IJVAR International Journal of Veterinary and Animal Research

Journal homepage: https://ijvar.org/index.php/ijvar

RESEARCH ARTICLE

Antimicrobial Efficacy of Sevoflurane in Infected Wounds

Zeynep Cengiz[1]✉, Ali Belge[1], Zeynep Bozkan Ünal[1], Hafize Tuğba Yüksel Dolgun[2], Büşra Kibar[1]

[1]Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Surgery, Aydın, Türkiye
[2]Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Microbiology, Aydın, Türkiye

ARTICLE INFO

Received: 20/08/2025
Accepted: 18/03/2026

DOI: 10.71336/ijvar.702

✉**Corresponding Author:** zeynep.bilgen@adu.edu.tr

Keywords

Antimicrobial activity
Skin lesions
Methicillin-resistant
Staphylococcus aureus
Topical sevoflurane

Cite this article as: *Cengiz Z. et al. 2026. Antimicrobial Efficacy of Sevoflurane in Infected Wounds. International Journal of Veterinary and Animal Research, 9(1): 18-22. DOI: 10.71336/ijvar.702.*

ABSTRACT

The aim of this study was to investigate the antimicrobial efficacy of sevoflurane in wounds infected with *Staphylococcus aureus*, a species known for rapid antibiotic resistance. The study material was formed of 80 healthy, male Sprague-Dawley rats. A wound was created in each animal, and then infected with methicillin-sensitive *Staphyloccocus aureus* and with methicillin-resistant *Staphyloccocus aureus*. Isotonic sodium chloride, hypochlorous acid and liquid sevoflurane were applied to the wounds. Our results show that sevoflurane exhibited greater antimicrobial efficacy than both hypochlorous acid and isotonic sodium chloride in wounds infected with *Staphyloccocus aureus*. Therefore, topical use of sevoflurane could be considered a viable alternative, particularly for methicillin-resistant *Staphyloccocus aureus* infections. The wound healing with topical liquid sevoflurane was also seen to be more rapid than those with hypochlorous acid and isotonic sodium chloride.

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is an important pathogen causing infections in the skin and soft tissue (Cheng et al., 2011). In a previous study, the microorganism most often causing wound infections was reported to be *S. aureus* at the rate of 41.4% (Turhanoglu et al., 2018). Antibiotic-resistant *Staphylococcus* species have been isolated from skin lesions such as pyoderma in dogs (Rosser, 2006).

The solutions to be used in irrigation should be isotonic solutions to avoid causing osmotic damage in healing tissues. Lactate Ringer solution at 45°C or isotonic sodium chloride can be used for this purpose. The addition of antiseptics not only physically removes the bacteria causing the contamination but also provides antisepsis. Antiseptics such as hypochlorous acid can be used (Sakarya et al., 2014). However, the use of antibiotics can cause side-effects or the development of antibiotic resistance (Gottlieb et al., 2018). *S. aureus* have the ability to rapidly develop resistance to antibiotics. Therefore, alternative techniques independent of antibiotics have been sought for treatment or prevention (Kobayashi et al., 2015).

Topical application of liquid sevoflurane has been observed to provide healing in wounds infected with antibiotic-resistant micro-organisms (Rueda-Martinez et al., 2014).

Although there is a limited number of case reports in literature related to the antimicrobial effect of sevoflurane, and there are no controlled experimental model studies.

MATERIALS AND METHODS

Ethics and animals

Ethical approval for this study was obtained from Experimental Animals Local Ethics Committee of Aydin Adnan Menderes University (Approval number: 64583101/2020/136).

The study material was formed of 80 healthy male Sprague-Dawley rats (mean body weight 360.11±49.4 g). Animals had ad libitum access to food and water and were housed under controlled environmental conditions (22±2 °C, 50–55% relative humidity, 12-h light/12-h dark cycle). All procedures were performed in the Experimental Animals Unit, Faculty of Veterinary Medicine, Aydın Adnan Menderes University.

