Effects of dorsal root ganglion destruction by adriamycin in patients with postherpetic neuralgia

Efeitos da destruição da raiz dorsal ganglionar pela adriamicina em pacientes com neuralgia pós-herpética

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ABSTRACT

PURPOSE: To investigate the effects of dorsal root ganglion destruction in patients with postherpetic neuralgia (PHN).

METHODS: Seventy-two patients with PHN selected were randomly divided into two groups (n=36). Group A was the control group (treated by injection) and group B was the group of dorsal root ganglion destruction by adriamycin. Visual analog scale scores (VAS), SAS, SF-MPQ scores. Clinical effects and therapy safety were evaluated before therapy, one week, three and six months after therapy. Forty-four patients were available for intention-to-treat analysis.

RESULTS: The average pain scores on the Likert scale were significantly reduced at each point in group B. Patients in group B reported clinical effectiveness at six months as excellent response, good response, improved but unsatisfactory or unchanged 16, 12 and 8.VAS scores at each time point after the operation were lower than that before operation and in group A, there was significant difference. Patients showed significant improvement in sleep scores in group B. There was significant difference at T2 in group A than T1. There was no significant difference in group A at T3, T4 after the operation than that before operation. Between group comparison: there was significant difference between group A and group B at each time point after the operation.

CONCLUSIONS: Dorsal root ganglion destruction by adriamycin under guidance of C-arm perspective, the puncture operation was accurate without any adverse reaction or serious complications, which could effectively relieve pain of patients with postherpetic neuralgia, but the long-term effects needed further study.

Key words: Neuralgia, Postherpetic. Ganglia, Spinal. Doxorubicin.

RESUMO

OBJETIVO: Investigar os efeitos da destruição da raiz dorsal ganglionar em pacientes com neuralgia pós-herpética.

MÉTODOS: Setenta e dois pacientes selecionados com neuralgia pós-herpética foram randomicamente distribuídos em dois grupos (n=36). Grupo A foi o grupo controle (tratado por injeção) e o grupo B foi o grupo com destruição da raiz dorsal do gânglio pela adriamicina. Os escores da Escala Analógica Visual (VAS), SAS, SF-MPQ escores, efeitos clínicos e segurança terapêutica foram avaliados as antes da terapia, uma semana, três e seis meses após a terapia. Quarenta e quatro pacientes foram avaliados pela análise de intenção-em-tratar.

RESULTADOS: A média dos escores de dor na escala de Likert foi significativamente reduzida em cada ponto no grupo B. Pacientes no grupo B relataram efetividade clínica aos seis meses com excelente resposta (16), boa resposta (12), melhora mais insatisfatória ou sem modificações (8). Escores VAS a cada tempo após o procedimento foram melhores em comparação ao pré-operatório. No grupo A não foi observada diferença significativa. Pacientes mostraram melhora nos escores de dormir no grupo B. Houve diferença significante no T2 no grupo A que T1. Não houve diferença significante no grupo A nos tempos T3 e T4 após a cirurgia em relação a antes. Comparação entre os grupos: houve diferença significante entre os grupos A e B a cada tempo após a cirurgia.

CONCLUSÕES: A destruição da raiz dorsal ganglionar pela adriamicina sob perspectiva guiada pelo C-arm, a cirurgia pontual foi acurada sem qualquer reação adversa ou complicação séria, que pode efetivamente aliviar a dor em pacientes com neuralgia pós-herpética, mas os efeitos de longo prazo necessitam mais estudos.

Key words: Neuralgia Pós-Herpética. Gânglios Espinhais. Doxorrubicina.

