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***Original Article** / Özgün Makale*

Does locally administered gentamicin affect the incidence of sternal wound infections after coronary artery bypass graft surgery?

Lokal gentamisin uygulaması koroner arter baypas greftleme ameliyatı sonrası sternal yara yeri enfeksiyonu insidansını etkiliyor mu?

Ozan Onur Balkanay,[1] Deniz Göksedef,[2] Safa Göde,[3] Zeki Kılıç,[4] Suat Nail Ömeroğlu,[2] Gökhan İpek[2]

Institution where the research was done:
Cerrahpaşa Medical Faculty, İstanbul University, İstanbul, Turkey

Author Affiliations:
[1]Department of Cardiovascular Surgery, Manisa State Hospital, Manisa, Turkey
[2]Department of Cardiovascular Surgery, Cerrahpaşa Medical Faculty, İstanbul University, İstanbul, Turkey
[3]Department of Cardiovascular Surgery, İstanbul Mehmet Akif Ersoy Training and Research Hospital, İstanbul, Turkey
[4]Department of Cardiovascular Surgery, Şırnak State Hospital, Şırnak, Turkey

ABSTRACT

Background: This study aims to investigate whether the use of gentamicin-soaked sponges during coronary artery bypass graft (CABG) surgery has a protective effect against sternal wound infection (SWI).

Methods: We included 100 consecutive CABG patients in a double-blind and placebo controlled study. Patients were randomized into two groups as gentamicin and placebo groups. During surgery, gentamicin/isotonic solution absorbed sponges were placed beneath the edges of the sternum-retractor. Primary end points were the development of SWI, wound revision, and mortality within the first 30 days after CABG. Two groups were compared statistically.

Results: Sternal wound infection developed in six patients. The impact in three patients was superficial, and no wound revision was required. In the other three patients, both cutaneous and subcutaneous layers of the skin were involved, and they all needed revision. All SWI cases were in the placebo group, and there was a significant difference between the groups ($p=0.027$). No mortality was observed in any patient.

Conclusion: The statistical comparison between gentamicin and placebo groups showed a significant difference. This result revealed that local use of gentamicin-sponges can be at least as effective as the use of gentamicin-collagen implants. Therefore, placing gentamicin-soaked sponges beneath the sternum-retractor during CABG can be beneficial to decrease SWI rates.

Keywords: Antibiotic prophylaxis; cardiac surgical procedures; gentamicin; surgical wound infection.

ÖZ

Amaç: Bu çalışmada koroner arter baypas greftleme (KABG) ameliyatında gentamisin emdirilmiş gaz kullanımının sternal yara yeri enfeksiyonuna (SYYE) karşı koruyucu etkisi olup olmadığı araştırıldı.

Çalışma planı: Çift-kör ve plasebo kontrollü çalışmaya 100 ardışık KABG hastası dahil edildi. Hastalar gentamisin ve plasebo grupları olmak üzere iki gruba ayrıldı. Cerrahi sırasında, gentamisin/izotonik solüsyon emdirilmiş gazlar sternum ekartörünün kenarlarının altına yerleştirildi. Primer sonlanım noktaları SYYE gelişimi, yara revizyonu ve KABG sonrası ilk 30 gün içinde mortalite idi. İki grup istatistiksel olarak karşılaştırıldı.

Bulgular: Altı hastada SYYE gelişti. Bu hastaların üçünde etkilenme yüzeyeldi ve yara revizyonu gerekmedi. Diğer üç hastada hem ciltte hem de ciltaltı tabakalarda tutulum vardı ve bu hastaların tümünde revizyon gerekti. Tüm SYYE olguları plasebo grubundaydı ve gruplar arasında anlamlı farklılık vardı ($p=0.027$). Hiçbir hastada mortalite gözlenmedi.

Sonuç: Gentamisin ve plasebo grupları arasındaki istatistiksel karşılaştırma anlamlı bir farklılık gösterdi. Bu sonuç, lokal gentamisinli gaz kullanımının en az gentamisin-kollajen implant kullanımı kadar etkili olduğunu ortaya koydu. Dolayısıyla, KABG sırasında sternum ekartörü altına gentamisin emdirilmiş gaz yerleştirilmesi SYYE oranlarının azaltılmasında faydalı olabilir.

