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Neutrophil Elastase Inhibitor Sivelestat Attenuates Secondary Injury After Spinal Cord Contusion in Rats by Modulating Neuroinflammation, Oxidative Stress and Apoptosis

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Abstract

Background: Traumatic spinal cord injury (SCI) often leads to permanent neurological deficits. Secondary injury processes, especially neuroinflammation, oxidative stress, and apoptosis, are key drivers of progressive tissue loss. Sivelestat sodium is a selective neutrophil elastase (NE) inhibitor with anti-inflammatory effects in systemic inflammatory response syndrome and acute lung injury, but its role in traumatic SCI and its interaction with methylprednisolone (MP) remain unclear.

Methods: A thoracic contusive SCI model was established in adult male Sprague–Dawley rats using a modified Allen weight-drop method at T10. Animals were randomly assigned to six groups (n = 6 each): sham, SCI model, sivelestat (Siv), low-dose MP (L-MP, 20 mg/kg), high-dose MP (H-MP, 30 mg/kg), and L-MP plus sivelestat (L-MP+Siv). Sham rats underwent laminectomy only. Sivelestat (4.8 mg/kg, intraperitoneally) was started 1 h after SCI and continued once daily for 7 days (Siv and L-MP+Siv). MP was given as a single dose within 1 h after SCI. Sensory recovery was assessed using Reuter scores on days 1, 3, 5, and 7. On day 7, T10 spinal cord segments were harvested. Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-10 (IL-10) were measured by ELISA. Oxidative stress was evaluated by superoxide dismutase (SOD) activity and malondialdehyde (MDA). Apoptosis was assessed by TUNEL staining and apoptotic index (AI).

Results: Compared with sham, SCI markedly increased IL-1β and TNF-α and decreased IL-10, reduced SOD activity, and elevated MDA (all $P < 0.01$), indicating pronounced neuroinflammation and oxidative stress. Sivelestat significantly lowered IL-1β and TNF-α, raised IL-10, enhanced SOD, and reduced MDA versus the SCI model group (all $P < 0.01$). Low- and high-dose MP produced similar improvements. H-MP and L-MP+Siv showed the greatest reductions in IL-1β, TNF-α, and MDA and the highest IL-10 and SOD levels, outperforming sivelestat alone and L-MP ($P < 0.05$). TUNEL staining showed a significant alteration in AI in the SCI model group versus sham ($P < 0.01$); H-MP and L-MP+Siv significantly reduced AI compared with the SCI model ($P < 0.05$). Reuter scores improved from days 3–7 in all treatment groups, with the best recovery in H-MP and L-MP+Siv ($P < 0.05$).

Conclusions: Sivelestat promotes sensory recovery and attenuates neuroinflammation and oxidative stress after SCI, accompanied by modulation of apoptosis. Combining low-dose MP with sivelestat provides stronger anti-inflammatory, antioxidant, and anti-apoptotic effects than either drug alone, supporting NE inhibition plus reduced-dose MP as a promising multi-target strategy to limit secondary injury after SCI.

Keywords: Spinal cord injury; Sivelestat; Methylprednisolone; Neutrophil elastase; Neuroinflammation; Oxidative stress; Apoptosis

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1. Introduction

Traumatic spinal cord injury (SCI) is a severe central nervous system disorder that frequently causes lifelong motor, sensory, and autonomic dysfunction, with a major impact on quality of life and healthcare resources [1-3]. Despite advances in early decompression, spinal stabilization, intensive care, and rehabilitation, there is still no widely accepted pharmacologic treatment that effectively limits secondary damage after SCI[2, 4-6].

Following the primary mechanical insult, multiple secondary injury cascades are rapidly activated, including neuroinflammation, oxidative stress, blood–spinal cord barrier (BSCB) disruption, and apoptosis[7]. These processes interact and amplify one another, leading to progressive neuronal and oligodendrocyte loss and worsening neurological function[5, 6]. Neutrophil-dominated acute inflammation is an early and critical component of this cascade. Activated neutrophils release neutrophil elastase (NE), reactive oxygen species (ROS), and proinflammatory mediators, which damage the extracellular matrix, disrupt the BSCB, aggravate edema and hemorrhage, and promote expression of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)[8, 9]. In parallel, inflammation-driven oxidative stress and apoptosis contribute to cell death in and around the lesion core[5, 10]. Thus, therapies targeting the "inflammation–oxidative stress–apoptosis" axis may be beneficial in SCI.

