

## A comparison of the efficacies of heterologous blood, rifamycin, and talc as pleural sclerosants in rabbits: An experimental study

*Tavşanlarda plevral sklerozan ajan olarak heterolog kan, rifamisin ve talk'ın etkinliğinin karşılaştırılması: Deneysel çalışma*

İsa Döngel,<sup>1</sup> Güven Sadi Sunam,<sup>2</sup> Özgür Külahcı,<sup>3</sup> Sami Ceran<sup>4</sup>

<sup>1</sup>Department of Thoracic Surgery, Sivas Numune Hospital, Sivas, Turkey

<sup>2</sup>Department of Thoracic Surgery, Medical Faculty of Selçuklu University, Konya, Turkey;

<sup>3</sup>Department of Pathology, Samandağı State Hospital, Hatay, Turkey;

<sup>4</sup>Department of Thoracic Surgery, Medical Faculty of Meram University, Konya, Turkey

**Background:** In this study, we aimed to investigate the efficacy of rifamycin pleurodesis in rabbits.

**Methods:** A total of 21 male New Zealand-type albino rabbits with an average weight of 3433 grams, were used in the study. One rabbit was used for blood supply. The other 20 rabbits were divided into four groups, including the control group, the heterologous blood group, the rifamycin group, and the talc group. Distilled water, heterologous fresh blood, rifamycin, and sterile liquid talc were administered through the catheter to the left hemithorax of rabbits. The rabbits were sacrificed using high-dose anesthesia on day 28. The pleural spaces were grossly assessed for evidence of pleurodesis and microscopic thickness of the pleura, and evidence of inflammation and fibrosis were examined. The degree of pleurodesis was rated on a scale of 0 to 4.

**Results:** No statistically significant differences were observed between the control and heterologous blood groups at the macroscopic and microscopic level ( $p>0.05$ ). The degree of pleurodesis in the talc and rifamycin groups was higher than in the control and heterologous blood group ( $p=0.04$ ). No significant difference was observed between the talc and rifamycin groups in terms of macroscopic and microscopic examination ( $p>0.05$ ). The median values of fibrosis thickness of the control, heterologous blood, rifamycin, and talc groups were 10 (10-29), 26 (10-71), 312 (264-351) and 304 (238-331)  $\mu\text{m}$ , respectively.

**Conclusion:** The efficacy of rifamycin pleurodesis in rabbits was microscopically and macroscopically similar to the talc group and superior to the control and heterologous blood group.

**Key words:** Rifamycin; heterologous blood; pleurodesis; talc.

**Amaç:** Bu çalışmada tavşanlarda rifamisin plörodezis etkinliği araştırıldı.

**Çalışma planı:** Çalışmada ortalama ağırlıkları 3433 g olan toplam 21 adet erkek Yeni Zelanda türü albino tavşan kullanıldı. Bir adet tavşan kan temininde kullanıldı. Diğer 20 tavşan kontrol grubu, heterolog kan grubu, rifamisin grubu ve talk grubu olarak dört gruba ayrıldı. Tavşanlara gruplarına göre sol hemitoraksa takılan katederden distile su, heterolog taze kan, rifamisin ve steril sıvı talk verildi. Yirmi sekizinci günde tavşanlar yüksek doz anestezi ile sakrifiye edildi. Plevrada makroskopik olarak plörodezis varlığı ve mikroskopik olarak plevral kalınlıkları ölçüldü ve inflamasyon ve fibrozis bulguları araştırıldı. Plörodezis derecesi 0'dan 4'e kadar olan skalada değerlendirildi.

**Bulgular:** Makroskopik ve mikroskopik seviyede kontrol grubu ile heterolog kan grubu arasında istatistiksel olarak anlamlı fark bulunmadı ( $p>0.05$ ). Talk ve rifamisin grubunda plörodezis derecesi kontrol ve heterolog kan grubundan daha yüksek idi ( $p=0.04$ ). Rifamisin grubu ile talk grubu arasında makroskopik ve mikroskopik incelemede anlamlı fark bulunmadı ( $p>0.05$ ). Plevral fibrozis kalınlığının medyan değerleri kontrol, heterolog kan, rifamisin ve talk grupları için sırasıyla 10 (10-29), 26 (10-71), 312 (264-351) ve 304 (238-331)  $\mu\text{m}$  ölçüldü.

