

## Histopathological effects of intramuscular metamizole sodium on rat sciatic nerve

Abdurrahman Emir <sup>1\*</sup>, Yıldıray Kalkan <sup>2</sup>, Habib Bostan <sup>3</sup>

<sup>1</sup> Bitlis Branch Directorate, Council of Forensic Medicine, The Ministry of Justice, Bitlis, Turkey

<sup>2</sup> Department of Histology, Medical Faculty, Recep Tayyip Erdoğan University, Rize, Turkey

<sup>3</sup> The Ministry of Justice, Council of Forensic Medicine, Istanbul, Turkey

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### ABSTRACT

**Objective(s):** We investigated the histopathological effects of metamizole sodium (MS) on the sciatic nerve.

**Materials and Methods:** This study was performed using 48 adult male Wistar albino rats. Ten groups were constituted with 6 rats in each group. MS injection into the sciatic nerve (group 1), MS injection into the muscle [group 3 (50 mg/kg, 0.4 ml) and group 5 (50 mg/kg, 0.8 ml)], MS injection into the muscle cavity in the vicinity of the sciatic nerve [group 2 (50 mg/kg, 0.4 ml) and group 4 (50 mg/kg, 0.8 ml)], normal saline injection into the muscle in the vicinity of the sciatic nerve [group 6A (0.4 ml) and 6B (0.8 ml)], subjected to injury by drilling the entire layer of nerve without injecting any drug, normal saline injection in the sciatic nerve, and control group. Nerve and muscle samples were taken 7 days after administrations. Tissue sections were stained using a hematoxylin and eosin-Luxol® fast blue stain, assessed by a histologist.

**Results:** The levels of axonal degeneration of the rats in groups 1, 2, 3, 4, 5, 6A, and 8 were found to be significantly higher compared to the levels of the rats in the control group ( $P<0.05$ ). Myelin degeneration of the rats in all groups was found to be significantly higher compared to myelin degeneration of the rats in the control group ( $P<0.05$ ).

**Conclusion:** It was observed that MS could lead to injury in the sciatic nerve with a toxic effect due to diffusion.

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### Introduction

During administration of drugs to patients, oral, topical, or parenteral routes can be given preference. Intramuscular (IM) injections are commonly used for the treatment of acute or chronic diseases and during vaccine administrations. Following IM administration of drugs, negative effects such as abscess, necrosis, infection, tissue irritation, contracture, hematoma, chronic pain, periostitis, and injuries to the blood vessels, bone, or nerves may occur at the injection site. Sciatic nerve injury is the most important among these negative effects (1-4). The drugs most commonly causing sciatic neuropathy via the IM route are antibiotics and analgesics (5).

Metamizole sodium (MS), a member of the pyrazolone group of non-steroidal anti-inflammatory drugs (NSAIDs), is still commonly used (6, 7). There is no mention of the neurotoxic effects of MS in the package insert, but cases of injection neuropathy caused by MS have been reported. In a study performed by Unal *et al*, it was reported that MS was administered alone in 5 of 121 cases experiencing

injection neuropathy and in combination with other drugs, in 10 of them. In another study, it was reported that dipyrone (MS) was administered alone in 10 of 28 cases developing sciatic neuropathy following injection and when dipyrone (MS) was used in combination with cefazolin, in 1 of them (8, 9).

Rat sciatic nerve is commonly used in the peripheral nerve injury or regeneration studies. Axonal degeneration occurs in the distal part of the axon with the nerve tissue invasion of macrophages and damage of myelin sheath after the sciatic nerve crush injury (10). Toxic drugs cause several histopathological changes in the nerve after injection as follows: degeneration of the axon and myelin, cellular swelling, vacuolization, and loss of Schwann cells. Axonal regeneration starts 1-2 weeks after this damage (11).

In this study, pathological effects of MS, a drug frequently used as an IM analgesic agent in medical practice, on rat sciatic nerves were investigated. Using this constituted animal model, histopathological effects of the drug depending on the site of administration were compared.

