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Antifibrotic Effect of Topical 2-Mercaptoethanesulfonate (Mesna) in a Rat Craniectomy Model

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Abstract:

Objective: Epidural adhesions that develop after decompressive craniectomy may complicate subsequent procedures by increasing operative difficulty and the risk of tissue injury. Mechanical barrier materials are commonly used, yet they do not directly modulate the inflammatory and fibrotic processes responsible for scar formation. This study investigated whether topical 2-Mercaptoethanesulfonate (Mesna) could reduce postoperative epidural fibrosis and adhesion formation in a rat craniectomy model.

Methods: Twenty-one adult male Wistar rats were randomly assigned to three groups (n=7 each): Sham, Vehicle (saline-soaked gelatin sponge), and Mesna (Mesna-soaked gelatin sponge). In the survival groups, re-exploration was performed after 4 weeks. Macroscopic adhesions were graded intraoperatively using the Rydell classification. Histopathological fibrosis and chronic inflammation were evaluated using Hematoxylin–Eosin and Masson's Trichrome staining. Nonparametric statistical tests were applied.

Results: The Mesna group showed significantly lower adhesion scores compared with the Vehicle group (median 1.0 vs 3.0, P=0.019). Fibrosis and chronic inflammation scores were also significantly reduced in the Mesna group across both staining methods (all P<0.05). Adhesion severity correlated positively with fibrosis and inflammatory scores.

Conclusion: Topical Mesna application was associated with significantly lower macroscopic adhesion severity, histopathological fibrosis, and chronic inflammation in this experimental craniectomy model. These findings suggest a potential antifibrotic effect supported by macroscopic and histopathological parameters; however, the underlying molecular mechanisms remain to be clarified. Further dose-response, safety, mechanistic, and translational studies are required before clinical application.

Keywords: Craniectomy, Cranioplasty, Fibrosis, Adhesions, 2-Mercaptoethanesulfonate, Mesna

Cranioplasty is performed after decompressive craniectomy to restore cerebral protection and improve cosmetic appearance. However, dense peridural adhesions that develop between the dura and the overlying soft tissues at the defect site can make secondary surgery technically challenging and

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increase the risk of surgical morbidity [1, 2]. Pro-inflammatory responses that develop secondary to surgical trauma, along with excessive accumulation of extracellular matrix (ECM) components in the wound bed, tend to promote a pathological fibrotic process rather than normal tissue repair [3-6]. The dense scar tissue encountered during cranioplasty dissection significantly prolongs operative time and increases the incidence of dural tears, brain parenchymal injury, cortical bleeding, and postoperative cerebrospinal fluid leakage [1, 2, 7].

Although physical dural barriers such as polytetrafluoroethylene, silicone elastomers, and various biological grafts are currently used to mechanically prevent these adhesions, no optimal standard has been established. These synthetic and biological materials may increase the risk of infection and trigger foreign body reactions. More importantly, they do not address the underlying molecular mechanisms of fibrosis. This limitation highlights the translational need for pharmacologic and mechanism-based strategies rather than relying solely on mechanical separation [8-10].

Sodium 2-mercaptoethanesulfonate (Mesna) is a potent antioxidant and mucolytic agent. Through its free sulfhydryl group, it scavenges reactive oxygen species (ROS) and reduces disulfide bonds between protein chains and ECM proteoglycans [11, 12]. Mesna is used systemically in clinical practice to prevent chemotherapy-induced urotoxicity. Owing to its molecular mechanism of action, it has recently been introduced into surgical practice as a chemical dissector to facilitate separation of tissue planes [12, 13]. Experimental studies and clinical reports have shown that topical Mesna does not cause toxicity in neural or neurovascular tissues. It has also been shown to significantly reduce epidural fibrosis and chronic inflammation after laminectomy in spinal surgery [12, 14]. Although its neuroprotective and antifibrotic properties have been reported, experimental studies evaluating the pharmacological modulation of epidural fibrosis in craniectomy models remain limited.

The aim of this study was to evaluate the effects of a Mesna-soaked gelatin sponge placed intraoperatively in the epidural space in a rat craniectomy model on postoperative macroscopic adhesions, histopathologic fibrosis, and chronic inflammation. Although topical Mesna has been investigated in several experimental surgical settings, its specific role in craniectomy-related epidural fibrosis remains insufficiently explored. We hypothesized that local Mesna application would reduce histopathological fibrosis and chronic inflammatory cell infiltration after craniectomy.

