EXPERIMENTAL STUDY

Antifibrotic and anti-inflammatory properties of halofuginone in a rat craniectomy model

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ABSTRACT

BACKGROUND: Cranioplasty is the process of closing a defect after craniectomy using various materials. This procedure carries risks due to adhesions formed by fibrous scar tissue after craniectomy, which can lead to complications such as cerebrospinal fluid (CSF) fistula from dural damage and cerebral hematoma contusion from parenchymal damage, which can have serious consequences. Halofuginone, a low-molecular-weight molecule derived from Dichroa febrifuga, has demonstrated antifibrotic and anti-inflammatory properties by inhibiting type I collagen synthesis and the transforming growth factor-beta (TGF-β) signaling pathway. This study aimed to investigate the effects of halofuginone on fibrotic tissue formation following craniectomy in a rat model.

METHODS: Twenty male Wistar rats underwent bilateral frontoparietal craniectomies and were divided into two groups: a control group treated with saline and a halofuginone group receiving oral halofuginone (1 mg/kg/day) for one week post-surgery. After 30 days, histopathological and ultrastructural analyses were performed to evaluate dura mater thickness, epidural fibrosis, arachnoid involvement, and bone regeneration.

RESULTS: Halofuginone significantly reduced dura mater thickness (19.3±6.51 µm vs. 51.29±14.3 µm in controls, $p<0.05$) and epidural fibrosis grades, with fewer arachnoid adhesions observed in the halofuginone group ($p<0.05$). Electron microscopy revealed fewer active fibroblasts and thinner, disorganized collagen fibers in halofuginone-treated rats, suggesting inhibition of fibroblast activity and collagen production. No significant difference in bone regeneration was observed between the groups.

CONCLUSION: These findings indicate that halofuginone effectively reduces fibrotic tissue formation at craniectomy sites, potentially by suppressing collagen synthesis and inflammatory responses. Further studies are warranted to explore its clinical applications in preventing postoperative fibrosis.

Keywords: Antifibrotic; cranioplasty; halofuginone; rat craniectomy model.

INTRODUCTION

Cranioplasty is a surgical procedure performed to repair or reconstruct missing or damaged bone in the skull.[1] Surgical decompression is often required after severe traumatic brain injury (TBI), ischemic stroke, subarachnoid hemorrhage, dural sinus thrombosis, or infection, and cranioplasty is subsequently needed.[2] Cranioplasty not only protects the brain from external trauma but also restores cranial shape for cosmetic purposes. Furthermore, it serves as a therapeutic interven-

Cite this article as: Taşcıoğlu T, Şahin Ö, Çaydere M, Fırat A, Sürücü HS, Cemil DB. Antifibrotic and anti-inflammatory properties of halofuginone in a rat craniectomy model. Ulus Travma Acil Cerrahi Derg 2025;31:1069-1074.

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Ulus Travma Acil Cerrahi Derg 2025;31(11):1069-1074 DOI: 10.14744/tjtes.2025.70707
Submitted: 02.04.2025 Revised: 06.05.2025 Accepted: 12.08.2025 Published: 03.11.2025

tion by regulating cerebrospinal fluid (CSF) dynamics, cerebral blood flow, and metabolic activity within the brain. It improves patients' psychological well-being while enhancing their social performance.[3,4]

Fibrosis refers to the process in which normal tissue architecture is replaced by abnormal, dysfunctional, and excessive scar tissue. This excessive scar formation is associated with a range of clinical issues and health complications.[5] Following craniectomy, extensive adhesions may form between soft tissue structures, particularly the dura, temporal muscle, and galea, during cranioplasty. Fibrotic tissue that develops between bone surfaces after bone flap replacement can also inhibit bone fusion.[6]

Halofuginone, a low-molecular-weight compound isolated from Dichroa febrifuga, is a specific inhibitor of type I collagen synthesis. By inhibiting the transforming growth factor-beta (TGF-β) pathway, it may exert antifibrotic effects in vivo.[7] Since fibrosis results from elevated type I collagen levels, it has been proposed that synthesizing type I collagen could selectively hinder the development of fibrosis.[8] The goal of our research was to explore the impact of halofuginone on wound healing at the craniectomy site in a rat craniectomy model.

