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Original Article

A comparison of analgesic effects between intradermal injection and epidural block of lidocaine for postherpetic neuralgia

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Abstract: Objective: The aim of this study was to evaluate the clinical efficiency of intradermal injection and epidural block of lidocaine for postherpetic neuralgia (PHN) treatment. Methods: Fifty PHN patients were randomly assigned to two groups. Group I received intradermal injection of 0.5% lidocaine with drug therapy and group II underwent epidural block of 0.8% lidocaine with drug therapy. The primary efficacy outcome was the changes in Visual Analog Scale (VAS), Short-Form McGill Pain Questionnaire (SF-MPQ) score and Sleep interference scores (SIS) between group I and group II when assigned patients were discharged. Then we recorded the use of dezocine for assistant analgesia and the complication of two groups in hospitalization. Results: Comparing with pretreatment, VAS, SF-MPQ and SIS scores decreased remarkably in each group when assigned patients were discharged ($P < 0.05$). It was observed that there were no significant difference in VAS, SF-MPQ, SIS scores between group I and II ($P > 0.05$). In hospitalization, groups I and II had similar frequency of injecting dezocine ($P > 0.05$). More complications were found in group II. At 1 month after hospital discharge, VAS, SF-MPQ and SIS scores of two groups were lower than the scores when patients were discharged ($P < 0.05$), and the three scores between group I and group II were still similar ($P > 0.05$). Conclusion: The efficacy of lidocaine by intradermal injection and continuous epidural block is similar in the treatment of PHN. Intradermal injection of lidocaine may be more useful in PHN management.

Keywords: Pregabalin, intradermal injection, epidural block, lidocaine, postherpetic neuralgia

Introduction

Postherpetic neuralgia (PHN) is a nerve pain due to damage caused by the varicella zoster virus, which commonly last for several months to years after skin herpes subsided. The pain lasting more than three months can be diagnosed as PHN [1]. It is a common chronic neuropathic pain and 9-30% of acute herpes zoster (HZ) patients will develop PHN [2].

PHN mainly affects elderly patients and it is reported that up to 50% of patients with acute HZ were ≥ 60 years old [3]. PHN results in poor quality of life and the level of pain may interfere with daily life, sleep, mood and enjoyment [4]. Recently, treatment guidelines of neuropathic pains including PHN have been developed and updated [5-7]. Unfortunately, simple oral medication PHN obtains unsatisfied clinical effects. Furthermore, it is always restricted to patients who are very old or accompanied by other complications to receive drug treatment [8, 9]. Thus, in recent years, the clinical treatment of PHN commonly combines drugs with partial minimally invasive treatment to rapidly relieve pain and improve efficacy, such as spinal block, sympathetic blockade, paraspinal nerve block or peripheral nerve radiofrequency surgery, peripheral nerve damage drugs surgery, electrical nerve stimulation [10]. Continuous epidural anesthetic is one of the most minimally invasive methods for treatment of PHN pain by its affirmed efficacy. A widely used continuous epidural drug is 0.8% lidocaine [10-13]. But continuous epidural block therapy still has its drawbacks, such as technically demanding operation, high risk of infection, epidural catheter. Particularly, epidural catheter is easy to fall off, which is inconvenient in clinical practice.

