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THE EFFECTS OF SUPEROXIDE DISMUTASE AND METHYLPREDNISOLONE ADMINISTRATION ON HISTOPATHOLOGICAL FINDINGS IN A RAT MODEL OF OPTIC NEURITIS

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ABSTRACT
Optic neuritis (ON) is an idiopathic inflammatory demyelinating condition of the optic nerve, vulnerable to degeneration due to energy depletion, reactive oxygen species (ROS) accumulation, and mitochondrial dysfunction. Superoxide dismutase (SOD) may offer neuroprotective benefits by targeting redox dysregulation, helping to halt retinal and retinal ganglion cell (RGC) degeneration. When combined with methylprednisolone (MP), which reduces inflammation, this therapy may accelerate recovery and minimize optic nerve damage. The ASK1-p38 pathway further supports this combined mechanism. To evaluate the effects of SOD and MP administration on optic nerve damage in a rat model of optic neuritis. This randomized post-test only control group laboratory experiment involved 35 male Wistar rats allocated into five groups: sham, control, SOD, MP, and combination therapy. Optic neuritis was induced by lipopolysaccharide (LPS) injection into the optic nerve. Histopathological data were collected after 14 days of treatment through microscopic evaluation of retinal ganglion cell (RGC) counts, optic nerve edema, demyelination, and hemorrhage. Data were analyzed using One-Way ANOVA or Kruskal-Wallis tests. The combination group demonstrated the most favorable outcomes, with the highest average RGC count (195 cells), minimal optic nerve edema ($p<0.001$), and demyelination levels similar to normal. Combined administration of SOD and MP provided better histopathological outcomes—reflected in ganglion cell preservation, reduced edema, and minimal demyelination—than either treatment alone in this rat model of optic neuritis.

Keywords: methylprednisolone; optic neuritis; superoxide dismutase

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INTRODUCTION

Optic neuritis (ON) is an idiopathic inflammatory demyelinating disease of the optic nerve, which may be associated with neuromyelitis optic or present as an early sign of multiple sclerosis (MS), a chronic demyelinating disorder of the central nervous system. Several risk factors have been reported, including granulomatous diseases, infections, and autoimmune conditions. Its pathogenesis involves activated T cells releasing inflammatory cytokines, leading to demyelination, blood-optic barrier disruption, and loss of retinal ganglion cells (RGCs) with optic nerve head (ONH) atrophy (Buonfiglio et al.,2023; Abel et al.,2019).

Optic Neuritis typically affects young adults, predominantly women (3:1), aged 20–45 years, and presents with acute unilateral vision loss, relative afferent pupillary defect, ocular pain, and color perception changes. Diagnosis is aided by fundoscopy and OCT, which reveal ONH anomalies and retinal nerve fiber layer (RNFL) thinning. OCT studies have shown up to 33% RNFL reduction compared to controls and 27% between affected and unaffected eyes. RNFL thinning is observed in 85% of ON patients within 3–6 months of onset. Perimetry and cranial MRI are also essential for visual field assessment and MS association (Buonfiglio et al.,2023)

The optic nerve is highly energy-dependent and vulnerable to degeneration due to oxidative stress and mitochondrial dysfunction. Antioxidants, including enzymatic types like superoxide dismutase (SOD), play a critical protective role (Alsemeh et al.,2023; Amore et al.,2021). SOD catalyzes the conversion of superoxide radicals to oxygen and hydrogen peroxide, activating endogenous antioxidant defenses. The three isoforms—SOD1, SOD2, and SOD3—differ in structure, metal cofactors, cellular location, and gene regulation but share common transcription factor binding sites. Studies in both humans and animal models highlight SOD's neuroprotective effects and its role in heavy metal detoxification. Therapeutically, SOD may reduce RGC death and optic nerve demyelination through the ASK1-p38 pathway in ON. (Rosa et al.,2021; Tan et al., 2015; Kumar et al.,2020).

