Int J Clin Exp Med 2020;13(8):6182-6189
www.ijcem.com /ISSN:1940-5901/IJCEM0111412

Review Article

Lidocaine gel combined with foscarnet sodium can reduce the pain level and adverse reactions of patients in the treatment of herpes zoster

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Received March 25, 2020; Accepted June 1, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Lidocaine gel combined with foscarnet sodium can reduce the pain level and adverse reactions of patients in the treatment of herpes zoster. Totally 167 cases of herpes zoster patients treated in our hospital were collected as research subjects, among which 75 cases treated with foscarnet sodium were enrolled in the CG (CG), and another 92 cases treated with lidocaine combined with foscarnet sodium were included in the research group (RG). Curative effect and the improvement of skin lesions in both groups were observed, and the VAS score and NRS score of the two groups before and after treatment were compared. Adverse reactions, postherpetic neuralgia (PHN), and quality of life after treatment of the two groups in both groups were recorded. The total effective rate of the RG was higher than that in the CG ($P<0.05$). The improvement of skin lesions after treatment in the RG was better than that in the CG ($P<0.05$). After treatment, VAS score and NRS score in the RG were remarkably lower than those in the CG ($P<0.05$). There was no statistical difference in the occurrence of adverse reactions between the two groups ($P>0.05$). There was no statistical difference in the incidence of PHN between the two groups ($P>0.05$). The pain score in the RG was notably lower than that of the CG ($P<0.05$). Quality of life of the RG was notably higher than that of the CG ($P<0.05$). Lidocaine gel combined with foscarnet sodium has a significant effect on the treatment of herpes zoster patients, with reduced pain level and less adverse reactions, which is worthy of clinical promotion.

Keywords: Lidocaine gel, foscarnet sodium, herpes zoster, pain level, adverse reactions

Introduction

Herpes zoster is an acute infectious skin disease caused by varicella zoster virus [1]. The virus enters the blood through respiratory mucosa to form viremia, and children without immunity to the virus will develop chicken pox after infection [2]. After being infected, some patients become carriers of the virus without symptoms [3]. The virus can be long-term latent in the posterior root ganglion or cranial nerve sensory ganglion. When the body is exposed to a stimulus that leads to a decrease in body resistance, the latent virus is activated and then travels down the sensory nerve axons to replicate in the skin of the nerve region, thus producing blisters [4, 5]. At the same time, inflammation, necrosis and neuralgia occur in the affected nerve. The older the patient is, the more severe the neuralgia becomes, and the incidence of neuralgia increases significantly with age [6]. Persistent pain severely affects the patients' quality of life.

Clinically, there is no specific and effective antiviral drug for herpes zoster [7], and the current treatment for this disease is still to alleviate symptoms, reduce pain and prevent infection [8]. Lidocaine is an amide local anesthetic that may produce an analgesic effect by blocking the occurrence and conduction of neuronal impulses on hyperactive or damaged nociceptors [9]. Lidocaine gel is a targeted peripheral analgesic that acts directly on local nociceptors to relieve pain [10]. Second, the plaster acts as a barrier to protect the skin from painful mechanical irritants [11]. Data show that lidocaine gel has significant analgesic effect in a variety of diseases [12]. For example, Torky et al. elaborated in their study that lidocaine gel

Table 1. Curative effect evaluation

Curative effect	
Recovered	The lesions subsided and the pain subsided
Markedly effective	Most of the lesions subsided and the local pain significantly reduced
Improved	The lesions partially subsided and the pain eased
Ineffective	A small part of the lesion subsided, but the pain did not abate

Note: Total effective rate = (recovered + markedly effective + improved)/number needed to treat.

Table 2. General data

	RG (n=92)	CG (n=75)	t or X^2	P
Age (years)	54.2±5.8	53.3±6.3	0.960	0.339
BMI (KG/cm^2)	23.52±3.05	24.46±4.72	1.554	0.122
Gender			0.074	0.786
Male	51 (55.43)	40 (53.33)		
Female	41 (44.57)	35 (46.67)		
Living environment			0.621	0.431
Town	63 (68.48)	47 (62.67)		
Countryside	29 (31.52)	28 (37.33)		
Educational level			2.242	0.134
< high school	72 (78.26)	51 (68.00)		
≥ high school	20 (21.74)	24 (32.00)		
Smoking history			0.212	0.645
With	47 (51.09)	41 (54.67)		
Without	45 (48.91)	34 (45.33)		
Excessive drinking history			0.214	0.644
With	36 (39.13)	32 (42.67)		
Without	56 (60.87)	43 (57.33)		
Family medical history			0.062	0.804
With	17 (18.48)	15 (20.00)		
Without	75 (81.52)	60 (80.00)		
Nation			0.035	0.851
Han	83 (90.22)	67 (89.33)		
Minority	9 (9.78)	8 (10.67)		

