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Treatment Analysis of Patients Followed up With Postherpetic Neuralgia in Nothern Cyprus

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ABSTRACT

Background: Postherpetic neuralgia (PHN) is a frequent complication of herpes zoster (HZ). Treatment of this chronic pain syndrome and results are often not clear. Tricyclic antidepressants, gabapentinoids and potent opioids are first-line treatments and are highly effective, but their use is limited due to adverse effects that may occur in elderly patients with significant medical comorbidities or interaction due to multiple drug use. There are no head-to-head comparisons of non medical treatments. Dry needling appears comparable to conventional physical therapy for treating PHN. **Objective:** Our aim is to determine the incidence of PHN in our population and to compare the treatments in patients with postherpetic neuralgia. **Methods:** A search for HZ and PHN was conducted in a general practice research database, comprising 2 general practices (dermatologist and physiatrist) and representing 5600 people. We analyzed a retrospective 37 case with PNH of 170 herpes zoster patient admmited to the dermatology and physical therapy and rehabilitation outpatient clinic between October 2018 and October 2020. Dry needling and physical therapy methods applied in addition to medical treatment in PHN treatment were compared. **Results:** In patients with postherpetic neuralgia, both dry needling therapy group and physical therapy group LANSS scores decreased significantly in the first week and in the third week compared to baseline. Dry needling therapy group has also similar results in VAS scores in the first and third week. But in physical therapy group, the VAS score did not show a significant decrease in the first week compared to the baseline, but it decreased significantly in the third week. **Conclusion:** PHN is a complex, difficult to treat and severe neuropathic pain that affects patients' daily function and quality of life. Various agents and methods are available to relieve the symptoms of PHN. This study shows as both physical therapy and dry needling therapy are effective treatment for postherpetic nevralgia..

Keywords: Postherpetic nevralgia, physical therapy, dry needling.

1. BACKGROUND

Reactivation of varicella zoster virus which is the causative agent of chickenpox, yields herpes zoster (HZ) or shingles causes a painful, blistering skin rash.

The most common complication of HZ is postherpetic nevralgia, and it is defined as pain in a dermatomal distribution that is continued for at least 30-90 days after the rash. These patients often complain of persistent or spontaneous burning or describe pain and sharp or burning pain with light touch of the affected skin (dynamic mechanical allodynia) (Baron 1996). The mechanism of pathophysiology underlying the ongoing symptoms is unclear. Postherpetic neuralgia is seen in 20% of patients with herpes zoster and 80% of cases occur in patients 50 years or older (1-3). Postherpetic neuralgia develops secondary to inflammation in the nerve (1).Older age, severe prodrome or rash, severe acute zoster pain, ophthalmic involvement, immunosuppression, and chronic conditions such as diabetes mellitus and lupus are risk factors (2, 4).

The treatment management of PHN is complex and difficult due to the lack of a definitive treatment algorithm for patients with PHN. In recent years, there have been a number of published guidelines recommended for the management of neuropathic pain in general. These guidelines equally recommend tricyclic antidepressants (TCAs), and anticonvulsants as first-

line treatment options for the treatment of neuropathic pain. In primary or secondary recommendations, depending on the source, topical treatments (eg topical lidocaine) are in the foreground (5). Although the response rates are less than ideal and these medications are often fraught with intolerable side effects in older adults. Despite this a substantial number of older adults continue to suffer with refractory pain (6).Due to the often treatment-resistant nature of PHN, we present this study not only for sensory neuropathy, but in the hope of encouraging physicians to think broadly about older adult patients with PHN. This encourage researchers to develop and test the effectiveness of wider treatment programs such as physical therapy and dry needling program. The aim of this study was to define retrospectively the presentation and characteristic features of PHN and to compare the outcome of treatments.

2. OBJECTIVE

The aim of this study was to define retrospectively the presentation and characteristic features of PHN and to compare the outcome of treatments. In this analysis included only patients who began treatment 1 or more 3 months after HZ that are considered to have had PHN.

