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Original Article

Long-Term Results of Sodium 2-Mercaptoethane Sulfonate Usage on Cholesteatoma Surgery

Serdal Celik[1,2], M. Zeki Yalcın[3], Osman Kılıc[2], Mehmet Tan[3], Mahmut Tayyar Kalcioglu[1,2]

[1]Department of Otorhinolaryngology, Istanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye
[2]Göztepe Süleyman Yalçın City Hospital, Ear Nose Throat Clinic, İstanbul, Türkiye
[3]Department of Otorhinolaryngology, İnönü University Faculty of Medicine, Malatya, Türkiye

ORCID iDs of the authors: S.C. 0000-0001-8469-1547, M.Z.Y. 0000-0002-4943-4577, O.K. 0000-0001-5352-1035, M.T. 0000-0001-8557-0886, M.T.K. 0000-0002-6803-5467.

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BACKGROUND: Although advanced technologies and surgical procedures are used, cholesteatoma is a disease with the possibility of recurrence. The aim of this study was to determine the long-term effect of sodium 2-mercaptoethane sulfonate (MESNA) on cholesteatoma surgery.

METHODS: Patients who underwent cholesteatoma surgery between January 2009 and July 2014 by the same surgeon were divided into 2 groups: those where MESNA was used and those where it was not. Otomicroscopic examinations were performed to see the presence of cholesteatoma recurrence in the patients who had surgery at least 8 years ago. Pure-tone audiometry was performed to evaluate the hearing results.

RESULTS: Sodium 2-mercaptoethane sulfonate was used in 23 patients and was not used in 39 patients who came to the control. In the MESNA-used group, cholesteatoma was seen in only 1 of the patients who underwent a canal wall-down (CWD) mastoidectomy. In the MESNA non-used group, cholesteatoma was seen in 3 patients who underwent CWD. The difference was not statistically significant.

CONCLUSION: Although there was no statistically significant difference, recurrence of cholesteatoma was seen less frequently in patients who received MESNA during surgery. Studies to be conducted in larger patient series may clarify this issue.

KEYWORDS: Cholesteatoma, mastoidectomy, MESNA

INTRODUCTION

Cholesteatoma is a common ear disease that can result in serious complications when left untreated.[1] Today, the only treatment for cholesteatoma is surgery. Although advanced technologies and surgical procedures are used, cholesteatoma is a disease with the possibility of recurrence.[2] The different techniques used in cholesteatoma surgery aim to reduce the likelihood of recurrence or residual cholesteatoma while minimizing functional loss.

Sodium 2-mercaptoethane sulfonate (MESNA) has been used in a variety of disorders, such as a mucolytic agent for pulmonary disorders and as a protective agent against the toxicity of some chemotherapeutic agents. It is a synthetic sulfur compound belonging to a class of thiol compounds that produce mucolysis by disrupting the disulfide bonds of the mucous polypeptide chains. Studies show that MESNA can be used as a chemical dissecting agent in cholesteatoma surgery due to its ability to break the disulfide bonds in the cysteine-rich keratin in the cholesteatoma.[3-5] In addition to facilitating dissection, MESNA may also prevent the formation of cholesteatoma. In one of these studies, MESNA was shown to be highly effective in preventing the formation of propylene glycol-induced cholesteatoma in rats.[6] Sodium 2-mercaptoethanesulfonate has been proven by experimental studies to be non-ototoxic, and in some clinics, such as ours, it is used in the surgical treatment of cholesteatoma. It has been reported in short-term follow-up studies that MESNA is effective enough to reduce residual cholesteatoma.[3] Another study evaluated the concentrations and ototoxic effects of MESNA when used in otologic surgery. In the study conducted by Doğan et al, MESNA concentrations of 50% and 100% were compared with saline. No ototoxic effects were observed at either concentration.[7] Similarly, Kokten et al conducted another study using a 100% concentration and found no ototoxic effects.[6] Another aspect to consider with the increasing

Corresponding author: Mahmut Tayyar Kalcioglu, e-mail: mtkalcioglu@hotmail.com
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popularity of MESNA use in otologic surgery is its potential toxic effect on the facial nerve. In a study by Baklacı et al, they investigated the effects of 25% and 100% concentrations of MESNA on the facial nerve and reported that MESNA had no toxic effect on the facial nerve.[8] However, long-term follow-up results should be evaluated to be considered a successful treatment, especially in ear surgery. To the best of our knowledge, no study in the literature provides long-term follow-up results of MESNA application in cholesteatoma surgery. The current study is the first that compares such long-term follow-ups and discusses the evaluation made at the end of an average follow-up period of 10 years.

