Randomized Trial

The Effect of Repeated Paravertebral Injections with Local Anesthetics and Steroids on Prevention of Post-herpetic Neuralgia

Mohamed Younis Makharita, MD[1] and Yasser M. Amr, MD[2]

From: [1]Professor from the Departments of Anesthesiology and Surgical Intensive Care, Faculty of Medicine, Mansoura University, Egypt; [2]Professor from the Departments of Anesthesiology and Surgical Intensive Care, Faculty of Medicine, Tanta University, Egypt

Address Correspondence: Mohamed Younis Makharita, MD Professor from the Departments of Anesthesiology and Surgical Intensive Care, Faculty of Medicine, Mansoura University, Egypt Email: m_younis24@yahoo.com

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Background: The usefulness of early sympathetic blockade in the prevention of postherpetic neuralgia (PHN) has been reported. However, the optimal duration and frequency of paravertebral blocks that prevent or maximally reduce the incidence of PHN need to be clarified.

Objectives: To assess the impact of weekly separated 2 versus 3 paravertebral injections using local anesthetic and steroids, early in the course of acute thoracic herpes zoster, on the incidence of postherpetic neuralgia.

Study Design: Randomized single-blind study.

Setting: University hospitals.

Methods: Eighty patients suffering from acute thoracic herpes zoster eruption were randomly allocated into 2 groups. Group I received paravertebral block using 25 mg bupivacaine plus 8 mg dexamethasone in a total volume of 10 mL twice one week apart. Group II received paravertebral block using 25 mg bupivacaine plus 8 mg dexamethasone in a total volume of 10 mL 3 times one week apart. All patients received daily 300 mg pregabalin in divided doses (150 mg/12 hours). Pain scores were evaluated during each visit. Once the patient reported mild pain, the trial for reducing the pregabalin dose was done. Acetaminophen was available as a rescue analgesia. At each assessment visit, the total analgesic consumption was recorded. The times of the complete resolution of the pain and the skin eruption were recorded. The incidence of PHN after 3, 6, and 12 months was also reported.

Results: Pre-eruptive pain severity and duration were comparable between both groups. There was no statistically significant difference between both groups with respect to the day of the block, the total duration of pain until the first block, and eruptive and herpetic pain duration parameters. The severity of skin lesions was comparable among both groups. Four patients (10.5%) had PHN in group I versus 3 patients (8.1%) in group II after 3 months of follow-up. Meanwhile, these numbers were 3 patients (7.9%) and 2 patients (5.4%) at 6 and 12 months in both groups, respectively. Compared with basal parameters, effective pain control was noticed in both groups with no significant difference between groups.

Limitations: Small size, lack of complete blindness, and the use of fluoroscopy in block performance in the era of performing this block under ultrasound.

Conclusions: Repeated paravertebral blocks using local anesthetic and steroids weekly over 2 or 3 weeks in the management of acute thoracic herpes zoster can provide safe and effective pain relief and minimize the incidence of PHN. However, no added benefit was detected from repeated blocks more than twice.

Key words: Repeated paravertebral injections, acute thoracic herpes zoster, pain, postherpetic neuralgia, prevention

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Varicella-zoster virus (VZV) is the causal agent of chickenpox during childhood and herpes zoster (HZ) in adults and the elderly (1). Acute herpes zoster (AHZ) is an infectious disease caused by reactivation of the dormant VZV virus in the ganglia of sensory cranial nerves and spinal dorsal root ganglia (DRG) (2). The decline of the cellular immunity to VZV that occurs with age or because of immunosuppression allows the possibility of virus reactivation. Subsequently, the virus replicates and migrates along the sensory nerves to the skin producing pre-eruptive pain that precedes the characteristic skin eruption by several days (3).

The concomitant inflammation of the peripheral nerve (ganglionitis and neuritis) and the skin damage in AHZ are supposedly responsible for the acute pain (4).

