



RESEARCH ARTICLE

LONG TERM EFFECTS OF ALLANTOIN ON PERIPHERAL NERVE HEALING: AN ELECTROPHYSIOLOGICAL STUDY

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Abstract

Background: Peripheral nerve injuries are a common health problem resulting in a decreased quality of life. Treatment of peripheral nerve injuries is complex and depends on location, intensity, and type of nerve injury. Allantoin is an antioxidant found in plants that enhance wound healing. It promotes the proliferation of cells by improving peripheral nerve function. This study aimed to investigate the long term effects of intraperitoneal (i.p.) administration of allantoin on peripheral nerve healing in an experimental sciatic nerve crush in a rat model.

Materials and Methods: Twenty male Wistar albino rats were randomly divided into four groups. Control (Cont) Group did not receive any special protocol for 60 days. Crush (Cr) Group was induced to crush. Allantoin (A) Group received 10 mg/kg of allantoin i.p. for 60 days. Crush + Allantoin (Cr+A) Group was induced to crush and given 10 mg/kg of allantoin i.p. for 60 days. After 60 days all rats were sacrificed following electromyography (EMG).

Results: Allantoin was revealed to enhance the peripheral nerve function in terms of amplitude and latency.

Conclusion: The i.p. administration of allantoin may have a positive effect on peripheral nerve healing.

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Introduction:-

Peripheral nerve injuries are a common health problem (Hussain et al., 2020). Crush injuries can result in a variety of levels of neurological damage. Peripheral nerve injuries are frequently resulting in a decreased quality of life (Menorca, Fussell, & Elfar, 2013). The majority of peripheral nerve injuries are caused by a combination of factors. Thorough knowledge of how peripheral nerves respond to damage could help researchers fully understand peripheral nerve healing (Mead, 2020). Treatment of peripheral nerve injuries is complex and depends on location, intensity, and type of nerve injury (Hussain et al., 2020). Treatments that guarantee full functional recovery are rare and tough to obtain (Menorca et al., 2013). The use of intraoperative electrophysiological assessment as a technique in the treatment has been widely recognized. EMG equipment and two electrodes are used for the electrophysiological evaluation (Martins, Bastos, Siqueira, Heise, & Teixeira, 2013).

Allantoin is a purine byproduct present in the plant's herbal extract as well as most animals' urine. Allantoin is a well-known and safe wound healing agent that promotes the development of new tissue (Ünsal, Bayram, Akay, & Yaşar, 2021). Allantoin has the molecular formula C₄H₆N₄O₃ as shown in Figure 1 and is also known as 5-

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ureidohydantoin or glyoxyldiureide. Wound healing is a physiological process that allows injured tissues to be repaired. Allantoin has a variety of pharmacological effects, including wound healing, cell mitotic stimulation, and epithelial stimulation promoter. It has been utilized as a wound healing enhancer for many years (Araújo, Grabe-Guimarães, Mosqueira, Carneiro, & Silva-Barcellos, 2010). Since allantoin exhibits antioxidant properties, it has also been used in cosmetics and topical medicinal preparations to treat skin conditions (Selamoglu, Dugun, Akgul, & Gulhan, 2017). Allantoin is a safe treatment that promotes cell division and epithelial tissue formation while accelerating the healing of damaged skin (Elzbieta, 2012).

In the present study, we hypothesized that long term i.p. administration of allantoin may have a beneficial effect on peripheral nerve healing due to its tissue-repair properties. In this study, we investigated the long term effects of i.p. administration of allantoin on peripheral nerve healing in an experimental sciatic nerve crush in a rat model.

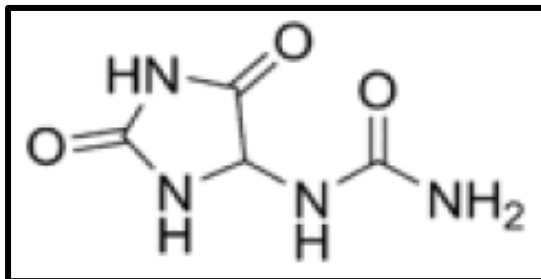


Figure 1:- Allantoin structure, 5-ureidohydantoin (Araújo et al., 2010).