could effectively reduce the pain during intrauterine device insertion [13]. Foscarnet sodium is a novel non-nucleoside broad-spectrum antiviral drug that directly inhibits viral DNA polymerase synthesis to inhibit viral replication without relying on the phosphorylation and activation of thymidine kinase [14]. It has been reported clinically that foscarnet sodium has good efficacy and safety in the treatment of herpes zoster [15]. Other studies have shown that glucocorticoid is more effective in treating herpes zoster [16]. Therefore, the treatment of herpes zoster is still controversial. We speculate that lidocaine gel combined with foscarnet sodium may have a better effect in the treatment of herpes zoster. In order to verify our speculation, this study investigated the treatment of herpes zoster with lidocaine gel combined with foscarnet sodium and observed the pain level and adverse reactions of patients, thereby providing reference and guidance for the future clinical treatment of herpes zoster.

Methods

Data of patients

A total of 167 cases of patients with herpes zoster receiving treatment in Jiaozhou Municipal People's Hospital from May 2016 to May 2018 were collected as study subjects. Among them, 75 cases of patients treated with foscarnet sodium were enrolled in the CG (CG), with an average age of 53.3±6.3 years. Another 92 cases of patients receiving treatment of lidocaine combined with foscarnet sodium were included in the research group (RG), with a mean age of 54.2±5.8 years. This study has been approved by the medical ethics committee, and all patients have been informed and signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria: All patients were treated in Jiaozhou Municipal People's Hospital for the first time and were diagnosed as herpes zoster in our hospital; patients with complete clinical data; patients cooperated with the follow-up; patients knew the purpose of the study and signed the informed consent.

Exclusion criteria: Patients with allergy to lidocaine gel and foscarnet sodium; patients with

Table 3. Curative effect evaluation after operation of the RG and the CG [n (%)]

	Observation group (n=92)	CG (n=75)	X^2 value	*P* value
Recovered	66 (71.74)	34 (45.33)	11.990	0.001
Markedly effective	20 (21.74)	23 (30.67)	1.722	0.189
Improved	4 (4.35)	10 (13.33)	4.343	0.037
Ineffective	2 (2.17)	8 (10.67)	5.294	0.021
Total effective	90 (97.83)	67 (89.33)	5.294	0.021

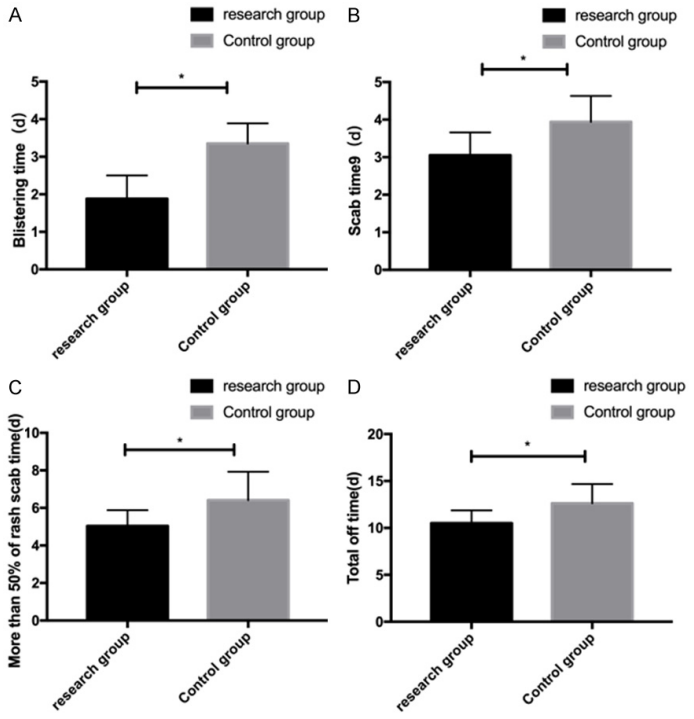

Figure 1. Comparison of the improvement of skin lesions after treatment between the two groups. A. Bleb-stopping time of patients after treatment. B. Scab-forming time of patients after treatment. C. Time of scab-forming of rash more than 50% of patients after treatment. D. Total decrustation time of patients after treatment. * denotes P<0.05.

diabetes, severe hypertension, active gastric ulcer, mental disorder or severe immunodeficiency; patients with liver, kidney and other impaired functions; patients in lactation period or gestation period.