Glucocorticoid therapy remains the standard treatment for acute ON and other CNS autoimmune exacerbations, exerting anti-inflammatory effects via genomic mechanisms.8 Standard treatment includes high-dose IV methylprednisolone (MP) (1000 mg/day for 3 days), shown to restore vision and stabilize the blood-optic barrier (Buonfiglio et al.,2023; Huang et al.,2017). However, MP lacks neuroprotective properties and may even increase neuronal apoptosis (Diem et al.,2003; Huang et al.,2017; Huang et al.,2011). No studies to date have evaluated MP combined with SOD, though such combination may enhance recovery by modulating inflammation and reducing damage to RGCs and ON (Buonfiglio et al.,2023). Based on this background, this study aims to investigate the effects of SOD and MP on optic nerve damage recovery in a rat model of optic neuritis, as both agents have shown antioxidant and neuro-regenerative potential. The general objective of this study is to To evaluate the effects of SOD and MP administration on optic nerve damage in a rat model of optic neuritis

METHOD

Study Design and Participants

This study employed a randomized post-test only control group laboratory experimental design using an animal model. The objective was to evaluate the effect of superoxide dismutase (SOD) and methylprednisolone (MP) on optic nerve (ON) damage in lipopolysaccharide (LPS)-induced optic neuritis (ON) in Wistar rats, with histopathological assessment conducted after treatment. All procedures adhered to institutional and ARRIVE guidelines. Ethical approval was granted by the Ethics Committee of Universitas Sumatera Utara with letter number : 1075/KEPK/USU/2024. Animals were humanely euthanized and disposed of using a diesel-powered incinerator.

Study Location and Duration

The study was conducted from October to December 2024 at Universitas Sumatera Utara. Induction procedures were performed at the Laboratory of Pharmaceutical Preparation Technology, Faculty of Pharmacy, while treatment administration was carried out at the Clinical Pharmacology Laboratory, Faculty of Medicine. Histological evaluations were conducted at the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Sumatera Utara.

Animal Model

Thirty-five male Wistar rats (Rattus norvegicus), aged 2–3 months and weighing 280–310 grams, were used. Animals were deemed healthy based on activity and absence of physical defects. Inclusion, exclusion, and drop-out criteria were strictly followed, and sample size was calculated using the Federer formula to ensure adequate power (n = 7 per group, 5 groups, with 30% drop-out margin).

Group Allocation and Treatment

Animals were randomly assigned to five groups: a sham group of healthy rats without intervention; a control group of optic neuritis (ON) model rats receiving no treatment; a P1 group treated with superoxide dismutase (SOD) 100 mg/kg/day intraperitoneally for 14 days; a P2 group treated with

methylprednisolone (MP) at an initial bolus dose of 30 mg/kg followed by tapering doses over 14 days; and a P3 group receiving combination therapy consisting of SOD 50 mg/kg/day and MP 15 mg/kg/day with dose tapering for 14 days.

Optic Neuritis Induction Procedure

Rats were anesthetized with ketamine (150 mg/kg) and xylazine (2 mg/kg) IP. A lateral canthotomy was performed, exposing 3 mm of the retrobulbar optic nerve under a surgical microscope. The optic nerve sheath was incised longitudinally, and 1 µL of 4.5 µg/µL *Salmonella typhimurium* LPS was injected into the optic nerve using a 30G Hamilton syringe.

Tissue Preparation and Histopathology

After 14 days of treatment, animals were sacrificed using chloroform anesthesia followed by cremation. The optic nerve (5–7 mm segment) was harvested, fixed in 4% paraformaldehyde, dehydrated in 30% sucrose, and stored at −20°C. Retinal eyecups were processed for histological analysis using H&E staining. Histological scoring of ON included assessment of edema, demyelination, mononuclear inflammatory infiltrates, and hemorrhage on a 0–3 scale. Retinal ganglion cell (RGC) density was determined by counting cells in three random 1-mm fields at 800 µm from the optic disc center, using 400× magnification.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Numerical data, including retinal ganglion cell (RGC) counts, were presented as mean ± standard deviation (SD). Data normality was assessed using the Shapiro–Wilk test. Comparisons among groups were performed using One-Way Analysis of Variance (ANOVA) for normally distributed data, followed by Bonferroni post hoc testing. Ordinal histopathological variables, including optic nerve edema, demyelination, and hemorrhage scores, were analyzed using the Kruskal–Wallis test, followed by Mann–Whitney U tests for pairwise comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULT

