ROLE OF GABAPENTIN AS ADJUVANT ANALGESIC WITH OPIOIDS FOR NEUROPATHIC CANCER PAIN WHEN COMBINED WITH LOW-DOSE AMITRIPTYLINE IN CANCER SUBJECTS OF TRIPURA, A NORTH EASTERN STATE OF INDIA
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ABSTRACT: INTRODUCTION: Neuropathic cancer pain is often refractory to standard opioid therapy. The use of adjuvant analgesics for neuropathic cancer pain is largely empirical. Although gabapentin is effective in the treatment of neuropathic cancer pain, some patients experience intolerable side effects sufficient to warrant discontinuation. This study aimed to compare the efficacy and safety of gabapentin when combined with low dose amitriptyline as adjuvant analgesic to opioid for neuropathic cancer pain. METHODS: It was a double blind placebo controlled Randomized Control Trial. 80 patients were randomized in four groups and intervention was given for 14 days. Primary and secondary outcome variables were assessed on day 8 and day 15 for statistical significance by ANOVA or chi square test as applicable. Group A: Gabapentin 100 mg b.d. + Amitriptyline 10 mg b.d.; Group B: Gabapentine 100 mg b.d. + placebo of Amitriptyline; Group C: Placebo of Gabapentine + Amitriptyline 10 mg b.d.; Group D: Placebo of Gabapentine + Placebo of Amitriptyline. RESULTS: 74 subjects completed the treatment. Worst pain score, Least Pain score, Average Pain score and current pain score in Numerical Rating Scale (NRS) by Brief Pain Inventory (BPI) in last 24 hour at enrolment, after 7 and 14 days of intervention has been measured as primary outcome variable and there were no significant difference of pain score in NRS between the groups. Among the secondary end point outcome variables only daily paroxysmal pain was significantly less (P = 0.02) in Gabapentin – amitriptyline + opioid group compared to only opioid group. CONCLUSION: Although gabapentin might be regarded as a promising new adjuvant analgesic for neuropathic cancer pain, our results indicated minimal clinical benefit. So controlled trial with higher dose of gabapentin is needed to establish its efficacy.

KEYWORDS: Neuropathic cancer pain, Gabapentin, Amitriptyline, NRS, BPI.

INTRODUCTION: Despite of great advances in the fields of pain management, pain associated with a cancer remains significantly under treated.¹ Neuropathic pain is regarded as one of the main causes of cancer pain refractory to standard opioid therapy in palliative care. The use of adjuvant analgesics for neuropathic cancer pain is largely empirical and the true efficacy of these adjuvant analgesics has been unknown. Gabapentin is one of the new promising anticonvulsant drugs as an adjuvant analgesic for neuropathic cancer pain.² Its exact mechanism of action is unknown, but its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels.³
Painful neuropathic conditions of cancer pain often show little response to non-opioid and opioid analgesics but may be eased by antidepressants and anticonvulsants. Although gabapentin is effective in the treatment of neuropathic pain in patients with cancer, some patients experience intolerable side effects sufficient to warrant discontinuation but when gabapentin dose is less than 600 mg and are combined with antidepressants, it is effective in treating cancer related neuropathic pain without severe side effects.\textsuperscript{4,5}

Opioids in adequate doses not only elicit some degree of pain relief but also may cause increased side effects. Therefore neuromodulatory nonopioid adjuvant drugs are often required to complement opioid therapy for the management of neuropathic pain in cancer patients.

Tricyclic antidepressants (TCAs) have efficacy in treatment the neuropathic pain and associated co-morbid depression. The doses effective for neuropathic pain are usually lower than those used for depression. The management of pain is an important goal in the holistic care of patients with cancer.\textsuperscript{6}

Although gabapentin was effective in relieving certain neuropathic pain symptoms, more evidence are needed to support the notion that gabapentin is the first-line treatment for neuropathic pain with a better efficacy, fewer side effects, and a favorable cost/efficiency ratio.\textsuperscript{7}

There are few effective pharmacological options to treat symptoms due to Chemotherapy induced peripheral neuropathy (CIPN). Tricyclic antidepressants (eg, nortriptyline and amitriptyline) have been suggested as therapeutic options for neuropathy; however, there are few data to support their use in CIPN. The identification of alternate treatment strategies would be a welcome development for patients afflicted with CIPN.\textsuperscript{8}

So necessity of randomized clinical trials has been to assess the clinical usefulness, including efficacy and safety of gabapentin in combination with other adjuvant analgesics for neuropathic cancer pain. So the present study was taken up with the aim to assess the efficacy and safety of the addition of gabapentin and/ or amitriptyline as adjuvant to opioids for neuropathic cancer pain.

