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A Prospective Observational Study On Pattern Of Drug Use For Neuropathic Pain In A Tertiary Hospital.

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Abstract

Neuropathic pain (NP) is a chronic condition caused by damage or disease affecting the somatosensory nervous system and may be associated with abnormal sensations or pain from normally non-painful stimuli. It is usually associated with impaired quality of life (QoL) which can potentially progress to a stage in which the patient is physically and psychologically distressed and also, the global burden of the disease conditions attributable to neuropathic pain are increasing over the past decade for reasons unknown. This study was conducted to determine the prescribing pattern for neuropathic pain and to assess the improvement and tolerability of the prescribed medications in neuropathic pain.100 consecutive subjects of either gender aged 18-65 years with newly diagnosed neuropathic pain, who attended Pain Super Specialty Outpatient Department at KIMS Hospital and Research Centre, Bangalore were assessed for the pattern of drugs prescribed and improvement of pain and overall health was estimated by using Short-Form McGILL Pain Questionnaire. The mean age group of study subjects was 44.68 years, majority of which, were between 31-50 years with more preponderance among male subjects. The response to combination therapy with 1st line drugs were better when compared to monotherapy in effectively managing all the dimensions of pain. The response to NP was higher in subjects with younger age group, good socio-economic status, familial support, good awareness and functional status, regular follow-up visits. Poor response was related to advancing age, lack of family/social support, multiple illnesses and medications and adverse effects.

Keywords: Neuropathic Pain, SF McGILL Pain Questionnaire, Pain clinic

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INTRODUCTION

Pain is a complex constellation of unpleasant, distressing sensory experiences provoked by actual or potential tissue damage that depends very strongly on one's biological, cognitive, emotional, financial, spiritual, cultural and educational influences [1] and is the most prevalent universal form of human distress posing a major challenging condition to modern medical therapies [2]. The reported prevalence of Neuropathic pain is high and ranges between 6.9 -17.9% of the general population in India and worldwide [3]. Pain with Neuropathic characteristics is more severe and is usually associated with worsening health in every measured dimension of life (significantly impacts on one's familial, social, economic and psychological well- being) [4]. Overall, this constitutes to a significant burden for the patient, the society and also the health care system in terms of impaired QoL and the cost of the therapies [5,6]. Because of its wide range of etiologies, it is difficult to diagnose and treat NP and only 40-60% of patients on treatment may attain partial relief of pain symptoms. Despite advances in the understanding of the neurobiology of pain signaling and its central processing, the clinical management to Neuropathic pain conditions remains insufficient, difficult and is aimed often at symptomatic relief rather than being curative [7]. In addition, medications used in the management of NP offer only moderate benefit with associated adverse side effects. As there is inconsistent data from the developing countries regarding the actual implementation of the therapeutic guidelines and also very few studies reported in Indian literature to assess the prevailing pattern of prescribing drugs in Neuropathic pain, there was a need for more systematic studies and hence this study was taken up. This study was conducted to determine the prescribing pattern for neuropathic pain and to assess the improvement and tolerability of the prescribed medications in neuropathic pain.

MATERIALS AND METHODS

This prospective, observational study was conducted on 100 subjects newly diagnosed with neuropathic pain attending Pain Super-Specialty Clinic on Out Patient Department basis at KIMS Hospital and Research Center Bangalore by the study investigator after coordinating and confirming the diagnosis with Pain specialist. Subjects were assessed for the pattern of drugs prescribed and overall health by using Short-Form McGill Pain Questionnaire after approval and clearance from the Institutional Ethics Committee (KIMS/IEC/D-10/11/2018). Study subjects were recruited by purposive sampling method from January 2019- June 2020 (18 months). Written informed consent was obtained from all the study subjects after fully explaining the study procedure to their satisfaction, in both English and vernacular language. Subjects fulfilling the inclusion criteria were included into the study i.e., Study subjects of either gender, aged 18-65 years, newly diagnosed with neuropathic pain, willingness to give written informed consent. Patients with the following conditions were excluded from the study i.e., Subjects with acute complications such as Cerebro-vascular events, injuries, fractures etc., patients with terminal illnesses i.e., malignancy, subjects with psychiatric illnesses, severe cognitive impairment, drug addicts and Pregnant and lactating women. A detailed present and past medical/surgical history, personal (including lifestyle), family and the drug history etc. was recorded from all the study subjects. The available medical records of the subjects were thoroughly scrutinized to obtain any relevant information about the previous and the ongoing drug therapy. Anonymity, confidentiality and professional secrecy was maintained for all the study subjects. The details of the current therapy for neuropathic pain including the number of drugs/ drug combinations used, therapeutic class, route of administration, dose, frequency and duration of administration etc. were documented. Any discontinuation or change in the medications and the reason for the same was documented. Subjects who were unable to attend OPD for follow-up were communicated through telephonic conversation and also followed up for subsequent visits. The improvement to the medications used for neuropathic pain was assessed by using **Short-Form McGill Pain Questionnaire**. The tolerability of the medications was assessed by patients reporting any side effects or by the history of drug related adverse events. Pain Questionnaire was administered on baseline visit (before starting the medications) and on follow-up visits (1st week and 6th week). The data collected was entered into Microsoft Excel data sheet and was analyzed using SPSS software 19.0 version. Categorical data was represented in the form of Frequencies and Proportions. Chi-square test was used as test of significance for Qualitative data. Student's paired t- test was used to analyze Quantitative data. All values are expressed using certain descriptive statistics namely mean, proportion, standard deviation, percentages. The results were also depicted in the form of tables and graphs. P value (Probability that the result is true) of < 0.05 was considered statistically significant after assuming all the rules of statistical tests.