Animal Model and Experimental Groups

A total of 35 Wistar rats were initially included in the study, but 10 rats were excluded due to dropouts. During the adaptation phase, 2 rats died, followed by 7 rats after the optic neuritis induction, and 1 rat during the treatment and monitoring phase. Therefore, 25 rats remained in the study, with 5 rats in each treatment group. Histopathological evaluations were performed on the optic nerve, assessing parameters such as retinal ganglion cell count, edema, demyelination, and hemorrhage.

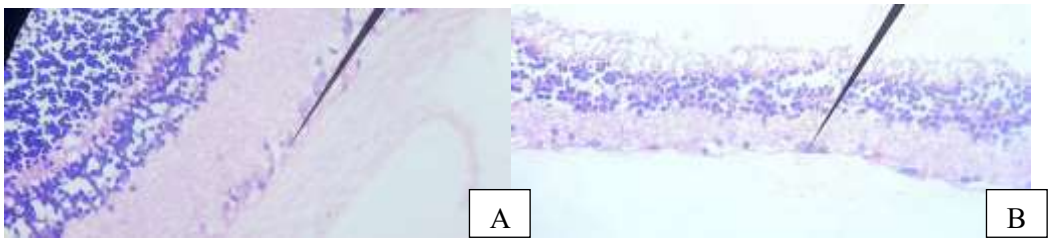


Figure1. Histological Appearance of Retinal Ganglion Cells in the Sham Group (A) and Retinal Ganglion Cells in the Control Group (B)

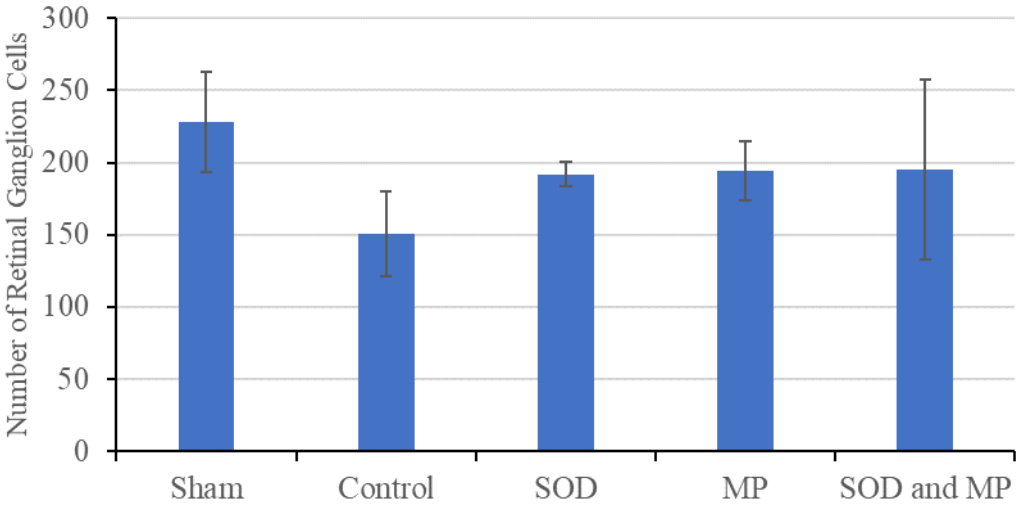


Figure 2. Graph of the Number of Retinal Ganglion Cells Between Groups

Table 1.
Number of Retinal Ganglion Cells Between Groups

Group	n	Mean ± SD	Median (Min – Max)	p
Sham	5	228 ± 34,65	220 (185 – 279)	0,045
Control	5	150,4 ± 29,38	154 (102 – 181)	
SOD	5	191,8 ± 8,44	195 (181 – 201)	
MP	5	194,4 ± 20,49	189 (175 – 227)	
SOD and MP	5	195 ± 62,16	192 (121 – 293)	

**Oneway Anova*

Based on Figure 1, Figure 2, and Table 1, histopathological examination revealed a significant difference in the number of retinal ganglion cells between the treatment groups. The sham group had the highest number of ganglion cells (228 ± 34.65), significantly greater than the control group, which had the lowest number (150.4 ± 29.38) (p = 0.045). The groups treated with SOD (191.8 ± 8.44), MP (194.4 ± 20.49), and SOD + MP (195 ± 62.16) showed no significant differences from the sham group.