If adequate pain reduction is not achieved within the acute phase of HZ, a state of central sensitization due to persistent nociceptive signaling from damaged neurons may be initiated which predisposes to pain chronicity. Post-herpetic neuralgia (PHN) is the most common complication of HZ and can impair quality of life due to pain (5). Multiple studies have reported the usefulness of providing early sympathetic block in the prevention of PHN (6-10). Although the number and extent of the sympathetic blockade vary between the providers, we can infer that the longer the duration of the sympathetic blockade, the lower the incidence of PHN encountered (11,12).

Recent meta-analysis reported favorable outcomes for early nerve blocks and confirmed a positive impact on the prevention of PHN (11). It also reported that the preventive effects of early nerve block may be more potent when performed with repetitive/continuous treatment modalities than single administration (6-10,13). However, the number, frequency, and duration of the blocks have not been justified (12). Therefore, the optimal duration and frequency of nerve blocks that prevent or maximally reduce the incidence of PHN need to be clarified.

This study tries to investigate whether weekly separated 2 versus 3 paravertebral injections using local anesthetic and steroids at an early point in the course of thoracic HZ would reduce the incidence of PHN. The primary objective was the incidence of PHN after 3 months of the onset of herpetic eruption. The secondary objectives were the influence of injections on visual analog scale (VAS), medications, and the incidence of PHN after 6 and 12 months.

Methods

The study protocol of this randomized clinical trial was approved by the Institutional Research Board (IRB) in Mansoura and Tanta universities and was registered on ANZCTR, with a registration number ACTRN12614000377639. The study was carried out from 3/1/2015 to 7/1/2018.

Adult patients suffering from acute onset HZ infection of the thoracic wall were sent to the chronic pain management outpatient clinic from the dermatology clinic on the same day at which they presented to the dermatology clinic, after having been given the suitable antiviral therapy.

The candidate patients aged greater than 50 years who had developed thoracic wall herpetic eruption for a duration shorter than one week and were under appropriate antiviral therapy were included in this study. Meanwhile, patients who had an eruption for longer than 7 days, patients who had not administered the appropriate anti-viral treatment, candidates who had extensive skin lesions (i.e., there was no clean area to insert and manipulate the needle) or infection at the injection sites, and patients with mild pain and who refused to participate in this study were excluded from the study. We also excluded patients who had a history of kidney or liver diseases, coagulopathy, diabetes mellitus, corticosteroid treatment, cancer, and patients under chemo- or radiotherapy.

Patient Evaluation

At the pain clinic, medical history was taken and a thorough clinical examination was performed. The side and dermatomal levels of eruption, duration of pre-eruptive pain, and the time elapsed since the eruption occurred were also reported. The severity of the herpetic skin lesions was assessed and classified as mild (< 25 lesions), moderate (25–50 lesions), or severe (> 50 lesions) according to the number of papules, vesicles, ulcers, and crusts within the affected dermatome (6).

Pain severity was evaluated using a VAS, (10 cm unmarked line in which 0 = no pain and 10 = worst pain imaginable), and basal VAS was recorded. Complete blood count, random blood glucose, urine analysis, and prothrombin time and activity were requested. After explaining the study procedures to the patients (injection and follow-up), all participants signed a written informed consent. Eligible patients were scheduled for injection after at least 24 hours of the antivirus therapy administration.

One hundred and eight patients were referred to the pain clinic during the recruitment period. Twenty-eight patients were excluded because of diabetes in 18 patients, hepatic illness in 3 patients, renal impairment in one patient; one received steroids, and 5 patients refused participation in the study. Meanwhile, 80 patients fulfilled the inclusion criteria. However, 5 patients dropped out during the follow-up of the study. Finally, 75 participants successfully completed a follow-up period of one year and have been included in the statistical analysis (Fig. 1).

Study Procedures

A blinded pain physician had determined eligibility for inclusion in the trial. The patients' randomization into 2 equal groups was done using a computer-generated random number table and closed sealed opaque envelopes. A blinded chief nurse who did not participate in the study or data collection opened the envelopes and determined group assignment.