Introduction

Postherpetic neuralgia(PHN) is often characterized by a combination of throbbing or burning pain, intermittent sharp pains, altered sensory perception, including paresthesia and allodynia (painful response to an innocuous stimulus[1].The pain may extend beyond the borders of the original zoster rash. The variety of symptoms likely result from injury to the dorsal root ganglia and dorsal horn as well as injury to the peripheral nerves. The incidence, duration and severity are all related to increasing age; in fact, PHN is uncommon in those less than 60 years of age[2-4]. Presence of pain prior to rash eruption, rash severity, and inflammation and fever are thought to all have an effect on PHN, pain is often severe, unrelenting, and exhausting. As a result, PHN can dramatically affect a patient's quality of life and function The pain is neuropathic in nature and may have a significant impact on the patient's quality of life and functional status, particularly in the elderly in whom postherpetic neuralgia is more prevalent[5,6].

Unfortunately, there is no intervention that reliably relieves the pain of PHN. Successful management of PHN can be complicated and challenging, especially with the fact that there is no definitive treatment algorithm specifically for patients with PHN. In recent years, there have been a number of published guidelines proposed for the treatment of neuropathic pain in general[7-10]. Effective therapy often requires multiple drugs. The treatments currently recommended and most frequently prescribed for PHN are tricyclic antidepressant and anticonvulsants[11]. However, in clinical practice these agents frequently result in poor pain relief and intolerable side-effects. Long-acting oxycodone was shown to result in PHN pain relief in a controlled clinical trial[12]. But opiates also frequently cause intolerable side effects; in addition, many patients and physicians are still reticent to utilize opiates for chronic nonmalignant pain. Thus, there exists a need for more effective and better-tolerated therapies. Among invasive therapies, repetitive peripheral nerve and sympathetic blocks have few advocates once PHN is fully established. Destructive procedures like nerve sectioning, DREZ (dorsal root rhizotomy) lesions, cordotomy cannot be recommended[13]. Implantable spinal infusion devices, neural stimulators, and skin resection have also been used in the treatment of severe or intractable postherpetic neuralgia. But nonpharmacologic therapies are not first-line treatment options till today, The aim of the present study is to investigate the effects of dorsal root ganglion destruction by adriamycin in patients with postherpetic neuralgia.

Methods

The study was performed at Department of Anesthesiology, People's Hospital of Guizhou Province, China. It was a randomized, parallel-group trial of three years duration. The protocol was approved by the institution Ethics Committee and the national regulator authority, written informed consent was obtained from a legal surrogate, all patients signed informed consent. Seventy-two patients (31 male cases and 41 female cases and age between 48-86 years old) suffering from postherpetic neuralgia were screened for eligibility between January 2004 and January 2007.

Inclusive criteria

Patients with PHN, at least 18 years of age with history of >12 weeks of PHN pain after healing of rash, a pain intensity of at least 40 mm on a 100 mm visual analog scale at screening and at randomization, and average pain score of at least 4 on the Likert scale during the baseline week were included in the study.

Exclusion criteria

Head and face postherpetic neuralgia, neurolytic or neurosurgical therapy for PHN, an immunocompromised state, hepatic or renal insufficiency and significant hematological disease, history of severe pain other than that caused by PHN, or history of use of experimental drugs or participation in a clinical study within two months of screening, a history of illicit drug or alcohol abuse within the last year, any serious or unstable medical or psychological condition.

In the operation, the patient was asked to lie in a lateral position with painful side upwards, then 3-5 segments were selected according to the painful positions and the corresponding spinous process was remarked. After local anesthesia of the patients, the puncture needle (Type: 7#) was punctured into intervertebral foramen at 0.5-2.0cm adjacent to spinous by fluroscopy. When the puncture needle arrived at the intervertebral foramen and then gas injection had no resistance and no blood or cerebrospinal fluid (CSF)was sucked out (Figure 1), and 1% lidocaine 2ml (testing dose) was injected subsequently, after 20min observation, if pain alleviated or disappeared in patients with the assurance of no all-lumbar anesthesia, no adverse reaction, no dysesthesia of lower limbs or no dyskinesia, 0.25% adriamycin 1ml (Zhejiang Hisun Pharmaceutical Co, Ltd) and 2.5mg dexamethasone was injected in each intervertebral foramen of the patients in Group B, however, only 2.5mg dexamethasone was injected in each intervertebral foramen of the patients in Group A (Figure 2). BP, HR and SpO$_2$

of the patients were monitored within 4h from the beginning of the operation and then the muscle strength of limbs of the patients were observed. Patients with unsatisfactory treatment effects accepted injection one week later.