The Primary objectives of the study were (i) to measure and compare the pain score by Numerical rating scale\textsuperscript{6} (NRS) 0 – 10 using Brief pain Inventory (BPI) at day 0, 8 and 15 day after intervention with gabapentin 100mg b.d. or/ and amitriptyline 10 mg b.d. as adjuvant analgesic with opioids for neuropathic cancer pain. (ii)Assessment of interference of activity by pain during past 24 hour using Brief pain Inventory (BPI)\textsuperscript{9} at day 0, 8 and 15 day after intervention with gabapentin or/ and amitriptyline.

Secondary Objectives were to evaluate and compare the efficacy and safety profile of interventional therapy among the different treatment group subjects, following secondary objective variables also will be assessed at day 0, 8 and 15.

i. Average daily paroxysmal pain (Shooting and Lancinating) episodes.
ii. Previous 24 hour opioid rescue dose.
iii. Assessment of quality of pain relief by using “Pain relief scale” (PRS) and “Patient’s global impression change”(PGIC).
METHODOLOGY:

Study Design: This was a single center, double blind, placebo controlled, parallel group, hospital based Randomized control trial (RCT) to evaluate and compare the efficacy and safety of opioid monotherapy with that of gabapentin and/or amitriptyline as adjuvant analgesic with opioids for neuropathic cancer pain in cancer subjects attending a tertiary care hospital. This protocol was approved by the independent Institutional Ethical Committee.

Duration of Study: Total 2 years. After screening, gabapentin or/and amitriptyline or placebo was given orally as adjuvant with opioid with no other changes to standard protocol of cancer treatment care. Patients were followed up for 0 to 15 days after interventional trial for assessment of primary and secondary objectives.

Participants: Cancer related neuropathic pain was defined as pain resulting from nerve injury or compression by a neoplastic lesion or anti-cancer therapy with at least one of the following symptoms or signs referred to the pain area: continuous sensory disturbance (dysesthesia, hyperesthesia, allodyna, burning pain), or incidental pain (shooting, lancinating pain).

Inclusion Criteria Were: Age ≥ 18 years; Worst pain intensity ≥ 5 on a NRS from 0 – 10, in the 24 hour period to study entry; Stable dose of regularly scheduled systemic opioid therapy (Morphine ≥ 60 mg/24 hour without sufficient analgesia for at least 24 hour; Life expectancy ≥ 30 days; Karnofsky performance status (KPS) ≥ 40.

Exclusion Criteria Were: Serum creatinine > 2 times the upper limit of normal; Serum liver enzyme > 5 times the upper limit of normal; Serum sodium < 130 m Eq; Unable to take medication orally; Pregnant and lactating subjects; Other organ dysfunction; Chemotherapy from 3 days before screening; Radiotherapy to the pain producing lesion from 15 days before screening; Patients unable to communicate fluency in Bengali or Hindi or English; Patients with history of epilepsy or use of anti-epileptic drugs or neuropathic analgesics other than opioids.

Intervention: Eligible subjects were allocated at a 1:1:1:1 ratio in to four interventions arms to receive Group A: gabapentin 100mg 12 hourly along with amitriptylin 10 mg 12 hourly Group B: Gabapentin 100 mg 12 hourly with Placebo of amitriptylin 10 mg 12 hourly Group C: Amitriptylin 10 mg 12 hourly with placebo of Gabapentin 100 mg 12 hourly or GroupD: Placebo of both trial medicines, orally 12 hourly daily for 14 days, all in combination with opioids as standard analgesic for treatment of cancer pain. Placebo was procured from manufacturers of gabapentin and amitriptyline (KC Laboratory, Mumbai) for matched placebo.

The primary endpoint outcome variables were: (a). Pain score (burning and shooting) by Numerical rating scale (NRS) 0 – 10 using Brief pain Inventory (BPI) at day 0, 8 and 15 day after intervention. (b). Assessment of interference of activity by pain during past 24 hour at day 0, 8 and 15 day after intervention by BPI. The secondary end point outcome variables were: (i) Recording of average daily paroxysmal pain (shooting and Lancinating) episodes. (ii). Previous 24 hour opioid rescue dose. (iii). Assessment of quality of pain relief by using “Pain relief scale” (PRS) and “Patient’s global impression change” (PGIC).
**Sample Size & Sampling Unit:** A sample size of 20 in each group assumed to be sufficient to detect a clinically important difference of \((\mu_1 - \mu_2)\) 2 points on the Numerical Rating Scale (NRS) scale of pain, assumed a standard deviation(\(\sigma\)) 1.5 with a power of 90% and a significance level of 1 %. A total of 80 patients (20 in each of the four groups) were selected from a Regional Cancer Center Hospital of North Eastern State.