Patients were randomly assigned into 2 groups. Group I received fluoroscopically guided paravertebral block using 25 mg bupivacaine plus 8 mg dexamethasone in a total volume of 10 mL twice one week apart. Group II received fluoroscopically guided paravertebral block using 25 mg bupivacaine 0.5% plus 8 mg dexamethasone in a total volume of 10 mL 3 times one week apart.

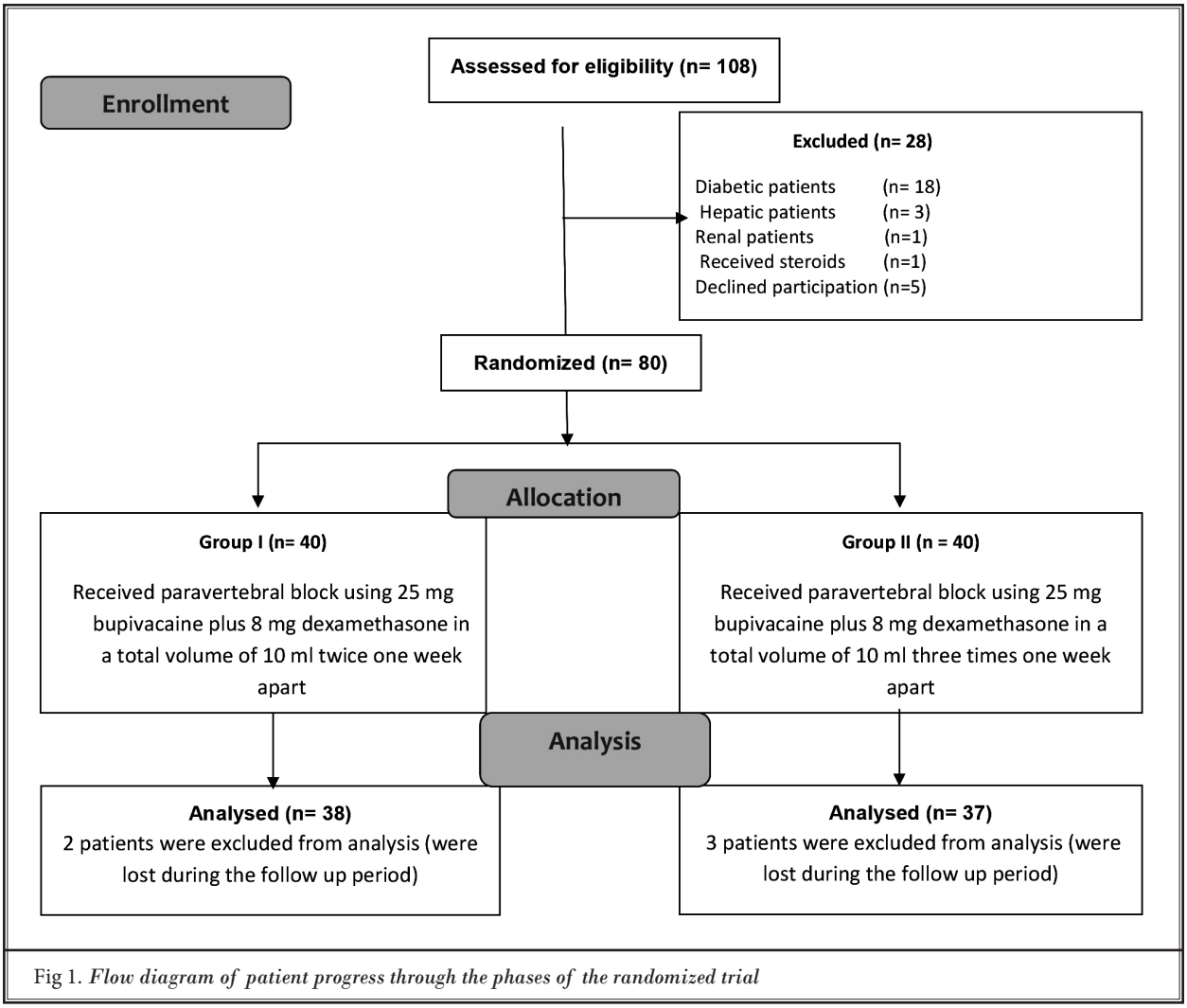

Fig 1. *Flow diagram of patient progress through the phases of the randomized trial*

Technique

An intravenous line was secured and an intravenous infusion drip was initiated using 500 mL saline (NaCl 0.9%). Thoracic paravertebral block was performed under fluoroscopy with the patient in a prone position. Antero-posterior view was obtained at the targeted level with suitable cephalo-caudal orientation. The back was sterilized and draped. A 22 G spinal needle was introduced in a tunnel view 2 – 3 cm lateral to the spinous process after local anesthetic infiltration targeting the transverse process which was contacted at a depth of 2 to 5 cm and then the needle was angled to walk off the superior border of the transverse process and advanced 1 – 1.5 cm with loss of resistance to air confirming entry of the space. Five mL of (Omnipaque 300mg/mL) was injected to confirm needle position (9).

In the recovery room, all patients were monitored for 2 hours. The severity of pain after 60 minutes was evaluated and documented. Data collection was achieved by a pain clinic resident who was not involved in any other parts of the study procedures.

Evaluation Parameters and Follow-ups

A pain physician blinded to the assignment groups was responsible for the follow-up of the patients, review of patients' responses to treatment, and data collection. Patients were evaluated for pain severity using VAS before the block (basal), one hour after the intervention, then every week for 2 months, fortnightly for 4 months, and every month for another 6 months, while the study values at basal, one hour, one, 2, 3, 4, 8, 12, 24 weeks, and after 12 months were included in the statistical analysis.

