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Sympathetic nerve blocks for the management of postherpetic neuralgia – 19 years of pain clinic experience

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Abstract

Background: Sympathetic system involvement in postherpetic neuralgia (PHN) has been targeted using peripheral sympathetic nerve blocks for a number of years with variable efficacy. The aim of this report is to present the outcomes of PHN management with concomitant use of pharmacological treatment and sympathetic nerve blocks.

Methods: We retrospectively evaluated clinical data on 563 patients with PHN symptoms treated in the pain clinic and identified cases in which sympathetic nerve blocks were implemented in the years 1992–2010. A Numeric Rating Scale was used as a pain severity assessment, with a reduction to values under 3 considered a positive therapy result. Three time intervals were considered: years 1992–1997 (I), 1998–2002 (II) and 2003–2010 (III).

Results: In group I, 27% of patients had poor treatment results, while in group II, the failure rate dropped to 18%. The same 18% failure rate was observed in group III as well. Treatment introduced early yielded the best results, but there was no difference among groups with a similar duration from herpes zoster onset to treatment commencement in the time periods assessed; however, from 1998 onward, the same rate of poor outcomes was also noted in the groups who started the sympathetic blockade, which aided pain clinic treatment up to 3 months and between 3 and 6 months from the onset of herpes zoster.

Conclusion: Major progress in the pharmacological treatment of PHN appears to be an obvious factor contributing to the overall improvement in PHN management (introduction of gabapentin). Nevertheless, safely administered regional anaesthesia techniques, although performed in a very similar manner for many years, appear to provide some support as part of a multimodal approach to PHN management.

Key words: postherpetic neuralgia, numeric rating scale, sympathetic nerve blocks, gabapentin, tricyclic antidepressants

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Postherpetic neuralgia (PHN) is described as unilateral pain localised in the area of herpes zoster (HZ), which includes the affected dermatomes and persists beyond the acute phase of HZ and healing of the skin lesions (for more than 30 days or 4 months according to the International Association for the Study of Pain [IASP]). The presence of a painful prodrome preceding the rash stems from early degenerative changes in sensory ganglia, while an extensive rash is a consequence of epidermal nerve fibre destruction. Acute pain in the early stage of shingles results from the onset of central sensitisation and destructive changes in the dorsal horn [1, 2]. The reason why some HZ cases convert to

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PHN is unknown. Viral infection followed by inflammation may cause destruction of the sensory and motor fibres, with subsequent permanent damage to peripheral nerve trunci, dorsal root ganglions (DRG), dorsal roots and dorsal horns. Inflammation – driven changes result in a disintegration of the nervous system. PHN is prevalent in 9–34% of HZ patients [3]. To date, a number of risk factors for PHN have been identified, including older age, female gender, painful prodrome, affected first branch of the trigeminal nerve, coexistent immunodeficiency and greater acute pain and rash severity [4]. From the list of risk factors, older age was the first to be named and still appears to be the most relevant. Its significance might be explained by age-related underlying subclinical polyneuropathy, which requires less viral damage to cause PHN [5]. The management of PHN depends on the pain characteristics and time from the onset of HZ symptoms; in addition, PHN management is guided by frequently published meta-analyses and recommendations that focus on the various types of chronic pain [6–11]. A modern comprehensive approach to PHN management requires the introduction of potent systemic drugs such as antidepressants, anticonvulsants and opioids, and in particular cases should be aided by topical lidocaine and capsaicin preparations; however, the role of interventional pain management techniques for PHN is still disputed [11].

In this retrospective study, we aimed to compare the efficacy of PHN management strategies employed over the years, which varied as to available pharmacological therapy options but had one common feature used throughout: nerve blocks that affect the sympathetic system.

