Retrospective Study

Efficacy of Patient-Controlled Intravenous Analgesia with Esketamine for Herpes Zoster Associated with Breakthrough Pain

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Background: Some patients with herpes zoster (HZ) experience an intermittent spontaneous, short-lived and severe pain, which is called breakthrough pain (BTP). The effect of analgesic drugs and invasive procedures is not significant. Therefore, treatment of HZ associated with BTP is challenging. Esketamine is a new N-methyl-D-aspartate receptor antagonist, with enhanced analgesic effects. This study aimed to evaluate the efficacy and adverse reactions of patient-controlled intravenous analgesia (PCIA) with low-dose esketamine for HZ associated with BTP.

Objectives: To evaluate the efficacy and adverse reactions of PCIA with low-dose esketamine for HZ associated with BTP.

Study Design: A retrospective, observational study.

Setting: The study was carried out in the Pain Department of the Affiliated Hospital of Jiaxing University in Jiaxing, China.

Methods: The clinical data of HZ associated with BTP treated by PCIA with low-dose esketamine at the Pain Department of the Affiliated Hospital of Jiaxing University, between October 2015 to October 2021, were collected retrospectively. The Numeric Rating Scale (NRS-11) scores of rest pain (RP) and BTP, frequency of BTP, Pittsburgh Sleep Quality Index (PSQI) score, and fasting blood glucose (FBG) were recorded and analyzed before treatment (T0) and on days one (T1) and 3 (T2), week one (T3), months one (T4), 3 (T5), and 6 (T6) after treatment. Adverse reactions during the treatment were recorded.

Results: Twenty-five patients treated by PCIA with low-dose esketamine were included finally. Compared with T0, the NRS-11 scores of RP at T2, T3, T4, T5, and T6 decreased significantly ($P < 0.05$). The NRS-11 score of RP at T4 was significantly lower than that of T3 ($P < 0.001$), but there was no statistical difference between T5 and T4 ($P > 0.05$), the efficacy of esketamine in the treatment of RP was stable at one month after treatment. Likewise, compared with T0, the NRS-11 scores of BTP, frequency of BTP, and PSQI score decreased significantly at each time point after treatment ($P < 0.05$). These at T5 were significantly lower than T4 ($P < 0.05$), but there was no statistical difference between T6 and T5 ($P > 0.05$), the efficacy of esketamine was stable at 3 months after treatment. FBG also decreased significantly at each time point after treatment ($P < 0.05$), it tended to be normal and stable one month after treatment. All patients had mild symptoms of dizziness during treatment, and though a slight increase in noninvasive blood pressure (BP) was noted in all, the elevated BP did not exceed 30% of the baseline value. Four patients (16%) developed nausea without vomiting. There were no serious adverse reactions, such as respiratory depression.

Limitations: The nonrandomized, single-center, small sample size, retrospective design is a major limitation of this study.

Conclusions: PCIA with low-dose esketamine has a significant and long-term effect in the treatment of HZ associated with BTP. The RP was controlled, and the degree and frequency of BTP were significantly reduced after treatment, leading to improved quality of life. There were no serious adverse reactions worthy of clinical promotion.

Key words: Patient-controlled intravenous analgesia, esketamine, herpes zoster, breakthrough pain

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Herpes zoster (HZ) is caused by the reactivation of the varicella-zoster virus (VZV) latent in the sensory ganglia (1,2). The virus often invades the unilateral nerve segment and mainly manifests as herpes along the corresponding segment of the sensory nerve accompanied by severe pain (2-4). Most of them are persistent spontaneous burning and stabbing-like pain (5).

Breakthrough pain (BTP) is an intermittent spontaneous pain that refers to short-lived and severe pain that occurs despite adequate treatment of rest pain (RP) with opioids (6,7). Clinically, some patients with HZ experience a similar BTP. The effect of oral nonsteroidal and opioid drugs is not significant, and that of invasive procedures, such as peripheral nerve blocks (NBs) and pulsed radiofrequency (PRF), are not ideal (8). Therefore, treatment of HZ associated with BTP is challenging.