Anahtar sözcükler: Antibiyotik profilaksisi; kardiyak cerrahi işlemler; gentamisin; cerrahi yara enfeksiyonu.

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Correspondence: Ozan Onur Balkanay, M.D. Manisa Devlet Hastanesi Kalp ve Damar Cerrahisi Kliniği, 45020 Manisa, Turkey.
Tel: +90 236 - 231 45 96 / 224 e-mail: balkanay@doctor.com

Modern cardiac surgical procedures have low morbidity and mortality rates because of recent major improvements in operational techniques and technology along with increased surgical experience.[1] Despite all of these advancements, the frequency of sternal wound infections (SWIs) has not decreased[1-4] with overall incidence rates ranging from 0.3-8.2% after open heart surgery.[5] However, depending on the patient's risk factors, the rates can be as high as 12-20%.[6] In addition, SWIs significantly influence both early and late mortality rates.

The major risk factors that affect the incidence of SWI are diabetes mellitus (DM), obesity, technical errors in sternal wiring, and early revision, but the use of the bilateral internal thoracic artery as well as renal failure, smoking, male gender, low left ventricular ejection fraction (LVEF), and prolonged length of intensive care unit (ICU) stay can also be found.[7] Currently, more complex and redo operations are being performed on a daily basis.[1] Although prophylactic antibiotics are routinely used, SWI remains a leading factor that affects morbidity and mortality rates among cardiac surgery patients.[1,5,8] If mediastinitis, the most advanced form of SWI, is included in the figures, the mortality rate increases markedly to as high as 50%.[9] In addition, this most severe form of SWI also decreases the long-term survival rates after open heart surgery.[10] For all of these reasons, additional methods of treatment are needed for SWIs.[1] Besides controlling risk factors and using systemic antibiotics, previous studies have tested the efficacy of nasal antibiotics to counteract SWIs with the goal of eradicating methicillin-resistant *Staphylococcus aureus* (MRSA). Previous studies have also investigated the effects of topical antibiotics (e.g., vancomycin and gentamicin) on the frequency of SWIs after heart surgery.[11,12] Recent studies have also used gentamicin-impregnated collagen implants while closing the sternum to reduce the frequency of mediastinitis, and locally administered prophylactic antibiotics have been widely used for soft tissue and bone infections. In addition, they have been utilized during surgery as well.[2,13] Moreover, a previous study reported a significant decrease in the frequency of mediastinitis after the use of local gentamicin-collagen implants.[14] After these reports, multiple studies and a recent meta-analysis were then carried out which have confirmed the possible positive effects of locally administered gentamicin in cardiac surgery.[1,2,5] Undergoing surgical procedures with topical local gentamicin also decreases the incidence of postoperative infection, and this served as the starting point of this study.[15] Our aim was to investigate whether the use of gentamicin-soaked sponges during coronary artery bypass graft surgery (CABG) had a protective effect on SWI.

PATIENTS AND METHODS

This double-blinded, randomized, placebo-controlled study (Figure 1) was conducted in the cardiovascular surgery department of a tertiary healthcare center. A total of 100 consecutive CABG patients (26 females, 74 males; mean age 57.6±11.6 years) who were operated on in our clinic between October 2008 and April 2009 were included in this study, and the patients were randomized into two groups using the block method, which featured two permutations, after

