

The effectiveness of repetitive paravertebral block with ropivacaine and dexmedetomidine for the prevention of postherpetic neuralgia in patients with acute herpes zoster

Fan Yang¹, Pingsheng Liao¹, Yujuan You², Yingping Liang², Yanhui Hu²

¹Pain Department, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi Province, China

²Anaesthesiology Department, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi Province, China

Adv Dermatol Allergol 2022; XXXIX (1): 116–120

DOI: <https://doi.org/10.5114/ada.2021.106021>

Abstract

Introduction: Herpes zoster (HZ) is a disease caused by the reactivation of the varicella zoster virus. Postherpetic neuralgia (PHN) is the most common complication of HZ.

Aim: Repetitive paravertebral block with local anaesthetics and dexmedetomidine for the prevention of PHN in patients with acute herpes zoster.

Material and methods: 104 patients with acute herpes zoster were randomly divided into two groups. Group Rop received repetitive paravertebral block with 0.25% ropivacaine 20 ml per 72 h three times. Group Dex received repetitive paravertebral block with a mixture of 0.25% ropivacaine 20 ml and dexmedetomidine 20 µg per 72 h three times. Patients were permitted to take tramadol when the visual analogue scale (VAS) \geq 4. The incidence of zoster-related pain was recorded at 1, 3, and 6 months after the end of treatments; VAS scores and the dose of rescue drug were recorded at 1 week, 2 weeks, 1 month, 3 months, and 6 months after the end of treatments.

Results: At 1 month post therapy, the incidence of zoster-related pain was 11% in Group Dex, compared with 35% in Group Rop ($p = 0.005$). At 3 months post therapy, the incidence of zoster-related pain in Group Dex was still significantly lower than in Group Rop. The VAS scores and the dose of rescue drug in Group Dex were also significantly lower than in Group Rop at each time point ($p < 0.05$).

Conclusions: Repetitive paravertebral block with local anaesthetics and dexmedetomidine in patients with acute herpes zoster can significantly reduce the incidence of zoster-related pain.

Key words: herpes zoster, nerve block, local anaesthetics, α_2 receptor agonists.

Introduction

Herpes zoster (HZ) is a disease caused by the reactivation of the varicella zoster virus. The global incidence of HZ is 3–5 per 1000 person-years. Herpes zoster is an acute infectious skin-neurological disease caused by reactivation of the varicella zoster virus. After initial infection (chickenpox) or vaccination, the virus remains latent inside the posterior-sensory root ganglion cells. As cellular immunity decreases, the latent virus reactivates, then multiplies inside the posterior-sensory root ganglion cells and migrates back to the sensory nerves of the skin, leading to shingles [1]. Postherpetic neuralgia

(PHN) is the most common and the most serious complication of HZ [2]. A study shows that the incidence of PHN in patients with HZ above 50 years old is 49%, and the incidence in patients above 70 years is 74% [3]. PHN decreases the life quality of patients and increases the economic burden of health care [4, 5]. Hence, prevention of PHN is the focus in our treatment for HZ.

Nerve block is a common means to avoid PHN. Some researches have indicated that continuous epidural block, repetitive paravertebral block (PVB), and sympathetic block can effectively reduce the incidence of PHN in patients with acute HZ [6, 7].

Address for correspondence: Yingping Liang, Yanhui Hu, Anaesthesiology Department, the Second Affiliated Hospital of Nanchang University, 330000 Nanchang, Jiangxi Province, China, e-mail: dryanhuihu@gmail.com

Received: 1.11.2020, **accepted:** 14.11.2020.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License (<http://creativecommons.org/licenses/by-nc-sa/4.0/>)

Dexmedetomidine (Dex) is a highly selective α_2 receptor agonist, currently widely used in regional anaesthesia as an adjuvant. In two basic studies, Dex shows its analgesic potency in vincristine-evoked painful neuropathic rats and spinal nerve ligation model rats [8, 9]. But the efficacy of Dex in the prevention and therapy for human neuropathic pain still lacks relevant research.

Aim

Therefore, this study aims to evaluate the effectiveness of repetitive paravertebral block with ropivacaine (Rop) and Dex for the prevention of PHN in patients with acute HZ.

Material and methods

This study was a prospective, randomised, clinical trial with a 6-month follow-up period. The protocol of the study was approved by the Human Ethics Committee of the Second.

