Randomized Trial

Subcutaneous Injection of Triamcinolone and Lidocaine to Prevent Postherpetic Neuralgia

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Background: Herpes zoster (HZ) is associated with inflammation of the peripheral nerves, which is considered to be an important cause of postherpetic neuralgia (PHN). Interventions aimed at reducing this inflammation could prevent PHN. One option is the epidural administration of corticosteroid and local anesthetic. However, several authors have reported a risk of arachnoiditis with epidural corticosteroids. Subcutaneous injection in an outpatient setting is a safer option. However, there is limited evidence of the effectiveness of this alternative for preventing PHN.

Objectives: The aim of this study was to assess the effectiveness of subcutaneous injection of triamcinolone and lidocaine for the prevention of PHN in elderly HZ patients.

Study Design: Randomized, single-center, clinical trial.

Setting: Department of pain management of a teaching hospital in Beijing, China.

Methods: Patients with acute HZ with rash < 7 days (n = 100) were randomly assigned to receive either standard therapy (oral antivirals and analgesics) alone or standard therapy plus subcutaneous injection of triamcinolone and lidocaine. The severity of pain was assessed using a numeric rating scale (NRS) at enrollment and at one, 3, and 6 months after rash onset. Quality of life (QoL) was evaluated by the SF-36 before treatment and at 3 and 6 months after rash onset. The primary endpoint was the presence of zoster-associated pain (ZAP) at 3 months after rash onset.

Results: At enrollment, all patients reported ZAP with average NRS scores of 6.64 ± 1.44 and 7.16 ± 1.22 in the standard group and subcutaneous group, respectively. At 3 and 6 months after rash onset, the pain had decreased in both groups, but the decrease was significantly greater in the subcutaneous injection group. At 3 months, 2 (4%) patients in the subcutaneous injection group vs. 10 (20%) patients in the standard group had ZAP with NRS > 3 ($P = 0.014$). Both groups showed significant improvement in QoL at 3 and 6 months. No patient had major adverse events related to the subcutaneous injection.

Limitations: The main limitation of the study was the absence of a placebo subcutaneous injection in the standard group.

Conclusion: Subcutaneous injection of triamcinolone and lidocaine in the acute phase of HZ can reduce ZAP more effectively than oral antivirals and analgesics alone, and may be a feasible method to prevent PHN.

Key words: Subcutaneous injection, lidocaine, triamcinolone, postherpetic neuralgia, prevention

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Postherpetic neuralgia (PHN), a common complication of herpes zoster (HZ), is diagnosed when zoster-associated pain persists beyond 90 days after rash onset (1,2). PHN is uncommon in people under 50 years, but occurs in 20% of those aged between 50 and 80 years and up to 35% in those aged > 80 years (3-5). The pain of PHN can be severe enough to affect all aspects of daily life

(6). Once the symptom has developed, the effect of treatment is disappointing, and hence the importance of preventive strategies (7,8).

HZ is associated with inflammation of the dorsal root ganglion and peripheral nerves, and this inflammation is considered to be an important causative factor for PHN (9). Interventions aimed at reducing this inflammation should therefore be effective in decreasing the likelihood of developing PHN. Epidural administration of corticosteroids and local anesthetics has been shown to be effective, but is associated with the risk of arachnoiditis (10-12). Subcutaneous injection in an outpatient setting may be effective in preventing PHN and is also considerably safer (13). However, there is limited evidence of the effectiveness of this treatment. This study was designed to examine the effectiveness of subcutaneous injection of triamcinolone and lidocaine in preventing PHN.

Methods

This randomized prospective clinical trial was conducted between May 1, 2014, and April 30, 2015, at the Department of Pain Management of a teaching hospital in Beijing, China. The study was approved by the local Ethics Committee, and informed consent was obtained from each patient.

Patients

Consecutive patients with HZ-associated pain (n = 100) were enrolled for the study. Inclusion criteria were 1) HZ infection (with rash duration < 7 days); 2) pain numerical rating scale (NRS) score > 3; 3) age ≥ 50 years; and 4) willingness to comply with the allocated treatment and follow-up measurements. Exclusion criteria were 1) coagulation abnormalities, including use of coumarin anticoagulants (salicylates were allowed); 2) bacterial infection of the skin of the affected dermatome; 3) allergy to triamcinolone acetonide or lidocaine; and 4) known serious disorder of immunity (e.g., AIDS).

