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THE TREATMENT OF TRAMADOL WITH CREAM CONTAINING 3.33% DOXEPIN AND 0.05% CAPSAICIN ON THE OVERALL IMPROVEMENT OF QUALITY OF LIFE IN POST HERPETIC NEURALGIA PATIENTS

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ABSTRACT: The main purpose of the study was to examine the effect of QoL of PHN patients after the treatment of tramadol (50mg-200mg), with topical cream containing 3.33% doxepin and 0.05% capsaicin and clinical correlations with CYP2D6 polymorphism. The study was prospective, non-responders versus responders, conducted in 246 outpatients of PHN undergoing tramadol treatment for 4 weeks. Rescue analgesia given in the form of the topical cream consisting of the combination of 3.33% doxepin and 0.05% capsaicin to the affected areas of patients along with tramadol therapy. The QoL as per WHO QoL BREF Questionnaire was evaluated in all the study participants. All samples were analyzed for CYP2D6 (*2,*4 and *10) polymorphism using PCR-RFLP method. Although the QoL score showed magnitude of improvement was higher in responders as compared to non-responders. Insignificant interactions were found in all domains of QoL with respect to CYP2D6*2 and CYP2D6*4 polymorphism. However, a significant ($p<0.001$) interaction was found in CYP2D6*10 polymorphism with respect to environmental domain of QoL. A significant interaction was found with CYP2D6*10 allele with respect to environmental domain of QoL whereas lack of an association was found between CYP2D6*2 and *4 polymorphisms with QoL in PHN patients.

INTRODUCTION: Postherpetic neuralgia (PHN) a sequel of acute herpes zoster, may be associated with severe pain and sensory abnormalities that adversely affect a patient's QOL [1]. The effects of neuropathic pain on WHO QOLBREF are well known [2] and although clinical intuition would suggest that reducing neuropathic pain would improve these broader indices of well-being [3].

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Current evidence indicates that pain reduction is not always accompanied by the improvement in domains of QOL [4-6]. Such discrepancies could be explained by adverse treatment effects and/or concurrent chronic illness. The herpes zostar (HZ) and PHN can have a devastating effect on QOL, affecting physical, functional, psychological and social domains [7-14]. Patients have reduced functional ability, with many becoming inactive or housebound. QOL seems to be a particular problem in patients whose pain persists as PHN [8-10, 15-17]. Opioids such as tramadol are receiving greater consideration for the treatment of PHN type of pain [18-21]. Tramadol is a weak μ -opioid agonist that

inhibits the reuptake of norepinephrine and serotonin.

The results of randomized control trials in patients with PHN, painful DPN, painful polyneuropathies, PHN of different etiologies, and postamputation pain demonstrated that tramadol reduced pain and improved some aspects of health-related quality of life [18-20, 22-25]. But it has developed lots of drug-induced adverse side-effects such as somnolence, dizziness, local site reaction, headache, hypotension, nausea and vomiting [20, 26-30]. Tramadol is metabolized by the CYP2D6 enzyme [31, 20, 21]. The CYP2D6 polymorphism has been reported to significantly affect the pharmacokinetics of tramadol [32]. The variation in CYP2D6 activity may impact upon a patients pain level and may contribute to interindividual variation in their response to opioids [33,34,20,21]. This enzyme plays a vital role in deciding doses of tramadol in PHN patients.

Currently, in the Indian scenario, few studies has been published to establish the clinical utility of CYP2D6 genotyping determining in relation to tramadol therapy with respect to QOL. The present study was designed to impact on QOL treated with oral tramadol (50mg-200mg) and topical application of a cream consisting of the combination of 3.33% doxepin and 0.05% capsaicin. In addition, the relationship between the clinical efficacy of QOL and CYP2D6 (*2, *4 and *10) polymorphism in PHN patients repeated administration for 4 weeks between non-responders and responders.

MATERIAL AND METHODS:

Study design:

The study was a prospective, non-responders versus responders in the treatment of PHN and consisted of oral administration of tramadol (short acting) for 4 weeks with day 0 (baseline) considered as a baseline. A total of 270 patients were initially enrolled for the treatment of which 15 patients did not fit the inclusion criteria and 9 patients did not receive tramadol therapy, according to the study design. This prospective study included 246 patients (age group 20-80 years) of PHN patients reported with less than 50% pain relief were categorized as “non- responders” (72 males and 51 females), and patients reported with 50% pain relief with 14 days of tramadol were categorized as “responders” (76 males, and 47 females).