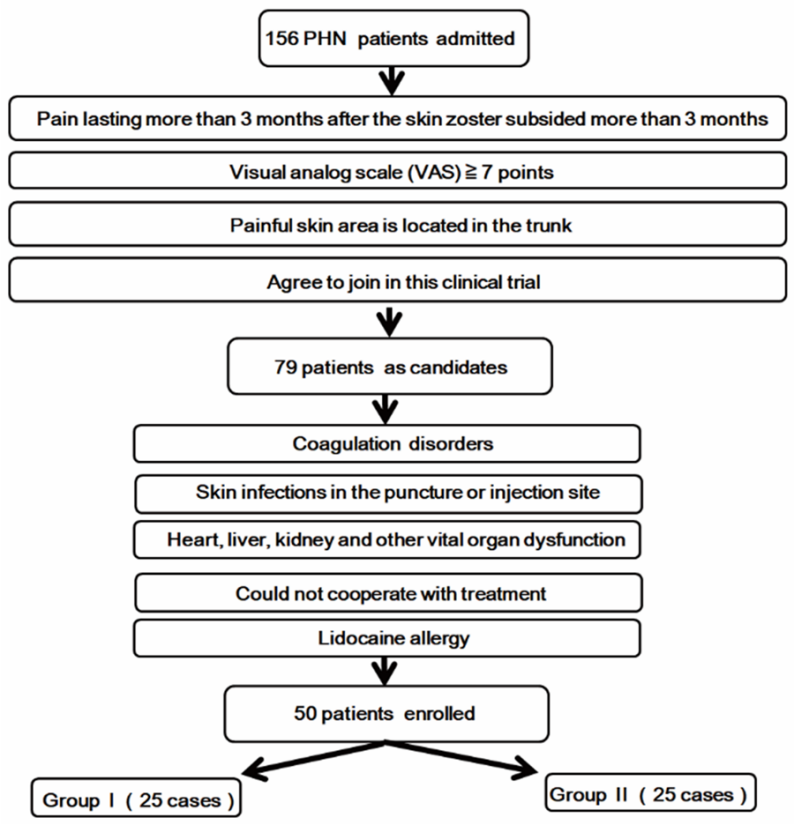

Figure 1. Flow chart of participant recruitment.

Intradermal injection is one kind of partial minimally invasive treatment methods and easy to be operated. Although intradermal injection is widely used in many types of treatment, it has not been taken seriously in the treatment of PHN. This study was aimed to compare the efficacy of PHN management with lidocaine between intradermal injection and epidural block, and evaluate the clinical efficiency of intradermal injection.

Materials and methods

Patients

From Mar 2014 to Mar 2016, a total of 156 patients who were diagnosed as PHN have been hospitalized to the First Affiliated Hospital of Wenzhou Medical University. They were taken as the candidates and the flow chart of participant recruitment used is illustrated in **Figure 1**. Finally, 50 patients were enrolled in this double-blind study. Neither the quizzes nor the subjects knew the group of the participants (the experimental group or control group). Selected cases were randomly divided into groups I and II with 25 cases in each group according to random numbers. Patients of group I were subcutaneously injected with 0.5% lidocaine combined with pregabalin and methylcobalamin treatment. Patients of group II received 0.8% lidocaine (5 ml/h) continuous epidural block combined with pregabalin and methylcobalamin treatment. Prior written and informed consent were obtained from this patient and the study was approved by the ethics review board of Wenzhou Medical University.

Lidocaine administration methods

Record information on admission was as follow: (1) General information: name, sex, age and complications; (2) Pain: pain location, time of pain, VAS [14], simple McGill Pain Questionnaire (SF-MPQ) score [15], sleep disturbance score (SIS) [16].

For intradermal injection method, the painful area of skin was confirmed and marked. Then 1% povidone iodine was used for skin disinfection. The syringe needle (25GA) was used to perform intradermal injection. When the needle bevel facing upward until the needle bevel into the skin, the needle was stopped and 0.5% lidocaine was injected intradermally to cause orange peel-like formation with the size of nearly 1 cm^2 Picchu, each Picchu apart 0.5-1.0 cm [17], and gradually to the central injection pain along the perimeter marked area until the pain Picchu covered the entire area. The injection of lidocaine was below 400 mg once in two days.

For epidural method, the epidural puncture point was determined according to the affected spinal nerve segment with corresponding to the pain region of patients, and the puncture site and subcutaneous tunnel connection were marked. After successful puncture, 3-4 cm epidural catheter was fixed and 3 ml 1% lidocaine was given.

Table 1. Patients' information on admission

Information	Group I	Group II
Cases	25	25
Gender (male/female)	10/15	12/13
Age (years)	65.85±8.95	63.50±6.24
Duration (month)	7.50±2.72	7.00±2.03
The number of segments involved	2.70±0.73	2.60±0.60
Past history of prednisone, amoxicillin (cases)	25	25

Outcome measurements

VAS, SF-MPQ and SIS in both groups I and II were measured. Using a 10 cm long ruler, mark 0 cm as "no pain" and 10 cm as "worst pain". The patient marked calibration position corresponding to the intensity of pain according to his/her judgment, and the distance from the left end position of the measurement is the VAS score [14]. For SF-MPQ measurement, the main component of the SF-MPQ consisted of 15 descriptors (11 sensory; 4 affective) which were rated to an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores were derived from the sum of the intensity rank values of the words chosen for sensory, affective and total descriptors (0-45) [15]. Then SIS evaluation method was similar with numeric rating scale (NRS) [14]. Patients based on subjective feeling to evaluate the degree of pain on sleep: 0 was completely free from pain, 10 was sleep disturbances, could not sleep because of pain [16].

