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Randomized Trial

Effect of Early Stellate Ganglion Blockade for Facial Pain from Acute Herpes Zoster and Incidence of Postherpetic Neuralgia

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Background: The incidence of postherpetic neuralgia (PHN) has been reported to be 25% among those over the age of 50 years treated with antiviral medication. The role of sympathetic block in its prevention remains questionable.

Objectives: The aim of this study is to determine whether early stellate ganglion blockade for acute herpes zoster of the face will reduce the intensity and duration of acute herpetic pain, and if the blockade has the potential to prevent or reduce the incidence and/or severity of PHN.

Study Design: Randomized, controlled, double blind trial.

Setting: Hospital, outpatient setting.

Methods: Sixty-four patients over 50 years were assigned to receive a stellate ganglion block using either 8 mL saline (Group 1) or 6 mL bupivacaine 0.125% and 8 mg dexamethasone in a total volume of 8 mL (Group 2). All procedures were performed under fluoroscopy.

All patients received pregabalin in a dose of 150 mg twice daily. Acetaminophen was available as needed. Pain assessment using the visual analog scale and amount of analgesic being taken was measured at the initial visit (basal), weekly for 6 weeks after the procedure and after 2, 3, and 6 months. Once a patient reported mild pain during the trial, pregabalin was tapered by 75 mg every other day; the patients who succeeded in this step were recorded in each group. The time of complete resolution of pain and incidence of persistent postherpetic pain was reported. Each patient's satisfaction was evaluated.

Results: There was a significantly shorter duration of pain noticed in Group 2 ($P = 0.002$). A significantly lower incidence of PHN was encountered in Group 2 after 3 months ($P = 0.043$) and 6 months ($P = 0.035$). Significantly more patient satisfaction was reported in Group 2 after 3 and 6 months. By the fourth week, 29 patients in Group 2 reported no pain. Two patients reported mild pain after 3 months which was resolved by the sixth month. In Group 1, 22 patients reported no pain by the sixth week and 8 patients reported moderate pain after 2 and 3 months; by the sixth month, 4 out of those 8 patients showed spontaneous remission of pain. There was a significant reduction in the total doses of pregabalin and acetaminophen in Group 2 ($P < 0.001$). No serious adverse effects were reported during the study period.

Limitations: The sample size was determined using the incidence of PHN (chronic pain) as a main hypothesis. Meanwhile, this study determined the incidence of acute pain as well, which may lead to bias to the results of acute pain.

Conclusion: Early stellate ganglion blockade, in combination with an antiviral agent, is a very effective treatment modality; it dramatically decreases the intensity of acute pain and shortens its duration and reduces the incidence of postherpetic neuralgia.

Key words: Stellate, blockade, herpes zoster, face.

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Herpes zoster (HZ) is a painful vesiculobullous skin disease caused by reactivation of a latent varicella zoster virus in dorsal root ganglia (1). In some individuals, a decrease in cell-mediated immunity allows the virus to multiply in ganglia and travel along the peripheral or cranial sensory pathways to the nerve endings, producing the pain and the skin lesions characteristic of shingles (2). The most common complication of HZ is postherpetic neuralgia (PHN). The incidence of PHN, defined as pain 3 months after rash onset, has been reported to be 25% among those over the age of 50 treated with antiviral medication (3,4).

The pathophysiology of PHN remains unclear. Severe ganglionitis and neuritis of the affected nerve results in profound sympathetic stimulation that leads to reduced intraneural blood flow, resulting in nerve ischemia. If ischemia is allowed to persist, endoneural edema forms with an increase in endoneural pressure causing a further decrease in endoneural blood flow, and finally irreversible nerve damage will result (2). Sympathetic blocks can be used to prevent the vasoconstriction that is thought to cause pain and nerve damage. Although many authors advocate the use of sympathetic nerve blocks for the treatment of acute pain in HZ patients (5-7), whether sympathetic nerve blocks administered early prevent PHN or reduce the likelihood of its occurrence remains a controversial issue (8-10).

