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Original Article

Effects of repetitive transcranial magnetic stimulation combined with acupuncture on NLRP3 inflammasome and protease levels in patients with neuropathic pain

Zanhua Wu[1], Qinghua Liu[1,2]

[1]*Department of Rehabilitation Medicine, People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530000, Guangxi, The People's Republic of China;* [2]*Department of Orthopaedics, Hanzhong 3201 Hospital, Hanzhong 723000, Shaanxi, The People's Republic of China*

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Abstract: Purpose: This study aimed to investigate whether repetitive transcranial magnetic stimulation (rTMS) combined with acupuncture could alleviate pain in patients suffering from postherpetic neuralgia (PHN) by inhibiting NOD-like receptor 3 (NLRP3) inflammasome activation. Methods: Data of 92 PHN patients were retrospectively collected. The patients were grouped as control (nerve block), rTMS, and rTMS + acupuncture groups according to treatment methods. The visual analogue scale (VAS) score, as well as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, NLRP3, and Caspase-1 levels of patients in each group prior and post-treatment were analyzed. Results: The rTMS + acupuncture group showed higher efficacy than the rTMS group and the control group, contributing to markedly lower VAS score, as well as TNF-α, IL-1β, IL-6, NLRP3 and Caspase-1 levels than the other two groups ($P < 0.05$). Conclusion: rTMS plus acupuncture can reduce the inflammatory immune response and ease the pain in patients by inhibiting NLRP3 inflammasome and its resulting inflammatory factors, Caspase-1 and IL-1β.

Keywords: Repetitive transcranial magnetic stimulation, acupuncture, neuropathic pain, IGF-1, NLRP3, inflammatory factor

Introduction

Neuropathic pain (NP) is caused by direct damage to the somatosensory system or diseases [1]. The patients can present with severe pain, even "extraordinary pain" for a long time. Often after the primary disease is cured, the pain still exists for another several months, years, or even throughout life [2]. Clinically, various diseases can cause NP, such as cancer, diabetes, infectious diseases, autoimmune diseases, and peripheral nerve damage diseases [3]. Epidemiological surveys indicate that the prevalence of postherpetic neuralgia (PHN) was 8-10% [4]. It severely affects the quality of life of affected patients and causes social and economic burdens [5]. However, traditional painkillers, like opioids and non-steroidal anti-inflammatory drugs (NSAIDs), are often ineffective in treating PHN. The efficacy of targeting drugs in the treatment of PHN is also unclear, and their use can lead to various adverse reactions [6]. Therefore, actively searching for effective treatments for PHN is of great significance to patients' prognosis and quality of life.

Repetitive transcranial magnetic stimulation (rTMS) is a painless treatment that has recently emerged. Its working principle is to transmit magnetic signals to neurons in the cerebral cortex through the skull, stimulate the brain, and affect the brain's metabolism and neural electrical activities, thereby causing physiological and biochemical reactions [7]. Using different stimulation parameters, rTMS can produce distinct neurophysiological actions, with low-frequency modes eliciting cortical inhibition and high-frequency patterns evoking excitation. Recently, it has been proven that high-frequency continuous repetitive stimulation can relieve pain, with advantages of non-invasiveness, safety, fewer side effects, and rapid onset of action [8-10].

Acupuncture, guided by the traditional Chinese medicine theory, inserts filigree needles into the skin at a certain angle, after which appropriate needle techniques (twisting and lifting, etc.) are utilized to stimulate specific acupoints to cure diseases. Moxibustion a therapeutic technique that involves applying heat stimulation to acupoints on the body surface by burning moxibustion sticks or grass for the prevention and treatment of various diseases. Studies have shown that acupuncture can activate the nervous system, and its analgesic mechanism involves peripheral nervous system, central nervous system and related biologically active substances. Acupuncture can signally improve the symptoms of NP [11]. Dyson-Hudson et al. [12] found that acupuncture was able to relieve chronic shoulder and back pain caused by spinal cord injury. A systematic review by Qin et al. [13] showed that acupuncture could signally relieve low back pain comparing with NSAIDs.