Preparation of inoculum

The standard methicillin-sensitive *S. aureus* ATCC 29213 and methicillin-resistant *S. aureus* ATCC 43300 strains were seeded in blood agar containing 5% sheep blood in the Microbiology Department, Veterinary Faculty, Adnan Menderes University, and incubated aerobically at 37°C for 24 hours. At the end of the incubation period, colonies were

observed on the blood agar, and a bacterial suspension was prepared in nutrient broth to a 0.5 McFarland turbidity for the *S. aureus* colonies. The prepared suspensions were adjusted to a rate of 2 X 10^8 kob/ml and prepared for immediate use at a volume of 100 µl (Mölne and Tarkowski, 2000; Winn et al., 2006).

Wound model, experimental groups and treatments

After a 2 week adaptation period, anesthesia was induced by isoflurane (FORANE, Abbott, Illinois, USA) using a drop jar method. The dorsal inter-scapular region of each animal was shaved with an electric cliper. Then skin was cleaned by povidone-iodine (POVIIODEKS, Tıpkimsan, İstanbul, Türkiye) and 70% isopropyl alcohol (ISOPROPYL ALCOHOL, Lepus Kimya, Tekirdağ, Türkiye). The skin was stabilized by one hand and a circular full thickness skin wound of 6 mm diameter was formed with a sterile punch biopsy (BIOPSY PUNCH-6mm, Kai Medical, Seki City, Japan). Wounds of the same size were thus created in all animals.

Immediately after the wounds were formed, rats were assigned to eight groups by simple randomization. At the same time, methicillin-sensitive *S. aureus* (MSSA) was inoculated on the wounds of 4 groups (Group 1, 2, 3 and 4) and methicillin-resistant *S. aureus* (MRSA) on the wounds of the other 4 groups (Group 5, 6, 7 and 8).

Immediately before inoculation (day 0), photographs of each wound were taken with a paper ruler placed next to the wound. The same procedure was repeated on day 3 and day 7. In this manner, the wound areas for each animal were calculated with the Image J (IMAGE J, Version 1.x, Loci, University of Wisconsin, USA). Wound healing was assessed by comparing wound areas between days 0 and 3, and 7.

Wound care started 24 h after in vivo infection and was performed twice daily by gently wiping the wound with a sterile 5×5 cm gauze pad moistened with equal volumes (5 mL) of isotonic saline (Group 2 and 6), hypochlorous acid (Group 3 and 7), or liquid sevoflurane (Group 4 and 8). For standardization Group 1 and 5 were control groups and no treatment was applied.

At the beginning of the study (day 0), the body temperature (T) and the bodyweight (BW) were measured, and the same procedures were repeated on days 3 and 7.

Post-treatment bacterial isolation and identification

On day 7 of the experiment, samples were collected for bacterial isolation and identification using a sterile transport swab (CULTIPLAST®, LP Italiana SPA, Milano, Italy) from the wounds. The obtained samples were sent to the Microbiology Department laboratories of the Veterinary Faculty at Aydın Adnan Menderes University for biochemical and carbohydrate fermentation tests and microbiological analysis for the isolation and identification of *S. aureus*.

Sheep blood agar (5%) was used for incubation in an aerobic environment at 37°C for 24 hours. After incubation, the colonies isolated were tested with a gram stain. Under light microscopy, colonies identified as Gram-positive were subjected to catalase and coagulase tests. Colonies determined as positive in the catalase and coagulase tests were confirmed with the Phoenix Automated Identification System (BD PHOENIX™, BD Biosciences, USA). For this, suspected colonies were purified on trypticase soy agar and incubated at 37°C for 24 hours. At the end of the incubation, suspensions were prepared at 0.5 McFarland density with ID broth prepared in test tubes from fresh cultures. The Phoenix PMIC/ID87 (BD PHOENIX™ PMIC/ID87, BD Biosciences, USA) panel was used for the identification of Gram-positive bacterial isolates.