Affiliated Hospital of Nanchang University. All the patients signed an informed consent form before they received PVB.

Patients

From January 2018 to December 2019, 122 patients with HZ-associated pain in the Pain Department of the Second Affiliated Hospital of Nanchang University were enrolled in this trial. Inclusion criteria were HZ within 30 days after onset of the rash, rash on the trunk and extremities, age older than 50 years, history of antiviral medication (acyclovir 800 mg five times daily for 7 days or valacyclovir 1000 mg three times daily for 7 days), and no history of bradycardia or hypotension. Exclusion criteria were HZ over 30 days after onset of the rash, rash on perineum, head, and face, age less than 50 years, history of bradycardia or hypotension, and inability to correctly express the severity of pain. Eighteen patients were excluded because they did not meet the inclusion criteria; finally, 104 patients were enrolled in this trial, including 51 males and 53 females.

Protocol

All the patients were randomly divided into two groups. Before the therapy, all of them were taught how to use the VAS to assess their severity of pain by the same doctor, and the initial VAS scores were recorded.

Group Rop ($n = 53$) were allowed to take tramadol when $VAS \geq 4$; the dose depended on the requirements of the patient (the permitted maximum daily dose was 400 mg). In addition, all the patients accepted PVB once per 72 h 3 times; every time before PVB we chose two adjacent paravertebral spaces according to nerve segments of the pain, and the injection was 0.25% ropivacaine 10 ml per space.

Group Dex ($n = 54$) received the same drug and PVB treatment. The injection in this group was a mixture of 0.25% ropivacaine 10 ml and 10 ug dexmedetomidine per space.

A 10 cm, 22G needle was punctured to each paravertebral space under the guidance of CT (as Figure 1 shows). After aspiration of the syringe, the drug was injected. All injections were administered by the same physician.

Outcome measures

Pain severity was evaluated by using VAS (0 = no pain, 10 = worst pain imaginable) score. VAS scores were assessed at the initial visit (basal) and 7 days, 14 days, 30 days, 60 days, and 180 days after the end of PVB treatment. The incidence of zoster-related pain (defined as burning and lancinating pain that was accompanied by allodynia and that was restricted to the dermatomes involved in the original eruption of HZ) was evaluated at 1, 3, and 6 months after treatment.

The dose of tramadol (mg/day) for each patient was also recorded, but the use of tramadol was not permitted during the 24 h before each evaluation. All of the assessments were completed by the same physician.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). Measurement data were expressed as mean and standard deviation. Frequency and proportion were used for enumeration data. For measurement data, an independent sample test was used to compare the two groups. For enumeration data, Fisher's exact test and the χ^2 test were used. $P < 0.05$ was considered statistically significant.

Results

At 1-month follow-up, all the patients completed the assessment. At 3-month follow-up, 1 patient in Group Rop

