Efficacy of Cryoanalgesia versus Systemic Gabapentin in the Treatment of Post Herpetic Neuralgia: A Randomised Control Trial

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Abstract
Introduction: PHN is defined as pain persisting for more than 4 weeks after the rash has healed. Despite increasing understanding of pathophysiology and advances in therapy the quest for the penultimate therapy for PHN still remains elusive. Out of various treatment options available anticonvulsants or tricyclic-antidepressants drugs are preferred. Cryoanalgesia is routinely used in interventional pain management settings. Recently it has been successfully used in treating PHN by Calandria L.

Material & Methods: 50 Patients of PHN on daily oral amitriptyline (25mg) were randomly divided into two groups of 25 each; group ‘A’ received weekly cryoanalgesia (60-90 seconds by non-freezing cryo (liquid nitrogen) spray) and group ‘B’ received daily oral gabapentin (600mg) for 8 weeks. Efficacy was studied by a blinded investigator using visual analogue score (VAS), SF- McGill pain questionnaire (SF-MGPQ). Safety was studied by appropriate investigations.

Results: Baseline mean VAS and Sf-MGPQ of group A and B were 100& 0.90 and 100& 0.90 respectively. At the end of 8 weeks mean VAS and Sf-MGPQ of group A and B were reduced to 14& 0.13 and10.4& 0.07 respectively. The difference in both the groups was not statistically significant (P=0.39)

Conclusion: Combination of cryoanalgesia and amitriptyline is well tolerated and its efficacy is equivalent to conventional therapy of gabapentin and amitriptyline.

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. Common sequelae to herpes zoster infection are occurrence of Post-herpetic neuralgia, which is a chronic debilitating problem.1

The characteristic appearance of lesions is usually sufficient to make an accurate clinical diagnosis of herpes zoster. However on the contrary diagnosis of Post herpetic neuralgia (PHN) is primarily done on the basis of a positive history of herpes zoster followed by persistent pain lasting for more than 4 weeks (1 month)2,3 in the corresponding dermatome often described as sharp, burning, aching, or shooting type and is commonly accompanied by concomitant sensory defects.4

Dermatologists often encounter patients suffering from PHN in whom no relief has been obtained by use of non-steroidal pain killers or conventional analgesics. So the main objective of the treatment revolves around pain alleviation and improvement in the quality of life.5 Pain relief in PHN with
Currently available therapies is often unsatisfactory as exact pathophysiology of PHN is still elusive. The various armamentarium available for treating PHN ranges from pharmacologic agents e.g. opioids, tricyclic antidepressants (TCAs), antiepileptic drugs and topical agents e.g. lidocaine patches, capsaicin creams along with a wide variety of interventional options ranging from sympathetic / other nerve blocks, intrathecal injections and spinal cord stimulations. Treatment of PHN with newer treatments modalities ranging from Botulinum toxin to lasers to Cryoanalgesia (Non Freezing Technique) is fast emerging with many reports showing there efficacy and safety.

It is known to man since ages that cold can be used for treating pain. The cryoanalgesia is a technique where there is direct freezing of nerve fibers and it provides a long term pain relief in interventional pain management settings when pain has been shown to be caused by sensory nerves. There were increasing doubts whether non-direct cryoanalgesia given to the surface of skin without exposing nerve will also be effective and if cold could be used without causing tissue injury. Thus came the concept of “non-freezing technique” (NFT) in which there is no permanent residual nerve damage in comparison with the older freezing techniques. Calandria L demonstrated the benefit of cryoanalgesia in treating PNH. However, it was neither blinded nor comparative study. Thus there is need for comparing this newer modality for treating PHN and to establish its safety and efficacy.

Material and Methods
This was a hospital based investigator blind randomized controlled comparative study of eight weeks duration. A total of 50 patients diagnosed as case of PHN on daily oral amitriptyline 25 mg at bed time were included in this study after a proper informed written and signed consent. 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. The patients who fulfilled the inclusion and exclusion criteria were randomly included in the two groups i.e. either group A or group B. Group A (study group) received cryoanalgesia once a week by non-freezing spray technique for a period of 60 to 90 seconds. In this NFT method liquid nitrogen LN₂ (pressurized nitrogen gas at -196 °C) was used and was applied over the skin surface of the affected dermatome by means of a portable cryosurgery unit. It is applied perpendicular to the skin over the affected site for about 60 to 90 seconds in circular motions or strokes. Care must be taken to cover the entire affected area with LN₂ producing a cloud of it and subsequently resultant cooling zone taking care of not freezing the underlying skin. Patients were followed up every week for the next 8 weeks.

Group B (control group) received conventional treatment with Oral Gabapentin (600mg/day) in divided doses daily and patients were followed up every week for the next 8 weeks.

Further patients were instructed not to disclose the modality of treatment to the co-investigator who will assess the safety and efficacy of treatment by Visual Analogous score (VAS). Physician global assessment at each visit and by Short form Mc-GILL Pain Questionnaire (Sf-MGPQ) on baseline, 4th and last visit and relevant laboratory investigations every alternate week. All adverse events, whether or not considered causally related to the study drug were documented by the investigator.

Statistical Analysis was done by Comparing the two groups by unpaired ‘t’ test for the variables of VAS, SF-MGPQ & blood investigations and one way ANOVA test for comparing standard deviation of VAS within both the groups.
Observation and Results

Mean age, gender distribution and mean duration of PHN were all comparable at baseline. Maximum cases belonged to 60 to 70 years of age group and T10-T11 was the most commonly affected dermatome in the study. Mean duration of disease in group A was 7.16 months and 7.54 months in group B. The difference was statistically insignificant (Figure 1).