\*Corresponding author: Abdurrahman Emir. Bitlis Branch Directorate, Council of Forensic Medicine, The Ministry of Justice, Bitlis, Turkey. Tel: +90-434-2266300; Fax: +90-434-2266303; email: abdurrahmanemir@gmail.com

## Materials and Methods

The study protocol was approved by the Local Ethics Committee of Recep Tayyip Erdogan University, Rize, Turkey (February 21, 2014; decision number: 2014/15). The study was performed at the Experimental Animal Implementation Unit of Recep Tayyip Erdogan University by using a total of 48 adult male Wistar albino rats weighing between 281 and 457 g with a mean weight of 365 g. After allowing a sufficient period of time to allow them to adapt to the laboratory conditions, the experimental animals were randomly divided into the groups shown in Table 1. All animals were fed *ad libitum* in the sterile experimental animal environment with a cycle of 12 hr of light and 12 hr of darkness at a relative humidity of 55–60% and  $22\pm 3$  °C room temperature. Applications were performed under anesthesia provided via intraperitoneal administration of 50 mg/kg of Ketalar® Vial M (ketamine HCl-Pfizer) and 10 mg/kg Rompun 25 ml 2% w/v solution for injection (xylazine hydrochloride-Bayer). All surgical procedures were performed by the same surgeon and using standard surgical techniques. After shaving the gluteal region and cleaning the surgical area with a betadine solution, an oblique skin incision was made over the lateral aspect of the gluteal region. Muscle tissues were opened with a blunt dissection. The sciatic nerve was observed and the applications seen in Table 1 were performed. All applications were performed by using 30 gauge insulin needles (BD Micro-Fine™ Plus). In group 1, when 0.1 ml was injected, nerve tissue became swollen due to the structure of the sciatic nerve, and portions of the drug could not be administered intraneurally (Figure 1). In groups 2 and 4, muscle tissue was opened and the drug was administered within muscle space around nerve tissue (Figure 2). The muscles and the skin were sutured in an orderly manner after the application. The muscle layers were opened and then they were closed by suturing without performing any procedure in the control group. After leaving them alone in their cages for 7 days, the rats were sacrificed using a high dose (150 mg/kg) of ketamine HCl, and the lower extremities together with their muscle and nerve tissues were taken for histopathological examination.



**Figure 1.** Metamizole sodium injection into the sciatic nerve and swollen nerve tissue

### Histopathological investigation

The muscle and the sciatic nerve samples obtained from the rats in all groups were labeled with a given code number and group name and stored in special bottles containing 10% formaldehyde. After leaving them in the fixative for approximately twenty-four hr, the samples were washed with running tap water for 4–6 hr and then were rinsed in a series of increasing concentrations of alcohol (50%, 70%, 80%, and 96%, pure alcohol) and xylene. Then, the samples were passed through an automated tissue processor (Citadel 2000, Thermo Fisher Scientific Shandon, England) and were embedded in liquid paraffin. Tissues were cut 4–6  $\mu$ m thick for routine hematoxylin-eosin staining (H&E) and Luxol® fast blue staining. Selected areas were examined under a light microscope at different magnifications and images were taken. A blind grading was performed by a histopathologist as follows: grade 0: no pathological change was observed; grade 1: < 1–20%; grade 2: < 21–40%; grade 3: < 41–60%; grade 4: < 61–80%; grade 5: < 81–100%. Histopathological findings such as myelin degeneration, axonal degeneration, lymphocytic infiltration, vacuolization, dilatation, and edema were evaluated.

**Table 1.** Experimental groups, drugs administered, and their doses

Experimental and control groups	N	Total
Group 1: Metamizole sodium (Dose: 50 mg/kg, vo: 0.1 ml) injection into the sciatic nerve	6	
Group 2: Metamizole sodium (Dose: 50 mg/kg, vo: 0.4 ml) injection into the muscle cavity in the vicinity of the sciatic nerve	6	
Group 3: Metamizole sodium (Dose: 50 mg/kg, vo: 0.4 ml) injection into the muscle in the vicinity of the sciatic nerve	6	
Group 4: Metamizole sodium (Dose: 50 mg/kg, vo: 0.8 ml) injection into the muscle cavity in the vicinity of the sciatic nerve	6	
Group 5: Metamizole sodium (Dose: 50 mg/kg, vo: 0.8 ml) injection into the muscle in the vicinity of the sciatic nerve	6	
Group 6: A) Normal saline injection into the muscle in the vicinity of the right sciatic nerve (vo: 0.4 ml), B) Normal saline injection into the muscle in the vicinity of the left sciatic nerve (vo: 0.8 ml)	6	
Group 7: An injury was performed by drilling the entire layer of the nerve by using a 1 ml insulin needle without injection drug into the right sciatic nerve	6	
Group 8: A 0.1 ml volume of normal saline injection in the sciatic nerve	6	
Group 9: Control group (left sciatic nerve and muscle of the animals in group 8 were sampled)		48