METHODS

Ethical Approval and Experimental Animals

The study was conducted in accordance with institutional and national guidelines for the care and use of laboratory animals and complied with the Animal Research: Reporting of In Vivo Experiments (ARRIVE 2.0) guidelines and the International Council for Laboratory Animal Science (ICLAS) principles. Ethical approval was obtained from the NESA Experimental Animals Laboratory Local Ethics Committee (Decision Date: January 5, 2024; Approval No: 033). All procedures were performed under appropriate anesthesia, and efforts were made to minimize animal suffering.

Twenty-one adult male Wistar albino rats (6 months old; 205–300 g) were included. Animals were housed under controlled laboratory conditions (22–25°C, 12-hour light/dark cycle, standard humidity) with ad libitum access to food and water. All procedures were performed to minimize animal suffering and reduce the number of animals used.

Animals were randomly allocated into three groups (n=7 per group) using a computer-generated randomization sequence: Sham, Vehicle, and Mesna.

Surgical Procedure

All animals received intramuscular cefazolin sodium one hour prior to surgery for antibiotic prophylaxis and intraperitoneal paracetamol for analgesia. General anesthesia was induced using intraperitoneal thiopental sodium (30 mg/kg), and spontaneous respiration was maintained throughout the procedure.

Animals were positioned prone and secured. After shaving and sterile preparation with povidone-iodine, a midline linear scalp incision was performed. Soft tissues were dissected subperiosteally under microscopic magnification. A 5–6 mm right frontoparietal craniectomy was created using a high-speed drill, with

preservation of dural integrity in all cases. No intraoperative complications occurred in any group.

Group-Specific Interventions

Sham Group

Immediately after creating the cranial defect, an en bloc specimen including scalp, subcutaneous tissue, bone, and dura was harvested and animals were euthanized at the index surgery (thiopental sodium, 150 mg/kg). This group was intentionally designed to provide a baseline histological reference for native epidural tissue architecture and background tissue appearance at time zero. It was not intended to serve as a postoperative adhesion control group; therefore, no survival period, re-exploration, or macroscopic adhesion grading was performed in the Sham group.

Vehicle Group

After craniectomy, a gelatin sponge (Spongostan®, Ethicon, Somerville, NJ, USA) trimmed to match the defect size was impregnated with 1 mL sterile saline and placed epidurally over the intact dura. Wounds were closed in anatomical layers using 4-0 polypropylene sutures.

Mesna Group

After craniectomy, a gelatin sponge was impregnated with 1 mL Mesna solution (100 mg; derived from a 400 mg/4 mL preparation, Uromitexan® (Baxter Oncology GmbH, Halle/Westfalen, Germany) and placed epidurally over the intact dura. The selected 1 mL volume was matched to the Vehicle group to control for local fluid volume. The 100 mg dose corresponded to the available 100 mg/mL Mesna preparation and was selected in accordance with previous experimental studies using topical Mesna in surgical and neural tissue models [11, 14, 15]. Closure was performed identically to the Vehicle group.

Postoperative Period and Re-exploration

Animals in the Vehicle and Mesna groups were housed individually and monitored daily for wound healing, infection, and general condition. No procedure-related morbidity or mortality occurred. A 4-week healing period was allowed to ensure adequate maturation of epidural fibrotic tissue in accordance with established experimental models. At 4 weeks, animals were re-anesthetized with intraperitoneal thiopental sodium (30 mg/kg), and re-entry was performed through the previous incision. Macroscopic adhesion grading was conducted intraoperatively by the same neurosurgeon, who remained blinded to group allocation; animals were coded by an independent investigator prior to re-exploration. Macroscopic scoring was performed exclusively in the Vehicle and Mesna groups, as the Sham group did not undergo re-exploration. Adhesions were evaluated according to the Rydell classification (Table 1) [16]. Immediately after macroscopic assessment, animals were euthanized with intraperitoneal thiopental sodium (150 mg/kg), and en bloc specimens including scalp, subcutaneous tissue, bone, dura, and epidural tissue were harvested.

TABLE 1. Rydell Classification System Used for Intraoperative Macroscopic Adhesion Assessment [16]

Grade	Definition
0	No adhesion
1	Adhesion easily dissected
2	Adhesion requiring blunt dissection
3	Dense adhesion requiring sharp dissection or inseparable

Macroscopic epidural adhesion severity was graded intraoperatively according to the Rydell classification system, with higher grades indicating more dense and surgically challenging adhesions.