The present study was carried out with the help of pain clinic, Department of Anesthesiology, Department of Dermatology and all molecular biology analysis were carried out in Environmental Biochemistry and Molecular Biology Laboratory, Department of Biochemistry and Department of Pharmacology at University College of Medical Sciences (University of Delhi) & Guru Teg Bahadur Hospital, New Delhi- 110095, India during the period January 2009 to January 2012. Prior approval of Institutional Ethics Committee – Human Research was received and patients consent was taken in written in the printed Performa.

In our previous published papers have already discussed duration of oral tramadol treatment were 4 weeks from day 0 (inclusion visit) to day 28 (the day before the end visit), dose incrementation, inclusion criteria and exlusion criteria [19-21]. All the patients in group non-responders and responders who were not satisfied with recommended tramadol therapy, were provided rescue analgesia, which consisted of a cream containing 3.33% doxepin (a long acting tricyclic) and 0.05% capsaicin applied topically four times a day to affected areas continuously for 4 weeks. A record of pain management with rescue analgesia cream was maintained in the case record form of each patient**.**

Quality of Life (QOL) Scores:

The Quality of life of PHN patients was studied using WHO QOL-BREF questionnaire which consisted of four domains: Domain 1 (physical health); domain 2 (psychological health); domain 3 (social relationships); and domain 4 (environmental health). The above mentioned measurements were recorded on scheduled visits: inclusion visit on day 0, follow-up visits on day 14 and end visit on day 28 [35].

Genotyping:

5 ml of blood was taken out from each patient and collected in EDTA coated vials. DNA was extracted using commercially available DNA extraction kit (Hi- Media Mini preparation kit, Hi-Media Laboratories Pvt. Ltd. Mumbai, India). The

PCR-RFLP was done by digesting PCR product with their respective restriction enzyme that determines the polymorphic site depending on the presence or absence of its recognition sequence **(Table 1).** The UM, EM, IM and PM patients were categorized based on genetic analysis (PCR-RFLP Method) [20, 21, 36, 37].

TABLE 1: PRIMER SEQUENCES AND PCR-RFLP DETECTION METHOD USING THEIR RESPECTIVE ENZYMES

Sr. No.	Assay	Primer Sequences	Detection Method
1	*2	5'GCTGGGGCCTGAGACTT'3 5'GGCTATCACCAGGTGCTGGTGCT3'	PCR-RFLP using *Hhal*
2	*4	5' TGCCGCCTTCGCCAACCACT3' 5'TCGCCCTGCAGAGACTCCTC3'	PCR-RFLP using *BstNI*
3	*10	5'GTGCTGAGAGTGTCCTGCC3' 5' CACCCACCATCCATGTTTGC3'	PCR-RFLP using *HphI*

TABLE 2: MEAN WHOBREF –QOL SCORES AT VARIOUS TIME INTERVALS AMONG NON-RESPONDERS AND RESPONDERS WITH GENDERS

QoL Domains	Groups	Genders	Baseline	Second week	p-value	Forth week	p- value
Sociological Domain	NR (n=123)	Male (n=72)	49.22±5.444	56.71±9.132	p<0.001	60.04±9.890	p<0.001
		Female (n=51)	46.96±5.506	55.67±9.232		58.80±9.942	
		p-value	p=0.026	p=0.537		p=0.497	
	R (n=123)	Male (n=77)	57.29±6.565	64.22±6.445		72.12±7.397	
		Female (n=46)	56.20±6.510	63.63±6.939		72.22±7.823	
		p-value	p=0.425	p=0.715		p=0.857	
Physiological Domain	NR (n=123)	Male (n=72)	41.89±5.264	49.14±8.345	p=0.625	52.51±10.578	p<0.001
		Female (n=51)	41.25±5.713	48.37±9.099		50.39±9.733	
		p-value	p=0.533	p=0.635		p=0.253	
	R (n=123)	Male (n=77)	44.32±6.847	50.01±6.713		56.09±7.068	
		Female (n=46)	42.26±5.230	48.09±5.391		54.74±5.717	
		p-value	p=0.071	p=0.106		p=0.288	
Psychological Domain	NR (n=123)	Male (n=72)	44.61±5.266	52.31±8.735	p<0.001	53.79±10.289	p<0.001
		Female (n=51)	43.88±5.512	51.00±8.514		53.41±10.306	
		p-value	p=0.464	p=0.409		p=0.841	
	R (n=123)	Male (n=77)	51.17±6.590	57.27±6.227		63.94±6.804	
		Female (n=46)	49.39±6.323	56.02±5.998		63.67±6.922	
		p-value	p=0.169	P=0.319		P=0.904	
Environmental Domain	NR (n=123)	Male (n=72)	53.08±5.109	60.82±9.155	p<0.001	64.68±8.968	p<0.001
		Female (n=51)	51.45±6.287	59.39±8.994		64.29±9.377	
		p-value	p=0.129	p=0.391		p=0.819	
	R (n=123)	Male (n=77)	64.18±6.920	72.23±7.312		80.44±8.416	
		Female (n=46)	63.87±7.664	72.04±7.665		81.72±8.482	
		p -value	p=0.924	p=0.965		p=0.367	

