# Complications and therapeutic approaches in a sciatic nerve injury rat model

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**Abstract**
Sciatic nerve injury (SNI) is a common model for studying peripheral nerve damage and regeneration. This study investigates the complications associated with acute nerve injury (ANI) by laceration of sciatic nerve in rats including infection, edema, and cannibalism, and evaluates the effectiveness of therapeutic interventions to modulate the observed complications. For this purpose eighteen female wistar albino rats were divided into three groups: control, sham-operated, and ANI. The ANI model induced with dissection and repair of the right sciatic nerve. Post-surgical care included the administration of diclofenac sodium for pain management. Observations were made for signs of infection, edema, hematoma, and survival rates within 10 days. The ANI group showed significant complications, including a 41.6% incidence of symptoms of pain (paraesthesia, allodynia, hyperalgesia, decreased activity, piloerection, excessive licking, un-groomed appearance) within 3 days, which increased to 60% by day 5. Edema was observed in 8.3% of the ANI rats, and 33.3% developed hematomas. Cannibalism rates also increased, particularly within 10 days post-injury. Survival rates in the ANI group decreased to 16.6% by day 10, indicating severe post-operative complications. The current study highlights the critical complications associated with ANI in rats, particularly the high rates of pain related symptoms (i.e. paresthesia and cannibalism). These findings suggest the need for improved post-operative care and highlight the importance of therapeutic interventions like opioid analgesics to mitigate these complications and enhance recovery outcomes in peripheral nerve injury models.

***Keywords:*** *Complications, laboratory animal models, sciatic nerve injury, survival*

## *INTRODUCTION*

Sciatic nerve injury (SNI) often occurs due to trauma, disc herniations, or prolonged pressure, leading to pain, numbness, and muscle weakness in the lower extremities. Current medical treatment for sciatic nerve injury focuses on pain relief and functional restoration. Initial management often includes physical therapy and pain medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Minimally invasive procedures like nerve blocks can also provide relief. In severe cases, surgical intervention may be necessary to repair nerve damage (Ellis & Bennett, 2013). Emerging treatments, are being explored for their potential to reduce inflammation and promote nerve healing, offering hope for improved outcomes in the future. The ANI model of the sciatic nerve is widely used; however, there is limited information available regarding complications associated with ANI in rats.

Complications arising from sciatic nerve injury in rats encompass a range of physiological and behavioral issues, including infection, cannibalism, and altered recovery dynamics. The sciatic nerve injury model is widely utilized in research to explore the mechanisms of nerve regeneration and the associated complications. Infection is a significant concern following sciatic nerve injury, particularly in experimental settings where surgical procedures may introduce pathogens (Zhang et al., 2020) including peripheral nerve repair and regeneration. Symptoms of pain in rodent model of nerve injuries include paraesthesia, allodynia, hyperalgesia, decreased activity, piloerection, excessive licking, un-groomed appearance (Austin et al., 2012). Cannibalism, particularly in the context of maternal behavior, can also emerge as a complication in animal models. Research has shown that stressors, including those induced by environmental changes or injury, can lead to increased rates of cannibalism among rat mothers, particularly towards their offspring (Kusama-Eguchi et al., 2016). To sum up, complications following nerve injury in rats, including infection and cannibalism, are influenced by a myriad of factors such as inflammation, hormonal responses, and age-related changes in regenerative capacity. Understanding these complexities is essential for developing effective therapeutic strategies to enhance recovery and mitigate adverse outcomes in both experimental and clinical settings.

The aim of the present study is to investigate the observable complications and survival rates in rats subjected to acute nerve injury induced by sciatic nerve laceration.

## *MATERIALS AND METHODS*

The experimental protocol of this study was approved by the Local Animal Studies Local Ethics Committee (No: 2024-027). Eighteen female rats (Wistar albino, 220-300 g) used in the study were individually housed during the experiment under standard controlled conditions (12 hrs dark/light cycle, at 22±2EC). Rats freely accessed food and water during housing. All procedures were performed according to the 'Principles of Laboratory Animal

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Care' by the 'National Institute of Health' publication.

### *Experimental groups*

Animals were randomly separated into 3 experimental groups, 1. Control (n = 3), 2. Sham-operated (n = 3), 3. Acute nerve injury (ANI, n=12) + Diclofenac (10 mg/kg/day, s.c.). Diclofenac sodium (Deva®), Ceftriaxone (Menarini®), Isoflurane (Adeka ®) were used for experiments. 0,9% NaCl were administered for controls, sham-operated and ANI groups (Bostan et al., 2018).