At present, the treatments for BTP at home and abroad include oral, intravenous, or subcutaneous injection of short-acting opioids. Due to the first-pass effect and slow onset, patients usually do not want to use oral analgesics. A single intravenous or subcutaneous injection usually causes additional pain at the injection site, so patient-controlled intravenous analgesia (PCIA) is considered a feasible option. Opioids are commonly used in analgesia at present, but they are prone to adverse reactions, such as excessive sedation, respiratory depression, nausea and vomiting, and skin itching. Therefore, there is an urgent need to find effective analgesic drugs with few adverse reactions.

Some studies (9-14,24) have shown that N-methyl-D-aspartate receptor (NMDAR) antagonists can effectively block spontaneous pain and hyperalgesia, and the incidence of adverse reactions, such as respiratory depression and skin pruritus is low. Esketamine, an isomer of ketamine, is a new NMDAR antagonist (9-13), with enhanced analgesic and sedative effects (14). Until now, there are only a few reports of esketamine for the treatment of HZ associated with BTP. This study aimed to evaluate the efficacy and adverse reactions of PCIA with low-dose esketamine for HZ associated with BTP.

Methods

Patients

A total of 25 patients of HZ associated with BTP treated by PCIA with low-dose esketamine in the Affiliated Hospital of Jiaxing University, between October 2015 to October 2021, were enrolled (Table 1).

Inclusion criteria: 1) those with HZ neuralgia and intermittent BTP; and 2) those who responded poorly to drugs and peripheral nerve interventional therapy.

Exclusion criteria: 1) heart, lung, brain, and other organ failures; 2) infection or tumor at the lesion site; and 3) mental health problems or refusal to participate in the study.

Treatment

Medications

All patients were treated with medications. In addition to the routine antiviral and neurotrophic therapy, analgesic therapy mainly included pregabalin capsules, tramadol hydrochloride sustained-release tablets, and morphine hydrochloride tablets. Following treatment with high-dose analgesics, it was anticipated that the patients would not be relieved of pain, especially in terms of the degree and frequency of BTP.

Peripheral Nerve Interventional Therapy

All patients received combined interventional therapy, including computed tomography (CT)-guided supraorbital nerve PRF via the supraorbital foramen (Fig. 1A), maxillary nerve PRF via the round foramen (Fig. 1B), mandibular nerve PRF via the foramen ovale (Fig. 1C), and dorsal root ganglion PRF (Fig. 1D) or NB. However, despite invasive interventional therapy, pain relief was not obvious.

PCIA with Low-dose Esketamine

All patients stopped using potent as well as weak opioids. They were routinely monitored using an electrocardiogram and oxygen inhalation by nasal catheters. PCIA with low-dose esketamine was initiated in patients without severe cardio-cerebrovascular disease, respiratory disease, or severe hypertension. The drug comprised 550 mg esketamine + 5 mg midazolam diluted to 275 mL (the concentration of esketamine is 2 mg/mL); parameter setting: continuous pumping 8 mg/h, additional 10 mg/h with a locking time of 30 minutes. Each patient was continuously treated with 2 analgesic pumps. During treatment with esketamine, the compound sodium chloride injection (500 mL) was dripped slowly to ensure that the venous pathway was unobstructed. When patients predicted or felt BTP, the additional button of the analgesic pump was pressed. If the pulse oxygen saturation (SPO_2) of the patient decreased ≤ 94% during the course of treatment, an oxygen mask was immediately used, and tracheal intubation equipment was prepared; if the

blood pressure (BP) of the patient exceeded 30% of the basic value or the systolic BP (SBP) reaches 180 mm Hg, urapidil hydrochloride 15 mg was administered intravenously for symptomatic treatment; if the patient complained of nausea and vomiting, metoclopramide 4 mg intravenous injection was immediately administered (Table 2).

Data Collection

Pain Indicators

Included the Numeric Rating Scale (NRS-11) scores of RP and BTP, and frequency of BTP. BTP was defined as a sudden increase in pain that occurs either spontaneously or suddenly under the induction of certain predictable or unpredictable factors. The observation times were before treatment (T0) and one day (T1), 3 days (T2), one week (T3), one month (T4), 3 months (T5), and 6 months (T6) after treatment.

