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Combination of low frequency electroacupuncture plus subdissociative doses of ketamine in post-herpetic neuralgia patients. A pilot study

[Combinación de electroacupuntura de baja frecuencia más ketamina a bajas dosis subdisociativas en pacientes con neuralgia post-herpética. Estudio piloto]

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Abstract|

Context: Pain processing implicates multiple concurrent mechanisms of nociceptive transmission and modulation. Electroacupuncture (EA) analgesia involves mainly the activation of the endogenous anti-nociceptive systems that modulate pain transmission in addition to the regulation of glial activity and inhibition of pro-inflammatory cytokines in the spinal cord.

Aims: To examine the potential anti-hyperalgesic effects the EA and the combination EA-ketamine in patients with post-herpetic neuralgia (PHN).

Methods: Sixty-eight patients with PHN irritable nociceptor type were randomly allocated to 3 groups: group I (n=26), that received treatment with EA (10 Hz, 2-3 mA, 0.5 ms, 20 min/15 sessions) alone, group II (n=21) with a combination EA-ketamine (0.25-0.5 mg/kg, i.m.) or group III (n=21) with sham EA-ketamine for 15 days. The average daily pain score (ADPS) using the Likert scale, area and rate of dynamic allodynia, the rate of thermal allodynia, and frequency of intermittent lancinating pain were evaluated during five visits – before treatment and at 15, 30, 60, 90 days.

Results: ADPS and sensory abnormalities decreased significantly concerning baseline data at 90 days in the three groups, but patients treated with the combination EA-ketamine significantly improved compared with the other groups.

Conclusions: These results suggest that the combination EA-ketamine shows an early and long-term anti-hyperalgesic effect in PHN patients. However, a controlled clinical trial is necessary to confirm this hypothesis.

Keywords: acupuncture; electroacupuncture; herpes zoster; neuropathic pain; post-herpetic neuralgia.

Resumen

Contexto: El procesamiento del dolor implica múltiples mecanismos concurrentes de la transmisión y modulación nociceptiva. La analgesia inducida por la electrocaupuntura (EA) involucra principalmente la activación de los sistemas antinociceptivos endógenos que modulan la transmisión del dolor, además la regulación de la actividad glial y la inhibición de las citocinas pro-inflamatorias en la médula espinal.

Objetivos: Examinar los efectos anti-hiperalgésicos potenciales de la EA y la combinación EA-ketamina en pacientes con neuralgia post-herpética (NPH).

Métodos: Sesenta y ocho pacientes portadores de NPH tipo nociceptor irritable fueron aleatoriamente asignados a tres grupos: grupo I (n=26), con tratamiento de EA (10 Hz, 2-3 mA, 0.5 ms, 20 min/15 sesiones); grupo II (n=21), combinación de EA-ketamina (0.25-0.5 mg/kg, i.m.); o grupo III (n=21), falsa EA-ketamina durante 15 días. Las variables evaluadas fueron: puntuaciones diarias medias de dolor (PDMD) mediante una escala de Likert, área e intensidad de la alodinia dinámica, intensidad de la alodinia termal y frecuencia del dolor lancinante intermitente durante cinco consultas, antes del tratamiento y a los 15, 30, 60 y 90 días.

Resultados: Las PDMD y las anormalidades sensoriales disminuyeron significativamente con respecto a los valores basales a los 90 días en los tres grupos, no obstante, los pacientes tratados con la combinación EA-ketamina mejoraron significativamente comparados con los asignados a los otros grupos.

Conclusiones: Estos resultados sugieren que la combinación EA-ketamina muestra un efecto anti-hiperalgésico temprano y a largo plazo en pacientes con NPH. Sin embargo, se hace necesario un ensayo clínico controlado para confirmar esta hipótesis.

Palabras Clave: acupuntura; dolor neuropático; electroacupuntura; herpes zoster; neuralgia post-herpética.

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INTRODUCTION

Post-herpetic neuralgia (PHN) is the most common chronic complication of herpes zoster (Johnson and Rice, 2014). It constitutes an intractable form of neuropathic pain (NP) that causes substantial interference with physical, emotional, and social functioning (Petersen and Rowbotham, 2010; Dworkin et al., 2008). PHN is defined as pain that persists 120 days or more after rash onset and this condition is characterized by burning, lancinating, or stabbing pain (Dworkin et al., 2008). In addition to abnormalities of sensation such as allodynia and hyperaesthesia of the affected dermatome (Fields et al., 1998). Although tricyclic antidepressants, topical lidocaine or capsaicin, gabapentin, pregabalin, and oxycodone are effective in alleviating this condition, many patients remain refractory to current pharmacologic and interventional therapies (Rice and Maton, 2001; Baron et al., 2009; Finnerup et al., 2015). Unfortunately, their use may be limited by side effects, particularly in elderly patients, which may be more prone to the anticholinergic side effects of tricyclic antidepressants and have cardiovascular and renal comorbidities (Finnerup et al., 2015). On the other hand, clinical studies showing that N-methyl-D-aspartate (NMDA) receptor antagonists as ketamine, can reduce both mechanical allodynia and hyperalgesia in patients with NP (Eide et al., 1995). Previous studies in animals have been shown a pivotal role of NMDA receptors in the generation and maintenance of central hyperexcitability (Woolf and Salter, 2000). The current literature suggests that ketamine in subanesthetic doses can provide short-term relief of refractory NP in some patients. The size and scope of controlled clinical trials, to this date, are insufficient to support longer-term use in any particular chronic pain disorder (Bell, 2009; Finnerup et al., 2015). Frequent abuse of ketamine has been shown to cause long-lasting memory impairment and altered prefrontal dopaminergic function (Bell, 2009). Then these safety aspects have limited the use of NMDA antagonists in this condition.