METHODS

STUDY POPULATION AND DATA COLLECTION

The protocol was reviewed and approved by the Institutional Ethics Committee of the Medical Center for Postgraduate Education in Warsaw. Medical notes of the patients treated in the Pain Clinic due to PHN symptoms during the years 1992–2010 were identified and reviewed. We aimed to assess PHN patients' demographics, prior medical history, PHN treatment preceding the pain clinic referral (use of antiviral agents and neuropathic pain management), and details of the treatment introduced and its outcome. A total of 563 PHN cases were identified, in which at least one form of regional anaesthesia was implemented. PHN was defined as a pain of typical character (constant burning pain or intermittent stabbing and shooting pain, and allodynia) persisting beyond the healing of herpetic skin lesions (more than 4 weeks after the rash onset). This criterion is the same utilised for defining PHN in our pain clinic. Another proposed definition of herpes-related pain is sub-acute herpetic neuralgia 30 to 120 days from HZ, and PHN if the pain persists beyond 3 months. It has also been proposed that PHN should only be diagnosed 6 months after HZ onset [1]. As defining PHN itself is clearly challenging, we decided to apply the less complex form of the definition because it does not influence the choice of treatment and avoids confusion. For the purpose of analysis, these cases were divided into 3 groups depending on the time period when pain clinic care was commenced, which determined pharmacological therapy options. As to pharmacological treatment, in the years 1992–1997 (group I), the most commonly used regime was amitriptyline and/or carbamazepine supported with opioid-based analgesics. In the years 1998–2002 (group II), the introduction of gabapentin caused a significant shift in PHN management, as it largely superseded carbamazepine. The years 2003–2010 (group III) were a time period when the new treatment options became available: pregabalin, duloxetine, transdermal buprenorphine, controlled-release oxycodone and dihydrocodeine. Unfortunately, at this point, it would be extremely difficult to evaluate pharmacological treatment in a quantitative manner; in addition, it would be even more challenging to present these results. Thus, although aware of the fact that the lack of quantitative analyses will influence this paper's scientific value, the data on the pharmacological treatment used will be limited to the description given above. Pain severity was assessed using an 11-point numeric rating scale (NRS) ranging from 0-10, where 0 represents no pain and 10 represents the worst pain possible. Only patients with an initial NRS score greater than 4 (5–10) were included in the data analysis. The cut-off NRS value for a good PHN management result was set at 3 (scores 0–2) [11]. Additionally, to identify outstanding treatment outcomes, we arbitrarily considered an NRS of 0 to indicate excellent results and NRS of 1–2 to indicate positive results. Patients unable to understand or utilise the NRS were excluded from the data analysis. Subjects with diabetes mellitus could be included provided they did not have any clinical signs of diabetic neuropathy prior to HZ.

CRITERIA FOR SYMPATHETIC NERVE BLOCK-BASED MANAGEMENT

A review of the available medical notes revealed that during the time period assessed, surprisingly similar criteria were applied to determine candidacy for a nerve block, and only minor occasional discrepancies were detected: diagnosed PHN as well as no more than 12 months from the first clinical signs of HZ, unless after 12 months the pain was still accompanied by allodynia. In all of the patients who started pain clinic treatment up to 6 months after the onset of HZ, a course of 3 to 10 nerve blocks was administered. The number of interventional procedures was limited by their effectiveness: at the first pain clinic visit, the block was placed, and subsequent blocks were considered depending on the outcome of the first and were performed either on

Table 1. Demographics of the study population

	Period of time		
	1992–1997	**1998–2002**	**2003–2010**
Age range (years)	23–97	19–92	40–92
No. of patients/No. of cases treated with SNB's	159/153	132/127	272/272
Sex (F/M)	118/41 (74/26%)	94/38 (71/29%)	179/93 (66/34%)
Prior treatment (Y/N)	101/58 (64/36%)	92/40 (71/29%)	243/29 (89/11%)
Area affected (HN/UL/CH/LL) (%)	25/13/53/9	25/7/60/8	24/16/54/6

HN — head and neck; UL — upper limb; CH — chest; LL — lower limb

alternate days or every three days, up to 10 procedures in total (Monday – Wednesday – Friday). If significant pain relief was reported (NRS score of less than 3) during the course of treatment, then one more block was placed, and further therapy relied on pharmacological options only. If more than 6 but less than 12 months had passed since the acute phase of the disease, two blocks were administered to aid diagnosis and estimate possible therapy outcomes. If a favourable result was noted with one or two blocks in place, additional blocks were subsequently placed (up to 10 in total), with NRS < 3 being the goal; an NRS < 3 effectively ended the course. Regardless of the number of blocks for these cases, the clinical data was used in our final analysis. In cases where treatment was commenced after more than a year from HZ, nerve blocks were rarely used because, in these PHN patients, the related pain was seldom accompanied by allodynia. Pharmacological treatment was then aided by local infiltration of the affected area with 1% lidocaine with methylprednisolone (up to 80 mg), using multiple injections to raise a wheal of subcutaneously injected LA/steroid solution around the affected area. It was obviously impossible to avoid some deviations from the above-mentioned protocol over so many years of clinical practice, of which missed appointments were noted as being the most common. More than three appointments missed in a row resulted in exclusion from the analysis.