**Sonuç:** Tavşanlarda rifamisin plörodezis etkinliği mikroskopik ve makroskopik olarak talk grubu ile benzer; kontrol ve heterolog kan grubuna göre daha üstün bulundu.

**Anahtar sözcükler:** Rifamisin; heterolog kan; plörodezis; talk.



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Correspondence: İsa Döngel, M.D. Sivas Numune Hastanesi Göğüs Cerrahisi Kliniği, 58040 Sivas, Turkey.

Tel: +90 505 - 222 83 88 e-mail: drdongel@hotmail.com

To stimulate chemical pleurodesis, pleural fibrosis is used to create the adherence of pleural leaves by applying a chemically efficient sclerosant to the pleural cavity. This is carried out by making use of various cytostatic and sclerotic agents through pleurodesis performed via thoracotomy or a tube thoracostomy.

Although there are many clinical and experimental studies on inflammation created by pleurodesis, they provide no detailed explanations. With this aim in mind, substances like blight, formalin, paraffine, eucalyptus oil, Sudan IIIA, magnesium oxide, alcohol, and ether have been tried. Other currently used agents, such as talc, antineoplastic drugs, tetracycline and its derivatives, and *Corynebacterium parvum* have also been employed; however, there is still no consensus on which agent should be employed for pleurodesis.

In our clinical experiences, we observed that rifamycin leads to inflammation and fibrosis during the healing of wounds. Therefore, we aimed to compare two easily available simple new agents: heterologous blood, which is known to be efficient in the pleurodesis of rabbits, and rifamycin, which is thought to have the same quality. Furthermore, they appear to have no significant side effects and can be administered painlessly with talc, which is known to be the most efficient agent for this application.

## MATERIALS AND METHODS

This study was carried out in Selçuk University Experimental Medicine and Application Center, the Department of Thoracic Surgery, Meram Faculty of Medicine. Pathological specimens were examined in the pathology department at the university.

### Ethical board and scientific research project support

After the study plan was devised, it was approved by the Experimental Animal Ethics Board at the Experimental Medicine Research and Application Center, Selçuk University (Issue No: 18/02/2008-02), and funding for this project was obtained from the Scientific Research Project (SRP) Coordinator.

### Experimental animals

In this study, 21 New Zealand male albino rabbits with an average weight of 3433 grams were used. The ease of the surgical procedure and the availability of the rabbits were criteria for the selection of the experimental animals. During the study, the ethical rules and concerns of the Society for the Prevention of Cruelty to Animals were taken into consideration.

### Anesthesia

The animals were subjected to general anesthesia with ketamine hydrochloride (HCL) (ketamine: 2-5%) at a concentration of 35 mg/kg via intramuscular injection. Xylazine (Rompun® 250 ml Bayer Corp., İstanbul, Turkey) was administered at 5 mg/kg for sustained intramuscular effects.

### Surgical protocol

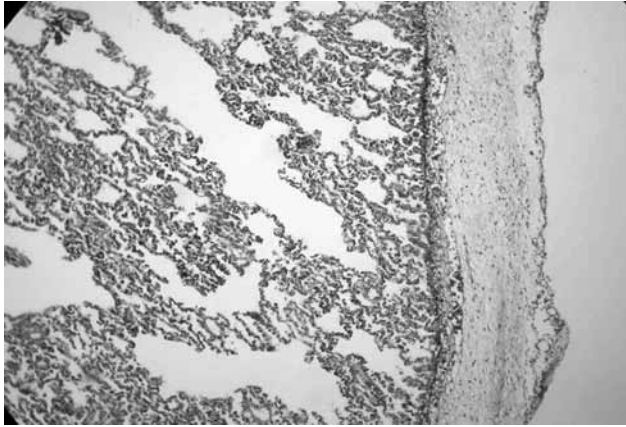
One rabbit was used as a fresh blood source. The other 20 rabbits were divided into four groups so that the number of rabbits in each group was equal (n=5).

