MHA MEDIHEALTH ACADEMY

Eurasian Journal of
Anesthesiology & Intensive Care

Original Article

doi
10.51271/EAJAIC-0021

From anesthesia to healing: the potential of topical sevoflurane in enhancing wound repair

Erdi Çelik[1], Sehbal Arslankoz[2], Pınar Koyuncu[3], Elmas Öğüş[3], Reyhan Polat[1], Aslı Dönmez[1]

[1]Department of Anesthesiology and Reanimation, Ankara Etlik City Hospital, Ankara, Turkiye
[2]Department of Pathology, Ankara Etlik City Hospital, Ankara, Turkiye
[3]Department of Biochemistry, Ankara Etlik City Hospital, Ankara, Turkiye

Cite this article: Çelik E, Arslankoz S, Koyuncu P, Öğüş E, Polat R, Dönmez A. From anesthesia to healing: the potential of topical sevoflurane in enhancing wound repair. *Eur J Anesthesiol Intens Care.* 2025;2(1):1-6.

Corresponding Author: Aslı Dönmez, aslidonmez@hotmail.com

Received: 01/10/2024 ◆ **Accepted**: 04/11/2024 ◆ **Published**: 03/02/2025

ABSTRACT

Aims: Sevoflurane is a volatile anesthetic agent commonly used for the induction and maintenance of general anesthesia. Recent case reports and case series have highlighted the analgesic and anti-inflammatory properties of sevoflurane when applied topically to venous ulcers, diabetic wounds, and infected wounds. This study investigates the therapeutic effects of topically applied sevoflurane on thermal burn wounds in rats, focusing on inflammatory responses and wound healing processes.

Methods: Twenty-one male Wistar Albino rats underwent the induction of a second-degree thermal burn covering 3 cm^2 on the interscapular skin. The animals were randomized into three groups: the experimental group (group S) received 3 ml of topical sevoflurane (1 ml/cm^2), the control group (group I) received 3 ml of isotonic saline, and the sham group (group K) received no treatment. Plasma concentrations of TNF-α, IL-1β, IL-6, and IL-10 were measured at baseline, and on days 7 and 14 post-injury. Histopathological evaluations of the burn sites were conducted on day 14, assessing for active and chronic inflammation, granulation, and fibrosis.

Results: All rats in the study maintained similar age and weight profiles across the groups. Histologically, the sevoflurane group exhibited significantly reduced chronic inflammation and enhanced granulation and fibrosis compared to controls. Immunologically, IL-6 and IL-10 levels were elevated in the isotonic group but did not differ significantly from baseline in other groups. Plasma cytokine levels were comparable across all groups.

Conclusion: Topical sevoflurane appears to promote wound healing by modulating inflammatory responses and enhancing tissue repair processes in a rat burn model. These findings indicate that sevoflurane may serve as a beneficial adjunctive therapy in the management of burn injuries and general wound care. Given its established anti-inflammatory effects when inhaled, there is a compelling need for further research to investigate the potential benefits and mechanisms of topical sevoflurane application. Such studies could provide valuable insights into optimizing wound healing processes and improving patient outcomes.

Keywords: Inflammation, sevoflurane, topical application, wound healing

INTRODUCTION

Sevoflurane is a volatile anesthetic agent commonly used for the induction and maintenance of general anesthesia. Recent literature has reported its potential as a topical treatment for venous ulcers, diabetic wounds, and infected wounds, demonstrating analgesic and anti-inflammatory effects that contribute to wound healing.[1-3]

Although the exact anti-inflammatory mechanisms of sevoflurane are not fully elucidated, hypotheses suggest it may modulate pro-inflammatory cytokine levels and stimulate anti-inflammatory pathways, particularly influencing IL-10 production.[4-6] Despite anecdotal evidence supporting topical sevoflurane's efficacy in analgesia and wound repair, a gap remains in clinical research regarding its healing effects. Wound healing is a complex process, critically involving inflammatory cell migration and signaling molecule expression, which are integral to tissue restoration following injury.[7]

This study aims to explore the impact of topical sevoflurane on wound healing by evaluating histopathological and immunochemical responses in a controlled rat model.