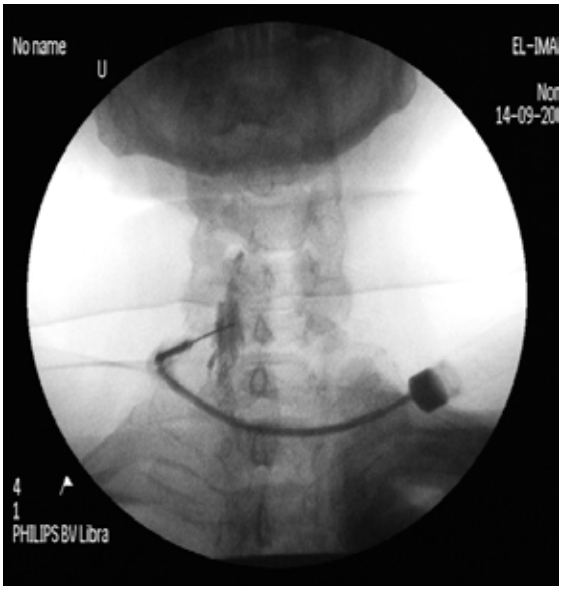

Fig. 1. *Under direct anteroposterior fluoroscopy, the C6 vertebral body is identified. The tip of the needle is at the junction of the transverse process with the vertebral body.*

The aim of this study was to determine whether early stellate ganglion blockade for acute HZ of the face reduces the intensity and duration of acute herpetic pain and if it has the potential to prevent or reduce the incidence and/or severity of PHN.

Methods

After approval from the local ethics committee, 64 adult patients with acute HZ of the face were referred from the dermatology clinic after having been given the appropriate antiviral therapy. Inclusion criteria included patients who had a herpetic eruption of less than 2 weeks, those under or who received appropriate antiviral therapy, and aged over 50 years. Exclusion criteria included patient refusal, an eruption of more than 2 weeks duration, patients who did not receive appropriate antiviral therapy, a preexisting neurological deficit in the face or upper extremities, infection at the site of injection, a history of renal or hepatic diseases or coagulopathy, diabetes, and patients with malignancies.

In the first pain clinic visit, after taking an adequate medical history and thorough clinical examination, we explained the study procedures (injections and follow-up) for the patient and then written, informed consent was obtained. The time of the first block (the day on which the patient received the first stellate ganglion block in relation to appearance of the rash and confirmation of the diagnosis of acute herpes zoster) was recorded.

The patients were randomly assigned using a computer-generated random number assignment to receive a stellate ganglion block using either 8 mL saline as placebo (Group 1) or 6 mL bupivacaine 0.125% plus 8 mg dexamethasone in a total volume of 8 mL (Group 2). Injections were performed under fluoroscopy in both groups. The syringes which contained the solutions of local anesthetic plus steroid or saline, were prepared by an anesthesiologist who did not participate in the study or data collection. Each patient received 2 stellate ganglion injections one week apart.

The method of stellate ganglion block has been described by Schürmann et al (11). The patient is placed in the supine position with the cervical spine in the neutral position. Under direct anteroposterior fluoroscopy, the C6 vertebral body is identified. The skin is numbed with one mL of local anesthetic. A 22-gauge, B-bevel needle is inserted through a skin wheal to contact the body of C6 at the junction of the transverse process with the vertebral body (Fig. 1). Depth and direction should be confirmed with both anteroposterior and lateral views

(Fig. 2). An intravenous extension should be attached to the needle and used for injection. Approximately 5 mL of water-soluble, nonionic contrast medium is injected after negative aspiration. If good spread of the contrast medium is visualized, a mixture of local anesthetic and steroid or saline is injected. After injection, the patient remains supine with the head elevated slightly for approximately 30 minutes.

All patients received pregabalin in a dose of 150 mg/ twice daily. Acetaminophen was available for as-needed analgesia: 1,000 mg on request with 4,000 mg as a maximum daily dose.

Patients were evaluated for pain severity using the visual analog scale (VAS, 10 cm unmarked line in which 0 = no pain and 10 cm = worst pain imaginable). VAS evaluations were made at the initial visit (basal), weekly for 6 weeks after the procedure and after 2, 3 and 6 months. At each assessment visit, calculation of the amount of on-request analgesia used was done. Once a patient reported mild pain (VAS $\leq$ 3), a trial for reducing the pregabalin dose was done by reducing 75 mg every other day. The result was reported and the number of patients who succeeded in this step were recorded in each group. The time of complete resolution of pain was recorded in each patient and the incidence of persistent herpetic pain after 3 and 6 months was reported as PHN. Patient satisfaction was evaluated by the following score (not satisfied = 0, mild satisfaction = 1, moderate satisfaction = 2 and strongly satisfied = 3) at 3 and 6 months.