### *Experimental procedure*

An experimental ANI model was performed. Rats in all experimental groups were anesthetized with 5% isoflurane and 1.5-2% oxygen concentration before surgery and maintained with 1.5-2% isoflurane and 1.5-2% oxygen concentration. Ceftriaxone (30 mg/kg, intraperitoneal,i.p.) was administered prophylactically to the groups before surgery. For the SNI group, the right sciatic nerve in each rat was dissected and cut to create a sciatic nerve injury model ((Bostan et al., 2018; Sonohata et al., 2023), and then repaired with sutures. All surgical procedures were performed by a single surgeon who is experienced on microsurgery (hand surgeon) using a standard surgical microscope. The right sciatic nerve was dissected and cut with a scalpel near the popliteal bifurcation through a skin incision. Subsequently, all injured nerves were repaired with primary end-to-end epineural sutures (Ethilon 8-0, Ethicon) (Figure 1). Rats received Diclofenac sodium (40 mg/kg) intraoperatively in operation area and the wounds were closed with 9-0 Vicryl (H. Kaya et al., 2021).

### *Post-experimental procedure and surgical care*

All surgical procedures were performed under aseptic conditions. Rats received Diclofenac sodium (40 mg/kg/day) every 8 hours for three doses for postoperative pain. After surgery, all rats were given at least 3-4 hours of recovery and then placed in their individual cages (Bostan et al., 2018; Sonohata et al., 2023). Diclofenac sodium (40 mg/kg/day) administered once daily for 7 days after the protocol (Kaya et al., 2021; Kaya & Alizade, 2022).

Throughout the experimental process, changes in the animals were monitored and recorded by the facility's veterinarians and the researchers. Indicators of infection, such as hypothermia, reduced food and water intake, postural disturbances, blood in the stool, and decreased activity, were carefully documented. Signs of pain were evaluated through behavioral and physical indicators, including vocalization, guarding of the affected limb, reluctance to move or bear weight, postural disturbances, and decreased activity levels.

Edema was assessed through visual inspection for soft, swollen tissue at the injury site or along the hind limb, complemented by palpation. Paresthesia was evaluated based on behavioral signs, including excessive grooming or biting of the affected limb, as well as hypersensitivity or withdrawal reflexes in response to sensory stimuli, such as touch. Cannibalism was identified by the presence of self-inflicted wounds or missing tissue, particularly in the area surrounding the nerve injury.

### *Statistical Analysis*

Statistical analysis was conducted using GraphPad Prism. Descriptive variables were presented as percentage distributions. Chi-square test is used for statistical analysis. A p-value of less than 0.05 was considered significant.

## *RESULTS*

Paresthesia and cannibalism observed in the same ratio in the same animals in the operated legs. Similarly excessive licking, allodynia and need of stitches of operated legs also started within 3 days (Figure 2). Edema and hematoma only observed within 3-7 days. Signs of infection including hypothermia, decreased food and water intake, sign of disturbances in posture, blood in stool and decreased activity (as a sign of pain and infection) started in 3$^{rd}$ day of operation and observed in 10 days (Table 1). Cannibalism, a serious complication observed in this study, led to the sacrifice of animals during the 10-day experimental period in accordance with ethical guidelines. The inclusion of the 3-10 day range for edema and hematoma in the table was likely chosen based on the observed timeline of the onset of these complications and progression. In this study, edema and hematoma were not present within the initial 0-3 day period but were observed between 3-10 days post-injury. Therefore, this timeframe is critical to capture the development of these complications.

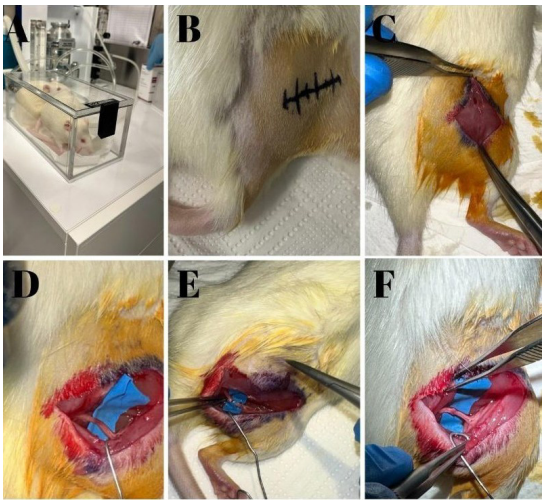


***Figure 1.*** *SNI operation of rats. Shown are steps development of SNI model in rats; Anesthesia (A), Marking (B), Skin dissection(C), Isolation of sciatic nerve (D-F)*