Statistical analysis

An a priori power analysis was conducted for a repeated-measures, between-factors design with 8 groups and 5 measurements to detect a medium-to-large effect size ($f = 0.35$) at $\alpha = 0.05$ with power = 0.80. The total sample size was determined to be 80 (10 per group). Analysis used F-tests for repeated measures with between-subject factors. The power analysis was performed with G*Power 3.1, and the actual power for the specified design was 0.816.

Standardization was applied to avoid bias originating from differences in wound areas between the groups, and the wound tissue healing was expressed as percentages. As there were 8 groups and the standardization method was used, the Kruskal-Wallis test was applied in the statistical analysis of the wound areas. To determine which groups differed, post hoc comparisons were conducted using the Dwass–Steel–Critchlow–Flignet (Dwass–Steel–Critchlow–Fligner) method. Statistical analyses of the data were performed using SPSS (SPSS® Statistics version14.1, Licence No. 9869264, International Business Machines®, New York, USA) and R software. A value of $p<0.05$ was considered statistically significant.

RESULTS

The mean bodyweight (BW) and temperature (T) values for the groups and the changes between days 0, 3, and 7, are shown in Tables 1 and 2, respectively.

On day 7 of wound treatment, the wounds had markedly reduced in size, and it was determined that wound cleaning would be ineffective on subsequent days due to thickening of the scab; as a result, sampling with a swab was not feasible without disturbing the scab, and wound care was terminated on day 7. Wound photographs from days 0, 3, and 7 are presented in Figure 1.

Healing percentages for the study groups are shown in Table 3 and Figure 2. On day 3, there was a statistically significant difference in wound healing between Group 1 and Group 3, and between Group 3 and Group 5. The healing percentage in Group 3 was higher than in Groups 1 and 5. When the day 7 wound data were evaluated, the healing percentage of Group 4 was statistically significantly higher than that of Groups 1, 2, 3, 5, 6, and 7, and the healing percentage of Group 8 was statistically significantly higher than that of Groups 1, 3, and 7.

Regarding bacterial isolation and identification on day 7, animals treated with sevoflurane showed greater improvement, with negative cultures. The proportions of positive and negative *S. aureus* cultures are presented in Table 4.