Before the experiment, the rabbits had number tags attached to their ears, and their weights were recorded in grams. Under general anesthesia, the left hemithorax was shaved and cleaned with polyvinylpyrrolidone solution. Under sterile conditions, a 16 F thorax catheter was in to the left hemithorax of all the rabbits while lying on their right side. The control group received 10 ml of distilled water from the catheter. Heterologous fresh blood at 1 ml/kg was added to the distilled water up to 10 ml and given through a catheter to the animals in the heterologous group while 20 mg/kg rifamycin was added to the distilled water, with 10 ml being given through a catheter to the animals in the rifamycin group. Sterile liquid talc at 70 mg/kg was added to the distilled water, and 10 ml was given through the catheter. Since the rifamycin contained lidocaine, the same amount of this anesthetic was added to the other groups.

After the thoracic catheters were inserted and removed postoperatively, chest X-rays were taken to assess the position of the drains and the presence of pneumothorax.

After 28 days, the 20 rabbits were sacrificed with a high dosage of anesthesia. Afterwards, macroscopic adhesion in the rifamycin administered hemithorax was observed in each group via a sternotomy. Pathological specimens were stained with hematoxylin and eosin (H-E) and Masson's Trichrome (MT). They were then sent to the pathology department for microscopic examination. The degree of inflammation and fibrosis was evaluated blindly by a pathologist, and a semi-quantitative evaluation was performed. The thickness of pleural fibrosis was measured microscopically (Figure 1), and it was graded as none (0=0-25  $\mu\text{m}$ ), equivocal (1=25-50  $\mu\text{m}$ ), mild (2=50-150  $\mu\text{m}$ ), moderate (3=150-300  $\mu\text{m}$ ), and marked (4=300  $\mu\text{m}$  and over).

Macroscopic and microscopic scoring of the groups was carried out by observing the criteria listed in Table 1. The degree of gross pleurodesis was graded according to the following scheme: 0= normal pleural space,



**Figure 1.** Marked pleural fibrosis due to rifamycin as seen under microscopic examination (M-T 400).

1= no adhesions, but the pleural space was inflamed as evidenced by roughness and fibrin deposition, 2= a few scattered adhesions, 3= generalized scattered adhesions, and 4= complete obliteration of the pleural space by adhesions (Figures 2a and b).

**Statistical analysis**

For analysis of the data, the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 13.0 software program was used. The Kruskal-Wallis variation analysis was used to compare the groups. For two-way comparisons, the Mann-Whitney U-test was used with Bonferroni correction, and  $p < 0.05$  was accepted as the significance level.

**RESULTS**

The distribution of the macroscopic and microscopic inflammation and fibrosis scale scores by groups are summarized in Table 2, and these scores were higher in the rifamycin and talc groups than in the control and heterologous blood groups for both macroscopic and microscopic two-way comparisons ( $p = 0.04$ ). However, there were no significant differences between the

fibrosis and inflammation scores of the rifamycin and talc groups for the same two-way comparisons ( $p > 0.05$ ).

A macroscopic lung abscess showing complete obliteration at the macroscopic and microscopic levels of the abscess wall developed in one of the rabbits in the talc group; necrosis was observed and verified microscopically.

Due to fibrosis and inflammation, the thickness of the pleura in the rifamycin and talc groups was higher than what was found in the control and heterologous blood groups ( $p = 0.008$ ). However, there were no significant differences between the thickness of fibrosis and inflammation scores in the rifamycin and talc groups the macroscopic and microscopic two-way comparisons were done ( $p > 0.05$ ; Figure 3). The medians of the fibrosis thickness of the control, heterologous blood, rifamycin, and talc groups were 10 (range 10-29), 26 (range 10-71), 312 (range 264-351), and 304 (range 238-331)  $\mu\text{m}$ , respectively.