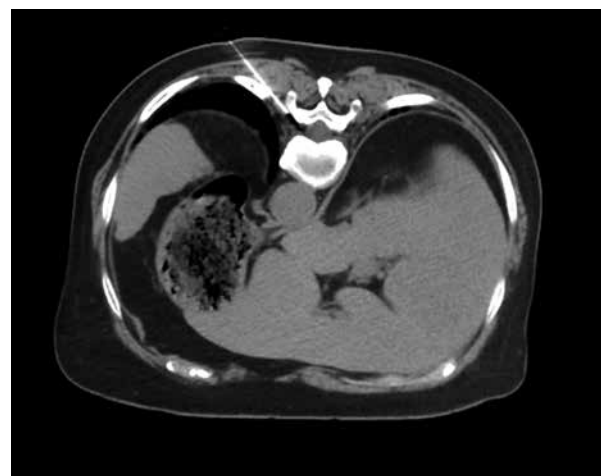


Figure 1. The needle position in paravertebral block

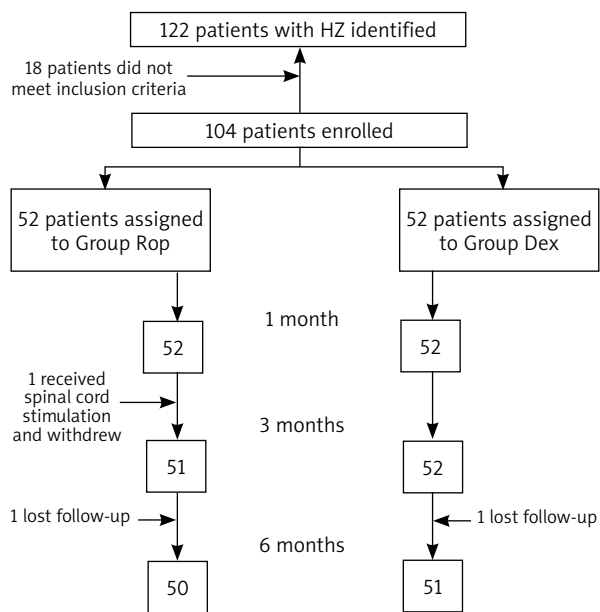


Figure 2. Trial profile

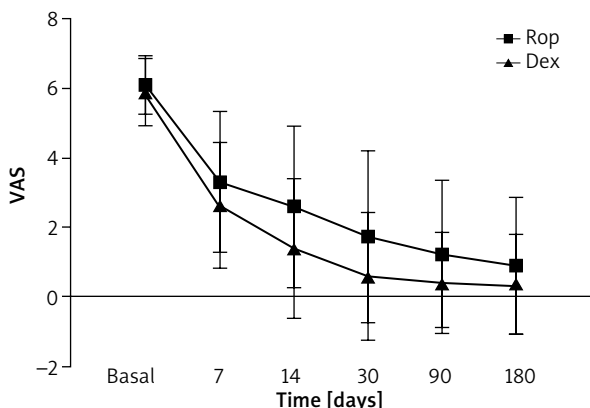


Figure 4. The VAS scores in the two groups at each time point

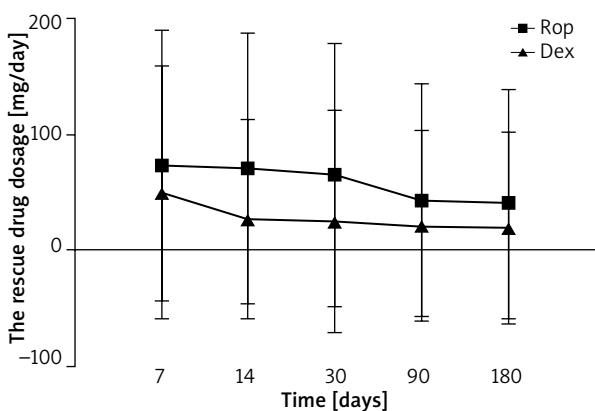


Figure 5. The dosage of rescue drug in the two groups at each time point

Table 1. Demographic and baseline patient characteristics

| Parameter | Group Rop (n = 53) | Group Dex (n = 54) | P-values |
|--------------------|--------------------|--------------------|----------|
| Age [years] | 70.6 ±8.4 | 68.8 ±8.8 | 0.259 |
| Sexy (male/female) | 22/31 | 24/30 | 0.846 |
| NRS scores | 6.1 ±1.2 | 6.1 ±1.3 | 0.941 |
| Days to block | 4.0 ±1.4 | 4.1 ±1.2 | 0.770 |

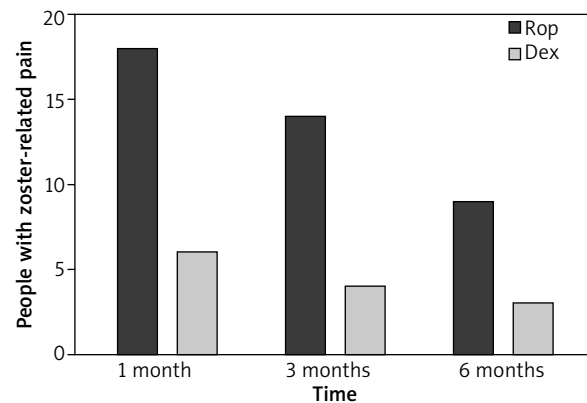


Figure 3. The incidence of zoster-related pain in the studied groups

received spinal cord stimulation and withdrew. There was 1 patient lost to follow-up in both two groups at 6-month follow-up (Figure 2). There were no statistically significant differences between the two groups with respect to demographic and clinical characteristics (Table 1).