Statistical methods

SPSS 17.0 statistical software (SPSS Inc, Chicago, IL, USA) was used for data analysis. Numerical variables were described by mean ± standard deviation (SD), and categorical data was described by the number or percentage of cases. Intra-group comparison of numerical variables were calculated using pairing t-testing and comparison between groups was performed using independent samples T test. Categorical variables were compared using chi-square test data. $P < 0.05$ was considered statistically significant.

Results

Patient demographics

The original data of the patients are provided in Supplementary Tables 1, 2, 3. On admission, gender, age, duration and scope of pain had no significant difference between group I and group II ($P > 0.05$, **Table 1**). A total of 77.5% patients accompanied by other complications, including COPD, diabetes, cardiovascular disease, cancer. Moreover, 80% patients in group I and 84% patients in group II had pains mainly in chest and back, while the other patients had pains mainly in waist and abdomen. As shown in **Table 1**, all the enrolled patients had previous history of medications (such as prednisone, amoxicillin).

VAS, SF-MPQ and SIS score before and after treatment

VAS score, SF-MPQ score and SIS scores of patients in two groups on admission had no significant difference ($P > 0.05$, **Figure 2** and Supplementary Table 4). All patients had severe pain on admission, and there were many kinds of pain existing in both groups. Average hospitalization time was 17.60±2.35 days in group I and 18.25±2.15 days in group II ($P > 0.05$, ns). For both groups, the VAS score, SF-MPQ score and SIS scores after treatment were lower than those before treatment ($P < 0.05$, **Figure 2** and Supplementary Table 4). Before the treatment, the VAS score, SF-MPQ score and SIS scores of the two groups had no significant difference, which was the same after treatment ($P > 0.05$, **Figure 2** and Supplementary Table 4).

Remedy drug use during treatment

During treatment, the frequency of dezocine injection was 2.50±1.05 times in group I, and 2.10±0.97 times in group II. There is no significant difference between two groups ($P > 0.05$).

Adverse reactions and complications

One patient in each group had slight dizziness after taking pregabalin, and no special treatment had been taken. There was no other adverse reaction appearing such as drowsiness, dry mouth or peripheral edema pregabalin. Patients in group I had obvious injection pain during intradermal injection, which was stopped after the injection. Two patients in group II had nausea after epidural block, and it was improved after symptomatic treatment.