Procedures

At enrollment, pain duration, severity and localization of the rash, and quality of life (QoL) were recorded. Patients were asked to quantify the average pain experienced in the last 24 hours on a numeric rating scale (NRS) that ranged from 0 for "no pain" to 10 for "worst ever pain." QoL was measured by the Medical Outcomes Study Short-Form 36 (SF-36). The SF-36 comprises 36 categories, 35 of which are grouped into 8 multi-item scales: physical functioning (PF; 10 items); role physical (RP; 4 items); bodily pain (BP; 2 items); general health (GH; 5 items); vitality (VT; 4 items); social functioning (SF; 2 items); role emotional (RE; 3 items); and mental health (MH; 5 items). The scores for the 8 scales range from 0 (worst QoL) to 100 (best QoL). The remaining category concerns the experience of change in general health during the previous year.

The enrolled patients were allocated to receive either standard treatment (standard group) or standard treatment plus subcutaneous injection (subcutaneous injection group) in a 1:1 ratio, using a computer program and block randomization. All patients received the current standard treatment for HZ, which included analgesics (as needed) and antiviral medication (oral acyclovir 800 mg 5 times daily, if the rash had been present for less than 72 hours). Patients in the subcutaneous injection group received, in addition, a combination of triamcinolone (10 mg) and lidocaine (0.5%), injected subcutaneously in the affected area at the points where the patients experienced the worst pain (2 mL per point, with up to 10 points to cover the whole area of pain). The injections were administered once per week for 3 weeks, using 25G needles and sterile hypodermic syringes.

Follow-up

At follow-up at one, 3, and 6 months after rash onset, patients were asked to assess the severity of zoster-associated pain (ZAP) in the past 24 hours. The primary endpoint was the presence of ZAP with an NRS score of > 3 at 3 months after rash onset. SF-36 scores were assessed at 3 and 6 months after rash onset to evaluate QoL. Side effects during the treatment period and follow-up were recorded. Data entry was done by administrative assistants, blinded to the assigned treatment.

Statistical Analysis

A sample size of 47 patients per group was calculated to be necessary to detect a decrease of 20% in the incidence of PHN with a power of 80% and alpha error of 5%. The intention-to-treat approach was used for analysis. Quantitative data were expressed as means ± standard deviations and categorical data as percentages. The t-test was used to compare quantitative variables and Fisher's exact test or the chi-square test for categorical variables. The repeated measures analysis of variance (ANOVA) was used to assess the differences over time between the groups in the NRS and SF-36 scores. A 2-tailed $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using

GraphPad Prism, version 5.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

Figure 1 shows the trial profile. A total of 124 patients with HZ were recruited during the 12-month enrollment period. Of these, 24 patients were excluded for various reasons, leaving 100 patients for the final analysis. The baseline demographic and clinical characteristics of the patients did not differ significantly between the 2 groups (Table 1).

The incidence of ZAP was significantly lower in the subcutaneous injection group than in the standard group at each follow-up time point (Table 2).

Figure 2 shows the intensity of pain at the different time points. The NRS scores were significantly lower in the subcutaneous injection group at all 3 follow-up time points.

