Use of high-voltage cathodic current for pain in experimental nerve compression

Gladson Ricardo Flor Bertolini[1], Cassiane Merigo do Nascimento[2], Daniela Martins Cunha[2], Elisangela Lourdes Artifon[2], Anamaria Meireles[3]

ABSTRACT

Objective: To assess the effect of high-voltage cathodic current on pain from a sciatica experimental model. **Methods:** A total of 16 male Wistar rats were submitted to the sciatica experimental model in the right hind paw. They were divided into sham group (GS) and group treated with cathodic current (GP-) for 20 min/daily, for 10 days). The model of sciatic compression was performed with a 4.0-chromic catgut thread tie in four points of the sciatic nerve. Assessment of nociception was performed by measuring the time during which the animal held its hind paw in a guarded position (THHP) and the pressure withdrawal threshold, by use of a digital electronic analgesymeter. Data collection was carried out before the sciatica experimental model (AS1), three days after compression (before, AS2, and after treatment, AS3), and five and 10 days after treatment (AS4 and AS5, respectively). **Results:** According to the functional disability test, both groups showed an increase in nociception, with no reduction at any assessment time. Submitted to pressure, however, GS showed a reduction in the hind paw withdrawal threshold at all assessment times, while GP- showed a reduction in the hind paw withdrawal threshold only initially – at AS5, the threshold was restored. **Conclusion:** No change in nociception was observed on functional assessment; however, on pressure hind paw withdrawal assessment, the treatment with cathodic current showed to be effective with the summation of therapies.

Keywords: transcutaneous electric nerve stimulation, sciatic neuropathy, pain measurement.

INTRODUCTION

Patients with symptoms of low back pain report a substantial improvement in pain and function with either surgical or conservative treatment.[1] Sciatica, however, is an important factor of worse prognosis in such cases,[2] because it generates higher financial cost, in addition to greater disability for work and absenteeism at work.[3]

Sciatica can be defined as neuropathic pain originating from injury to the nervous system, caused by compression, *diabetes mellitus*, infection, trauma, and autoimmune diseases.[4] For some authors, the term refers only to radiculopathies. However, sciatica is widely known as the pain arising from the lower back, or along the nerve trajectory, and radiating down to the leg.[5] It is associated with paresthesia and possible neurological deficit, such as paresis and reflex alterations. The major cause of symptoms is an inflammatory reaction that results in nerve irritation or compression. The prevalence of symptoms varies in the literature from 1.6% to 46%, and that can be explained by differences in the definitions used, data collection methods, and populations studied. Disc herniation and lumbar or foraminal stenoses are typical diseases that cause sciatica; however, there are several other reasons, such as extraspinal tumors and cysts.[3] Awkward posture, exposure to whole body vibration, and long periods in a seated position have also been related to a higher risk for developing sciatica.[6]

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Laboratório de Estudo das Lesões e Recursos Fisioterapêuticos, Universidade Estadual do Oeste do Paraná – Unioeste.
1. PhD in Health Sciences Applied to the Musculoskeletal System, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo – FMRP-USP; Adjunct Professor, Universidade Estadual do Oeste do Paraná – Unioeste
2. Physical Therapist, Unioeste
3. Undergraduate student of Physical Therapy, Unioeste
Correspondence to: Gladson Ricardo Flor Bertolini. Rua Universitária, 2069 – Jardim Universitário. Colegiado de Fisioterapia. CEP: 85819-110. Caixa Postal: 711. Cascavel, PR, Brasil. E-mail: gladson_ricardo@yahoo.com.br

Treatments vary. Medicamentous therapy, although being the most commonly used treatment, has adverse side effects that jeopardize the risk/benefit ratio.[7] Non-surgical interventional therapies also exist, but few of them have shown to be effective.[8] In the short run, the surgical treatment is the most effective, but, on the long run, its benefits decrease.[9] Finally, there is the conservative, non-pharmacological treatment, which includes physical therapy modalities, whose risks are rare and evidence of efficacy is still insufficient.[10]

Thus, studies on the physical therapy modalities for the treatment of sciatica are necessary. The use of experimental animals has shown to be useful for the pre-clinical assessment of the nociception caused by nerve injuries,[11] such as the nerve compression model reported by Bennett and Xie,[12] which simulates sciatica findings.