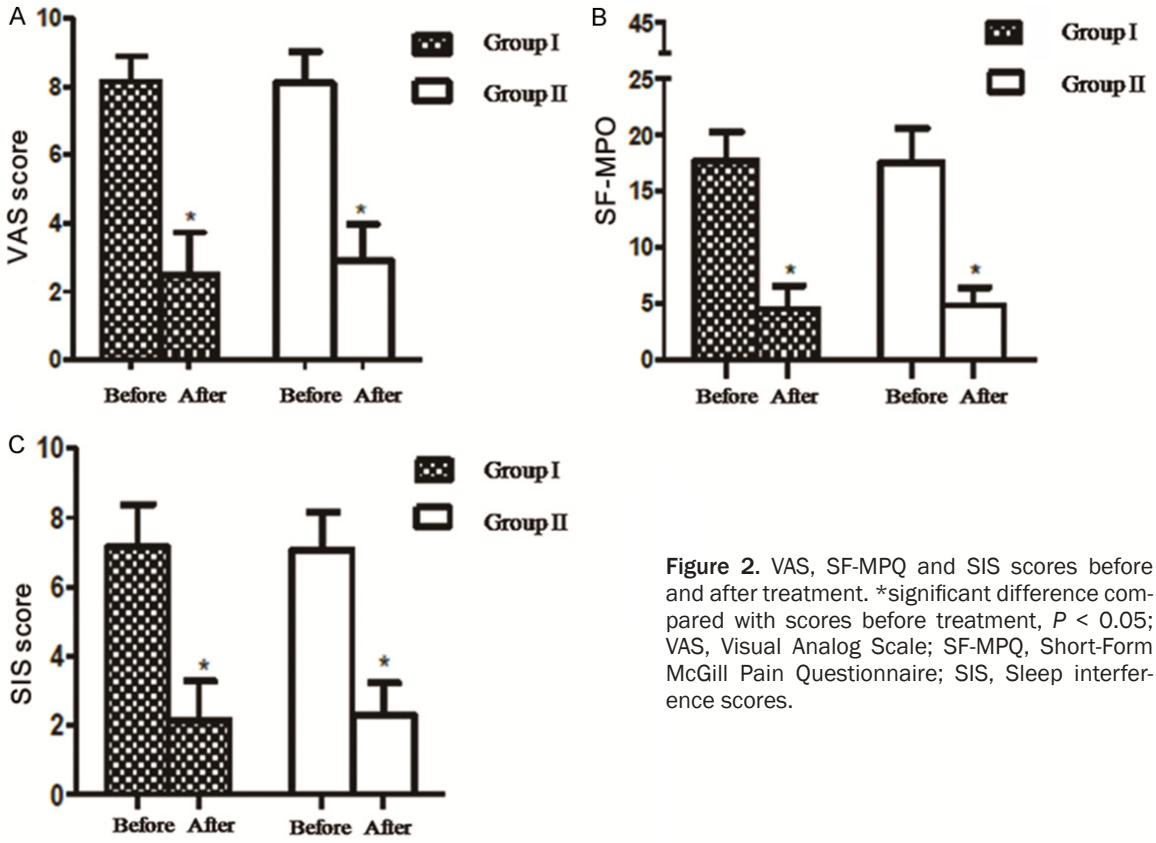

Figure 2. VAS, SF-MPQ and SIS scores before and after treatment. *significant difference compared with scores before treatment, $P < 0.05$; VAS, Visual Analog Scale; SF-MPQ, Short-Form McGill Pain Questionnaire; SIS, Sleep interference scores.

Table 2. Adverse reactions and complications

Complications	Group I	Group II
Local anesthetic toxicity	0	0
Nausea	0	2*
Breathing difficulties	0	0
Dysuria	0	3*
Lower limb movement disorder	0	0
Infection	0	0

Note: *significant difference compared with Group I.

Three patients in group II had dysuria being retained catheterization. After all, there were no severe complications appearing in both groups such as tongue numbness, dizziness and other local anesthetic toxicity, breathing difficulties, lower limb movement disorder, local skin puncture and spinal infection (**Table 2**).

One month follow-up after discharge

Twenty-one patients were successfully followed up in group I, and 20 in group II. One month after discharge, VAS, SF-MPQ and SIS scores were lower than those at discharge in both groups ($P < 0.05$, Supplementary Table 4). But VAS, SF-MPQ and SIS scores had significant difference between the two groups ($P < 0.05$, **Figure 2** and Supplementary Table 4).

Discussion

PHN is a typical peripheral neuropathic pain. Patients often suffer from severe pain and troubling abnormal sensation, which brings tremendous burden in life. Simple oral drug treatments have poor effects on most patients with PHN, which often require hospitalization in combination with other treatment methods for comprehensive treatment. As a part of comprehensive treatment, minimally invasive treatment can provide faster and better analgesic therapy effect [18].

Currently, minimally invasive treatments for PHN contain nerve block (including epidural anesthesia, sympathetic block and other peripheral nerve block) [19], nerve radiofrequency ablation and electrical nerve stimulation therapy. Although prospective studies suggest that electrical nerve stimulation therapy and radiofrequency treatment for PHN are effective, the two treatments in clinical efficacy are still

unclear. Moreover, they have high requirements for Physicians' technology and equipment, and their cost is relatively expensive. In contrast, epidural anesthesia or sympathetic nerve and other peripheral nerve block have been widely used in the actual clinical treatment. Nerve block treatment requires accurate judgments of affected nerve which needs experienced puncture skills. The ultrasound or core-needle X-ray imaging technology is needed sometimes. In addition, intradermal injection, a local minimally invasive treatment method, precisely delivers drugs into the painful area of skin, which has low requirements of technology and equipment.

Pathogenesis of PHN may be as follows: (1) Pain is related to the afferent nerve; (2) Peripheral sensitization associated afferent fibers; (3) Central sensitization occurs in the spinal cord [20]. Pregabalin is the first-line treatment of herpes zoster neuralgia internationally, whose mechanism may be directly work on the calcium channels of central nervous system (including the spinal cord and brain). Pregabalin has a high affinity with calcium ion channel subunit α2δ protein, and the combination with subunit α2δ can reduce the release of excitatory neurotransmitters to produce an analgesic effect [21]. Methylcobalamin is the neural active form of vitamin B12 which protects the integrityof nerve function, which is also one of the commonly used drugs of various therapeutic neuralgias.

