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Randomized Trial

# Efficacy of Intrathecal Midazolam with or without Epidural Methylprednisolone for Management of Post-Herpetic Neuralgia Involving Lumbosacral Dermatomes

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**Background:** Post herpetic neuralgia is a chronic neuropathic pain syndrome which remains one of the most difficult pain disorders to treat. Epidural injection of methylprednisolone with or without local anesthetic provides relief for neuralgia for a short duration only. Recent studies have shown a promising anti nociceptive effect for intrathecal midazolam, a water soluble benzodiazepine, due to its interaction with benzodiazepine-GABA-A receptor complex within the spinal cord.

**Study Design:** A randomized, double blind study was conducted at 2 different centers in India.

**Setting:** Two different interventional pain practice centers in India.

**Objectives:** To quantify the effectiveness of a single intrathecal injection of midazolam 2 mg with and without epidural methylprednisolone 60 mg for management of pain and allodynia in 150 adult patients with postherpetic neuralgia of 3-6 months duration involving lumbosacral dermatomes.

**Methods:** Patients in Group M-0 (n=50) received epidural methylprednisolone (60 mg), patients in group M-1 (n=50) received midazolam 2 mg in the intrathecal space while patients in Group M-2 (n=50) received methylprednisolone (60 mg) in the epidural space plus midazolam 2 mg in the intrathecal space.

**Results:** The administration of intrathecal midazolam (2 mg) provided short term improvement in post herpetic neuralgia similar to epidural methylprednisolone. However, the combination of intrathecal midazolam with epidural methylprednisolone resulted in prolonged duration of analgesia in patients with post herpetic neuralgia. The need for analgesics was also significantly less in patients who received the combination compared to those who received either intrathecal midazolam or epidural methylprednisolone. No serious adverse effect was reported with the use of intrathecal midazolam except a mild degree of sedation.

**Conclusion:** The combination of intrathecal midazolam with epidural methylprednisolone resulted in prolonged duration of analgesia in patients with post herpetic neuralgia of lumbosacral dermatomes due to the complementary anti nociceptive action of intrathecal midazolam with epidural methylprednisolone on spinal nerve roots.

**Limitations:** The dose-response relationship of intrathecal midazolam was not evaluated in our study, so further study should be conducted with different doses of intrathecal midazolam for management of PHN.

**Key words:** postherpetic neuralgia, lumbosacral, midazolam, intrathecal, methylprednisolone, epidural, pain, allodynia, sedation, neurological sequelae.

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Post herpetic neuralgia (PHN) is the most common sequelae of herpes zoster (1), commonly affecting elderly patients (2). It presents as pain that persists after the resolution of the rash caused by herpes zoster. Different authors have proposed different time durations for labelling the pain of herpes zoster as PHN; varying from 3-6 months after the onset of skin lesions (3-6). The pain of PHN usually follows the typical dermatomal distribution of the rash caused by herpes zoster and is accompanied by allodynia and hyperalgesia. The most frequently involved dermatomes with PHN are the thoracic dermatomes (53%) while the lumbar and sacral dermatomes are affected in 21% and 8% of patients, respectively (7).

Commonly prescribed medications for pain relief of PHN include opioids (8), antidepressants (9), anticonvulsants (10,11) and topical application of local anesthetic (12) and capsaicin (13). Cases refractory to these medications received epidural (12) and intrathecal (14,15) injections of corticosteroids with or without local anaesthetics. However, both of these therapeutic interventions did not provide long lasting pain relief and were associated with the risk of neurological complications.

Midazolam, a water soluble benzodiazepine, has been used via intrathecal route in the management of acute (perioperative) (16,17), chronic (18) and cancer (19) pain. Goodchild and Noble (16) were the first to demonstrate the role of intrathecal midazolam in relieving the pain of somatic origin in humans. It was suggested that this effect of intrathecal midazolam was produced due to its action on benzodiazepine-GABA-A receptor complex within the spinal cord (20), which lead to enhanced activity of GABA, an inhibitory neurotransmitter, in the primary afferent neurons. The localization of a specific benzodiazepine binding site on a subunit of GABA-A receptor in the dorsal root ganglia and on spinal neurons of mammalian spinal cord by Bohlhalter et al (21) clearly established that the antinociceptive action of intrathecal midazolam was produced due to its action on the benzodiazepine-GABA-A receptor complex within the spinal cord.