However, there are few reports on the efficacy of acupuncture combined with rTMS in treating PHN, but its therapeutic mechanism on the inflammatory immune response of nerve tissue remains unclear. A wide array of studies have confirmed that the inflammatory immune response of nerve tissue caused by the release of proinflammatory cytokines after the activation of glial cells is one of the important mechanisms of NP [14, 15]. Hence, this study investigated the effect of rTMS plus acupuncture on inflammatory immune response to understand the related mechanism. Tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, proinflammatory cytokines and key inflammation-related pain factors, have been reported to be actively involved in promoting NP progression [16]. IL-1β is produced in an inactive precursor form (pro-IL-1β), and its maturation and secretion are tightly regulated by the body, mainly primarily through the action of inflammasomes. Inflammasomes are cytoplasmic macromolecule protein complex involved in the activation of pro-IL-1β into biologically active IL-1β. One of the inflammasomes is the NOD-like receptor 3 (NLRP3), which consists of an adaptor protein called apoptosis-related speck-like protein and an effector protein known as cysteine protease 1 precursor (pro-caspase-1). Inhibition of spinal NLRP3 inflammasome activation can attenuate NP induced by chronic contractile injury [17]. Based on the above theory, this article focuses on NLRP3 inflammasome and pro-inflammatory cytokines to explore the mechanism of action of rTMS + acupuncture in modulating inflammatory immune responses in PHN, so as to provide insights for guiding PHN treatment.

Materials and methods

Research subjects

In this study, data of 92 patients with PHN treated at the People's Hospital of Guangxi Zhuang Autonomous Region between January 2019 and January 2021 were retrospectively collected. The patients were grouped as control (n=30), rTMS (n=31), and rTMS + acupuncture (n=31) groups according to the treatment methods. Among the 92 patients, there were 48 males and 44 females, aged 36-75 (57.33±7.10) years, with a disease duration of 12.21±2.58 months. The three groups exhibited no significant difference in terms of sex, age, course of disease, and other general data ($P < 0.05$), as shown in **Table 1**.

Inclusion criteria: (1) patients who met the diagnostic criteria of PHN (previous history of acute herpes zoster disease; spontaneous, knife-like, tight-bundle pain on the skin for more than one month; pain sensation and paresthesia in the innervated area) [18]; (2) patients with complete data; (3) patients with a Visual Analogue Scale (VAS) score of greater than 5 points; (4) patients who met the indications of rTMS or acupuncture and received rTMS or/and acupuncture treatment. Exclusion criteria: patients who were not tested for levels of TNF-α, IL-1β, IL-6, NLRP3, and Caspase-1, with incomplete data. The Medical Ethics Committee at People's Hospital of Guangxi Zhuang Autonomous Region approved this study.

Data collection

Pain assessment was conducted prior-treatment, at 2 weeks of intervention, at 4 weeks of intervention, and 2 weeks after the treatment using VAS, which was the primary outcome measure. The VAS score ranges from 0 (no pain) to 10 (worst possible pain) points. A total score of 1-2 points means slight pain, 3-4 means moderate pain, 5-6 means severe pain, 7-8 means grievous pain, 9-10 means unbearable pain.

Table 1. Demographics and characteristics of patients (n=92)

	Control (n=30)	rTMS (n=31)	rTMS + acupuncture (n=31)	Total
Age (years)				
Mean	57.23	57.45	57.32	57.33
Standard deviation	7.59	7.69	6.15	7.10
Sex (M/F)				
Male	16	15	17	48
Female	14	16	14	44
Education level (No.)				
Elementary school	6	3	7	16
Middle school	12	18	12	42
High school	8	8	8	24
College	4	2	4	10
Race (No.)				
Asian	30	31	31	92
Course of disease (months)				
Mean	12.06	12.42	11.84	12.11
Standard deviation	2.66	2.64	2.68	2.64
Baseline VAS (points)				8.61
Mean	8.60	8.64	8.58	
Range	7-10	6-10	6-10	6-10

Note: rTMS: Repetitive transcranial magnetic stimulation; VAS: Visual analogue scale.