N- Non-responders, R-responders; All values are expressed as numbers and mean ± standard deviation

Statistical analysis:

The unpaired t-test was used to compare all mean differences between the two groups on day 14. One-factor repeated measure analysis of variance (ANOVA) was used to compare the means within the group at different time intervals with Bonferroni adjustment (α=0.05) in both the groups separately. Analysis of covariance was used to compare QOL in responders and non-responders after adjusting for baseline values, age and sex. Fisher's exact test was carried out, to find an association between sex and metabolizers.

Two-factor repeated measure ANOVA was used to compare QOL within, and among metabolizers with Bonferroni adjustment (α= 0.05) in both groups.Three factor repeated measure ANOVA was applied taking time as a repeated factor, group and metabolizer as a fix factor. We report multivariate (Wilks' Lambda test) analysis since the Mauchly's test of Sphericity was found to significant in all QOL variables.

RESULTS:

Patient data:

Both the groups (123 non- responders and 123 responders) of PHN patients were comparable with respect to age and gender ratio. The total gender means in non-responders were 53.33±12.47 (males 53.94±13.24; females 52.45±11.35) and total mean in responders were 52.23±12.08 (males 53.50±12.72; females 50.17±10.79.33). The mean age (in years) of patients in non-responders were 53.33±12.47 and in responders were 52.23±12.08. The mean weight (in kg) in group, non-responders were 56.28±10.95 and in responders were 51.23±11.45. The mean duration of disease (in months) of patients in non-responders were 4.79±3.48 and in responders were 4.23±4.47. The gender ratio (Male: Female) in non-responders and responders were 72:51 and 76:47 respectively.

WHO QOL BREF Scores Clinically:

In the four domains of quality of life, there was no statistical difference in the groups at baseline (p>0.05). There was a significant improvement in all the domains of quality of life in responders as compared to non-responders at the end of 2nd week and 4th week of treatment after adjusting their baseline values **(Figure 1).**

WHOQOL BREF Scores with respect to Genders:

In all the four domains of QOL, there was no statistical significant difference in the genders at baseline, 2nd and 4th week (p>0.05). At the end of 2nd week, all domains except physiological domain was statistically significant between the groups (p<0.05). The improvement in all the domains of QOL was statistically significant in responders as compared to non-responders at the end of 4th week of treatment **(Table 2).**

WHO QOL BREF with respect to CYP2D6 Polymorphism:

In CYP2D6*2 allele, PMs in non-responders group were found higher in numbers than responders group whereas high numbers of EMs were found in responders than non-responders. Clinically overall there was significant (p<0.001) change observed in all domains of QOL. Three way repeated measure ANOVA was carried out to find out interactions between time, group and metabolize using Wilks's Lambda for repeated measures analysis. No significant interaction was found in CYP2D6*2 allele in all domains of QOL.

In CYP2D6*4 allele, in non-responders no UMs was observed whereas in responders eight patients were found. Clinically, significant (p<0.001) improvement observed in all domains of QOL. The multivariate analysis with CYP2D6*4 allele showed no significant interaction in all domains of QOL.