The study conducted by Kontinen and Dickensen (22) demonstrated that midazolam could play an important role in the management of neuropathic pain due to its action on the GABAergic system within the spinal cord. A continuous intrathecal infusion of midazolam was used for the relief of neurogenic pain without any toxic effect on nerve roots (23).

Serrao et al (18) compared the action of intrathecal midazolam with epidural methylprednisolone in patients with chronic mechanical low back pain. They reported that intrathecal midazolam provided similar improvement in pain and physical activity of patients as epidural methylpredinsolone; however, the requirement of analgesic medication was significantly reduced in patients who received intrathecal midazolam, while no change in the intake of analgesics was noted in the steroid group.

Since PHN is a state of persistent inflammatory response to spinal nerve roots, we investigated the possible role of intrathecal midazolam with or without epidural methylpredinsolone in the management of pain and allodynia in patients with post herpetic neuralgia involving lumbar and sacral dermatomes.

## Methods

After obtaining approval from the hospital ethics committee, a randomized, double blind study was conducted at 2 different centers, Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh, India; and Delhi Pain Management Centre, New Delhi, India.

### Participants

The study enrolled 150 patients aged 35-70 with pain and allodynia due to herpes zoster of 3-6 months duration involving only the lumbosacral dermatomes. Patients with coexisting systemic diseases, coagulation abnormalities, neurological diseases, immune disorders, or those who had already received spinal injections or nerve blocks for pain relief were excluded from the study.

### Randomization

The patients were then randomly divided into 3 groups of 50 patients, using computer generated randomization schedule. Patients in Group M-0 received methylprednisolone (60 mg) suspended in 10 mL of normal saline in the epidural space and preservative free normal saline 2 mL in the intrathecal space. Patients in Group M-1 received normal saline 10 ml in the epidural space and midazolam 2 mL (one mg/mL, preservative free) in the intrathecal space while patients in Group M-2 received methylprednisolone (60 mg) suspended in 10 mL normal saline in the epidural space plus midazolam 2 mL (one mg/mL) in the intrathecal space.

### Interventions

All patients were advised to stop all other medications except tablet paracetamol 650 mg at 6 hour

intervals 2 weeks prior to the date of injection. However, patients were not allowed to take any analgesic medication 24 hours before the administration of study drugs. The injections were given independently by 2 physicians at 2 study centers. Each physician had experience performing spinal and epidural blocks under the guidance of image intensifier (C-arm). The patients were kept in the left or right lateral position with the affected side down. The epidural injections were given either at the L1-L2 or L2-L3 intervertebral space. An 18-gauge Tuohy needle was used for injection into the epidural space which was identified by the loss of resistance technique. A non ionized contrast agent (iohexol 300 mg I/mL) was injected to confirm the epidural space before administrating the study drugs. The intrathecal injections were given at one segment lower than epidural injections i.e. L2-L3 or L3-L4 intervertebral space using a 23-gauge, Quincke spinal needle. The intrathecal injection was given after confirming the free flow of cerebrospinal fluid (CSF) through the spinal needle.

After the injections, the patients were monitored in the recovery room by an observer blinded to the study groups for level of sedation and any post procedural complications such as hypotension, bradycardia, respiratory depression (respiratory rate < 8 per minunte), nausea and vomiting, headache, back or leg pain/weakness, and urinary or faecal dysfunction. Sedation was assessed using a 4-point scale (24), 1 = responds readily to name spoken in a normal tone, 2 = lethargic response to a name spoken in a normal tone, 3 = responds only after name is called loudly and 4 = responds only after mild prodding or shaking.

### Outcomes

The severity of pain and allodynia was assessed by the same blinded observer using a visual analog scale (VAS) of 0-10 (0= no pain, 10 = worst imaginable pain). The allodynia was elicited by stroking the skin with a 2 cm wide electrical toothbrush (Oral-B, Procter and Gamble Ltd). The area of allodynia was calculated after marking the skin in 8 directions as described by Kotani et al (15). The assessment was done just before the administration of the study drugs, at the time of discharge from the hospital, at weekly intervals for 4 weeks, and then at 8 weeks and 12 weeks by an observer unaware of the study groups assigned.