Statistical Analysis

The sample size was determined assuming that the expected incidence of PHN in patients above 50 years old in the control group was 25%, according to the study done by Wood et al (3). Our aim was to lower the incidence to less than 5% at a 95% confidence interval (CI) and power of study 85% (α = 0.05, β = 0.1). A calculated sample size of 29 patients in each group was needed. Allowing for 10% loss of follow-up, 64 patients were included.

A statistical analysis was carried out using SPSS version 16 (SPSS Inc., Chicago, IL). The descriptions of data were done in the form of mean (+/-) standard deviation for quantitative data and in frequency and proportion for qualitative data. Data analysis was done to test statistically significant differences between the groups. For quantitative data, Student's t-test was used to compare the 2 groups. For qualitative data, chi-square test was used. *P* value was considered significant if $\leq$ 0.05 at 95% CI.

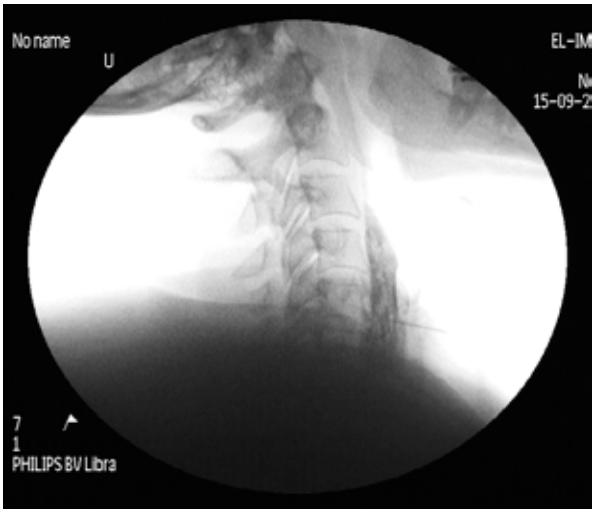

Fig. 2. *Lateral view showed the needle at the level of C6 and dye distributed up and down.*

Results

Sixty-four adult patients above 50 years old were randomly assigned into 2 groups (32 in each). Two patients in Group 1 and one patient in Group 2 were unavailable for follow-up and excluded from the study. The demographic characteristics of the remaining 61 patients are summarized in Table 1. There were no significant differences in the distribution of age, gender, and the affected side of the face between the 2 groups. There was no significant difference in the time of the first block between the studied groups (5.17 ± 0.8 vs 6.26 ± 0.6 days). There was a significantly shorter duration of pain noticed in Group 2 (43.6 ± 28.7 vs 23.8 ± 18 days, *P* = 0.002) (Table 1). A significantly lower incidence of PHN was encountered in Group 2 after 3 months (6.5% vs 26.7%, *P* = 0.043) and 6 months (0% vs 13.3%, *P* = 0.035) (Table 1). Significantly more patient satisfaction was reported in Group 2 after 3 and 6 months (Table 1).

Regarding the severity of pain, a significantly lower VAS was noticed in Group 2 throughout the study period (Table 2). Also, according to pain severity as measured by the VAS, patients statistically were stratified into 4 categories where VAS 0 = no pain, VAS < 4 = mild pain, VAS 4-6 = moderate pain, and VAS $\geq$ 7 = severe pain. By the fourth week, 29 patients (93.5%) in Group 2 reported no pain while 2 patients (6.5%) reported mild pain after 3 months until the sixth month

Table 1. *Demographic data and patient's outcome in the studied groups. Values are in mean ±SD and in number (%). Group 1: placebo group. Group 2: stellate ganglion block group.*