One of the electrostimulation modalities used in clinical practice is high-voltage current. According to Davini et al.,[13] there is evidence that such therapy decreases pain and improves tissue repair. The high-voltage current can be described as pulsed, monophasic, double peak, high voltage (over 100 V), with pulse duration of 5–100 μs and high peak amplitude. Such characteristics provide a relatively pleasant stimulation, capable of reaching not only sensory and motor nerve fibers, but also those responsible for conducting nociceptive impulses. The high-voltage current finds application especially in cases of cutaneous ulcers and edema reduction, mainly with cathodic stimulation. Thus, the present study aimed at assessing, by using cathodic high-voltage current, the increase in nociception due to experimental sciatica.

MATERIALS AND METHODS

Experimental groups

This study assessed 16 male Wistar rats (*Rattus norvegicus*), whose mean weight was 376.80 ± 24.68 g, and mean age, 14 ± 2 weeks. The animals were maintained in polypropylene cages, submitted to light/dark cycles of 12 hours and temperature of 25 ± 1 ºC, and had free access to water and food during the entire experiment.

The animals were randomly divided into two groups:

- Sham group (GS, n = 8): submitted to sciatica in the right hind paw and placebo treatment;
- Group treated with cathodic current (GP-, n = 8): submitted to sciatica and treated with cathodic current in the surgical site.

The project was conducted according to the international guidelines of ethics in animal experimentation and approved by the Animal Experimentation Ethics Committee (protocol #0209) of the Universidade Estadual do Oeste do Paraná (Unioeste).

Table 1 shows the time sequence of the study.

Table 1
Times of the assessments and procedures performed in the study

	Study day	PO day	Type of assessment
AS1	1st day		THHP, pressure
Injury	1st day		
AS2	4th day	3rd PO	THHP, pressure
Treatment	4th day	3rd PO	3rd PO
AS3	4th day	3rd PO	THHP, pressure
AS4	8th day	7th PO	THHP, pressure
AS5	13th day	12th PO	THHP, pressure

AS: assessment; THHP: time during which the animal held its hind paw in a guarded position (functional disability test); PO: post-operative; pressure: assessment of the hind paw withdrawal threshold.

Experimental injury protocol

The animals were anesthetized with intraperitoneal xylazine (12 mg/kg) and ketamine (95 mg/kg), and, then, epilation was performed on the surgical site. An incision parallel to the fibers of the biceps femoris muscle of the right thigh was performed, thus exposing the sciatic nerve. In accordance with the model described by Bennett and Xie,[12] compression around the nerve was performed in four distinct points, with an approximate distance of 1 mm between them, by using chromic catgut 4.0, reproducing the symptoms of sciatica. Then, suture in layers was performed.

Functional disability test

The animals underwent the functional disability test, originally described by Tonussi and Ferreira.[14] Their nociception was assessed while they walked over a cylinder of 30-cm diameter, covered with a stainless steel net and rotating at 3 rpm, powered by an electric engine. The hind paws received metallic boots. The right boot conducted information from the right hind paw to a computer. The computer ran a program that measured the time during which the boot did not contact the cylinder while the animal walked over the cylinder for one minute. Thus, the time (in seconds) during which the right hind paw contacted the cylinder and the time during which the animal held its hind paw in a guarded

position (THHP) could be measured. The boot remained on the left hind paw, but provided no input to the computer, so that both limbs experienced the same sensations. Tonussi and Ferreira[14] have reported that, while walking over the cylinder for one minute, animals with no alterations usually hold their hind paw in a guarded position for approximately 10 seconds.

The experiment began after the third day of training, which consisted in walking over the cylinder. Data collection was initiated before surgery (first assessment, AS1). On the day following the end of training, the sciatica experimental model was performed, and functional disability test data were collected on the third post-operative day, before and after the first treatment (AS2 and ASV3, respectively), after the fifth day of treatment (AS4), and, finally, right after the tenth day of treatment (AS5). The assessments after therapy were performed 30 minutes after the animals recovered from anesthesia.

Assessment of the hind paw withdrawal threshold

Nociception was also assessed through the hind paw withdrawal threshold in response to a mechanical stimulus. The device used in the nociception test was the electronic pressure analgesymeter (Insight®). It consists in a transducer arm with a disposable polypropylene pointer (0.1-1.000-g variation), connected with an amplifying box, and measuring the pressure applied to the animal's surface.

The animals were contained manually, and the polypropylene pointer was perpendicularly applied to the nerve compression region, with gradual increase in pressure. As soon as the animal withdrew its right hind paw, the test was interrupted, and withdrawal threshold was recorded. Animal adaptation and training lasted three days. The assessments were always performed in THHP sequence.

Treatment protocol

Treatment was initiated on the third post-operative day, and performed daily, for 10 consecutive days, with 20-minute sessions. A high-voltage device (Neurodyn High Volt, IBRAMED®) was used, with calibration certificate valid for the study period.