The patients were discharged from the recovery room after they were fully awake and oriented (sedation scale = 1) and no adverse effects were noted for 6-8 hours after the injection of the study drugs. The patients were allowed to take tablet paracetamol 650 mg as required during the study period with a minimum interval of 6 hours between doses. For any breakthrough pain during this period, tablet tramadol 50 mg was given as a rescue analgesic. However, patients were not allowed to take any analgesic medication one day before evaluation.

A diary was maintained by every patient starting one week prior to the study period to record the number of doses of tablet paracetamol consumed each day, necessity of the rescue analgesic for breakthrough pain during the first 4 weeks of the study period, and quality of sleep as measured on a scale of 1 (very poor sleep) to 5 (slept very well).

An overall improvement in the condition of patients was evaluated with the help of global pain relief score as excellent (>75% pain relief), good (50%-74% pain relief), fair (25%-49% pain relief), and poor (<25% pain relief). The score was recorded at weekly intervals for 4 weeks and then at the eigthth and twelfth week.

### Sample size

The sample size was calculated on the basis of a pilot study with 10 patients in each group. The minimum number of patients required was found to be 42 to achieve a difference of 20% in pain relief between the groups with power of at least 80% and *P* value of 0.05. Considering any loss of subject during the study we have enroled 50 patients in each group. The data from the patients in the pilot study were incorporated in the main study.

### Statistical Methods

All data were expressed as mean ± S.D. Analysis of variance (ANOVA) test was used to measure differences among the study groups. The differences in VAS scores among the study groups were analyzed by Mann-Whitney U-test. Global pain relief was evaluated by Fisher's exact test. Values of $P < 0.05$ were considered statistically significant.

## Results

### Participant Flow

One patient in Group M-0 and 2 patients each in Groups M-1 and M-2 did not turn up in the follow up period and were therefore excluded from the study.

## Evaluation of Demographic Variables

The study groups were comparable with respect to age, sex and duration of PHN (Table 1).

Table 1. *Demographic Characteristics.*

| | M-0 (n=49) | M-1 (n=48) | M-2 (n=48) |
|---|---|---|---|
| Age (yrs) | 57.3±7.9 | 57.9±7.8 | 57.0±8.4 |
| Gender (M/F) | 26/23 | 26/22 | 27/21 |
| Duration of symptoms (days) | 126±26 | 132±25 | 139±23 |

## Control of Pain and Allodynia

Patients who received intrathecal midazolam (Groups M-1 and M-2) reported significantly better relief in pain and allodynia at the time of discharge from the hospital as compared to patients who received only epidural methylpredinsolone (Group M-0). The improvement in pain and allodynia was more or less similar at the first, second and third week of the study period in the 3 study groups, however, at the fourth, eighth and twelfth week of study, the patients in Group M-2 (epidural methylpredinsolone +intrathecal midazolam) showed significantly better scores of pain and allodynia compared with patients in Groups M-0 and M-1 (Figs. 1, 2). A significant decrease in the area of allodynia was