vo: volume



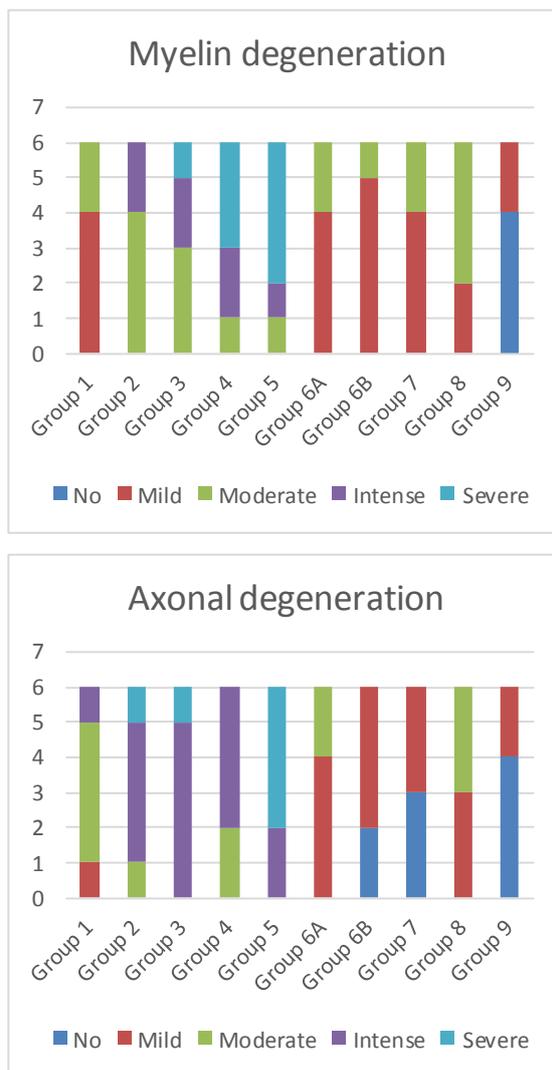
**Figure 2.** Metamizole sodium injection into the muscle cavity in the vicinity of the sciatic nerve

**Statistical evaluations**

NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programs were used for statistical analysis. During evaluation of the study data, the Mann-Whitney U test was used for the intergroup comparisons of descriptive statistical methods (mean, standard deviation (SD), median, frequency, ratio, minimum, and maximum) as well as comparisons of parameters without normal distribution. Significance was evaluated at the levels of  $P < 0.01$  and  $P < 0.05$ .