FIGURE 1 - Later radiograph showing the needle placed at the anterosuperior of foramen.

FIGURE 2 - Anteroposterior radiograph of patient showing the needle placed at the foramen.

Pain intensity was assessed using a horizontal 100mm visual analog scale (VAS). The subject indicated the severity of his or her pain with a mark along the line between 0=no pain and 100=worst pain imaginable. Visual Analogue Scale was made before the operation (T1), and one week (T2), three month (T3) and six months (T4) after the operation.

Sleep, disability and clinical effectiveness were evaluated as described previously[14]. Sleep was assessed using a 100mm visual analog scale (VAS) with "slept well" on one end and "did not sleep at all" on the other end. Disability was rated according to a categorical scale of "no, mild, moderate and severe

disability implied patient was in bed with pain for part or all of the day. Moderate disability implied pain significantly interfered with or prevented activities of daily living such as dressing, wearing clothes, eating, cleaning or shopping Mild disability implied pain that interfered only with some activities such as exercise.

The SF-MPQ[10] was used to assess pain at all four visits. Fifteen pain descriptors (11 sensory, 4 affective) are rated by the subjects on a four-point intensity scale (0 = none to 3 = severe) regarding the preceding week. For data analysis, three scores are derived: (1) sensory score (descriptors: 'throbbing', 'shooting', 'stabbing', 'sharp', 'cramping', 'gnawing', 'hot-burning', 'aching', 'heavy', 'tender', and 'splitting'); (2) affective score (descriptors: 'tiring-exhausting', 'sickening', 'fearful', and 'punishing-cruel'); and (3) total score (sensory plus affective score).

Clinical effectiveness was determined by categorizing patients as depending upon response into "excellent, good, improved but unsatisfactory or unchanged[12].An excellent response implied no pain and tolerable side effects, no disability, no insomnia and an expression of satisfaction with the degree of pain relief. A good response implied that pain was never worse than mild and VAS marked within the one-thirds of the 'NO PAIN" end. This category also implied at least 70% pain relief, mild disability, VAS marked within the one -third of the "slept well" end and patient expressing satisfaction with the degree of pain relief and low level of side effects. An unsatisfactory response implied 25% improvement in VAS but with some significant, intolerable side effects persisting, moderate or greater disability or an expression of dissatisfaction with pain relief.

Any side effects reported by the patient were recorded. Furthermore, a checklist of side effects of both medications was given at baseline and at each visit.

Data collection and statistical analysis

Study population was analyzed on an intention-to-treat basis. The sample size calculation was based on the primary efficacy variable with an assumption of a 1:1 randomization ration of group A and group B. Assuming a standard deviation of 1.5 and normally distributed responses, a sample size of 25 randomized patients per group was calculated to provide 90% power to detect a difference of 1.25 in the end point in the two groups, with 2-sided testing at the 0.05 level. Assuming a 30% patient dropout rate, a total sample size of about 35 randomized patients per group was required to demonstrate significant difference in efficacy between the two groups. The null hypothesis for the study was that here is no significant difference between the two groups in reducing the 11-point pain intensity score in patients with post-herpetic

neuralgia.

Each treatment arm was assessed by comparing the results to the baseline results using repeated measures ANOVA. Between-groups comparison was done by using ANOVA. Global impression of therapy was analyzed using Chi-square test. A 2-sided p value of less than 0.05 was considered statistically significant.

Results

The baseline demographic and clinical characteristics of the two groups were similar (Table 1). There was no statistically significant difference in the distribution of age, sex. Herpes involved areas were: 32 cases of back thoracic, abdominal waist of 40 cases, 31 patients involving the scope of herper in 1-3 spinal segments, 41 patients involving the scope of more than three spinal segments.