We hypothesize that the topical application of sevoflurane will significantly improve wound healing in a rat thermal burn model. This improvement is theorized to manifest through a quantifiable reduction in chronic inflammation and an increase in granulation tissue and fibrosis, as observed in histopathological evaluations. Furthermore, we posit that sevoflurane will modulate the expression of key immunochemical markers, including pro-inflammatory and anti-inflammatory cytokines, contributing to the complex physiological process of tissue repair and integrity restoration post-injury.

METHODS

Approval for this investigation was obtained from the Animal Experiments Local Ethics Committee of Ankara Training and Research Hospital (Date: 26.11.2020, Decision No: 0063-646). The study was undertaken at the Animal Research Centre of Ankara Training and Research Hospital and was financially supported by the Scientific Research Projects Coordination Unit of Health Sciences University Dışkapı Yıldırım Beyazıt Health Applications and Research Centre (BAP No: 78/03). We included 21 male Wistar albino rats, aged between 10-12 weeks, each weighing 250-300 grams. The subjects were randomly assigned into three distinct groups, identifiable by numbered tail labels, and comprised of the experimental group (group S, n=7), the control group (group I, n=7), and the sham group (group K, n=7). All rats were anesthetized with an intramuscular injection of 50 mg/kg ketamine (Ketalar flacon, Pfizer Pharma GMBH, Germany) and 10 mg/kg xylazine hydrochloride (Alfazyne 2%, Alfasan International, Holland). The back region of each rat was shaved, and a second-degree thermal burn measuring 3 cm^2 was induced on the shaved interscapular region using a heated metal plate. Group S received a topical dose of 3 ml (1 ml/cm^2) sevoflurane (Sevorane 100% 250 ml. solution, Abbvie Laboratories, IL, USA) applied as a liquid to the burn area. Sponges soaked with sevoflurane were held on the wound by the practitioner's gloved hand until the sevoflurane evaporated or the rats' respiratory patterns were disrupted by the evaporating sevoflurane. Group I received the same volume of isotonic saline, and group K received no intervention. Wound care was repeated every other day.

All rats were maintained under veterinary supervision for 14 days in the same environment, with identical food and water, in temperature-controlled cages with a 12-hour light-dark cycle. No antibiotics were administered to the rats at any time, and there were no animal losses during this period.

Intracardiac blood samples were collected from all rats on days 0,7, and 14. These blood samples were centrifuged at 3500 rpm for 10 minutes, and serum was separated and stored at -80°C until analysis. IL-1β, IL-6, IL-10, and TNF-α concentrations in the serum samples were analyzed using the Enzyme linked immunosorbent assay (ELISA) method (USCN, Wuhan, Hubei, PRC). Optical density (OD) measurements were taken for samples bound with biotinylated antibodies using an EL-800 ELISA reader, and cytokine concentrations were determined by comparing the OD of the samples with the OD curve of a standard sample.

On the 14th day, after deep anesthesia, the rats were sacrificed through intracardiac exsanguination and biopsy samples were obtained from the incision line, forming 2x2 cm^2 strips that included healthy tissue. After fixation in formalin, routine tissue processing was applied to all samples, and paraffin blocks were prepared. Two slices, each 4-5 μm in thickness, were sectioned from the paraffin blocks. One slice was stained with hematoxylin eosin (HE), and the other with Masson's trichrome stain (BESLAB, Histo-Med, Ankara, Turkey).

Additionally, on the tenth day, tissue samples were also scored for histopathological evaluation, including active inflammation, chronic inflammation, granulation tissue, and fibrosis, scored using a semi-quantitative method (0: none, 1: mild, 2: moderate, 3: severe).