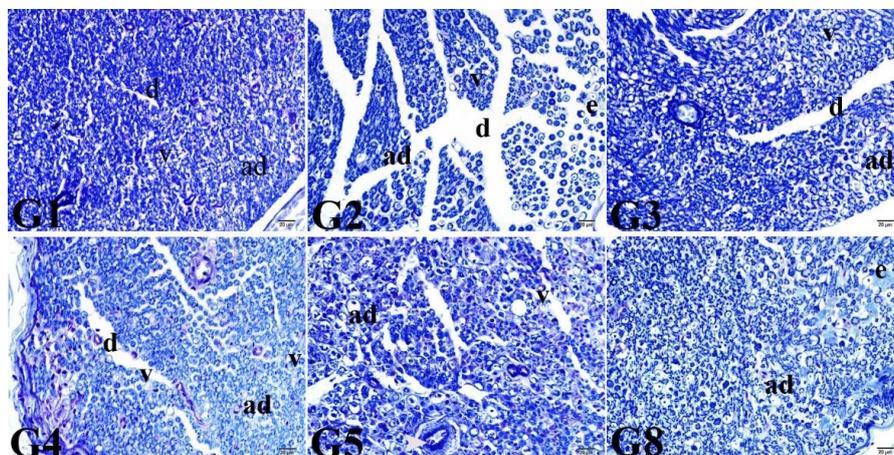
**Results**

All of the histopathological parameters are shown in Table 2 and Figure 3. In group 1, it was determined that mild axonal degenerations, severe dilatations, and edema were observed in nerve epineuriums and moderate degeneration was seen only in epineuriums of nerve samples (33%) obtained from two animals. In group 3, it was determined that edema areas and dilatations were marked, and also myelin degenerations and axonal degenerations were intense in the areas close to the application areas. In group 5, it was determined that edema areas and dilatations were more marked, and also myelin degenerations and axonal degenerations were more intense in the areas close to the application areas compared to group 3. In



**Figure 3.** Distribution of axonal and myelin degeneration in the groups

group 8, while edema areas and dilatations were observed more markedly in the areas close to the application areas, it was determined that myelin degenerations and axonal degenerations were also seen more intensely in the areas close to these areas (Figures 4 and 5).



**Figure 4.** G 1, G2, G3, G 4, G5, G8 nerve tissue, ad: axonal degeneration, d: dilatation, e: edema, v: vacuolization, Luxol Fast Blue x40

**Table 2.** Median  $\pm$ SD values of the histopathological findings according to the groups

	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	Gr 6A	Gr 6B	Gr 7	Gr 8	Control
ad	2,00 $\pm$ 0,63 (2,0) %66	3,00 $\pm$ 0,63 (3,0) %66	3,17 $\pm$ 0,41 (3,0) %83	2,67 $\pm$ 0,52 (3,0) %66	3,67 $\pm$ 0,52 (4,0) %66	1,33 $\pm$ 0,52 (1,0) %66	0,67 $\pm$ 0,52 (1,0) %66	0,50 $\pm$ 0,55 (0,5) %50	1,50 $\pm$ 0,55 (1,5) %50	0,33 $\pm$ 0,52 (0,0) %66
md	1,33 $\pm$ 0,52 (1,0) %66	2,33 $\pm$ 0,52 (2,0) %66	2,67 $\pm$ 0,82 (2,5) %50	3,33 $\pm$ 0,82 (3,5) %50	3,50 $\pm$ 0,84 (4,0) %66	1,33 $\pm$ 0,52 (1,0) %66	1,17 $\pm$ 0,41 (1,0) %83	1,33 $\pm$ 0,52 (1,0) %66	1,67 $\pm$ 0,52 (2,0) %66	0,33 $\pm$ 0,52 (0,0) %66
li	1,83 $\pm$ 0,41 (2,0) %83	3,50 $\pm$ 0,84 (4,0) %66	3,67 $\pm$ 0,52 (4,0) %66	3,67 $\pm$ 0,52 (4,0) %66	4,50 $\pm$ 0,84 (5,0) %66	1,17 $\pm$ 0,41 (1,0) %83	0,33 $\pm$ 0,52 (0,0) %66	2,00 $\pm$ 0,63 (2,0) %66	2,50 $\pm$ 0,55 (2,5) %50	0,50 $\pm$ 0,55 (0,5) %50
e	3,00 $\pm$ 0,63 (3,0) %66	3,17 $\pm$ 0,75 (3,0) %50	2,67 $\pm$ 0,52 (3,0) %66	2,83 $\pm$ 0,41 (3,0) %83	3,00 $\pm$ 0,00 (3,0) %100	2,17 $\pm$ 0,41 (2,0) %83	0,67 $\pm$ 0,52 (1,0) %66	1,33 $\pm$ 0,52 (1,0) %66	1,67 $\pm$ 0,52 (2,0) %66	0,17 $\pm$ 0,41 (0,0) %83
d	2,83 $\pm$ 0,75 (3,0) %50	3,00 $\pm$ 0,63 (3,0) %66	2,67 $\pm$ 0,52 (3,0) %66	2,83 $\pm$ 0,41 (3,0) %83	3,67 $\pm$ 0,52 (4,0) %66	2,17 $\pm$ 0,41 (2,0) %83	1,83 $\pm$ 0,75 (2,0) %50	2,00 $\pm$ 0,00 (2,0) %100	2,50 $\pm$ 0,55 (2,5) %50	0,33 $\pm$ 0,52 (0,0) %66
v	2,00 $\pm$ 0,63 (2,0) %66	3,00 $\pm$ 0,63 (3,0) %66	3,50 $\pm$ 0,55 (3,5) %50	3,67 $\pm$ 0,52 (4,0) %66	4,50 $\pm$ 0,55 (4,5) %50	2,17 $\pm$ 0,41 (2,0) %83	1,33 $\pm$ 0,52 (1,0) %66	1,50 $\pm$ 0,55 (1,5) %50	2,50 $\pm$ 0,55 (2,5) %50	0,17 $\pm$ 0,41 (0,0) %83