For applying the high-voltage current specifically over the surgical incision, the animals were anesthetized and put in the left lateral decubitus position. Silicone-gum electrodes were positioned over the surgical incision site and the lumbar region of the animals. The area of the active electrode (surgical site) was 1 cm^2, and that of the passive electrode (lumbar region), 4 cm^2. The intensity of the current was increased until a muscle contraction was observed, being then reduced by 10% of such value, producing, thus, stimulation only at the sensitive level. The frequency used was 50 Hz.

Analysis of results

The normality of the results was analyzed by use of the Kolmogorov-Smirnov test. Because of their normality, they were expressed by use of descriptive statistics (mean and standard deviation) and analyzed by use of inferential statistics, with repeated measures analysis of variance, Tukey test for intragroup analysis, and non-paired *t* test for intergroup analysis. For both tests, the significance level adopted was $\alpha = 0.05$.

RESULTS

Functional disability test

The results were analyzed by comparing the pre-injury assessment with the post-injury assessment, and the post-injury assessment with the subsequent ones. In the GS, a significant increase in nociception was observed between the pre-injury assessment and all subsequent ones. No significant decrease was observed when comparing the assessment prior to the first treatment (AS2) and the subsequent ones (Figure 1).

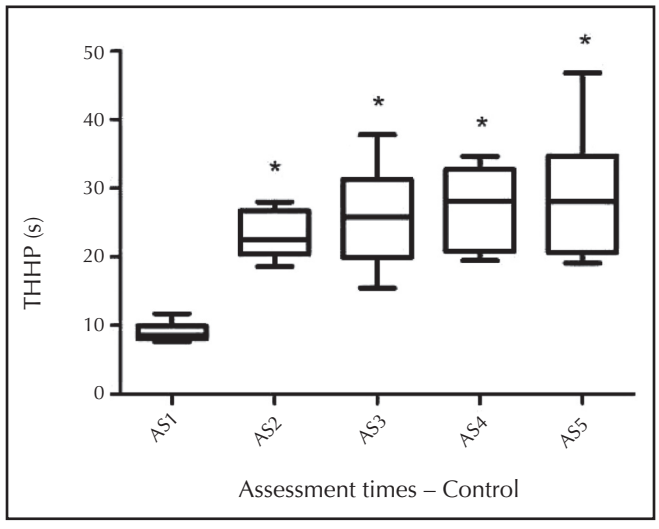

Figure 1
Assessment of the functional disability test for the sham group, with time during which the animal held its hind paw in a guarded position (THHP), according to the different assessment times (AS).
* Statistically significant variation as compared with AS1.

The functional disability test showed that the cathodic current produced no significant reduction in nociception. After AS1, no restoration of the values occurred. No significant decrease was observed when comparing AS2 (prior to first therapy) with the following assessments, nor when comparing AS2 with GS. Thus, functionality remained impaired by the increased nociception perceived by the animals due to experimental sciatica (Figure 2).

No significant variation was observed when comparing GS and GP- at the different assessing times.

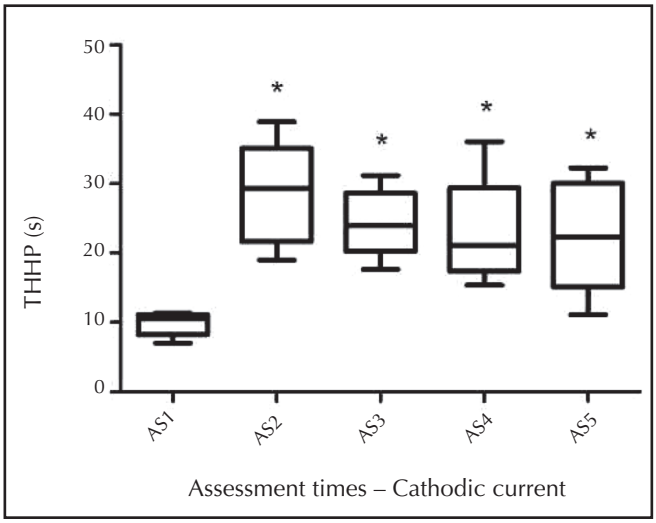

Figure 2
Assessment of the functional disability test for the cathodic current group, with time during which the animal held its hind paw in a guarded position (THHP), according to the different assessment times (AS).
* Statistically significant variation as compared with AS1.