This study was approved by Ethics Committee of Jiaozhou Municipal People's Hospital and was in accordance with Helsinki Declaration.

Therapies

Patients in the CG receiving treatment of foscarnet sodium were given intravenous infusion of foscarnet sodium and sodium chloride injection (Wuhan Docan Pharmaceutical Co., Ltd., SFDA approval number: H20066684) 250 mL: 3 g, 1 time/1 d, 1 time/12 h, continuing for 7 days. During the infusion, care was taken to ensure that the patient drunk more than 2 L of water, and the slow infusion was not less than 2 h. On the basis of the CG, a 3 g lidocaine gel (Beijing Zizhu Pharmaceutical Co., Ltd., SFDA approval number: H11022396) was taken and applied to the thin layer of non-woven gauze of patients in the RG (treated with lidocaine gel combined with foscarnet sodium). Then the non-woven gauze was wrapped with plastic wrap and pasted on the affected area for 2-3 times a day. Lidocaine gel ointment was applied to the affected area for a maximum of 12 h/d for 4 weeks.

Outcome measures

Main outcome measures: the curative effect of the two groups of patients (as shown in **Table 1**). The improvement of skin lesions after treatment between the two groups was compared. Visual analogue scale (VAS) [17] and numerical rating scale (NRS) [18] were used to evaluate neuralgia before and after treatment in the two groups. Adverse reactions were observed in the two groups.

Secondary outcome measures: the incidence of sequela was assessed using EORTC-QLQ-C30 score, and the quality of life of patients in both groups after treatment was observed.

Statistical analysis

Analysis of data was conducted with the help of SPSS22.0 statistical software, and Graphpad7 was applied to graph the data results. Enumeration data were expressed as rate, and inter-group comparison was performed using chi-square test. Measurement data were expressed by mean ± standard deviation, and t

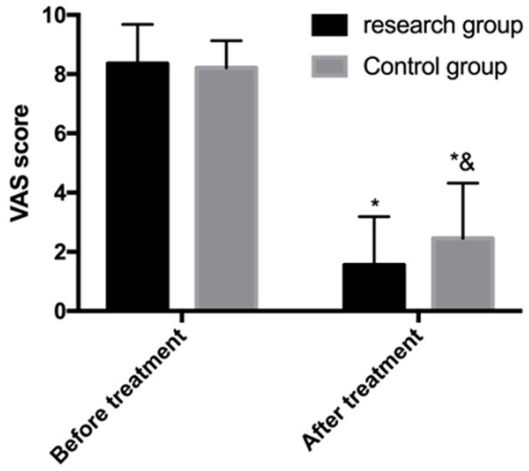

Figure 2. Comparison of VAS scores before and after treatment between the two groups. * denotes comparison with before treatment, & denotes comparison with the RG.

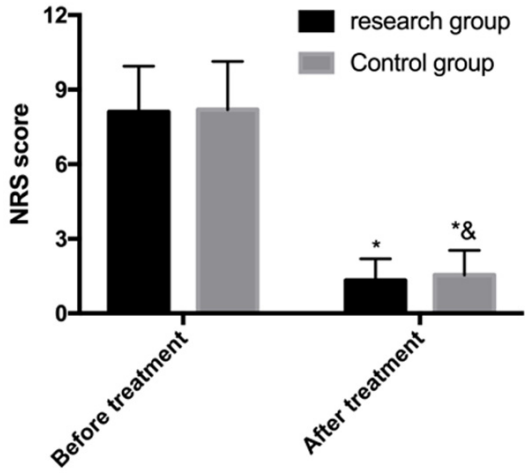

Figure 3. Comparison of NRS scores before and after treatment between the two groups. * denotes comparison with before treatment, & denotes comparison with the RG.

test was used for inter-group comparison. P<0.05 was considered statistically significant.

Results

General data

There was no difference in age, BMI, gender, living environment, education level, smoking history, drinking history, family medical history and nation between the two groups (P>0.05). See **Table 2**.