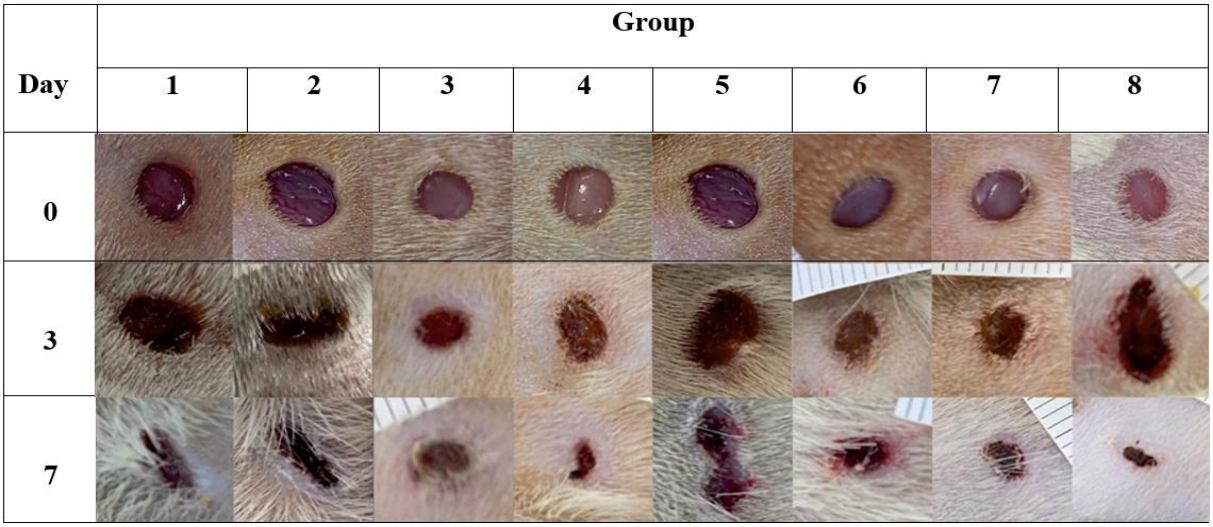

Figure 1. Photographs of the wounds at 0, 3 and days 7 of the study

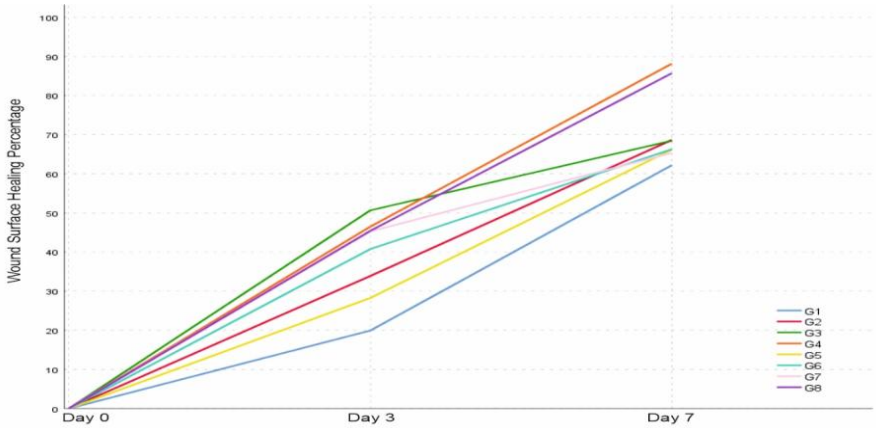

Figure 2. The healing percentages of the study groups according days

Table 1. The mean bodyweights of the groups by days

	Time (Day)			p	
Group	**0**	**3**	**7**	**Group**	**Day**
Group 1	332.5±28.54^{cd}	363.2±25.31^{b}	363.9±28.98^{b}		
Group 2	307.7±17.73^{d}	356±24.78^{b}	375.4±19.56^{b}		
Group 3	364.4±27.61^{b}	383±32^{ab}	388.6±32.28^{ab}		
Group 4	432±36.03^{a}	411.5±47.14^{a}	424.3±29.96^{a}		
Group 5	301.7±22.16^{d}	350.4±35.18^{b}	374.8±32.18^{b}	<0.001	<0.001
Group 6	371.5±20.02^{bc}	393.5±18.96^{ab}	396.5±20.24^{ab}		
Group 7	382±30.86^{b}	396±42.38^{ab}	389.8±26.48^{ab}		
Group 8	389.1±36.41^{b}	396.5±37.1^{ab}	399.5±36.16^{ab}		
All Groups	360.11±49.4^{C}	381.26±38.61^{B}	389.1±32.58^{A}		

a, b, c, d: Different letters in the same column indicate statistically significant difference in groups ($p<0.05$).
A, B, C: Different letters on the same line indicate statistically significant difference in time ($p<0.05$).

Table 2. The mean body temperature of the groups by days

	Time (Day)			p	
Group	**0**	**3**	**7**	**Group**	**Day**
Group 1	26.57±0.8^{a}	26.94±0.95^{b}	30.07±1.19^{a}		
Group 2	28.55±1.22^{a}	27.86±0.76^{ab}	29.77±1.24^{ab}		
Group 3	28.15±0.88^{a}	28.84±1.33^{a}	27.49±1.41^{c}		
Group 4	28.02±0.71^{a}	27.73±0.64^{ab}	27.74±1.14^{c}		
Group 5	27.9±0.68^{ab}	28.63±0.52^{a}	28.17±1.23^{bc}	<0.001	0,221
Group 6	27.59±0.65^{b}	28.31±1.05^{b}	27.94±0.67^{c}		
Group 7	28.36±0.71^{a}	28.05±0.94^{b}	28.12±1.58^{c}		
Group 8	29.03±1.81^{a}	28.32±0.8^{b}	27.52±0.68^{c}		
All Groups	28.02±1.18	28.09±1.15	28.35±1.47		

a, b, c: Different letters in the same column indicate statistically significant difference in groups ($p<0.05$)