TECHNIQUES

The method of nerve block placement was similar for a given pain location. With the exception of lumbar epidural and sciatic nerve blocks, the local anaesthetic used was bupivacaine 2.5 mg mL^{-1} (0.25%) with epinephrine 2.5 µg mL^{-1}. For PHN of the first trigeminal (ophthalmic) nerve, an isolated blockade with 5 mL of bupivacaine with epinephrine was administered. If the second and/or third trigeminal nerve branch were affected, or if neck and upper extremity PHN was present, a stellate ganglion block was indicated, for which the modified blind paratracheal approach technique described by Carron [12] was employed with 5 mL of bupivacaine with epinephrine. The block was considered successful if ipsilateral Horner's syndrome (miosis, ptosis) developed, with or without paraesthesia, and the rate of successful blocks was nearly 100% when validated in the above-described manner. In the most commonly occurring chest wall PHN, blocks of the corresponding intercostal nerves were placed using the same concentration of local anaesthetic. Three to five intercostal blocks with 3 mL of local anaesthetic solution each were typically performed along the scapular line, with the patient in a sitting position. In rare cases of gluteal and sacral region PHN, a single-dose lumbar epidural injection with 3 mL of 2% lidocaine and 40 mg methylprednisolone was implemented. For a sciatic nerve block to treat an affected lower extremity, 20 mL of plain 0.0625% bupivacaine was routinely utilised using a Labat modified by Winnie approach [13]. Low concentrations of the local anaesthetic in this case allowed the block to be performed in an outpatient clinic setting with no need for hospital admission. At this point, it should be noted that the term "sympathetic nerve block" may not be appropriate in the case of an ophthalmic nerve block. Unlike other structures, blockades of which are described above (intercostal nerves, sciatic nerve, lumbar epidural or purely sympathetic stellate ganglion block), the ophthalmic nerve is purely sensory, and thus, blocking it does not affect the sympathetic system. Nevertheless, it is an interventional treatment directed towards PHN and has been evaluated with sympathetic system blocking procedures.

We analysed the available data to determine the influence of age and time to treatment commencement on the outcomes of the employed therapy. Statistica 10 (StatSoft, Tulsa, USA) software was used for data analysis. The χ^2 test was employed to analyse the differences in success rates between the groups, with a Yates correction when appropriate. *P* values < 0.05 were considered significant.

RESULTS

Demographic information, number and type of affected dermatomes, time from HZ onset to therapy commencement and the proportion of previously treated patients are presented in Table 1. The groups were similar in age,

Table 2. Overall results in the time intervals assessed

Result	Period of time		
	1992–1997	1998–2002	2003–2010
Good	112 (73%)*	104 (82%)	224 (82%)*
Excellent	73 (48%)	81 (64%)	129 (47%)
Positive	39 (25%)	23 (18%)	95 (35%)
Poor	41 (27%)	23 (18%)	48 (18%)

* $P < 0.02$

male/female ratio and area of affected dermatomes. There were significant differences in the proportion of previously treated patients between the groups: 36% of patients in group I, 29% in group II and only 11% in group III had no previous pain treatment. The most commonly affected PHN area was the chest, followed by the head and neck and extremities. The overall results of the employed therapy indicate an improvement when groups I and III were considered, but no significant differences in success rate between groups II and III. After applying the NRS-based criteria for excellent and positive therapy outcomes, it was found that the best results were achieved in the years 1998–2002, when excellent were reported in 64% of cases (compared with 48% of patients treated before and 47% of patients treated after that period of time; Table 2). As age and time from HZ onset are known to be major contributors to possible outcomes of PHN treatment, the former and latter for each period of time were recorded and are summarised in Tables 3 and 4, respectively. As shown, the efficacy of PHN management tended to diminish with age, with the highest rates of favourable outcomes observed in younger patients. Although the latter groups (up to 49 and 50–59 years of age) were relatively small in size compared to the older patient groups, the tendency appears to be obvious. Considering the results in the same age groups over time, similar success rates in the 60–69 and 70-79 age groups were noted (87.5% vs. 93.7% vs. 91.6%% and 69.8% vs. 79.3% vs. 77.9%, respectively), while in the oldest groups (> 80 years) the chance of a good treatment outcome significantly increased over the last 19 years (the rate of favourable treatment results was 32.1% vs. 61.1% vs. 73.1%, respectively). In the years 2003–2010, the success rate of PHN treatment in this age group was shown to be similar to the rate observed in younger subjects. The findings of the analysis of time from the rash onset to treatment commencement and therapy outcomes are given in Table 4. As expected, treatment was most efficacious when started earlier than 3 months from the rash onset, regardless of the period of study considered, and diminished with time. If more than 12 months had passed before the PHN treatment was started, the treatment success rate was always lower, even though the chances for an effective treatment in this difficult group of patients have improved over the years, although not significantly (29.4% vs. 40% vs. 48.5%, respectively, $P > 0.05$) (Table 4).