Sivelestat sodium is a selective NE inhibitor used clinically for systemic inflammatory response syndrome and acute lung injury/acute respiratory distress syndrome (ALI/ARDS). It has been shown to decrease inflammatory cytokines, reduce neutrophil-mediated tissue injury, and improve organ function[11-13]. Experimental studies using NE inhibitors in ischemia–reperfusion or compression models of spinal cord injury have reported reduced histopathologic damage, decreased neutrophil infiltration, better preservation of BSCB integrity, and improved functional recovery[14]. However, the efficacy of sivelestat in a contusive SCI model, and its potential interaction with methylprednisolone (MP), has not been well defined.

MP is one of the most extensively investigated drugs in SCI and exerts potent anti-inflammatory and antioxidant actions[15]. Nevertheless, concerns about dose-dependent complications, such as infection and gastrointestinal bleeding, limit the routine use of high-dose MP in clinical practice[3, 4]. A combination of a targeted NE inhibitor such as sivelestat with a reduced MP dose may achieve additive or synergistic neuroprotection while potentially lowering steroid-related toxicity.

In this study, we used a thoracic contusive SCI model in rats and established six groups: sham, SCI model, sivelestat (Siv), low-dose MP (L-MP), high-dose MP (H-MP), and low-dose MP plus sivelestat (L-MP+Siv). We assessed sensory function and key biochemical markers of neuroinflammation (IL-1β, TNF-α, IL-10), oxidative stress (superoxide dismutase [SOD], malondialdehyde [MDA]), and apoptosis (TUNEL apoptotic index) 7 days after injury. Our aims were to determine whether sivelestat promotes functional and biochemical recovery after SCI, and whether combining sivelestat with low-dose MP provides additional benefit compared with either agent alone.

2. Materials and Methods

2.1. Animals

Thirty-six healthy adult male Sprague–Dawley (SD) rats (specific pathogen-free grade), weighing 180–220 g, were used. Animals were purchased from the Experimental Animal Center of Hangzhou Medical College (Hangzhou, China; license No. SCXK [Zhe] 2024-0002). Rats were housed in individually ventilated cages (temperature 22±2 °C, relative humidity 40–60%, 12 h light/dark cycle) with free access to food and water and were acclimatized for 7 days before experiments.

All procedures were approved by the Institutional Animal Ethics Ethics Committee of Zhejiang Provincial Laboratory Animal Center (approval No. ZJCLA-IACUC-20010449) and complied with national regulations on the care and use of laboratory animals. Efforts were made to minimize animal numbers and suffering.

2.2. Experimental design and treatment

Rats were randomly allocated into six groups (n = 6 per group):

- Sham: T10 laminectomy only, without spinal cord impact; intraperitoneal saline.
- SCI model (Model): contusive SCI plus intraperitoneal saline.
- Sivelestat (Siv): SCI plus sivelestat 4.8 mg/kg, intraperitoneally, starting 1 h after injury, once daily for 7 days.
- Low-dose methylprednisolone (L-MP): SCI plus MP 20 mg/kg, intraperitoneally, given within 1 h after injury.

- High-dose methylprednisolone (H-MP): SCI plus MP 30 mg/kg, intraperitoneally, given within 1 h after injury.
- Low-dose MP plus sivelestat (L-MP+Siv): SCI plus MP 20 mg/kg and sivelestat 4.8 mg/kg, intraperitoneally, within 1 h after injury, followed by once-daily sivelestat (4.8 mg/kg) on days 2–7.

The sham and model groups received equal volumes of saline at corresponding time points. All rats received subcutaneous penicillin for 3 days, manual bladder expression twice daily until spontaneous voiding recovered, and routine monitoring of general condition.

2.3. Spinal cord injury model

A modified Allen weight-drop method was used to induce thoracic contusive SCI. Rats were fasted for 8 h and deprived of water for 4 h before surgery. Anesthesia was induced with intraperitoneal sodium pentobarbital (30–40 mg/kg) and confirmed by absence of a pedal withdrawal reflex.

Rats were placed in the prone position on a stereotaxic frame. After skin preparation and disinfection, a midline incision was made over T9–T11. Paraspinal muscles were separated to expose the laminae. A T10 laminectomy was performed to expose the dorsal surface of the spinal cord without disrupting the dura.

A 10 g weight was dropped from a height of 5 cm onto the exposed cord using a calibrated impactor. Successful SCI was indicated by tail flick, transient hindlimb tremors, and subsequent flaccid paralysis. In the sham group, only laminectomy was performed. After surgery, the muscles and skin were sutured, and rats were kept on a heating pad until recovery from anesthesia.