Clinical and scientific interest in acupuncture-related techniques such as electroacupuncture (EA) has been increasing dramatically in the last decades (Han, 2011). EA analgesia involved the activation of the endogenous descending modulatory system that regulates nociceptive pain transmission by means of multi-synaptic pathways and various neurotransmitters/neuromodulators. Mostly including endogenous opioid peptides, glutamate, glial cell-derived neurotrophic factor, serotonin, noradrenaline and their receptors (Pomeranz and Chiu, 1976; Han, 2003; Huang et al., 2004; Choi et al., 2005a; Dong et al., 2005; Kim et al., 2005). EA analgesia is also linked to the regulation of glial activation and inhibition of inflammatory cytokines in the spinal cord (Sun et al., 2006; 2007). Moreover, its neuroprotective and regenerative abilities following neurological lesions are reported (Wang et al., 2009). However, many negative reports in large-scale clinical trials have also been published (Scharf et al., 2006). In general, the effectiveness of acupuncture-related techniques in the treatment of chronic pain mainly has been studied in musculoskeletal pain (low back, neck, and shoulder), osteoarthritis of the knee, and headache/migraine (McPherson et al., 2017). Particularly a few clinical studies in PHN patients have been published (Takahashi 2007). A recent systematic review was inconclusive, due to the heterogeneity in the forms of acupuncture therapies and the qualities of methodology (Li et al., 2014). Nevertheless, neuroimaging research demonstrated that long-term acupuncture treatment in chronic NP patients has been found to alter cortical somatosensory processing and produces beneficial changes in somatotopy (Napadow et al., 2007). The heterogeneity of NP syndromes, as PHN, probably reflecting various subjacent mechanisms could have a strong influence on the variability of these results. Many recent trials using drugs that expected to be effective in NP are negative on the primary outcome (Attal and Bouhassira, 2015). Also, the heterogeneity of diagnostic criteria and an inadequate classification of patients in clinical trials to identify responder populations could be the major reason of trial failure (Finnerup et al., 2015; Attal and Bouhassira, 2015). Hence the design of clinical trials in both NP and EA should be improved to reduce possible therapeutic failures.

Nowadays the knowledge of pain processing that implicates multiple concurrent mechanisms of nociceptive transmission and modulation constitutes the support for synergist multimodal analgesia (Gilron et al., 2013). Besides the development of more effective strategies for the prevention and treatment

of PHN is an important public health necessity. Therefore, an alternative and complementary approach using EA or its combination with conventional drugs could be a rational and safe possibility. Then a relatively innocuous procedure, which targeting multiple mechanisms through nociceptive pathway as EA, is attractive to be combined with other drugs (Huang et al., 2004; Zhang et al., 2004; Liang et al. 2010). It might provide superior analgesia and fewer side-effects than any monotherapy. The present study aimed to collect the preliminary information on the possible efficacy and safety of EA and its combination with ketamine at low doses in patients with PHN irritable nociceptor type. With the purpose of distinguishing its activity according to the heterogenic pain condition mechanism-based classification.

MATERIAL AND METHODS

Patients

A total of 68 patients with PHN irritable nociceptor type were recruited from the Pain Clinic of '10 de Octubre' Hospital, from January 2000 to June 2006. The study was approved by the hospital's Ethics Committee in accordance with the Declaration of Helsinki (protocol number: SC00401). Written informed consent was obtained from each patient.

Study design

The study was conducted in adult patients of both sexes, who were diagnosed with PHN type irritable nociceptor with clinic evolution <6 months, which reported exquisite mechanical dynamic allodynia or hyperalgesia to mechanical stimuli, as well as a relatively preserved sensory function in the painful area.

The diagnostic was corroborated by infiltration of the most painful skin areas with a local anesthetic (0.5% lidocaine) that provides complete or almost complete relief of both ongoing pain and allodynia (Fields et al., 1998). The intensity of the initial spontaneous pain should have been 4 or more on a 10-point numeric scale (Likert scale). Patients who received treatment with antiviral, opioid, and immunosuppressive agents up to 6 months before the study were excluded. Patients were also excluded if they used a pacemaker or suffered from cardiovascular diseases (unstable angina, recent heart attack, non-treated arterial hypertension), stroke, active malignancy, hyperthyroidism, psychiatric disease or skin sepsis. As well as, patients with antecedents of sensitivity or contraindication for the use of ketamine. The primary outcome measure was the change in the average daily pain score (ADPS) using the Likert scale (baseline week *versus* final week of study); 0 indicated the absence of pain and 10 showed unbearable pain (Rice and Maton, 2001). The patients individually evaluated the pain that corresponded to the previous 24 h, in the morning, and the initial or baseline score consisted of the average pain daily registered in the week before the beginning of the study (enrolment visit). The final pain score was the mean of the daily pain registered in the week before the final visit of the 90-day period. The area and rate of dynamic allodynia, the rate of thermal allodynia, and frequency of spontaneous lancinating pain were other outcomes evaluated in addition to ADPS. The estimated boundaries of the area of allodynia were determined with a cotton bud. Then a regular grid (2-cm intervals) was marked on the skin, and the cotton was used to lightly stroke (2–3 cm/s) from a distant site into the affected dermatome. The subject was asked to report if the sensation was normal or unpleasant and painful. The intensity of allodynia in 2 points of this area was determined according to the Likert scale, and the average of both scores was calculated (Besson et al., 2005). Equally, the intensity of thermal allodynia was determined; the heat was produced by an incandescent lamp (60 W) placed at a 15-cm distance from the skin over 20 s to provide a warm innocuous stimulus. Furthermore, the patients were asked to report the number of intermittent lancinating pain within a 24-hour period (Garrido-Suárez et al., 2011). Outcomes were evaluated during five visits [before treatment and at 15, 30, 60 and 90 days (final visit)]. In all cases, information on dosage and administration frequency of accepted analgesic drugs were collected.