Table 3. The healing percentages of the study groups

Group	N	3rd day healing %	7th day healing %
1	10	18 (15.4-23.9) [cd]	59.8(57.2-69.7) [c]
2	10	29.8 (28.1-40.7) [acd]	66.3(63.8-74.4) [bc]
3	10	50.9 (46.7-59.2) [ab]	69.1(64.8-73.4) [c]
4	10	48.6 (41.1-53.6) [abd]	89.6(86.4-91.4) [a]
5	10	30.2 (20.4-36.6) [cd]	64.2(57.9-76.8) [bc]
6	10	46.2 (23.8-55.5) [abcd]	64.8(60.1-66.5) [bc]
7	10	42.6 (39.8-55.5) [abd]	70.2(59.1-71.2) [c]
8	10	46 (36.2-55.3) [abd]	83.8(82.2-93.8) [ab]

a, b, c, d: Different lettering in the same column indicates statistically significant difference

Table 4. The rate of positive and negative *S. aureus* cultures after treatment

Group	Negative culture (%)	Positive culture (%)
1	-	100
2	-	100
3	20	80
4	79	21
5	30	70
6	10	90
7	60	40
8	90	10

DISCUSSION AND CONCLUSION

The healing effect of liquid sevoflurane arises from several properties: a direct antimicrobial effect, a local anesthetic effect, and, theoretically, a vasodilatory effect. The local anesthetic effect has been shown to facilitate irrigation and to permit higher-quality irrigation. (Rueda-Martinez et al., 2014).

Martinez-Monsalve et al. (2018) applied topical sevoflurane during surgical debridement and reported that the analgesic effect of sevoflurane began rapidly, was long-lasting, and was adequate. In the current study, in contrast to the information in literature, desensitization, licking/chewing movements, aggressive behavior or findings of pain such as writhing were not observed in any rat during wound care, which prevented evaluation of the local anaesthetic effect of sevoflurane, and it was thought that this was due to the animals not feeling pain as the acute wounds were only cleaned by wiping rather than performing abscess irigation or wound debridement. Moreover, when the mean body weight values of the groups were examined, the changes did not indicate loss of appetite.

Although there were statistically significant differences between the groups in respect of the mean body temperatures, the group mean values were not outside the limits of normal values, and thus it was concluded that the change in body temperatures did not indicate clinical significance.

In studies conducted on methicillin-resistant *S. aureus,* Imbernon-Moya et al. (2017) applied local sevoflurane without any systemic antibiotics in 3 patients with chronic venous ulcers in the extremities infected with antibiotic-resistant *Pseudomonas aeruginosa* and MRSA. It was reported that sevoflurane reduced bacteria colonization, foul smell, and exudation. At the end of the first month, the wound in the patient infected with MRSA was fully closed and no bacteria were isolated. In the present study, it was observed that wound healing up to day 3 was better in the hypochlorous acid–treated group than in the 0.9% NaCl–treated group. Wound cleaning with liquid sevoflurane in the groups infected with the MRSA was seen to provide greater healing than in group treated with hypochlorous acid. In the wounds treated with sevoflurane, there was seen to be healing of 83.8% (Group 8) of the wound area on day 7, and this rate was <70.2% in the other groups.