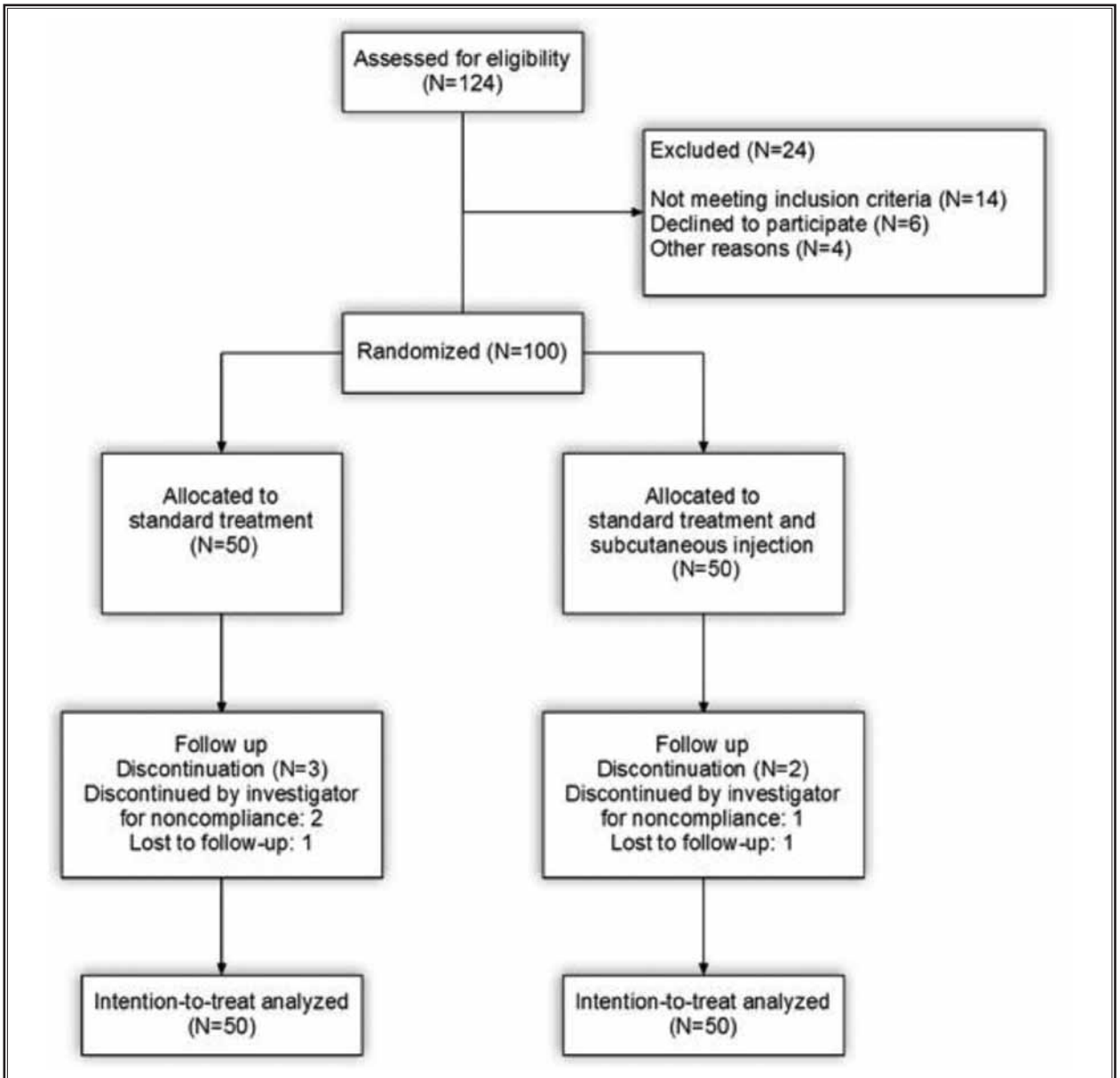

Fig. 1. *Trial profile.*

Table 1. *Clinical characteristics of patients at inclusion.*

	Standard group (n = 50	Subcutaneous group (n = 50)
Age at rash onset (mean ± SD)	63.84 ± 10.20	65.86 ± 10.19
Gender (male/female)	23/27	24/26
Duration of pain after rash onset (days; mean ± SD)	3.20 ± 1.96	3.36 ± 1.35
Pain NRS at inclusion (mean ± SD)	6.64 ± 1.44	7.16 ± 1.22
Localization		
Face	8 (16%)	7 (14%)
Cervical region	5 (10%)	2 (4%)
Thoracic region	23 (46%)	31 (62%)
Lumbar region	14 (28%)	10 (20%)

SD = standard deviation; NRS = numeric rating scale

Table 2. *Results at different time points after inclusion.*

Patients with ZAP (%)	1 month	3 months	6 months
Standard therapy group	12 (24%)	10 (20%)	9 (18%)
Subcutaneous injection group	3 (6%)	2 (4%)	2 (4%)
RR (95%CI)	0.81 (0.68 to 0.96)	0.83 (0.72 to 0.97)	0.85 (0.74 to 0.98)
P	0.012	0.014	0.025

ZAP = zoster-associated pain; RR = relative risk.

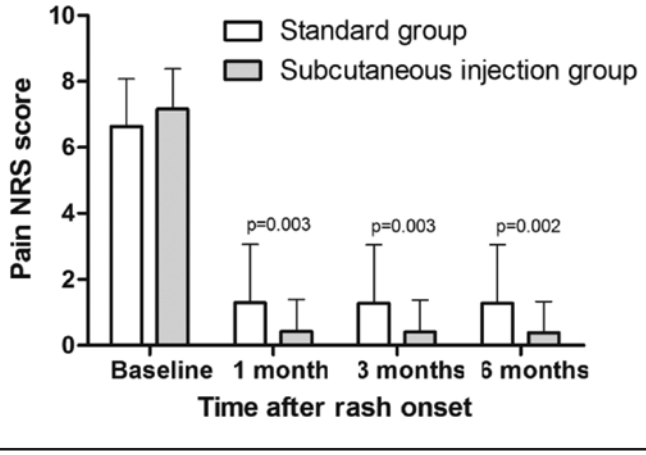

Fig. 2. *NRS ratings of pain intensity at different time points.*

The QoL, as assessed by the SF-36, was not significantly different between the groups across subscales at baseline, and showed significant improvement from baseline in both groups at 3 and 6 months (Fig. 3). The subcutaneous injection group showed significantly greater improvement in the subscales of PF, RP, BP, VT, and MH at 3 and 6 months than the standard group.