TABLE 1 - Demographic characteristics at inclusion (n=36).

Variable		A	B
Age(years)	Mean(SD)	68.4(12.3)	69.2 (11.8)
Male(%)		38.89%	30.56%
Weight(kg)	Mean(SD)	68.3(11.2)	65.5(11.7)
Time since rash in months	Mean(SD)	12.6 (4.8)	13.2(4.9)
Pain VAS score	Mean(SD)	7.55(1.44)	7.64(1.99)

SD: Standard Deviation

Success rate of puncture was 100%. In group B, one case missed follow-up one month after the operation and three cases missed follow-up three months after the operation. Eight patients accepted twice operation (one patient recurrence one month after operation and was released after the second operation), two patients accepted three time operation. In group A, two cases missed follow-up one month after the operation and three cases missed follow-up three months after the operation. Nine patients accepted twice operation, two patients accepted three time operation

No serious complication, dyskinesia, cardiovascular system reaction, nausea or vomitting presented in patients after the operation in both group. Sixteen cases had postoperative local numbness and hypoesthesia in group B.

The average pain scores on the Likert scale were significantly reduced at each point in group B. Patients in group B reported clinical effectiveness at six months as excellent response, good response, improved but unsatisfactory or unchanged 16, 12, 8.VAS scores at each time point after the operation were lower than that before operation and in group A, there was significant difference (Table 2). Patients showed significant improvement in sleep scores in group B. There was significant difference at T2 in group A than T1. There was no significant difference in group A at T3, T4 after the operation than that before operation. Between group comparison: there was significant difference between group A and group B at each time point after the operation.

TABLE 2 - Comparison of VAS, SAS, SF-MPQ before and after therapy (n=36).

		T1	T2	T3	T4
VAS	A	7.55±1.44	4.91±1.85*	7.28±1.42	7.23±1.31
	B	7.64±1.19	2.64±3.05*#	1.45±2.50*#	1.14±2.23*#
SAS	A	3.32±1.91	2.64±1.65	2.77±1.66	3.00±1.75
	B	3.50±1.47	1.45±1.22*	1.64±1.47*	1.27±1.12*#
SF-MPQ	A	9.64±2.32	7.78±2.58*	9.09±1.93	9.27±2.00
	B	10.32±2.21	2.82±3.67*#	2.09±3.57*#	1.82±3.54*#

Note: compared to the T1,*p<0.05. Compared to the Group A, #p <0.05.

Discussion

Our study showed dorsal root ganglion destruction by adriamycin is significantly more efficious than dexamethasone only in reducing pain of PHN, without any serious side-effect. It was a safe and effective micro-traumatic intervention treatment and can relieve the pain of PHN effectively. Patients could accepted the second or third operation when the pain returned (one patient experienced the recurrence of symptoms in group B 1 month after the first operation) or they still feel pain after the first operation. In group A, the average pain scores on the Likert scale were significantly reduced at T2, but no significantly reduced at T3, T4. This short time pain relieve may contribute to the application of corticosteroids at the dorsal root ganglion.

But in our study, the pain of two patients was not relieved, this suggest that the mechanism of postherpetic neuralgia is complex. Both peripheral and central pathophsiological mechanisms contribute to PHN pain. The mechanisms of PHN include both peripheral and central mechanisms. Peripheral mechanisms of pain are most clearly present when patients exhibit marked allodynia, prolonged relief from local anest hetic skin infiltration; and capsaicin induced burning[16-18]. It has been