3. PATIENTS AND SETTING

Data were collected from the General Practice Research Database. All HZ patients diagnosed between 30.10.2018 and 31.10.2020 were identified by search- ing the database for the ICPC code B0.09, B0.01 (HZ) and for free text ('zoster'). Patients admitted to hospital and diagnosed with these ICD codes were included in the study. During the study, two authors, one of whom was a dermatologist and the other a physiatrist, made general practices and examined the full-text medical records of the selected patients. The duration of pain was recorded for each HZ patient. In this study, PHN was defined as any pain that persists for at least 1 month after the diagnosis of HZ. Patients with still pain 3 months after the diagnosis of HZ were also recorded. Patients' age, gender, localization, presence of prodrome pain, time between symptom and presentation, co-morbidity pain severity, medication for HZ (systemic local) were questioned. Relevant co-morbidity included diabetes mellitus (DM), Hypertension, cardiovascular disease, HİV and Malignancy, at the time of HZ diagnosis.

All patients undergo physical examination and had answered pain questionnaires (VAS and LANNS). 37 patients suffering from postherpetic nevralgia treated with dry needling (N=18) therapy/conventional physical therapy (N=19). Additionally during this time, all patients were using pregabalin (75-150mg/daily). Dry needling was done to trigger pain point and perineural stimulation during three weeks total 10 sessions. We use 25x0.25mm gauge needle for dry needling. Depending on the number of active trigger point, 4-5 needles were applied to the patients at intervals of 5-10 minutes. Conventional physical therapy program consist of TENS(transcutaneuos electrical nevre stimulation) 70-100Hz frequency, duration of 20 minutes, therapeutic ultrasound (1watt/cm2) 5-8 minutes and home-exercise program (stretching and strengthing effected muscles). Physiotherapy program consists of 15 sessions, in three weeks. After three weeks of treatment we again performed physical examination and questionnaries for patient in each visit.

Statistical analysis

All analyzes were performed on SPSS v15 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to determine whether variables are normally distributed. Number, percentage, mean, standard deviation (SD), median, minimum and maximum values were used in the evaluation of descriptive data. Categorical data were compared using Chi-square test and continuous data were compared with Student's t or Mann Whitney U tests according to the distribution. Univariate and Multivariate Logistic Regression Analysis was performed to determine risk factors for postherpetic neuralgia and sequelae after Herpes Zoster

	Post-infectious sequelae		p
	Absent	Present	
Age, median (min-max)	43.0 (5.0-88.0)	69.0 (20.0-84.0)	<0.001
Duration of HZ infection (day), median (min-max)	3.0 (1.0-22.0)	14.0 (1.0-25.0)	<0.001
VAS-baseline,median (min-max)	6.0 (0.0-10.0)	9.0 (3.0-10.0)	<0.001
LANSS-baseline,median (min-max)	10.0 (0.0-24.0)	24.0 (10.0-24.0)	<0.001
Age groups, n (%)			
<18	4 (3.2)	0 (0.0)	0.574
⩾18	121 (96.8)	45 (100.0)	
Gender, n (%)			
Male	50 (40.0)	26 (57.8)	0.040
Female	75 (60.0)	19 (42.2)	
Comorbidity, n (%)			
Absent	72 (57.6)	4 (8.9)	<0.001
Present	53 (42.4)	41 (91.1)	
Prodromal sign, n (%)			
Absent	50 (40.0)	3 (6.7)	<0.001
Present	75 (60.0	42 (93.3)	
Treatment method, n(%)			
Topical	29 (23.2)	0 (0.0)	<0.001
Medical	96 (76.8)	45 (100.0)	
Dermatome, n (%)			
Cranial	17 (13.6)	4 (8.9)	0.004
Lumbar	25 (20.0)	14 (31.1)	
Sacral	26 (20.8)	2 (4.4)	
Cervical*	7 (5.6)	9 (20.0)	
Thoracic	50 (40.0)	16 (35.6)	

VAS:visual analog scale, LANSS:Leeds Assessment of Neuropathic Symptoms & Signs, *region with similar distribution between groups

Table 1. Comparison of patients with and without post-infectious sequelae in terms of characteristics after shingles infection

infection.

4. RESULTS

A total of 170 patients with herpes zoster were reviewed, 37 of whom had PHN (20 (54.1%) male, 17 (45.3%) female), with an incidence rate of 21.8%.