The HE-stained slices were evaluated for active inflammation, chronic inflammation, and granulation tissue formation, while the Masson's trichrome-stained slices were assessed for fibrosis. The severity of acute and chronic inflammation was determined by roughly counting the proportion of neutrophil leukocytes for acute inflammation and mature lymphocytes and plasma cells for chronic inflammation observed in a high-power field. The formation of granulation tissue was evaluated according to the intensity of small vessel proliferation observed in a high magnification field. Fibrosis was graded according to fibroblastic activity beneath the wound tissue and collagenization. All parameters were scored semi-quantitatively as follows: 0 (none), 1 (mild), 2 (moderate), and 3 (severe). For acute inflammation: 0 (none): neutrophil leukocyte <5; 1 (mild): 10-50 neutrophils leukocytes; 2 (moderate): >50 neutrophils; 3 (severe): abscess formation or plate-forming neutrophil leukocyte observation. For chronic inflammation: 0 (none): <5 mature lymphocytes or plasma cells; 1 (mild): 5-50 mature lymphocytes or plasma cells; 2 (moderate); clustered mature lymphocytes and/or plasma cells; 3 (severe); diffuse infiltration of mature lymphocytes and/or plasma cells. Granulation tissue: 0 (none): no small vessel proliferation; 1 (mild): a few congested small vessel proliferations that do not form clusters in one high power field; 2 (moderate); proliferation of several small vessels arranged back-to-back in a high magnification field; 3 (severe): numerous small-diameter vascular structures in one high-power field. Fibrosis: 0 (none); No trichome staining was observed; 1 (mild); presence of sparse thin collagen fibers; 2 (moderate); the presence of collagen fibers that are coarsened but do not form bundles; 3 (severe): presence of coarse collagen fibers in bundles. Stained sections were examined independently by two pathologists.

Statistical Analysis

The data analysis was performed using SPSS for Windows version 21.0 software (Statistical Package for Social Sciences). Data did not conform to a normal distribution based on the Shapiro-Wilk test. Descriptive statistics are presented as median and interquartile range (IOR) values for continuous variables. Kruskal-Wallis test was applied for comparisons among the experiment, control, and sham groups, Friedman test for within-group comparisons, and ANOVA for the evaluation of all groups in repeated measurements. The Fisher Exact test was used for the comparison of categorical variables. A 95% confidence interval was used for result evaluation, and a p-value less than 0.05 was considered statistically significant in all analyses.

RESULTS

All rats in the study maintained similar age and weight profiles across the groups.

The histopathological findings of the groups and the distribution of inflammation severity are shown in Table 1. When statistical evaluations were made between the groups in terms of active inflammation, chronic inflammation, granulation, and fibrosis (Table 2), a difference in the severity of active inflammation was noted between the experimental, control, and sham groups, but it was not statistically significant (p>0.05). The severity of chronic inflammation was significantly lower in the sevoflurane group compared to the other two groups (p=0.011). Severe chronic inflammation was observed in 2 subjects in the sham group but was absent in the sevoflurane and isotonic groups. Mild chronic inflammation was observed in 6 subjects in the sevoflurane group, 2 subjects in the isotonic group, and 5 subjects in the sham group (Figure 1).

Granulation severity was significantly higher in the sevoflurane group compared to the other two groups (p=0.005). Severe granulation findings were observed in 4 subjects in the sevoflurane group, but none in the isotonic and sham groups. Mild granulation findings were observed in 4 subjects in the sham group and 1 subject in the isotonic group; no mild granulation was observed in the sevoflurane group (Figure 2).

Fibrosis severity was significantly higher in the sevoflurane group compared to the other two groups (p=0.018). Severe fibrosis findings were found in 5 subjects in the sevoflurane group, and in one subject each in the isotonic and sham groups. Mild fibrosis was observed in 1 subject in the sevoflurane group, 3 subjects in the isotonic group, and 6 subjects in the sham group (Figure 3).

When examining median (IQR) values, descriptive statistics, and comparative analyses for TNF-α, no statistically significant differences were found between the experimental, control, and sham groups at any time points examined (p>0.05). For IL-1β, no statistically significant differences were detected between the experimental, control, and sham groups at any time points examined (p>0.05). For IL-6, a statistically significant difference was observed in the isotonic group at the 14-day mark (p=0.012), but no significant changes were noted in IL-6 levels in the sham and sevoflurane groups (p>0.05). For IL-10, a statistically significant difference was found in the isotonic group at the 14-day mark (p=0.021), while no significant changes were noted in IL-10 levels in the sham and sevoflurane groups (p > 0.05) (Table 3).