suggested that in these patients damaged (irritable) primary afferent nociceptors that remain in continuity with their central targets provide continuous input to the dorsal horn[19]. Such increased nociceptor input from peripheral sources into spinal dorsal horn neurons can result in central sensitization[20]. Marked allodynia may therefore be explained by augmented and spontaneous activation of damaged C-nociceptors providing continuous input into the spinal cord and thereby maintaining central sensitization. Other peripheral mechanisms accounting for pain and allodynia in PHN may include sensitization of peripheral nociceptors, increased adrenergic activation of C-fibers, regeneration of damaged axons leading to neuromas or abnormal sprouting, and collateral innervation of denervated areas by neighboring axons. There is also compelling evidence that central mechanisms contribute to PHN. It has been suggested that deafferentation induced CNS abnormalities are an important mechanism[21,22]and that patients with marked sensory deficits, minimal allodynia, and little relief from local anesthetic skin infiltration provide the clearest evidence of deafferentation. In these patients, peripheral nociceptive C-fiber function and peripheral sympathetic input provide minimal contribution to spontaneous PHN pain. C-fiber degeneration accompanied by central hyperexitability is thought to explain predominantly continuous or shooting pain and the relative absence of allodynia[23]. Other central mechanisms of PHN may be present in these patients. Postmortem studies of patients with PHN have revealed degenerative changes in spinal gray matter following herpes zoster, intraspinal neuronal death (especially of inhibitory interneurons), either directly by inflammation or indirectly by primary afferent neuronal death, may result in development of increased excitability. Dorsal root ganglion (DRG), also named as ganglia or sensory ganglia, is located in the spinal nerve dorsal root between intervertebral foramens. DRG cells are physical and visceral sensory primary afferent neurons which play an important role in the occurrence and maintenance of neuropathic pain. DRG sensory neurons' peripheral processes terminate at physical and visceral peripheral pain receptors in the distributed areas, and central processes enter into spinal dorsal horn, so via neurons exchange of the second and third grade afferent neurons pain signals reflecting to cerebral cortex induce location pain and emotional reaction. If DRG is blocked upload of pain stimulating signals at the initial end of a pain transduction pathway will be cut down to relieve pain in corresponding distributed areas[24] description of damage to the nervous system from acute zoster has been confirmed and expanded upon by many authors. At time periods of up to one year after AHZ, some excised DRGs and peripheral nerves are still infiltrated with chronic inflammatory

cells. In late cases, DRGs may have 'ghosts' of sensory neurons, extensive collagen replacement, or even be grossly cystic. Peripheral nerves may show thinning of the myelin sheath in many axons, and in distal branches nearly complete transformation into collagen has been documented. Maybe some kind of pain of the patients cannot be relieved by dorsal root ganglion destruction; this still need more study.

Adriamycin can be absorbed by peripherals of nervous fibers and retrogradely transport along axoplasm to corresponding distributed neurons resulting in neuronal degeneration and necrosis, which is named as fatal and retrograde axoplasm transportation and suicidal transportation effect[25]. The present study showed that low dose and low concentration adriamycin injected in paravertebral intervertebral foramen immediately aggregated in ipsilateral DRG causing cell degeneration and necrosis without any influence on exercise-induced ventral root and corresponding spinal segments[26]. Saiki *et al.*[27] reported after intranerual injection of adriamycin, once symptoms of PHN patients had disappeared, no recurrence of symptoms was experienced. But in our study, one patient had a recurrence one month after operation, and was released after the second operation this maybe connected with the dose of adriamycin. How much adriamycin is consequently able to induce degeneration of the neurons without any systemic side effects needs further study.

Conclusions

Dorsal root ganglion destruction by adriamycin effectively relieve pain of patients with postherpetic neuralgia .It is a safe and effective treatment without any adverse reaction or serious complications.However,the long-term effects needed further study.

References

1. Argoff CE, Katz N, Backonja M. Treatment of postherpetic neuralgia: a review of therapeutic options. J Pain Symptom Manage. 2004;28:396-411.

2. Bader MS, McKinsey DS. Viral infections in the elderly. The challenges of managing herpes zoster, influenza, and RSV. Postgrad Med. 2005;118:45-8.

3. Stacey BR, Glanzman RL. Use of gabapentin for postherpetic neuralgia: results of two randomized, placebo-controlled studies. Clin Ther. 2003;25:2597-608.