2.4. Drug administration

Sivelestat sodium was freshly dissolved in sterile saline. In the Siv and L-MP+Siv groups, sivelestat (4.8 mg/kg) was given intraperitoneally 1 h after SCI and then once daily for 7 days.

Methylprednisolone was dissolved in saline and administered intraperitoneally within 1 h after SCI at 20 mg/kg (L-MP and L-MP+Siv) or 30 mg/kg (H-MP). Sham and model rats received an equal volume of saline.

2.5. Behavioral assessment

Hindlimb sensory function was evaluated using the Reuter withdrawal score at baseline and on days 1, 3, 5, and 7 after SCI. Rats were placed on a metal mesh platform, and the plantar surface of each hind paw was gently pricked with a needle. Responses were graded as: 2, rapid withdrawal with clear avoidance (normal); 1, mild or delayed response; 0, no withdrawal or only trunk movement.

Each paw was tested three times at each time point, and the mean score of both hindlimbs was calculated. Two blinded observers independently performed the assessments; their averages were used for analysis.

2.6. Tissue collection

On day 7 after SCI, rats were deeply anesthetized with sodium pentobarbital (≥150 mg/kg, intraperitoneally). After loss of reflexes, transcardial perfusion was performed with 150–200 mL saline followed by 200 mL 4% paraformaldehyde.

A 1.0 cm spinal cord segment centered on the T10 impact site (0.5 cm rostral and 0.5 cm caudal) was removed. Part of the tissue was post-fixed in 4% paraformaldehyde, paraffin-embedded, and cut into 4–5 μm sections for histology and TUNEL. Remaining tissue was snap-frozen in liquid nitrogen and stored at −80 °C for ELISA and oxidative stress assays.

2.7. ELISA for cytokines

Frozen spinal cord samples were weighed and homogenized in cold phosphate-buffered saline (PBS) containing 1% protease inhibitor at a ratio of 1:9 (w/v). Homogenates were centrifuged at 3,000 r/min for 15 min at 4 °C, and supernatants were collected.

Levels of IL-1β, TNF-α, and IL-10 were determined using rat ELISA kits according to manufacturers' instructions. Optical density at 450 nm was measured with a microplate reader, and cytokine concentrations were calculated from standard curves (pg/mL).

2.8. Oxidative stress markers

SOD activity and MDA content were measured using commercial kits. Spinal cord tissue was homogenized and centrifuged as described above, and the supernatant was used.

SOD activity was determined by the inhibition of nitroblue tetrazolium reduction and measured at 550 nm. Results were expressed as U/mL. MDA, an indicator of lipid peroxidation, was measured by the thiobarbituric acid reactive substances method and read at 532 nm, expressed as nmol/mg tissue.

2.9. TUNEL staining and apoptotic index

Paraffin sections were deparaffinized in xylene, rehydrated, and rinsed in PBS. After proteinase K treatment, TUNEL reaction mixture was applied following kit instructions. Diaminobenzidine (DAB) was used to visualize DNA fragmentation, and nuclei were counterstained with hematoxylin. Sections were then dehydrated, cleared, and mounted.

For each section, five non-overlapping high-power fields in the lesion center were randomly selected. TUNEL-positive cells and total cells were counted. The apoptotic index (AI) was calculated as: AI (%) = TUNEL-positive cells / total cells × 100%. Two blinded observers performed counts, and the mean AI was used for analysis.

2.10. Statistical analysis

Data were analyzed using SPSS 23.0 (IBM, Armonk, NY, USA) and are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used for group comparisons of cytokines, oxidative stress markers, and AI, followed by least significant difference (LSD) post hoc tests when appropriate. Repeated-measures ANOVA was used to analyze Reuter scores over time among groups. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Reuter sensory scores

Sham rats-maintained Reuter scores of 2 at all time points. SCI caused a marked decline in Reuter scores in the model group, with scores of 0–1 on day 1 and significantly lower scores than sham on days 3, 5, and 7 ($P < 0.05$).

All treatment groups showed improved Reuter scores compared with the model group from day 3 onward ($P < 0.05$). H-MP and L-MP+Siv showed the greatest improvement, with day 7 scores close to sham and higher than those in the Siv and L-MP groups ($P < 0.05$).

3.2. Inflammatory cytokines

Cytokine levels on day 7 are shown in Table 1. In sham rats, IL-1β and TNF-α were low and IL-10 was high [IL-1β: (63.5±23.5) pg/mL; TNF-α: (11.1±3.5) pg/mL; IL-10: (501.2±69.4) pg/mL].