Table 1. Comparative analysis of plasma TNF-α, IL-1β, IL-6, IL-10 levels

	Sham (n=7)	Isotonic (n=7)	Sevoflurane (n=7)	p*	p**
TNF-α (day 0) (pg/ml)	26.40 (76.32)	80.84 (73.00)	104.92 (198.28)	0.301	
TNF-α (day 7) (pg/ml)	116.16 (131.52)	225.92 (214.60)	160.86 (343.04)	0.572	0.732
TNF-α (day 14) (pg/ml)	133.14 (113.36)	157.60 (52.78)	141.30 (117.68)	0.925	
p* **	0.066	0.156	0.867		
IL-1β (day 0) (pg/ml)	7.12 (5.10)	9.16 (7.46)	5.08 (3.40)	0.291	
IL-1β(7.gün) (pg/ml)	8.14 (3.72)	9.48 (10.18)	9.16 (4.08)	0.476	0.738
IL-1β (day 14) (pg/ml)	7.80 (3.06)	6.78 (2.38)	8.82 (7.46)	0.477	
p* **	0.368	0.158	0.156		
IL-6 (day 0) (pg/ml)	4.26 (5.20)	4.72 (1.76)	4.26 (8.52)	0.687	
IL-6 (day 7) (pg/ml)	6.14 (5.44)	8.52 (2.58)	5.78 (1.56)	0.279	0.380
IL-6 (day 14) (pg/ml)	6.14 (3.08)	6.86 (2.60)	6.14 (4.02)	0.762	
p* **	0.368	**0.012**	0.867		
IL-10 (day 0) (pg/ml)	9.30 (0.00)	5.32 (7.98)	8.62 (5.98)	0.386	
IL-10 (day 7) (pg/ml)	11.94 (7.94)	15.92 (13.94)	14.60 (13.94)	0.360	0.691
IL-10 (day 14) (pg/ml)	15.26 (27.40)	19.26 (13.26)	24.56 (25.10)	0.669	
p* **	0.254	**0.021**	0.180		

Descriptive statistics were stated as median (IQR), p*: Intergroup comparisons over the same time period, p**: Intergroup comparisons across all time periods, p***: Within-group comparisons across all time periods

Table 2. Distribution and degree of histopathological findings

	Active inflammation	Chronic inflammation	Granulation	Fibrosis
Sham (n=7)				
K1	1	3	2	1
K2	2	1	1	1
K3	3	3	1	3
K4	3	1	2	1
K5	2	1	1	1
K6	3	1	1	1
K7	2	1	2	1
Isotonic (n=7)				
I1	1	2	2	2
I2	2	1	1	1
I3	2	2	2	3
I4	1	2	2	2
I5	3	1	2	1
I6	2	2	2	1
I7	1	2	2	2
Sevoflurane (n=7)				
S1	2	1	2	3
S2	1	1	3	3
S3	3	1	2	3
S4	3	1	3	3
S5	1	1	2	3
S6	3	2	3	2
S7	1	1	3	1

K: Sham group, I: Isotonic group, S: Sevoflurane group Histopathological evaluation: 0=none,1=mild, 2=moderate, 3=severe

DISCUSSION

The results of this study demonstrate that topical application of sevoflurane on thermal burn wounds in a rat model has a positive impact on wound healing. This impact is characterized by a reduction in chronic inflammation and an increase in granulation and fibrosis, as observed in the histopathological evaluation. However, there were no significant changes in the plasma levels of IL-6, IL-8, IL-10, and TNF-α when measured immunochemically.