Table 2.
Posthoc Test of Differences in Number of Retinal Ganglion Cell Between Groups

Group	Posthoc*			
	Control	SOD	MP	SOD and MP
Sham	0,027	1,000	1,000	1,000
Control		0,827	0,664	0.631
SOD			1,000	1,000
MP				1,000
SOD and MP				

**Bonferroni*

Table 2, post hoc analysis confirmed a significant difference between the sham and control groups (p = 0.027), but no significant difference between the sham group and the treatment groups. The number of retinal ganglion cells in the treatment groups did not significantly differ from each other.

Edema of the Optic Nerve

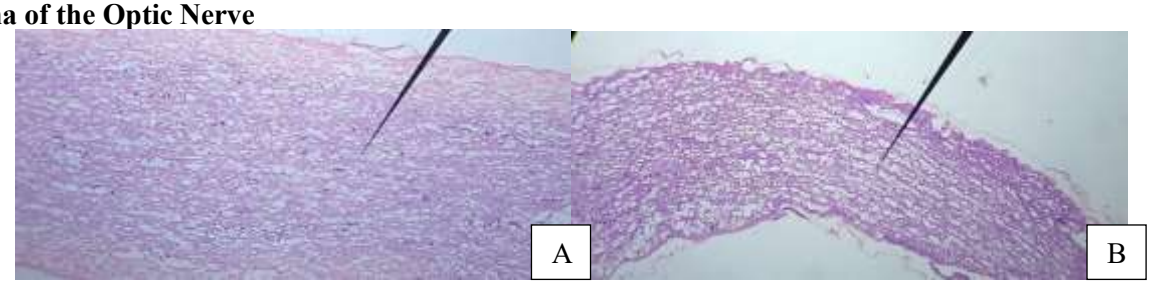


Figure 3. Histological Appearance of Optic Nerve Edema in the Sham Group (A) and Optic Nerve in the Control Group (B)

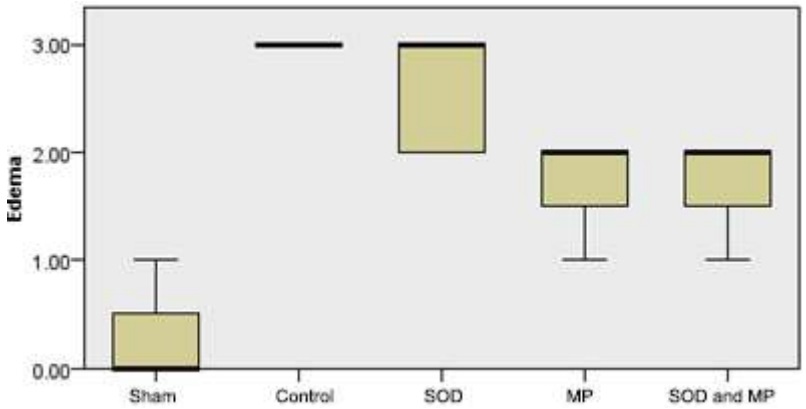


Figure 4. Graph of Differences in Optic Nerve Edema Between Groups

Table 3.
Optic Nerve Edema Between Groups

Group	n	Optic Nerve Edema				p
		0	1	2	3	
Sham	5	4 (80)	1 (20)	0	0	<0,001
Control	5	0	0	0	5 (100)	
SOD	5	0	0	2 (40)	3 (60)	
MP	5	0	1 (20)	4 (80)	0	
SOD and MP	5	0	1 (20)	4 (80)	0	