We carried out enzyme-linked immunosorbent assays to determine TNF-α, IL-1β, IL-6, NLRP3, and Caspase-1 levels at the above mentioned time points. Fasting venous blood (5 mL) was collected from each subject and centrifuged to obtain serum, which was placed in a -20°C freezer for testing. Beijing Biolab Technology Co., Ltd. provided detection kits for human IL-1β (ZN2236-KFO), human IL-6 (ZN2272-OHR), and human TNF-α (ZN2479-GEV). While human NLRP3 (ab274401) and Caspase-1 (ab219633) kits were purchased from Abcam, USA. The testing procedures strictly followed the kit manuals.

Treatment methods

The control group was treated with a nerve block and pregabalin. The nerve block segment was determined based on the pain location. Nerve trunk block was used for head and face pain, and paravertebral nerve block was used for chest, back, and waist pain. After the segment was determined, the patients received a combination of 7 mg of compound betamethasone (Chongqing Huabang Pharmaceutical Co., Ltd., H20093412), 2 ml of 2% lidocaine (Jichuan Pharmaceutical Group Co., Ltd., H10960193), and 20 ml of adenosine Cobalamin 1 mg analgesic compound solution (Yangzijiang Pharmaceutical Group Nanjing Hailing Pharmaceutical Co., Ltd., H20058993) for nerve block once a week. Additionally, they were prescribed 150 mg oral pregabalin (Germany Pfizer GmbH, Betriebsstatte Freiburg, J20160021) to be taken twice daily, in the morning and evening. The treatment was continued for four weeks.

The rTMS group received rTMS on the basis of the control group. The patients received magnetic stimulation therapy (magnetic stimulator, MT10, Beijing Naotai Technology Development Co., Ltd.) at the same time each day. The rTMS treatment parameters were as follows, stimulation frequency: 10 Hz, stimulation intensity: 80%-100%, total number of MT pulses: 1200, stimulation site: motor cortex M1 area, stimulation time: 20 min. rTMS was given once a day for four consecutive weeks.

In the rTMS + acupuncture group, patients received additional acupuncture on the basis of the rTMS group. The main acupuncture point was Zusanli, and the auxiliary points were selected around the skin lesions, including Jiaji, Waiguan, Zhigou, Quchi, Ashi points, etc. For

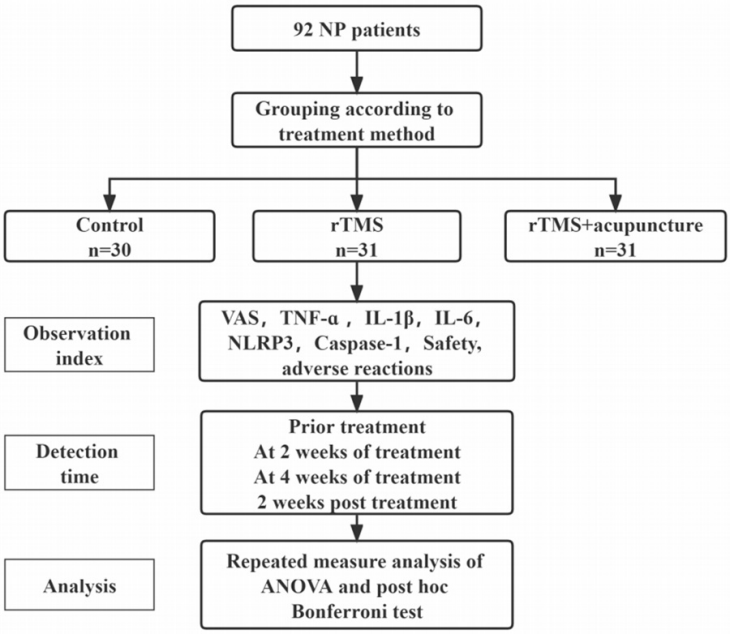

Figure 1. Flow chart. NP: Neuropathic pain; rTMS: Repetitive transcranial magnetic stimulation; VAS: Visual analogue scale; TNF-α: Tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6; NLRP3: NOD-like receptor 3; ANOVA: Analysis of variance.

acupuncture and moxibustion, a lateral decubitus position was used. When acupuncture at the Ashi point, the center of the skin lesion should be punctured at the junction of the abnormal skin and the normal skin, with a depth of about 1.0-1.5 cun (1 cun = 3.33 cm). The Jiaji point was acupunctured with a depth of 1.0 cun using levelling, supplementing, and reducing methods. For Zusanli acupoint, the supplementing method was adopted. The other acupoints were treated with lifting, thrusting and reducing methods. The needles were retained for 30 min, and patients received rTMS and acupuncture at a specified time every day for 4 weeks.