**Randomization:** Sequence generation: Permutated fixed block randomization in a block of 8. Allocation concealment mechanism: Sequentially numbered sealed opaque envelope. Implementation: Random allocation sequence was generated by a faculty member of the Dept. of Community Medicine independent to investigator. Participants were enrolled and assigned intervention by a particular investigator. Blinding: Double blind (both patient and investigator) by matched placebo.

**Study Conduct:** Cancer patients diagnosed as having neuropathic pain that was not completely controlled with opioid analgesics (Morphine ≥ 60mg) with or without non-steroidal anti-inflammatory drugs (NSAIDS) and attended in Regional Cancer Centre were enrolled in this study. Patients satisfying the inclusion criteria were recruited in the present study. Patients, receiving non-opioid analgesics at baseline and steroid therapy were considered as eligible if administration of these drugs had not been initiated or increased in the 24 prior to study entry. Baseline assessment including diagnostic work-up and laboratory assessments was done.

A full voluntary written informed consent was obtained from each patient after explaining the benefit and harm of joining the study. Study was conducted following the principles of Helsinki after getting approval from “Institutional Ethics Committee, Agartala Govt. Medical College”. Before enrolment of first patient this clinical trial was registered vide No. CTRI/2012/12/002182. The trial was comprised of complete medical history and physical examination and screening. Investigative work-up consisting of estimation of Hb%, FBS, KFT, LFT. The eligible participants were placed for randomization.

- **Visit 1(-1week):** The patients were screened for suitability to the study.
- **Visit 2 (0 day):** Eligible patients were randomized and allocated in a block of eight in 1:1:1:1 pattern to four interventions arms to receive trial medication or placebo, all in combination with opioids and opioid dose was kept constant at same as dose receiving at the entry in study. Additional rescue opioid analgesic was allowed in subjects of all the groups whenever required. All the patients were assessed for primary and secondary objective variables, safety data and laboratory data on 0 day.
- **Visit 3(8 day):** Patients were assessed for disease status. Laboratory work up along with assessment of efficacy and safety parameters of the intervention were recorded.
- **Visit 4(15 day):** Patients were assessed for disease status and then efficacy and safety of the intervention along with laboratory work up data were recorded.
- **All the patients were assessed for primary and secondary outcome variables on 0, 8, and 15 days. Pain intensity (burning and shooting pain), the primary endpoint variable by the NRS of 0–10 were assessed using the modified brief pain inventory (BPI). Assessments of interference of activities by pain, during past 24 hour were also recorded by using BPI at...**
day 0, 8 and 15 days. Toxicity based on the following symptoms were recorded in the pain diary on a four-point scale as “none”, “mild”, “moderate”, or “severe” for constipation, nausea, drowsiness, dizziness, headache, and peripheral edema. The quality of pain relief during the study period were also assessed by the patients using the pain relief scale (PRS; a 5-point categorical scale, which indicates 0 (none), 1 (slight), 2 (moderate), 3 (lots), and 4 (complete) and the patient global impression of change (PGIC; a 7-point categorical scale that rates change in overall status from the beginning of the study with choices of 1 (much improved), 2 (moderately improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (moderately worse), or 7 (much worse). Average daily paroxysmal pain (shooting and Lancinating) episodes, Presence and absence of allodynia and previous 24 hour opioid rescue dose, Physician’s Global Impression also were recorded at 0, 8 and 15 days after intervention.

The physician’s Global Assessment (GI) of efficacy and safety was graded on a four-point scale as no response (0), fair (1), good (2), and excellent (4). Although data acquisition for the trial was no longer done after 15days, all patients received palliative care thereafter from Palliative care OPD, Radiotherapy department. They also received palliative radiotherapy/chemotherapy, if indicated.

**Statistical Analysis:** Nonparametric data were compared between the groups by Chi square Test or Kruskal-Wallis, One way ANOVA which ever applicable, with \( P < 0.05 \) as the cut-off level for significance, which was followed by a post hoc Turke’s Test as post adhoc. Comparisons were two-tailed. Data analysis was carried out in SPSS17 and Statistica version 6.