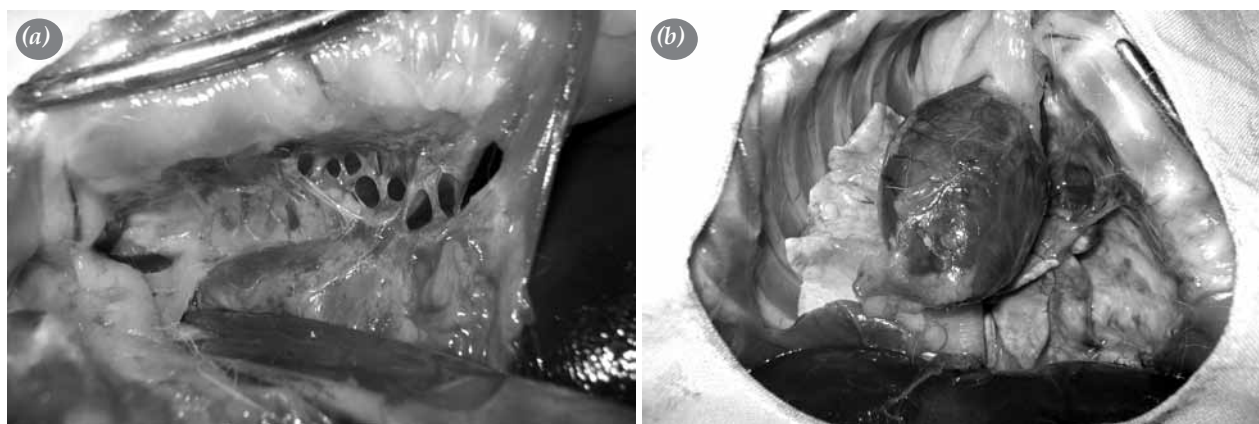
**DISCUSSION**

The procedure of sticking pleural leaves to each other by applying a substance with a sclerosant effect to the pleural cavity of expansible lungs is called chemical pleurodesis. Before pleurodesis is carried out, the lungs must be able to completely re-expanded. If the lungs re-expanded, fully when the main bronchus is completely occluded or when the lungs are trapped, pleurodesis will not be effective. Therefore, it is important that the patients who are being considered for pleurodesis show significant decreases in complaints of dyspnea after thoracentesis or show no expansion deficiencies on a lung graph.

There have been various studies and points of view about sclerotic agents and potential methods which are inapplicable to the pleurodesis procedure. Although various chemicals are used for pleurodesis, there is no true sclerosant that is currently recommended. It

**Table 1. Macroscopic and microscopic scores of the groups**

	Macroscopic	Microscopic
Score 0	Normal pleural cavity	Inflammation and fibrosis= None (0=0-25 $\mu\text{m}$ )
Score 1	Inflammation of pleural cavity; no adhesion	Inflammation and fibrosis= Equivocal (1=25-50 $\mu\text{m}$ )
Score 2	A few scattered adhesions	Inflammation and fibrosis= Mild (2=50-150 $\mu\text{m}$ )
Score 3	Common scattered adhesions	Inflammation and fibrosis= Moderate (3=150-300 $\mu\text{m}$ )
Score 4	Full obliteration of the pleural cavity with adhesion	Inflammation and fibrosis= Marked (4=300 $\mu\text{m}$ and over)



**Figure 2.** (a) The macroscopic appearance of adhesions due to rifamycin. (b) The comparative macroscopic appearance of the thoracic wall is shown along with obvious pleural thickening. There is adhesion on the left side, which was administered rifamycin, but there is no evidence of pleural adhesion and thickening on the right side.

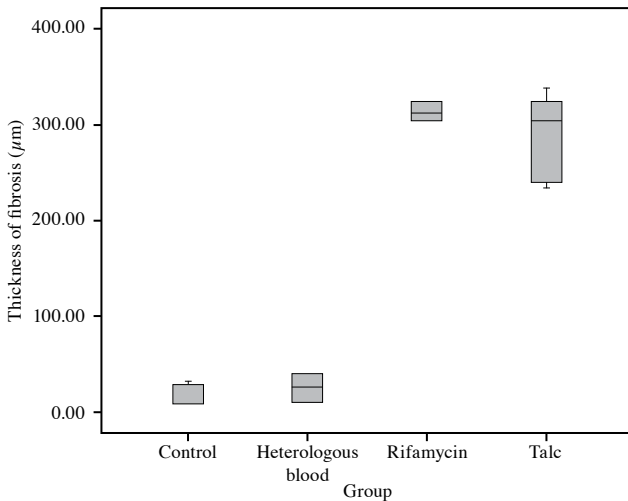
is difficult to make adequate assessments of specific chemical agents because of the low number of patients, different techniques, and criteria for success in these studies along with the lack of comparative randomized studies.<sup>[1,2]</sup> Sterile asbestos, free talc, tetracycline, doxycycline, antineoplastic agents (bleomycin, cisplatin, and cytosine arabinoside), *Corynebacterium parvum*, interferon- $\alpha$ , interferon- $\beta$ , interleukins (IL-2), collagen dust, silver nitrate, and homologous blood are among these chemical agents which have been used.<sup>[1,2]</sup> In our experimental study, we utilized New Zealand albino rabbits to compare the pleurodesis efficiency of talc with two new agents, rifamycin and heterologous blood, which had not been previously studied. Besides their availability and low cost, the fact that the drainage of rifamycin heals the wound faster allowed us to speculate that it could be an effective agent in pleurodesis.