In CYP2D6*10 allele, overall significant change in QOL scores was observed with respect to time (p<0.001) in all domains. Since the Mauchly's Test of Sphericity was found to be significant, we report the multivariate test for repeated measures analysis. The multivariate analysis using Wilks's Lambda test insignificant interaction was found between group and metabolizers (p=0.279) also among time, group and metabolizers (p=0.282) whereas significant interaction was found between time and group (p=0.010) in sociological domain. In psychological domain, we observed significant interaction with group (p=0.033) but in the physiological domain no interaction was found to be significant. Interaction between time, group and

metabolizers (p=0.048) and between time and metabolizers (p<0.001) were found to be significant in environmental domain **(Table 3-5).**

TABLE 3: WHO-BREF (QoL) SCORES AND CYP2D6*2 POLYMORPHISM

WHO-BREF (QoL)	Group	Metabolizers	Baseline	2nd Week	4th Week	P value
Sociological Domain	NR	UM(n=4)	48.50±9.037	47.00±6.976	61.50±12.369	p=0.001[a]
		EM(n=56)	48.95±5.913	57.46±9.177	60.16 ±10.160	p=0.217[b]
		IM(n=30)	47.30±5.402	56.53±8.500	58.20±10.226	p=0.805[c]
		PM(n=33)	48.03±4.687	55.15±9.477	59.42±9.138	p=0.448[d]
		Total (n=123)	48.28±5.561	56.28±9.150	59.53±9.890	
	R	UM(n=3)	63.67±8.963	71.00±9.644	76.33±8.505	
		EM(n=65)	56.95±6.138	64.06±6.324	72.09 ±7.414	
		IM(n=41)	56.66±6.829	63.49±6.896	72.32±7.738	
		PM(n=14)	55.71±6.911	63.71±6.366	71.07±7.770	
		Total (n=123)	56.88±6.539	64.00±6.612	72.15±7.527	p=0.001[a]
Physiological Domain	NR	UM(n=4)	42.50±10.247	44.75±11.673	52.50±10.599	p=0.531[b]
		EM(n=56)	41.95±5.405	49.45±8.697	51.66±10.277	p=0.932[c]
		IM(n=30)	41.57±6.151	49.50±8.480	51.60±11.205	p=0.968[d]
		PM(n=33)	41.03±4.224	47.64±8.477	51.52±9.722	
		Total (n=123)	41.63±5.440	48.82±8.638	51.63±10.249	
	R	UM(n=3)	43.00±4.583	47.33±3.055	53.33±4.509	
		EM(n=65)	43.75±6.070	49.46±6.049	56.02±6.606	
		IM(n=41)	43.56±6.823	49.34±6.905	55.27±6.786	
		PM(n=14)	42.71±7.021	48.79±6.530	55.00±6.839	
		Total (n=123)	43.55±6.348	49.29±6.298	55.59±6.603	
Psychological Domain	NR	UM(n=4)	44.75±10.046	44.50±6.856	55.50±10.630	p=0.001[a]
		EM(n=56)	44.61±5.287	52.32±8.458	54.21±10.350	p=0.288[b]
		IM(n=30)	43.90±5.671	52.80±8.930	52.97±11.059	p=0.843[c]
		PM(n=33)	44.12±4.742	50.76±8.678	53.03±9.681	p=0.592[d]
		Total (n=123)	44.31±5.359	51.76±8.633	53.63±10.255	
	R	UM(n=3)	53.00±5.568	59.33±3.215	63.00±2.646	
		EM(n=65)	50.77±6.446	56.78±5.920	63.78±6.800	
		IM(n=41)	50.27±6.793	56.83±6.752	64.20±7.184	
		PM(n=14)	49.43±6.688	56.29±6.207	63.21±6.941	
		Total (n=123)	50.50±6.523	56.80±6.148	63.84±6.821	
Environmental Domain	NR	UM(n=4)	52.75±7.41	54.00±7.394	65.25±8.694	p=0.001[a]
		EM(n=56)	53.20±6.07	60.71±9.376	65.48±8.737	p=0.126[b]
		IM(n=30)	52.17±5.93	61.17±8.346	63.23±10.251	p=0.722[c]
		PM(n=33)	51.24±4.37	59.30±9.376	63.97±8.883	p=0.709[d]
		Total (n=123)	52.41±5.66	60.23±9.079	64.52±9.104	
	R	UM(n=3)	74..33±12.70	81.00±8.660	87.67±7.234	
		EM(n=65)	63.98±6.88	72.12±7.116	81.29±8.591	
		IM(n=41)	63.85±7.04	71.61±7.733	80.54±8.491	
		PM(n=14)	62.86±6.84	72.07±7.227	78.86±7.564	
		Total (n=123)	64.07±7.17	72.16±7.416	80.92±8.429	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders; a-interaction with time; b-interaction with group (non-responders versus responders); c- interaction with metabolizers and group; d- interaction with group (non-responders versus responders), metabolizers and time; Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test.