As shown in Figure 3, compared to Group Rop, Group Dex reported a lower incidence of zoster-related pain at each time point. At 1 month post therapy, the incidence in Group Dex was significantly lower than Group Rop (6/52 vs. 18/52, $p = 0.005$). At 3 months post therapy, the people with zoster-related pain in Group Dex were still significantly fewer than Group Rop (4/52 vs. 14/51, $p = 0.008$), but there were no statistically significant differences between the two groups at 6 months after treatment (3/51 vs. 9/50, $p = 0.06$).

Regarding the VAS scores in the two groups, Group Dex showed significantly lower scores than Group Rop at 1, 3, and 6 months after treatment (Figure 4). In the comparison of rescue drug in the two groups, significantly lower doses were noted in Group Dex at 2 weeks, 1 month, 3 months, and 6 months post therapy (Figure 5).

It is worth noting that common complications of Dex are bradycardia and hypotension; therefore, we recorded the heart rate and blood pressure of each patient a 1, 3, and 6 h after PVB. However, no bradycardia and hypotension occurred in Group Dex – of course, the same as Group Rop.

Discussion

This clinical randomised trial shows that compared to using Rop only, repetitive paravertebral block with a combination of Rop and Dex in patients with acute herpes

zoster can significantly reduce the incidence of zoster-related pain.

Acute HZ is usually defined as occurring up to 30 days after rash onset, the subacute phase and PHN are often defined as 30–90 days, and the pain persists for ≥ 90 days after rash onset [10, 11]. In this study, we chose the patients who were within 30 days of onset of rash. Because current research indicates that decreasing repetitive painful stimuli during the early phase of HZ substantially reduces the incidence of development of chronic pain, and some of the patients with a long-term zoster-related pain had already developed into central sensitisation, the efficacy of nerve block in these patients is always pessimistic [12, 13].

Nerve block has been used to treat and prevent PHN for a long time, including epidural block, PVB, and sympathetic block, but only continuous epidural block, repetitive PVB, and repetitive sympathetic block show effectiveness in the prevention of PHN [6, 7, 14, 15]. In the patients with single epidural block, PVB, and sympathetic block, the incidence of PHN has no significant difference compared to the patients with simple drug therapy [14–16]. Therefore, the project of repetitive PVB 3 times was adopted.

α_2 -Adrenoceptor has been confirmed as an important target in neuropathic pain treatment [17, 18]. Feng *et al.* found that intrathecal clonidine in a rat model of partial sciatic nerve ligation-induced hypersensitivity could attenuate mechanical and thermal hyperalgesia [19], and in a clinical study, Kaygusuz *et al.* demonstrated that a mixture of local anaesthetics and Dex in regional anaesthesia was able to effectively prolong the anaesthesia time and significantly decrease post-operative pain [20].

Based on animal and clinical research, we suggest that the nerve block with an injection of mixed Rop and Dex in early HZ can efficiently reduce the incidence of PHN, and our findings confirm this suggestion. There are some probable mechanisms: first, Dex may directly act on the dorsal root ganglion and cause the inhibition of substance P release in the nociceptive pathway; second, Dex could also act on the presynaptic α_2 -adrenoceptor to reduce neurotransmitter release by inhibiting calcium influx.

However, in traditional studies the usual nerve block drug is a mixture of local anaesthetics and steroids. Steroids are eutherapeutic in preventing PHN because they can decrease neuronal damage and inhibit the inflammatory process [21]. But systemic absorption of corticosteroid may still increase the risk of infection; in order to avoid these risks, we explored more choices and possibilities. If the additional Dex can furtherly reduce the incidence of PHN, compared to Rop combined with corticosteroid, we need more studies. Our study showed that repetitive paravertebral block with local anaesthetics and dexmedetomidine in patients with acute herpes zoster can significantly reduce the incidence of zoster-related pain.

The common side effects of Dex are dose-dependent bradycardia and hypotension. In order to avert severe bradycardia and hypotension, we abandoned intravenous injection. We used 10 μg dexmedetomidine for each paravertebral space only and did not find haemodynamic side-effects, which supports the safety profile of our study medication regime.