Light et al.<sup>[3]</sup> studied the efficiency of talc at various dosages. In their study, they introduced talc into the pleura through a small catheter and sacrificed the rabbits 28 days later. They found that inflammation and fibrosis increased macroscopically and microscopically in a dose-dependent manner. The fact that the fibrothorax

and hemothorax did not develop, contrary to when derivatives of tetracycline were used, showed that talc was an efficient pleurodesis-causing agent in rabbit models. However, they pointed out that it led to respiratory insufficiency, acute pneumonia, and adult respiratory distress syndrome (ARDS), and the efficiency of talc in pleurodesis increased with the dose. In our study, we observed that rifamycin was microscopically and macroscopically as efficient as talc in rabbit models. Although our study was not a dose-dependent study, we did not observe any complications at the dosages we used. Rehse et al.<sup>[4]</sup> who studied patients that had developed respiratory insufficiency after talc pleurodesis reported that 33% of 78 patients had respiratory complications or died, and 9% developed ARDS. They pointed out that talc is an efficient sclerosant and that respiratory insufficiency and severe pneumonia can develop when talc pleurodesis is applied. It is important to inform patients about the risks, and bilateral talc pleurodesis application should be avoided. Hunt et al.<sup>[5]</sup> in their study on the safety of talc pleurodesis in young patients after primary spontaneous pneumothorax pointed out that there were no studies on the side effects of talc that show

**Table 2. Macroscopic and microscopic inflammation and fibrosis scores of the different groups**

Score	Groups			
	Control	Heterologous blood	Rifamycin	Talc
0	5/3	2/2	0/0	0/0
1	0/2	2/2	0/0	0/0
2	0/0	1/1	0/0	2/0
3	0/0	0/0	1/1	1/2
4	0/0	0/0	4/4	2/3
Mean	0/0.4	0.8/0.8	3.8/3.8	3.0/3.6



**Figure 3.** The box plots represent the median and interquartiles of the thickness of fibrosis for each group. The thickness of fibrosis in the rifamycin and talc groups was higher than in the control and heterologous blood groups ( $p=0.008$ ). There were no significant differences between the thickness of fibrosis in the rifamycin and talc groups ( $p>0.05$ ).

systemic side effects. A study conducted by Yildirim et al.<sup>[6]</sup> on 49 patients to determine the side effects due to talc pleurodesis found a pleurodesis success rate of 81.6%. The most common side effects were fever (42.9%), chest pain (14.3%), and vomiting (4.1%) while one patient had temporary atrial arrhythmia, hypotension, and convulsion that developed 12 hours after the operation. Ahmadzadehfar et al.<sup>[7]</sup> reported increased fluorine-18-deoxyglucose (FDG) accumulation in the lung parenchyma, mediastinum, and pleura of a patient who was subjected to talc pleurodesis due to bullous lung. In this case, a needle biopsy was performed on the lesions, and the histopathological diagnosis revealed talc granuloma. As seen here, benign diseases can exhibit radiological errors in late-period follow-ups due to talc granuloma formation.

Bilgin et al.<sup>[8]</sup> in their pleurodesis study on the treatment of repeated primary spontaneous pneumothorax with autologous blood showed a 78.8% rate of success for pleurodesis and found no death or complications related to the operation. Furthermore, they stated that pleurodesis was a simple, painless, and inexpensive alternative. Mitchem et al.<sup>[9]</sup> performed their experimental study on rabbits given autologous blood, talc, and doxycycline through a chest tube. Macroscopic and microscopic assessments after 30 days revealed mediastinal thickness and adhesion similar to the doxycycline and talc treatments. The autologous blood was only found to be more effective than the treatment with a catheter. It was observed that