Table 3. Therapeutic results and patient age (data given as count and rate in parentheses, when applicable)

Therapy outcome	Age (years)				
	1992–1997 (n: 153)				
	23–49	50-59	60–69	70–79	80+
Good	2 (100%)	22 (100%)	42 (87.5%)	37 (69.8%)	9 (32.1%)
Excellent	1	14	27	25	6
Positive	1	8	15	12	3
Poor	0	0	6	16	19
	1998–2002 (n: 127)				
	19–49	50–59	60–69	70–79	80+
Good	8 (100%)	5 (83.3%)	30 (93.7%)	50 (79.3%)	11 (61.1%)
Excellent	6	4	7	38	8
Positive	2	1	23	12	3
Poor	0	1	2	13	7
	2003–2010 (n: 272)				
	40–49	50–59	60–69	70–79	80+
Good	5 (100%)	23 (82.1%)	55 (91.6%)	92 (77.9%)	49 (73.1%)
Excellent	3	17	38	45	23
Positive	2	6	17	47	26
Poor	0	5	5	26	18

Table 4. Therapy outcomes depending on the time from the onset of HZ to treatment commencement (data given as count and rate in parentheses, when applicable)

Therapy outcome	Time from HZ onset			
	Up to 3 months	3–6 months	6–12 months	12 months+
	1992–1997 (n: 153)			
Good	78 (91.7%)*	23 (71.8%)*^	6 (31.5%)^	5 (29.4%)
Excellent	51	15	4	3
Positive	27	8	2	2
Poor	7	9	13	12
	1998–2002 (n: 127)			
Good	69 (88.4%)	24 (82.7%)	7 (70%)	4 (40%)
Excellent	58	15	5	3
Positive	11	9	2	1
Poor	9	5	3	6
	2003–2010 (n: 272)			
Good	145 (92.3%)#	49 (85.9%)	13 (56.5%)#	17 (48.5%)
Excellent	97	25	1	6
Positive	48	24	12	11
Poor	12	8	10	18

* $P < 0.01$, ^ $P < 0.01$, # $P < 0.0001$

DISCUSSION

Management of the acute phase of HZ aims to effectively alleviate pain and avoid possible complications (PHN), regardless of the area affected. Most pain specialists currently agree that treatment introduced early should decrease the risk of PHN. It appears that this approach is of special value to the elderly, as older age is undeniably the most relevant risk factor for PHN, in patients with a severe acute phase of the disease, with affected facial and neck areas, as well as in non-immunocompetent subjects. The best effect is achieved when aggressive treatment is introduced within 48 hours of rash onset, although early treatment does not provide sufficient protection against complications [1, 3, 4]. Once preventive measures fail and PHN develops, there is still no advisable "one size fits all" management strategy in place. In this report, we present our experience with sympathetic nerve block techniques employed as an adjunct therapy directed at this serious sequela of HZ.