Assessment of the hind paw withdrawal threshold

Assessment of the pressure nociceptive threshold showed a decrease in the hind paw withdrawal threshold for both groups – when comparing the pre-surgery values (AS1) with pre-treatment values on the third post-operative day (AS2) a significant reduction was observed, a fact that remained after the first therapy (AS3). However, GP- (Figure 3) showed recovery of the initial values in the assessments after the fifth and tenth therapies, which was not observed for GS (Figure 4), which continued statistically different as compared with AS1. In addition, in GP-, the AS5 significantly differed from AS2, showing a significant increase in the pressure nociceptive threshold. When GS and GP- were compared in the different assessment times, no significant difference was observed from AS1 to AS4, except for AS5.

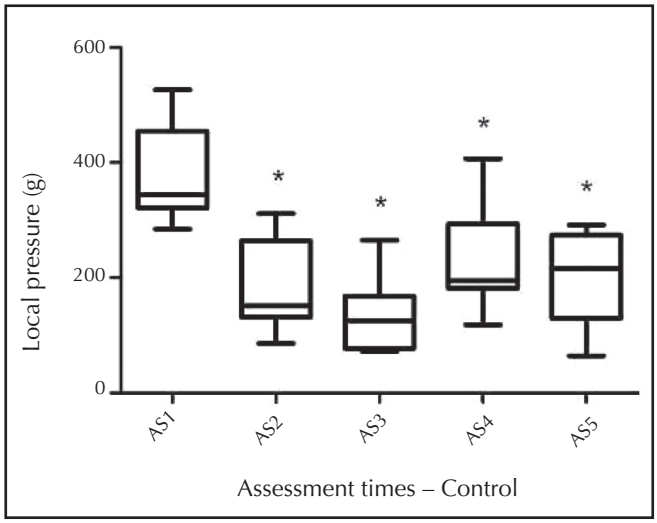

Figure 3
Assessment of pressure on the nerve compression region for the different assessment times (AS) of the sham group.
*Statistically significant variation as compared with AS1.

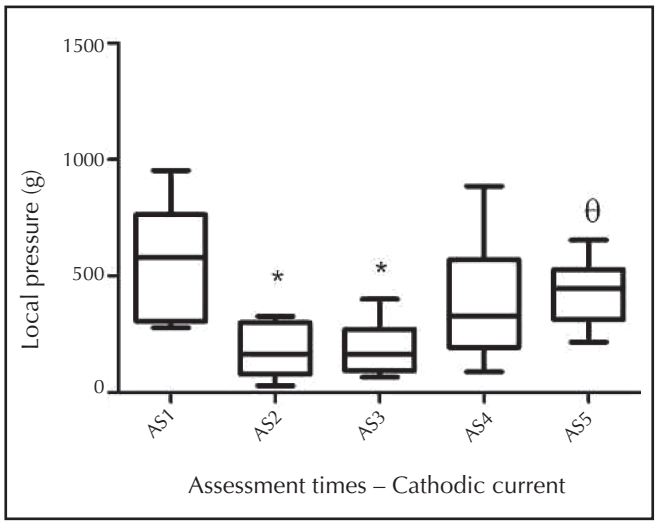

Figure 4
Assessment of pressure on the nerve compression region for the different assessment times (AS) of the cathodic current group.
* Statistically significant variation as compared with AS1.
θ Statistically significant variation as compared with AS2.

DISCUSSION

Considering that the sciatic nerve is the largest nerve of the human body, and is subjected to several types of injury, such as smashing, transection, stretch, and freezing, studies on treatment methods for its injuries are required. Experimental nerve compression models in rats are used due to its similarity

with the human nerve.[15] It is worth noting that experiments with animals, in addition to generating knowledge, can be reproducible, serving as a valuable source of information for general health – experiments with behavioral measures of neuropathic pain in animals have become increasingly common.[11] In this study, we chose the nerve compression model described by Bennett and Xie,[12] which reproduces the symptoms of sciatica, aiming at assessing the high-voltage current effect, by using the negative pole acting as the active pole (cathodic current), on the evolution of nociception with two different stimuli – one functional and the other by pressure. It is worth emphasizing that nociception is defined as "a response to stimuli potentially capable of tissue damage".[16] Thus, the nociception process is aimed at detecting present or potential damage stimuli.[17] According to Sandercock et al.,[18] changes in the mechanical nociceptive threshold can demonstrate primary hyperalgesia or its reduction, that is, the increase in the mechanical threshold can show a decrease in hyperalgesia findings.