Materials and Methods:-

Animals

In the present study, 20 male Wistar albino rats aged 10 ± 2 weeks (weighing 200 ± 50 g) were obtained from the animal and experimental research center, Ondokuz Mayıs University (OMU), Samsun, Turkey. The experimental research was approved by the Ethical Committee of Ondokuz Mayıs University (OMU) under the project of long term effects of allantoin on peripheral nerve healing (number 36).

Rats were randomly divided into four groups. Each group consisted of five animals. Control (Cont) Group did not receive any special protocol for 60 days. Crush (Cr) Group was induced to crush. Allantoin (A) Group received 10 mg/kg of allantoin i.p. for 60 days. Crush + Allantoin (Cr+A) Group was induced to crush and given 10 mg/kg of allantoin i.p. for 60 days. After 60 days all rats were sacrificed.

Surgical Procedures

The surgical procedure in the study was carried out at the animal and experimental research center, Ondokuz Mayıs University (OMU), Samsun, Turkey. The rats of the crush groups were anesthetized with a mixture of ketamine and xylazine 0.1 mg/kg - 0.4 mg/kg i.p. The surgical procedure was performed on the right hind limb. The area over the right hind limb was shaved and sterilized. A small incision was made to the skin of the shaved area and the right sciatic nerve was exposed in the gluteal muscle. The nerve was crushed with hemostatic forceps for 5 seconds of 50 Newton pressure. Then the incised site was sutured and sterilized.

Electrophysiological analysis

The electrophysiological analysis was done by using EMG before sacrifice. The rats were anesthetized and the area over the right hind limb was shaved and sterilized. An incision was made to the skin and the right sciatic nerve was exposed. A needle wire was placed 10 mm distal from the sciatic notch, and two monopolar electrodes were placed on the gastrocnemius rim at a distance of 2.5 cm from the needle wire. The compound muscle action potential (CMAP) was then measured on the gastrocnemius by stimulating a voltage between 0.01 mV and 10 mV.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21. One-way analysis of variance (ANOVA) and Tukey's post hoc test for statistical differences was used. Data are presented as mean \pm SD, and a P value of less than 0.05 was considered statistically significant.

Results:-

Electrophysiological Results

CMAP Latency

The comparison of mean latency values is shown in Table 1 and Figure 2. There was a highly significant difference between Cont and Cr groups ($p < 0.01$). There was a highly significant difference between Cont and Cr+A groups ($p < 0.01$). There was a highly significant difference between Cr and A groups ($p < 0.01$). There was a highly significant difference between Cr and Cr+A groups ($p < 0.01$). There was a highly significant difference between the A and Cr+A groups ($p < 0.01$). A significant difference was not found between Cont and A.

Table 1:- Shows the mean of latency (SD, standard deviation and CV, coefficient of variation).

Group	Latency (s) (Mean \pm SD)	CV
Cont	0.53 \pm 0.04	0.07
Cr	4.18 \pm 0.41	0.08
A	0.5 \pm 0.03	0.06
Cr+A	3.606 \pm 0.45	0.11