Life Quality Assessment

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) score, and the total score ranged from 0 to 21. The higher the score, the worse is the sleep quality. The time for patients to complete the evaluation was 5-10 minutes. The observation times were similar to the pain indicators (Table 3).

Table 1. *Patient demographic data.*

	Patients
Age (y)	67.72 ± 10.027
Gender	
Men	11 (44%)
Women	14 (56%)
Course of Disease (d)	19.88 ± 7.513
Involved Dermatome	
Cervical	5 (20%)
Thoracic	8 (32%)
Trigeminal Nerve VI	8 (32%)
Trigeminal Nerve VII	3 (12%)
Trigeminal Nerve VIII	1 (4%)
Underlying Disease	
DM	9 (36%)
HTN & DM	12 (48%)
Cancer & DM	1 (4%)
Cancer & HTN & DM	1 (4%)
CVD & HTN & DM	2 (8%)
Analgesics Before Esketamine	
Opioids With NB	10 (40%)
Opioids With PRF	15 (60%)

Results are expressed as mean ± SD, percentages.
Abbreviations: y: years; d: days; DM: diabetes mellitus; HTN: hypertension; CVD: cardiovascular diseases; NB: nerve block; PRF: pulsed radiofrequency; SD: standard deviation.

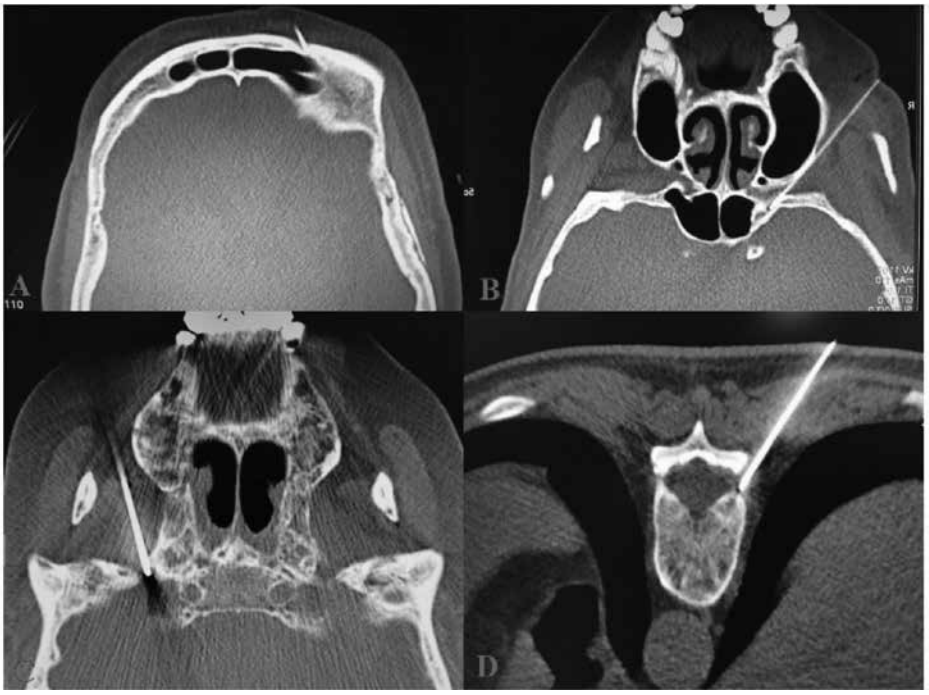

Fig. 1. *Peripheral nerve interventional therapy. CT-guided supraorbital PRF via the supraorbital foramen (A), maxillary nerve PRF via the round foramen (B), mandibular nerve PRF via the foramen ovale (C), and dorsal root ganglion PRF (D).*
CT: computed tomography; PRF: nerve pulsed radiofrequency.

Fasting Blood Glucose (FBG) Assessment

Since all the patients have diabetes in our study, the FBG of the patients during treatment is routinely monitored during the treatment and followed up after discharge. The observation times were similar to the pain indicators.