4. Mounsey AL, Matthew LG, Slawson DC. Herpes zoster and postherpetic neuralgia: prevention and management. Am Fam Physician. 2005;72:1075-80.

5. Sabatowski R, Gálvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, Versavel M; 1008-045 Study Group. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-

controlled clinical trial. Pain. 2004;109:26-35.

6. Engberg B, Grondahl GB, Thibom K. Patients' experience of herpes zoster and postherpetic neuralgia. J Adv Nurs. 1995;21:427-33.

7. Moulin DE, Clark AJ, Gilron MD. Pharmacological management of chronic neuropathic pain-Consensus statement and guidelines from the Canadian Pain Society. Pain Res Manage. 2007;12:13-21.

8. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol. 2003;60:1524-34.

9. Attal N, Cruccu G, Haanpää M,Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P, EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006;13:1153-69.

10. Gore M, Sadosky A, Tai KS, Stacey B. A retrospective evaluation of the use of gabapentin and pregabalin in patients with postherpetic neuralgia in usual-care settings. Clin Ther. 2007;29:1655-70.

11. Watson CPN. Medical treatment of postherpetic neuralgia. In: Watson CPN (editor). Herpes zoster and postherpeic neuralgia. 1ed. Netherlands: Elsevier; 1993. p.205-19.

12. Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology. 1998;50(6)1837-41.

13. Loeser JD. Surgery for postherpetic neuralgia. In: Watson CPN (editor). Herpes zoster and postherpetic neuralgia. Amsterdam: Elsevier; 1993. p.221-37.

14. Watson CPN, Vernich L, Chipman M, Reed K. Notriptyline versus amitriptyline in post-herpetic neuralgia a randomized trial. Neurology. 1998;51:1166-71

15. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987;30:191-7.

16. Rowbothm MC, Fields HL. The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia. Brain. 1996;119:347-53.

17. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol. 1995;37:246-53.

18. Watson CPN, Deck JH. The neuropathology of herpes zoster with particular reference to postherpetic neuralgia. Amsterdam: Elsevier; 1993. p.139-57.

19. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis. 1998;5:209-27.

20. Pierce PA, Brose WG. Causalgia/reflex sympathetic dystrophy. In: Yaksh TL, Lynch C, Zapol WM, Maze M, Biebuyck JF, Saidman LJ (editors). Anesthesia: biologic foundations. Philadephia: Lippincott-Raven Publishers; 1998. p.889-904.

21. Bennett GJ. Hypothesis on the pathogenesis of herpes zoster-associated pain. Ann Neurol. 1994;35:S38-41.

22. Baron R, Saguer M. Postherpetic neuralgia: are C-nociceptors involved in signaling and maitenance of tactile allodynia? Brain. 1993;116:1477-96.

23. Nurmikko T, Wells C, Bowsher D. Pain and allodynia in postherpetic neuralgia: role of somatic and sympathetic nervous systems. Acta Neurol Scand. 1991;84:146-52.

24. Holmes FE, Bacon A, Pope RJ, Vanderplank PA, Kerr NC, Sukumaran M, Pachnis V, Wynick D. Transgenic overexpression of galanin in the dorsal root ganglia modulates pain-related behavior. Proc Natl Acad Sci USA. 2003;100(10):6180-5.

25. Bridges D, Thompson SW, Rice AS. Mechanisms of neuropathic pain. Br J Anaesth. 2001;87:12-26.

26. Xu J, Zheng B, Xue Y, Deng F. Selective effect of paravertebral injection with adriamycin on rabbits dorsal root ganglion. Chinese J

Anaesth. 2004;24(9):714-5.

27. Saiki M, Kondo A, Kinuta Y, Iwasaki K, Kobata H, Hasegawa K, Chin M, Nakano I, Yamamoto T. Treatment of intractable postherpetic neuralgia and blepharospasm: intraneural injection of adriamycin. No Shinkei Geka. 1995;23(2):125-30

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