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RESULTS AND DISCUSSION

Table 1 shows the age and gender distribution in the study subjects. The mean age for males was **44.72±12.48** years and for females was **44.58±11.28** years. Majority of the subjects (54%) were in the age group between 31-50 years, higher prevalence of NP was similarly reported in another study done by Thomas Eko Purwata [8]. Out of the total, 69.0% of the subjects were male and 31.0% were female. The relative male preponderance was also observed in other studies.[8] However, some studies have reported a relatively higher incidence of reporting of neuropathic pain in females than in males [9, 10]. **Figure-1** summarizes the **sensory characteristics of neuropathic pain** in the study subjects. The finding was similar to a study conducted by Daniel Bates et al. and Thomas Eko Purwata et al [8, 11]. **Table -2 summarizes the Ongoing therapy (**prescription pattern of drugs) from Baseline visit to Week 6. In the present study the most commonly prescribed drugs were NSAIDs among which Paracetamol, Aceclofenac, Diclofenac and Etricoxib were given in different combinations. Similar pattern was also observed in few other studies, substantiating the fact that simple analgesics, even though ineffective in the treatment of NP may help relieve a coexisting nociceptive component of pain, which may be considered at any stage of treatment [12-14]. Among the first line agents, most of the subjects received Pregabalin, followed by Amitriptyline, Nortriptyline and Gabapentin respectively as Monotherapy. Several other studies also reported that drugs most effective as monotherapy were consistent with our prescription pattern [12, 13, 15]. The dosing of Pregabalin was initiated at 75 mg/day, Amitriptyline at 10 mg/day and Gabapentin to 150-300 mg/day. Dosing preference in our study was also consistent with another study done by Kamble SV et al [16]. The dose / strength of Gabapentin and Pregabalin were increased over time in our study in subsequent weeks depending on the improvement and / or due to minimal improvement in response to pain which was consistent to another study with similar pattern of prescription [17]. Polytherapy with the combination of 2 or 3 drugs with TCA'S + Gabapentinoids was prescribed in patients who could not tolerate higher doses or who did not have sufficient pain relief with monotherapy. Studies conducted by Gilron et al. and Holbech et al. and Daniel Bates et al. inferred that the combination of TCA'S + Gabapentinoids showed significant effect than monotherapy [11, 18, 19]. Most frequently prescribed drugs in 2nd line of therapy were topical preparations, Lidocaine 5% gel/cream, Capsaicin 0.008-8 % cream. Studies done by Casale R et al., Meier T et al. and Irving GA et al. found a favorable response when the above topical preparation were used as add-ons treatment to oral therapy for localized NP conditions [20-22]. Also, a study conducted by Mick G, Correa Illanes indicated the use of topical lidocaine and capsaicin in post-surgery NP cases [23]. Among the 3rd line therapy, Strong Opioids like Fentanyl (0.5 mcg/kg/dose) i.v was administered to subjects on Post-operative Day-1. Studies conducted by Clarke H et al., indicated that post-operative administration of Gabapentinoids like Pregabalin and Gabapentin is associated with lower incidence of chronic postsurgical pain [24]. All the drugs were prescribed with greater caution by prescribers due to their association with high risk of adverse drug reactions and keeping age of patient in view. All the drugs were prescribed in the approved and recommended standard doses depending upon the nature and severity of the condition. **Table 3 displays** the improvement in pain symptoms to the prescribed medications evaluated by SF-MPQ and **Table 4 summarizes** the assessment of scores with Monotherapy with 1st line drugs measured by **Short Form McGill Pain Questionnaire (SF-MPQ).** Components evaluated were; Present Pain Intensity (PPI), Visual Analogue Scale (VAS), Affective Dimension (AD) and Sensory Dimension (SD) of pain and improvement was compared from Baseline to Week 6 visit. In our study, the difference in the mean total scores of PPI, SD, AD and VAS scales at Baseline visit and Week 6 of therapy was found to be statistically significantly ($p < 0.001$) indicating there was improvement in all the dimensions of pain. The assessment of SF-MPQ scores with Monotherapy of 1st line drugs showed that subjects on Amitriptyline responded better in relieving the SD and PPI component of Pain, whereas subjects on Gabapentin showed improvement in the SD component of pain more that the PPI and Nortriptyline and Pregabalin proved to be effective in improving the SD, PPI and AD components of pain with no positive outcome in VAS score. Among the Combination therapy, Amitriptyline + Gabapentin and Pregabalin + Nortriptyline was found to be significantly successful in alleviating pain in SD, AD and PPI components with minimal improvement in VAS scores. SF-MPQ, an extensive yet comprehensive questionnaire, employed in multi-dimensional assessment of pain experience, involving cognitive evaluation of pain, sensory component, and intensity of pain and gauging its emotional impact was forethoughtfully considered in the present study. Ours is the first study to extensively analyze all the above said components and there are no studies available to correlate our results. **Figure-2 summarizes the type of surgical interventions** that subjects underwent either due to poor response to medical therapy or who directly preferred surgery in the course of treatment due to unmanageable pain symptoms. Most of the subjects with surgical interventional therapy reported a major improvement in pain symptoms i.e., > 50% improvement in pain and better QoL in