ad: axonal degeneration, md: myelin degeneration, li: lymphocytic infiltration in the muscles, e: edema, d: dilatation, v: vacuolization

In group 6A, while it was observed that edema areas and dilatations were more marked, it was determined that myelin degenerations and axonal degenerations were also more intense in the areas close to the application areas. In group 6B, while it was observed that dilatations were more marked, it was determined that there was no degeneration in myelin and axons. In group 7, it was determined that while axonal loss occurred at the places coinciding with the nerve injury, the nerves had normal histological morphology in the other areas. In the control group, it was determined that neural cells were regularly placed and axons, myelin sheaths, and Schwann cells had a normal morphological appearance and with no structural irregularity (Figure 6).

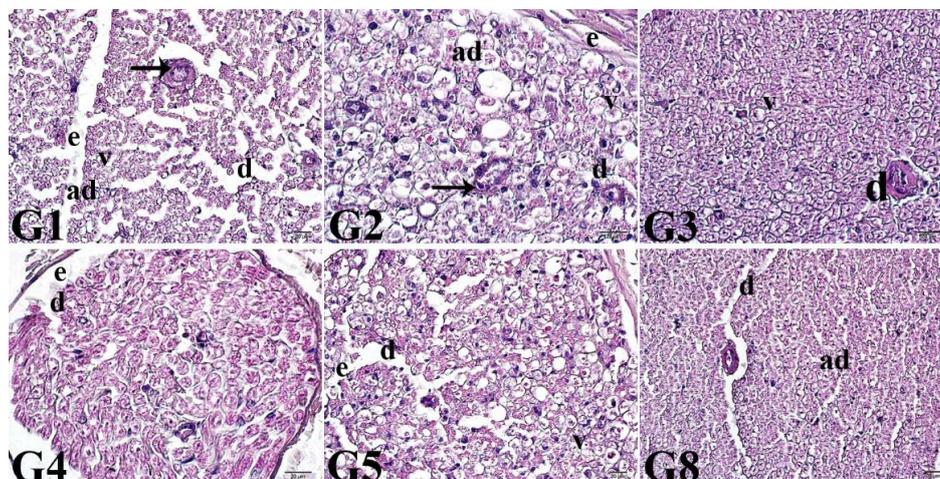
#### Comparison of application groups with control group

The levels of axonal degeneration of the rats in group 1, group 2, group 3, group 4, group 5, group 6A and group 8 were found to be significantly higher compared to the controls ( $P<0.05$ ). No statistically significant difference was determined between the rats in group 6B, group 7 and the rats in the control group, regarding the levels of axonal degeneration ( $P>0.05$ ). Myelin degeneration of the rats in all

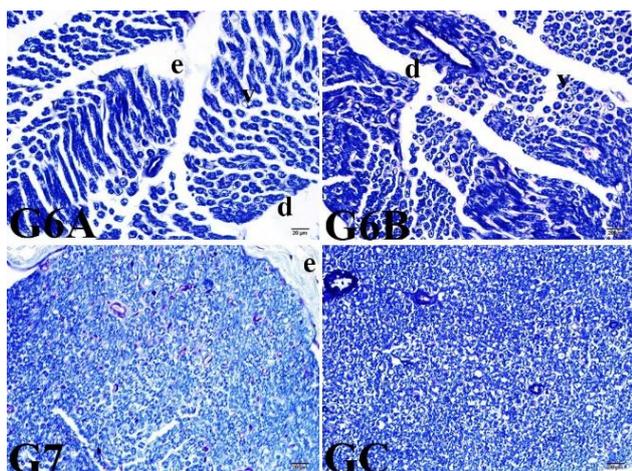
groups was found to be significantly higher compared to myelin degeneration of the rats in the control group ( $P<0.05$ ). The levels of dilatation and vacuolization of the rats in all groups were found to be significantly higher compared with the rats in the control group ( $P<0.01$ ).