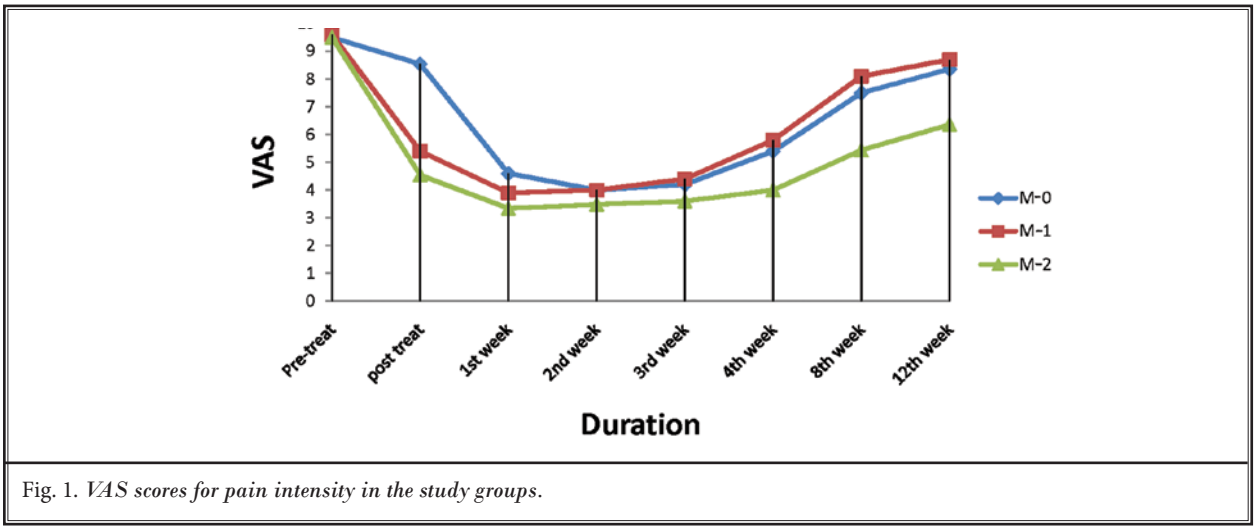


Fig. 1. *VAS scores for pain intensity in the study groups.*

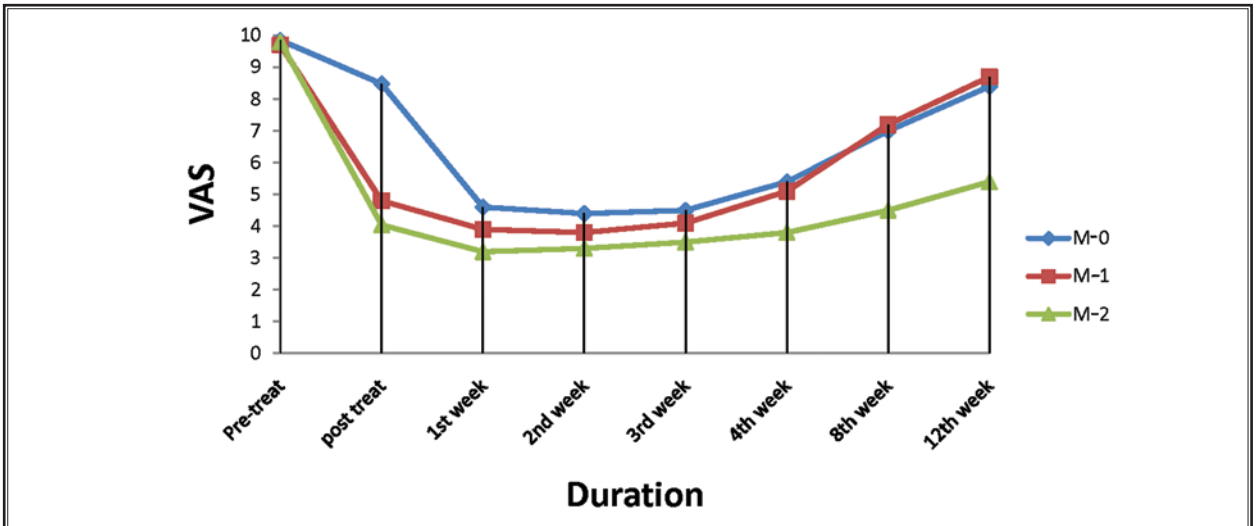


Fig. 2. *VAS scores for allodynia in the study groups.*

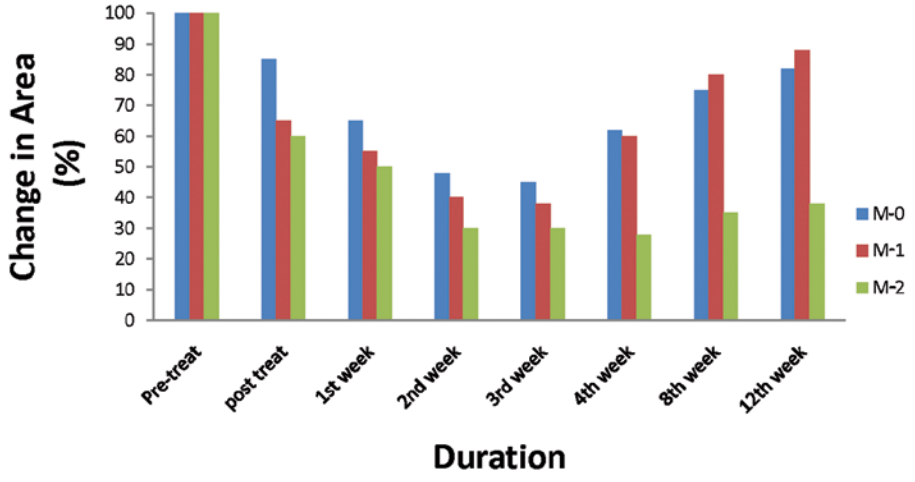


Fig. 3. *Changes in the areas of allodynia in the study groups.*

Table 2. *Global Pain Relief*

| | 1st week | | 2nd week | | 3rd week | | 4th week | | 8th week | | 12th week | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | excellent to good | fair to poor | excellent to good | fair to poor | excellent to good | fair to poor | excellent to good | fair to poor | excellent to good | fair to poor | excellent to good | fair to poor |
| Group M-0 (n=49) | 21 | 28 | 28 | 21 | 31 | 18 | 17 | 32 | 7 | 42 | 5 | 44 |
| Group M-1 (n=48) | 31* | 17 | 33 | 15 | 27 | 21 | 13 | 35 | 5 | 43 | 3 | 45 |
| Group M-2 (n=48) | 41*# | 7 | 42*# | 6 | 39*# | 9 | 30*# | 18 | 24*# | 24 | 19*# | 29 |

*$P$ <0.05 vs M0, #$P$ <0.05 vs M-1

also noted in all study groups during the first 3 weeks of the study period; however, at the fourth and eighth week a significant increase in the area of allodynia was noted in Groups M-0 and M-1 from the previous weeks; no significant change was noted in patients of Group M-2 (Fig. 3).