Adverse Reactions

The occurrence of adverse reactions, such as dizziness, elevated BP, nausea and vomiting, and respiratory depression, during treatment was recorded (Table 2).

Statistical Analysis

Statistical analyses were performed using the SPSS software (Version 26.0; IBM Corporation, Armonk, NY). All data were tested for normality using the Shapiro-Wilk test and histograms. Normally distributed continuous data are presented as mean ± standard deviation (SD), nonnormally distributed continuous data are provided as medians and interquartile ranges, and categorical data are expressed as numbers and percentages (%). An independent t test was used to compare normally distributed continuous data, and the Mann-Whitney U test was employed for nonnormally distributed continuous data. Statistical significance was set at $P < 0.05$.

Table 2. *Adverse reactions recorded during treatment.*

	Number of Patients	Intervention
Mild Dizziness	25 (100%)	stay in bed and strengthen monitoring
Nausea	4 (16%)	metoclopramide 4 mg intravenous injection
Vomit	0 (0)	metoclopramide 4 mg intravenous injection
Elevated BP	25 (100%)	BP ≥ 30% of the basic value or the SBP ≥ 180 mm Hg, use urapidil hydrochloride 15 mg intravenous injection
Respiratory Depression	0 (0)	SpO_2 ≤ 94%, use the mask to inhale oxygen and prepare the tracheal intubation equipment

Abbreviations: BP: blood pressure; SBP: systolic blood pressure; SpO_2: pulse oxygen saturation.

Results

Patient Characteristics

Among the 26 patients treated with low-dose esketamine, one patient was lost to follow-up. Finally, 25 patients (11 men, 14 women) were included in the study. The age ranged from 42 to 80 years, and the course of disease was ranged from 7 to 30 days. The results of baseline demographics are shown in Table 1.

Changes in Pain Indicators

Compared to T0, the NRS-11 scores of RP at T2, T3, T4, T5, and T6 decreased, and the difference was statistically significant ($P < 0.05$). The NRS-11 score of RP at T4 was significantly lower than that of T3 ($P < 0.001$), but there was no statistical difference between T5 and T4 ($P > 0.05$), the efficacy of esketamine in the treatment of RP was stable at one month after treatment (T4). The details are presented in Table 4 and Fig 2A.

Similarly, compared to T0, the NRS-11 scores and frequency of BTP declined significantly at each time point after treatment ($P < 0.05$). These at T5 were significantly lower than T4 ($P < 0.05$), but there was no statistical difference between T6 and T5 ($P > 0.05$), the efficacy of esketamine for BTP was stable at 3 months after treatment (T5). The details are presented in Table 2, Fig. 2B, and Fig. 2C.

Changes in Life Quality

Compared to T0, the PSQI scores at different time points after esketamine treatment were significantly lower ($P < 0.05$). PSQI scores at T5 were significantly lower than T4 ($P < 0.001$), but there was no statistical difference between T6 and T5 ($P > 0.05$). Life quality was stable at 3 months after treatment (T5). The details have been depicted in Table 3 and Fig. 2D.

Changes in FBG

Compared to T0, FBG levels at different time points

Table 3. *Changes in life quality and FBG before and after treatment.*

	T0	T1	T2	T3	T4	T5	T6
PSQI Score	16.04 ± 2.491	8.92 ± 1.552	6.72 ± 0.980	5.88 ± 1.013	3.68 ± 1.180	1.60 ± 0.957	0.72 ± 0.678
FBG	11.88 ± 2.108	9.00 ± 1.780	7.76 ± 0.879	6.24 ± 1.165	5.24 ± 0.879	5.96 ± 0.978	5.84 ± 0.943

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; FBG: fasting blood glucose; T0: before treatment; T1: one day after treatment; T2: 3 days after treatment; T3: one week after treatment; T4: one month after treatment; T5: 3 months after treatment; T6: 6 months after treatment.