MATERIALS AND METHODS

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Animal Population

Twenty male Wistar rats, approximately 1 year old and weighing an average of 300 grams, were included. Ethical approval was obtained from the Local Ethics Committee (authorization number 774).

Surgical Procedure

Prior to surgery, the frontal regions of the rats were shaved and disinfected with povidone. A drill system was used to create bilateral frontoparietal craniectomies, measuring 7-8 mm. The dura mater was exposed without damage. The rats were then randomly allocated into two distinct groups:

1. Control Group (n=10): Saline-soaked cotton pads (0.5×0.5 cm) were applied to the dura mater for 5 minutes.

2. Halofuginone Group (n=10): Following the procedure, halofuginone was administered via oral gavage at a daily dose of 1 mg/kg for one week.[9]

All rats demonstrated satisfactory postoperative recovery with no observable neurologic deficits. They were maintained under uniform conditions and fed a standard diet. Animals were euthanized 30 days after surgery. Cranial bones, including the scalp, were harvested in blocks; one hemisphere was fixed in 10% buffered formalin, while the other was placed in 2.5% glutaraldehyde for 48 hours and then post-fixed with osmium tetroxide.

Epidural Fibrosis Evaluation

Before pathological analysis, tissue samples were processed through decalcification, dehydration, and paraffin embedding. Axial sections 4 µm thick were prepared and stained with hematoxylin-eosin and Masson's trichrome. The stained slides were examined by a pathologist who was unaware of the group assignments, ensuring a blinded assessment. The evaluation focused on quantifying dura mater thickness, assessing the density of epidural fibrosis, and determining whether the arachnoid mater was involved. Dura mater thickness was calculated as the average of four random measurements. Epidural fibrosis was graded according to the classification system established by He et al.:[10]

- Grade 0: No scar tissue,
- Grade I: Thin fibrous bands between fibrous tissue and dura mater,
- Grade II: Adhesions covering less than two-thirds of the craniectomy defect,
- Grade III: Extensive fibrous tissue with adhesions covering more than two-thirds of the craniectomy defect.

Additionally, the analysis included recording the presence or absence of arachnoid involvement and bone regeneration.

Evaluation Using Transmission Electron Microscopy

Following fixation, the samples underwent dehydration through a graded series of alcohol concentrations before being embedded in Araldite CY212 resin. Sections approximately 2 µm thick were prepared and treated with 1% methylene blue stain. These sections, mounted on slides, were then heated on a hot plate at 100-110°C for 40-45 seconds and then rinsed with tap water. Preliminary examinations for descriptive analysis were performed using a light microscope. Regions deemed significant for ultrathin section preparation were pinpointed. Using a LEICA EM UC7 ultramicrotome, ultrathin sections measuring 60 x 90 nm were prepared. These sections were stained with uranyl acetate and lead citrate, and visualized with a HITACHI HT7800 transmission electron microscope operating at 120 kV.

Statistical Analysis

Statistical analysis was performed using two methods. Dura mater thickness was assessed with the Mann-Whitney U test, while dura mater fibrosis and arachnoid involvement were evaluated with a chi-square test. A significance level of $p<0.05$ was set. Analyses were conducted with IBM SPPS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, 2015).

RESULTS

Examination of the surgical sites revealed no evidence of superficial or deep infections. No signs of erythema, hematoma, or CSF leakage were observed.

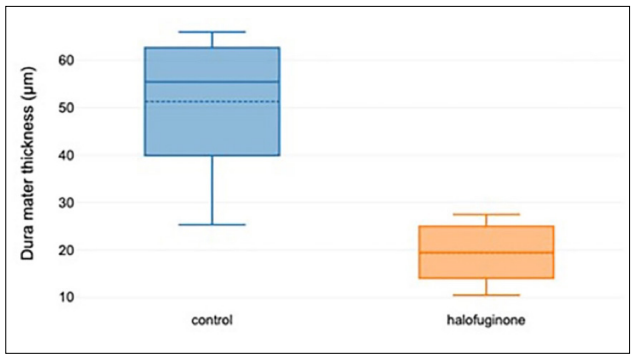

Figure 1. Box-plot graph showing differences in dura mater thickness between the halofuginone and control groups. The difference between the halofuginone group and the control group was statistically significant ($p<0.05$).