## Global Pain Relief

Global pain relief was graded as excellent or good by a significantly large number of patients at the first, second, third, fourth, eighth and twelfth weeks of study in Group M-2 compared with Group M-0 and Group M-1 (Table 2). Moreover, a significant difference in global pain relief was found at the first week between Groups M-0 and M-1 as well.

## Analgesic Requirement

The number of doses of paracetamol required during the first 3 weeks of the study period was significantly less in all 3 groups from the prestudy period, but at the fourth week of the study, a significant increase in doses was noted from the previous week in Group M-0 and Group M-1, but not in Group M-2 (Fig. 4). The need for rescue analgesic (tramadol) for breakthrough pain was also significantly less in Group M-2 compared with Groups M-0 and M-1 during the fourth week of the study (Fig. 5).

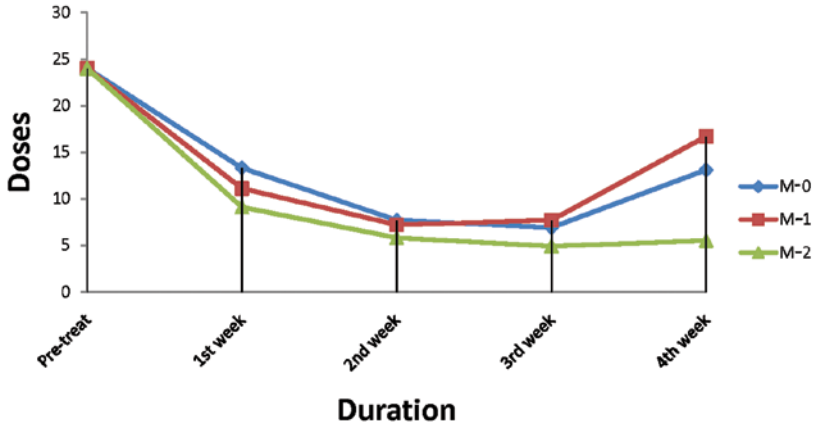


Fig. 4. *Requirement of paracetamol (doses per week) during first 4 weeks.*

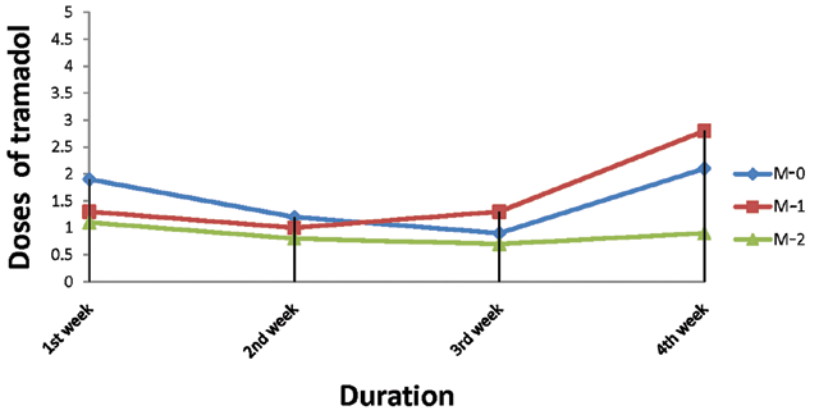


Fig. 5. *Requirement of tramadol (doses per week) during first 4 weeks.*

## Quality of Sleep

The quality of sleep was significantly improved from the pretreatment period in all 3 groups but in Groups M-0 and M-1, the quality of sleep deteriorated after the third week while patients in Group M-2 enjoyed a similar quality of sleep throughout the study period (Fig. 6).