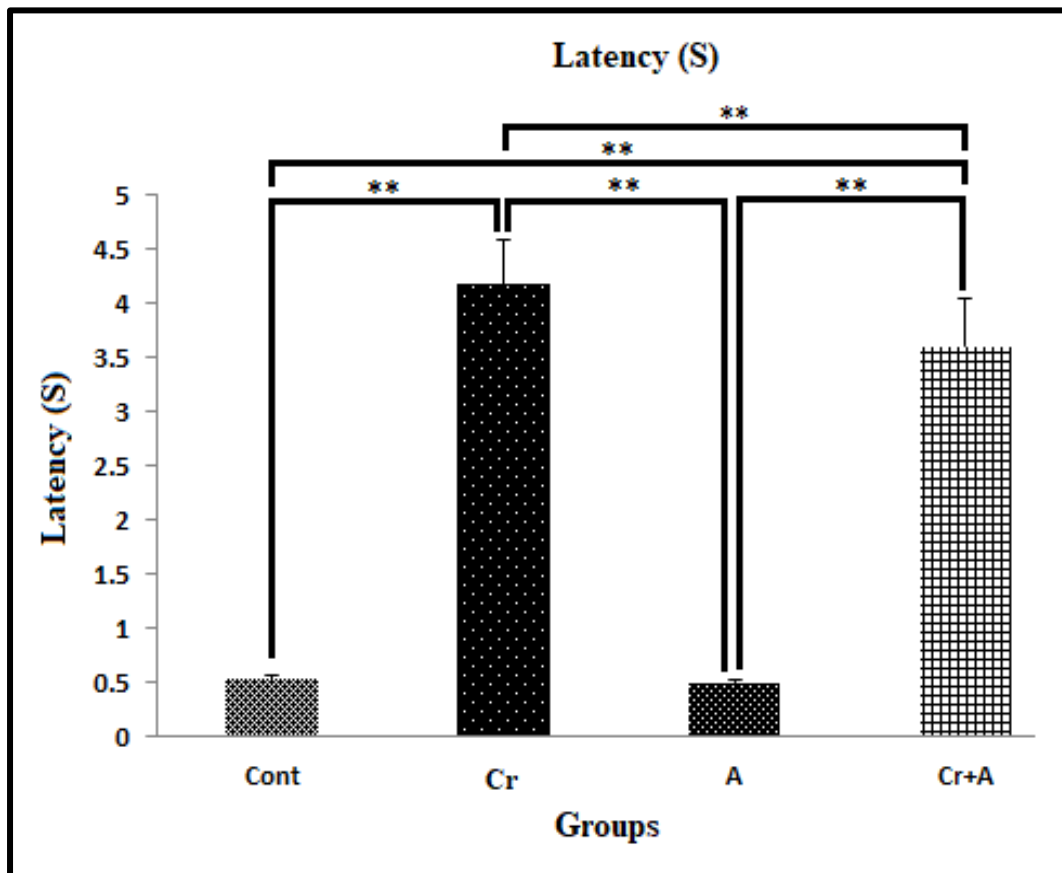


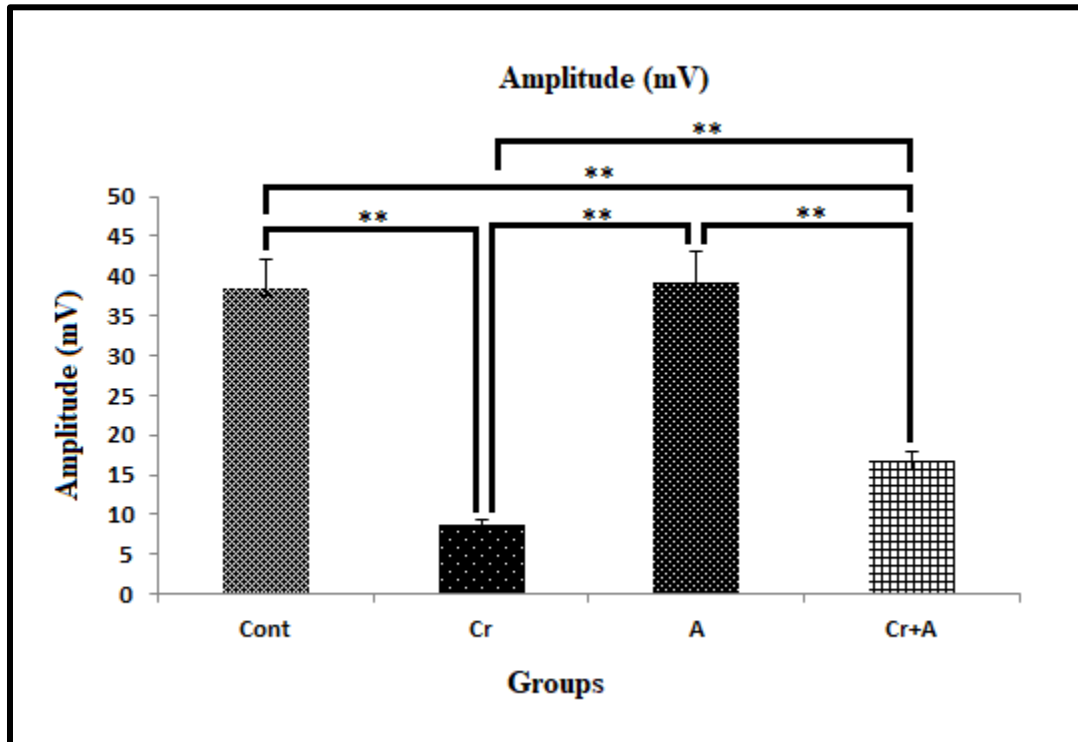
Figure 2:- Latency values between groups. Significant differences at $p < 0.01$ are shown by (**).