Continuous epidural pain is one of the commonly used treatments for PHN, our finding suggests that continuous epidural anesthesia is effective in treating PHN, which is consistent with preliminary results of clinical trials in our department and other studies [10-13]. The mechanism of epidural block in the treatment of PHN may be: (1) Blocking abnormal PHN pain signals in the spinal cord or dorsal root ganglion conduction, and the vicious cycle of pain messages conduction; (2) Blocking the contact of sensory neurons and sympathetic; (3) Generating sympathetic blockade, expand local pain area vessels, and improving blood circulation to ease the pain [13].

Intradermal injection of lidocaine mainly acts on a large number of sensory nerve fibers in the dermis or subcutaneous tissue. PHN spontaneous pain was mainly led by the abnormal electrical signal of affected areas in skin sensory nerve fibers, and abnormal electrical signal generation and conduction are dependent on sodium channels [22]. PHN affected areas of the skin sensory nerve fiber always has increased sodium channels mRNA levels, and a large number of sodium ion channels gather such action potential threshold values decrease. Thus, spontaneous activity increases and a peripheral nervous "sensitive phenomenon" forms [20]. Lidocaine may be prioritized on the skin of high excitability of nerve fibers, working on the sensitive or high excitability of the specific voltage-gated sodium channels to inhibit their spontaneous activity. Lidocaine can also reduce the level the sodium channel mRNA of local nerve fibers, reducing spontaneous activity and signal transmission. Moreover, intradermal injection of lidocaine can improve local blood circulation and produce anti-inflammatory effects [23]. Since local skin keratinocytes and other skin immune cells are related to PHN, several studies suggest that intradermal injection of local anesthetic may be effective on local skin keratinocytes, or other immune cells to reduce PHN [24]. In addition, some researchers propose that dorsal root ganglia may also be the destination of lidocaine by intradermal injection, and a report demonstrated that intradermal injected lidocaine can be transported to the dorsal root ganglia in animals. Thus, intradermal injection of lidocaine may work in the dorsal root ganglia to reduce PHN [25].

This study mainly used 0.5% lidocaine as intradermal injection drug, because that low concentrations of lidocaine as intradermal injection of drugs can produce better analgesia effect. While producing effective analgesia effect, low concentrations of local anesthetics can also avoid motor block caused by high concentrations.

This study suggests that the analgesic effect of lidocaine by injection and continuous epidural block is similar. Certainly, intradermal injection need many times repeated and injection pain is a widespread problem. But some methods such as using fine needle, injected slowly can minimize the pain on injection. In this study, both intradermal injection and continuous epidural block had no serious complications in the treatment process. Additionally, intradermal injection is much easier to operate and the equipment requirement is less. It can also be

implemented even in the pain clinic. Thus, intradermal injection is more suitable for clinical treatment of PHN. However, intradermal injection in the treatment of PHN is still in the exploratory stage. It still needs more comprehensive trails with larger sample size to evaluate the clinical value.

Conclusions

In summary, the efficacy of lidocaine by intradermal injection and continuous epidural block is similar in the treatment of PHN. Since intradermal injection in the treatment of PHN is safe and effective, simply operated, it is worth clinical promotion.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Patients' information

Group	Number	Gender	Age (year)	Duration (month)	Number of segments involved	Past history of prednisone, amoxicillin
1	1	Male	67	9	4	1
1	2	Female	69	14	2	1
1	3	Female	73	5	3	1
1	4	Male	64	6	3	1
1	5	Male	66	16	2	1
1	6	Female	66	11	2	1
1	7	Female	69	3	3	1
1	8	Male	71	10	3	1
1	9	Female	78	1	3	1
1	10	Male	61	5	2	1
1	11	Female	62	9	3	1
1	12	Male	59	3	1	1
1	13	Female	63	2	2	1
1	14	Female	62	8	3	1
1	15	Female	64	9	3	1
1	16	Male	61	11	3	1
1	17	Female	65	12	3	1
1	18	Male	63	6	4	1
1	19	Female	66	2	3	1
1	20	Female	67	1	3	1
1	21	Male	65	11	3	1
1	22	Female	69	13	3	1
1	23	Female	64	6	2	1
1	24	Male	66	6	3	1
1	25	Female	66	7	3	1
2	1	Male	68	7	3	1
2	2	Female	62	9	3	1
2	3	Male	58	13	2	1
2	4	Male	67	2	3	1
2	5	Female	71	1	2	1
2	6	Female	62	16	3	1
2	7	Male	59	18	2	1
2	8	Female	63	2	2	1
2	9	Female	64	8	3	1
2	10	Female	68	2	2	1
2	11	Male	69	5	4	1
2	12	Female	66	2	3	1
2	13	Female	59	1	2	1
2	14	Male	57	11	3	1
2	15	Male	66	4	2	1
2	16	Female	64	9	4	1
2	17	Female	61	7	2	1
2	18	Male	62	8	3	1
2	19	Male	64	9	2	1
2	20	Female	65	6	3	1
2	21	Male	66	10	2	1
2	22	Female	61	3	2	1