**RESULTS AND OBSERVATIONS:** In this study out of the total 107 cancer patients screened, only 80 eligible patients were randomized in four groups. 78 subjects completed 7 days treatment and only 74 patients completed 14 days treatment hence completed the study. The four groups were comparable with respect to age, gender distribution, smoking habit and other baseline clinical characteristics. (Table 1)

Worst pain score, Least Pain score, Average Pain score and Current pain score in Numerical Rating Scale (NRS) by Brief Pain Inventory (BPI) in last 24 hour at enrolment, after 7 and 14 days of intervention has been recorded and shown in Table-2. There was no significant difference of Worst pain score, Least Pain score, Average Pain score and Current pain score in last 24 hour, between the groups after intervention on 8th day and 15th day following treatment.

Assessments of interference of activity by pain during past 24 hour at day 0, day 8 and day 15 after intervention by Brief Pain Inventory (BPI) was also done. But there was no significant difference between the groups.

Average Daily Paroxymal pain episode and Amount of Morphine Dose, Percentage of Relief of pain, Number of opioid rescue dose, Total Amount of rescue opioid analgesics in Previous 24 hour, following intervention has been recorded on day 0, day 8 and day 15 and shown in Table 3. Except “Average Daily Paroxymal pain episode” there was no significant statistical difference between the groups after intervention on 8th day and 15 day. The average Daily Paroxymal pain episode was significantly less (\( P = 0.02 \)) in gabapentin combined with Amitryptyline group when compared with placebo group i.e. only opioid group at 15th day.
Following assessment of quality of pain relief by using “Pain relief scale’ (PRS) at the end of 14 day intervention in gabapentin and amitriptyline group, out of 18 patients who completed the study, 12 patients rated the pain relief as lots, 1 patient as complete relief and 5 patients as moderate relief. Whereas placebo group (N=18) rated the pain relief as 1 as complete, 5 as lots, 5 as moderate 4 as slight 2 as none and it was observed that PRS score between the groups did not reach significant level of difference at any study point.

**Table 1:** Gabapentin or/ and amitriptyline as adjuvant for neuropathic cancer pain – demographic and baseline clinical characteristics.

| Variables                          | Gabapentin & Amitriptyline | Gabapentin | Amitriptyline | Placebo | Remarks     |
|-----------------------------------|-----------------------------|------------|---------------|---------|-------------|
| Randomized Subjects               | 20                          | 20         | 20            | 20      | Total 80    |
| Age (Mean± SD) in years           | 51.7± 10.83                 | 51.3±8.75  | 51.75±14.11   | 52.05±9.83 | P= 0.997    |
| Male                              | 10                          | 15         | 10            | 13      | Chi square  |
| Female                            | 10                          | 5          | 10            | 7       | p = 0.14    |
| Non smoker                        | 12                          | 10         | 13            | 9       | Chi square  |
| Smoker                            | 8                           | 10         | 7             | 11      | p = 0.59    |
| Dose of Morphine in last 24 hour at Day0 (Mean± SD) in mg | 78.50±32.61 | 70.0±24.06 | 63.75±10.11 | 73±20.42 | P= 0.25    |
| Percentage of Relief of pain in last 24 hour at Day 0 (Mean± SD) | 45±23.06 | 52.5±21.98 | 51.0±17.74 | 47.5±23.59 | P= 0.69    |
| Allodyna at 0 hour Present: Absent | 3:17                        | 1:19       | 6:14          | 12:68   | Chi square p = 0.14 |
| Average Daily Paroxymal Pain at Day 0 (Mean± SD) in NRS | 3.60±1.1.54 | 3.35±1.04 | 3.40±1.47 | 3.25±1.16 | P= 0.86    |
| In Previous 24 hour, Number of opioid rescue dose at Day 0 (Mean± SD) | 0.10±0.30 | 0.05±0.22 | 0.10±0.30 | 0.10±0.45 | P=0.95     |
| Amount of rescue opioid analgesics at Day 0 (Mean± SD) in mg | 2.00± 6.16 | 1.5±6.70 | 1.5±4.89 | 2.0 ± 8.94 | P=0.99     |
| No of subjects completed treatment at day 15 | 18          | 20         | 19            | 17      | Total 74    |

Table 1
After assessment of Allodyna and quality of pain relief by using “Patient’s Global impression change” (PGIC) at different time, it was observed that except Allodyna on day 8, the findings did not indicate any significant difference between the groups at different study point. Allodyna was absent in 19 subjects in Gabapentin + Amitryptyline group (N=20) and in amitriptyline group allodyna was absent in 15 subjects out of 20 (p = 0.03).