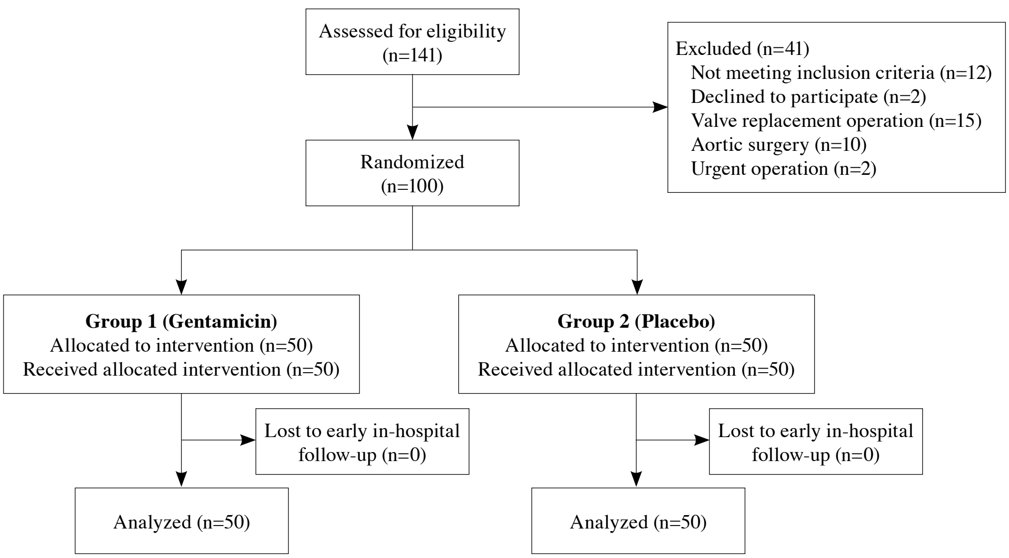

Figure 1. Flow chart of the study.

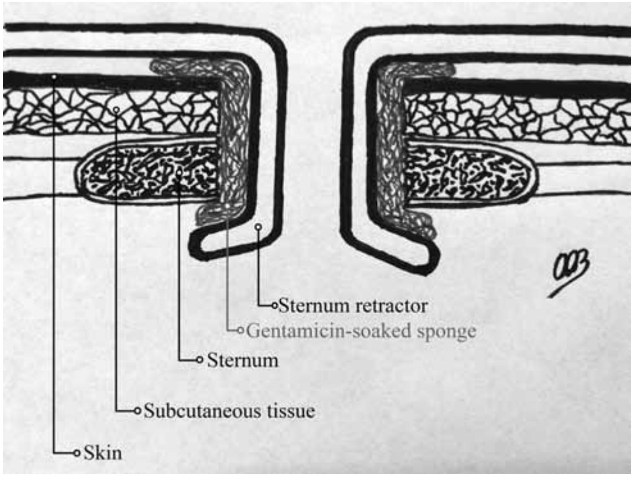

Figure 2. Cross-sectional view of the surgical site.

receiving the approval of the local ethics committee and obtaining the patients' informed consent. Patients who were allergic to gentamicin as well as those with a need for emergency surgery, those who needed open heart surgery other than CABG, those who did not give their informed consent, those under the age of 18, those with chronic kidney failure requiring renal replacement therapy, and those with intraoperative mortality were excluded from the study.

An independent nurse prepared the gentamicin/placebo solutions. The applied solvent for the gentamicin group (group 1) included a total of 320 mg of gentamicin in 250 ml of an isotonic solution while the solvent for the placebo group (group 2) contained 250 ml of a saline solution. During surgery, we placed the solution-absorbed sponges beneath the edges of the sternum retractor, and these were in contact with all layers of the skin, subcutaneous tissues, and both sides of the sternum (Figure 2). If the sponges needed to be replaced, new ones were inserted. The sponges were applied from the very beginning of the procedure after the sternotomy and were not withdrawn until the retractor was removed.

Intravenous prophylactic antibiotics were given to all of the patients, with cefazolin being administered to 98 patients (98%) and vancomycin to two patients (2%) with a beta (β)-lactam antibiotic allergy. The patients were followed up while they were in the intensive care unit (ICU) as well as during the entire hospitalization process and for three months postoperatively.

All of the operations were performed by the same surgical team using on-pump CABG. Mild hypothermia was attained using a body temperature of 32 °C in all patients, and myocardial protection was achieved via both antegrade and retrograde cold blood cardioplegia. Proximal and distal anastomoses was performed using a cross-clamp, and left internal mammary artery-left anterior descending coronary artery (LIMA-LAD) anastomosis was utilized for all of the patients.

We accepted the development of SWI, wound revision, and mortality within the first 30 days after CABG as the primary end points of the study, and the secondary end points included other morbidity factors such as postoperative renal functions, revision rates, and length of hospital stay.