Minor complications were seen in 15 of the 50 patients who received subcutaneous injection: 8 (16%) patients had self-limiting subcutaneous hemorrhage and 7 (14%) complained of pain at the injection point. No major adverse events, such as acute lidocaine intoxication, dysesthesias, infection, or dissemination of zoster, were seen.

Discussion

In this study, we examined whether subcutaneous injection of triamcinolone and lidocaine during acute HZ would be effective in reducing the incidence of PHN. We followed up patients for 6 months and found that PHN developed in 4% of those who received the subcutaneous injection group vs. 20% in those who did not receive the injection.

Treatment of PHN can be rather disappointing (14), and efforts are therefore being directed toward prevention. It is believed that repetitive pain stimuli reaching the central nervous system lead to sensitization of the nociceptive system (15). Therefore, strategies to reduce acute pain during HZ can help prevent PHN (16).

Varicella-zoster vaccine is one option that

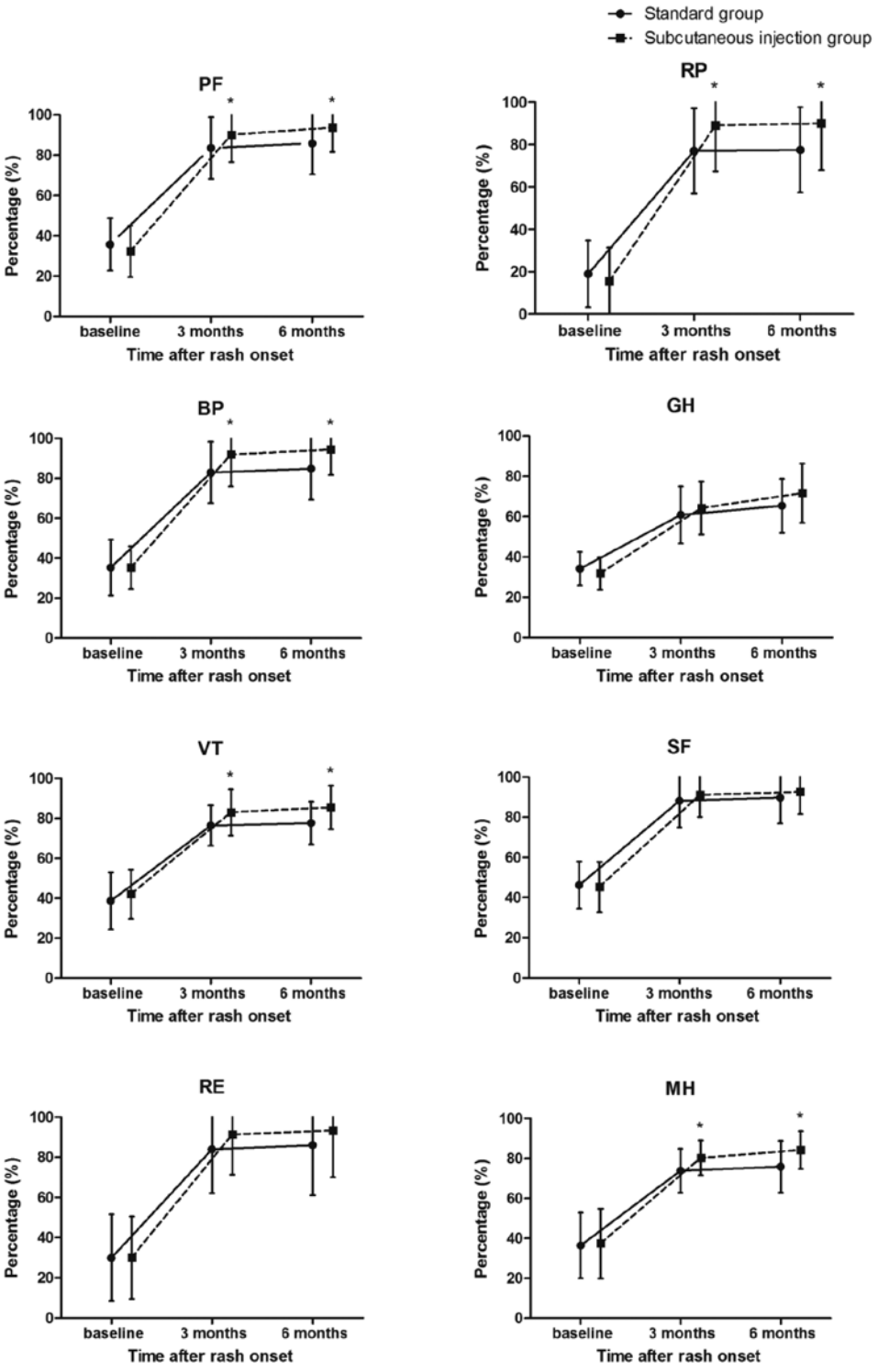

Fig. 3. *Quality of life (SF-36) before and after intervention. PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health.*

has shown promise in the prevention of PHN (17), but it is not a cost-effective measure; as many as 10 individuals have to be vaccinated to avoid one HZ case and 144 to avoid one PHN case (18). The accumulation of sodium channels at the injury sites and concomitant inflammation of the peripheral nerve are supposedly responsible for the acute pain of HZ (19,20). Lidocaine is thought to act by selective, but only partial, inhibition of voltage-gated sodium channels of damaged or dysfunctional unmyelinated C fibers and small myelinated A fibers (21). Corticosteroids exert a potent anti-inflammatory action, which might minimize nerve damage and thereby relieve HZ pain and prevent PHN (22). High-dose oral corticosteroids have been shown to produce a modest reduction in acute pain though no effect on the incidence of PHN has been demonstrated (23,24). In 1976, Epstein (25) demonstrated that intradermal injection of triamcinolone and procaine is an effective treatment for ZAP. Since then, there have been a few similar reports. Nerve block, in combination with corticosteroids, is now widely used in the treatment of the pain of HZ and PHN (25-27).