**Table 2:** Gabapentin or/ and amitriptyline as adjuvant for neuropathic cancer pain – Measurement of Worst Pain Score, Least Pain score, Average pain score in last 24 hour and pain at the time of assessment in Numerical Rating Scale (NRS) 0 to 10 by Brief Pain Inventory (BPI) at enrollment i.e. at day 0, day 8 and at day 15 after intervention.

| Variables                        | Days | Gabapentin & Amitryptyline | Gabapentin | Amitryptyline | Placebo | Remarks |
|----------------------------------|------|-----------------------------|------------|---------------|---------|---------|
| Worst Pain Score in last 24 hour | 0    | 8.80±0.95                  | 7.90±1.29  | 8.40±1.00     | 8.35±1.04 | P=0.081 |
|                                  | 8    | 6.50±1.73                  | 6.25±2.12  | 6.75±1.41     | 7.28±1.40 | P=0.297 |
|                                  | 15   | 5.44±1.85                  | 5.30±2.18  | 6.05±1.96     | 6.35±2.00 | P=0.343 |
| Least Pain score in last 24 hour | 0    | 4.60±2.35                  | 3.00±1.72  | 3.85±1.84     | 3.65±2.20 | P=0.110 |
|                                  | 8    | 1.75±1.91                  | 1.65±1.46  | 2.30±1.38     | 2.44±1.42 | P=0.306 |
|                                  | 15   | 1.11±1.08                  | 1.10±1.30  | 1.84±1.46     | 1.71±1.31 | P=0.177 |
| Average pain score in last 24 hour| 0    | 6.90±1.45                  | 5.65±1.57  | 5.85±1.69     | 6.25±1.62 | P=0.072 |
|                                  | 8    | 3.95±1.99                  | 3.65±2.03  | 4.40±1.53     | 4.89±1.61 | P=0.178 |
|                                  | 15   | 2.83±1.33                  | 3.25±2.02  | 3.84±1.61     | 4.41±2.03 | P=0.054 |
| Pain Score at the time of assessment in last 24 hour | 0    | 5.70±2.20                  | 3.90±1.68  | 4.95±1.85     | 4.90±2.55 | P=0.068 |
|                                  | 8    | 3.15±2.32                  | 2.45±2.37  | 3.00±1.41     | 3.56±2.281| P=0.455 |
|                                  | 15   | 1.56±1.20                  | 2.00±1.80  | 2.68±1.97     | 2.47±1.42 | P=0.170 |

Tests of Significance done by One-way Anova.

Table 4 and 5 shows that after 8 days and 15 days of intervention, except nausea at day 15 and drowsiness at day 8, there were no other significant differences between the groups regarding adverse effects like constipation, nausea, drowsiness, dizziness, headache and edema in different study point.

Assessment of efficacy (Global assessment) by the physician, after 14 days of intervention has been shown in Table 6. The overall assessment of efficacy (Global assessment) by the physician after intervention was significantly better (p< 0.05) in intervention group than the placebo group.
Regarding the assessment of overall safety of the formulation by the physician, the results do not indicate any significant difference between the formulations.

**Table 3:** Gabapentin or/ and amitriptyline as adjuvant for neuropathic cancer pain – Amount of Morphine Dose in last 24 hour, Percentage of Relief of pain in last 24 hour, Average Daily Paroxymal pain episode, Number of Previous 24 hour opioid rescue dose, Total Amount of rescue opioid analgesics.

| Variables                          | Days | Gabapentin & Amitriptyline | Gabapentin | Amitriptyline | Placebo | Remarks |
|-----------------------------------|------|----------------------------|------------|---------------|---------|---------|
| **Amount of Morphine Dose in mg** | 0    | 78.50±32.61                | 70.00±24.06| 63.75±10.11   | 73.00±20.41 | P=0.1259 |
| (Mean ± SD)                       | 8    | 76.50±32.45                | 70.00±24.06| 63.75±10.11   | 75.56±20.79 | P=0.0931 |
|                                  | 15   | 78.61±34.46                | 70.00±24.06| 63.95±10.35   | 75.59±21.42 | P=0.1197 |
| Percentage of pain Relief         | 0    | 45.00±23.06                | 52.50±21.98| 51.00±17.74   | 47.50±23.59 | P=0.692  |
| (Mean ± SD)                       | 8    | 77.00±15.93                | 71.00±17.44| 65.00±17.01   | 63.89±19.45 | P=0.080  |
|                                  | 15   | 82.78±13.20                | 75.50±16.05| 73.16±13.36   | 71.76±20.69 | P=0.180  |
| Average Daily Paroxymal pain episode | 0    | 3.60±1.54                  | 3.35±1.04  | 3.40±1.47     | 3.25±1.164 | P=0.861  |
| (Mean ± SD)                       | 8    | 2.10±1.02                  | 2.45±0.89  | 2.50±1.051    | 2.67±1.41  | P=0.444  |
|                                  | 15   | *1.33±0.84                 | 1.85±0.93  | 2.05±1.27     | *2.47±1.23 | *P=0.02  |
| **Number of Previous 24 hour opioid rescue dose. (Mean ± SD)** | 0    | 0.10±0.308                 | 0.05±0.22  | 0.10±0.31     | 0.10±0.48  | P=0.8863 |
|                                  | 8    | 0.05±0.22                  | 0.10±0.31  | 0.20±0.41     | 0.28±0.67  | P=0.4941 |
|                                  | 15   | 0.06±0.24                  | 0.10±0.31  | 0.11±0.32     | 0.29±0.69  | P=0.7162 |
| **Total Amount of rescue opioid analgesics. (Mean ± SD)** | 0    | 2.00±6.16                  | 1.50±6.71  | 1.50±4.89     | 2.00±8.94  | P=0.9018 |
|                                  | 8    | 0.50±2.24                  | 2.50±7.86  | 3.00±6.57     | 4.72±11.44 | P=0.4941 |
|                                  | 15   | 2.78±11.79                 | 2.50±7.86  | 2.11±6.31     | 4.71±11.25 | P=0.7469 |