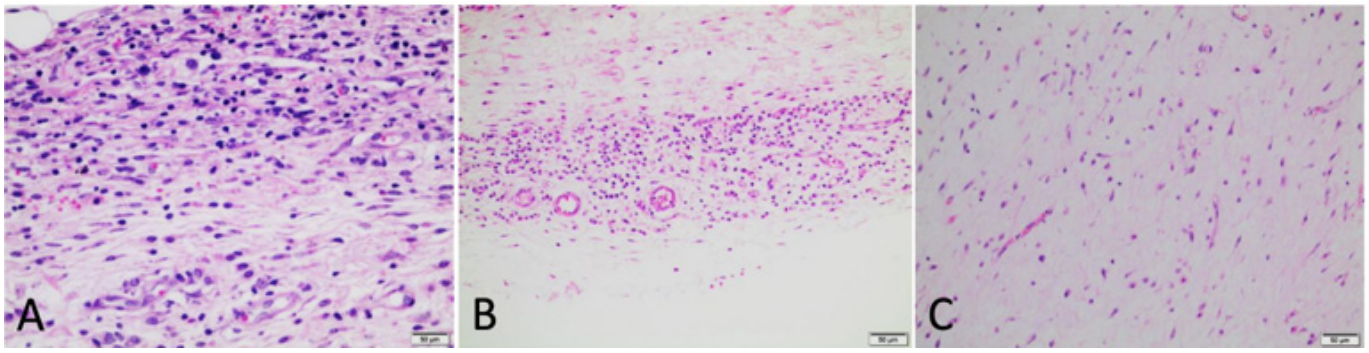

Figure 1. Histopathological evaluation of chronic inflammation, **A.** Severe chronic inflammation (H&E X200) observed in the Sham group. **B.** Severe chronic inflammation at the wound base in group I (H&E X200). **C.** Mild chronic inflammation noted in group S (H&E X200).

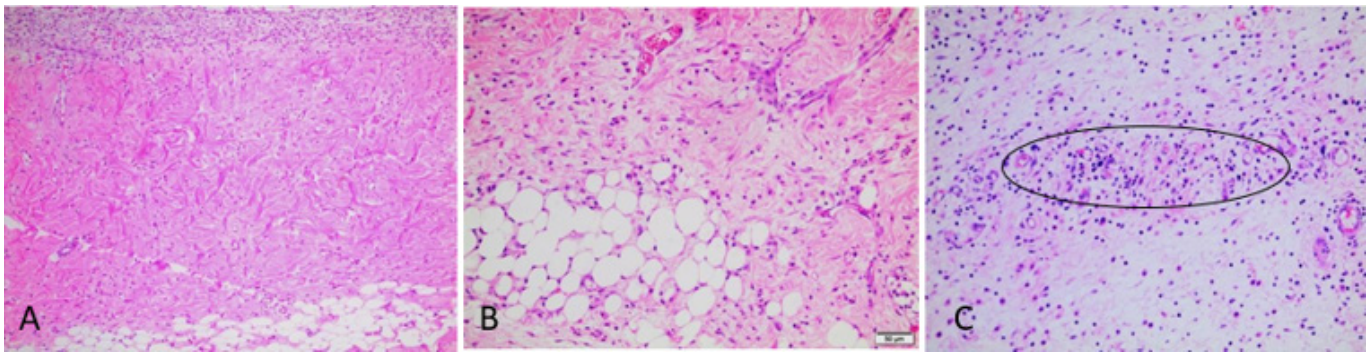

Figure 2. Analysis of granulation tissue formation, **A.** Signs of chronic inflammation in the upper part of the image with no granulation tissue development in group 0 (H&E X200). **B.** Chronic inflammation at the wound base without granulation tissue formation in group I (H&E X200). **C.** Proliferating vascular structures indicating granulation tissue in group S (H&E X200).

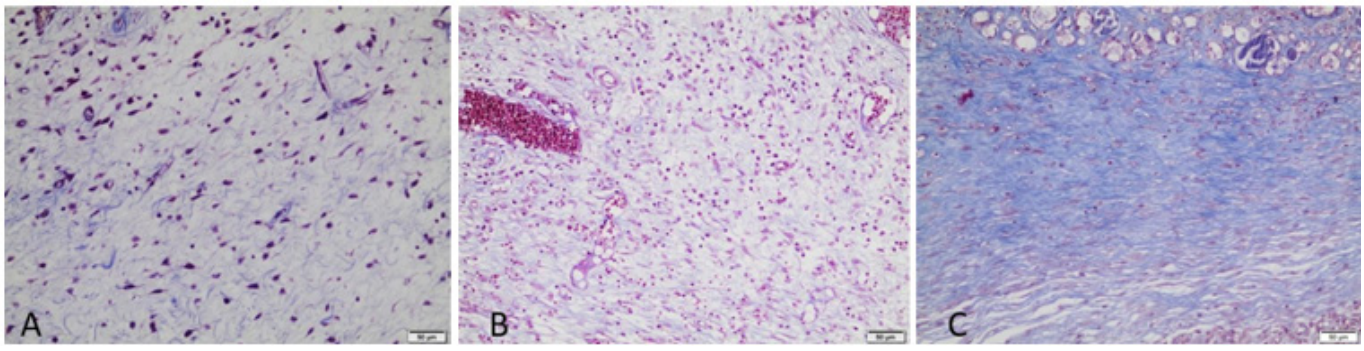

Figure 3. Evaluation of fibrosis, **A.** Mild fibrosis and a small number of stained collagen fibers observed in group 0 (Masson Trichrome X200). **B.** Minimal increase in collagen fibers at the wound base in group I (Masson Trichrome X 200). **C.** Severe fibrosis in group S, characterized by a notable increase in collagen fibers stained blue (Masson Trichrome X200).