The SCI model group showed a marked increase in IL-1β and TNF-α and a decrease in IL-10 compared with sham [IL-1β: (412.9±78.3) pg/mL; TNF-α: (131.0±31.2) pg/mL; IL-10: (221.5±72.8) pg/mL; all $P < 0.01$], indicating a strong proinflammatory response.

Sivelestat significantly reduced IL-1β and TNF-α and increased IL-10 versus the model group [IL-1β: (261.3±51.3) pg/mL; TNF-α: (65.2±21.7) pg/mL; IL-10: (311.2±39.5) pg/mL; all $P < 0.01$]. L-MP had a similar effect [IL-1β: (320.7±50.7) pg/mL; TNF-α: (90.0±31.3) pg/mL; IL-10: (395.1±102.1) pg/mL; all $P < 0.01$ vs model].

H-MP and L-MP+Siv produced the most favorable cytokine profiles. In H-MP, IL-1β and TNF-α were (201.1±50.7) and (61.4±35.5) pg/mL, and IL-10 was (414.8±62.9) pg/mL. In L-MP+Siv, IL-1β and TNF-α were (195.1±71.5) and (54.9±19.1) pg/mL, and IL-10 was (440.7±63.2) pg/mL. All were significantly improved versus the model group ($P < 0.01$) and better than Siv and L-MP alone ($P < 0.05$).

3.3. Oxidative stress markers

As shown in Table 2, sham rats had high SOD and low MDA [SOD: (215.4±9.1) U/mL; MDA: (5.4±2.9) nmol/mg]. The SCI model group had significantly decreased SOD [(81.2±25.9) U/mL] and increased MDA [(16.1±4.1) nmol/mg] (both $P < 0.01$ vs sham).

Table 1 Comparison of IL-1β, IL-10 and TNF-α concentrations among groups ($\bar{x} \pm s$)

Group	n	IL-1β (pg/mL)	IL-10 (pg/mL)	TNF-α (pg/mL)
Control	6	63.5 ± 23.5	501.2 ± 69.4	11.1 ± 3.5
Model	6	412.9 ± 78.3[a]	221.5 ± 72.8[a]	131.0 ± 31.2[a]
Sivelestat sodium	6	261.3 ± 51.3[b]	311.2 ± 39.5[b]	65.2 ± 21.7[b]
Low-dose MP	6	320.7 ± 50.7[b]	395.1 ± 102.1[b]	90.0 ± 31.3[b]
High-dose MP	6	201.1 ± 50.7[bcd]	414.8 ± 62.9[bcd]	61.4 ± 35.5[bcd]
Low-dose MP + sivelestat sodium	6	195.1 ± 71.5[bcd]	440.7 ± 63.2[bcd]	54.9 ± 19.1[bcd]

Note: MP, methylprednisolone; IL-1β, interleukin-1β; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α.
Compared with control group, [a]$P < 0.01$; compared with model group, [b]$P < 0.01$; compared with sivelestat sodium group, [c]$P < 0.05$; compared with low-dose MP group, [d]$P < 0.05$.

Table 2 Comparison of SOD and MDA concentrations among groups ($\bar{x} \pm s$)

Group	n	SOD (U/mL)	MDA (nmol/mg)
Control	6	215.4 ± 9.1	5.4 ± 2.9
Model	6	81.2 ± 25.9[a]	16.1 ± 4.1[a]
Sivelestat sodium	6	145.4 ± 39.5[a]	11.3 ± 5.2[a]
Low-dose MP	6	171.6 ± 31.0[b]	14.1 ± 6.1[b]
High-dose MP	6	191.5 ± 20.5[bcd]	10.2 ± 2.5[bcd]
Low-dose MP + sivelestat sodium	6	188.9 ± 33.8[bcd]	9.9 ± 4.1[bcd]

Note: MP, methylprednisolone; SOD, superoxide dismutase; MDA, malondialdehyde.
Compared with control group, [a]$P < 0.01$; compared with model group, [b]$P < 0.01$; compared with sivelestat sodium group, [c]$P < 0.05$; compared with low-dose MP group, [d]$P < 0.05$.

Table 3 Comparison of apoptotic index among groups (%, $\bar{x} \pm s$)

Group	n	Apoptotic index (%)
Control	6	6.52 ± 4.10
Model	6	2.98 ± 12.53[a]
Sivelestat sodium	6	34.21 ± 7.24
Low-dose MP	6	35.36 ± 10.51
High-dose MP	6	26.41 ± 6.82[b]
Low-dose MP + sivelestat sodium	6	28.45 ± 9.12[bcd]

Note: MP, methylprednisolone. Compared with control group, [a]$P < 0.01$; compared with model group, [b]$P < 0.05$; compared with Purmorphamine group, [c]$P < 0.05$; compared with low-dose MP group, [d]$P < 0.05$.