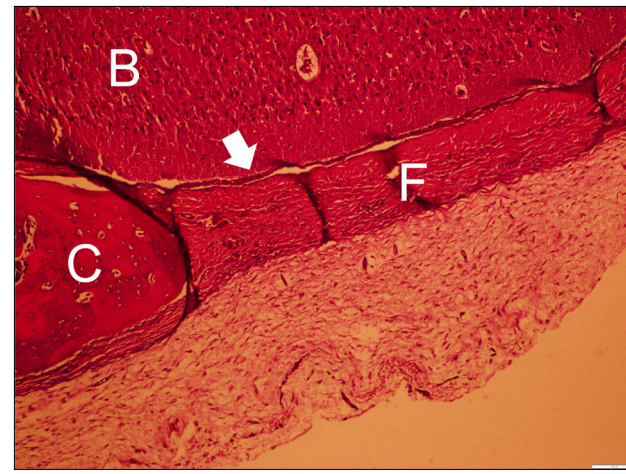

Figure 2. Grade 3 control group sections showing fibrous tissue with adhesions extending more than two-thirds of the craniectomy defect (Hematoxylin-Eosin). B: Brain tissue; C: Craniectomy defect; F: Fibrotic tissue; White arrow: Thickened dura mater.

Results regarding dura mater thickness are illustrated in Figure 1. On average, dura mater thickness in the halofuginone-treated group was 19.3±6.51 µm, compared to 51.29±14.3 µm in the control group. The difference in dura mater thickness between the halofuginone and control groups was statistically significant ($p<0.05$).

Analysis of axial sections stained using hematoxylin and eosin (HE) revealed grade 3 epidural fibrosis in seven rats from the control group (Fig. 2), while seven rats in the halofuginone group exhibited grade 1 epidural fibrosis (Fig. 3). Evaluation of the epidural fibrosis grades, detailed in Table 1, showed statistically significant differences between the two experimental groups ($p<0.05$). Assessment of arachnoidal involvement, presented in Table 2, also demonstrated statistically significant differences between the halofuginone-treated and control groups ($p<0.05$). In contrast, comparison of bone regeneration results showed no statistically significant difference between the experimental groups ($p>0.05$) (Table 3). In the electron microscopy samples, neural tissues were not evaluated due to improper fixation. The dural membrane and epidural ultrastructure were compared between the control and halofuginone groups. In the control group, active fibroblasts with rough endoplasmic reticulum occupying large cytoplasmic areas were observed. These cells were embedded in thick bundles of parallel collagen fibers (Fig. 4). In the halofuginone group, fibroblasts were less active, with sparse cytoplasm and few organelles. The collagen fibers in these

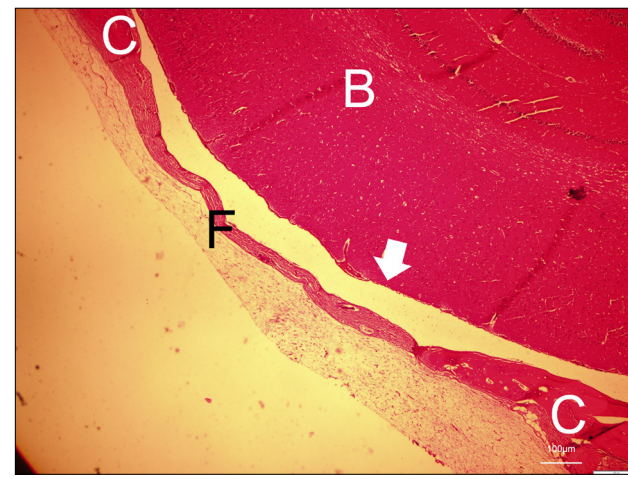

Figure 3. Grade 2 halofuginone group sections showing fibrotic adhesions covering less than two-thirds of the craniectomy defect with no dura mater adhesion. B: Brain tissue; C: Craniectomy defect; F: Fibrotic tissue; White arrow: Dura mater.

samples were thinner and oriented in multiple directions (Fig. 5). Ultrastructural examination indicated that halofuginone treatment prevents fibrosis and collagen formation, possibly by inhibiting fibroblast growth.