In the study group, 37 patients with postherpetic neuralgia after herpes zoster infection had significantly higher medians of age (p<0.001), duration of shingles infection(p<0.001), VAS-baseline (p<0.001), LANSS-baseline (p<0.001) than those without postherpetic neuralgia. In patients with postherpetic neuralgia, the frequency of comorbidity (p<0.001), the frequency of prodromal findings (p<0.001), and the frequency of receiving medical treatment (p=0.002) were statistically significantly higher. The distribution of HZ dermatome outside the cervical region was found to be significantly different in patients with and without postherpetic neuralgia (p=0.005 (Table 2).

The medians of age (p<0.001), duration of disease (p<0.001), VAS-baseline (p<0.001), and LANSS-baseline (p<0.001) of patients with sequelae after shingles infection were higher than those without sequelae. The majority of patients with sequelae were male (57.8%) (p=0.04). The frequency of comorbidity (p<0.001) and the frequency of prodromal signs (p<0.001) were higher in patients with sequelae after HZ infection. All of the patients (100%) with sequelae were those who received medical treatment (p<0.001). The distribution of regions other than the cervical region was different between the groups with and without sequelae (p=0.004 (Table 1).In the univariate logistic regression analysis performed for factors affecting the development of postherpetic neuralgia after shingles infection, increased age (p<0.001), increased shingles infection duration (p<0.001), increased VAS-baseline (p<0.001), increased LANSS-baseline (p<0.001), having comorbidity (p<0.001), having shingles in the cervical dermatome (p=0.012) were found to be risky in terms of postherpetic neuralgia. In the multivariate logistic regression model, which was created with factors found to be effective in univariate analysis, increased age (p=0.019), increased shingles infection duration (p<0.001), increased LANSS-baseline (p=0.013), and had shingles infection in the cervical dermatome (p=0.040). increased the risk of developing postherpetic neuralgia. It was found that the risk of postherpetic neuralgia increased 1.05 (1.01-1.10)-fold with one-unit age increase, 1.22 (1.09-1.36)-fold with one-unit increase in duration of infection, and 1.23 (1.05-1.45)-fold with one-unit increase in LANS-baseline. It was found that having a shingles infection in the cervical dermatome carries a 60.79 (1.21-3057.21) fold postherpetic neuralgia risk compared to the cranial dermatoma (Table 2).

	Univariatelogistic regression analysis		Multivariate logistic regression analysis	
	Exp B (95% CI)	p	Exp B (95% CI)	p
Postherpetic neuralgia				
Age	1.07 (1.04-1.09)	<0.001	1.05 (1.01-1.10)	0.019
Gender (male)	1.62 (0.78-3.36)	0.198		
Duration of disease	1.33 (1.21-1.45)	<0.001	1.22 (1.09-1.36)	<0.001
VAS-baseline	1.53 (1.24-1.89)	<0.001	0.77 (0.49-123)	0.274
LANSS-baseline	1.24 (1.11-1.38)	<0.001	1.23 (1.05-1.45)	0.013
Comorbidity	21.95 (5.07-95.03)	<0.001	21.75 (0.66-719.29)	0.085
Lumbar	4.22 (0.85-21.08)	0.080	1.15 (0.13-10.64)	0.898
Sacral	0.73 (0.09-5.66)	0.764	0.85 (0.06-11.17)	0.901
Cervical	9.50 (1.64-54.99)	0.012	60.79 (1.21-3057.21)	0.040
Toracal	2.33 (0.48-11.29)	0.293	0.67 (0.08-5.32)	0.707
Post-infectious sequelae				
Age	1.06 (1.04-1.09)	<0.001	1.04 (1.00-1.08)	0.047
Gender (male)	2.05 (1.03-4.10)	0.041	6.16 (1.73-21.93)	0.005
Duration of disease	1.27 (1.17-1.37)	<0.001	1.17 (1.04-1.32)	0.010
VAS-baseline	1.53 (1.26-1.85)	<0.001	0.84 (0.55-1.29)	0.430
LANSS-baseline	1.20 (1.11-1.29)	<0.001	1.19 (1.04-1.36)	0.009
Comorbidity	13.92 (4.70-41.26)	<0.001	5.82 (0.96-35.41)	0.056
Proromal sign	9.33 (2.74-31.76)	<0.001	4.53 (0.81-25.50)	0.086
Lumbar	2.38 (0.67-8.48)	0.181	1.21 (0.19-7.77)	0.842
Sacral	0.33 (0.05-2.00)	0.225	0.23 (0.03-2.01)	0.184
Cervical	5.46 (1.26-23.77)	0.024	20.17 (1.13-359.22)	0.041
Toracal	1.36 (0.40-4.63)	0.623	0.77 (0.13-4.51)	0.770