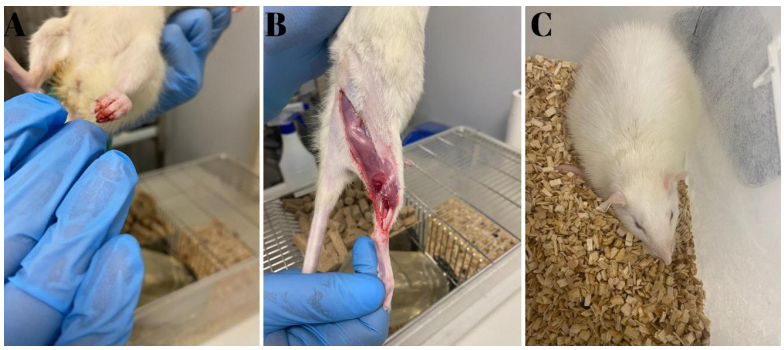


***Figure 2.*** *Complications observed in rats with SNI. Shown are excessive licking (A), cannibalism (B) and piloerection with disturbance in posture (C)*

***Table 1.*** *Observed complications of the experimental groups*

| N (%) | Control (N=3) | Sham (N=3) | SNI (N=12) | p |
|---|---|---|---|---|
| Signs of infection within 3 days* | 0/3 (0) | 0/3 (0) | 5/12 (41,6) | |
| Signs of infection within 5 days* | 0/3 (0) | 1/3 (33,3%) | 6/10 (60%) | < 0.0001*** |
| Signs of infection within 10 days* | 0/3 (0) | 2/3 (66,6%) | 4/6 (33,3%) | |
| Edema within 3-5 days | 0/3 (0) | 0/3 (0) | 1/10 (10%) | |
| Hematoma within 3-5 days | 0/3 (0) | 0/3 (0) | 3/10 (30%) | |
| Paresthesia within 3 days | 0/3 (0) | 0/3 (0) | 0/12 (0) | |
| Paresthesia within 5 days | 0/3 (0) | 0/3 (0) | 1/10 (10%) | < 0.0001*** |
| Paresthesia within 10 days | 0/3 (0) | 0/3 (0) | 4/6 (66,6%) | |
| Allodynia in operated leg within 3 days | 0/3 (0) | 0/3 (0) | 5/12 (41,6) | |
| Allodynia in operated leg within 5 days | 0/3 (0) | 0/3 (0) | 6/10 (60%) | 0.0002*** |
| Allodynia in operated leg within 10 days | 0/3 (0) | 0/3 (0) | 4/6 (66,6%) | |
| Decreased activity within 3 days | 0/3 (0) | 0/3 (0) | 5 (41,6) | |
| Decreased activity within 5 days | 0/3 (0) | 1/3 (33,3%) | 6 (60%) | 0.0002*** |
| Decreased activity within 10 days | 0/3 (0) | 2/3 (66,6%) | 4/6 (66,6%) | |
| Piloerection within 3 days | 0/3 (0) | 0/3 (0) | 5/12 (41,6) | |
| Piloerection within 5 days | 0/3 (0) | 0/3 (0) | 6/10 (60%) | 0.0700 |
| Piloerection within 10 days | 0/3 (0) | 1/6 (33,3%) | 4/6 (66,6%) | |
| Excessive licking within 3 days | 0/3 (0) | 0/3 (0) | 1/12 (8,33%) | |
| Excessive licking within 5 days | 0/3 (0) | 0/3 (0) | 1/10 (10%) | < 0.0001*** |
| Excessive licking within 10 days | 0/3 (0) | 0/3 (0) | 4/6 (66,6%) | |
| Un-groomed appearance within 3 days | 0/3 (0) | 0/3 (0) | 5/12 (41,6) | |
| Un-groomed appearance within 5 days | 0/3 (0) | 1/3 (33,3%) | 6/10 (60%) | 0.0002*** |
| Un-groomed appearance within 10 days | 0/3 (0) | 2 /3 (66,6%) | 4/6 (66,6%) | |
| Cannibalism within 3 days | 0/3 (0) | 0/3 (0) | 0/3 (0) | |
| Cannibalism within 5 days | 0/3 (0) | 0/3 (0) | 1/10 (10%) | < 0.0001*** |
| Cannibalism within 10 days | 0/3 (0) | 0/3 (0) | 4/6 (66,6%) | |
| Survival (N,%) within 3 days | 3/3 (100%) | 3/3 (100%) | 10/12 (83,3%) | |
| Survival (N,%) within 5 days | 3/3 (100%) | 3/3 (100%) | 6/12 (50%) | < 0.0001*** |
| Survival (N,%) within 10 days | 3/3 (100%) | 2/3 (66,6%) | 2/12 (16,6%) | |
| Need of stitches within 3 days | 0/3 (0) | 0/3 (0) | 2/12 (16,6%) | |
| Need of stitches within 5 days | 0/3 (0) | 0/3 (0) | 4/10 (40%) | 0.0017** |
| Need of stitches within 10 days | 0/3 (0) | 0/3 (0) | 4/6 (66,6%) | |