Drugs

Ketamine hydrochloride (50 mg/mL, 10 mL) (Laboratorios Liorad, La Habana, Cuba) was injected by intramuscular route (0.25-0.5 mg/kg, i.m.).

However, due to ethical reasons patients were asked of three groups to take accepted concomitant medication and analgesic rescues during the study period if the pain was unbearable. Also, if they did not want to continue with the study, they could leave at any time. The introduction of concomitant medication, relative to opioids, tricyclic antidepressants or antiepileptic's drugs constituted a control outcome in this study. The administration of dipyrone (300 mg tablets) as analgesic rescue dosage was also controlled.

Treatments

Patients were randomized sequentially into three groups using a computer-generated randomization list (Fig. 1): group I (n=26), that received treatment with EA alone, group II (n=21) with a combination EA-ketamine or group III (n=21) with a sham EA-ketamine diary for 15 days. The mean of ketamine dose by i.m. route about (0.44 mg/kg) was used because it is ideal for ambulatory procedures. This dose was selected according to previous reports, and it was not associated with loss of conscience or psychomotor agitation (Sadove et al., 1971).

Electroacupuncture

The needles were inserted into acupuncture points, but small crocodile clips were then attached to the ends of needles to connect them to an electroacupuncture device. A qualified acupuncturist carried out 15 acupuncture sessions in total on each patient with one session every day. The duration of every session was 20 min with the patients sitting or recumbent comfortably in a bed located in a private room each. Acupuncture needles of 30 mm size were used. The needles were inserted into the specific points on the surface of the skin (10–30 mm depth in the electroacupuncture group and a *De Qi* sensation was ensured in this group (Fig. 2).

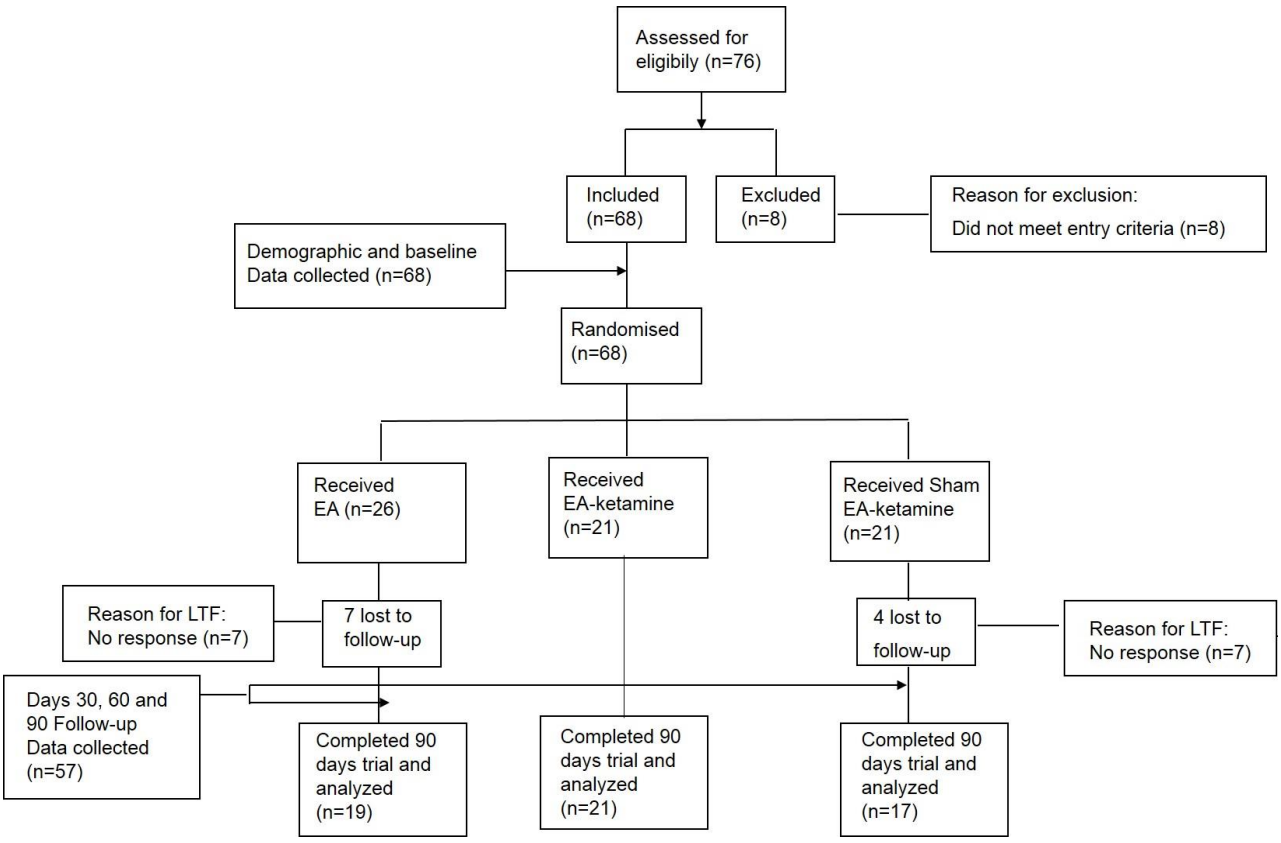

Figure 1. Flow of the patients through the trial.