Table 1. Preoperative variables

Variable	Group 1* (n=50)					Group 2† (n=50)					Total (n=100)					
	n	%	Mean±SD	Med.	Min.-Max.	n	%	Mean±SD	Med.	Min.-Max.	n	%	Mean±SD	Med.	Min.-Max.	*p*
Age (years)			56.4±12.5		38-79			58.9±10.7		26-77			57.6±11.6		26-79	0.288
Gender																
Female	13	26				13	26				26	26				
Male	37	74				37	74				74	74				
DM	18	36				15	30				33	33				0.523
Hyperlipidemia	27	54				31	62				58	58				0.418
Hypertension	28	56				32	64				60	60				0.414
COPD	4	8				1	2				5	5				0.362
PAD	3	6				7	14				10	10				0.182
CAD**	5	10				3	6				8	8				0.715
Smoking	31	62				32	64				63	63				0.836
Preoperative MI	21	42				23	46				44	44				0.687
LVD	8	16				5	10				13	13				0.372
NYHA classification			1.9±0.7	2				2±0.9	2				1.9±0.8	2		0.801
CCI classification			1.9±0.7	2				1.8±0.7	2				1.9±0.7	2		0.263
EF			55.2±9.5		40-72			55.3±7.7		35-72			55.3±8.6		35-72	0.936

* Gentamicin group; † Placebo group; SD: Standard deviation; Med.: Median; Min.: Minimum; Max.: Maximum; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; PAD: Peripheral artery disease; CAD: Carotid artery disease; MI: Myocardial infarction; LVD: Left ventricular dysfunction; NYHA: New York Heart Association; CCI: Canadian Classification of Health Interventions; LVEF: Left ventricular ejection fraction.

Table 2. Renal function tests

Variable	Group 1* (n=50)				Group 2† (n=50)				Total (n=100)				
	n	%	Mean±SD	Min.-Max.	n	%	Mean±SD	Min.-Max.	n	%	Mean±SD	Min.-Max.	*p*
Preoperative BUN (mg/dL)			42.1±19.8	15-171			42.1±22.9	16-150			42.1±21.3	15-171	0.996
Preoperative blood creatinine (mg/dL)			1.2±1	0.5-2.1			1.1±0.3	0.7-3			1.1±0.8	0.5-3	0.688
Preoperative chronic renal dysfunction	1	2			2	4			3	3			0.558
Postoperative BUN (mg/dL)			55.6±36.2	13-98			50.4±22.7	17-189			53±30.2	13-189	0.390
Postoperative blood creatinine (mg/dL)			1.2±0.8	0.5-2.3			1.2±0.4	0.6-3.2			1.2±0.6	0.5-3.2	0.475
Postoperative renal dysfunction	2	4			3	6			5	5			0.646

* Gentamicin group; † Placebo group; SD: Standard deviation; Min.: Minimum; Max.: Maximum; BUN: Blood urea nitrogen.

Statistical analysis

All categorized variables were presented as numbers and percentages (n, %), and all numerical variables were expressed as mean ± standard deviation (SD). Ordinal variables were expressed as mean ± SD with median values. In addition, we compared the parametric continuous variables using Student's T-test and the non-parametric variables via the Mann-Whitney U test. Furthermore, a chi-square or Fisher's exact test were used to compare the categorical variables. The statistical power of the study was represented by the presence of SWI, and this was calculated as 92.2% [for an alpha (α) error level of 5%]. The percentage of patients with SWI in groups 1 and 2 (50 patients each) was 0% (accepted as <1%) and 12%, respectively.

RESULTS

We found that 33 patients had DM, 58 had hyperlipidemia, 60 had hypertension (HT), five had chronic obstructive pulmonary disease (COPD), 10 had peripheral artery disease (PAD), and eight had carotid artery disease (CAD) (Table 1). In addition, there was no distinction between the preoperative comorbidity factors and demographic values between the groups (p>0.05) (Table 1), and there were no statistically significant differences between the renal function tests and intraoperative values (p>0.05) (Tables 2 and 3). For the entire group of patients in the ICU, the mean follow-up time was 43.2±5.9 hours, and the postoperative total bleeding was 1017±629 mL. In addition, no significant differences were seen between the groups with regard to the amount of bleeding and the number of blood products used (p>0.05) (Table 4). Fifteen patients required an insulin perfusion protocol to control their blood glucose levels in the early postoperative period, but there were no statistically significant differences between the groups in terms of insulin usage (Table 4). Moreover, 21 patients experienced atrial fibrillation (AF) during the postoperative period, and 11 of these (52.4%) recovered via the use of an amiodarone infusion protocol. However, there were no significant differences between the groups regarding the development of AF (p=0.806) (Table 4). Furthermore, no meaningful differences were noted between the groups with respect to the need for inotropic drugs or an intra-aortic balloon pump postoperatively (p>0.05) (Table 4). There were also no statistically significant differences between groups concerning the need for a reoperation (Table 4). Additionally, no patients had any postoperative acute kidney injuries. The mean hospital stay was 8.1±3.8 days, but this did not account for any statistically significant differences between the groups (p=0.690) (Table 4).