The follow-up evaluation was carried out two weeks after the treatment. The research process is shown in **Figure 1**.

Statistical analyses

Quantitative and qualitative data were described as mean ± standard deviation and n (%), respectively. Chi-square tests were performed for between-group comparisons of qualitative data. For quantitative data, t-test and two-way analysis of variance (ANOVA) were employed for between-group and multi-group (three or more groups) comparisons, respectively. Repeated measures ANOVA followed by post hoc Bonferroni test was used for analyzing data with repeated measurements. Statistical significance was considered when the *P*-value was less than 0.05. All data processing was carried out using SPSS 23.0, and graphing was performed using with GraphPad Prism 8.0.

Results

During the study, four patients withdrew. Two cases withdrew in the control group and were lost to follow-up or received other treatment due to relocation at 1-week follow-up and 2-week follow-up, respectively. One case each withdrew in the rTMS group and the rTMS + acupuncture group, which was lost to follow-up at 1-week and 2-week follow-up, respectively.

VAS scores prior and post treatment

Pain assessment was conducted prior-treatment, at 2 weeks of intervention, at 4 weeks of intervention, and 2 weeks after the treatment using VAS. Statistical significance was identified in VAS scores among the groups ($P < 0.001$). No statistical difference was identified in pre-treatment VAS scores among the groups. After treatment, the VAS scores were found to be significantly reduced in the three groups, with lower scores in the rTMS + acupuncture group than that in the other two groups at 4 weeks of treatment and 2 weeks after treatment ($P < 0.05$), as shown in **Table 2**. See **Figure 2** for the changes in the levels of observation indicators prior and post-treatment.

Levels of inflammatory factors in the three groups prior and post treatment

TNF-α, IL-1β, and IL-6 levels were statistically different among the groups ($F(3, 356)=8.614$, $P < 0.001$; $F(3, 356)=16.010$, $P < 0.001$; $F(3, 356)=22.550$, $P < 0.001$). No statistical difference was observed in pre-treatment serum TNF-α, IL-1β, and IL-6 levels among the groups ($P > 0.05$). After treatment, the serum levels of TNF-α, IL-1β, and IL-6 were markedly reduced in the three groups. Serum levels of TNF-α, IL-1β,

Table 2. Comparison of VAS scores among the three groups prior and post treatment (points)

Group	Prior treatment	At 2 weeks of treatment	At 4 weeks of treatment	2 weeks post treatment	F_{time}	P
Control (n=30)	8.60±0.85	5.96±0.96	5.60±0.67	5.36±0.61	109.600	< 0.001
rTMS (n=31)	8.64±1.14	5.03±0.98*	4.38±0.80*	3.70±0.86*	165.300	< 0.001
rTMS + acupuncture (n=31)	8.58±1.06	4.0±1.0*,#	2.45±0.76*,#	1.74±0.68*,#	370.200	< 0.001
F_{group}	0.032	30.581	136.606	189.159		
P	0.968	< 0.001	< 0.001	< 0.001		

Note: *P < 0.05, indicating comparison with control group; #P < 0.05, indicating comparison with rTMS group. VAS: Visual analogue scale; rTMS: Repetitive transcranial magnetic stimulation.