*Signs of infection: hypothermia, decreased food and water intake, sign of disturbances in posture, blood in stool

Chi-square test is used for statistical analysis. p<0.01: **; p<0.001: ***

## *DISCUSSION*

ANI of sciatic nerve is a widely used model for studying peripheral nerve injuries due to its reproducibility and relevance to clinical conditions. However, the high mortality and morbidity rates observed in this study underscore the need for improved surgical techniques, postoperative care protocols, and preventive strategies. By understanding the complications and risks associated with ANI models, future studies can refine methodologies and contribute to the development of safer and more effective experimental designs. The complications observed during the study were meticulously documented and analyzed across experimental groups. These findings not only provide critical reference data for researchers conducting similar studies but also highlight the importance of addressing the challenges associated with experimental models like ANI.

Paresthesia and allodynia are common complications following sciatic nerve injury in rats, often resulting from neuropathic pain mechanisms that arise during the regeneration process. Paresthesia refers to abnormal sensations such as tingling or prickling, while allodynia is characterized by pain from stimuli that do not normally provoke pain. These phenomena are frequently observed in rodent models of peripheral nerve injury, including those involving the sciatic nerve, where nerve damage can lead to significant alterations in sensory processing and pain perception (Guo & Gu, 2014; Liu et al., 2019). Research indicates that following sciatic nerve injury, there is a marked increase in the expression of proteins associated with inflammation and nerve regeneration, which can contribute to the development of neuropathic. For instance, the upregulation of immune-related genes and inflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-10 (IL-10), has been documented in the context of nerve injury, suggesting a robust immune response that may exacerbate pain conditions like allodynia (Huang et al., 2023; Xing et al., 2017). Moreover, cannibalism, or self-mutilation behavior, is another severe consequence observed in rodent models following sciatic nerve injury which may require sacrification during the experimental processes in accordance to ethical concerns, as in this study. This behavior is often linked to the intense pain and sensory abnormalities that arise from nerve damage, leading to self-inflicted injuries as the animals attempt to alleviate their discomfort (Heinzel et al., 2020). The phenomenon of autotomy, where animals remove or injure their own limbs, is particularly noted in cases of severe neuropathic pain, which can be induced by various types of nerve injuries, including complete transection or chronic constriction injuries (Andersson et al., 2018; Guo & Gu, 2014).

Observational studies of rats with sciatic nerve injury reveal significant complications such as edema and necrosis, which are critical to understanding the underlying mechanisms of nerve damage and recovery. The sciatic nerve, being the largest peripheral nerve, is particularly susceptible to injury due to its anatomical location and the nature of trauma it often endures. In experimental models, such as those involving sciatic nerve crush injuries, the immediate response includes inflammation characterized by edema, which is a common reaction to nerve trauma. This inflammatory response is mediated by various cytokines, including tumor necrosis factor-alpha (TNF-α), which plays a pivotal role in the pathophysiology of nerve injury and subsequent regeneration (Zhang et al., 2020). Furthermore, the upregulation of pro-inflammatory cytokines such as IL-1β and IL-6 has been documented in the context of peripheral nerve injuries, contributing to both edema and necrosis (Yu et al., 2023). Although inflammatory processes are considered one of the primary contributors to pain, NSAIDs may not be sufficient for managing pain and inflammation in the case of SNI. This insufficiency was also observed in the operated animals in this study, which showed signs of inflammation, pain, edema, and necrosis. Opioids may be more effective for SNI-related pain; however, the role of inflammation should not be overlooked. Adjuvant corticosteroid therapy could be considered part of the standard treatment protocol, although further studies are needed to establish solid evidence for its routine use in SNI models in rats.