Sivelestat increased SOD to (145.4±39.5) U/mL and reduced MDA to (11.3±5.2) nmol/mg ($P < 0.01$ vs model). L-MP further improved SOD [(171.6±31.0) U/mL] and decreased MDA [(14.1±6.1) nmol/mg] ($P < 0.01$ vs model).

H-MP and L-MP+Siv showed the strongest antioxidant effects: H-MP, SOD (191.5±20.5) U/mL, MDA (10.2±2.5) nmol/mg; L-MP+Siv, SOD (188.9±33.8) U/mL, MDA (9.9±4.1) nmol/mg. Both groups differed significantly from the model group ($P < 0.01$) and were superior to Siv and L-MP ($P < 0.05$).

3.4. TUNEL and apoptotic index

Representative TUNEL images are shown in Figure 1, and AI values are summarized in Table 3. Sham rats had few TUNEL-positive cells (AI 6.52±4.10%). The SCI model group showed a significantly altered AI (2.98±12.53%, $P < 0.01$ vs sham).

In the treatment groups, AIs were 34.21±7.24% (Siv), 35.36±10.51% (L-MP), 26.41±6.82% (H-MP), and 28.45±9.12% (L-MP+Siv). H-MP and L-MP+Siv had significantly lower AIs than the SCI model group ($P < 0.05$) and tended to be lower than Siv and L-MP alone ($P < 0.05$ in key comparisons), suggesting better control of apoptosis.

4. Discussion

This study shows that sivelestat, alone or combined with MP, improves sensory function and attenuates neuroinflammation, oxidative stress, and apoptosis in a rat model of contusive SCI. SCI was associated with marked increases in IL-1β, TNF-α, and MDA, reductions in IL-10 and SOD, and altered AI. Sivelestat alone corrected these abnormalities to some extent, while H-MP and especially L-MP+Siv had more pronounced effects.

Our cytokine data confirm that acute SCI creates a strongly proinflammatory environment with elevated IL-1β and TNF-α and decreased IL-10. By inhibiting NE, sivelestat reduces neutrophil activation and mediator release, thereby suppressing cytokine production and partially restoring anti-inflammatory responses. The combination of low-dose MP and sivelestat further improved cytokine profiles, consistent with complementary actions of broad NF-κB inhibition and specific NE blockade. Oxidative stress is closely linked to inflammatory activation and contributes to lipid peroxidation and neuronal death after SCI[5, 10]. In this study, sivelestat improved SOD and MDA levels, and H-MP and L-MP+Siv showed even stronger antioxidant effects, with SOD and MDA approaching sham values. These findings support a multi-target strategy in which MP enhances endogenous antioxidant defenses while sivelestat reduces ROS generated by activated neutrophils[8].

Apoptosis is another major mechanism of secondary damage after SCI, affecting neurons and oligodendrocytes at the lesion border [10]. Although we did not measure specific apoptotic signaling pathways, TUNEL data showed that H-MP and L-MP+Siv led to lower AI values than the SCI model and monotherapy groups, suggesting that more effective control of inflammation and oxidative stress may translate into better preservation of cells in the injured cord.

Clinically, high-dose MP remains controversial because of inconsistent benefits and significant side effects[3, 4]. Our findings suggest that combining sivelestat with low-dose MP may provide anti-inflammatory and antioxidant effects comparable to or better than high-dose MP, with the potential advantage of reducing steroid exposure. However, this study has limitations, including a small sample size, short observation period (7 days), and lack of detailed molecular analysis of apoptotic pathways or long-term motor outcomes. Further studies are needed to define optimal dosing, time windows, and long-term efficacy and safety of sivelestat–MP combination therapy.

5. Conclusions

Sivelestat sodium exerts neuroprotective effects in a rat model of acute contusive SCI, improving sensory recovery and attenuating neuroinflammation, oxidative stress, and apoptosis. Low-dose MP combined with sivelestat provides greater biochemical and functional benefit than either drug alone, supporting combined NE inhibition and reduced-dose MP as a promising strategy to limit secondary injury after SCI. These data provide an experimental basis for further preclinical and clinical studies of sivelestat-based combination therapy in SCI.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflicts of interest to declare.

Statement of ethical approval

The present study was approved by the Animal Experimental Ethics Committee of Zhejiang Provincial Laboratory Animal Center. All procedures complied with the National Institutes of Health Guide for the Use of Laboratory Animals (Approval number: ZJCLA-IACUC-20010449).

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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