TABLE 2. Histopathological Fibrosis Scoring System According to Nahm *et al.* [17]

Grade	Histopathological Criteria
0	No fibrosis
1	Loose or focal fibrosis
2	Loose and diffuse fibrosis (>50% of the examined area)
3	Dense or focal fibrosis
4	Dense and diffuse fibrosis

Histopathological fibrosis was graded according to the scoring system described by Nahm *et al.* [17], based on the density (loose vs dense) and distribution (focal vs diffuse) of fibrotic tissue within the examined area.

Histopathological Evaluation

All specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 5 µm thickness. Sections were stained with Hematoxylin–Eosin and Masson's Trichrome. Slides were coded and evaluated by an experienced pathologist blinded to group allocation. Fibrosis was graded according to the scoring system described by Nahm *et al*., incorporating both density (loose vs dense) and distribution (focal vs diffuse), on a 0–4 scale (0 = no fibrosis; 4 = dense and diffuse fibrosis) (Table 2) [17]. Chronic inflammation was graded according to the criteria described by Salafia *et al*., based on the extent of mononuclear inflammatory cell infiltration (0–4 scale) (Table 3) [18]. Acute inflammation was not assessed, as no neutrophil infiltration was observed in any specimen.

Statistical Analysis

All macroscopic and histopathological scores were entered into a coded dataset after completion of blinded assessments and before statistical analysis. Group identities were used only after finalization of the primary statistical comparisons. Statistical analyses were performed using IBM SPSS Statistics (Version 25.0; IBM Corp., Armonk, NY, USA). Rydell adhesion scores were compared between the Vehicle and Mesna groups using the Mann–Whitney U test. Fibrosis and chronic inflammation scores were analyzed as ordinal variables using the Kruskal–Wallis test, followed by Bonferroni-corrected Mann–Whitney U tests for pairwise comparisons when appropriate. Effect sizes (r and ε^2) were reported for primary nonparametric analyses. Data were presented as median (interquartile range). Correlations between adhesion severity and histopathological parameters were assessed using Spearman's rank correlation within the survival cohorts. For post-hoc pairwise comparisons, significance was assessed using Bonferroni-adjusted P values (α adjusted accordingly). A two-sided $P<0.05$ was considered statistically significant. Sample size (n= 7 per group) was determined based on comparable experimental studies and ethical principles aimed at minimizing animal use [11, 19-21].

TABLE 3. Chronic Inflammation Scoring System According to Salafia *et al.* [18]

Grade	Histopathological Criteria
0	No chronic inflammation
1	One focus (minimum 5 mononuclear cells)
2	More than one Grade 1 focus or at least one focus containing 5–20 cells
3	Multiple confluent foci corresponding to Grade 2
4	Dense and diffuse inflammatory infiltration

Chronic inflammation was graded according to the criteria described by Salafia *et al.* [18], based on the extent and distribution of mononuclear inflammatory cell infiltration within the examined tissue sections.

RESULTS

All animals tolerated the procedures without intraoperative complications or postoperative mortality. The main findings are summarized in Table 4.

Macroscopic Adhesion

Macroscopic adhesion severity, assessed using the Rydell classification, was significantly lower in the Mesna group compared with the Vehicle group. The median Rydell score was 3.0 (IQR: 2.0–3.0) in the Vehicle group and 1.0 (IQR: 1.0–1.5) in the Mesna group (Mann–Whitney U = 42.5, P=0.019), corresponding to a moderate-to-large effect size (r = 0.60).

Fibrosis – Hematoxylin–Eosin (H&E)

Fibrosis scores differed significantly among the three groups (Kruskal–Wallis H = 16.01, $P<0.001$, $\varepsilon^2 = 0.78$). Median fibrosis scores were 0.0 (IQR: 0.0–0.0) in the Sham group, 4.0 (IQR: 3.5–4.0) in the Vehicle group, and 1.0 (IQR: 0.5–1.0) in the Mesna group. Post hoc analysis confirmed significantly lower fibrosis scores in the Mesna group compared with the Vehicle group after Bonferroni correction (P=0.006) (Figure 1).