All patients received daily 300 mg pregabalin in divided doses (150 mg/12 hours). Pain score was evaluated at each visit. Once the patient reported mild pain (VAS $\leq$ 3), the trial for reducing the pregabalin dose was done by reducing the dose by 75 mg every other day, only if the pain score was still $\leq$ 3 with each reduction. We provided acetaminophen as a rescue analgesic at a dose of 1000 mg PRN, limited by 4000 mg as a maximum daily dose. For the sake of safety, telephone consultations were allowed if any increase in pain occurred during follow-up.

During every evaluation visit, the total pain medicine consumption was documented. The study values at one, 2, 3, 4, 8, 12, 24 weeks, and after 12 months were included in the statistical analysis. The time points of the full resolution of pain (from the day of the intervention until the complete disappearance of pain resulting from AHZ) and skin eruption (identified by falling of the last crust) were recorded. Persistent herpetic pain after 3, 6, and 12 months was also recorded as an incidence of PHN.

Statistical Analysis

The sample size was calculated assuming that the expected incidence of PHN (pain after 3 months of infection) in patients above 50 years old in the control group was 22.1% to 30% (7-10,13) with an average incidence of 26%. The aim was to lower the incidence to less than 5% with the power of the study at 90% (α = 0.05, β = 0.1). A calculated sample size of 34 patients in each group was needed. Eighty patients were included to overcome losses during the follow-up period.

The statistical analysis was done using SPSS software version 16 (SPSS Inc., Chicago, IL, USA). Mean (standard deviation) was used to summarize continuous quantitative data, while frequency and proportion were used for qualitative data. The analysis of the data was done to test statistically significant differences between the 2 groups. For quantitative data, unpaired student t-test was used to compare between the 2 groups. For qualitative data, chi-square test was used. A *P*-value < 0.05 was considered significant.