The nociceptive system exists to concentrate attention on a harmful stimulus, initiate a flight response or suppress reflexes to allow for a better organized motor response. The painful stimulus is transmitted from the periphery to the spinal cord and brainstem via small myelinated Aδ fibers and unmyelinated C fibers. The first fibers recruited have high threshold, and the Aδ fibers transmit the "first pain", perceived as clearly localized and discriminated by its duration, proportional to the application of the painful stimulus. In case of more intense stimuli, the activation of polymodal nociceptors promotes an unpleasant and persistent diffusion of the painful sensation, with longer duration than that of acute pain and with a slight delay in its beginning. That "second pain" is associated with affective characteristics and motivational aspects, and might become prominent during the course of chronic pain.[16]

The assessments showed an increase in nociception on the third PO day in both groups, because the values of both the THHP and the pressure necessary for hind paw withdrawal significantly differed from their initial values. According to Bertolini et al.,[19] in animals undergoing the nerve compression model, the THHP values are greater than 10 seconds, considering that for animals without increased nociception values close to 10 seconds are expected.[14] This is in accordance with the findings of both groups in this study.

The functional disability test showed that the cathodic current produced no reduction in nociception. That is, the animals continued to limp because of the increase in nociception perceived by the animal due to experimental sciatica, indicating that THHP, although used in other studies to assess the neuropathic pain of the sciatic nerve,[19,20] has lower sensitivity to small variations, such as the local pressure assessment. Identical result was found when similar methodology of injury was used, but with treatment with anodic high-voltage current.[20]

According to Bennett and Xie,[12] the animals showed, after the sciatic nerve compression model, claudication of the paw submitted to surgery. Both humans and animals tend to show dysfunction when using the injured limb. Bennett[21] has reported that the increase in nociception in animals begins from the second PO day onwards, reaching its maximum around the 10th to 14th day. Thus, in the present study, nociception and the effect of treatment were assessed from the third PO day onwards, encompassing a period in which, according to the literature, a reduction in the nociceptive threshold occurs. Such alterations were assessed in this study, and directly reflected on the contact of the paw with the ground observed in the tests before and after surgery.

Both groups showed a decrease in the pressure nociceptive threshold. Such decrease was maintained in the GS, while in the GP-, the values significantly increased after the fifth and tenth therapies. That indicated that, if no restoration of the values occurred, at least the threshold that was low on the third PO day increased as compared with the values of the eighth and 13th PO days. That difference between the groups was evident when comparing both in the AS5, because GP- showed a higher nociceptive threshold, indicating, thus, a summation analgesic effect of the current. It is worth noting that the animals were assessed only after recovering from anesthesia, and no analgesia was observed after the first therapy, requiring, thus, summation of therapies. Thus, probable analgesic effects, such as the floodgate theory or nerve conduction block, can be ruled out as the cause of the nociception reduction found in this study.[22]

Several studies have reported positive effects of the high-voltage current when used with cathodic current stimulation.[23–27] The present study aimed at assessing the use of that current on the nociception of animals submitted to experimental sciatica, both with functional assessment and local pressure assessment.

According to Davini et al.,[13] there is evidence that the high-voltage current can reduce pain. However, further studies are required regarding the use of high-voltage current in cases of sciatica, experimental or clinical, and even regarding analgesia in experimental models.

Stralka et al.,[28] using high voltage in individuals with repetitive strain injury, have reported, in addition to edema

reduction and strength gain, pain reduction. However, Holcomb et al.,[29] using cathodic high-voltage current to inhibit the painful stimulus of neuromuscular electrostimulation, providing, thus, greater intensity of current and, consequently, greater muscle torque, have not observed facilitation of the neuromuscular response. It is worth noting that those authors assessed healthy individuals, who had no pain-inducing disease, because what they wanted was to alter the threshold of pain perception. The occurrence of probable anti-inflammatory effects of the current, such as an increase in lymphatic flow,[30] a reduction in edema,[23–27] and acceleration in tissue repair, can be infered.[31] Such effects might have aided in removing pain-producing substances and in reducing stasis, favoring a possible analgesic effect of the current, although insufficient to improve a functional test, such as THHP.

Regarding the technical limitations of the present study, neither histological nor electrophysiological parameters, which would deepen the responses about the effect mechanisms, were assessed. This is a suggestion for future studies. In addition, electrostimulation with high-voltage current should be compared with other forms already established for sciatica treatment, such as non-steroidal anti-inflammatory drugs.

CONCLUSION

In conclusion, based on the results obtained and the methodology used, no reduction in nociception, favoring the animal's function, was observed. However, the pressure nociceptive threshold was significantly reduced after five and 10 days of therapy.

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