**Kruskal-Wallis*

Figure 3, Figure 4, and Table 3, optic nerve edema was assessed across the groups. In the sham group, 80% of rats exhibited no edema, while 20% had mild, focal edema (score 1). In contrast, the control group showed severe, diffuse edema (score 4) in all rats. The SOD group had 60% of rats with severe edema (score 3) and 40% with moderate, multifocal edema (score 2). The MP and SOD + MP groups exhibited similar results, with 80% of rats showing moderate edema (score 2) and 20% showing mild edema (score 1). Statistical analysis using the Kruskal-Wallis test showed significant differences in optic nerve edema between groups ($p<0.001$).

Tabel 4.
Posthoc Test of Differences in Optic Nerve Edema Between Groups

Group	Posthoc*			
	Control	SOD	MP	SOD and MP
Sham	<0,001	0,009	0,699	0,699
Control		1,000	0,196	0,196
SOD			1,000	1,000
MP				1,000
SOD and MP				

**Mann-Whitney*

Table 4, post hoc analysis using the Mann-Whitney test showed significant differences in edema between the sham and control groups ($p < 0.001$), and between the sham and SOD groups ($p = 0.009$). No significant differences were observed between the sham and MP or SOD + MP groups, nor between the treatment groups themselves.

Demyelination of the Optic Nerve

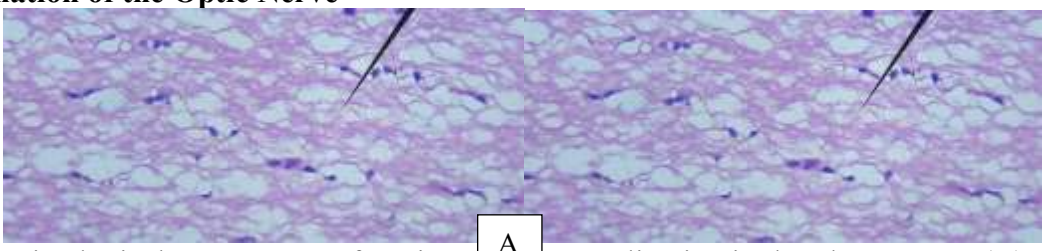


Figure 5. Histological Appearance of Optic Nerve Demyelination in the Sham Group (A) and Optic Nerve Demyelination in the Control Group (B)