Curative effect evaluation after operation of the RG and the CG

By comparing the curative effect evaluation, it was found that the total effective rate of the RG was 97.83%, and that in the CG was 89.33%, which was higher in the RG than the CG, with statistically significant differences (P<0.05). See **Table 3**.

Improvement of skin lesions after treatment between the two groups

After treatment, the time of bleb-stopping, scab-forming, scab-forming of rash more than 50%, and total decrustation of patients in the RG were all shorter than those in the CG, with a statistical difference, P<0.05. See **Figure 1**.

Comparison of VAS scores before and after treatment between the two groups

VAS scores before and after treatment were compared between the two groups, and the results exhibited that there was no remarkable difference between the RG and the CG before treatment (P>0.05), while the VAS score in the RG was notably lower than that in the CG after treatment (P<0.05). See **Figure 2**.

Comparison of NRS scores before and after treatment between the two groups

NRS scores before and after treatment were compared between the two groups, and the results exhibited that there was no notably difference between the RG and the CG before treatment (P>0.05), while the NRS score in the RG was significantly lower than that in the CG after treatment (P<0.05). See **Figure 3**.

Adverse reactions in the two groups

By observing the adverse reactions such as increased serum creatinine (Cr), increased blood urea nitrogen, weak and dizzy, loss of appetite, nausea, and constipation, it was found that the total incidence of adverse reactions in the RG was 9.78%, while that in the CG was 14.67%. The total incidence of adverse reactions in the RG was lower than that in the CG, without statistical difference, P>0.05. See **Table 4**.

Table 4. Comparison of adverse reactions between the two groups [n (%)]

	RG (n=92)	CG (n=75)	X^2	P
Increased Cr	1 (1.09)	2 (2.67)		
Increased blood urea nitrogen	2 (2.17)	2 (2.67)		
weak and dizzy	2 (2.17)	2 (2.67)		
Loss of appetite	2 (2.17)	1 (1.33)		
Nausea	1 (1.09)	2 (2.67)		
Constipation	1 (1.09)	2 (2.67)		
Adverse reaction rate (%)	9.78	14.67	0.935	0.334

Table 5. The incidence of sequela

	RG (n=92)	CG (n=75)	X^2	P
PHN	8 (8.70)	9 (12.00)	0.493	0.482
Cutaneous necrosis	2 (2.17)	2 (2.67)	0.043	0.836
Cicatrization	5 (5.43)	3 (4.00)	0.187	0.666

The incidence of sequela in the two groups

After 3 months of treatment, there was no remarkable difference in PHN, cutaneous necrosis, cicatrization and other sequelae between the two groups. See **Table 5**.

Quality of life after treatment in the two groups

There were no significant differences in the symptom field of fatigue, nausea, vomiting, and loss of appetite, functional domains of cognitive function and social function EORTC-QLQ-C30 scores between the two groups ($P>0.05$). While the pain score in the symptom field of the RG was remarkably lower than that of the CG ($P<0.05$). The emotional functioning, physical function and role function in the functional domain of the RG were remarkably higher than those of the CG ($P<0.05$). See **Table 6**.

Discussion

Herpes zoster associated pain is a short-term or long-term pain caused by reactivation of varicella zoster virus that lurks in the sensory ganglia [19]. The pain is often characterized by typical pathologic neuralgia [20]. The treatment is mainly antiviral therapy [21]. Studies have reported that most patients lack effective pain treatment, and the pain lasts for months or even years [22]. It seriously affects patients' quality of life and brings a heavy burden to their families and even the society. Hence, relief of neuralgia caused by herpes zoster is particularly important for patients. At present, there are a variety of clinical treatments for herpes zoster. In order to find a timely and effective treatment for pain relief related to herpes zoster, this study applied lidocaine gel combined with foscarnet sodium to treat herpes zoster and observed the degree of pain relief for patients.