Fibrosis – Masson's Trichrome (M-T)

A significant overall group difference was observed (Kruskal–Wallis H = 18.11, $P<0.001$, $\varepsilon^2 = 0.90$). Median fibrosis scores were 0.0 (IQR: 0.0–0.0)

TABLE 4. Summary of Macroscopic and Histopathological Findings

Parameter	Sham (n=7)	Vehicle (n=7)	Mesna (n=7)	P-value (overall)	Post-hoc
Adhesion score (Rydell)	—	3.0 (2.0–3.0)	1.0 (1.0–1.5)	—	**0.019**
Fibrosis (H&E)	0.0 (0.0–0.0)	4.0 (3.5–4.0)	1.0 (0.5–1.0)	**<0.001**	**0.006**
Fibrosis (M-T)	0.0 (0.0–0.0)	4.0 (3.5–4.0)	1.0 (1.0–1.0)	**<0.001**	**0.003**
CI (H&E)	0.0 (0.0–0.0)	4.0 (3.5–4.0)	1.0 (1.0–1.5)	**<0.001**	**0.004**
CI (M-T)	0.0 (0.0–0.0)	4.0 (4.0–4.0)	1.0 (1.0–1.0)	**<0.001**	**0.003**

CI, chronic inflammation; H&E, hematoxylin–eosin; M-T, Masson's trichrome.
Statistically significant P-values are shown in bold.

in the Sham group, 4.0 (IQR: 3.5–4.0) in the Vehicle group, and 1.0 (IQR: 1.0–1.0) in the Mesna group. The difference between the Vehicle and Mesna groups remained significant after Bonferroni adjustment (P=0.003) (Figure 1).

Chronic Inflammation – Hematoxylin–Eosin (H&E)

Chronic inflammation scores showed a significant difference among groups (Kruskal–Wallis H = 18.03, P<0.001, $\varepsilon^2 = 0.89$). Median scores were 0.0 (IQR: 0.0–0.0) in the Sham group, 4.0 (IQR: 3.5–4.0) in the Vehicle group, and 1.0 (IQR: 1.0–1.5) in the Mesna group. Inflammation severity was significantly reduced in the Mesna group compared with the Vehicle group following Bonferroni correction (P=0.004) (Figure 1).

Chronic Inflammation – Masson's Trichrome (M-T)

A significant overall difference was detected

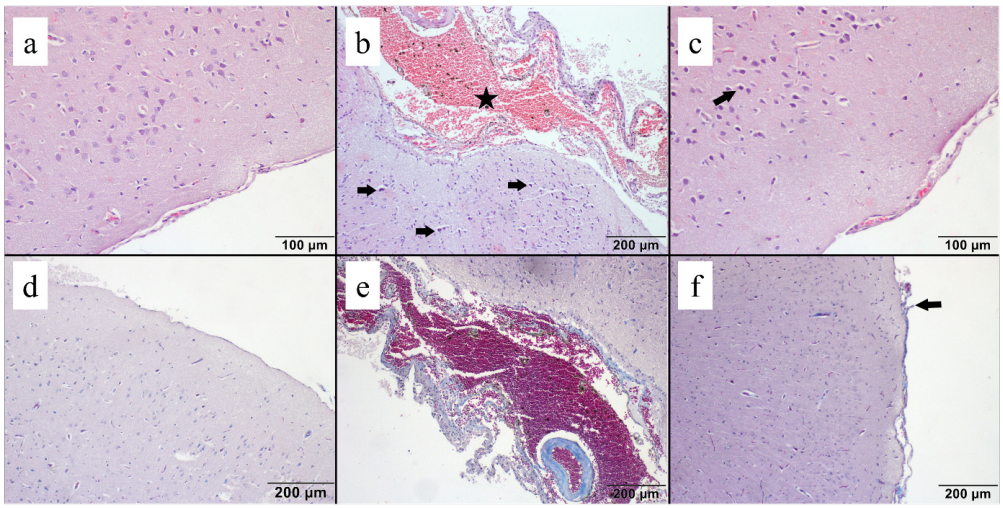

FIGURE 1. Histopathological evaluation of epidural tissue following craniectomy. (a–c) Hematoxylin–Eosin (H&E) staining; (d–f) Masson's Trichrome staining. (a, d) In the Sham group, normal epidural tissue architecture is preserved without evident fibrosis or inflammatory cell infiltration. (b, e) In the Vehicle group, prominent fibrotic tissue formation and increased cellularity are observed between the dura and the overlying soft tissues; the star marks a region of dense inflammatory and fibrotic change. Masson's Trichrome staining demonstrates marked collagen deposition. (c, f) In the Mesna group, epidural fibrosis, collagen deposition, and cellular infiltration are reduced compared with the Vehicle group, and tissue planes appear more clearly preserved. Arrows highlight representative areas of fibrotic and inflammatory tissue change. Scale bars represent 100 µm in a and c, and 200 µm in b, d, e, and f.

among the groups (Kruskal–Wallis H = 17.17, P<0.001, $\varepsilon^2 = 0.84$). Median inflammation scores were 0.0 (IQR: 0.0–0.0) in the Sham group, 4.0 (IQR: 4.0–4.0) in the Vehicle group, and 1.0 (IQR: 1.0–1.0) in the Mesna group. The Mesna group demonstrated significantly lower inflammation scores compared with the Vehicle group (P=0.003) (Figure 1).