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subsequent visits. **Table-5 summarizes drug related adverse reactions** in the study subjects, 32.0% subjects in the study presented with adverse drug reactions related to various classes of drugs, of which none were life threatening and mostly related to Gastrointestinal system and Central nervous system, implicated to TCA's most commonly. These findings were consistent with another study conducted by Subransu Sekhar et al [25]. Appropriate measures like reduction in the dose, titration of dose and rescue medications were considered and action taken to avert the ADRs.

Figure 1: NP Sensory Characteristics (N=100)

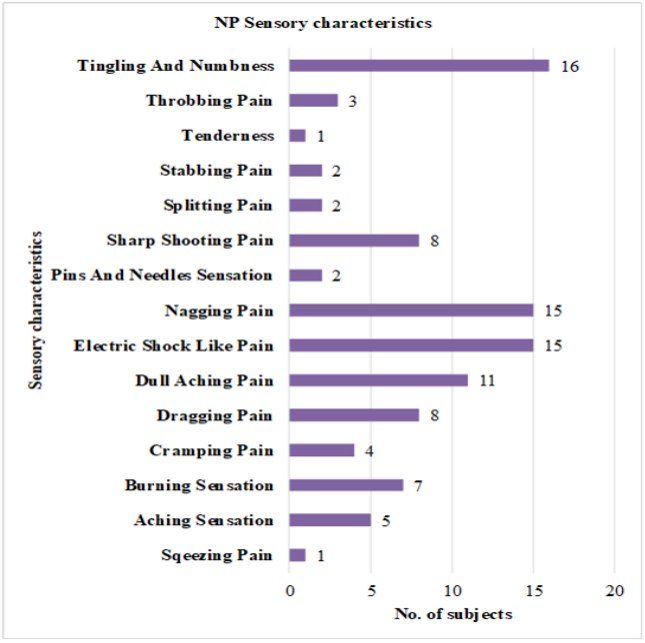
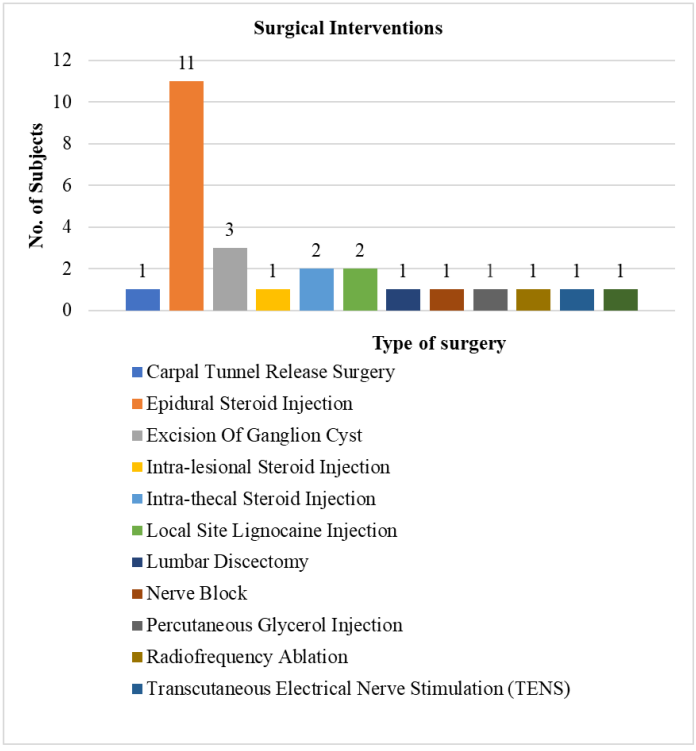