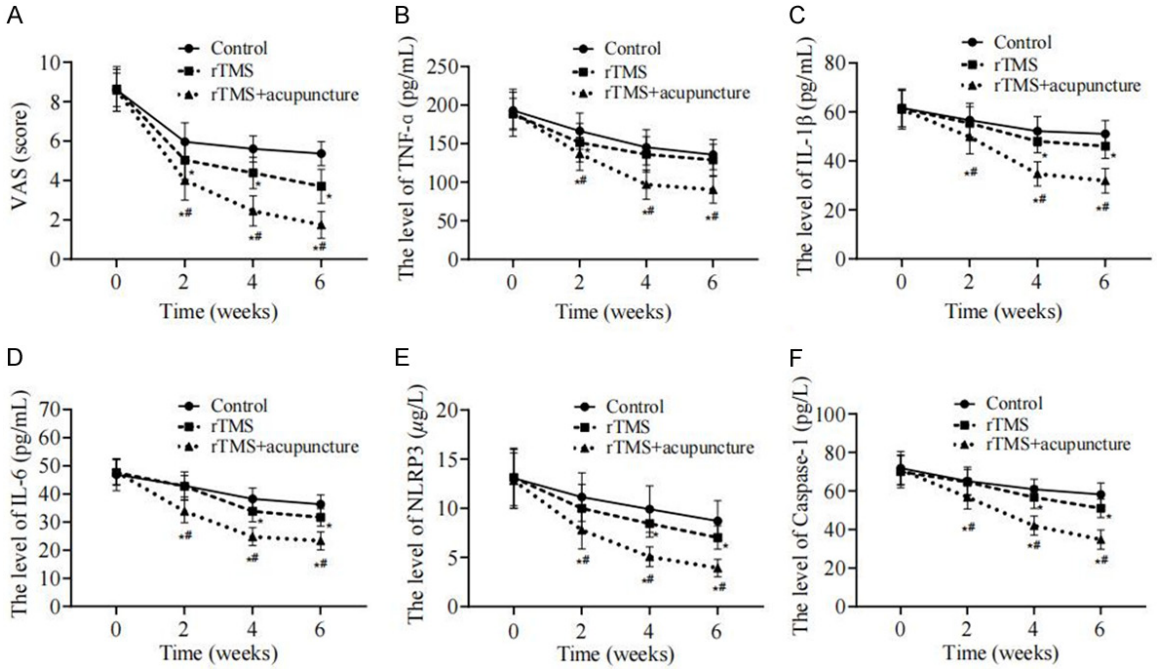

Figure 2. Changes in the observed indicators of the three groups of patients. (A) Pain score, (B) TNF-α, (C) IL-1β, (D) IL-6, (E) NLRP3, (F) Caspase-1. Note: *P < 0.05, indicating comparison with control group; #P < 0.05, indicating comparison with rTMS group. VAS: Visual analogue scale; rTMS: Repetitive transcranial magnetic stimulation; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; NLRP3: NOD-like receptor 3.

and IL-6 were signally lower in the rTMS + acupuncture group than those in the other two groups at 4 weeks of treatment and 2 weeks after treatment (P < 0.05), as shown in **Tables 3**-**5**.

Levels of inflammasome and protease in the three groups prior and post treatment

NLRP3 and Caspase-1 were markedly different among the groups (F(3, 356)=7.817, P < 0.001; F(3, 356)=20.990, P < 0.001). No statistical difference was identified in pre-treatment serum NLRP3 and Caspase-1 levels among the groups (P > 0.05). After treatment, the NLRP3 and Caspase-1 levels were markedly reduced in all the three groups. The rTMS + acupuncture group exhibited lower NLRP3 and Caspase-1 levels than the other two groups at 4 weeks of treatment and 2 weeks after treatment (P < 0.05). See **Tables 6** and **7**.

Comparison of adverse reactions

One patient in the rTMS + acupuncture group developed skin erythema due to acupuncture and moxibustion. The erythema was relieved without special treatment. The other groups showed no adverse reactions.

Table 3. Comparison of TNF-α levels among the three groups prior and post treatment (pg/ml)

Group	Prior treatment	At 2 weeks of treatment	At 4 weeks of treatment	2 weeks post treatment	F_{time}	*P*
Control (n=30)	192.96±23.72	166.26±23.41	145.25±22.83	135.81±19.47	38.350	< 0.001
rTMS (n=31)	188.40±20.49	151.35±24.99*	136.14±22.86	128.87±20.21	44.140	< 0.001
rTMS + acupuncture (n=31)	189.99±30.48	136.78±21.51*,#	96.98±19.04*,#	90.27±17.36*,#	126.800	< 0.001
F_{group}	0.255	12.150	44.659	50.969		
P	0.776	< 0.001	< 0.001	< 0.001		

Note: *$P < 0.05$, indicating comparison with control group; #$P < 0.05$, indicating comparison with rTMS group. TNF-α: Tumor necrosis factor-α; rTMS: Repetitive transcranial magnetic stimulation.