The use of sympathetic nerve blocks for the treatment of early postherpetic pain was first reported back in 1938, and regional anaesthesia techniques have been used for sub-acute and chronic HZ–related pain management ever since [14]. Significant effort has been made to identify the nature of the interaction between the sympathetic system and neuropathic pain, as there is no communication between the peripheral sympathetic system and primary sensory fibres under normal conditions [15]. The results of experimental studies suggest a possible role of abnormal, direct links between afferent neurons of the pain pathway and efferent sympathetic fibres that may stem from abnormal neuronal sprouting at the site of neuronal or tissue damage [15]. Direct biochemical interactions are most likely to be mediated by noradrenaline, and there is substantial evidence for abnormal α-adrenergic sensitivity of the injured nociceptive fibres, resulting from α-receptor synthesis and/or activation [16]. This phenomenon is most likely significant in PHN because pain and allodynia may be worsened by the local administration of adrenergic agonists [17]. Recent guidelines regarding pharmacological treatment of neuropathic pain identify management with topical lidocaine preparations as part of a comprehensive first-line therapy, with capsaicin patches identified as second-line options [7, 8]. Although sympathetic nerve blocks are not recommended in the 2013 guidelines [11], when considering our local circumstances, they still appear to be the most affordable treatment option. Our previously developed routine of implementing sympathetic nerve blocks in all PHN cases with no contraindications to regional anaesthesia techniques (as employed in cases reported in this study) is now being amended. We aim not to replace sympathetic nerve blocks with 5% lidocaine plasters but to use regional procedures in cases where topical lidocaine and/or capsaicin preparations are not indicated, effective, or otherwise feasible due to their poor availability or lack patient consent. This change means that in a high number of our PHN patients, sympathetic nerve blocks are still a major part of the therapeutic process.

Although the possible mechanisms are still under investigation, sympathetic system involvement is traditionally

targeted in PHN management with varying efficacy. Numerous reports are available validating the use of sympathetic nerve blocks in prevention of PHN, while recent studies describing their application in established neuralgia are scarce and mostly limited to case reports and small trials [18–21]. Although the results of these studies are not consistent and data from large randomised controlled trials are lacking, our long-standing experience supports the substantial clinical value of sympathetic nerve blocks in daily pain clinic practice. In two early retrospective studies, Colding [22, 23] reported on the efficacy of blocking the peripheral sympathetic system in acute HZ and established PHN, with 34 (mean duration of symptoms approximately 2 years) and 69 cases (symptoms duration from 2 months to 2 years, and 11 years in one of the subjects) of PHN treated with sympathetic blocks. Although initially promising, the results eventually led to the conclusion that blocking sympathetic ganglions in diagnosed PHN may not be advisable, as significant pain relief was noted to be short-lived. The authors' theory that sympathetically mediated disturbances in neuronal blood supply would lead to time-related damage resulting in neuropathic pain was eventually validated by a retrospective study by Winnie et al. [24], which identified time from HZ onset as critical in decision making in regard to implementing sympathetic nerve blocks in the prevention and treatment of PHN. Similar conclusions can be drawn from our results, as the most favourable outcomes were observed in the groups treated within three months of rash onset. Treatment that commenced in the following three months was highly efficacious as well, with no significant differences in treatment outcomes between patients with blocks performed up to three months and between three and six months of the rash onset from 1998 onwards. It should be acknowledged at this stage that the introduction of more potent pharmacological options, especially gabapentinoids, could have played a role in the above results, as the shift towards longer periods of time from the onset of the herpetic rash and positive outcome of supplemented nerve block therapy occurred after the introduction these potent neuropathic pain medications. Unfortunately, it is impossible to quantify the extent of the pharmacological treatments' influence, but considering the results of previous studies, our own experience and some existing data on the successful use of sympathetic blockade in cases of intractable PHN [18, 25], the sole pharmacological treatment might not have been that successful.

It is both significant and disappointing that the number of patients treated for PHN before a pain clinic referral increased over the 19-year period. This finding is notable due to the rise in PHN from 64% in group I to 89% in group III; however, the number of patients whose treatment commenced more than 12 months after the appearance of HZ remains disappointingly high, as the chances of a positive therapy outcome in this group are low.

Our report is not free of methodological concerns. Differences in the areas affected, differences in the time from HZ onset, concomitant use of pharmacological therapy and lacking a means of validating our results against the outcomes of a control group limit the value of the majority of studies of sympathetic nerve blocks in PHN. However, because reports focused on the use of sympathetic blockade in PHN are usually based on smaller than our groups of patients, we believe that our experience may be of significant value for pain specialists who employ interventional techniques in their practice.

In conclusion, after 20 years of experience, we find sympathetic nerve blocks to be feasible and effective in aiding PHN management. Nerve blocks appear to be a very handy tool in the repertoire of possible therapy options. Regardless of the multitude of advanced pharmacological options, it is still awareness of the problem and prompt introduction of treatment that appear to be most relevant in optimising postherpetic neuralgia management.

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