CI:Confidence interval, VAS: visual analog scale, LANSS: Leeds Assessment of Neuropathic Symptoms & Signs

Table 2. Univariate and multivariate logistic regression analysis of factors affecting postherpetic neuralgia and post-infectious sequelae

	Dry needling	Physical therapy and rehabilitation	p
VAS-baseline	9 (8-10)[a]	9 (7-10)[a]	0.575
VAS-first week	7 (6-9)[b]	8 (5-10)[a]	0.294
VAS-third week	4 (1-8)[c]	4 (1-9)[b]	0.868
p	<0.001	<0.001	
LANSS-baseline	24 (22-24)[a]	24 (10-24)[a]	0.476
LANSS-first week	18 (10-24)[b]	18 (5-24)[b]	0.534
LANSS-third week	10 (0-18)[c]	10 (0-18)[c]	0.964
p	<0.001	<0.001	

VAS: visual analog scale, LANSS: Leeds Assessment of Neuropathic Symptoms & Signs, superscript letters were used to show the difference of variables in columns

Table 3.Comparison of dry needling and physical therapy and rehabilitation in PNH treatment

Table 2. Univariate and multivariate logistic regression analysis of factors affecting postherpetic neuralgia and post-infectious sequelae. UnivariatIn patients with postherpetic neuralgia, with dry needling therapy, VAS (p<0.001) and LANSS(p<0.001) scores decreased significantly in the first week and in the third week. In postherpetic neuralgia cases undergoing physical therapy and rehabilitation, the VAS score did not show a significant decrease

in the first week compared to the baseline, but it decreased significantly in the third week (p<0.001). It was found that the LANSS scores of the patients who received physical therapy and rehabilitation significantly decreased in the first and third weeks compared to the baseline (p<0.001). In the dry needling and physical therapy and rehabilitation groups, the baseline (respectively p=0.575, p=0.476), first week (respectively p=0.294, p=0.534) ve third week (respectively p=0.868, p=0.964) medians of the VAS and LANSS scores were similar (Table 3).

Limitations and Deficiencies

This is a retrospective study that has certain limitations. The first is that the sample size included in the study is not large enough. With more sample data, the likelihood to reflect the real situations is greater.

5. DISCUSSION

Several studies have analyzed risk factors associated with PHN using epidemiological questionnaires. These studies help us to understand which features of PHN appear more frequently in HZ patients (7). As PHN mainly affects more elderly populations, safety and tolerability of pharmacological treatments are important issues to be considered (1, 2). The anticonvulsants are approved for treatment of postherpetic neuralgia. Several meta-analyses have shown that gabapentin (1,800 to 3,600 mg per day; NNT = 8; 95% CI, 5 to 14) and pregabalin (600 mg per day; NNT = 4; 95% CI, 3 to 9) were more effective than placebo in achieving 50% reduction in pain (8). Despite their effectiveness, these agents needed time to titrate to an effective dose (up to 10 weeks) and their adverse effects (e.g., somnolence) are disadvantages (9). In our study, pregabalin 75-300 mg was given to all patients who developed PNH. Despite this treatment, patients with recurrent pain and current comorbidities were included in the our nonmedical treatment group.

Since the early 1980s, many anti-depressants at a lower dose that provide analgesia have been used in neuropathic pain caused by PHN. A high quality of evidence for the first-line use of the tricyclic anti-depressants (TCA) such as serotonin norepinephrine reuptake inhibitors duloxetine or venlafaxine found in the recent systematic review and meta-analysis of pharmacotherapies for neuropathic pain . TCAs should be started at a dose of 10-25 mg before bedtime and gradually increased in 3-7 days up to a maximum dose of 150 mg. (10). In our study, there was no patient using medication in the antidepressant group.

