International Journal of Medical and Health Research
ISSN: 2454-9142
Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 4; Issue 1; January 2018; Page No. 136-139

Efficacy and safety of cryoanalgesia in treating post herpetic neuralgia

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Abstract
Treatment of PHN with newer treatments modalities ranging from Botulinum toxin to laser to Cryoanalgesia (Non Freezing Technique) is fast emerging with many reports showing there efficacy and safety. Till date, there is only one study demonstrating the benefit of cryoanalgesia thus there is a need for comparing this newer modality in treating PHN and to establish its safety and efficacy. A total of 50 patients diagnosed as case of PHN on daily oral amitriptyline 25mg at bed time were included in this study from the patients attending the outpatient department of dermatology at Krishna Hospital, Karad after a proper informed written and signed consent.

Keywords: PHN, botulinum toxin, cryoanalgesia, nonfreezing technique

1. Introduction
Herpes zoster is caused by reactivation of a varicella zoster virus (VZV) which after a primary infection of chicken pox attains latency in the dorsal root ganglia of the spinal cord. Predominantly it affects older individuals whose immunity for the virus has waned over the period of time. Common sequelae to herpes zoster infection are occurrence of Post-herpetic neuralgia, which is a chronic debilitating problem [1]. the characteristic appearance of herpes zoster (rash with redness, papules, and vesicles involving a dermatome, and healing with crust formation) is usually sufficient to make an accurate clinical diagnosis. The rash is generally unilateral and does not cross the midline of the body. However diagnosis of Post herpetic neuralgia (PHN) is primarily a clinical one which is done on the basis of a positive history of herpes zoster followed by persistent pain lasting for more than 4weeks (1month) in the corresponding dermatome often described as sharp, burning, aching, or shooting type and is commonly accompanied by concomitant sensory defects [2]. Treatment of PHN with newer treatments modalities ranging from Botulinum toxin [3]. to lasers [4]. to Cryoanalgesia (Nonfreezing Technique) is fast emerging with many reports showing there efficacy and safety. Till date, there is only few study demonstrating the benefit of cryoanalgesia thus there is a need for comparing this newer modality in treating PHN and to establish its safety and efficacy. Major breakthrough came when the virus was isolated from patients suffering from varicella and zoster in the year 1952 by Weller and Stoddard and further in year 1958 they recognized the same virus was responsible for causing both diseases. [5]. as in that era concept was Z-varicella (Varicella as a result of exposure to HZ) and O-varicella (ordinary childhood disease) was prevalent and both were thought to be separate entities. However existence of link between these two was suggested by an experiment in which healthy children were inoculated with HZ fluid and subsequently the infected children developed a condition identical to varicella and interestingly they were able to transmit the condition to other children in their contact [6].

Objectives
The safety and efficacy of cryoanalgesia with established treatment modality of Gabapentin

Material and Methods
A total of 50 patients diagnosed as case of PHN on daily oral amitriptyline 25mg at bed time were included in this study from the patients attending the outpatient department of dermatology at Krishna Hospital, Karad after a proper informed written and signed consent. The patients who fulfilled the inclusion and exclusion criteria were randomly included in the two groups i.e. either group A or group B. Before treatment patients were examined thoroughly using clinical and by laboratory measures for presence of any underlying disease. All previous systemic or topical therapies for PHN were stopped at least a month before start of study. Use of concomitant topical treatments or any systemic treatments that could affect the outcome of PHN was not permitted until the end of study.
This was a hospital based investigator blind randomized controlled comparative study of eight weeks duration. Inclusion criteria to enrol the patient in study patient -

A. Must have given written consent before any treatment commenced.
B. Diagnosed to be suffering from PHN clinically (pain persisting more than 4 weeks after healing of HZ infection).
C. Should be completed 18 years of age.
D. Must not have any active infection at the dermatome to be treated
E. Must have to stop any other modality of treatment one

month prior to the inclusion in study.

- Should be able and willing, in the view of investigator, to comply all study procedure.

Exclusion criteria following patient will be excluded from study

A. Patient with hypersensitivity to drug or patient intolerant to the study medication.
B. Pregnant and lactating patient.
C. Unrealistic expectations of patients.
D. Not willing for regular follow up.
E. Other neuropathies or neuralgia not due to HZ
F. Patient suffering from Raynaud's phenomenon.
G. Patients having PHN close to vital organs like eyes and ears

Result and discussion

Of the 50 patients enrolled, 25 patients (group A) received cryoanalgesia (LN2 spray, non-freezing technique) for a period of 90 to 120 seconds weekly for a period of 8 weeks and 25 patients (group B) received daily oral gabapentin in a divided doses of 600 mg/day for 8 weeks. In addition to the above said group medicines both the groups were given fixed daily doses of oral amitriptyline 25mg daily. All the patients completed 8 weeks of treatment. No patients withdrew from the study. Demographic data results in group a, 36 % were female and 64 % were male. In group B 44 % were male and 56 % were female. This was not statistically significant. Mean age of the patient in group A was 59.8 years and in group B was 55.6. This was not statistically significant. According to age wise distribution maximum patients were found in between 60 – 70 years of age group (17/50). According to dermatomal involvement of skin Thoracic dermatome was the most commonly affected and majority of patients were of T10-T11 dermatomal involvement. Mean duration of disease in group A was 7.16 months and 7.54 months in group B. The difference was statistically insignificant. Thus demographic data of both the groups was comparable at baseline.