Table 3. The severity of acute inflammation, chronic inflammation, granulation, and fibrosis

	Sham (n=7)	Isotonic (n=7)	Sevoflurane (n=7)	p*
Active inflammation				
None	0	0	0	**0.443**
Mild	1	3	3	
Moderate	3	3	1	
Severe	3	1	3	
Chronic Inflammation				
None	0	0	0	**0.013**
Mild	5	2	6	
Moderate	0	5	1	
Severe	2	0	0	
Granulation				
None	0	0	0	**0.006**
Mild	4	1	0	
Moderate	3	6	3	
Severe	0	0	4	
Fibrosis				
None	0	0	0	**0.023**
Mild	6	3	1	
Moderate	0	3	1	
Severe	1	1	5	

*Fisher Exact test was used for the comparisons of categorical variables. A value of $p<0.05$ was accepted as statistically significant in all the analyses

While the FDA currently approves only the inhalation form of sevoflurane, there are documented case reports that highlight the benefits of topical sevoflurane use. Such cases involve venous and ischemic ulcers that exhibit resistance to standard treatments and showcase improved wound healing and reduced analgesia requirements.[8-11] Additionally, there are publications in the literature describing the use of topical sevoflurane in surgical wounds infected with multidrug-resistant microorganisms[2], vascular ulcers[12], and cancer wounds.[1] These are clinical case reports and case series with small sample sizes, but the consistent theme is that topical sevoflurane application leads to accelerated wound healing, rapid and long-lasting pain reduction, and reduced reliance on traditional analgesics. The simplicity and safety of application make it well-tolerated by patients.[8,11,12] However, the specific mechanism of action of topically applied sevoflurane remains unclear.

To the best of our knowledge, there have been no previous studies examining the effects of topical sevoflurane on wound healing in rats. However, a previous study examining the effects

of inhaled sevoflurane on wound healing in rats reported a significantly decreased expression rate of procollagen 1 and 3, reflecting the rates of growth factor (bFGF) and collagen expression, in the group exposed to long-term (8 hours) sevoflurane compared to the group with a shorter exposure.[13] Researchers suggested that these findings might be related to the duration of sevoflurane exposure and its systemic immunosuppressive effects.

In the current study, the effects of topical sevoflurane on active inflammation, chronic inflammation, granulation tissue, and fibrosis were assessed histopathologically. The results revealed that while there were differences among the groups in terms of active inflammation, these differences were not statistically significant. However, the severity of chronic inflammation was significantly lower in the sevoflurane group compared to the other two groups. The reduced chronic inflammation observed in the sevoflurane group supports the anti-inflammatory potential of sevoflurane. Additionally, the level of granulation tissue, marked by fibroplasia, giant cells, and increased vascularization, was significantly higher in the sevoflurane group compared to the other groups. The greater extent of fibrosis in the sevoflurane group can be interpreted as wound size reduction and accelerated wound healing. It's worth noting that the study was terminated on the 14th day due to ethical considerations and logistical challenges, preventing the evaluation of sevoflurane's effects on wound dimensions. This aspect could be explored in longer-term studies with larger sample sizes.

Prior studies have demonstrated the anti-inflammatory properties of inhaled sevoflurane.[14-16] It has been shown to decrease the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8 and reduce microglial migration caused by pro-inflammatory cytokine production. While IL-1β is considered harmful in wound repair, it is necessary in the early stages of inflammation for wound healing. Similarly, pro-inflammatory cytokines like IL-1β, TNF-α, and IFN-γ have been found to be essential in the early stages of wound healing, demonstrating that they are not detrimental to wound repair. Furthermore, IL-6 and IL-8 levels have been shown to decrease in patients administered intraoperative sevoflurane, indicating its suppressive effects on pro-inflammatory cytokines. IL-10, another inflammatory cytokine, has anti-inflammatory properties by suppressing the production of inflammatory cytokines and plays a crucial role in regulating pro-inflammatory cytokine expression in wounds, contributing to scar-free healing.