Results

Eighty patients fulfilled the inclusion criteria and were assigned to participate in the current clinical trial (40 participants in each group). Two patients in Group I and 3 patients in Group II dropped out during the follow-up period. Seventy-five patients completed the current clinical trial (38 participants in Group I and 37 participants in Group II) and have been included in the statistical analysis (Fig. 1). Patient demographics are shown in Table 1. Statistical analysis showed no differences among groups regarding demographic data.

Clinical variables are illustrated in Table 2, with no significant differences between the 2 groups. Pre-eruptive pain severity and duration scores were comparable

Table 1. *Demographic data in the studied groups. Values are presented as mean ± SD and number.*

	Group I (n = 38)	Group II (n = 37)	*P* value
Age:	57.82 ± 2.58	57.18 ± 3.45	0.38
Gender: *M/F*	16/22	19/18	0.42
Side: *Right/Left*	21/17	25/12	0.27

between both groups (P = 0.79, 0.44, respectively). There were no statistically significant differences between both groups with respect to the day of the block, the total duration of pain until the first block, and eruptive and herpetic pain duration parameters as shown in Table 2. The severity of skin lesions was comparable among both groups as shown in Table 2.

Four patients had PHN in Group I versus 3 in Group II after 3 months of follow-up; however, 3 and 2 patients after 6 and 12 months in Group I and Group II, respectively, had PHN; there were no statistical significant differences in the incidence of PHN at all measure times.

Compared with basal parameters, a significant reduction of pain score (VAS) in both groups, $P < 0.05$, was found. Effective pain control was noticed in both groups with no significant difference between groups, $P > 0.05$, as shown in Table 3. Comparison of both groups throughout the study duration showed no significant difference regarding acetaminophen and pregabalin post-procedural consumption (Tables 4, 5).

Regarding the adverse effects reported during the study period, none of the studied patients in either group developed edema. There was an insignificant difference between groups regarding the incidence of drowsiness during the first and second weeks (42.1% vs 37.8%, P = 0.7 and 13.2% vs 10.8%, P = 0.8, respectively). None of the patients developed drowsiness in either group in the third week. Twenty-one point one percent of the patients in Group I and 27% of the patients in Group II developed mild local pain at the site of injection in the third week of the study, P = 0.55.

Discussion

The results of the current randomized clinical trial reported a comparable decrease in the incidence of thoracic PHN in both groups using either weekly injection of local anesthetic and steroids in the paravertebral space for 2 or 3 weeks. Both groups showed an inability to eliminate or prevent the possibility and risk of PHN even when the injection was started early during the first week following the appearance of the herpetic rash.

Table 2. *Herpes zoster and block characters in the studied groups. Values are presented as mean±SD, median (min-max) and number.*

	Group I (n = 38)	Group II (n = 37)	*P* value
Pre-eruptive pain severity	5 (4-7) 5.26 ± 0.98	5 (4-7) 5.19 ± 1.08	0.79 0.76
Pre-eruptive pain duration	3.82 ± 0.69	3.95 ± 0.74	0.44
Day of block	4(3-6) 4.32 ± 0.8	4(3-6) 4.13 ± 0.9	0.31 0.36
Total duration of pain till onset of 1st block (days)	8.13 ± 1.17	8.08 ± 1.21	0.86
Herpetic Pain duration (days)	18 (16-90) 25.37 ± 22.5	17(16-90) 23.24 ± 20.15	0.15 0.67
Eruption duration (days)	22.50 ± 3.61	21.32 ± 2.91	0.13
Severity of skin lesion: Mild Moderate Severe	 2 (5.3%) 19 (50.0%) 17 (44.7%)	 3 (8.1%) 18(48.6%) 16(43.2%)	0.89
PHN incidence at 3 months	4 (10.5%)	3 (8.1%)	0.72
PHN incidence at 6 months	3 (7.9%)	2 (5.4%)	0.67
PHN incidence at 12 months	3 (7.9%)	2 (5.4%)	0.67