Recently, epidural, intrathecal, and paravertebral nerve blocks have been reported to be effective in reducing ZAP and preventing PHN (10,27). Pasqualucci and colleagues (10) randomized 600 patients with severe ZAP to receive either acyclovir plus prednisolone intravenously, or methylprednisolone plus bupivacaine via an epidural catheter, for periods ranging from 7 to 21 days. After one month, the incidence of ZAP was 8% in the epidural group and 41% in the intravenous therapy group. Several authors have, however, reported a risk of arachnoiditis with the use of epidural corticosteroids, which limits the widespread adoption of this technique (11,12,28). The other option, paravertebral injection, is relatively complex, with potential for injury to nerve roots and adjacent tissues (such as the pleura in thoracic paravertebral injection, and the vertebral artery in a cervical paravertebral injection). In comparison, subcutaneous injection of lidocaine and triamcinolone is a simple and safe method to block affected peripheral nerves and reduce inflammation. In our study, the pain NRS score decreased significantly in all HZ patients one month after rash onset, but patients who received standard treatment plus subcutaneous injection showed significantly greater improvement in pain score than those who received standard treatment alone.

It has been recommended that HZ patients who are older and have severe pain during HZ should be targeted for interventions designed to prevent PHN (29). For this study, we therefore chose patients aged ≥ 50 years with pain NRS scores > 3.

There is some controversy regarding the definition of PHN. We chose to define it as ZAP with NRS score > 3 at 3 months after rash onset. In a previous case series of 272 patients with acute HZ who were treated with subcutaneous injection of triamcinolone mixture under the areas of eruption, only 2.9% developed PHN (30). In our study, 4% developed PHN in the subcutaneous injection group compared with 20% in the standard group. However, a major drawback in this study was the lack of a proper control group. Ideally, the standard group in this study should have received a placebo subcutaneous injection (of saline); however, maintenance of blinding would have been impossible because of the absence of immediate local analgesia with the placebo.

Dissemination of the viral infection following subcutaneous injection has been observed by earlier investigators (31), but there is not sufficient evidence to establish it (22). In this study, a few patients had minor complaints but there were no complications, such as dissemination of the viral infection, acute lidocaine intoxication, excessive sensory loss, or paresthesia.

Conclusion

In conclusion, this single-center trial suggests that subcutaneous injection of triamcinolone and lidocaine in combination with standard treatment (acyclovir and analgesics) is effective and safe for treating pain caused by HZ and for preventing PHN. A large-scale multicenter clinical trial is needed to confirm our findings.

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