Sternal wound infection occurred in six patients. Three of these were type A and three were type B, but none had type C SWI (Table 5). Moreover, all of the SWI patients were in group 2, and there was a statistically significant difference between the two groups (p=0.027) (Table 6). Wound revisions were needed in all three patients with type B SWI. Furthermore, the groups had similar saphenous vein harvesting site infection rates (Table 6). No mortality was detected among the patients in our study.

Table 3. Intraoperative variables

Variable	Group 1* (n=50)			Group 2† (n=50)			Total (n=100)			
	Mean±SD	Median	Min.-Max.	Mean±SD	Median	Min.-Max.	Mean±SD	Median	Min.-Max.	*p*
Distal bypass	2.8±0.7	3		2.6±0.8	3		2.7±0.8	3		0.447
ACCT (min)	67.9±27.2		12-113	68±27		15-127	68±27		12-127	0.997
TPT (min)	98±31.5		35-166	95.9±29.5		37-154	97±30.4		35-166	0.727

*: Gentamicin group; †: Placebo group; SD: Standard deviation; Min.: Minimum; Max.: Maximum; ACCT: Aortic cross clamp time; TPT: Total perfusion time.

Table 4. Postoperative variables

Variable	Group 1* (n=50)					Group 2† (n=50)					Total (n=100)					
	n	%	Mean±SD	Med.	Min.-Max.	n	%	Mean±SD	Med.	Min.-Max.	n	%	Mean±SD	Med.	Min.-Max.	*p*
Total bleeding (mL)			1050±626		100-1850			985±636		300-2000			1017±629		100-2000	0.606
ES (unit)			1.9±1.7	2				1.5±1.2	2				1.7±1.5	2		0.225
FFP (unit)			0.7±1.4	0				0.4±0.7	0				0.6±1.1	0		0.226
Fresh total blood (unit)			0.2±0.5	0				0.2±0.5	0				0.2±0.5	0		0.853
ICU follow-up (h)			43.1±5		39-67			43.3±6.8		24-67			43.2±5.9		24-67	0.834
Sternal wire#			8.2±1.5	8				8.2±1	8				8.2±1.7	8		0.905
Insulin	11	22				4	8				15	15				0.050
Atrial fibrillation	10	20				11	22				21	21				0.806
Ventricular fibrillation	0	0				1	2				1	1				1.000
Inotropic drug use	20	40				19	38				39	39				0.838
Perioperative MI	5	10				0	0				5	5				0.056
IABP	5	10				2	4				7	7				0.436
Reoperation	2	4				2	4				4	4				1.000
Hospital-stay (days)			8.2±4.7	7				7.9±2.7	7				8.1±3.8	7		0.690

* Gentamicin group; † Placebo group; SD: Standard deviation; Med.: Median; Min.: Minimum; Max.: Maximum; ES: Erythrocyte suspension; FFP: Fresh frozen plasm; ICU: Intensive care unit; #: Total number of metal sutures used for wiring the sternum; MI: Myocardial infarction; IABP: Intra-aortic balloon pump.

DISCUSSION

Sternal wound infection can be divided into three subgroups using the Centers for Disease Control (CDC) classification system (Table 5).[16] For clinical practice, some clinicians use just two subgroups in which one consists of patients with superficial SWI that involves the skin and/or subcutaneous tissue and the other is composed of those with deep SWI that involves the sternum and/or mediastinitis.[8,17] As previously mentioned, patient risk factors can increase the incidence of SWI to between 12 and 20%. This can be explained by the expanded presence of multiple risk factors and comorbidities among cardiac surgery candidates.[8,17,18] Our patient population in group 2 demonstrated a higher rate of SWI when compared with the overall incidence rate in our study, but when the rate in group 2 was compared with the rates for the patients who had risk factors, they were similar (Table 6).