Table 1. Epidural fibrosis grades in the halofuginone and control groups

Epidural Fibrosis Grades	N	Grade 0	Grade 1	Grade 2	Grade 3
Control Group	10	0	1	2	7
Halofuginone Group	10	0	7	3	0

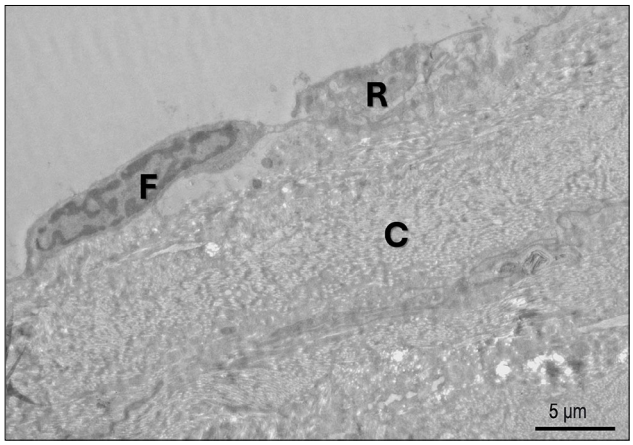

Figure 4. Fibroblast (F) with active rough endoplasmic reticulum (R) at the border of the dura mater. Thick bundles of collagen fibers (C) are observed below.

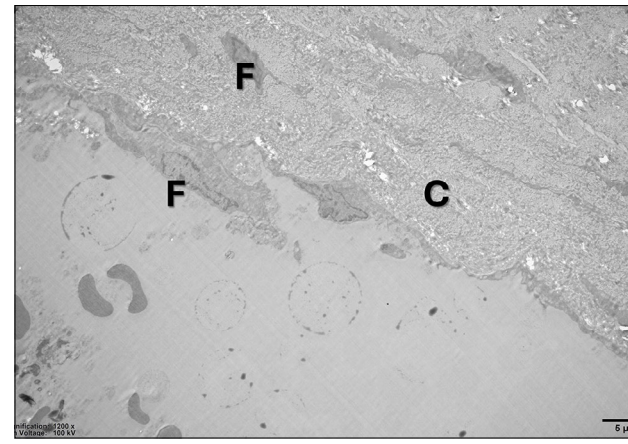

Figure 5. Inactive fibroblasts (F) with small or absent cytoplasm. Collagen fibers (C) beneath are oriented in various directions.

Table 2. Arachnoid adhesion results in the halofuginone and control groups

Arachnoid Adhesion	N	Yes	No
Control Group	10	9	1
Halofuginone Group	10	2	8

Table 3. Bone regeneration results in the halofuginone and control groups

Bone Regeneration	N	Yes	No
Control Group	10	7	3
Halofuginone Group	10	9	1

DISCUSSION

In this study, we evaluated the advantageous effects of halofuginone in preventing fibrotic adhesions in the epidural space after craniectomy. Such adhesions form as a consequence of inflammation induced by surgical trauma, leading to increased synthesis of the extracellular matrix. This process can subsequently cause technical difficulties during tissue separation and negatively affect the operative course. As a result, operative time increases and the risk of dural perforation rises. Additionally, adhesions result in greater residual soft tissues beneath the bone flap and may contribute to poorer aesthetic outcomes of the surgery due to inadequate tissue coverage for the bone flap.[6]