2	23	Male	63	12	3	1
2	24	Female	64	4	2	1
2	25	Male	63	6	4	1

Note: 1: group 1; 2: group 2, Pasthistory (Past history of prednisone, amoxicillin: 1: yes; 2: no.

Supplementary Table 2. Data of VAS, SF-MPQ and SIS scores at different times

Group	Number	VAS_b	VAS_a	VAS_d	VAS_1 m	SFMPQ_b	SFMPQ_a	SFMPQ_d	SFMPQ_1 m	SIS_b	SIS_a	SIS_d	SIS_1 m
1	1	9	3	2	2	14	7	6	3	7	3	2	0
1	2	9	5	3	2	18	3	8	6	7	2	3	2
1	3	8	0	2	1	17	3	3	2	9	2	0	
1	4	8	3	1		15	0	3	3	7	1		1
1	5	8	1	5	2	17	3	5		9	3	2	0
1	6	8	1		3	19	2		2	9	3	3	2
1	7	8	1	3	2	14	5	5	4	8	1	1	3
1	8	7	3	2	1	20	4	3	5	8	2	3	1
1	9	8	3	2	2	21	4			4	3	2	
1	10	8	4	3	2	19	7	6	4	5	2		2
1	11	8	2		1	19	3	4	5	10	4	2	3
1	12	9	3	1	1	19	2	5	4	9	1	1	0
1	13	8	2	2	3	20	3		3	4	3	3	3
1	14	8	3	3	2	15	4	6	4	8	2	1	2
1	15	9	2	1	3	15	5	0		6	1	1	
1	16	9	4	4	1	22	9	5	2	8	2		2
1	17	7	2		2	17	3	4	6	6	3	1	3
1	18	7	1	3		21	3	6	6	6	1	3	0
1	19	8	1	3		20	2	4	2	6	3		1
1	20	8	3		2	15	2	3	3	6	2	3	1
1	21	9	3	3	1	19	4	2	5	6	3	1	
1	22	9	4	2	2	19	9	2	3	9	2	3	2
1	23	8	2	3	1	19	5	2	3	8	1	4	2
1	24	8	3	2		17	7			8	0	1	2
1	25	9	2	3	3	14	8	9	2	8	2	3	2
2	1	9	4	4	3	23	7	6	3	7	2	3	1
2	2	7	3	2	2	16	6	7	5	8	2	3	2
2	3	10	3	3	1	22	8	5	3	5	3	2	
2	4	7	2	3		13	3	5	4	6	2		4
2	5	8	4	2	2	16	5	3	5	7	4	3	1
2	6	7	2	3	3	18	4			5	2	2	3
2	7	8	3	5	2	16	6	8	6	9	4	2	2
2	8	10	3		2	22	5	4		6	2		1
2	9	8	2	2		13	2		4	7	3	2	1
2	10	8	4	4	1	18	5	3	6	8	4	2	2
2	11	9	3	3		20	3	6	2	7	2	1	2
2	12	8	3		3	18	7	3	2	6	1		
2	13	10	4	4	2	17	5		3	9	3	1	1
2	14	7	5	2	1	17	6	4		6	4	3	1
2	15	8	3	1	1	15	5	3	8	8	2	3	2
2	16	9	4	4	2	18	8	3	3	7	3		
2	17	8	2	2	2	18	6	4		6	1	3	2
2	18	7	2			20	5	7	1	10	3	4	1
2	19	8	3	3	4	18	6		3	7	2	2	
2	20	7	2			14	5	6	5	8	3		1
2	21	8	2	2	1	20	9	5	4	8	2	3	3
2	22	7	4	3	4	19	6	4		7	1	1	3
2	23	8	3	4	3	18	9		3	6	4	3	1
2	24	8	2		1	15	3	3	4	8	3	2	