Our study still has some limitations. Firstly, we selected the patients within 30 days after the onset of rash, and the effect of this method in patients with a long-term zoster related pain is still unclear. Secondly, further studies are required to observe the efficacy of Dex in epidural block and sympathetic block.

Conclusions

Our study demonstrated that repetitive PVB with ropivacaine and dexmedetomidine in patients with acute HZ could effectively reduce the incidence of PHN, and decrease the VAS scores and the dosage of rescue drugs.

Conflict of interest

The authors declare no conflict of interest.

References

1. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014; 4: e004833.
2. Opstelten W, Zuithoff NP, van Essen GA, et al. Predicting postherpetic neuralgia in elderly primary care patients with herpes zoster: prospective prognostic study. *Pain* 2007; 132 Suppl 1: S52-9.
3. Dworkin RH, Perkins FM, Nagasako EM. Prospects for the prevention of postherpetic neuralgia in herpes zoster patients. *Clin J Pain* 2000; 16 (2 Suppl): S90-100.
4. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. *CMAJ* 2010; 182: 1731-6.
5. Johnson RW, Bouhassira D, Kassianos G, et al. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. *BMC Med* 2010; 8: 37.
6. Ji G, Niu J, Shi Y, et al. The effectiveness of repetitive paravertebral injections with local anesthetics and steroids for the prevention of postherpetic neuralgia in patients with acute herpes zoster. *Anesth Analg* 2009; 109: 1651-5.
7. Pasqualucci A, Pasqualucci V, Galla F, et al. Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. *Acta Anaesthesiol Scand* 2000; 44: 910-8.
8. Lee HG, Choi JJ, Kim YO, Yoon MH. The role of alpha-2 adrenoceptor subtype in the antiallodynic effect of intraplantar dexmedetomidine in a rat spinal nerve ligation model. *Neurosci Lett* 2013; 557: 118-22.
9. Park HJ, Kim YH, Koh HJ, et al. Analgesic effects of dexmedetomidine in vincristine-evoked painful neuropathic rats. *J Korean Med Sci* 2012; 27: 1411-7.
10. Opstelten W, Mauritz JW, de Wit NJ, et al. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using

- a general practice research database. *Fam Pract* 2002; 19: 471-5.
11. Schmader K, Gnann JW Jr, Watson CP. The epidemiological, clinical, and pathological rationale for the herpes zoster vaccine. *J Infect Dis* 2008; 197 Suppl 2: S207-15.
 12. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth* 2001; 48: 1000-10.
 13. Johnson RW. Consequences and management of pain in herpes zoster. *J Infect Dis* 2002; 186 Suppl 1: S83-90.
 14. Makharita MY, Amr YM, El-Bayoumy Y. Effect of early stellate ganglion blockade for facial pain from acute herpes zoster and incidence of postherpetic neuralgia. *Pain Physician* 2012; 15: 467-74.
 15. Kim HJ, Ahn HS, Lee JY, et al. Effects of applying nerve blocks to prevent postherpetic neuralgia in patients with acute herpes zoster: a systematic review and meta-analysis. *Korean J Pain* 2017; 30: 3-17.
 16. van Wijck AJ, Opstelten W, Moons KG, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. *Lancet* 2006; 367: 219-24.
 17. Di Cesare Mannelli L, Micheli L, Crocetti L, et al. alpha2-adrenoceptor: a target for neuropathic pain treatment. *Mini Rev Med Chem* 2017; 17: 95-107.
 18. Bahari Z, Meftahi GH. Spinal alpha2-adrenoceptors and neuropathic pain modulation; therapeutic target. *Br J Pharmacol* 2019; 176: 2366-81.
 19. Feng X, Zhang F, Dong R, et al. Intrathecal administration of clonidine attenuates spinal neuroimmune activation in a rat model of neuropathic pain with existing hyperalgesia. *Eur J Pharmacol* 2009; 614: 38-43.
 20. Kaygusuz K, Kol IO, Duger C, et al. Effects of adding dexmedetomidine to levobupivacaine in axillary brachial plexus block. *Curr Ther Res Clin Exp* 2012; 73: 103-11.
 21. Cui JZ, Zhang XB, Zhu P, et al. Effect of repetitive intracutaneous injections with local anesthetics and steroids for acute thoracic herpes zoster and incidence of postherpetic neuralgia. *Pain Med* 2017; 18: 1566-72.