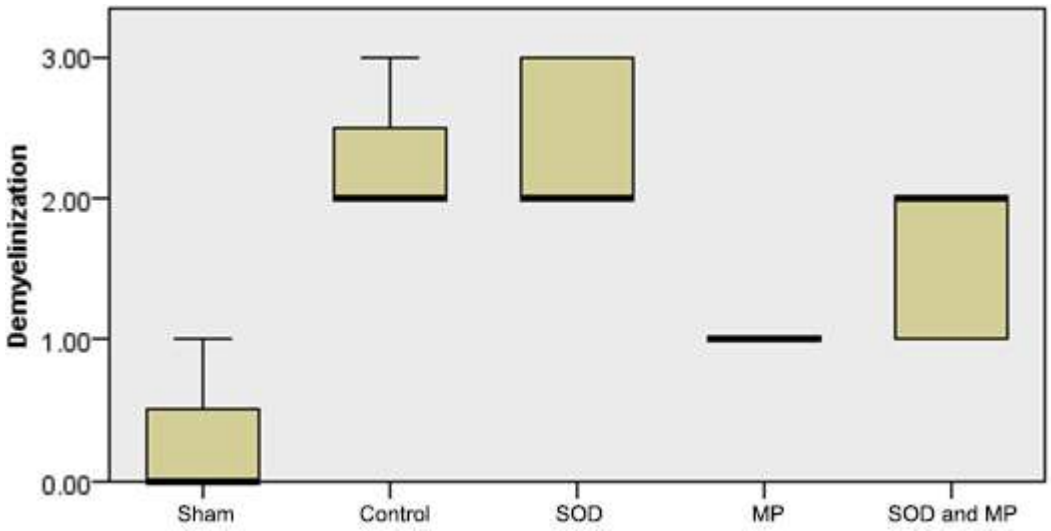


Figure 6. Graph of Differences in Optic Nerve Demyelination Between Groups

Table 5.
Optic Nerve Demyelination Between Groups

Group	n	Optic Nerve Demyelination Score				p
		0	1	2	3	
Sham	5	4 (80)	1 (20)	0	0	0,001
Control	5	0	0	4 (80)	1 (20)	
SOD	5	0	0	3 (60)	2 (40)	
MP	5	0	5 (100)	0	0	
SOD and MP	5	0	2 (40)	3 (60)	0	

**Kruskal-Wallis*

Figure 4, Figure 5, and Table 5, the degree of demyelination was also evaluated in all groups. In the sham group, 80% of rats showed no demyelination, and 20% exhibited mild, focal demyelination (score 1). The control group, however, displayed severe, widespread demyelination in 80% of rats (score 3), with 20% showing moderate demyelination (score 2). The SOD group showed 60% of rats with severe demyelination (score 3) and 40% with moderate demyelination (score 2). The MP group showed 100% of rats with moderate demyelination (score 2). The SOD + MP group showed 40% of rats with moderate demyelination (score 2) and 20% with mild demyelination (score 1).

Tabel 6.
Posthoc Test of Differences in Optic Nerve Demyelination Between Groups

Group	Posthoc*			
	Control	SOD	MP	SOD and MP
Sham	0,005	0,002	1,000	0,208
Control		1,000	0,196	1,000
SOD			0,086	1,000
MP				1,000
SOD and MP				

**Mann-Whitney*

Table 6, the post hoc test using Mann-Whitney revealed significant differences in demyelination between the sham and control groups ($p = 0.005$), and between the sham and SOD groups ($p = 0.002$), but no significant differences between the sham and MP or SOD + MP groups. There were no significant differences between the treatment groups.

Hemorrhage of the Optic Nerve

Table 7, there is no hemorrhage was observed in any of the experimental groups, including the sham, control, SOD, MP, and SOD + MP groups.

Table 7.
Optic Nerve Hemorrhage Between Groups

Group	n	Optic Nerve Hemorrhage Score				p
		0	1	2	3	
Sham	5	5 (100)	0	0	0	-
Control	5	5 (100)	0	0	0	
SOD	5	5 (100)	0	0	0	
MP	5	5 (100)	0	0	0	
SOD and MP	5	5 (100)	0	0	0	

**Kruskal-Wallis*

DISCUSSION

Our study demonstrated a significant reduction in RGC counts in the untreated optic neuritis (ON) group (mean: 150.4) compared to the sham group (228; p=0.045). Notably, the sham group had significantly higher RGC counts than the control group (p=0.027), but no significant differences were observed between the sham group and any of the treatment groups. This suggests that RGCs are highly vulnerable to ON-induced injury, consistent with previous findings that implicate reactive oxygen species (ROS) as major contributors to ON pathogenesis (Qi et al.,2003; Yang et al.,2024).

Among the treatment groups, the combination of SOD and methylprednisolone (MP) yielded the highest RGC preservation (mean: 195), supporting previous studies that highlight the role of inflammation and ROS in ON damage. For instance, Zhang et al. demonstrated that gypenoside reduced ROS production and inflammation, preventing RGC apoptosis (Zhang et al.,2020). Similarly, recent studies have demonstrated that antioxidant-based therapies can attenuate retinal ganglion cell (RGC) loss and reduce demyelination by suppressing oxidative stress and neuroinflammatory pathways. Yang et al. (2024) reported that mitochondrial dysfunction and excessive reactive oxygen species (ROS) production play a central role in RGC degeneration, highlighting the therapeutic potential of antioxidant interventions. Furthermore, Buonfiglio et al. (2023) emphasized that targeting oxidative stress may preserve neuronal integrity and reduce inflammatory damage in optic nerve diseases. Despite differences in therapeutic approaches, these findings support the rationale for combining ROS inhibition with anti-inflammatory strategies, such as corticosteroid therapy, to improve outcomes in optic neuritis.