This study first compared the efficacy of the two groups of patients, and found that the total effective rate of patients treated with lidocaine gel combined with foscarnet sodium was higher than that of patients treated with foscarnet sodium alone. At the same time, time of bleb-stopping, scab-forming, scab-forming of rash more than 50% and total decrustation of patients treated with lidocaine gel combined with foscarnet sodium were shorter than those of the patients treated with foscarnet sodium alone, suggesting that lidocaine gel combined with foscarnet sodium had a better curative effect for herpes zoster patients, bringing more stable improvement of skin lesions in patients in shorter time. According to previous studies, it was found that lidocaine gel and its excipients could make drugs uniformly adhere to the surface of skin and mucosa, delay drug release, slow down the absorption of drugs by skin and mucosa, and prolong the drug action time [23], with strong antibacterial properties, low toxicity and strong anesthetic depth. LU et al. showed in their study that lidocaine gel has high sensitivity, strong penetrability, long duration of anesthesia, high safety, and low incidence of allergic reactions in the treatment of recurrent oral ulcers [24]. It can effectively produce the local analgesic effect, along with durable drug force, thus significantly improve the patients' symptoms. This is consistent with our findings. Foscarnet sodium is a non-nucleoside antiviral that can directly target viral DNA polymerase and inhibit viral DNA synthesis [25]. Relevant data have elaborated that foscarnet sodium has certain advantages in the antiviral treatment of herpes zoster [26]. In the study of Sauerbrei et al. [27], the curative effect and

Table 6. Comparison of EORTC-QLQ-C30 scores

		RG (n=92)	CG (n=75)	t	P
Symptom field	Fatigue	11.85±6.01	12.05±5.24	0.226	0.821
	Pain	1.68±1.12	3.28±1.47	7.980	<0.001
	Nausea	8.66±1.54	8.59±2.04	0.253	0.801
	Vomiting	6.42±3.84	6.82±4.02	0.656	0.513
	Loss of appetite	6.04±2.15	6.16±2.08	0.364	0.716
	Insomnia and dreamful sleep	12.25±5.52	21.58±6.28	10.210	<0.001
Functional domain	Cognitive function	74.63±6.94	75.13±7.05	0.460	0.646
	Emotional functioning	68.14±5.95	52.86±8.94	13.200	<0.001
	Physical function	72.82±4.82	61.84±6.27	12.79	<0.001
	Social functioning	76.59±7.05	75.93±7.46	0.586	0.559
	Role function	68.25±5.84	60.41±7.57	7.554	<0.001

safety of foscarnet sodium in treating herpes zoster were clearly pointed out, which further confirms our findings. Therefore, lidocaine gel combined with foscarnet sodium has a good effect in the treatment of herpes zoster. We speculated that lidocaine gel sped up metabolism, effectively promoted wound healing in rashes, and foscarnet sodium inhibited virus production. Anti-virus and pain relief were carried out simultaneously, which greatly improved the compliance of patients, alleviated their pain, and significantly improved the treatment effect. The VAS and NRS scores of the patients were then statistically analyzed, and the results showed that the pain of patients receiving treatment of lidocaine gel combined with foscarnet sodium was significantly reduced. This result further verified our above experiments. We speculated that the pain relief of patients was the result of the local anesthetic effect of lidocaine gel. After absorption of lidocaine, the tissue distribution was quick and wide, so that the effect was quick and the pain sensation was reduced. A review of the data revealed that Perez-Lopez et al. showed in their study that lidocaine gel could effectively reduce pain and pain score in patients after intrauterine device insertion [28]. This supports our experimental results. We further observed the occurrence of adverse reactions in patients. The results exhibited that the incidence of adverse reactions such as increased Cr, increased blood urea nitrogen, weakness and dizziness, loss of appetite, nausea, constipation was small, and the patients were tolerable, without affecting treatment. They were not treated specially and the conditions improved during or after treatment. This suggests that lidocaine gel combined with foscarnet sodium is of high safety and minimal side effects in treating herpes zoster patients, and has a high clinical application value. Finally, we followed up the patients for three months after the treatment, and found that the incidence of PHN was lower, which confirmed the above complication experiment, and the patients had better recovery effect. In the follow-up quality of life survey, the recovery of patients was further verified, and the quality of life of patients treated with lidocaine gel combined with foscarnet sodium was better.

In this study, the effect of lidocaine gel combined with foscarnet sodium on the pain level and adverse reactions of herpes zoster patients were investigated. However, there are still some deficiencies because of the limited experimental conditions. For example, there is no comparative analysis on the dosage of medication in this study, so it is not ruled out that there may be different results in different dosage of medication. And due to the short experimental period, we could not evaluate the effect of the two drug methods on the long-term prognosis of patients. We will conduct a more in-depth and comprehensive analysis on the above deficiencies as soon as possible to obtain better experimental results.

In conclusion, lidocaine gel combined with foscarnet sodium has a significant effect on the treatment of herpes zoster patients, with less pain level and adverse reactions, which is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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