Table 4. *Changes in pain indicators before and after treatment.*

	T0	T1	T2	T3	T4	T5	T6
NRS-11 Score of RP	3.88 ± 0.726	3.64 ± 0.700	3.48 ± 0.510	1.44 ± 0.583	0.48 ± 0.653	0.40 ± 0.500	0.36 ± 0.490
NRS-11 Score of BTP	8.84 ± 0.850	6.04 ± 0.790	4.92 ± 0.812	2.64 ± 0.810	0.80 ± 0.277	0.48 ± 0.823	0.00 ± 0.000
Frequency of BTP	7.68 ± 1.547	4.16 ± 1.028	2.28 ± 0.792	1.68 ± 0.748	0.80 ± 0.277	0.36 ± 0.569	0.00 ± 0.000

Abbreviations: NRS-11: Numeric Rating Scale; RP: rest pain; BTP: breakthrough pain;
T0: before treatment; T1: one day after treatment; T2: 3 days after treatment; T3: one week after treatment; T4: one month after treatment; T5: 3 months after treatment; T6: 6 months after treatment.

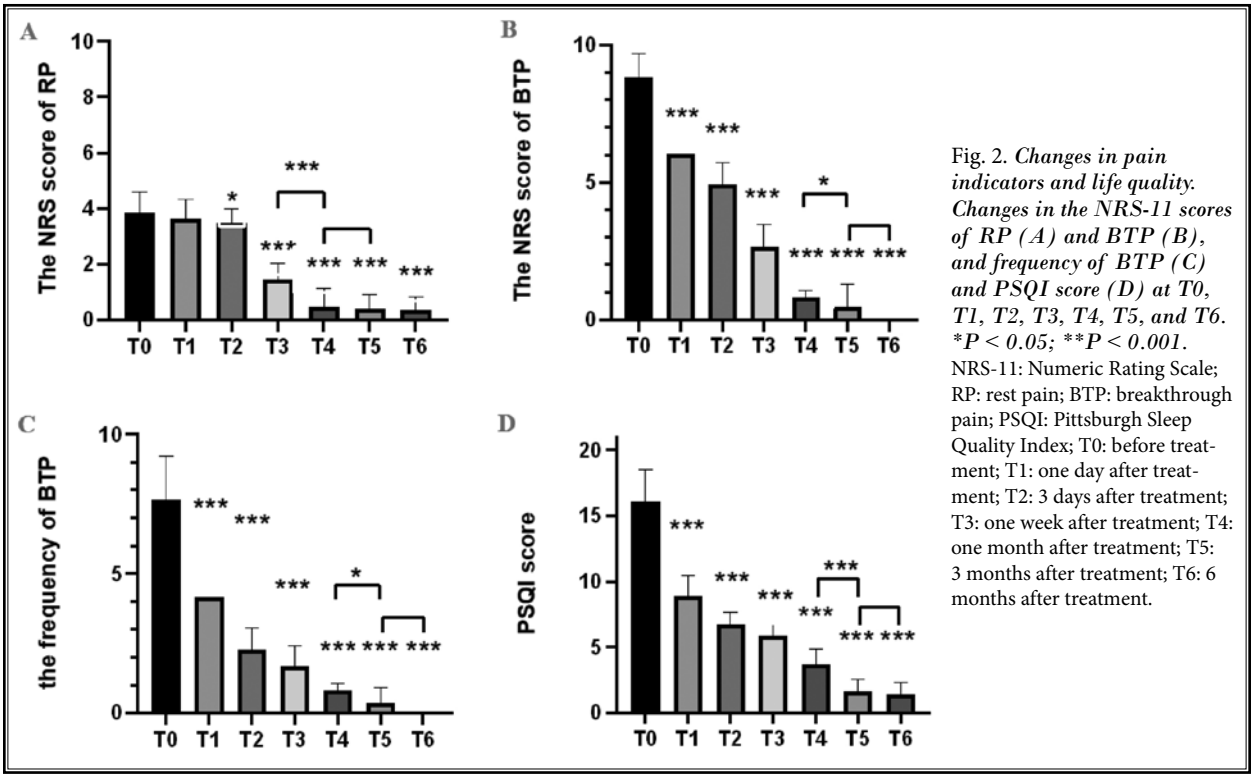

Fig. 2. *Changes in pain indicators and life quality. Changes in the NRS-11 scores of RP (A) and BTP (B), and frequency of BTP (C) and PSQI score (D) at T0, T1, T2, T3, T4, T5, and T6. *P < 0.05; **P < 0.001.* NRS-11: Numeric Rating Scale; RP: rest pain; BTP: breakthrough pain; PSQI: Pittsburgh Sleep Quality Index; T0: before treatment; T1: one day after treatment; T2: 3 days after treatment; T3: one week after treatment; T4: one month after treatment; T5: 3 months after treatment; T6: 6 months after treatment.

after esketamine treatment were significantly lower ($P < 0.05$). With regular hypoglycemic treatment, FBG levels returned to normal 1 month after treatment (T4). The details have been depicted in Table 3.

Adverse Reactions

During treatment, all patients had mild symptoms of dizziness. Additionally, although a slight increase in noninvasive BP was noted in all, the elevated BP was no more than 30% of the baseline value. Four patients (16%) developed nausea, which was relieved after intravenous injection of 4 mg metoclopramide. There was no incidence of vomiting or respiratory depression. The details are presented in Table 2.

Discussion

Currently, the pathogenesis of HZ neuralgia is unclear. When the human immune system is unbalanced, the VZV, which originally lurks in the dorsal root ganglion, begins to destroy the peripheral nerve fibers and the ascending inhibitory conduction of the spinal cord because of its neurophagia. This causes excessive excitatory signals to pass into the center, causing sympathetic efferent fibers to activate the peripheral receptors and increase the excitability of the primary receptors (15,16). Some researchers believe that in the process of the occurrence and development of HZ neuralgia, the mechanism of peripheral sensitization and central sensitization is the direct cause of pain (17).

BTP caused by HZ is related to the enhancement