Groups	Group 1 (n=30)	Group 2 (n=31)	*P* value
Age (years)	59.6 ± 3.2	60.6±2.2	0.14
Sex (male/ female)	14/16	13/18	0.71
Side (right/ left)	16/14	17/14	0.91
Incidence of PHN			
3 months	8/30 (26.7%)	2/31* (6.5%)	0.043
6 months	4/30 (13.3%)	0/31 * (0 %)	0.035
Patient Satisfaction Score			
3 months	2.2 ± 1.3	2.8 ± 1.1*	0.03
6 months	2.4 ± 0.5	3 ± 0.0*	0.004
Time of first block (days)	5.17 ± 0.8	6.26 ± 0.6	0.63
Duration of pain (days)	43.6 ± 28.7	23.8 ± 18*	0.002

* Significant when compared to the other group

Table 2. *Visual Analogue Score in the studied groups. Values are in mean ± SD. Group 1: placebo group. Group 2: stellate ganglion block group.*

	Basal	1 week	2 weeks	3 weeks	4 weeks	6 weeks	2 months	3 months	6 months
Group1	7.1 ± 1.1	4.7 ± 1.1	3.8 ± 1.3	2.8 ± 1.8	1.8 ± 2	1.1 ± 1.9	1.1 ± 1.9	1.1 ± 1.8	0.4 ± 1.1
Group2	7 ± 0.9	2.9 ± 0.6*	1.7 ± 0.8*	0.7 ± 1*	0.1 ± 0.6*	0.2 ± 0.7*	0.2 ± 0.5*	0.13 ± 0.5*	0 ± 0*
P value	0.79	< 0.001	< 0.001	< 0.001	< 0.001	0.014	0.015	0.007	0.042

* Significant when compared to the other group

when spontaneous remission of pain occurred.

In Group 1, 22 patients (73.3%) reported no pain by the sixth week and 8 patients (26.7%) reported moderate pain after 2 and 3 months; by the sixth month, 4 of those 8 patients showed spontaneous remission of pain and 4 of them (13.3%) reported persistent pain (PHN), 3 with mild pain and one report of moderate pain (Table 3).

Concerning the analgesic consumption per week, there was a significant reduction in the dose of pregabalin and acetaminophen taken by Group 2 throughout the study period, with a subsequent significant reduction of the total consumption of both drugs encountered in Group 2 ($P < 0.001$) (Tables 4,5).

No serious adverse effects were reported during the study period. Change in voice and difficulty swallowing were improved within 2 to 6 hours after injection. Local pain occurring at the site of injection extended to the second day after each injection. Drowsiness occurred in 66.7% of patients in Group 1 and 54.8% in Group 2 during the first week and dramatically improved in the second week. A mild degree of lower limbs edema occurred in one patient in Group 1 (Table 6).

Discussion

The findings of this randomized, placebo-controlled study show that early sympathetic blockade, within 2 weeks of rash onset, was not only effective for rapid relief from the acute pain of HZ but also significantly reduced and may prevent the incidence of PHN more effectively than standard treatment (oral administration of acyclovir and analgesics).

The pain that occurs during acute HZ is a result of inflammation of the ganglion and peripheral nerve as well as tissue damage (12). Inflammation and tissue damage produce nociceptor excitation and sensitization which lead to central hyperexcitability. In addition, severe ganglionitis and neuritis induce profound sympathetic stimulation with a subsequent reduction of intraneural blood flow, nerve ischemia, and damage (6).

Our rationale was that early interventions that decrease repetitive painful stimuli and prevent vasocon-

Table 3. Proportion of patients according to severity of pain over time. Data are in numbers. Group 1: placebo group. Group 2: stellate ganglion block group.

	Basal	1 week	2 weeks	3 weeks	4 weeks	6 weeks	2 months	3 months	6 months
Group 1 (30)									
No Pain	-	-	-	-	12	22	22	22	26
Mild	-	5	12	22	10	-	-	-	3
Moderate	10	25	18	8	8	8	8	8	1
Severe	20	-	-	-	-	-	-	-	-
Group 2 (31)									
No Pain	-	-	-	14	29	29	29	29	31
Mild	-	27	29	15	2	2	2	2	-
Moderate	9	4	2	2	-	-	-	-	-
Severe	22	-	-	-	-	-	-	-	-
***P* value**	0.72	<0.001*	<0.001*	<0.001*	<0.001*	0.004*	0.004*	0.004*	0.11

* Significant when compared to the other group

Table 4. *Pregabalin dose in mg/week in the studied groups. Values are in mean ± SD. Group 1: placebo group. Group 2: stellate ganglion block group.*