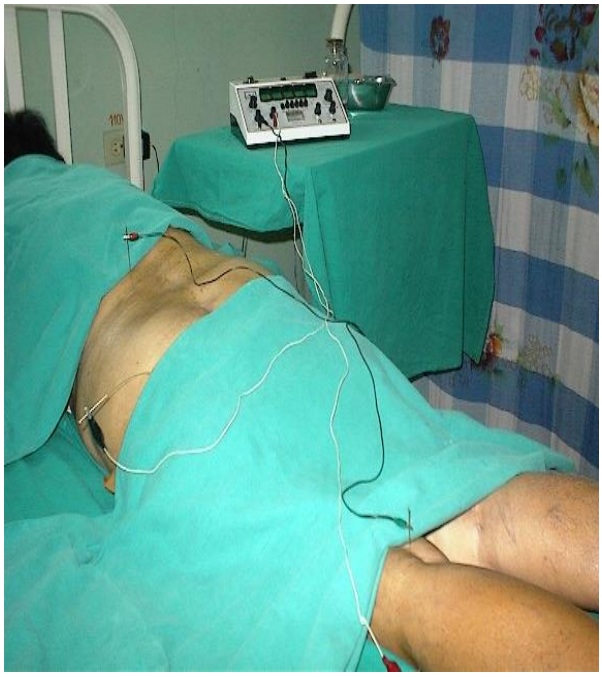

Figure 2. Patient under EA treatment protocol utilized in this study. In this case, 30th and 34th acupoints on the gallbladder meridian (GB30 and GB34), as well as 25th and 40th acupoints on the urinary bladder meridian (BL25 and BL40) were utilized.

Pain Clinic of 10 de Octubre Hospital. Photo: BB Garrido-Suárez.

The Gran Muralla KWD-808 II electrostimulator (10 Hz, 0.5 ms for 20 minutes) was used with the maximum tolerable intensity of current (2-3 mA). The points were selected according to topographic criteria of the Traditional Chinese Medicine meridian theory to treat regional pain (according to affected dermatomes) (Ahsin et al., 2009).

Sham electroacupuncture

Sham EA was administered with the same duration and frequency and by the same specialist who performed the genuine EA. The needles located into small adhesive cylinders were placed without perforating the skin (Ashin et al., 2009). The acupuncturist placed the needles at the same points as the genuine group and used the same pairs of electrodes to simulate the electrical connection. Patients were told that they may or may not feel an electrical current sensation in order to achieve a blind trial.

Statistical analysis

Data were analyzed using the statistical program Graph Pad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA). The difference between the mean of each outcome during five visits was evaluated. Pre-treatment means of outcome were compared to post-treatment means at 15, 30, 60, and 90 days with the non-parametric Friedman test followed by Dunn's or one-way analysis of variance test followed by Bonferroni's multiple comparison tests according to the sample size per groups. The Chi-square test was used to check the discrete variables, presented in proportion. The results are expressed as mean ± standard error of the mean (SEM). Values of $p<0.05$ were considered statistically significant.

RESULTS

Participants

In this study, 76 patients were screened, and eight patients that did not meet the inclusion criteria were excluded. Eligible 68 patients were randomly allocated to three groups: a group of EA (n=26), EA plus ketamine (n=21), and sham EA plus ketamine (n=21). During the first weeks of the study, a total of 11 (16.17%) patients withdrew from the trial (Fig. 1). The EA treatment group (7, 26.92%) had more discontinuations (due to no response) than the sham EA-ketamine treatment group (4, 19.04%). No withdrawal of patients was observed in EA-ketamine group. No statistically significant differences were found in the baseline demographic and clinical characteristics of the randomized treatment groups, as shown in Table 1.

Therapeutic effects

At the end of 15 sessions exclusivity the patients treated with the combination EA-ketamine reduced significantly ($p<0.001$) the ADPS concerning baseline data, this effect was increased ($p<0.001$) until the last evaluation at 90 days. Similarly, the ADPS in both, EA and sham-ketamine groups were reduced but from 60 days until 90 days ($p<0.001$) concerning baseline data. Through the trial, the EA-ketamine group was more efficient to reduce this outcome compared with EA group ($p<0.001$) and sham-ketamine ($p<0.05$) (Table 2 and Fig.3).

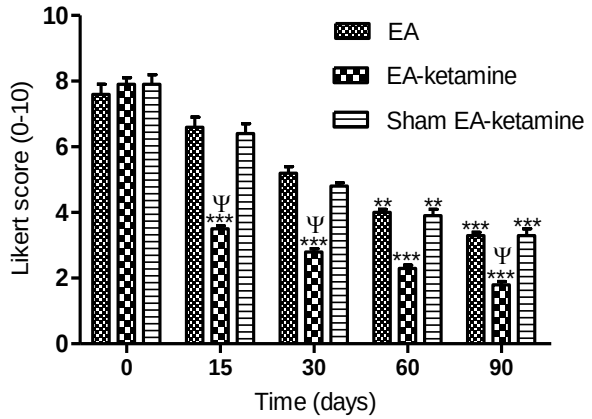

Figure 3. Change in average daily pain score (ADPS) in post-herpetic neuralgia (PHN) patients treated with electroacupuncture (EA, 10 Hz, 2-3 mA, 0.5 ms, 20 min/15 sessions) alone, a combination EA-ketamine (0.25-0.5 mg/kg, i.m.) or with sham EA-ketamine for 15 days.