Table 4. Comparison of IL-1β levels among the three groups prior and post treatment (pg/ml)

Group	Prior treatment	At 2 weeks of treatment	At 4 weeks of treatment	2 weeks post treatment	F_{time}	*P*
Control (n=30)	61.63±7.71	56.61±6.90	52.16±6.02	51.01±5.47	16.710	< 0.001
rTMS (n=31)	61.41±7.44	55.36±6.77	48.05±4.66*	46.03±4.97*	41.740	< 0.001
rTMS + acupuncture (n=31)	61.00±7.99	49.84±6.96*,#	34.73±4.93*,#	31.90±4.97*,#	142.200	< 0.001
F_{group}	0.051	8.430	93.240	114.200		
P	0.951	< 0.001	< 0.001	< 0.001		

Note: *$P < 0.05$, indicating comparison with control group; #$P < 0.05$, indicating comparison with rTMS group. IL-1β: interleukin-1β; rTMS: repetitive transcranial magnetic stimulation.

Table 5. Comparison of IL-6 levels among the three groups prior and post treatment (pg/ml)

Group	Prior treatment	At 2 weeks of treatment	At 4 weeks of treatment	2 weeks post treatment	F_{time}	*P*
Control (n=30)	46.86±5.70	42.87±4.97	38.23±3.86	36.29±3.35	32.490	< 0.001
rTMS (n=31)	47.59±4.49	42.70±3.81	33.81±3.76*	31.65±3.07*	119.50	< 0.001
rTMS + acupuncture (n=31)	47.83±4.52	33.79±3.99*,#	24.80±3.18*,#	23.33±3.22*,#	276.400	< 0.001
F_{group}	0.318	425.351	109.971	127.700		
P	0.729	< 0.001	< 0.001	< 0.001		

Note: *$P < 0.05$, indicating comparison with control group; #$P < 0.05$, indicating comparison with rTMS group. IL-6: interleukin-6; rTMS: repetitive transcranial magnetic stimulation.

Table 6. Comparison of NLRP3 levels among the three groups prior and post treatment (μg/L)

Group	Prior treatment	At 2 weeks of treatment	At 4 weeks of treatment	2 weeks post treatment	F_{time}	*P*
Control (n=30)	13.06±3.07	11.14±2.46	9.91±2.36	8.06±1.98	21.950	< 0.001
rTMS (n=31)	13.12±2.85	9.99±2.44	8.44±1.36*	7.03±1.19*	48.820	< 0.001
rTMS + acupuncture (n=31)	12.81±2.81	7.79±1.94*,#	5.07±1.0*,#	3.92±0.88*,#	144.500	< 0.001
F_{group}	0.095	16.893	67.970	70.700		
P	0.909	< 0.001	< 0.001	< 0.001		

Note: *$P < 0.05$, indicating comparison with control group; #$P < 0.05$, indicating comparison with rTMS group. NLRP3: NOD-like receptor 3; rTMS: Repetitive transcranial magnetic stimulation.

Correlation of NLRP3 inflammasome, inflammatory factors, and protease with VAS

This study analyzed the correlation of VAS score with TNF-α, IL-6, IL-1β, NLRP3, and Caspase-1 at two weeks after treatment. The results showed that the VAS score was significantly correlated with the above indexes ($P < 0.001$), as shown in **Figure 3**.

Discussion

Herpes zoster is a common infectious disease in dermatology. Its pathogenesis is that the

Table 7. Comparison of Caspase-1 levels among the three groups prior and post treatment (pg/L)

Group	Prior treatment	At 2 weeks of treatment	At 4 weeks of treatment	2 weeks post treatment	F_{time}	P
Control (n=30)	71.89±8.61	65.13±7.31	60.86±5.23	58.18±6.04	22.420	< 0.001
rTMS (n=31)	70.01±8.36	64.63±6.56	56.72±5.73*	51.03±4.79*	51.800	< 0.001
rTMS + acupuncture (n=31)	70.92±7.73	56.75±6.02*,#	41.99±4.93*,#	34.79±4.98*,#	220.40	< 0.001
F_{group}	0.397	15.409	107.200	157.300		
P	0.674	< 0.001	< 0.001	< 0.001		

Note: *P < 0.05, indicating comparison with control group; #P < 0.05, indicating comparison with rTMS group. rTMS: repetitive transcranial magnetic stimulation.