	Group 1	Group 2	*P* value
1 week	2100 ±0	2100 ±0	1
2 week	1900 ±455	1055 ±409*	< 0.001
3 weeks	1470 ±835	194 ±556*	< 0.001
4 weeks	860 ±855	97 ±405*	< 0.001
6 weeks	490 ±903	29 ±162*	0.007
2 months	560 ±945	0 ±0*	0.002
3 months	560 ±945	0 ±0*	0.002
6 months	560 ±945	0 ±0*	0.002
Total Dose	8110 ±4829	3474 ±1379*	<0.001

* Significant when compared to the other group

Table 5. *Acetaminophen dose in mg/week in the studied groups. Values are in mean ± SD. Group 1: placebo group. Group 2: stellate ganglion block group.*

	Group 1	Group 2	*P* value
1 week	22433 ±3588	16548 ±2718*	< 0.001
2 weeks	17433 ±6897	12226 ±2952*	< 0.001
3 weeks	13867 ±6755	4355 ±5206*	< 0.001
4 weeks	7967 ±9114	968 ±3497*	< 0.001
6 weeks	4700 ±7544	903 ±3496*	0.014
2 months	3967 ±6800	903 ±3496*	0.030
3 months	3733 ±6297	903 ±3496*	0.033
6 months	1867 ±4840	0 ±0*	0.036
Total Dose	74267 ±50543	36806 ±22885*	< 0.001

* Significant when compared to the other group

Table 6. *Adverse events of the studied patients groups. Data are in numbers and (%). Group 1: placebo group. Group 2: stellate ganglion block group.*

	Group 1		Group 2		*P* value
	No.	%	No.	%	
First Week					
Drowsiness	2 0/30	66.7%	17/31	54.8%	0.34
Local pain	7/30	23.3%	6/31	19.4%	0.71
Change in voice	0/30	0%	3/31	9.7%	0.08
Difficult swallow	5/30	16.6%	4/31	13%	0.87
Edema lower limb	1/30	3.3%	0/31	0%	0.3
Second Week					
Drowsiness	3/30	10%	2/31	6.5%	0.61
Local pain	6/30	20%	5/31	16.1%	0.69
Change in voice	0/30	0%	2/31	6.5%	0.16
Difficult swallow	4/30	13.3%	3/31	9.7%	0.72
Edema lower limb	1/30	3.3%	0/31	0%	0.3
Third Week					
Edema lower limb	1/30	3.3%	0/31	0%	0.3

striction during the acute phase of HZ may attenuate central sensitization, prevent nerve scarring, and substantially account for the prevention of PHN. This rationale was supported by several studies reflecting the efficacy of early sympathetic blockade on the reduction of the incidence of PHN (5-7) .

In the current study, sympathetic blockade of the face by stellate ganglion block resulted in significantly lower pain intensity (VAS) and rapid pain relief in Group 2 throughout the study period; this is in accordance with the observations in many studies which mentioned effective pain relief and reduction in the duration of acute HZ pain with the use of sympathetic blockade, although almost none of these studies carefully reported the effects on the intensity of acute pain (5-9,13). Moreover, the current study stratified the patient's pain - according to pain severity - into no pain, mild, moderate, and severe and represented the number of patients in each category throughout the whole study period. After one week of treatment, 27 patients (87%) in Group 2 reported mild pain (VAS 2.9) while in the control group 25 patients (83%) still suffered from moderate pain (VAS 4.7).

Twenty-nine patients (93.5%) in Group 2 reported complete pain relief (VAS = 0) by the fourth week, reflecting the significantly shorter duration of pain recorded in Group 2 when compared with Group 1 (23.8 vs 43.6 days). Higa and his colleagues (14) studied the effect of repeated regional sympathetic blockade using local anesthetic alone on the duration of pain in patients suffering from acute HZ pain. They did not receive antiviral agents and reported their pain duration as 24.2 days for mild pain, 41.3 days for moderate pain, and 77.3 days severe pain. Hwang and his coworkers (15) reported a shorter duration of pain in patients who received epidural blocks for 7 days plus intravenous acyclovir than those who received intravenous acyclovir alone (18.5 vs 31.6 days).