The results are presented as mean ± SEM. *p<0.05, **p<0.01, ***p<0.001 indicates significant differences with respect to baseline valor. Ψ indicates significant differences between groups.

The area of dynamic mechanical allodynia significantly decreased concerning baseline data from 60 days in EA-ketamine patients (p<0.01), this effect was increased at 90 days (p<0.001) (Fig. 4A). There was also a significant reduction in the allodynic areas in other groups at the end of study (p<0.001). As shown in Fig. 4B-C, the rate of dynamic and rate of thermal allodynia showed significant reduction through the study in all groups compared with its initial values. However, the combined group patients significantly improved mechanical allodynia rate from 30 days concerning other groups (p<0.05). The frequency of intermittent spontaneous lancinating pain significantly decreased (p<0.01) within the first month of treatment only in the combined group concerning baseline values. This effect also increased (p<0.05) during subsequent weeks as well observed in other groups (Fig. 4D). Patients receiving EA plus ketamine had significantly better results in all outcomes.

Concomitant treatments and adverse effects

As shown in Table 2 during the study, all patients treated only with EA required other 15 EA sessions after the first treatment. Also, 7 (33.3%) patients treated with sham EA-ketamine required the introduction of minor opioid or antiepileptic's drugs (p<0.001). These concomitant medications were maintained until the end of the study. Likewise, the rescue dosages of minor analgesics were further in sham EA-ketamine group compared with EA (70.6%, *vs.* 31.6%, p<0.001). Patients receiving EA plus ketamine did not use other medication. The incidence of adverse effects was low through the study. Nevertheless, adverse effects were observed in eight patients enrolled in sham EA-ketamine group, which also required mainly opioid medication with codeine. Principally, nausea, vomiting, constipation, and sedation were observed even though these patients completed the study.

DISCUSSION

Previous studies using quantitative testing of primary afferent function, skin biopsies, and controlled treatment trials have recognized that the heterogeneous mechanisms of neural dysfunction observed in PHN patients span a spectrum (Fields et al., 1998). However, both peripheral and central pathophysiological mechanisms contribute to PHN pain (Petersen and Rowbotham, 2010). Some patients have abnormal sensitization of unmyelinated cutaneous nociceptors (irritable nociceptors). Such patients characteristically have a minimal sensory loss (Fields et al., 1998; Johnson and Rice, 2014). This phenotype is characterized as having normal thermal detection thresholds and at least one sign suggestive of hypersensitivity in the painful area (dynamic mechanical allodynia, allodynia to mechanical, warm, or cold stimuli, or hyperalgesia to mechanical stimuli) (Petersen and Rowbotham 2010). Some types of mechanism may coexist in different skin regions in the same patient (Johnson and Rice 2014). In the present study, the sample was constituted by preponderantly irritable nociceptor patients, finding homogeneity for a more realistic therapeutic approach focused mainly on clinical phenotypes (Attal and Bouhassira 2015). In this condition, the spontaneous activity induced by axonal damage along the primary afferent as well as the upregulation of excitatory adrenergic receptors and neuroinflammation have been proposed as generating-mechanisms (Fields et al., 1998). The distal portion of injured nerve undergoes degeneration, exposing the surviving nerve fibers from an uninjured portion of the nerve a milieu of cytokines and growth factors, which produce peripheral sensitization (Berger et al., 2011). These fibers develop spontaneous activity (ectopic discharge) and increased sensitivity to chemical, thermal, and me-

chanical stimuli (Fields et al., 1998). Afterward, abnormal nociceptor function provides sufficient ongoing input to generate and maintain central sensitization (Berger et al., 2011). Then considering that the better-characterized mechanism of EA analgesia is the activation of the endogenous descending modulatory system, patients with a preserved, although hypersensitive, somatosensory system could provide a responder population for this trial. EA's analgesic effect occurs via the central release of endogenous opioids (Han, 2003), which exert inhibitory actions on excitatory transmissions in spinal dorsal horn neurons (Minami and Satoh, 1995).

Table 1. Demographic and clinical characteristics of patients with post-herpetic neuralgia at baseline.

Parameter	EA-group	EA-ketamine-group	Sham-ketamine-group	p
Age (years)	77.65 ± 1.6	75.81 ± 1.9	73.48 ± 1.3	NS
Women, n (%)	11 (42.3%)	12 (57.1%)	11 (52.4%)	NS
Men, n (%)	15 (57.7%)	9 (42.8%)	10 (47.6%)	NS
Time since symptom onset (days)	4.0 ± 0.2	4.0 ± 0.2	3.9 ± 0.2	NS
ADPS (Likert scale)	7.8 ± 0.4	8.0 ± 0.3	7.5 ± 0.3	NS
Area of affected dermatomes, n (%)				
Cervical	4 (15.4%)	1 (4.8%)	2 (9.5%)	NS
Dorsal	17 (65.4%)	14 (66.7%)	13 (61.9%)	NS
Lumbar-sacral	5 (19.2%)	6 (28.6%)	6 (28.6%)	NS
Trigeminal nerve	0 (%)	0 (%)	0 (%)	NS
Treatment at Inclusion, n (%)				
Amitriptyline	12 (46.1%)	12 (54.5%)	10 (47.6%)	NS
Dipyrone	26 (100%)	21 (100%)	21 (100%)	NS
Nerve blocks	5 (19.2%)	3 (13.6%)	3 (14.3%)	NS

ADPS: average daily pain score. Post-herpetic neuralgia (PHN). PHN defined as pain that persists 120 days or more after rash onset.

Table 2. Clinical characteristics of patients, concomitant treatments and adverse effects at the end of the study.