## Adverse Events

All patients were discharged from the hospital after 6-8 hours of observation without any adverse sequelae. One patient in Group M-2 complained of difficulty in breathing after the intrathecal injection. On examination, the patient had an increased respiratory rate and heart rate, but there was no change in mean arterial pressure and arterial oxygen saturation on air from the baseline value. The symptoms of the patient subsided within half an hour and all parameters returned to baseline without any intervention. The patient was discharged from the hospital after 8 hours of monitoring in the recovery room.

An increased level of sedation was noted in significantly more patients in Groups M-1 and M-2 compared

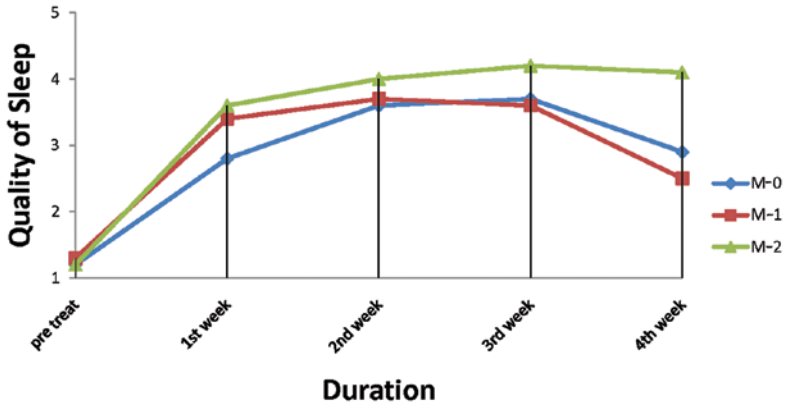


Fig. 6. *Changes in the quality of sleep in the study groups.*

with Group M-0 (Table 3). Post dural puncture headache (PDPH) was reported by 2 (4.2%) patients each in Groups M-1 and M-2 and 3 (6.1%) patients in Group M-0 during the study period, which was treated with NSAIDS and oral fluids. No neurological complication was reported during the follow up period of the study. The incidence of nausea and vomiting was comparable in all 3 groups of patients (M-0 = 4 [8.3%], M-1 = 3 [6.1%] and M-2 = 3 [6.1%]).

## Discussion

The findings of our study showed that intrathecal midazolam provided short-term improvement in pain and allodynia in patients with lumbosacral PHN. The improvement in symptoms was similar in patients who received either epidural methylprednisolone or intrathecal midazolam for PHN. Serrao et al (18) compared the analgesic efficacy of intrathecal midazolam with epidural methylprednisolone in patients with chronic mechanical low back pain. They reported similar improvement in symptoms in both groups of patients during the 2-month follow-up study period. In our study, unlike the sustained analgesia obtained in patients with chronic mechanical LBP by Serrao et al (18), the improvement in symptoms lasted for less than a month in majority of the patients of either group in our study.

A study conducted by Kikuchi et al (14) in patients with PHN observed an improvement in pain and allodynia for only one week after epidural injection of methylprednisolone. However, their study was conducted with patients in whom PHN had persisted for more than a year after herpes zoster while we enrolled patients with PHN of only 3-6 months duration.

Table 3. *Maximum Level of Sedation*

| Level of sedation | M-0 (n=49) | M-1* (n=48) | M-2* (n=48) |
|---|---|---|---|
| 1 | 35 | 5 | 6 |
| 2 | 14 | 41 | 39 |
| 3 | 0 | 2 | 3 |
| 4 | 0 | 0 | 0 |

*$P$ <0.05 vs M-0
(1=responds readily to name spoken in a normal tone, 2=lethargic response to a name spoken in a normal tone, 3=responds only after name is called loudly and 4=responds only after mild prodding or shaking)

Similar to the study of Serrao et al (18), an early improvement in pain and allodynia was observed in a significantly larger number of patients in our study after administration of intrathecal midazolam compared with those who received epidural methylprednisolone. This could be due to the direct action of midazolam on receptors involved in mediating analgesia within the spinal cord.