In recent years, evidence-based medicine has devoted more attention to the sodium chloride placebo effect. In a study carried out in patients undergoing an interventional block, sodium chloride produced a placebo effect in 13 – 15% of patients (16). However, this percentage was postulated to be less in the present study because the nature of the study was explained to the patients and the block was given in addition to analgesic medications (pregabalin and acetaminophen). Also, the clinicians explained to patients that they might have a 50% chance of receiving an intervention with an inactive ingredient (17). Overall, the contradictory literature on the placebo effect indicated that the effect was short-lived (17), and in the current study the follow-up period was extended to 6 months.

Acute pain severity is one of the most well established risk factors for PHN (18). In the current study, about two-thirds of the patients in each group had severe pain at onset, putting them at high risk for the development of PHN. Therefore, any intervention which reduces the intensity and/or duration of this pain- including sympathetic nerve blocks-has the potential to prevent or reduce the incidence or severity of PHN (19,20).

Antiviral agents that inhibit replication of the varicella-zoster virus has been shown to accelerate the overall resolution of pain in patients with HZ and decrease the incidence and duration of PHN (3,21,22) . Wood and his coworkers (3) reported the incidence of PHN to be 25% among those over the age of 50 years. Our study proved a significantly lower incidence of PHN in Group 2 after 3 and 6 months than the control group (6.5% vs 26.7% at 3 months and 0% versus 13.3% at 6 months). These findings are supported by previous studies reporting an incidence of 5% who developed PHN at 6 to 12 months if the injections were done between one and 21 days of the patient's symptoms (5), while virtually 100% success was obtained if the injections were done within 1-2 weeks after the onset of the lesions (6). The reported decrease in the incidence of PHN that occurred after 6 months in our study suggests that the long-term improvement in pain may reflect spontaneous resolution rather than the latent effect of sympathetic blockade; we suggest that this spontaneous resolution may occur fairly often in healthy non damaged nerve endings. The beneficial lower incidence of PHN encountered in our study highlighted the value of early sympathetic blockade used concomitant with an appropriate antiviral agent on the course of acute HZ.

More importantly, the significant rapid effective pain relief, shorter duration of the acute herpetic pain, and lower incidence of PHN were not only statistically but also clinically meaningful, defined in this study by the subsequent significant reduction of analgesic drug consumption (pregabalin and acetaminophen) throughout the study period. There was an effective cost reduction in addition to more patient satisfaction noted in Group 2. Apart from an insignificant high incidence of drowsiness that occurred in both groups in the first week, no serious adverse effects were reported in this study.

It is well known that PHN has an important effect on quality of life; many patients develop severe physi-

cal, occupational, and social disabilities as a result of the unceasing pain (23). Family and society are also affected in terms of cost and lost productivity.

Therefore, it is the desire to avoid this disastrous sequela to a usually benign self-limited disease that dictates all therapeutic effects for the patient suffering from acute herpes zoster (24). The most important risk factors for this pain syndrome include age and the severity of acute pain and inflammation during HZ. The incidence of PHN increases with age: 27% of untreated adults over 55 years old, 47% over 60, and 73% over 70 have postherpetic neuralgia (25,26). The intractability of the pain may also increase with age (25,27,28).

Pain lasting more than one year has been reported in 4% of patients under 20 years old, 22% over 55, and 48% over 70 (26,29). Thus, early aggressive treatment of this group is mandatory. Failure to use sympathetic blockade early and aggressively, especially in the elderly, may sentence the patients to a lifetime of suffering (24). Our results support the previous recommendations (5,6,15) for early sympathetic blockade for acute HZ in risky patients.

Finally, although our results proved the efficacy of early sympathetic blockade by a qualified pain physician for treating acute HZ pain and prevention of PHN, this treatment must be carefully weighed against potential serious complications and invasiveness, especially in younger patients who do not have risk factors for developing PHN. As noted, most patients with HZ have their acute pain resolved spontaneously within several weeks. A large multicenter study is needed to confirm our results.

Conclusion

In conclusion, for acute HZ of the face, early stellate ganglion blockade, in combination with an antiviral agent, is a very effective treatment modality that dramatically decreases the intensity of acute pain and shortens its duration. We believe it has preventive effects on PHN via reversing or preventing profound sympathetic stimulation and vasoconstriction, hence restoring intraneural blood flow and preventing nerve ischemia and damage.

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