2	25	7	3	2	1	14	6	5	3	6	3	2	1	

Note: VAS_b: VAS Before treatment; VAS_a: VAS After treatment; VAS_d: VAS Discharge; VAS_1 m: VAS 1 m after discharge; SFMPQ_b: SF-MPQ Before treatment; SFMPQ_a: SF-MPQ After treatment; SFMPQ_d: SF-MPQ Discharge; SFMPQ_1 m: SF-MPQ 1 m after discharge; SIS_b: SIS Before treatment; SIS_a: SIS After treatment; SIS_d: SIS Discharge; SIS_1 m: SIS 1 m after discharge.

Supplementary Table 3. Data of adverse reactions and complications

Group	Number	Local anesthetic toxicity*	Nausea*	Breathing difficulties*	Dysuria*	Lower limb movement disorder*	Infection*
1	1	2	2	2	2	2	2
1	2	2	2	2	2	2	2
1	3	2	2	2	2	2	2
1	4	2	2	2	2	2	2
1	5	2	2	2	2	2	2
1	6	2	2	2	2	2	2
1	7	2	2	2	2	2	2
1	8	2	2	2	2	2	2
1	9	2	2	2	2	2	2
1	10	2	2	2	2	2	2
1	11	2	2	2	2	2	2
1	12	2	2	2	2	2	2
1	13	2	2	2	2	2	2
1	14	2	2	2	2	2	2
1	15	2	2	2	2	2	2
1	16	2	2	2	2	2	2
1	17	2	2	2	2	2	2
1	18	2	2	2	2	2	2
1	19	2	2	2	2	2	2
1	20	2	2	2	2	2	2
1	21	2	2	2	2	2	2
1	22	2	2	2	2	2	2
1	23	2	2	2	2	2	2
1	24	2	2	2	2	2	2
1	25	2	2	2	2	2	2
2	1	2	2	2	2	2	2
2	2	2	2	2	2	2	2
2	3	2	2	2	2	2	2
2	4	2	2	2	2	2	2
2	5	2	2	2	2	2	2
2	6	2	2	2	2	2	2
2	7	2	1	2	2	2	2
2	8	2	2	2	1	2	2
2	9	2	2	2	2	2	2
2	10	2	2	2	2	2	2
2	11	2	2	2	2	2	2
2	12	2	2	2	2	2	2
2	13	2	2	2	2	2	2
2	14	2	2	2	2	2	2
2	15	2	2	2	1	2	2
2	16	2	2	2	2	2	2
2	17	2	2	2	2	2	2

2	18	2	2	2	2	2	2
2	19	2	2	2	2	2	2
2	20	2	2	2	1	2	2
2	21	2	2	2	2	2	2
2	22	2	1	2	2	2	2
2	23	2	2	2	2	2	2
2	24	2	2	2	2	2	2
2	25	2	2	2	2	2	2

Note: *1: yes; 2: no.

Supplementary Table 4. Comparison of VAS, SF-MPQ and SIS scores at different times

Groups	Cases	VAS	SF-MPQ	SIS
Group I				
Before treatment	25	8.14±0.56	17.76±2.37	7.16±1.57
After treatment	25	2.47±1.12$^{\#}$	4.51±2.36$^{\#}$	2.20±0.87$^{\#}$
Discharge	21	2.42±0.93	4.35±2.06	2.10±1.09
1 m after discharge	21	1.87±0.79*	3.69±1.37*	1.52±1.01*
Group II				
Before treatment	25	8.07±0.97	17.63±2.76	7.05±1.26
After treatment	25	2.89±0.92$^{\#,\Delta}$	4.79±2.03$^{\#,\Delta}$	2.31±0.84$^{\#,\Delta}$
Discharge	20	2.84±0.93	4.71±1.47	2.28±0.76
1 m after discharge	20	2.10±0.99*	3.87±1.451*	1.63±0.19*

Note: $^{\#}$significant difference compared with scores before treatment, $P < 0.05$; $^{\Delta}$significant difference compared with scores compared to Group I, $P < 0.05$; *significant difference compared with scores at discharge, $P < 0.05$; VAS, Visual Analog Scale; SF-MPQ, Short-Form McGill Pain Questionnaire; SIS, Sleep interference scores.