#### Comparison of the groups administered intraneural and intramuscular MS

The levels of axonal degeneration and vacuolization of the rats in group 1 were found to be significantly lower compared to the levels of axonal degeneration and vacuolization of the rats in groups 3 and 5 ( $P<0.01$ ). The levels of myelin degeneration and lymphocytic infiltration in the muscles of the rats in group 1 were found to be significantly lower compared to the levels of myelin degeneration and lymphocytic infiltration in the muscles of the rats in groups 3 and 5 ( $P<0.05$ ) (Figure 7). While no statistically significant difference was determined between the rats in groups 1, 3, and 5 regarding the levels of edema and dilatation ( $P>0.05$ ), the lower levels of dilatation of the rats in group 1 compared to the levels of dilatation of the rats in group 5 was striking ( $P>0.05$ ).



**Figure 5.** G 1, G2, G3, G 4, G5, G8 nerve tissue, arrow: swelling and loss in endothelial cells, ad: axonal degeneration, d: dilatation, e: edema, v: vacuolization, H-E X40



**Figure 6.** G 6A, G 6B, G 7, and control group's nerve tissue, d: dilatation, e: edema, v: vacuolization, Luxol Fast Blue x40

#### **Comparison of the groups administered intramuscular MS and intramuscular normal saline**

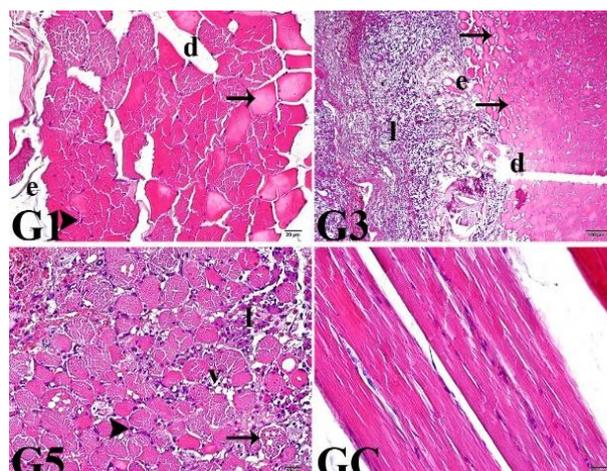
The levels of axonal degeneration, vacuolization and lymphocytic infiltration of the rats in group 3 were higher compared to the levels of the rats in group 6A, and the levels of axonal degeneration, myelin degeneration, and lymphocytic infiltration of the rats in group 5 were higher compared to the levels of the rats in group 6B ( $P < 0.01$ ). The levels of myelin degeneration of the rats in group 3 were significantly higher compared to the levels of the rats in group 6A ( $P < 0.05$ ). While no statistically significant difference was determined between the rats in group 3 and group 6A regarding the levels of edema and dilatation, higher levels of edema and dilatation of the rats in group 3 compared to the levels of dilatation of the rats in group 6A was striking ( $P > 0.05$ ). The levels of edema, vacuolization, and dilatation of the rats in group 5 were significantly higher compared to the levels of the rats in group 6B ( $P < 0.01$ ).

#### **Comparison of the groups administered MS intramuscularly and into the muscle cavity**

No statistically significant difference was determined between groups 2 and 3 regarding the levels of all histopathological parameters ( $P > 0.05$ ).

#### **Comparison of the Groups Administered MS Intramuscularly**

While no statistically significant difference was determined between groups 3 and 5 regarding the levels of axonal degeneration, myelin degeneration, lymphocytic infiltration, and edema, the lower levels of axonal degeneration and lymphocytic infiltration of the rats in group 3 compared to the levels of the rats in group 5 was striking ( $P > 0.05$ ). The levels of dilatation and vacuolization of the rats in group 3 were significantly lower compared to the levels of the rats in group 5 ( $P < 0.05$ ).