Amplitude

The comparison of mean latency values is shown in Table 2 and Figure 3. A highly significant difference was observed between Cont and Cr groups ($p < 0.01$). A highly significant difference was also observed between Cont and Cr+A groups ($p < 0.01$). There was a highly significant difference between Cr and A groups ($p < 0.01$). There was a highly significant difference between Cr and Cr+A groups ($p < 0.01$). There was a highly significant difference between the A and Cr+A groups ($p < 0.01$). Similar to latency, a significant difference was not found between Cont and A.

Table 2:- Shows the mean of amplitude (SD, standard deviation and CV, coefficient of variation).

Group	Latency (mV) (Mean \pm SD)	CV
Cont	38.516 \pm 3.52	0.08
Cr	8.653 \pm 0.73	0.07
A	39.17 \pm 3.94	0.09
Cr+A	16.762 \pm 1.25	0.06

**Figure 3:-** Amplitude values between groups. Significant differences at $p < 0.01$ are shown by (**).

Discussion:-

The peripheral nerves are affected by many different conditions (Chung, Prasad, & Lloyd, 2014). Since peripheral nerve injuries are frequent, electrophysiological analysis is important for assessing nerve injury (Elfayoumy, Elgendy, Saad, & Labib, 2020). In the present study, electrophysiological analysis of CMAP including latency and amplitude was measured. Latency was significantly higher in Cr and Cr+A groups and was lower in Cont and A groups. The amplitude was significantly higher in Cont and A groups and was lower in Cr and Cr+A groups. The Cr+A group showed improvement in both latency and amplitude if compared to the Cr group. These results indicate that myelination of the nerves was significantly improved in rats administered with allantoin. Kahraman and Kahveci (2015) investigated the effect of allantoin on peripheral nerve injuries in a rat model and found that allantoin has a positive effect on wound healing (Kahraman & Kahveci, 2015).

Delibas, Kuruoglu, Bereket, and Onger (2021) reported that allantoin was found to be effective in peripheral nerve healing. The authors proved that i.p. administration of 10 mg/kg of allantoin can accelerate peripheral nerve healing after crush injury (Delibas, Kuruoglu, Bereket, & Onger, 2021). N S, Mohamad, and Razdan (2019) found that latency and amplitude were restored in allantoin-treated rats (N S, Mohamad, & Razdan, 2019). Similarly, in the present study, allantoin showed improvement of latency and amplitude in the Cr+A group, this can be attributed to the positive effects of allantoin on the peripheral nerve healing after crush.

Conclusion:-

This study evaluated the effect of allantoin on peripheral nerve healing after sciatic nerve injury in rats by using electrophysiological methods. The results showed that allantoin has a positive effect on peripheral nerve healing

after sciatic nerve injury and enhanced peripheral nerve regeneration. The effect is based on electrophysiological data. More studies are needed to make clear the long term effects of allantoin on peripheral nerve injury.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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