Parameter	EA-group			EA-ketamine-group			Sham-EA-group			Among groups
	Baseline	90 days	p	Baseline	90 days	p	Baseline	90 days	p	p
ADPS	7.8 ± 0.4	3.3 ± 0.1	<0.001	7.9 ± 0.2	1.8 ± 0.1	<0.001	7.9 ± 0.3	3.3 ± 0.2	<0.001	<0.001
Mechanical allodynia	7.6 ± 0.2	3.5 ± 0.2	<0.001	6.8 ± 0.2	1.8 ± 0.1	<0.001	7.6 ± 0.3	3.4 ± 0.1	<0.001	
Thermal allodynia	7.8 ± 0.3	3.2 ± 0.1	<0.001	6.6 ± 0.2	1.7 ± 0.1	<0.001	7.2 ± 0.3	3.1 ± 0.1	<0.001	
Spontaneous lancinating pain	5.6 ± 0.4	0.8 ± 0.2	<0.001	6.9 ± 0.5	0.2 ± 0.1	<0.001	6.4 ± 0.2	1.5 ± 0.2	<0.01	
Other 15 sessions	-	19 (100%)		-	0 (%)			-		<0.001
Opioid analgesics or anticonvulsant	-	0 (%)		-	0 (%)			7 (33.3%)		<0.001
Analgesic rescue dosages	-	6 (31.6%)		-	0 (%)			12 (70.6%)		<0.001
Adverse effects	-	0 (%)			0 (%)			8 (47.0%)		<0.001

ADPS: average daily pain score. The results are presented as mean ± SEM. *p <0.01 and **p<0.001 indicate significant differences with respect to baseline valor of their respective group or among groups as shows the column at right. Friedman test followed by Dunn's or one-way analysis of variance test followed by Bonferroni's multiple comparison tests. The Chi-square test was used to check the discrete variables, presented in proportion.

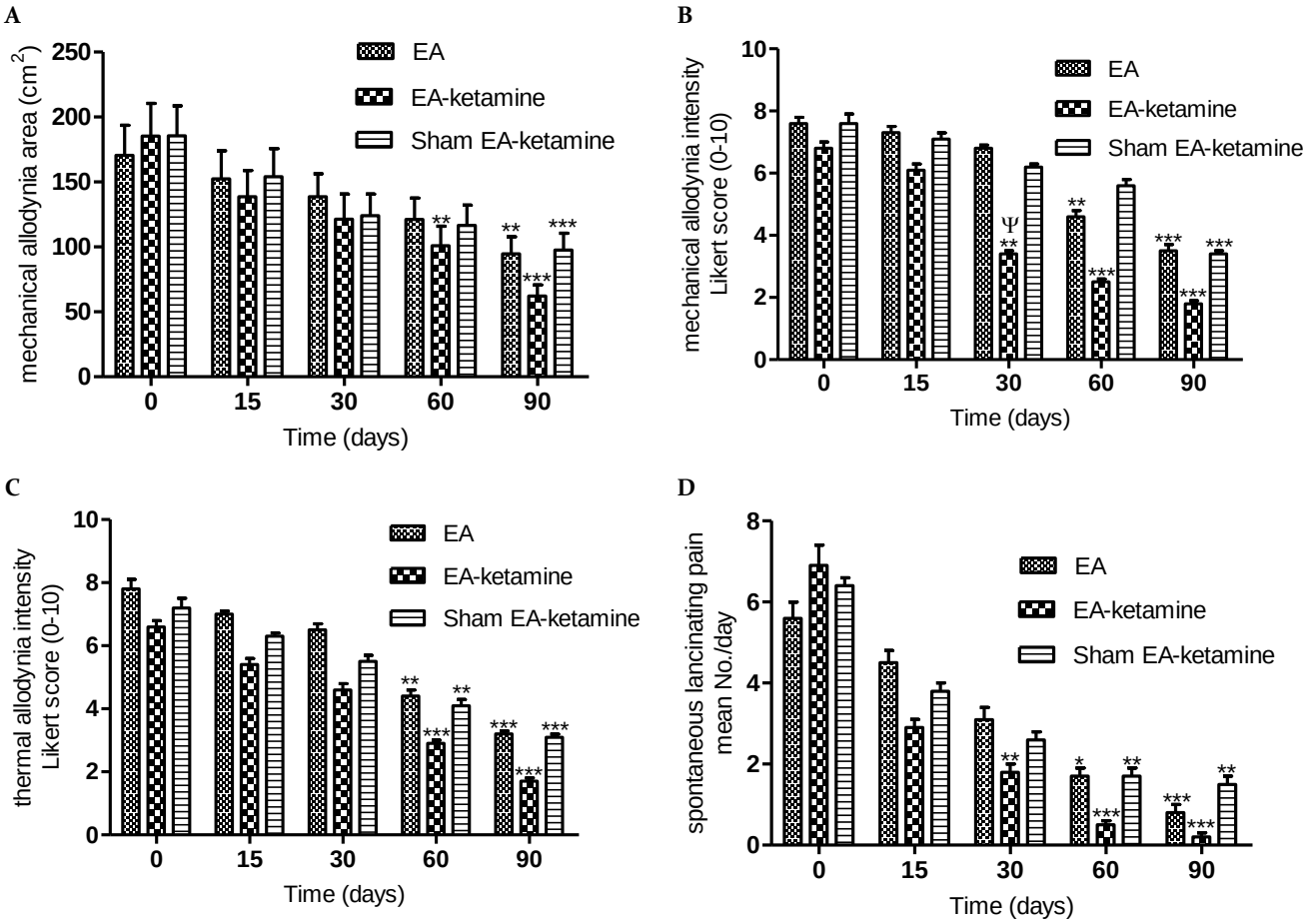

Figure 4. Change in area of dynamic mechanical allodynia **(A)**, mechanical allodynia **(B)**, thermal allodynia **(C)** intensities and spontaneous lancinating pain frequency **(D)** in post-herpetic neuralgia (PHN) patients treated with electroacupuncture (EA, 10 Hz, 2-3 mA, 0.5 ms, 20 min/15 sessions) alone, a combination EA-ketamine (0.25-0.5 mg/kg, i.m.) or with sham EA-ketamine for 15 days.