DISCUSSION: In the management of PHN, there is no better therapy or intervention approach. With most forms of neuropathic pain, the treatment response is best described as inconsistent. The chronic neuropathic pain present in the patients of PHN is mainly due to peripheral and central sensitization [38, 39]. The primary aim of this study was to find tramadol (50-200mg) with a topical cream containing 3.33% doxepin and 0.05% capsaicin administered over 4 weeks in patients suffering from PHN was improved on quality of life domains. The secondary aim of this study was clinically efficacy of QOL relationship with CYP2D6 *2, *4 and *10 polymorphism. The adoption of the single entity therapy approach in the present study results significantly improvement

quality of life which was evidenced by the significant ($p<0.001$) increase in scores of physical, psychological, social relationships, and environmental domains of WHO QOL BREF questionnaire in post herpetic neuralgia patients.

However, no statistical difference was found between responders and non-responders at baseline and gender wise no association was observed with all QOL domains. It also confirmed that the previous preliminary work reported orally administered tramadol (50–200 mg) over 4 weeks is safe and improved quality of life in PHN patients (32 non responders and 68 responders) [19].

TABLE 4: WHO-BREF (QoL) SCORES AND CYP2D6*4 POLYMORPHISM

WHO-BREF (QoL)	Group	Metabolizers	Baseline	2nd Week	4th Week	P value
Sociological Domain	NR	UM(n=0)	-	-	-	p=0.001[a]
		EM(n=77)	47.71±5.753	56.82±8.874	59.51±10.178	p=0.202[b]
		IM(n=34)	49.97±4.758	57.15±8.982	59.76±9.863	p=0.966[c]
		PM(n=12)	46.00±4.405	48.73±8.684	57.82±8.122	p=0.313[d]
		Total (n=123)	48.19±5.481	56.18±9.125	59.43±9.865	
	R	UM(n=8)	55.38±5.290	63.62±3.926	72.38±6.567	
		EM(n=92)	56.86±6.791	63.75±6.931	71.63±7.987	
		IM(n=21)	57.95±5.844	65.57±6.046	74.90±5.078	
		PM(n=2)	52.50±7.778	60.50±6.364	66.50±6.364	
		Total (n=123)	56.88±6.539	64.00±6.612	72.15±7.527	p=0.001[a]
Physiological Domain	NR	UM(n=0)	-	-	-	p=0.335[b]
		EM(n=77)	41.08±5.370	49.49±8.570	52.05±10.222	p=0.666[c]
		IM(n=34)	42.88±5.912	50.06±7.707	50.97±10.556	p=0.143[d]
		PM(n=12)	41.55±4.344	40.18±8.072	50.00±10.334	
		Total (n=123)	41.62±5.463	48.81±8.672	51.57±10.263	
	R	UM(n=8)	40.00±5.451	46.12±4.454	53.5±05.071	
		EM(n=92)	43.99±6.133	49.58±6.245	55.5±36.734	
		IM(n=21)	43.38±7.145	49.57±7.040	56.9±06.700	
		PM(n=2)	39.501±0.607	46.00±7.071	52.50±4.950	
		Total (n=123)	43.55±6.348	49.29±6.298	55.59±6.603	
Psychological Domain	NR	UM(n=0)	-	-	-	p=0.001[a]
		EM(n=77)	43.62±4.894	52.19±8.505	53.56±10.323	p=0.137[b]
		IM(n=34)	45.71±6.023	52.68±8.171	53.91±10.743	p=0.917[c]
		PM(n=12)	43.55±4.367	44.82±8.171	52.00±8.270	p=0.351[d]
		Total (n=123)	44.20±5.234	51.66±8.596	53.52±10.214	
	R	UM(n=8)	47.50±4.811	53.62±4.689	61.75±5.574	
		EM(n=92)	50.75±6.609	56.96±6.154	63.61±7.007	
		IM(n=21)	51.00±6.550	57.62±6.515	66.056.273	
		PM(n=2)	46.00±8.485	54.00±7.071	59.50±4.950	
		Total (n=123)	50.50±6.523	56.80±6.148	63.84±6.821	
Environmental Domain	NR	UM(n=0)	-	-	-	p=0.001[a]
		EM(n=77)	51.96±5.818	60.65±8.596	64.64±8.887	p=0.086[b]
		IM(n=34)	54.03±5.208	61.18±9.498	64.26±10.264	p=0.890[c]
		PM(n=12)	49.82±4.535	53.45±9.048	63.45±6.962	p=0.335[d]
		Total (n=123)	52.34±5.642	60.15±9.072	64.43±9.081	
	R	UM(n=8)	63.88±5.693	72.88±6.512	83.88±7.453	
		EM(n=92)	63.66±7.520	71.54±7.781	79.87±8.882	
		IM(n=21)	66.33±6.011	75.00±5.666	84.81±5.056	
		PM(n=2)	59.50±4.950	68.00±4.243	76.50±7.778	
		Total (n=123)	64.07±7.178	72.16±7.416	80.92±8.429	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders; a-interaction with time; b-interaction with group (non-responders versus responders); c- interaction with metabolizers and group; d- interaction with group (non-responders versus responders), metabolizers and time; Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test.