Clinical Efficacy Evaluation of efficacy of the drugs was done using visual analogue scale (VAS) and physician global assessment (PGA) at each visit. Additionally on baseline, 4th and 8th visit improvement in pain score was done using Sensory & Affective component of SF- Mc GIll Pain Questionnaire (Sf-MGPQ) along with present pain intensity. At baseline visit, mean VAS, Sf-MGPQ of group A (study group) was 100 and 0.90 (sensory) / 0.84 (affective) respectively and mean VAS, Sf-MGPQ of group B (control group) was 100 and 0.90(sensory) / 0.88 (affective) respectively. There was no statistically significant difference in VAS, Sf-MGPQ in study and control group. Physician global assessment (PGA) was graded as "Poor" for all patients (100%) at baseline. Group A There was steady and extremely significant reduction in the mean VAS and mean Sf-MGPQ at subsequent visits along with improvement in PGA from "Poor" to "Excellent" or "Clear" response. Clinically improvement was seen even after 7 days of treatment in group A. After 7 days, mean VAS was reduced from 100 to 84.6 (15.4% reduction (Table 8). 80 % patients showed poor response (0% - 25% improvements) and 12 % showed fair response (25% - 50% improvements). 8% patients showed good clinical response (50% - 75% improvements). None of the patient on1st visit showed excellent or clear response.

After 15 days (2weeks) mean VAS score further reduced to 65.8 (34.2% improvement). 64% patients showed fair response, 20% showed poor response. Good and excellent response was seen in 12% and 4% respectively. This trend of improvement was further followed in 3rd week with 46.2% reduction in mean VAS (53.8) score.52% patients showed good response and excellent response was seen in 8%. Poor and fair response was observed in 20% of patients. None showed clear response. After 4th week VAS score showed significant reduction by 58.2% (41.8). At this stage 48% showed good response with excellent response seen in 24% of patients. 20% showed fair response with 8% showing poor response. Mean Sf-MGPQ at this showed 55.5% (sensory) and 51% (affective) improvement from baseline. After 5th week VAS score was further reduced to 31.4 (68.6% improvement). At this stage 40% showed excellent response followed by 32% showing good response and 12% showed clear response (100% improvement). Only 4% showed poor response. At the end of 6th week VAS score showed excellent reduction with 79.2% improvement from base line (20.8). 36% patients showed excellent response with 28% showing clear response. None of the patients showed poor response. After 7 weeks of treatment mean VAS was 16.4 (83.6% improvement) and showed excellent reduction from baseline. At this stage 40% showed clear response with excellent and good response seen in 28% and 24% respectively. 12 % showed fair response and none had poor response. After last 8th visit there was significant amount of reduction in VAS from 100 to 14 (86% improvement). At the end of study 40% showed clear response followed by excellent response in 40% of patients. 16 % showed good response. However one patient (4%) still showed fair response at end of study with none showing poor response. And final improvement in Sf-MGPQ was 86.67% (sensory) and 83.3% (affective). There was consistently significant and steady improvement in the VAS and Sf-MGPQ at each visit in comparison with their baseline values. Improvements in the mean VAS score at Visit 1, 2, 3, 4, 5, 6, 7 and 8 was 15.4%, 34.2%, 46.2%, 58.2%, 68.6%, 79.2%, 83.6% and 86% respectively. Similarly, Improvements in the mean Sf-MGPQ sensory component from baseline at 4th and 8th was 55.5% and 86.7% respectively and mean improvement in affective component was 51% and 83.3% at 4th and 8th visit respectively. This difference in change of VAS, Sf-MGPQ (sensory & affective) was extremely significant statistically (one was ANNOVA) with p value = <.0001for each. There was no statistical difference noted between the various blood investigational parameters at the end of study (8th visit) when compared with their corresponding baseline values.