Figure 2: Surgical Interventions In The Course Of Therapy



Epidural Steroid Injection was preferred modality of surgery in 11 subjects of which, 8 had IVDP, 2 - Idiopathic coccydynia and 1- Failed Back Surgery Syndrome

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Table 1: Age And Gender Distribution (N=100)

Age (years)	Male - n (%)	Female - n (%)	Total - n (%)
18-30 years	9(75.0%)	3(25.0%)	12(100%)
31-50 years	36(66.7%)	18(33.3%)	54(100.0%)
51-65 years	24(70.6%)	10(29.4%)	34 (100%)
Total	69 (69.0%)	31(31.0%)	100 (100.0%)
Mean ± SD	44.72±12.48	44.58±11.28	44.68±12.071

Table 2: Ongoing NP Therapy- Week 0/ Baseline Visit - Week 6*

Group of drugs	Generic name	Week 0/ Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
NSAIDs	NSAIDS†	65	8	1	4	6	3	2
1st line Drugs								
TCA's	Amitriptyline	3	8	12	1	11	5	5
	Nortriptyline	2	6	10	6	10	10	10
Anticonvulsants	Pregabalin	19	49	45	34	34	28	28
	Gabapentin			1		2	1	1
TCA + Gabapentinoids	Nortriptyline+ Pregabalin	2	18	28	28	28	28	28
	Nortriptyline + Gabapentin	4	2	2	3	3	4	4
	Amitriptyline+ Gabapentin		15	15	15	9	9	9
2nd line drugs								
Weak Opioids	Tramadol		7	4	3	1		
	Tapentadol‡		7	4	2	2	1	
	Topical Lidocaine	7	11	20	20	43	43	22
	Topical Capsaicin			5	13	16	16	8
3rd line drugs								
Strong Opioids	Fentanyl§					2		

* According to International Association for Study of Pain Guidelines 2017 – NeuPSIG recommendations and others to assess NP in primary care – Indian expert panel modified recommendations (2018)
† most common NSAIDs combinations prescribed - aceclofenac 100 mg+ thiochochicoside 4 mg + paracetamol 325 mg followed by etricoxib 400mg+ thiocolchicoside 4 mg, ibuprofen+ paracetamol + caffeine
‡ Tapentadol –a novel weak μ receptor agonist and norepinephrine reuptake inhibitor, to relieve ongoing severe pain
§ Strong opioids – Inj.fentanyl restricted to intractable pain in (2) post- surgical cases on day 1 of surgery

Table 3: Short Form McGILL Pain Questionnaire - Assessment Of PPI, SD, AD And VAS Scales At Week 0 / Baseline Visit And Week 6 Of Therapy

COMPONENTS OF SF Mc GILL PAIN QUESTIONNAIRE		Minimum	Maximum	Mean	Std. Deviation	t	p value*
PRESENT PAIN INTENSITY	PPI Baseline	3	5	4.07	.582	37.489	<.001
	PPI Week 6	0	3	2.09	.561		
SENSORY DIMENSION	SD Baseline	2	27	14.70	3.592	25.641	<.001
	SD Week 6	0	15	7.39	2.600		
AFFECTIVE DIMENSION	AD Baseline	2	9	6.39	1.319	27.101	<.001
	AD Week 6	0	6	2.93	1.166		
VISUAL ANALOGUE SCALE	VAS Baseline	6	9	8.29	.721	40.403	<.001
	VAS Week 6	0	7	4.14	1.118		