talc increased the activity of the angiotensin-converting enzyme, changed the liver functions of doxycycline, and led to tissue toxicity. As a result, the authors noted that while doxycycline formed pleurodesis, it had serious, undesired systemic effects. Moreover, the autologous blood did not form pleurodesis during short exposure times. In our study, we observed lower levels of pleurodesis with heterologous blood compared with rifamycin and talc. To standardize the study, 1 ml/kg dosage of heterologous blood was brought up to 10 ml with distilled water. It is possible that the blood was too diluted, preventing the expected pleurodesis effect. This effect should be further studied. In their phase 3 study, Dresler et al.<sup>[10]</sup> compared talc poudrage insufflations and talc slurry application. Talc poudrage insufflations was more successful in primary lung and breast cancer. In their study on the extent to which talc and silver nitrate trigger systemic inflammation during the acute phase of experimental pleurodesis in rabbits, Marchi et al.<sup>[11]</sup> found that while talc temporarily increased white blood cell (WBC) and neutrophil percentages during the acute phase of pleural injection, silver nitrate produced a greater increase in lactate dehydrogenase (LDH) and interleukin-8 (IL-8) levels. They also revealed that they both increased the vascular endothelial growth factor (VEGF) levels at similar rates, and silver nitrate led to more significant acute pleural inflammation. The authors noted that these markers play a role in the pathogenesis of fever and ARDS due to pleurodesis via talc and silver nitrate. Tremblay et al.<sup>[12]</sup> reported that pleurodesis could be achieved by the daily use of silver nitrate with the lowest possible doses. They also mentioned that it was a more tolerable pleurodesis regimen.

Birgöl et al.<sup>[13]</sup> compared clarithromycin and bleomycin as pleural sclerosants in rabbits and noted that clarithromycin was more effective in creating fibrosis and was better tolerated. Miller et al.<sup>[14]</sup> compared pleurodesis with erythromycin, talc, doxycycline, and diazepam and found that pleurodesis did not develop in the control and diazepam-treated groups as shown by macroscopic examination on the 30<sup>th</sup> day. However, erythromycin led to minimal inflammation and maximum fibrosis between the parietal and visceral pleura in 75% of the animals in the treatment group, and there was 100% pleural adhesion and fibrosis in the doxycycline group. Talc caused 29% fibrosis, 14% inflammation, and 57% granulomatous disease in the lungs, diaphragm, and surrounding tissues. They identified severe local tissue damage with doxycycline and side effects with talc usage. In addition, a 0.4 mg/kg dosage of diazepam was ineffective at causing pleurodesis over a short period of time in

rabbits, and erythromycin was more efficient and safer than the other agents. In their study on harmful pleural liquids in patients in which they compared bleomycin with talc, Haddad et al.<sup>[15]</sup> found no difference between the two applications in terms of the pleurodesis success rate. They also discovered that while bleomycin was more expensive, talc was preferred. While one flacon of sterile talc costs 96 dollars in Turkey, and one vial of talc is used for each pleurodesis, one vial of rifamycin (250 mg) costs two dollars, and a patient weighing 70 kg needs six tubes of rifamycin at a dosage of 20 mg/kg, which only costs 12 dollars. Based on our study, rifamycin can be used as an alternative to talc for pleurodesis as it is easier to find, is less expensive, and has no known side effects. Additionally, in selected operable patients with lung expansion problems and prolonged air exhalation, washing inside the thorax with solutions including rifamycin before closing the intra-operative thorax wall can help to decrease the infection risk and exhalation problem.

We observed at both microscopic and macroscopic levels that rifamycin and sterile talc produced better adhesion, inflammation, and fibrosis in the pleural cavity compared with heterologous blood. Rifamycin, which has been used in tuberculosis treatment, has no significant side effects and is readily available, inexpensive and effective as an antibiotic. Rifamycin can be an alternative to talc in spite of its side effects in pleurodesis studies.

Currently, there are no studies on the pleurodesis effect of rifamycin in the literature. As we are the first to study rifamycin in pleurodesis, we are not able to give conclusive information about the its use in humans. We used rifamycin at 20 mg/kg, the maximum dosage for children, and concluded that further studies on dosage and clinical usage should shed light on whether rifamycin could be used as a potential agent for use in pleurodesis.

#### **Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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