According to the swab samples on day 7, there was negative *S. aureus* culture of 90% of animals treated with sevoflurane. However positive culture was determined in 40% of the rats where hypochlorous acid was used. Similar to the study by Imbernon-Moya (2017), it was concluded in the current study that *S. aureus* infections were brought under control more quickly with sevoflurane, primarily more successfully in methicillin-resistant strains.

For methicillin-susceptible *S. aureus*, The effect on wound healing of the use of hypochlorous acid was seen to be better up to day 3 compared with the control group. The use of hypochlorous acid on wounds infected with MSSA provided healing of 50.9% of the wound area in the first 3 days. In a case report Gencay (2019), applied local sevoflurane to a pressure ulcer, and necrotic tissues were cleared and wound culture was negative after one month. In our study, on day 7, wound cleaning with liquid sevoflurane in the groups infected with the MSSA was seen to provide greater healing than in all the other groups. This rate was 89.6% in wound care group with sevoflurane and was lower than 69.1% in the other groups.

According to swab samples collected on day 7, 79% of the animals treated with sevoflurane had negative *S. aureus* cultures. However, positive cultures were detected in 80% of the rats treated with hypochlorous acid. (Group 3). A study conducted on mice by Kuwabara et al. (2018) compared hypochlorous acid and pure water application in wounds infected with *P. aeruginosa.* It has been reported that hypochlorous acid is superior in both wound healing and infection control. In our study, when we examined the effect of hypochlorous acid on MSSA, on day 7 the percentage of wound healing was not statistically different from the control and the isotonic sodium chloride group. However, relative to these two groups, the hypochlorous acid group had a lower rate of positive cultures. In other words, for infection control, hypochlorous acid was more effective than isotonic saline but less effective than sevoflurane.

Lee et al. (2010) anesthetized wounded rats with sevoflurane in an anesthesia chamber, and reported that sevoflurane might alter the inflammatory phase and reduce collagen formation. Similarly, Cha et al. (2009) exposured rats to inhalant sevoflurane and reported that sevoflurane decreased blood flow in the wound and enlarged the wound area. In contrast to this studies, in our research sevoflurane was not applied via inhalation; it was applied topically as a liquid and was more effective in wound healing than other solutions. Simillary, according to Çelik et al. (2025), topical sevoflurane promotes burn injury healing by modulating inflammatory reponses and enhancing tissue repair.

In conclusion, topical sevoflurane was found to be superior in antimicrobial efficacy and wound healing rate compared with hypochlorous acid and isotonic sodium chloride in wounds infected with MRSA and MSSA. Wound care with liquid sevoflurane may be expensive but could offer an alternative for antibiotic-resistant bacteria.

In our study, wound care was performed with small amounts of sevoflurane, so the researcher applying the treatment was not exposed to the odor. However, when larger wounds require application, it is recommended to use a well-ventilated room to protect the operator.

As there are few studies related to the antimicrobial property of sevoflurane and the wound healing effect, the

current study can be considered a resource for future studies.

LIMITATIONS

This study did not assess the histopathological effects of sevoflurane, which is a limitation. It is also known that treatment of chronic wounds is more challenging than that of acute wounds. Therefore, future studies should investigate the effects of sevoflurane on chronic wounds and elucidate its histopathological effects.

Acknowledgement

The authors declare that there are no acknowledgements.

Ethical Declaration

Ethical approval for this study was obtained from Experimental Animals Local Ethics Committee of Aydin Adnan Menderes University (Approval number: 64583101/2020/136).

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authorship contributions

Concept: Z.C., Design: B.K.K., Z.C., Data Collection: Z.C., Z.B.Ü., B.K.K., Analysis: Z.C., H.T.Y.D., Literature Search: Z.C., A.B., Z.B.Ü., Writing: Z.C., A.B., H.T.Y.D.

Financial Support

This study was supported by Aydın Adnan Menderes University Scientific Research Fund (Project No. VTF-19033).

Additional informations.

This study does not cover any thesis. This study has not been previously presented at any congress/symposium or published in another journal.

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