* p= <0.001 is statistically significant with respect to components of SF McGILL Questionnaire to evaluate Present pain intensity (PPI), sensory dimension (SD), affective dimension (AD) and visual analogue scale (VAS) in relation to neuropathic pain. Paired t test was applied

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Table 4: Short Form McGILL Pain Questionnaire – Assessment Of Scales With Monotherapy With 1st Line Drugs At Week 0 / Baseline Visit And Week 6 Of Therapy

Component of SF Mc GILL Pain Questionnaire	Monotherapy	Mean	SD
PPI – Baseline	**Amitriptyline**	4.17	0.38
	Gabapentin	2.1	0.31
	Nortriptyline	4.3	0.48
	Pregabalin	4.2	0.63
PPI - Week 6	**Amitriptyline**	2	0.42
	Gabapentin	2.1	0.33
	Nortriptyline	2.2	0.42
	Pregabalin	2.18	0.59
SD – Baseline	**Amitriptyline**	16	2.69
	Gabapentin	15.67	2.08
	Nortriptyline	15	2.05
	Pregabalin	15.44	3.8
SD - Week 6	**Amitriptyline**	9.25	2.63
	Gabapentin	6.67	1.15
	Nortriptyline	7.9	1.85
	Pregabalin	7.44	2.49
AD – Baseline	**Amitriptyline**	6.83	0.71
	Gabapentin	6.67	0.667
	Nortriptyline	6.7	0.82
	Pregabalin	6.58	1.37
AD- Week 6	**Amitriptyline**	3.42	1.08
	Gabapentin	2.67	0.57
	Nortriptyline	3.3	0.82
	Pregabalin	2.8	1.19
VAS – Baseline	**Amitriptyline**	8.25	0.96
	Gabapentin	8.67	0.57
	Nortriptyline	8.3	0.48
	Pregabalin	8.24	0.77
VAS - Week 6	**Amitriptyline**	4.5	1.24
	Gabapentin	4.67	1.52
	Nortriptyline	4.3	0.335
	Pregabalin	3.98	1.02

Table 5: Drugs Related Adverse Reactions

Therapeutic class	Drugs prescribed	Side effects	n (%)
Tricyclic anti-depressants	**Amtriptyline**	constipation, dizziness	2(2.0)
	Nortriptyline	constipation	1(1.0)
Anti-convulsants	**Gabapentin**	dry mouth, redness of skin	2(2.0)
	Pregabalin	weakness, nausea, constipation	2(2.0)
Anti-parkinsons drug	**Levodopa+ carbidopa**	dry mouth, redness of skin	1(1.0)
Weak Opioids	**Topical capsaicin**	skin irritation, burning sensation, redness	7(7.0))
	Topical lidocaine	redness, itching, stinging sensation	4(4.0)
	Tramadol	nausea, vomiting	3(3.0)
	Tapentadol	nausea, headache	1(1.0)
Triptans	**Sumatriptan**	giddiness	1(1.0)
Corticosteroids	**Topical mometsone**	satellite lesions over skin	1(1.0)
Non-Opioid Analgesics	**NSAIDS**	gastritis	7(7.0)

CONCLUSIONS

The complexity of NP directed pharmacotherapy is yet a huge challenge, not only for the treating physicians but also the patients as a delineated effective therapeutic strategy is lacking. Our study intends to highlight the current therapeutic options in an OPD set-up and displays an actual, practical approach in

the effectual management of NP. Pharmacotherapy of NP in the present study, found that the response to Combination therapy with 1st line NP drugs Pregabalin + Nortriptyline and Gabapentin + Amitriptyline was better when compared to Monotherapy with Pregabalin, in effectively managing all the dimensions of pain i.e., SD, PPI, AD and VAS components. We also observed that the response to therapy was higher in subjects with younger age group, subjects with good awareness and who followed regular follow-up visits.

Strength of the study

This study is a first-of-a-kind study in our geographical region that allowed us to compare the use of different drugs targeted at Neuropathic Pain among the subjects diagnosed with varied NP conditions which may help in relooking, designing and developing a satisfactory regime to ensure uniformity and to harmonize the management of Neuropathic Pain.

Limitations

Short duration of over 6 weeks therapy may be insufficient to assess the precise response to pain.

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