TABLE 5: WHO-BREF (QoL) and CYP2D6*10 POLYMORPHISM

WHO-BREF (QoL)	Group	Metabolizers	Baseline	2nd Week	4th Week	P value
Sociological Domain	NR	EM(n=81)	52.68±5.935	55.75±9.481	59.06±10.053	p=0.001[a] p=0.010[b] p=0.279[c] p=0.282[d]
		IM(n=30)	51.90±4.664	58.50±8.170	62.13±9.126	
		PM(n=12)	51.83±6.351	54.25±8.884	56.17±9.889	
		Total (n=123)	52.41±5.661	56.28±9.150	59.53±9.890	
	R	EM(n=88)	64.44±7.606	64.40±6.669	72.26±7.672	
		IM(n=30)	63.57±6.235	63.33±6.890	72.17±7.702	
		PM(n=5)	60.40±3.050	61.00±2.000	70.20±3.564	
		Total (n=123)	64.07±7.178	64.00±6.612	72.15±7.527	
Psychological Domain	NR	EM(n=81)	44.74±5.698	51.42±8.913	52.78±10.705	p=0.001[a] p=0.033[b] p=0.351[c] p=0.168[d]
		IM(n=30)	43.10±3.595	53.23±7.815	56.47±8.737	
		PM(n=12)	44.42±6.557	50.42±8.888	52.33±10.129	
		Total (n=123)	44.31±5.359	51.76±8.633	53.63±10.255	
	R	EM(n=88)	50.86±6.601	57.23±6.346	64.19±7.043	
		IM(n=30)	50.20±6.467	56.13±5.835	63.30±6.603	
		PM(n=5)	46.00±4.243	53.40±2.881	60.80±2.775	
		Total (n=123)	50.50±6.523	56.80±6.148	63.84±6.821	
Physiological Domain	NR	UM(n=)	-	-	-	p=0.001[a] p=0.166[b] p=0.304[c] p=0.228[d]
		EM(n=81)	42.02±5.552	48.48±8.850	50.44±10.320	
		IM(n=30)	40.87±4.158	49.90±8.130	55.00±9.541	
		PM(n=12)	40.83±7.420	48.42±8.908	51.25±10.437	
		Total (n=123)	41.63±5.440	48.82±8.638	51.63±10.249	
	R	EM(n=88)	43.97±6.396	49.81±6.409	56.00±6.638	
		IM(n=30)	43.13±6.235	48.53±6.078	55.00±6.843	
		PM(n=5)	38.80±4.919	44.80±3.633	51.80±2.775	
		Total (n=123)	43.55±6.348	49.29±6.298	55.59±6.603	
Environmental Domain	NR	EM(n=81)	52.68±5.935	59.52±9.553	64.30±9.302	p=0.001[a] p=0.001[b] p=0.378[c] p=0.048[d]
		IM(n=30)	51.90±4.664	63.03±7.425	66.83±7.349	
		PM(n=12)	51.83±6.351	58.00±8.634	60.25±10.610	
		Total (n=123)	52.41±5.661	60.23±9.079	64.52±9.104	
	R	EM(n=88)	64.44±7.606	72.61±7.677	81.07±8.627	
		IM(n=30)	63.57±6.235	71.27±7.172	80.30±8.384	
		PM(n=5)	60.40±3.050	69.60±1.949	82.00±5.788	
		Total (n=123)	58.24±8.702	72.16±7.416	80.92±8.429	

All values are expressed in means and standard deviation; EM- Extensive metabolizers; IM- Intermediate Metabolizers; PM- Poor metabolizers; NR- non-responders and R-responders;a-interaction with time;b-interaction with group (non-responders versus responders);c-interaction with metabolizers and group;d- interaction with group (non-responders versus responders), metabolizers and time;Analysis was performed by Three Way Repeated measure ANOVA using Wilks's Lambda test.