It was further observed in our study that the set of patients who received the combination of intrathecal midazolam with epidural methylprednisolone (Group M-2) obtained consistent analgesia throughout the 3-month study period. This shows that the anti nociceptive action of intrathecal midazolam complemented the anti-inflammatory analgesic action of epidural methylprednisolone by reversing the state of neuronal hyper excitability (neuronal plasticity) in the spinal nerves,

leading to a long term blockade in the transmission of nociceptive signals in the spinal cord.

A similar decrease in the intake of analgesics was noted for the first 3 weeks in patients who received either intrathecal midazolam (Group M-1) or epidural methylprednisolone (Group M-0). This was in contrast to the study of Serrao et al (18) where almost half of the patients after intrathecal midazolam had a lesser requirement for analgesics throughout the 2-month study period while no change in the intake of analgesics was noted in patients who received epidural methylprednisolone.

The requirement for analgesics was significantly reduced throughout the study in patients who received the combination of intrathecal midazolam with epidural methylprednisolone (Group M-2). This was due to the synergistic analgesic action of methylprednisolone and midazolam leading to a prolonged blockade of nociceptive signals within the spinal cord.

The dose of intrathecal midazolam used in our study (2 mg) was not found to produce any respiratory depression in different clinical studies on acute and chronic pain management (16,25). None of the patients in our study had any adverse respiratory events after intrathecal injection of midazolam except one patient in Group M-2 who complained of difficulty in respiration after injection. Since no deterioration in the arterial oxygen saturation was noted on pulse oximetry and the vital parameters returned to normal within a few minutes without any intervention, this was most likely the result of a temporary anxiety reaction and not the effect of intrathecal administration of midazolam per se.

Although a mild degree of sedation was observed in significantly more patients who received intrathecal midazolam (Groups M-1 and M-2) as compared with the control group , none of the patients in either group had a profound degree of sedation (level 4). Goodchild and Noble (16) reported that up to 2 mg of intrathecal midazolam produced no sedative effect in humans while Yegin et al (17) observed a mild degree of sedation after intrathecal injection of 2 mg midazolam.

Thus 2 mg of midazolam produced considerable anti nociceptive effects in different acute and chronic pain conditions without compromising the well-being of individuals. However, a further study can be conducted with different doses of intrathecal midazolam to determine the dose-response relationship in patients with PHN.

We used 23-gauge Quincke needles for intrathecal injection in our study, while Serrao et al (18) advocated the use of a 22-gauge needle for intrathecal injection to ensure definite deposition of the drug inside the intrathecal space. However, compared to the incidence of PDPH in different groups in our study (4.2% to 6.1%), Serrao et al (18) reported an almost 50% incidence of PDPH in their study groups. This striking difference in the incidence of PDPH clearly demonstrates that the use of a 23-gauge spinal needle was the better choice to keep a balance between the success of the intrathecal injection and the risk of PDPH. However, in day-to-day practice, we recommend needle through needle technique for combined spinal-epidural injections. The use of a 27-gauge spinal needle for intrathecal injection in this technique could completely abolish the incidence of PDPH.

No evidence of any neurological insult was reported with the use of intrathecal midazolam in our study. Although few animal studies have highlighted the neurotoxic potential of intrathecal midazolam (26-28), none of the human studies (17,18,25,29) have shown any association between neurotoxicity and intrathecal midazolam. Moreover, the preparation of midazolam used in our study was a preservative free hydrochloride solution of midazolam. Although there is no formulation of midazolam meant specifically for intrathecal use, studies have shown that this preparation of midazolam can be safely used for intrathecal injection compared with sulphate preparation, which contains benzoate and is not safe for intrathecal injection (30).

## Conclusion

The administration of intrathecal midazolam (2 mg) provided short-term improvement in the pain and allodynia in patients of post herpetic neuralgia involving lumbosacral dermatomes. Although the onset of action of intrathecal midazolam was earlier than epidural methylprednisolone, the duration of analgesia was comparable with both drugs. However, the combination of intrathecal midazolam with epidural methylprednisolone resulted in a prolonged duration of analgesia in patients with post herpetic neuralgia of the lumbosacral dermatomes due to the complementary anti-nociceptive action of intrathecal midazolam with epidural methylprednisolone on affected spinal nerve roots and did not cause any serious adverse effects.

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