The results are presented as mean ± SEM. *p <0.05, ** p <0.01, *** p <0.001 indicate significant differences with respect to baseline valor. Ψ indicates significant differences between groups.

The opioid signaling decreases the release of excitatory neuropeptides/neurotransmitters, like substance P (SP) and glutamate respectively from the presynaptic terminals, causing an effect similar to calcium-channel $\alpha_2\delta$ binding drugs (gabapentin or pregabalin), which also reduces the release of presynaptic transmitters (Taylor, 2009). Also, EA produces an inhibition of the excitatory transmission in spinal postsynaptic dorsal horn neurons. Studies have shown that EA inhibits a tooth pulp stimulation-evoked release of SP and reduces electrophysiological spinal neuron response to noxious stimuli (Yonehara et al., 1992). Other authors demonstrate that this procedure selectively inhibits centrally mediated pain via suppressing central sensitization (Kim et al., 2009). EA suppress the expression of spinal neurokinin-1 (NK-1)/SP and ionotropic glutamate receptors, NMDA (NR-1, NR-2A) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA/Glu-R1) in inflammatory hyperalgesia models (Choi et al., 2005b; Zhang et al., 2005a). Several pre-clinical data showed the synergistic anti-hyperalgesic effect of EA combined with a sub-effective dose of MK-801, an NMDA antagonist in chronic inflammatory conditions (Zhang et al., 2005b). The functional potentiation between other glutamatergic antagonists (kynurenic acid, AP-5, DNQX) and EA in pathological conditions also are published (Zhang et al., 2002; 2003). Particularly in spinal nerve ligation, a neuropathic pain model, EA decreases mechanical allodynia in naloxone sensitive manner. Ketamine dose-dependently also inhibits allodynia, moreover, a sub-effective dose of ketamine potentiates the anti-allodynic effect of EA (Huang et al., 2004). Given that the interaction between ketamine and EA was similar to the one established between NMDA receptor

antagonists and exogenous opioids, this fact suggests a novel strategy using EA-ketamine to approach the opioid resistance in NP and decreases the side effects of drug therapy. The present clinical results are in agreement with this suggestion.

On the other hand, previous studies have demonstrated that healthy and pathological conditions respond differently to EA (Han, 2011). It has been demonstrated that EA anti-hyperalgesia is parameter-dependent, 10 Hz being more beneficial than 100 Hz in the long-term treatment of an inflammatory condition (Lao et al., 2004). Several studies have reported that the 2 Hz EA-induced long-term depression (LTD) in the spinal dorsal horn may be a potential mechanism for the analgesic effects of low-frequency EA on NP (Choi et al., 2005a; Xing et al., 2007). This effect depends on the induction of the NMDA receptor-dependent LTD via activation of the endogenous opioid peptides system. Therefore, the direction of the long-term synaptic plasticity like LTP or LTD in spinal dorsal horn might determine the development or avoidance of NP (Xing et al., 2007). Interestingly, spinal LTP, which might be induced by ectopic discharges plays an important role in the development and maintenance of central sensitization underlying in nociceptor irritable PHN patients, in the late stage (Latremoliere and Woolf 2009). Anti-allodynic effect of EA at low frequency (10 Hz) in this trial possibly could be explicated by this mechanism. Essentially because of its long-term effect observed at least 75 days after the completion of the treatment, since LTD of synaptic strength in the spinal dorsal horn may contribute to the long-lasting analgesic effects of EA at low frequency in NP conditions (Xing et al., 2007). According to a meta-analysis of patients with chronic pain, approximately 90% of the benefit of acupuncture relative to controls would be sustained about 12 months (McPherson et al., 2017). Thus, the present results are congruent with this evidence considering the extension of this study.