In contrast to some of these previous studies, the current study did not reveal statistically significant differences in the serum levels of TNF-α, IL-1β, IL-6, and IL-10 between the groups at the examined time points. This lack of significance could be attributed to the limited sample size in the study due to ethical regulations for laboratory animals. Additionally, there is a lack of knowledge regarding the peak and decline times of cytokine expression, potentially contributing to the absence of significant results. Future studies with larger sample sizes and longer observation periods may provide more meaningful results.

The specific mechanism of action of topically applied sevoflurane remains unclear. Some case studies have indicated that topical sevoflurane could be a therapeutic option for wounds infected with multidrug-resistant microorganisms and painful chronic venous ulcers.[2-4,8-10] There is also a case study of a patient with ulcerative necrobiosis lipoidica diabetorum, which successfully treated the condition with topical sevoflurane and punch grafting, resulting in full epithelialization.[1]

Limitations

The limitations of the current study include the small group sizes due to ethical constraints and the relatively short observation period of 14 days. To further understand the effects of topical sevoflurane, larger sample sizes and longer-term studies are needed.

This study pioneers the investigation of topical sevoflurane's effects on wound healing in a rat model, contrasting with prior research focusing on its inhaled form. Although the study is constrained by the limited subject number and duration due to ethical considerations, it opens avenues for future research to further elucidate the therapeutic potential of sevoflurane in wound management. We postulate that sevoflurane's wound healing properties may be attributed to its anti-inflammatory action, as reflected by the reduced chronic inflammation and pronounced fibroplastic activity. Such activity is crucial during the granulation phase, a pivotal stage in wound repair marked by neovascularisation and fibroplasia. The significant fibrosis observed suggests that sevoflurane may accelerate wound closure and tissue repair, a hypothesis warranting further long-term studies. Previous findings have corroborated the anti-inflammatory properties of inhaled sevoflurane,[4-6] yet this study's lack of significant changes in plasma cytokine levels calls for additional research. Considering the limitations of subject number and study duration, extended investigations could yield more definitive insights, particularly if tissue-level cytokine expressions are examined. In summary, while the topical application of sevoflurane demonstrates promising histopathological benefits in wound healing, corroborative immunochemical evidence remains to be established. Future research should aim to extend the monitoring period and include a broader range of immunochemical parameters to substantiate the preliminary findings observed herein.

CONCLUSION

In summation, this investigation supports the premise that topical sevoflurane positively influences wound healing in a rat burn model. The histopathological data underscores a beneficial effect characterized by reduced chronic inflammation and enhanced granulation and fibrosis. These observations suggest the potential of sevoflurane as an adjunctive therapy in the management of burn injuries and wound care. However, the anticipated immunochemical support for these findings was not substantiated in plasma cytokine analysis within the study's timeframe. The absence of significant immunochemical data underscores the need for extended observation periods and a more comprehensive examination of tissue-level cytokine profiles. Such future studies could provide the necessary empirical evidence to firmly establish the therapeutic efficacy of sevoflurane for wound healing. Given the recognized anti-inflammatory effects of sevoflurane when inhaled, further research is warranted to explore its topical benefits. The pursuit of such knowledge could potentially unveil a novel therapeutic application for sevoflurane, revolutionizing wound management strategies and improving patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval for this investigation was obtained from the Animal Experiments Local Ethics Committee of Ankara Training and Research Hospital (Date: 26.11.2020, Decision No: 0063-646).

Informed Consent

Since this study is an animal experiment, informed consent is not required.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The study was financially supported by the Scientific Research Projects Coordination Unit of Health Sciences University Dışkapı Yıldırım Beyazıt Health Applications and Research Centre (BAP no: 78/03).