**Group A** showed 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 were 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 (figure 2,3,4). This difference in change of VAS, Sf-MGPQ (sensory & affective) was extremely significant statistically (one-way ANNOVA) with p value = <.0001 for each.

The side effects observed were further divided into two parts i.e. one caused by local application of cryogen and other by co-administration of amitriptyline. Undesirable effects secondary to local cryospray were vasovagal like reactions and transient acute exacerbation in pain intensity were observed in 3 patients each. 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 due to 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.

**Group B** also showed a 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. 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 (Figure 2,3,4). This difference in change of VAS, Sf-MGPQ (sensory & affective) was extremely significant statistically (one was ANNOVA) with p value = <.0001 for each.

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.

**Comparison between both groups** 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 than cryoanalgesia at the end of study, it was not statistically significant. Similar reduction was also observed in Sf-MGPQ pain scores in both the groups but the difference was not statistically significant. The PGA at baseline was poor for all participants and by end of study there was significant reduction in pain and subsequently improvement in the PGA. At end of the study 40% showed excellent and clear response each in group A as compared to 52% and 40% excellent and clear response in group B. (Figure 5)
Figure 1

![Figure 1](image1)

Figure 2

![Figure 2](image2)

Figure 3

![Figure 3](image3)
Discussion
In 2010 Calandria L first reported the study of cryoanalgesia treatment in PHN. The author enrolled a total of 47 patients with a mean age of 73 years. Out of these 47 patients 19 had PHN duration of 1 week to 1 month. The author used LN$_2$ spray over the affected dermatome without allowing it to freeze thus forming a nitrogen cloud several times in roughly circular movements over the whole affected area for about 30s. The treatment cycle were repeated at weekly interval until pain improved to the acceptable level. Author used between one to 20 such sessions (mean 4.8) to attain acceptable pain relief. Author in end concluded that the technique doesn’t involve the freezing of skin, nor does it cause any type of burn or erythema and the mechanism triggered by cooling the affected dermatome is sufficient to attenuate the pain in all its facets. However there were some pitfalls in this study as author used 30s cycle to cool the affected dermatome, which probably is not sufficient time
to effectively cool larger areas thus requiring as much as 20 cycles in the published study. Secondly, 19 out of 47 patients (40.4%) were having pain duration of less than one month which by definition is acute herpetic neuralgia and not true PHN. Improvement in these cases can be due to self resolution of the disease and may be the reason for pain relief after one or two sessions as stated by author. Thirdly improvement was studied using numbered pain scale and final outcome solely dephen upon how the patient perceived his/her pain. Further, it was neither a comparative or blinded study, so question about investigator bias remains. Considering all these drawbacks and lack of clarity on few parameters some modifications were made in the current study to address the above mentioned issues. Treatment duration was increased from 30s to 60-90 seconds so as to completely cool the affected dermatome thus requiring lesser number of treatment cycles. The total number of visits was limited to 8 sessions as 20 sessions or 5 months is a long time and if there is no satisfactory response after a period of 2 months the efficacy of the treatment is itself questioned and during such a prolonged course there is definitely a chance of self recovery of PHN. Secondly only true cases of PHN were included in the study (average duration of PHN in our study was 7.4 months). Thirdly Amitriptyline was used as a nullifying agent in both the groups as efficacy of amitriptyline is well established and it was proved to be efficacious in treating PHN in a study by Watson CP et al.\textsuperscript{12} The aim of adding nullifying factor was based on ethical consideration. Placebo controlled trial was not ethically possible as cryoanalgesia is a newer therapeutic modality and there is little evidence to support this. In the absence of any double blind placebo control studies its efficacy by large has not been yet fully established.

On the other hand safety and efficacy of gabapentin in treatment of PHN is well established in the literature by two large trials by Rowbotham M et al.\textsuperscript{13} and Bonezzi C and Demartini L,\textsuperscript{14} and is considered as the 1\textsuperscript{st} line of therapy or the gold standard therapy for PHN and is currently being extensively used by dermatologists. We took this opportunity to compare the two different modalities in regard to their efficacy and tolerability in PHN. After the end of stipulated time frame of 8 weeks we observed that cryoanalgesia has almost similar efficacy in reducing VAS, PGA, SF-MGPQ pain score in cases of PHN in comparison with gabapentin. Gabapentin group although showed slightly better improvement at the end of study, (89.6% as compared to 86%) but the difference was statistically not significant. The similar reduction was seen in pain score On comparing the visit wise reduction early reduction in VAS score was observed in cryoanalgesia group as compared to gabapentin during the earlier visits however as sessions increased the more reduction was observed in gabapentin group during the last 2 weeks.

With this study we have successfully concluded that cryoanalgesia is effective in treating PHN and can be used as an adjuvant with other known modalities. However, we strongly recommend double blind placebo controlled future studies comparing the efficacy of cryoanalgesia with the established modalities. Also studies with a long follow up need to be taken up to comment upon the long term remission and relapse rates in treated patients of PHN.

**Conclusion**

Cryoanalgesia definitely has a place in the armamentarium of management of PHN as it is safe, barring few transient local side effects it is free from any long term side effects. Tolerability of cryoanalgesia definitely is superior to any other systemic drugs used in PHN like antiepileptics / TCAs as drugs can have systemic side effects and can effectively replace existing systemic therapies without their side effects. Cryoanalgesia is as effective as conventional therapy of gabapentin in reducing pain in PHN cases so can also be used along with other treatment modalities as an adjuvant for augmenting the pain relief.
References