*Turke’s Test as post adhoc test shows that there is significant difference.*

** Non parametric test Kruskal-Wallis Test ANOVA by Ranks done.
Table 4: Gabapentin or/ and amitriptyline as adjuvant for neuropathic cancer pain – Assessment of Adverse effects like constipation, Nausea and Drowsiness after intervention.

| Variables                  | Grades   | Gabapentin & Amitriptyline | Gabapentin | Amitriptyline | Placebo | Remarks                       |
|---------------------------|----------|----------------------------|------------|---------------|---------|-------------------------------|
| Constipation at Day 0      | None     | 3                          | 6          | 8             | 9       | Chi-square test p value 0.566 |
| (N = 80)                  | Mild     | 6                          | 7          | 6             | 5       |                               |
|                           | Moderate | 6                          | 5          | 5             | 5       |                               |
|                           | Severe   | 5                          | 2          | 1             | 1       |                               |
| Constipation at Day 8      | None     | 1                          | 3          | 5             | 5       | Chi-square test p value 0.172 |
| (N = 78)                  | Mild     | 6                          | 7          | 7             | 5       |                               |
|                           | Moderate | 7                          | 8          | 7             | 8       |                               |
|                           | Severe   | 6                          | 2          | 1             | 0       |                               |
| Constipation at Day 15     | None     | 1                          | 4          | 3             | 3       | Chi-square test p value 0.273 |
| (N=74)                    | Mild     | 1                          | 6          | 7             | 4       |                               |
|                           | Moderate | 14                         | 9          | 7             | 10      |                               |
|                           | Severe   | 2                          | 1          | 2             | 0       |                               |
| Nausea at Day 0            | None     | 13                         | 14         | 14            | 13      | Chi-square test p value 0.0566 |
| (N = 80)                  | Mild     | 3                          | 4          | 5             | 2       |                               |
|                           | Moderate | 3                          | 2          | 1             | 5       |                               |
|                           | Severe   | 1                          | 0          | 0             | 0       |                               |
| Nausea at Day 8            | None     | 12                         | 11         | 16            | 5       | Chi-square test p value 0.057 |
| (N = 78)                  | Mild     | 5                          | 8          | 3             | 10      |                               |
|                           | Moderate | 3                          | 1          | 1             | 3       |                               |
|                           | Severe   | 0                          | 0          | 0             | 0       |                               |
| Nausea at Day 15           | None     | 7                          | 17         | 15            | 8       | Chi-square test p value 0.028 |
| (N=74)                    | Mild     | 9                          | 3          | 4             | 5       |                               |
|                           | Moderate | 2                          | 0          | 0             | 3       |                               |
|                           | Severe   | 0                          | 0          | 0             | 1       |                               |
| Drowsiness at Day 0        | None     | 12                         | 15         | 11            | 14      | Chi-square test p value 0.810 |
| (N = 80)                  | Mild     | 5                          | 4          | 5             | 4       |                               |
|                           | Moderate | 3                          | 1          | 4             | 2       |                               |
|                           | Severe   | 0                          | 0          | 0             | 0       |                               |
| Drowsiness at Day 8        | None     | 5                          | 10         | 10            | 6       | Chi-square test p value 0.012 |
| (N = 78)                  | Mild     | 5                          | 6          | 9             | 11      |                               |
|                           | Moderate | 5                          | 3          | 1             | 1       |                               |
|                           | Severe   | 5                          | 1          | 0             | 0       |                               |
**Table 4**

| Drowsiness at Day 15 (N=74) | None | Mild | Moderate | Severe | Chi-square test p value |
|-----------------------------|------|------|----------|--------|-------------------------|
| None                        | 3    | 10   | 2        | 3      | 0.135                   |
| Mild                        | 7    | 9    | 2        | 2      |                         |
| Moderate                    | 11   | 8    | 0        | 0      |                         |
| Severe                      | 8    | 6    | 3        | 0      |                         |