**Figure 7.** G 1, G3, G5, and control group's muscle tissue, d: dilatation, e: edema, arrowhead: swollen muscle cell, arrow: degenerated muscle cells, l: lymphocytic infiltration, H-E X40

#### **Comparison of the groups administered normal saline intramuscularly**

While no statistically significant difference was determined between groups 6A and 6B regarding the levels of axonal degeneration, myelin degeneration, and dilatation ( $P > 0.05$ ), the levels of axonal degeneration of the rats in group 6A were strikingly higher compared to the levels of the rats in group 6B. The levels of vacuolization and lymphocytic infiltration of the rats in group 6A were found to be significantly higher compared to the levels of the rats in group 6B ( $P < 0.05$ ). The levels of edema of the rats in group 6A were found to be significantly higher compared to the levels of the rats in group 6B ( $P < 0.01$ ).

#### **Comparison of the groups administered intraneural MS and intraneural normal saline**

No statistically significant difference was determined between groups 1 and 8 regarding the levels of axonal degeneration, myelin degeneration, and vacuolization ( $P > 0.05$ ). The levels of lymphocytic infiltration in the muscles of the rats in group 1 were found to be significantly lower compared to the levels of the rats in group 8 ( $P < 0.05$ ). The levels of edema of the rats in group 1 were found to be significantly higher compared to the levels of the rats in group 8 ( $P < 0.01$ ). The levels of dilatation of the rats in group 1 were found to be significantly higher compared to the levels of the rats in group 8 ( $P < 0.05$ ).

#### **Comparison of the group subjected to injury by drilling the entire layer of nerve without injection into the sciatic nerve and the group administered intraneural MS**

The levels of axonal degeneration of the rats in group 1 were found to be significantly higher compared to the levels of the rats in group 7

( $P < 0.01$ ). No statistically significant difference was determined regarding the levels of myelin degeneration, lymphocytic infiltration, dilatation, and vacuolization ( $P > 0.05$ ). The levels of edema of the rats in group 1 were found to be significantly higher compared to the levels of the rats in group 7 ( $P < 0.01$ ).

**Comparison of the group subjected to injury by drilling the entire layer of nerve without injection into the sciatic nerve and the group administered intraneural normal saline**

The levels of axonal degeneration of the rats in group 7 were significantly lower compared to the levels of the rats in group 8 ( $P < 0.05$ ). While no statistically significant difference was determined regarding the levels of myelin degeneration, lymphocytic infiltration, edema, and dilatation ( $P > 0.05$ ); the levels of vacuolization of the rats in group 7 were significantly higher compared to the levels of the rats in group 8 ( $P < 0.05$ ).

## Discussion

Sciatic nerve injury due to IM injection is considered to be a significant health problem, especially in developing countries (12, 13). The World Health Organization reported that half of 12 billion injections given worldwide each year were performed unsafely (11). There are studies in the literature investigating whether or not many drugs have a toxic effect on the sciatic nerve (14-16). It has been reported that MS caused injection neuropathy (8, 9). However, no study indicating the mechanism of action of MS causing sciatic nerve neuropathy and its histopathological effect on the sciatic nerve was encountered in the literature.

In this study, during the comparison of all groups in which application was performed with the control group, axon, and/or myelin degeneration was found to be significantly higher. This indicates that all administration groups suffered damage in the sciatic nerve.

It was observed that administration of intraneural normal saline caused much more nerve damage than in the groups subjected to injury by drilling the entire layer without injecting any drug. This condition can be explained by the existence of a resistant perineurium tissue that suffered epineurial damage but not perineurial damage due to the needle penetration (17). Since the perineurium is a continuation of the blood-nerve barrier and limits the diffusion (18), perineurial damage plays an important role in nerve damage.

Determination of significantly higher axonal injury in the group administered MS intraneurally compared to the group subjected to injury by drilling the entire layer of nerve without injecting any drug suggests that administration of MS intraneurally

increases nerve damage. This is supported by the observation that administration of intraneural MS and intraneural normal saline caused much more nerve damage than in the groups subjected to injury performed by drilling the entire layer without injecting any drug.