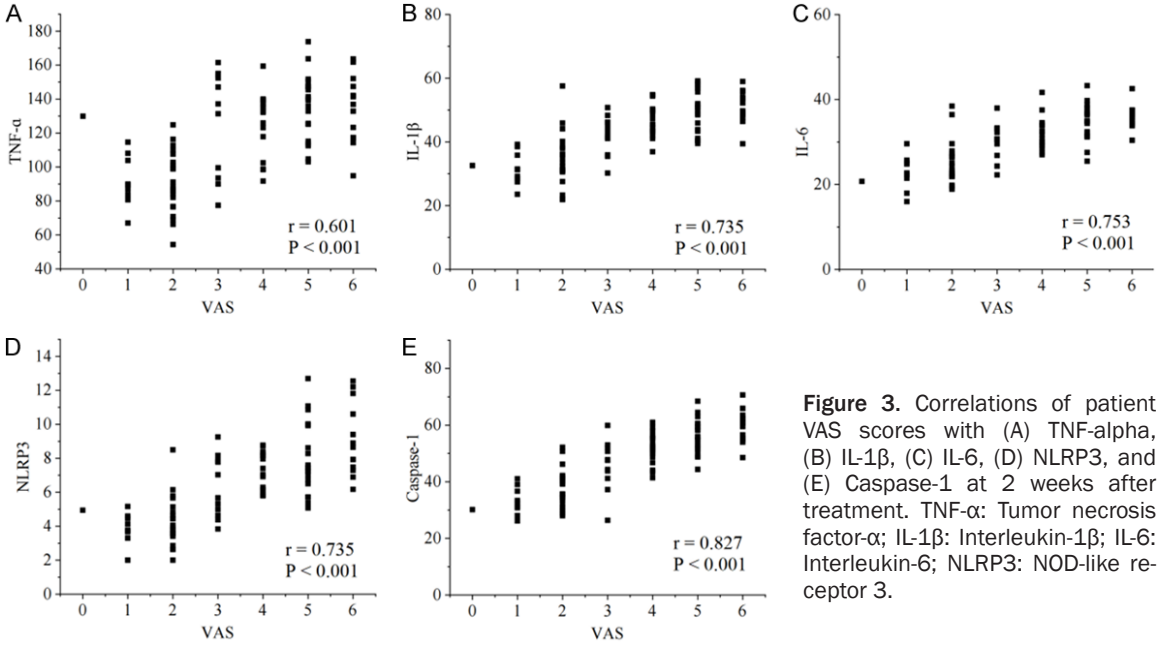

Figure 3. Correlations of patient VAS scores with (A) TNF-alpha, (B) IL-1β, (C) IL-6, (D) NLRP3, and (E) Caspase-1 at 2 weeks after treatment. TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; NLRP3: NOD-like receptor 3.

varicella-zoster virus invades the body and establishes a latent infection. It travels along the nerves and resides in the dorsal root ganglia of the spinal cord. During periods of weakened immune function, the virus within the ganglion can undergo multiplication. PHN, a clinically refractory chronic pain, is the most common complication of herpes zoster. Patients usually have persistent or paroxysmal pain, and some have sharp stabby pain [19]. In recent years, rTMS has been proven to relieve pain and has the advantages of non-invasiveness, safety, fewer side effects, and rapid onset of action [20, 21]. Acupuncture can also activate the nervous system and relieve pain [22]. However, there are few reports on treating postherpetic NP patients with rTMS plus acupuncture, so the therapeutic mechanism needs to be clarified. Some studies have suggested that NP after herpes zoster occurs due to inflammatory factors damaging nerve cells during the development of the infection. This damage can induce the formation of neurofibromas, which contribute to the development of nerve pain [23]. Based on the above reasons, this paper explored whether rTMS plus acupuncture can lessen the levels of inflammatory factors and inflammatory responses.