Understanding the mechanism of adhesion formation at the craniectomy site is key to implementing effective preventive measures. Postoperative fibrotic tissue formation occurs in three phases. The first phase begins with an early inflammatory reaction characterized by immune cell infiltration and activation caused by hemostasis, coagulation, and chemokine release. This occurs within the first 3-5 days. The second phase, lasting 2-3 weeks, involves the development of fibrotic tissue. At this stage, extracellular matrix is formed at the injury site under the influence of fibroblasts responding to cytokines such as transforming growth factor- β1 (TGF-β1), interleukin-6 (IL-6), and fibroblast growth factor. Finally, tissue remodeling occurs over months to years.[11] Although granulation tissue that develops at the surgical site may be considered a normal component of wound healing,[12] it is now widely accepted to be non-physiologic.[13]

Halofuginone has many interrelated positive biological activities. It has been officially approved for use as an anti-protozoal agent in both poultry and ruminant animals.[14] Derived from febrifugine, halofuginone has also shown effectiveness in experimental models for treating malaria.[15] The compound demonstrates potent suppression of angiogenesis in diverse tumor types, frequently linked to inhibition of fibroblast-to-myofibroblast transformation and reduction of tumor extracellular matrix content.[16,17] Additionally, halofuginone exhibits anti-fibrotic, anti-inflammatory, and immune-regulating activities.[18,19] The scientific literature proposes two distinct mechanisms to account for these actions:

1. By preventing Smad3 phosphorylation, halofuginone interferes with TGF-β-driven induction of the extracellular matrix and regulates tissue inhibitor genes related to collagen, plasminogen activator inhibitor-1, and metalloprotease-1. This ultimately inhibits epithelial–mesenchymal transition (EMT) and exerts anti-fibrotic effects.

2. Halofuginone blocks the activity of prolyl-tRNA synthetase (ProRS) during the erythrocytic phase of malaria infection and limits Th17 cell differentiation. This mechanism reduces inflammation and autoimmune reactions through activation of the amino acid deprivation pathway and integrated stress

response pathways.[20]

As described above, halofuginone is involved in regulating extracellular matrix formation and reducing inflammation. Therefore, we hypothesized that halofuginone could have positive effects in preventing fibrosis following craniectomy. To investigate the potential mechanisms underlying the reduction of fibrosis by halofuginone treatment after craniectomy, we first examined modifications in extracellular matrix constituents at the craniectomy site. Halofuginone's capacity to inhibit fibrosis was initially discovered by chance and has since been evaluated in numerous animal models as well as human clinical studies.[18,21] Its anti-fibrotic effect is thought to derive from its ability to suppress collagen synthesis, particularly type I collagen.[22] In our research, we first assessed pathologically how halofuginone altered fibrosis grades at the craniectomy site and whether arachnoid adhesions were also present. We then extended this evaluation and, for the first time in published research, investigated at the cellular level how halofuginone affected the extracellular region within the cell. The results showed that halofuginone significantly reduced fibrosis grades and arachnoid adhesions. On electron microscopy, it was associated with decreased collagen fibers. These findings suggest that halofuginone may alleviate fibrotic tissue formation by suppressing collagen production at the craniectomy site. As documented in prior studies, halofuginone has been shown to inhibit activation of the TGF-β signaling pathway by reducing levels of p-Smad3. The TGF-β pathway plays a crucial role in regulating extracellular matrix turnover,[23] and halofuginone has been observed to suppress collagen synthesis induced by TGF-β.[24] In summary, halofuginone potentially reduces fibrosis formation by decreasing collagen production, likely through inactivation of the TGF-β signaling pathway.[25]

The formation of adhesions after craniectomy results not only from an imbalance between synthesis and degradation of extracellular matrix (ECM) components but also from activation of the inflammatory response. Halofuginone has been reported to act on inflammatory mechanisms, leading us to hypothesize that halofuginone treatment may reduce fibrotic tissue formation by inhibiting inflammation. In our study, thickening of the dura mater was quantitatively assessed, and inflammatory cell status was examined by pathology and electron microscopy. As a result, significantly thinner dura mater was observed in the halofuginone group. In addition, electron microscopic examination revealed fewer inflammatory cells in the halofuginone group. Halofuginone had no significant effect on new bone formation in our study. In conclusion, halofuginone treatment inactivates multiple signaling pathways and reduces levels of pro-inflammatory cytokines, which may contribute to the suppression of inflammation.