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Quintana-Castanedo L, Recarte-Marín L, Pérez-Jerónimo L, Conde-Montero E, de la Cueva-Dobao P. Ulcerative necrobiosis lipoidica diabeticorum successfully treated with topical sevoflurane and punch grafting. *Int Wound J*. 2019;16(5):1234-1236. doi:10.1111/iwj.13179
2. Rueda-Martínez JL, Gerónimo-Pardo M, Martínez-Monsalve A, Martínez-Serrano M. Topical sevoflurane and healing of a post-operative surgical site superinfected by multi-drug-resistant *Pseudomonas aeruginosa* and susceptible *Staphylococcus aureus* in an immunocompromised patient. *Surg Infect (Larchmt)*. 2014;15(6):843-846. doi:10.1089/sur.2013.079
3. Imbernon-Moya A, Ortiz-de Frutos FJ, Sanjuan-Alvarez M, Portero-Sanchez I, Merinero-Palomares R, Alcazar V. Treatment of chronic venous ulcers with topical sevoflurane: a retrospective clinical study. *Br J Anaesth*. 2017;119(4):846-847. doi:10.1093/bja/aex269
4. Potočnik I, Novak Janković V, Šostarič M, et. al. Antiinflammatory effect of sevoflurane in open lung surgery with one-lung ventilation. *Croat Med J*. 2014;55(6):628-637. doi:10.3325/cmj.2014.55.628
5. Yu X, Zhang F, Shi J. Effect of sevoflurane treatment on microglia activation, NF-kB and MAPK activities. *Immunobiology*. 2019;224(5):638-644. doi:10.1016/j.imbio.2019.07.004
6. Yu QB, Li HM, Li LL, Wang SY, Wu YB. Sevoflurane downregulates interleukin-6 and interleukin-8 levels in patients after cardiopulmonary bypass surgery: a meta-analysis. *Genet Mol Res*. 2015;14(4):19016-19027. doi:10.4238/2015.December.29.9
7. Chhabra S, Chhabra N, Kaur A, Gupta N. Wound healing concepts in clinical practice of OMFS. *J Maxillofac Oral Surg*. 2017;16(4):403-423. doi:10.1007/s12663-016-0880-z
8. Imbernón A, Blázquez C, Puebla A, et. al. Chronic venous ulcer treatment with topical sevoflurane. *Int Wound J*. 2016;13(5):1060-1062. doi:10.1111/iwj.12474
9. Hidalgo-Doniga C, Lopez-Lopez C, Pajero Otero V, et. al. Use of topical sevoflurane in pressure ulcer treatment in a double-lung transplant patient. *J Tissue Viability*. 2021;30(1):124-127. doi:10.1016/j.jtv.2020.07.003
10. Fernández-Ginés FD, Cortiñas-Sáenz M, Agudo-Ponce D, et. al. Pain reduction of topical sevoflurane vs intravenous opioids in pressure ulcers. *Int Wound J*. 2020;17(1):83-90. doi:10.1111/iwj.13235
11. Su L, Zheng J, Wang Y, Zhang W, Hu D. Emerging progress on the mechanism and technology in wound repair. *Biomed Pharmacother.* 2019;117:109191. doi:10.1016/j.biopha.2019.109191
12. Dámaso Fernández-Ginés F, Cortiñas-Sáenz M, Mateo-Carrasco H, et. al. Efficacy and safety of topical sevoflurane in the treatment of chronic skin ulcers. *Am J Health Syst Pharm*. 2017;74(9):176-182. doi:10.2146/ajhp151008
13. Cha MS, Lee HJ, Bae JH, Yang WS, Baik SW. Effects of sevoflurane on wound healing process. *Korean J Anesthesiol*. 2009;57(1):78-83. doi:10.4097/kjae.2009.57.1.78
14. Khan J, Noboru N, Young A, Thomas D. Pro and anti-inflammatory cytokine levels (TNF-α, IL-1β, IL-6 and IL-10) in rat model of neuroma. *Pathophysiology*. 2017;24(3):155-159. doi:10.1016/j.pathophys.2017.04.001
15. Alzoghaibi MA, Al-Oraini AI, Al-Sagheir AI, Zubaidi AM. Temporal expression of IL-1β and IL-10 in rat skin, muscle, small bowel, and colon wounds: a correlative study. *J Basic Clin Physiol Pharmacol*. 2014;25(2):205-210. doi:10.1515/jbcpp-2013-0073
16. de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med*. 1991;174(5):1209-1220. doi:10.1084/jem.174.5.1209