Correlation Analysis

Within the survival cohorts (Vehicle and Mesna groups), macroscopic adhesion severity demonstrated significant positive correlations with fibrosis scores in both staining methods (Spearman's P=0.67 for Masson's Trichrome, P=0.008; P=0.66 for H&E, P=0.010). Adhesion severity also correlated positively with chronic inflammation scores (P=0.59 for Masson's Trichrome, P=0.028; P=0.56 for H&E, P=0.036). Strong correlations were observed between fibrosis and chronic inflammation scores across both staining methods (P>0.90 and P<0.001).

DISCUSSION

This experimental study demonstrated that topical application of a Mesna-soaked gelatin sponge in the epidural space during craniectomy was associated with significantly lower postoperative macroscopic adhesion severity, histopathologic fibrosis, and chronic inflammation compared with the Vehicle group. The strong positive correlations observed between macroscopic adhesion severity and histopathologic fibrosis and inflammation scores indicate that macroscopic adhesions reflect the underlying histopathological changes rather than representing an isolated mechanical phenomenon. Importantly, the Sham group in this study should be interpreted only as a baseline histological reference rather than as a postoperative adhesion control group. Because Sham animals were sacrificed at the index surgery, this group was used to document native epidural tissue architecture at time zero and was not intended to model postoperative adhesion formation. Therefore, the primary treatment-related interpretation of the study is based on the comparison between the Vehicle and Mesna groups, both of which underwent the same survival period, carrier placement, and re-exploration protocol.

From a macroscopic perspective, the significantly lower adhesion scores observed in the Mesna group suggest a more preserved epidural tissue plane. Adhesion formation is one of the most relevant consequences of postoperative fibrosis, and its reduction has been consistently reported in experimental studies investigating antifibrotic strategies [2, 6, 19, 22, 23]. In our study, the reduction in adhesion severity parallels the decrease in fibrosis and inflammation scores, supporting a coherent biological effect rather than a purely mechanical separation.

Histopathologically, Mesna was associated with a marked reduction in fibrosis across both staining methods. Epidural fibrosis is driven by excessive extracellular matrix accumulation following fibroblast activation [11, 22]. Experimental studies have shown that pharmacological interventions targeting this process can reduce fibrotic tissue formation, although no standard approach has been established [6, 12, 22, 24, 25]. The significantly lower fibrosis scores observed in the Mesna group are consistent with these findings and indicate that local application may attenuate fibrotic tissue development after surgical injury.

Similarly, chronic inflammation scores were significantly reduced in the Mesna group. Inflammatory cell infiltration plays a central role in initiating and sustaining the fibrotic cascade [3, 11]. Therefore, the observed reduction in chronic inflammation may be associated with the decreased fibrosis seen in our study. Although these findings are compatible with a potential antifibrotic and anti-inflammatory effect of topical Mesna, the present study did not include molecular analyses of fibrosis-related or inflammatory markers such as TGF-β, IL-6, TNF-α, Collagen I/III, or α-SMA. Therefore, the proposed mechanism should be considered indirect and hypothesis-generating, based on macroscopic adhesion grading and histopathological assessment rather than direct molecular pathway confirmation.

The pathophysiology of postoperative epidural fibrosis is characterized by a complex inflammatory cascade triggered by surgical trauma [19]. Surgical injury leads to the migration of inflammatory cells to the affected area and promotes the release of ROS [3, 26]. During this process, activated fibroblasts differentiate into myofibroblasts and lead to excessive accumulation of ECM components such as collagen,

dermatan sulfate, and fibronectin in the wound bed [11, 22]. In this context, the reduction in fibrosis and inflammation observed in our study suggests that Mesna may influence this pathological process; however, the exact mechanism cannot be determined without molecular analysis.