In this study, no significant difference was observed between the groups administered intraneural MS and intraneural normal saline regarding axon and myelin damage. In a study performed by Elizabeth L *et al*, the authors determined significantly higher nerve damage in the group that received an intrafascicular injection of 0.05 ml ropivacaine compared to the group that received an intrafascicular injection of normal saline (19). We think that the absence of any significant difference between groups 1 and 8 in regard to degeneration of the axon and myelin results from the lower dose of MS (approximately 5 mg) in group 1. The amount of drug injected is limited by the anatomical structure of the nerve. Therefore, we think that the amount of drug in the nerve remains in lower concentrations and reduces the possibility of causing damage in the groups administered intraneural MS.

In the study performed by Elizabeth L *et al*, the authors reported that intrafascicular injection of 0.05 ml normal saline in the groups resulted in only intraneural edema, and they did not determine demyelination or Wallerian degeneration (19). However, in the present study, edema, dilation, myelin, and axonal degeneration were observed. We think that this results from intraneural injection of higher volumes of normal saline (0.1 ml) in our study. The volume effect, in our opinion, is a more important factor in intraneural administrations compared to IM administrations regarding nerve damage.

In a study performed by Gentili *et al*, the authors reported that minor axonal and myelin changes were determined by using electron microscopy at the injection site 10 min after administration in the groups that received an intrafascicular injection of 0.25 ml normal saline, but no significant change was found using light microscopy (20).

Absence of any significant difference between axonal degeneration and myelin degeneration during the comparison of the groups administered IM normal saline and IM MS suggest that nerve damage due to mass effect is not increased. This case supports the neurotoxic effect of MS.

With respect to nerve damage, no observation of any significant difference between the groups administered IM MS and those administered MS into the muscle cavity in the vicinity of the nerve suggests that IM MS causes a toxic effect on the nerve through diffusion. Significantly higher rates of axon and myelin damage in the group administered IM MS

compared to the group administered intraneural MS shows that a higher dose of MS administered intramuscularly causes more toxic damage in the nerve through diffusion compared to a lower dose of MS administered intraneurally. Research showed that the amount of drug injected was one of the factors affecting the degree of nerve damage (21). This condition is also seen in the present study.

The determination of the occurrence of significant axonal and myelin damages in the group 3 (administered IM 0.4 ml MS) compared to the group administered IM 0.4 ml normal saline, and similarly the occurrence of higher rates of axonal damage in group 5 (administered IM 0.8 ml MS) compared to the group administered IM 0.8 ml normal saline supports the conclusion that IM MS has a toxic effect on the nerve through diffusion. The authors of a study reported that the effect of penicillin on the sciatic nerve is toxic rather than mechanical damage (22). In the study performed by Gentili *et al*, by using five drugs in current use and commonly administered by IM injection, the authors determined that the mechanism of injury caused by the drug occurred as a direct neurotoxic effect on the axon both in Schwann cells and in the nerve fiber, together with a breakdown in the blood-nerve barrier (20). In the present study, it has been shown that MS could cause toxic nerve damage through diffusion from the muscle tissue.

In one study, it was shown that maximal nerve injury was caused by the injection of penicillin, diazepam, and chlorpromazine, and minimal nerve injury resulted from the injection of iron-dextran, meperidine, and cephalothin (14). In the study performed by Unal *et al*, combined use was reported as follows: MS + ampicillin in 2 cases, MS + lincomycin in 2 cases, and MS + diazepam in 1 case (8). In the present study, it was demonstrated that MS had a toxic effect on the sciatic nerve. This suggests that combined use of MS together with drugs exerting toxic effects on the sciatic nerve may increase the risk of injury. However, we think that it would be advisable to perform further study to confirm this finding.

## Conclusion

It was observed that MS, whose use has been abolished in many countries and in others like Germany and Spain has also been banned in combination with other drugs, could cause nerve damage in the sciatic nerve due to its toxic effect. We think that the practice of IM administration of MS in the vicinity of peripheral nerves should be reconsidered.

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## Conflict of interest

The authors declare that there are no potential conflicts of interest.

## Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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