In our study, 80% of sham rats showed no optic nerve edema, while all control animals exhibited diffuse, severe edema (score 4). Both MP and combination groups showed mostly moderate edema (score 2 in 80% of animals; p<0.001). The sham group differed significantly from the control (p<0.001) and SOD (p=0.009) groups, but not from the MP or combination groups. Histopathologic findings are consistent with Manogaran et al., who observed myelin ballooning and nerve swelling in ON models at 11- and 28-days post-infection. Inflammatory infiltration near the optic nerve head (ONH) likely contributed to inner retinal layer (IRL) edema (Manogaran et al.,2019).

Corticosteroids are known to accelerate visual recovery in ON (Hickman & Petzold.,2022). In a study by Biotti et al. (2017) high-dose IV steroids reduced ON-related edema in 70% of patients, resulting in significant improvements in visual scores and RNFL thickness. Dahanayake et al. (2021) found substantial recovery in visual acuity and field by 1–3 months post-treatment. Moreover, Qi et al. (2007) showed that combined catalase gene therapy and ECSOD expression significantly reduced ONH edema by 34% (p<0.01). These findings affirm the role of corticosteroids and antioxidants in alleviating optic nerve edema, as reflected in our results.

Demyelination scores differed significantly between the sham group and both the control (p=0.005) and SOD (p=0.002) groups, but not with MP or combination groups. This suggests that MP, alone or with SOD, helps preserve myelin integrity. Recent studies have demonstrated that demyelination in optic neuritis is closely associated with neuroinflammation, axonal degeneration, and visual dysfunction, resulting in impaired neural signal transmission along the optic pathway (Hickman & Petzold, 2022; Buonfiglio et al., 2023).

Our findings align with this inflammatory demyelination pathway, even with differing inducers. Racic et al. (2021) found that fluorocortison reduced pro-inflammatory cytokine expression in Müller glia. Recent evidence has highlighted the central role of neuroinflammation, oxidative stress, and mitochondrial dysfunction in the pathogenesis of optic neuritis-induced demyelination. Inflammatory mediators contribute to myelin injury and axonal degeneration, whereas antioxidant and anti-inflammatory interventions may help preserve optic nerve integrity (Buonfiglio et al., 2023; Ciapă et al., 2022). Furthermore, current therapeutic strategies increasingly emphasize multimodal approaches that simultaneously target inflammation, oxidative stress, and neurodegeneration to achieve greater neuroprotection (Chaitanuwong et al., 2025). These findings support the rationale for combining antioxidant and anti-inflammatory therapies to protect against optic neuritis-associated demyelination (Yang et al., 2024).

No hemorrhage was observed in any group. This aligns with Qi et al. (2007) who found no optic nerve hemorrhage in SOD-treated rats. Nakazawa et al. (2021) also reported no hemorrhagic complications in ON patients treated with corticosteroids. Our results suggest that MP and SOD+MP treatments are not associated with hemorrhagic side effects in the optic nerve, though continued monitoring for other adverse effects is warranted.

CONCLUSION

The administration of SOD and MP significantly impacted the histopathological damage in the optic neuritis rat model, influencing the ganglion cell count, edema, and demyelination of the optic nerve. The results indicated a significant difference between the treatment groups and the control group, particularly in ganglion cell count and optic nerve edema. Specifically, the highest ganglion cell count was observed in the group treated with a combination of SOD and MP, while the control group showed the lowest count. Furthermore, significant differences were observed in optic nerve edema and demyelination among the groups, supporting the beneficial effects of SOD and MP. However, no hemorrhage was detected in the optic nerves of the rats, suggesting that these treatments did not induce further damage in this aspect. It is recommended to conduct further research investigating the effects of these therapies on biomarkers involved in the development of optic neuritis would provide deeper insights into their mechanisms. Lastly, studies using varying doses of treatment would be valuable in determining the most effective and optimal dosage for managing optic neuritis.

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