To date, mechanical dural barriers such as polytetrafluoroethylene, silicone elastomers, biological grafts including bovine pericardium and amniotic membrane, and various synthetic membranes have been used to prevent epidural adhesions after craniectomy [1, 24-26]. However, these materials primarily act as physical barriers and do not target the underlying cellular mechanisms of fibrosis [1, 10, 27]. Several experimental antifibrotic agents, including mitomycin C, esomeprazole, boric acid, halofuginone, and tranexamic acid, have been evaluated in epidural fibrosis models [6, 11, 19, 22, 23, 30]. Although promising results have been reported, no widely accepted strategy has been established. In this context, the findings of the present study suggest that Mesna may represent an additional pharmacological approach.

The use of a vehicle group consisting of a saline-soaked gelatin sponge allowed us to control for the potential effects of both the carrier material (Spongostan) and the injected fluid volume[20].

Epidural fibrosis is clinically relevant, particularly in the context of secondary procedures such as cranioplasty, where dense adhesions may complicate re-entry and increase surgical risk [1, 2]. Although reduced fibrosis and adhesion formation observed in this study may be associated with improved surgical conditions, operative parameters such as dissection difficulty, bleeding, or dural injury were not directly evaluated. Therefore, any potential clinical implications should be interpreted cautiously.

Strengths and Limitations

This study provides preliminary experimental evidence that topical Mesna is associated with reduced epidural fibrosis, chronic inflammation, and adhesion formation following craniectomy. These findings support further investigation of Mesna as a potential pharmacologic modulator of postoperative epidural fibrosis, but additional dose-response, safety, molecular, and translational studies are required before clinical application can be considered.

Despite these promising findings, several limitations should be acknowledged. First, this study was conducted in an animal model, and wound healing processes in rats may not fully reflect human physiology. Second, both survival groups received a gelatin sponge, and no additional survival group without implanted carrier material was included. Although the use of a saline-soaked gelatin sponge in the Vehicle group allowed partial control for the carrier and fluid volume, gelatin sponge itself may influence local wound healing, inflammatory response, and adhesion formation. Therefore, the independent contribution of the carrier material cannot be completely excluded. Third, molecular analyses of fibrosis-related and inflammatory pathways were not performed. In particular, markers such as TGF-β, IL-6, TNF-α, Collagen I/III, and α-SMA were not evaluated. This limits the ability to define the precise molecular mechanism underlying the observed reduction in fibrosis and inflammation. Finally, only a single dose and time point were evaluated.

CONCLUSION

In this experimental craniectomy model, topical Mesna application was associated with significantly lower macroscopic adhesion severity, histopathologic fibrosis, and chronic inflammation. These findings suggest a potential antifibrotic and anti-inflammatory effect supported by macroscopic and histopathological parameters. However, because molecular fibrosis markers were not evaluated, the underlying mechanism remains to be clarified. Further dose-response, safety, mechanistic, and translational studies are warranted before clinical applicability can be determined.

Ethics Approval and Consent to Participate

This study was approved by the NESA Experimental Animals Laboratory Local Ethics Committee (Decision No: 033; date: 05.01.2024). All experimental procedures involving animals were conducted in accordance with the ethical standards of the Guide for the Care and Use of Laboratory Animals published by the U.S.National Institutes of Health and

Institutional authority. All efforts were made to minimize animal suffering and to reduce the numberof animals used.

Clinical Trial Registration

Not Available.

Data Availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Authors' Contribution

Study Conception: MEE, ERY; Study Design: MEE, ERY; Supervision: ERY, MET; Funding: N/A; Materials: MEE, HD; Data Collection and/or Processing: MEE, HD; Statistical Analysis and/or Data Interpretation: MEE, ERY, MET; Literature Review: MEE, HD; Manuscript Preparation: MEE, ERY, HD, MET; and Critical Review: MEE, ERY, HD, MET.

Conflict of Interest

The author(s) disclosed no conflict of interest during the preparation or publication of this manuscript.

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Generative Artificial Intelligence Statement

During the preparation of this manuscript, the authors used ChatGPT (GPT-5, OpenAI) to assist with English language refinement, improvement of grammar and clarity, and structural organization of section headings. The AI tool was not used to generate scientific content, perform data analysis, interpret results, or draw conclusions. All content was critically reviewed, revised, and approved by the authors, who take full responsibility for the accuracy and integrity of the manuscript. The all content of the study was produced by the author(s) in accordance with scientific research methods and academic ethical principles.

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