Table 3. *Visual analog score in the studied groups. Values are mean ± SD.*

	Basal	1 hour	7 days	14 days	3 weeks	4 weeks	8 weeks	12 weeks	24 weeks	12 months
Group I (n = 38)	7.92 ± 0.99	2.63 ± 0.7*	2.8 ± 0.8*	2.0 ± 0.8*	0.53 ± 1.3*	0.42 ± 1.2*	0.42 ± 1.2*	0.39 ± 1.2*	0.29 ± 1.0*	0.24 ± 0.8*
Group II (n = 37)	7.78 ± 1.13	2.35 ± 0.9*	2.6 ± 0.9*	1.9 ± 0.8*	0.32 ± 1.1*	0.32 ± 1.1*	0.29 ± 1.0*	0.29 ± 1.0*	0.16 ± 0.7*	0.16 ± 0.7*
P value	0.57	0.15	0.27	0.38	0.47	0.72	0.64	0.70	0.53	0.67

P value = values for comparison for both groups at each time interval, all were $P > 0.05$.
* Significant when compared to the basal value within the same group, all were $P < 0.05$.

Table 4. *Pregabalin consumption/week in the studied groups. Values are mean ± SD.*

Pregabalin	Group I (n = 38)	Group II (n = 37)	*P* value
1 week	1863 ± 228	1800 ± 212	0.22
2 weeks	1125 ± 442	1001 ± 302	0.16
3 weeks	497 ± 584	407 ± 536	0.49
4 weeks	245 ± 648	199 ± 575	0.75
8 weeks	221 ± 653	146 ± 513	0.58
12 weeks	193 ± 591	142 ± 505	0.69
24 weeks	138 ± 499	114 ± 481	0.83
12 months	83 ± 287	57 ± 241	0.67

Table 5. *Acetaminophen consumption/week in the studied groups. Values are mean ± SD.*

Acetaminophen	Group I (n = 38)	Group II (n = 37)	*P* value
1 week	20921 ± 3605	20811 ± 4396	0.91
2 weeks	16026 ± 4187	15541 ± 4432	0.63
3 weeks	5842 ± 5946	5676 ± 4894	0.89
4 weeks	2500 ± 6509	2054 ± 5778	0.75
8 weeks	2211 ± 6531	1703 ± 5811	0.72
12 weeks	2026 ± 6069	1514 ± 5253	0.69
24 weeks	1474 ± 5187	757 ± 3209	0.47
12 months	1105 ± 3826	757 ± 3209	0.67

During the acute phase of HZ, virus replication and multiplication in the DRG resulted in ganglionitis, neuritis, and pain along the affected nerve. The progression of neurogenic inflammation induces profound sympathetic stimulation and vasospasm of endoneural arterioles. Persistent vasoconstriction and impairment in the intra-neural blood flow end by nervous tissue ischemia and damage (14).

The unique block quality of paravertebral block is of interest to clinicians and researchers as it produces combined somatosensory and sympathetic blockade. The use of local anesthetic and steroids in the paravertebral space allows adequate block of ongoing pain signals through the direct action of the local anesthetic on the spinal nerves including the dorsal rami, the rami communicants, and the sympathetic chain (15). Adding dexamethasone promotes a membrane-stabilizing effect on C fiber transmission resulting in hindering the transmission of the nociceptive signal and reducing or even preventing the arousal of ectopic neural discharge (16,17). Moreover, the inclusion of the steroids in the injectate might reduce the associated neuronal inflammation in the DRG and the distal part of the insulted nerve (9,11). Early paravertebral block during the course of AHZ could interrupt repetitive painful stimuli and reverse vasospasm. Therefore, paravertebral block may attenuate the central sensitization and prevent or minimize nerve ischemia accounting for PHN prevention (9). Missing the use of sympathetic blockade early in the high risk groups, including elderly patients, may lead to a long time of suffering for the affected patients and their families (18).