**Table 5:** Gabapentin or/ and amitriptyline as adjuvant for neuropathic cancer pain – Assessment of Adverse effects like dizziness, headache & peripheral edema after intervention.

| Variables          | Grades   | Gabapentin & Amitryptiline | Gabapentin | Amitryptiline | Placebo | Remarks             |
|--------------------|----------|----------------------------|------------|---------------|---------|---------------------|
| Dizziness at Day 0 (N = 80) | None     | 0                           | 0          | 15            | 12      | Chi-square test p value 0.019 |
|                    | Mild     | 12                          | 20         | 4             | 4       |                     |
|                    | Moderate | 7                           | 0          | 0             | 4       |                     |
|                    | Severe   | 1                           | 0          | 1             | 0       |                     |
| Dizziness at Day 8 (N = 78) | None     | 12                          | 15         | 13            | 9       | Chi-square test p value 0.627 |
|                    | Mild     | 7                           | 5          | 5             | 7       |                     |
|                    | Moderate | 1                           | 0          | 1             | 2       |                     |
|                    | Severe   | 0                           | 0          | 1             | 0       |                     |
| Dizziness at Day 15 (N=74) | None     | 12                          | 17         | 15            | 13      | Chi-square test p value 0.468 |
|                    | Mild     | 4                           | 3          | 2             | 4       |                     |
|                    | Moderate | 2                           | 0          | 2             | 0       |                     |
|                    | Severe   | 0                           | 0          | 0             | 0       |                     |
| Headache at Day 0 (N = 80) | None     | 13                          | 14         | 12            | 9       | Chi-square test p value 0.650 |
|                    | Mild     | 6                           | 4          | 6             | 9       |                     |
|                    | Moderate | 1                           | 2          | 2             | 1       |                     |
|                    | Severe   | 0                           | 0          | 0             | 1       |                     |
| Headache at Day 8 (N = 78) | None     | 13                          | 16         | 14            | 12      | Chi-square test p value 0.496 |
|                    | Mild     | 7                           | 2          | 4             | 4       |                     |
|                    | Moderate | 0                           | 2          | 2             | 2       |                     |
|                    | Severe   | 0                           | 0          | 0             | 0       |                     |
| Headache at Day 15 (N=74) | None     | 15                          | 14         | 12            | 13      | Chi-square test p value 0.796 |
|                    | Mild     | 3                           | 5          | 5             | 3       |                     |
|                    | Moderate | 0                           | 1          | 2             | 1       |                     |
|                    | Severe   | 0                           | 0          | 0             | 0       |                     |
| Peripheral         | None     | 18                          | 17         | 16            | 18      | Chi-square          |
Table 5:

| Variables                  | Grades | Gabapentin & Amitriptyline | Gabapentin | Amitriptyline | Placebo | Remarks |
|----------------------------|--------|-----------------------------|------------|---------------|---------|---------|
| overall assessment of efficacy at Day 15 (N=74) | No response | 1 | 3 | 2 | 4 | Chi-square test p value 0.045 |
|                            | Fair   | 1 | 3 | 10 | 5 |
|                            | Good   | 11 | 10 | 5 | 5 |
|                            | Excellent | 7 | 4 | 3 | 3 |

DISCUSSION: Pain management in cancer patients is challenging and continuous task and about 75% of cancer patients with pain require treatment with opioids as first line drug for severe pain. Neuropathic pain is frequently diagnosed as complication of cancer pain. Efficacy of opioids in neuropathic pain seems to be less optimal, and adjuvant drugs, mainly anticonvulsants and antidepressants are often combined with opioids.