Allodynia is present in at least 70% of patients and is usually considered to be the most distressing and debilitating PHN (Johnson and Rice, 2014). The patients significantly decreased the affected area in this study suggesting a synergy between peripheral and central mechanisms by EA and particularly in EA-ketamine group. The area of allodynia tested in the present study clinically reflects the level of central sensitization depending on C-nociceptor input from the periphery, which results in Aβ-mediated dynamic allodynia (Woolf and Salter, 2000; Besson et al., 2005). The enlargement of nociceptive neuron receptive fields and convention of spinal nociceptive specific neurons into wide dynamic neurons that could respond to both noxious and innocuous stimuli have been involved in this phenomenon (Latremoliere and Woolf 2009). NMDA antagonists prevent and reverse the hyperexcitability of nociceptive neurons induced by nociceptor conditioning inputs (Latremoliere and Woolf 2009). In addition, the ability of EA to activates endogenous glial cell line-derived neurotrophic factor (GDNF)/GDNF family receptor α-1 (GFR-α1) system (Dong et al., 2005; 2006) could be implicated in this beneficial effect. Given that GDNF protects against multiple phenotypic changes induced by peripheral nerve injury, particularly by preventing A-fibre sprouting into lamina II and blocking spontaneous ectopic discharges in large-diameter myelinated Aβ afferent fibers (Bennett et al., 1998). However, the peripheral inhibition of dysfunctional nociceptors by EA or systemic ketamine could also be implicated in the effect (Duarte et al., 1990; Fields et al., 1998). By means of controlled treatment trials, nowadays it is recognized that nociceptor-selective-inactivating agents when topically applied, provide significant relief for some patients (Watson et al., 1993; Baron et al., 2009). The capsaicin an agonist for transient receptor potential vanilloid type 1 (TRPV1) ligand-gated cation channels, which can lead to excitation and subsequent desensitization of nociceptive afferents, are being evaluated as potential analgesics in the irritable nociceptor type (Watson et al., 1993). Its effect depends on preserved and possibly sensitized primary afferent nociceptors that remain connected to their peripheral and central targets. TRPV1 receptor signaling increases the excitability of terminal unmyelinated C fibers and in these conditions dramatically increases pain and enlarges the area of dynamical allodynia (Petersen and Rowbotham, 2010). Nowadays, a high expression of TRPV1 endowed with nitric oxide synthase (nNOS) in subepidermal nerve fibers in the acupoints has been demonstrated (Abraham et al., 2011). Its upregulation after EA stimulation may play a key role in mediating the transduction of EA signals to the central

nervous system, early a similar effect to capsaicin was suggested for acupuncture (Zijlstra et al., 2003). EA mediated analgesic effect by L-arginine-nitric oxide (NO)-cGMP pathway has been previously reported (Almeida et al., 2008; Garrido-Suárez et al., 2009). Also, EA increases endogenous opioid (β endorphin) expression in keratinocytes and infiltrating immune cells at the inflammatory site through cannabinoids (CB2) receptors activation (Su et al., 2011). In concordance with these findings, EA induces a functional regulation of the nociceptors in addition to its central modulatory mechanisms that may facilitate the beneficial results observed in this study.

Furthermore, there is growing recognition that spinal glia contributes to the development and maintenance of central sensitization in chronic pain (De Leo et al., 2006). Subsequently, neuroimmune activation and neuron-glial interaction propose new targets for therapeutic intervention in neuropathic pain. In several inflammatory and neuropathic pain models, the activation of microglia and astrocytes was inhibited significantly by EA treatment (Sun et al. 2006; 2007; Tu et al., 2015). Analgesic effect of EA may be achieved through the inhibition pro-inflammatory interleukin 1 *beta* (IL-1*β*), IL-6 and tumor necrosis factor *alpha* (TNFα) expression in spinal cord (Sun et al., 2007). Thermal allodynia also showed significant reduction through of the study. Previously, was reported that EA improves thermal and mechanical sensitivities in a rat model of PHN by attenuating resiniferatoxin induced damage to sensory neurons (Wu et al., 2013). Specially neurotrophin-3 (NT-3) has been involved in the prevention of the development and maintenance of thermal hyperalgesia in NP and EA is able to upregulate its expression in dorsal root ganglion and spinal cord of mononeuropathic rats (Tu et al., 2015).

Through this trial, the spontaneous pain was also decreased. However, the patients treated with the combined therapy showed better and early results. After nerve injury, the voltage-gated sodium channels (Na^+ channels) accumulate mainly in the axon at the injury site resulting in foci of hyperexcitability (Fields et al., 1998). Particularly expression of the Nav1.3 and Nav1.8 sodium channels is markedly increased after varicella zoster virus (VZV) infection (Garry et al., 2005). Also, the spinal cord hyperexcitable neuron and pathologic loss of its inhibition (disinhibition) can also lead to increased spontaneous pain (Latremoliere and Woolf, 2009). Systemic or topical lidocaine may reduce ectopic discharges through its sodium channel–blocking properties (Finnerup et al., 2015).

Different subjacent mechanisms are present in our patients with this type of PHN, and its favorable response could relate with the additive and synergistic interaction between EA and ketamine. Ketamine is a multimodal drug with several targets additional to the inhibition of NMDA receptors, it also interacts with opioid, monoaminergic, cholinergic systems and decreases sodium-and voltage-dependent calcium channels activity (Eide et al., 1995; Bell, 2009). Also, acupuncture analgesia is closely related to the activation of α_2 adrenergic and serotonin (5-HT1A) receptors in the spinal dorsal horn (Kim et al., 2005).

CONCLUSIONS

In summary, patients with PHN nociceptor irritable type that received the three therapeutic strategies (genuine EA alone, its combination with low doses of ketamine and ketamine with sham EA) improved significantly in terms of ADPS and sensory abnormalities. These benefits persisted for at least 75 days after the completion of treatment. The combination EA (10 Hz)-ketamine at low doses was superior compared with other groups, EA requires a major number of sessions but also was an efficient treatment. Adverse events were observed exclusivity in patients treated with sham EA-ketamine, which required the association with opioids and anticonvulsant drugs. These results suggest that EA and its combination with ketamine might be useful to treat PHN. Nevertheless, the small amount of data is a limitation of this study. Although previously discussed pre-clinical data supports its indication in this subgroup of patients, more controlled clinical evidence and translational studies are necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Special thanks to Jorge Conde Garrido for advice on the correct use of the English language.

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Concepts or ideas	X						
Design	X						
Definition of intellectual content	X						
Literature search	X		X				
Clinical studies	X			X	X	X	
Data acquisition	X			X	X	X	
Data analysis	X						
Statistical analysis	X						
Manuscript preparation	X	X					
Manuscript editing	X	X					
Manuscript review	X	X					X

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