Non-steroidal anti-inflammatory drugs (NSAIDs), particularly diclofenac, are commonly used to alleviate pain and inflammation in sciatic nerve injury in clinical practice and in vivo studies. Diclofenac's potent anti-inflammatory effects help reduce nerve compression and associated discomfort (Kaya & Alizade, 2022). Inflammation is also a significant concern following sciatic nerve injury, particularly in experimental settings where surgical procedures may introduce pathogens that can also be controlled with NSAIDs. The inflammatory response triggered by nerve injury can create an environment conducive to inflammation, complicating recovery. For instance, cytokines play a crucial role in mediating inflammation and immune responses post-injury, with studies indicating that their expression patterns significantly change following nerve damage (Zhang et al., 2020). The presence of pro-inflammatory cytokines can exacerbate tissue damage and delay recovery, highlighting the importance of managing inflammation to prevent secondary complications such as infection (Feng & Yuan, 2015). Along with the other research studies our study demonstrated that inflammation might be considered as a risk factor in rats with SNI along with the pain that diclofenac use failed to control in this experimental process which is also observed in increasing mortality within 10-day period. This study demonstrated that, although previous research reported fewer complications and higher survival rates in rats with SNI, future studies should consider its potential impact on mortality. Researchers should also take precautions, such as closely monitoring for signs of inflammation or loss of sensation, particularly within the first five days post-operation.

Moreover, therapeutic strategies aimed at mitigating these complications have been explored. For example, the administration of anti-inflammatory agents like dexamethasone has shown promise in enhancing functional recovery and reducing the extent of edema and necrosis following SNI (Feng & Yuan, 2015; Sun et al., 2012). These treatments can help modulate the inflammatory response, thereby promoting a more conducive environment for nerve repair and improve survival although in case of systemic inflammation there is conflicting data that corticosteroid use (Feng & Yuan, 2015; Sun et al., 2012). These treatments can help regulate the inflammatory response, creating a more favorable environment for nerve repair. However, NSAIDs may not be the most

effective option for managing pain and inflammation in sciatic nerve injury (SNI). While opioids offer stronger pain relief, they should be used with caution. Adjuvant corticosteroid therapy may be beneficial in controlling inflammation. Additionally, post-operative use of extended spectrum antibiotics might be necessary, as pre-operative administration alone may not sufficiently prevent infections. Strict adherence to surgical sterilization protocols is crucial, and close monitoring of the wound site, particularly within the first 5 days after surgery, is essential. Frequent checks, ideally every 6 hours, are recommended to detect early signs of infection and enable timely intervention, which could improve overall recovery outcomes in SNI.

### *Limitations*

This study is observational, meaning no direct interventions were tested to address the complications. Therefore, while the findings are valuable for understanding the complications associated with sciatic nerve injury (SNI), the results may be limited in terms of establishing causality or offering definitive therapeutic solutions. Secondly, regular monitoring of biochemical parameters, such as inflammatory markers or cytokine levels, could provide additional insight into the physiological processes underlying complications like infection and inflammation. Lastly, the study only tracked complications over a 10-day period, which may not capture the long-term outcomes of sciatic nerve injury recovery. Extending the follow-up period could provide a more comprehensive understanding of both the progression of complications and the effectiveness of potential interventions over time for researchers.

## *CONCLUSION*

This study highlights the significant challenges associated with the acute sciatic nerve injury (ANI) model in rats, particularly the high mortality and morbidity rates observed during the postoperative period. Complications such as inflammation, edema, hematoma, paresthesia, allodynia, and cannibalism were meticulously recorded, providing critical insights into the pathophysiology and behavioral consequences of ANI. The findings demonstrate that while NSAIDs like diclofenac can offer some relief, they are insufficient in managing the severe pain and inflammation associated with this model. Alternative therapeutic strategies, such as the incorporation of opioids, corticosteroids, and enhanced postoperative care protocols, should be explored in future studies to improve survival rates and reduce complications.

Furthermore, the detailed documentation of observed complications contributes valuable reference data for researchers utilizing SNI models, emphasizing the need for close monitoring and improved pain management strategies in experimental settings. These results not only underscore the importance of refining surgical and postoperative care techniques but also pave the way for the development of safer and more effective therapeutic approaches in peripheral nerve injury research.

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The experimental protocol of this study was approved by the Local Animal Studies Local Ethics Committee (No: 2024-027). The authors would like to thank the veterinary scientists of Izmir Biomedicine and Genome Center for their technical support.

### *Financial Support*

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### *Conflict of Interest*

NA

### *Ethical Statement*

The experimental protocol of this study was approved by the Local Animal Studies Local Ethics Committee (No: 2024-027).

### *Author Contributions*

VO and AED completed the experimental model. EB conducted the statistical analyses and figures. All authors write the main article and revised.

### *Availability of Data and Materials*

The data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

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