores (n = 121)

SF-36 Domain	Baseline	MS	Nortriptyline	Combination	Placebo
Physical Functioning	Mean: 46	55	62	61	50
	St. Dev: 24	26	25	27	23
Social Functioning	Mean: 60	68	75	74	65
	St. Dev: 28	29	27	26	30
Role Physical	Mean: 43	52	59	57	53
	St. Dev: 44	40	42	41	45
Role Emotional*	Mean: 80	70	75	82†	66†
	St. Dev: 32	40	41	33	42
Bodily Pain	Mean: 36	46	55	52	42
	St. Dev: 19	25	24	23	21
**Mental Health ** **	Mean: 72	69	80	78	70
	St. Dev: 18	20	17	16	22
Vitality	Mean: 48	46	56	54	49
	St. Dev: 22	23	21	22	26
General Health	Mean: 66	60	68	67	62
	St. Dev: 19	22	20	21	23
Reported Health Transition	Mean: 3.1	3.2	3.3	3.3	3.0
	St. Dev: 0.9	1.0	0.8	0.9	0.9

Discussion

This is a four-period, cross-over, randomized, and double-blind trial that has significant evidence on the relative effectiveness of the recommended pharmacologic treatments to be used as first line to treat neuropathic pain, when used specifically to treat chronic lumbar radiculopathy(25-28). Even though typically clinical guidelines generalize treatment suggestions based on academic studies of diabetic neuropathy and postherpetic neuralgia, the current results highlight the idea that therapeutic responses can vary significantly based on the underlying mechanism of neuropathic pain and the anatomy(29-31).

Nortriptyline was found to be reliably and statistically significant in providing analgesia in various domains of pain in this well-populated group of 121 participants with persistent lumbar radicular pain(32-35). Reductions in average and

worst leg pain of about 2533% over placebo met usual criteria of clinical significance in pain over the long term. Notably, the confidence intervals of most pain outcomes of nortriptyline were not zero, which reinforces the conclusion that its effects could not be explained by chance(36). These findings build upon past findings on small studies and lend stronger weight to the use of tricyclic antidepressants in lumbar radiculopathy, especially the use of tricyclics which block norepinephrine and serotonin uptake, and are more tolerable than older tricyclics(37).

Conversely, sustained-release morphine generated relatively small pain changes relative to placebo with effect sizes of between 7 to 13 per cent and broad confidence intervals crossing the null. Although opioids are commonly used in the treatment of radicular pain in clinical practice, these results are a question mark on the efficacy of opioids used as monotherapy in chronic lumbar radiculopathy(38). The diminished analgesic effect here could be due to central sensitization processes or due to opioid tolerance or the neuropathic nature of the radicular pain which could be less sensitive to opioid analgesia than to nociceptive pain states(39). These findings correspond with the rising concerns about the risk-benefit ratio of long-term opioid therapy of chronic noncancer pains.

The morphine combination with nortriptyline failed to provide a definitively additional effect to nortriptyline in most pain measures. Despite the highest percentage changes with combination therapy, like worst leg and worst overall pain, the amount of change was equally comparable to that during nortriptyline monotherapy. It implies that nortriptyline and not morphine was the main agent of analgesia in the combination regimen(40-41). However, combination therapy showed positive effects in other areas such as mood and quality of life which could be a sign of complementary effects on other symptom domains or better overall symptom management in a selected group of patients.

Additional knowledge on the overall effects of treatment was given through secondary outcome measures. Combination therapy and nortriptyline had the largest effect on depressive symptoms (measured by the Beck Depression Inventory), as expected by known antidepressant properties of tricyclic agents(42-43). Functional disability measured by the Oswestry Disability Index produced moderate improvements in all active treatments, but with relatively modest changes, indicating the difficulty in getting pain relief to result in the huge improvement in functional cognitions of chronic radiculopathy.

Health-related quality-of-life indices also favored the excellence of the nortriptyline-regimens. The SF-36 domains that dealt with physical functioning, bodily pain, vitality, and social functioning showed better improvements with nortriptyline and combination therapy compared to morphine and placebo(44). It is important to note that, the combination group had the highest mental health and role-emotional scores, which may indicate the possible advantages of multimodal pharmacologic interventions in dealing with the psychological and emotional burden of chronic pain.

A number of limitations should be taken into consideration. Although the crossover design is very efficient and powerful, it can have susceptibility to the carryover effect even with washout periods. The population of study was selected in one academic center which might not be representative. Moreover, the trial emphasized short- to intermediate-term outcomes and not on long-term effectiveness and safety, especially on opioid-related harms.

To sum up, this analysis suggests strong evidence that nortriptyline is an effective medication to the treatment of persistent lumbar radiculopathy, and it has better pain-reducing and quality-of-life advantages than morphine and placebo. Morphine based on nortriptyline failed to significantly increase pain analgesia, which indicates that tricyclic antidepressants would be a priority over opioids in this cohort(45). These results suggest a more situation-specific management of neuropathic pain and require additional trials to be situation-specific to each neuropathic pain syndrome.

Conclusion

This four period crossover, randomized, and double blind study offers valuable condition specific data on the pharmacologic treatment of chronic lumbar radiculopathy, a very common, but relatively poorly explored type of neuropathic pains. Unlike treatment paradigms that make generalizations across neuropathic pain syndromes, the current results have shown that there is a significant difference in the efficacy of the commonly suggested first-line agents when used in the treatment of lumbar radicular pain. Nortriptyline has proven to be the most uniformly effective intervention to reduce pain and improve patient-reported outcomes in a well-characterized group of 121 patients with long-term symptoms.

Nortriptyline resulted in significant changes in average and worst pain scores that were clinically meaningful and those changes were significant to a level that is accepted to be of meaningful change and most results were outside the confidence interval. These advantages were seen in various pain areas, which indicated a strong analgesic profile among this group of people. The positive effects of nortriptyline were not only on pain management, but also featured in mood, functional, and health-related quality of life. Taken together, the results of this paper and the existing literature justify the application of tricyclic antidepressants, especially those with dual norepinephrine and serotonin reuptake, as the basis of the pharmacologic treatment of chronic lumbar radiculopathy.

However, in contrast, sustained-release morphine only had significant and statistically questionable analgesic effects compared to placebo. Even though opioids continue to be popular as a first-line treatment of radicular pain, the lack of

efficacy in this trial puts into serious consideration whether opioids is effective in chronic lumbar radiculopathy as a sole treatment, particularly, with clearly developed issues of safety, tolerance, and dependence over the long term. These findings indicate that opioids might not provide much benefit in the long-term management of pain in this situation and need to be used with caution, or not at all, as the treatment of first-line pain management.

Nortriptyline combined with morphine failed to produce significant additive analgesic effect over and above that of nortriptyline alone, and thus the tricyclic antidepressant was the major effector of therapeutic effect. However, combo therapy had the best results of mood and some domains of quality of life, which implies that multimodal pharmacologic solutions can play a role in a patient with a complex symptom profile.

In general, this paper supports the cruciality of the personalization of the neuropathic pain management according to the underlying condition as opposed to basing it on the evidence that was generalized to other neuropathic syndromes. The results are significant in their support of nortriptyline over opioid therapy in chronic lumbar radiculopathy and the necessity to continue with large-scale and condition-specific studies to help tailor treatment approaches and maximize long-term outcomes in this prevalent and debilitating disease.

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