Higher SWI rates increase both postoperative morbidity and mortality,[1] and despite routine systemic antimicrobial prophylaxis in open heart surgery, deep SWI and multiresistant bacteria have become more common.[1]

Gentamicin destabilizes bacterial membranes and inhibits protein synthesis.[1] Although this drug is normally used for infections caused by gram-negative agents, it also has bactericidal effects on many gram-positive agents that are directly proportional with gentamicin's peak level. The systemic use of gentamicin has three primary disadvantages. Not only is it highly toxic, but it has many side effects. Furthermore, bacterial resistance is possible when taking low doses. However, these disadvantages become advantages when gentamicin is used topically because higher local levels of this drug can be effective against bacteria that are resistant to its minimal inhibitory concentration levels.

Table 5. "Centers for Disease Control" classification of sternal wound infection

Type A:	Superficial infection effected the cutaneous and subcutaneous tissue
Type B:	Deep infection effected the subcutaneous tissue deep down to the bone
Type C:	Sternal osteomyelitis or mediastinitis

Besides prescribing gentamicin as a topical antibiotic for bone and soft tissue infections, recent studies have also focused on the use of local antibiotics like gentamicin in cardiac surgery,[1] with investigators usually preferring prophylactic antibiotic agents such as gentamicin-impregnated bone cement.[1] In addition, a recently published systematic review and meta-analysis of randomized trials showed a decrease in surgical site infections (SSIs) when gentamicin-collagen implants were used.[5] This study also demonstrated the possible positive effects associated with the local prophylactic use of gentamicin in surgical sites to decrease the rate of SWI. In our study, we preferred a different way of locally applying the gentamicin to the surgical site via the use of gentamicin-soaked sponges.

One of the main differences in our study was its double-blinded, placebo-controlled design. All of the previous studies that used local gentamicin-collagen implants compared these groups with a control group without an implant, which might have led to a procedural bias. In our study, the surgical team used sponges without any knowledge of whether they were soaked in gentamicin or the saline solution (placebo). The second major difference in our study was that we

Table 6. Variables concerning the surgical site infection

Variable	Group 1* (n=50)		Group 2† (n=50)		Total (n=100)		
	n	%	n	%	n	%	*p*
Sternal wound infection	0	0	6	12	6	6	0.027§
Saphenous site infection	0	0	1	2	1	1	1.000
Wound revision	0	0	3	6	3	3	0.242

*: Gentamicin group; †: Placebo group; §: Statistically significance (p<0.05).

used a solution that contained a saline solution with or without gentamicin, which meant a reasonable reduction in cost. When we compared the cost of locally administered gentamicin with a gentamicin-collagen implant, there was a nearly 30-fold difference, with the cost of our solution being $10 versus the implant cost of $300. Another difference in our study involved the time period that the gentamicin was locally applied. We used gentamicin-soaked sponges from soon after the sternotomy was performed until the sternal retractor was removed, which covered almost the whole operational process. This provided the ability to prevent microorganisms from colonizing while the operative site was open. All of the previous studies used the gentamicin-collagen implant just before the closure of the surgical site but not during the intraoperative period. Our unique study design offered another advantage in that the application area was nearly totally covered by all the incision layers on both sides. When the gentamicin-soaked sponges were inserted beneath the sternum-retractor, they covered all of the layers of skin and the sternum. Previous studies featured the use of the gentamicin-collagen implant at the posterior side of the sternum; thus, there was no contact with the anterior side of the bone, dermis, or hypodermic tissues. The most common type of SWI in cardiac surgery is type-A, which involves the skin and subcutaneous tissue. Hence, potentially, the superficial infection could then progress to deeper layers and lead to type-B SWI. Though a progression of this kind is not a guarantee, the ability of our procedure to prevent infection both superficially and at the deep surgical sides simultaneously is a major benefit.

Conclusion

Our results showed that the local use of gentamicin-soaked sponges can be at least as effective as the use of gentamicin-collagen implants, and they indicate that placing these sponges beneath the sternum retractor during CABG can decrease the rate of SWI. However, further multicenter, randomized studies featuring this technique should be conducted with a larger patient group to verify our results. Additional studies are also needed to evaluate the underlying mechanisms involved in this study since the results of previous studies that focused on the use of gentamicin were not as positive as ours.

Declaration of conflicting interests

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