CONCLUSION

Our study demonstrated that halofuginone effectively prevented fibrotic tissue formation in an experimental craniectomy model. Further research will help identify alternative agents capable of inhibiting the development of epidural fibrosis.

Ethics Committee Approval: This study was approved by the Health Sciences University Ankara Training and Research Hospital Ethics Committee (Date: 22.05.2024, Decision No: 774).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: T.T., D.B.C.; Design: T.T., D.B.C.; Supervision: T.T., D.B.C.; Resource: T.T., M.Ç., A.F., H.S.B.; Materials: H.S.B., A.F.; Data collection and/or processing: M.Ç., H.S.B., A.F.; Analysis and/or interpretation: T.T., D.B.C.; Literature review: T.T., D.B.C.; Critical review: D.B.C., T.T.

Conflict of Interest: None declared.

Financial Disclosure: The author declared that this study has received no financial support.

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DENEYSEL ÇALIŞMA - *ÖZ*

Halofuginonun sıçan kraniyektomi modelinde antifibrotik ve anti-inflamatuar özellikleri

AMAÇ: Kranioplasti, kraniektomi sonrası oluşan defektin çeşitli materyaller ile kapatılması işlemidir. Bu işlemin kraniektomi sonrası fibröz skarın oluşturduğu yapışıklıklar nedeniyle bazı komplikasyonları vardır. Bu komplikasyonlar arasında dura hasarı sonucu BOS fistülü ve parankim hasarı sonucu, kontüzyo ve serebral hematom yer almaktadır. Dichroa febrifuga'dan elde edilen düşük molekül ağırlıklı bir molekül olan halofuginon, tip I kolajen sentezini ve TGF-β sinyal yolunu inhibe ederek antifibrotik ve anti-inflamatuar özellikler göstermiştir. Bu çalışmanın amacı, halofuginonun kraniyektomi sonrası fibrotik doku oluşumu üzerindeki etkilerini bir sıçan modelinde araştırmaktır.
GEREÇ VE YÖNTEM: 20 erkek Wistar sıçana bilateral frontoparietal kraniektomi uygulandı ve iki gruba ayrıldı: serum fizyolojik ile tedavi edilen kontrol grubu ve ameliyat sonrası bir hafta boyunca oral halofuginon (1 mg/kg/gün) alan halofuginon grubu. 30 gün sonra, dura mater kalınlığı, epidural fibrozis, araknoid tutulumu ve kemik rejenerasyonunu değerlendirmek için histopatolojik ve ultrastrüktürel analizler yapıldı.
BULGULAR: Sonuçlar halofuginonun dura mater kalınlığını (19.3±6.51 µm'ye karşı kontrollerde 51.29±14.3 µm, $p<0.05$) ve epidural fibrozis derecelerini önemli ölçüde azalttığını ve halofuginon grubunda daha az araknoid yapışıklık gözlendiğini gösterdi ($p<0.05$). Elektron mikroskobu, halofuginon ile tedavi edilen sıçanlarda daha az aktif fibroblast ve daha ince, dağınık kolajen lifleri ortaya çıkardı, bu da fibroblast aktivitesinin ve kolajen üretiminin inhibisyonunu düşündürdü. Gruplar arasında kemik rejenerasyonunda anlamlı bir fark gözlenmedi.
SONUÇ: Bu bulgular, halofuginonun kraniyektomi bölgelerinde fibrotik doku oluşumunu, potansiyel olarak kolajen sentezini ve enflamatuar yanıtları baskılayarak etkili bir şekilde azalttığını göstermektedir. Ameliyat sonrası fibrozisi önlemede klinik uygulamalarını araştırmak için daha fazla çalışma yapılması gerekmektedir.

Anahtar sözcükler: Antifibrotik; halofuginon, kraniyoplasti; sıçan kraniyektomi modeli.

Ulus Travma Acil Cerrahi Derg 2025;31(11):1069-1074 DOI: 10.14744/tjtes.2025.70707