of pain signal transduction by central sensitization. Central sensitization manifests when the pain area is enlarged and explosive pain occurs repeatedly diminishing the patient's tolerance to pain (18). One study (19) has reported that HZ neuralgia is related to nerve fiber damage in the posterior root of the spinal cord, which is characterized by inflammatory demyelination. In this study, all patients with HZ had diabetes that was poorly controlled. It has been documented that VZV and high blood glucose levels promote inflammatory demyelination of nerve fibers and accelerate central sensitization. Hence, this may explain why HZ patients with diabetes are more prone to BTP than nondiabetics.

In addition to routine drug treatment, peripheral nerve interventional therapy has shown good results in patients with intractable HZ neuralgia (20-22). However, peripheral nerve interventional therapy is not effective for patients with HZ associated with BTP, especially with respect to the degree and frequency of BTP. To date, there are few clinical trials undertaken for HZ associated with BTP. Therefore, it is difficult to arrive at a treatment strategy. All patients in this study were treated with peripheral nerve interventional therapy, including PRF and NB, and RP relieved after therapy. However, the degree and frequency of BTP after therapy did not decrease significantly, the reasons could be that peripheral nerve modulation could not completely block central sensitization, and the BTP is still present.

NMDARs are widely distributed in the peripheral and central nervous systems and are important components of nociceptive signal transmission and pain reception. Studies have confirmed that NMDARs play an important role in the peripheral and central sensitization, which participates in the occurrence, development, and maintenance of chronic neuropathic pain. Ketamine, a nonselective NMDAR antagonist, acts on the phenylcyclohexyl piperidine site of the NMDAR complex channel, antagonizing the NMDAR by reducing the average open time and channel opening frequency (13,23). An animal and clinical study has confirmed that ketamine can produce obvious anti-injury and analgesic effects on neuropathic and other chronic pain (24). It has been reported that ketamine inhibits intracellular Ca^{2+} overload and lipid peroxidation and enhances the activity of antioxidant enzymes by acting on NMDARs. This, in turn, prevents the injury of neurons and astrocytes in the spinal dorsal horn of rats, and inhibits the secretion of interleukin-1β and tumor necrosis factor-α in astrocytes leading to relief in neuropathic pain (25). Esketamine is the dextral form of ketamine and has a high affinity for NMDARs. Therefore, the dose needed to produce an analgesic effect is lower, with a better analgesic effect and few adverse reactions. That is why we included esketamine in this study to relieve patients' BTP by blocking peripheral and central sensitization.