The side effects observed were further divided into two parts i.e. one caused by local application of cryogen and other by systemic addition of amitriptyline. Undesirable effects secondary to local cryospray were vasovagal like reactions seen in 3 out of 25 patients and also transient acute exacerbation in pain intensity was also observed in 3 patients. One patient developed cryospray induced blisters due to accidental freezing of affected dermatome and healed with

residual hypo-pigmentation. All the local side effects observed were transient and none warranted discontinuation of therapy. Side effects observed due to addition of amitriptyline were sedation and dry mouth observed in 3 patients each on 1st visit. As the duration of therapy increased patient became habitual to the sedation and dry mouth and subsequently nil side effects were observed from 6th visit onwards. This study concludes that Non-freezing cryoanalgesia is efficacious and safe in treating the established cases of PHN. Group B There was steady and highly significant reduction in the mean VAS and mean Sf-MGPQ at subsequent visits within the group along with improvement in PGA from "Poor" to "Excellent" or "Clear" response. Clinically improvement was seen even after 7 days of treatment in group B. After 7 days, mean VAS was reduced from 100 to 91.2 (8.8% reduction). 96 % patients showed poor response (0% - 25% improvements) and 4 % showed fair response (25% - 50% improvements). None of the patient on1st visit showed good, excellent or clear response. After 15 days (2weeks) mean VAS score further reduced to 74.8 (25.2% improvement). 52% patients showed poor response, 40 % showed fair response with good response in 8%. None showed excellent or clear response. This trend of improvement was further followed in 3rd week with 37% reduction in mean VAS (63) score. 56% patients showed fair response, 16 % had good response and excellent response in 4% of patients. However Poor response was observed in 24% of patients. None showed clear response. After 4th week VAS score showed significant reduction by 49.6% (50.4). At this stage 64% showed good response with excellent response seen in 4% of patients. 20% showed fair response with 12% showing poor response. Mean Sf-MGPQ showed 50% (sensory) and 44.3% (affective) improvement from baseline. After 5th week VAS score was further reduced to 36.4 (63.6% improvement). At this stage 60% showed good response followed by 20% showing excellent response, 16% showed fair response and 4% showed clear response (100% improvement). No one showed poor response. At the end of 6th week VAS score showed excellent reduction with 74.8% improvement from base line (25.2). 48% patients showed excellent response along with 44% showing good response and only 4% showing fair and clear response each. None of the patients showed poor response. After 7 weeks of treatment mean VAS was 14.4 (85.6% improvement) and showed excellent reduction from baseline. At this stage 24% showed clear response with excellent and good response seen in 60% and 16% respectively. None had poor or fair response. After last 8th visit, there was significant reduction in VAS from 100 to 10.4 (89.6% improvement). At the end of study 52% showed excellent response followed by clear response in 36% of patients and good response in 12 % of patients. None showed poor or fair response to therapy. And final improvement in Sf-MGPQ was 92% (sensory) 88.64% (afferent) from the baseline.

There was consistently significant and steady improvement in the VAS and Sf-MGPQ at each visit in comparison with their baseline values. Improvements in the mean VAS score at Visit 1, 2, 3, 4, 5, 6, 7 and 8 was 8.8%, 25.2%, 37%, 49.6%, 63.6%, 74.8%, 85.6% and 89.6% respectively. Similarly, Improvements in the mean Sf-MGPQ sensory component from baseline at 4th and 8th was 46.4% and 92% respectively and mean improvement in affective component was 44.3% and 88.6 % at 4th and 8th visit respectively. This difference in change of VAS, Sf-MGPQ (sensory & affective) was extremely significant statistically (one was ANNOVA) with p value = <.0001for each. There was no statistical difference noted between the various blood investigational parameters at the end of study (8th visit) when compared with their corresponding baseline values. The side effects observed were due to both gabapentin and amitriptyline. Sedation was most common side effects seen in 6 patients followed by dry mouth in 3 patient and nausea and headache in 2 patient each on 1st visit. Weight gain was observed in one patient on 5th visit. All observed side effects were mild and none warranted any discontinuation of therapy. This study concludes that gabapentin (600mg daily in divided doses) along with 25 mg amitriptyline is efficacious and safe in treating the established cases of PHN. Comparison between both groups

Mean VAS score for the two groups was similar and at each subsequent visit the difference in the mean VAS score of two groups was not statistically significant. At the end of study (8 weeks) cryoanalgesia grouped showed 86% reduction while gabapentin group showed 89.6% reduction from the baseline mean VAS. Although gabapentin group showed slightly better response in reducing mean baseline VAS score then cryoanalgesia at the end of study, it was not statistically significant. Cryoanalgesia is equally efficacious to gabapentin in reducing the VAS score in PHN. Similar reduction was also observed in Sf-MGPQ pain scores in both the groups but the difference was not statistically significant. At baseline all patients in both groups showed poor response however at end of study 40% showed excellent and clear response each in cryoanalgesia as compared to 52% and 40% excellent and clear response in gabapentin group. This study concluded that both cryoanalgesia and gabapentin are equally efficacious in treating PHN. The side effects observed in both the groups were mild and transient thus establishing the safety of both the group medications.

Conclusion

Cryoanalgesia is as effective as conventional therapy of gabapentin in reducing pain in PHN cases. Cryoanalgesia is safe, barring few transient side effects it is free from any long term side effects. Cryoanalgesia is a good alternative for treatment of PHN and can effectively replace existing systemic therapies without their side effects. Cryoanalgesia can also be used along with other treatment modalities as an adjuvant for augmenting the pain relief. Follow up studies are recommended to compare and observe the efficacy of cryoanalgesia in maintaining the remission in comparison with other established modalities.

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