Paravertebral block for treatment of AHZ pain and prevention of PHN had been used (8,9). A single fluoroscopically guided paravertebral block using local anesthetic and steroids early within the first week of AHZ was capable of reducing the incidence of PHN to 11.4% after 3 months and 5.7% after 6 months (9). Meanwhile, repetitive paravertebral block utilizing steroids added to a local anesthetic (4 times per week using a nerve stimulator) reported more effective prevention of PHN. An incidence of 7% after 3 months, 4% after 6 months, and only 2% after one year was reported (8). The current study reported nonstatistical significant difference in the incidence of PHN with the use of paravertebral blocks weekly either for 2 weeks (Group I) or for 3 weeks (Group II) early in the course of AHZ. An incidence of 10.5% after 3 months, 7.9% after 6 months, and 7.9% after 12 months was reported in the Group I; while an incidence of 8.1% after 3 months, 5.4% after 6 months, and 5.4% after 12 months was reported in the Group II. Similar low incidence of PHN was reported with the use of repetitive/continuous epidural injection using local anesthetic and steroids for treatment of AHZ (6,7). It is clear that the longer the block, the more beneficial preventive effect on PHN. Interruption of vasospasm of endoneural arterioles and prevention of the re-spasm in addition to the longer block of nociceptive input transmission and more attenuation of central sensitization may account for a lower incidence of PHN.

The results of the current study showed no significant difference in the incidence of PHN after 3, 6, and 12 months between the 2 studied groups. The occurrence of PHN in both groups in spite of long blockade may be attributed to the nerve insults that occurred in the nerve during pre-injection time (total duration of pain until onset of first block), which presented the sum of pre-eruptive pain duration and the time from the first day of eruption until the block day, estimated to

be about 8 days in the present study. Where the virus replication and multiplication in the DRG resulted in ganglionitis, neuritis, and pain along the affected nerve due to vasospasm of endoneural blood arterioles. The authors suggest that the earlier intervention without steroids (using local anesthetic alone or with adding dexmedetomidine or clonidine) during the first day of the eruption, without waiting to be under the cover of effective antiviral therapy, may result in less injury of the nerves. This could be attributed to the earlier interruption of the vasospasm which may minimize the incidence of PHN. The use of newly introduced easily performed ultrasound-guided erector spine block may enable pain physicians to perform the block earlier using local anesthetic alone even before or simultaneously with the use of antiviral therapy followed by the well-known effective paravertebral block using local anesthetic and steroids (19,20). The authors assume there is a limited chance for performing sympathetic blockade for PHN prevention because it must be performed as early as possible within the first week of skin eruption.

Moreover, this block must continue for at least 2 weeks to avoid re-spasm of the endoneural arterioles. Future research should focus on the introduction of the sympathetic blockade as early as possible and the trial of local anesthetics alone as early as possible or in combination with drugs which have the inherited character of sympathetic blockade like clonidine and dexmedetomidine. This new approach may allow earlier intervention at the time of patients' presentation and avoid precious time loss for fear of dissemination risk. Therefore, the progression of neurogenic inflammation is more likely to be interrupted early and effectively.

Regarding the pregabalin and acetaminophen consumption throughout the study period, no significant differences were reported between groups. There was no significant difference between the studied groups as regarded the incidence of drowsiness in the first and second weeks of the study. Meanwhile, a comparable incidence of mild local pain at the site of injection was reported in both groups in the third week of the study.

Limitations of the present study include small study size, lack of complete blindness because of variations in the number of injections in both groups and the use of fluoroscopy in block performance in the era of performing this block under ultrasound which the authors attributed to lack of tolerance of probe manipulation in the painful infected area.

Conclusion

Repeated paravertebral blocks using local anesthetic and steroids weekly over 2 or 3 weeks, early in the course of the acute thoracic herpetic eruption cannot eradicate the possibility of PHN. It can provide safe and effective pain relief and minimize the incidence of PHN. However, no added benefit was detected from repeated blocks more than twice.

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