In addition, a study (26) have shown that excessive activation of NMDARs and excessive release of glutamate also play important roles in the transmission of nociceptive information and central sensitization of diabetic neuralgia. Therefore, esketamine, being an NMDAR antagonist, can relieve diabetic neuralgia. Esketamine can relieve both HZ-related neuralgia and diabetic neuralgia, which provides a new treatment idea for these patients.

A previous study (27) have shown that the duration of relief from neuropathy is related to the total dose and duration of esketamine infusion. Furthermore, intravenous esketamine infusion for the treatment of refractory pain is included in the guidelines of the American Society of Anesthesiology and Pain Medicine (28). Therefore, in this case, the PCIA mode was chosen, which can accurately control the infusion speed and dose to achieve continuous analgesia.

Esketamine, a psychotropic drug, may cause adverse reactions, such as excessive sedation, dizziness, and hallucinations, which, to a certain extent, limits its clinical application. Benzodiazepines effectively alleviate the adverse effects of ketamine (29). In this study, continuous infusion of low-dose esketamine combined with midazolam not only had sedative and analgesic effects, but also reduced the severity of dizziness and hallucinations. When patients predicted or felt BTP, they press the add button of the analgesic pump, and esketamine immediately reaches the blood concentration of strong analgesia, thus having the effect of analgesia. The advantages of this therapy include complete analgesia, safety, convenience, and timely operation under constant monitoring.

In this study, it was found that the RP of the patients was obviously controlled 3 days after treatment, and the degree and frequency of BTP decreased one day after treatment significantly, which had an excellent effect on the patients with BTP, and the RP score tended to be stable one month after treatment. The degree and frequency of BTP also tended to be stable 3 months after treatment, indicating that the curative effect was stable. The sleep quality of the patients was also improved, the state of hyperglycemia was changed, and the blood glucose was controlled within the nor-

mal range, which may be related to the patient's return to normal life after pain relief. What's more, no serious adverse reactions occurred in any of the patients, and all experienced relief after symptomatic treatment, which provided a new treatment for patients with BTP.

Limitations

This study had some limitations. First, the sample size of this study was too small due to the low incidence rate. Second, no randomized controlled trials were conducted. Finally, since this study was a retrospective trial, some data, such as NRS-11 scores, may have recall bias, resulting in a lack of objectivity and accuracy of the results. In future, it will be necessary to conduct multicenter, prospective, large-sample clinical studies to make the results more objective and credible.

Conclusions

PCIA with low-dose esketamine is effective for HZ associated with BTP, with no serious adverse reactions, and is thus worthy of clinical consideration.