In addition, WHO QOL-BREF scores showed no significant ($P > 0.05$) difference was observed in all 4 domains of QOL in non responders and responders at day 0(baseline). Moreover, a significant ($P < 0.001$) improvement was observed in QOL scores in all 4 domains after weeks 2nd and 4th in both groups with respect to their respective baseline values only. A significant difference was observed between non responders and responders at days 14 and 28 in only 2 domains (ie, social and physical domains) [20, 21].

The single-entity therapy medications have consistently improved QOL of subjects. In the patients with PHN, the opioids [13, 40, 5] have all produced statistically significant improvements in QOL relative to placebo. Hence this study confirms that orally administered tramadol over 4 weeks is safe in PHN patients.

Two open-label, nonrandomized, prospective studies [41, 42] showed that the lidocaine patch 5% (applied over the area of maximal pain) reduced the intensity of moderate-to-severe PHN pain and improved quality of life [41].

The treatment of NP (neuropathic pain) is challenging and compared with non neuropathic chronic pain patients. Patients with NP seem to have higher average pain scores and lower HRQOL

(even after adjusting for pain scores); to require more medications; and to report less pain relief with treatment [43, 44]. The neuropathic pain has been shown to impair patients' overall health-related QOL, including important aspects of physical and emotional functioning such as mobility and ability to work [8, 45, 46, 47, 48]. It also generates substantial costs to society [48-51]. Albert et al. [39] observed that the QOL of PHN patients is affected not only because of the excruciating pain, but also because of the indirect effect of chronic fatigue, compromised mobility, and diminished social networking. Patients with PHN report difficulty in concentrating.

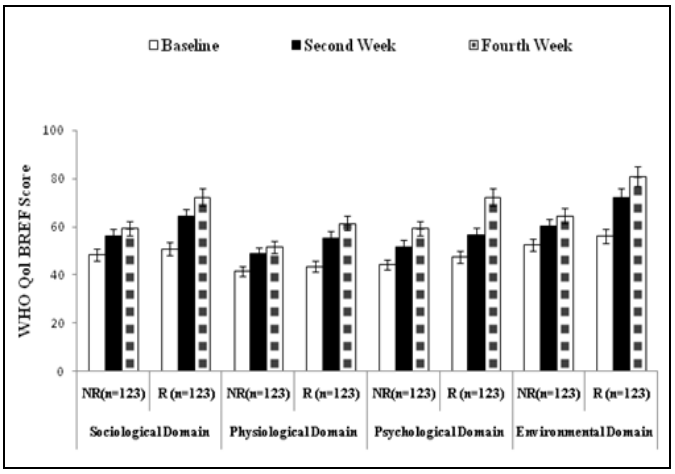

FIG.1: WHO QUALITY OF LIFE- BRIEF QUESTION ARE SCORES IN FOUR DIFFERENT DOMAINS AT DIFFERENT TIME INTERVALS AMONG NONRESPONDERS AND RESPONDERS

They also fear recurrences of PHN symptoms and may experience changes in their emotional roles within key relationship. Patients experienced average pain of moderate intensity most of the time. Psycho-social variables such as measures of role functioning, personality disorder symptoms and disease conviction may be additional risk factors for PHN [13]. This chronic complication remains refractory to pharmacological treatments and prevention strategies [53]. PHN causes a loss of physical function, with patients experiencing fatigue, anorexia, weight loss, reduced mobility, physical inactivity, sleep disturbance and reductions in overall health [8, 15]. It may also affect patients psychological well being [8].

The psychosocial scores improve in patients who fully recover from the acute symptoms of HZ, but they remain low in patients who develop PHN [54]. The results of a postal survey in the USA used pain and QOL questionnaire, as showing that patients commonly reported moderate and severe levels of pain despite receiving analgesic agents [8]. The increased awareness of the burden of HZ and PHN on QOL may lead to improve strategies for prevention and management. The goal of second objective was to provide data about the impact of differences in genetically polymorphic metabolic patterns of the CYP2D6 system and their role and relationship on QOL 4 week tramadol treated PHN patients.