The use of opioids in PHN treatment guidelines has moved from primary care to secondary or tertiary therapies due to their potential for abuse and side effects over time. Opioids (tramadol (Ultram, Conzip), oxycodone (Percocet, Roxicet) or morphine) provide analgesia by modulating pain through various opioid receptors such as mu, kappa, and delta both centrally and peripherally during an inflammatory response. Several clinical studies have shown that opioids are useful in the management of neuropathic pain, including PHN. A randomized controlled trial comparing placebo to opioids and TCAs in 2002 also showed that opioids and TCAs may provide better pain relief than a placebo. Some of the side effects of opioid use include; nausea, itching, drowsiness, constipation, and sedation (11).

Topical therapies such as capsaicin and lidocaine may be considered for patients with PHN who have mild to moderate localized pain and who are considered to be intolerant of treatment with oral medications. In a meta-analysis of four randomized, controlled trials involving 1,272 patients with PHN, overall efficacy results were significantly better in patients treated with a single application of 8% topical capsaicin compared to those treated with 0.014% topical capsaicin (12). In the practice of acupuncture, without the use of injectate the insertion of thin monofilament needles is named as 'Dry needling'. It is typically used for the management of a variety of neuromusculoskeletal pain syndrome for muscles, ligaments, tendons, subcutaneous fascia, scar tissue, peripheral nerves, and neurovascular bundles (13, 14). 'Intramuscular manual therapy' (IMT) or 'trigger point dry needling' (TDN) is a procedure of dry needling. IMT, or the insertion of needles into trigger point is not exact same with the term dry needling (15, 16).

'Intramuscular manual therapy is a physical intervention that uses a filiform needle no larger than a 25-gauge needle to stimulate trigger points, diagnose and treat neuromuscular pain and functional movement deficits according to Mississippi State Board of Physical Therapy (17, 18).

There is a high quality evidence of direct dry needling into myofascial trigger points for the purpose of short/long-term pain and disability reduction in patients with musculoskeletal pain syndromes (19, 20, 21).

Peri-neural needling of non-trigger point structures helps reduce pain and disability while improving sensory and motor nerve conduction velocities. Perineural needling has evidence to stimulate microcirculation in patients with mild to moderate carpal tunnel syndrome (22, 23, 24).

The optimum dosage (frequency of treatment sessions per week or month), duration (length of time the needles should remain in situ), and intensity (the number of needles used and degree of manual manipulation or electrical stimulation) has yet to be determined for many neuromusculoskeletal conditions (25, 26, 27). Majority of 'dry' needling randomized trials attempt to elicit a deqi response. Deqi has been defined as a dull ache, heaviness, distension, numbness, tingling, cramping, pressure, fullness, spreading, warmth, or coolness (28, 29).In our study, patients diagnosed with PNH were questioned for neuropathic pain by the physiartrist before starting treatment and at each visit and also was evaluated with VAS and LANSS scores. Out of 18 of patients take dry needling therapy for PHN. We applied a total of 10 sessions of dry needles to our patients for 3 weeks. 25x0.25mm gauge needle injected intramuscularly through the corresponding dermatome. Transcutaneous electrical nerve stimulation (TENS) is widely used as a non-pharmacological approach for pain relief in a variety of clinical conditions. Most clinical trials have demonstrated the efficacy of TENS in attenuating neuropathic pain (30).

In a study, TENS frequencies (110 or 4 Hz) and two intensities (strong but comfortable or highest tolerable) were applied at three sites relative to the measurement site (segmentally, extrasegmentally or a combination of these), for 30 min. The high frequency, high intensity segmental, and combined stimulation groups, showed rapid onset and significant hypoalgesic effects. All other TENS intervention

groups showed hypoalgesic responses similar to the sham TENS group, and none of these groups reached a clinically significant hypoalgesic level (31).

In our study, 19 of patients undergo conventional physical therapy treatment with therapeutic ultrasound, TENS and exercise therapy. We observed a significant reduction in neuropathic pain complaints in our patients with conventional physical therapy programs. In addition, it provides a good advantage, especially in the elderly patient group, as a method that has no side effects and is well tolerated.

6. CONCLUSION

Physical therapy and dry needling appear to be an effective option for the treatment of PHN. When we evaluate the systemic side effects and drug interactions of other drugs, the non-invasive nature of these treatments (Physical therapy program and dry needling) provides some advantages, especially in the elderly population with com-morbidity. Considering these advantages, longer-term studies are required to establish the long-term safety and efficacy of physical therapy and dry needling therapy in the treatment of PNH.

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