References

1. Choi WS, Kwon SS, Lee J, et al. Immunity and the burden of herpes zoster. *J Med Virol* 2014; 86:525-530.
2. Opstelten W, McElhaney J, Weinberger B, et al. The impact of varicella zoster virus: Chronic pain. *J Clin Virol* 2010; 48(suppl 1):S8-S13.
3. Gross GE, Eisert L, Doerr HW, et al. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. *J Dtsch Dermatol Ges* 2020; 18:55-78.
4. Johnson RW. Consequences and management of pain in herpes zoster. *J Infect Dis* 2002; 186(suppl 1):S83-S90.
5. Chen LK, Arai H, Chen LY, et al. Looking back to move forward: A twenty-year audit of herpes zoster in Asia-Pacific. *BMC Infect Dis* 2017; 17:213.
6. Greenfield K, Holley S, Schoth DE, et al. A protocol for a systematic review and meta-analysis to identify measures of breakthrough pain and evaluate their psychometric properties. *BMJ Open* 2020; 10:e035541.
7. Kang JH, Koh SJ, Oh SY, et al. Interference with daily functioning by breakthrough pain in patients with cancer. *Support Care Cancer* 2020; 28:5177-5183.
8. Hadley GR, Gayle JA, Ripoll J, et al. Post-Herpetic neuralgia: A review. *Curr Pain Headache Rep* 2016; 20:17.
9. Culp C, Kim HK, Abdi S. Ketamine use for cancer and chronic pain management. *Front Pharmacol* 2020; 11:599721.
10. Bredlau AL, Thakur R, Korones DN, et al. Ketamine for pain in adults and children with cancer: A systematic review and synthesis of the literature. *Pain Med* 2013; 14:1505-1517.
11. Kirkpatrick AF, Saghafi A, Yang K, et al. Optimizing the treatment of CRPS with ketamine. *Clin J Pain* 2020; 36:516-523.
12. Kiefer RT, Rohr P, Ploppa A, et al. Complete recovery from intractable complex regional pain syndrome, CRPS-type I, following anesthetic ketamine and midazolam. *Pain Pract* 2007; 7:147-150.
13. Sawynok J, Zinger C. Topical amitriptyline and ketamine for post-herpetic neuralgia and other forms of neuropathic pain. *Expert Opin Pharmacother* 2016; 17:601-609.
14. Wang Y, Zhang Q, Dai X, et al. Effect of low-dose esketamine on pain control and postpartum depression after cesarean section: A retrospective cohort study. *Ann Palliat Med* 2022; 11:45-57.
15. Klompas M, Kulldorff M, Vilk Y, et al. Herpes zoster and postherpetic neuralgia surveillance using structured electronic data. *Mayo Clin Proc* 2011; 86:1146-1153.
16. Kramer S, Baeumler P, Geber C, et al. Somatosensory profiles in acute herpes zoster and predictors of postherpetic neuralgia. *Pain* 2019; 160:882-894.
17. Tekin E, Ahiskalioglu A, Aydin ME, et al. High-Thoracic ultrasound-guided erector spinae plane block for acute herpes zoster pain management in emergency department. *Am J Emerg Med* 2019; 37:375.e1-375.e3.
18. Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: A review of prevalence, characteristics and mechanisms. *Eur J Pain* 2005; 9:195-206.
19. Ruppenthal M. Changes of the central nervous system in herpes zoster. *Acta Neuropathol* 1980; 52:59-68.
20. Zhang H, Ni H, Liu S, et al. Supraorbital nerve radiofrequency for severe neuralgia caused by herpes zoster ophthalmicus. *Pain Res Manag* 2020; 2020:3191782.
21. Zhu J, Fei Y, Deng J, et al. Application and therapeutic effect of puncturing of the costal transverse process for pulsed radiofrequency treated T1-T3 herpes zoster neuralgia. *J Pain Res* 2020; 13:2519-2527.
22. Harke H, Gretenkort P, Ladleif HU, et al. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. *Anesth Analg* 2002; 94:694-700.
23. Huge V, Lauchart M, Magerl W, et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. *Eur J Pain* 2010; 14:387-394.
24. Petrenko AB, Yamakura T, Baba H, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: A review. *Anesth Analg* 2003; 97:1108-1116.
25. Johnson JW, Glasgow NG, Povysheva NV. Recent insights into the mode of action of memantine and ketamine. *Curr Opin Pharmacol* 2015; 20:54-63.
26. Huang XT, Li C, Peng XP, et al. An excessive increase in glutamate contributes to glucose-toxicity in β-cells via activation of pancreatic NMDA receptors in rodent diabetes. *Scientific Reports* 2017:7.
27. Maher DP, Chen L, Mao J. Intravenous ketamine infusions for neuropathic pain management: A promising therapy in need of optimization. *Anesth Analg* 2017; 124:661-674.
28. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the

American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018; 43:456-466.

29. Oliveira Filho GR, Castilhos CM, Kriegl JP, et al. Oral preanesthetic medication in children - comparison between midazolam alone and in combination with ketamine: A systematic review and meta-analysis. *Braz J Anesthesiol* 2021. [Epub ahead of print]