Postherpetic NP is shown to be strongly associated with the level of inflammatory factors in the body [24]. The initiating factor of inflammatory response is TNF-α, which promotes the body to release a large amount of pro-inflammatory factors such as IL-1β, IL-6, and IL-10, and blocks the release of anti-inflammatory factors, thereby regulating the aggregation of macrophages and NP. This study showed that after 4 weeks of rTMS and acupuncture treatment, the pain scores, TNF-α, IL-1β, and IL-6

levels of postherpetic NP patients were signally lower than those prior treatment. Moreover, rTMS plus acupuncture treatment contributed to significantly better efficacy than the other two treatments. This study indicates that rTMS plus acupuncture can effectively regulate the levels of pro-inflammatory and anti-inflammatory factors, as well as relieve PHN. Acupuncture signals are transmitted to the central nervous system by acupoint receptors and peripheral nerves, and after integration, they are able to regulate the body's endocrine function. By reducing the production of TNF-α and suppressing the activation of Th1, the release of excessive pro-inflammatory factors, such as IL-1β and IL-6 can be inhibited. This reduction in immune responses and inflammatory mediators contributes to pain relief.

Studies have shown that a Nod-like receptor family is a group of intracytoplasmic pattern recognition receptors functioning as danger signal receptors in the cytoplasm. The NLRP3 inflammasome is a cytoplasmic protein complex consisting of NLRP3, pro-caspase-1, and apoptosis-associated speck-like protein (ASC). When NLRP3 detects intracellular activation signals, it undergoes oligomerization and recruits pro-caspase-1, forming inflammasomes with the assistance of the binding protein ASC. This process facilitates the self-cleavage of pro-caspase-1, resulting in the maturation of Caspase-1, which in turn plays a role in the maturation and secretion of IL-1β [25, 26]. By observing NLRP3 and Caspase-1 levels in postherpetic NP patients prior- and post-treatment, we analyzed the role of rTMS plus acupuncture treatment in inflammatory responses in patients. The results showed that the serum levels of NLRP3 and Caspase-1 signally decreased in the three groups after treatment, with the lowest levels found in the rTMS + acupuncture group at 4 weeks of treatment and 2 weeks after treatment. It is indicated that rTMS plus acupuncture can reduce the inflammatory immune response and improve pain by inhibiting the NLRP3 inflammasome and its resulting inflammatory factors like Caspase-1 and IL-1β. Liu et al. reported that NLRP3 inflammasome activation mediated the development of NP after chronic sciatic nerve contraction injury, and inhibition of NLRP3 inflammasome activation could alleviate NP [17]. Ju et al. also found a lower VAS score after intervention in the combined acupuncture group, which is consistent with our results [27]. Acupuncture also seemed to improve nerve conduction study parameters in both sensory and motor nerves, according to a meta-analysis [28].

Although this study suggests that rTMS plus acupuncture can alleviate pain in PHN patients and improve their quality of life in a short period of time, there are some limitations remain to be addressed. Firstly, this clinical study has a small number of cases in all three groups, so it is impossible to fully determine the therapeutic effect of rTMS on PHN. Therefore, future multicenter and large-sample studies are needed. Secondly, we only observed the short-term efficacy at 2 weeks after treatment. Whether there is a sustained analgesic effect and in a longer duration and the relapse rate remain unknown. Therefore, it is necessary to extend the follow-up time in further studies.

Conclusion

rTMS plus acupuncture contribute to better efficacy, as well as lower VAS score, and TNF-α, IL-1β, and IL-6 levels than rTMS or nerve block in treating PHN. In addition, the NLRP3 and Caspase-1 levels were significantly lower in the rTMS + acupuncture group than the rTMS and nerve block groups. It is indicated that rTMS plus acupuncture can reduce the inflammatory immune response and improve pain by inhibiting NLRP3 inflammasome and its resulting inflammatory factors like Caspase-1 and IL-1β. However, the small sample size of this study may cause certain bias in the results, so the sample size needs to be expanded in further studies.

Disclosure of conflict of interest

None.

Address correspondence to: Qinghua Liu, Department of Orthopaedics, Hanzhong 3201 Hospital, Hanzhong 723000, Shaanxi, The People's Republic of China. Tel: +86-0916-2383201; E-mail: 2792-286459@qq.com

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