In this study, QOL as per the WHO QOL BREF questionnaire was evaluated in all the study participants comparison with CYP2D6 polymorphism. The QOL status of PHN patients was not significantly associated with time, metabolizers and group. Insignificant interactions were found in all domains of QOL with respect to CYP2D6*2 and CYP2D6*4 alleles. However, a significant ($p<0.001$) interaction was found in CYP2D6*10 allele with respect to time, group and metabolizers in environmental domain of QOL.

To our knowledge, based on the genetic model of the CYP2D6 polymorphism, in present literature, it is hard to find QOL correlating with CYP2D6 genotypes of PHN patients.

In our previous study [20] reported relationship between the CYP2D6*4 polymorphism, interindividual differences in CYP2D6 activity and QOL in PHN patients receiving tramadol. The QOL scores obtained from 158 patients (78 non responders and 80 responders) who were treated with tramadol. In addition, the psychological, sociological and environmental domains demonstrated a significant ($p < 0.05$) association compared with the CYP2D6*4 allele using two-factor repeated measure analysis ANOVA. There was no association found between the physiological domain and the CYP2D6*4 allele ($p > 0.05$).

The impact of the CYP2D6 genotypes and phenotypes on tramadol pharmacokinetics among acute pain patients were reported by Gan et al [29]. However, genotyping for CYP2D6*10 alone is not sufficient to explain tramadol disposition. When

larger number of malysian patients were recruited (n=138), Gan et al[29] found that relationship with pharmacokinetic-pharmacodynamic of tramadol.

They observed that high frequency of the CYP2D6*10 allele found Malaysian patients. The UM and EM groups had 2.6- and 1.3-times faster CL, respectively, than the IM. CL was 16, 18, 23, and 42 L/h while mean half-lives were 7.1, 6.8, 5.6, and 3.8 hours among the IM, EM1, EM2, and UM groups, respectively. However, the analgesic effects of tramadol were not measured adequately among the postoperative patients to establish its full therapeutic effects. There were significant differences in the adverse-effect profiles amongst the various genotype groups with the IMs group experiencing more adverse effects than the EMs and the EMs having more adverse effects than the UMs.

Three studies reported the impact of the CYP2D6 genotypes and phenotypes on tramadol analgesia among acute pain patients [55-57]. Stamer et al [55] investigated whether the CYP2D6 genotype influenced the post-operative analgesia of tramadol (via IV bolus 100mg), PCA (combination of tramadol 20 mg/ml, dipyrone 200mg/ml and metoclopramide 0.4 mg/ml) and continuous infusion). They compared the pain scores analgesic consumption and need for resuce medication between heterozygous EMs and PMs. The hypothesis of reduced analgesic efficacy of tramadol in PMs was confirmed where they found that a well characterized group of PMs differed significantly in their response compared with the large group of patients carried at least one wild type of allele.

The perecentage of non responders was significantly higher in the PM (46.7%) compared with the EM (21.6%). Wang et al [56] found that the CYP2D6*10 allele has significant impact on analgesia with tramadol (10 mg/ml tramadol plus 0.3 mg/ml metoclopramide combination) via patient –controlled analgesia (PCA) in a Chinese population. Slanar et al [57] evaluated tramadol efficacy in relation to CYP2D6 and MDRI polymorphism. Tramadol was given on demand intramuscularly at a dosage of 100mg for one application or orally 50 mg in immediate relase formulation.

They found that the mean pain difference was lowest in the UM and highest in the PM. The pain difference varied significantly among the CYP2D6 subgroups with significant difference between homEMvs hetEM, hom EMvs. PM, and UMvs. PM subgroups. Finally they concluded that CYP2D6 plays a significant role in tramadol analgesic efficacy.

Zalina and Ismail [58], reviewed of the literature was the evidence on how CYP2D6 polymorphisms might influence pain sensititvity and clinical response to codaine and tramadol. Codaine and tramadol that are bioactivated by CYP2D6, PMs may cause no metabolite formation and lead to inadequate analgesia. Conversely, UMs may experience quicker analgesic effects but be prone to higher mu-opioid related toxicity. The literature suggested the potential uselfulness of the determination of CYP2D6 polymorphisms in elucidating serious adverse events and in preventing subsequent inappropriate selection or doses of codeine and tramadol.

CONCLUSION: Tramadol (50mg -200mg) with topical application of a cream consisting of the combination of 3.33% doxepin and 0.05% capsaicin treated PHN patients experienced maximum pain relief and improved quality of life in PHN patients. The CYP2D6*2 and *4 polymorphism may not be a predictor of treatment outcome of patients with QOL of PHN receiving tramadol.

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