Proper assessment of pain in the cancer is imperative because its failure can lead to an under treatment. Intensity of pain can be assessed by self-reporting by the patients but could be better assessed with visual analogue scales (VAS), numerical rated scales (NRS) and verbal rated scales (VRS). The Brief Pain Inventory (BPI) is a quickly administered assessment tool for capturing both the intensity of a patient’s cancer-related pain as well as the amount of interference in a patient’s life caused by pain. First developed in English, the BPI’s simple format and its focus on a limited number of relatively universal functions has made it easy to translate. Several studies have provided evidence that patients who are from different cultures and speak different languages rate the items in a similar fashion. The BPI can be thought of as consisting of
a pain severity subscale and a pain interference subscale. In this study BPI was translated in local languages, explained validated in present set up. Data was captured by research associate. Gabapentin is a centrally acting GABA agonist and promotes non-vesicular release of GABA. It interacts with N-methyl-D-aspartate receptor system. It also decreases the release of substance P and glutamate. Although Gabapentin has a role in treatment of painful diabetic neuropathy, post-herpetic neuralgia and cancer related neuropathic pain but there is lack of consensus with regard to dosage, indication for its use and some patients experience intolerable side effects sufficient to warrant discontinuation.

Amitriptyline, a tricyclic antidepressant, which is most widely, accepted adjuvant analgesic for neuropathic pain. It is also important to consider the balance between benefits and risks of adjuvant analgesics with opioids, because the efficacy of adjuvant analgesics is often limited by various side effects.

So it was assumed rational to study the efficacy of gabapentin and/or amitriptyline in low doses for relief of neuropathic cancer pain. Pain assessment also has been done by dependable and acceptable pain assessment tools like NRS and BPI.

The findings of this study indicate that there were no statistically significant effects on worst, least, average or current neuropathic pain in NRS after addition of gabapentin and/or Amitriptyline in low dose, 200 mg/ day and 20 mg/day respectively as adjuvant with opioids. This result is almost in consistent with the finding of Rao RD at al. 2007 and Shinde S et al. 2014. However our result is in contrast to finding of Keskinbora K 2007 and Banerjee M 2013 who found statistically significant low pain score by using high dose gabapentin 900 mg and 600 -1800 mg respectively. But Takahashi H and Shimoyama N, 2010 has demonstrated that statistically significant changes in NRS by gabapentin may not be sufficient in clinical practice.

The patient’s global impression change in this study failed to demonstrate any significant difference between the groups and this finding is comparable with the finding of Takahashi H, 2010 and Caraceni A, 2004 who also recorded no global impression change by the patient’s.

In accordance with the finding of Arai YC P et al. 2010, this study demonstrate that low dose gabapentin and amitriptyline in combination with opioids significantly decreased daily paroxysmal pain episodes when compared with only opioids. But there was no significant difference of percentage of pain relief, previous 24 hour opioid rescue dose and quality of pain relief by pain relief scale (PRS).

As found by the other workers the adverse effects experienced by patients in this study were of mild – to moderate degree and did not require discontinuation of therapy.

Insensitive difference between the groups may be due to small daily gabapentin dose (200mg/day) compared with higher dose titration that used in the other previous studies. Although there may be genetic or cultural differences from other populations that affect the response to gabapentine, a more aggressive titration schedule might be introduced for future trials.

In conclusion the role of gabapentin in expanding the efficacy of opioid analgesia in combined drug regimens has a rational basis but should be supported by clinical studies. In accordance to finding of other studies our results demonstrate a limited role of gabapentin as adjuvant to opioids for neuropathic cancer pain, although significant benefit could be seen in
some patients. So study with higher dose of adjuvant analgesic for long duration may be able to
demonstrate significant results of clinical importance.

**Study overview & treatment arm:**

- **Assessment for eligibility (107)**
- **Randomization N = 20 + 20 + 20 + 20 = 80**
- **Opioid analgesic (Morphine Tab) +**
  - Gabapentin 100mg + Amitriptyline 10mg For 14 days
  - Gabapentin 100mg + Placebo of Amitriptyline For 14 days
  - Gabapentin Placebo + Amitriptyline 10 mg For 14 days
  - Placebo of both Drugs For 14 days

- Measurement of pain score (burning & shooting) by Numerical rating scale (NRS) 0 – 10 using Brief pain Inventory (BPI) at day 0, 8 and 15 day after intervention.
- Assessment of interference of activity by pain during past 24 hour at day 0, 8 and 15 day after intervention

**Following secondary objective variables also will be assessed at day 0, 8 and 15 day after intervention**
- Recording of average daily paroxysmal pain (shooting and Lancinating) episodes.
- Previous 24 hour opioid rescue dose.
- Assessment of quality of pain relief by using “Pain relief scale” (PRS) and “Patient’s global impression change” (PGIC).
- Recording of toxicity based on four point scale.
- Presence and absence of allodynia.
- Amount of rescue opioid analgesics.

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