MATERIAL AND METHODS

The current study was designed to retrospectively examine the preoperative data and surgery reports of the patients to be included in the study and to prospectively evaluate their current otomicroscopic examinations and hearing evaluations. Approval for the study was obtained from the clinical research ethics committee of Istanbul MedeniyetUniversity Göztepe Prof. Dr. Süleyman Yalçın CityHospital (Approval No: 2021/0664; Date: December 22, 2021). Informed consent was obtained from the patients who agreed to take part in the study. Patients who underwent tympanomastoidectomy surgery performed by the same surgeon (MTK) at Istanbul Medeniyet University hospital and Inonu University hospital between January 2009 and July 2014 were included in the study.

The study included 62 patients who accepted our invitation and came for a control examination. All patients underwent preoperative computed tomography and magnetic resonance imaging (MRI) scans to confirm the presence of cholesteatoma and to determine the damage caused by cholesteatoma, and the presence of cholesteatoma was confirmed. Patients in whom MESNA was used for cholesteatoma dissection during surgery and patients in whom MESNA was not used were invited to participate in the study if they had regular follow-up after surgery. Patients with labyrinthine fistulas on preoperative or intraoperative evaluation were excluded. All of the patients aged 8 to 13 had undergone canal wall down (CWD) or canal wall up (CWU) mastoidectomy surgery for cholesteatoma. While the surgery was performed without MESNA application in 39 of 62 patients, there were surgeries performed in 23 patients using diluted MESNA (20% MESNA and 80% saline). In the MESNA-applied group, cholesteatoma debris was aspirated, and the cavity was filled with diluted MESNA for 5 minutes. The remaining cholesteatoma matrix was removed and dissected using a dissector or cotton. After debulking the cholesteatoma, MESNA was applied before removing the cholesteatoma matrix. All cholesteatoma cases were operated on under a microscope with special attention to the endoscopic evaluation of trap areas such as the tympanic sinus. The same surgical procedures were performed in the other group without MESNA. Sodium 2-mercaptoethanesulfonate used patients were randomly selected.

MAIN POINTS

- The use of MESNA may facilitate surgical dissection in cholesteatoma surgery.
- The use of MESNA may reduce cholesteatoma recurrence.
- MESNA, which is known to have no ototoxic effect, is safe to use and apply in cholesteatoma surgery.

Otomicroscopic examinations and pure-tone audiometry were performed. Preoperative and long-term after-surgery hearing evaluations, recurrence, and residual rates of colesteatoma in both groups were compared. Cholesteatoma was classified as recurrent if it recurred in the setting of developing retractions. In addition, if cholesteatoma was detected on a non-EPI diffusion MRI behind an intact cartilage graft or behind an obliterated mastoid cavity, it was classified as residual cholesteatoma.

Patients operated on for cholesteatoma in our clinic are routinely followed for 5 years. These follow-ups are performed postoperatively at 3 weeks, 3 months, 6 months, 1 year, and then annually. In all treated cholesteatoma cases, cholesteatoma control is performed with non-EPI diffusion MRI at 12 months postoperatively. The graft material of choice for tympanic membrane grafting in our clinic is cartilage, and every patient who has a CWD mastoidectomy has undergone cavity obliteration with bone pate and cartilage to reduce the cavity size and minimize potential problems with the large cavity, such as cleaning problems and problems with hearing aid use. Nowadays, it is possible to detect a possible recurrence or residual cholesteatoma with non-EPI diffusion MRI. In our clinic, patients who have no problems after 5 years of follow-up are removed from routine follow-up with instructions to contact us if they have any problems. None of the patients who agreed to participate in our study came to the hospital with any complaints after 5 years of routine follow-up. Our study includes a long follow-up period of 10 years on average. None of the patients included in the study had any postoperative problems during the 5-year follow-up period. When they were invited to the hospital after an average of more than 10 years postoperatively, they underwent auto-microscopic examinations and, if cholesteatoma was suspected, non-EPI diffusion MRI to investigate the possibility of cholesteatoma. To avoid unnecessary costs, repeat MRI imaging was not requested for patients in whom cholesteatoma was not suspected on otomicroscopic examination.

Statistical Analysis

Statistical Package for the Social Sciences Statistics software, version 24.0 (IBM SPSS Corp.; Armonk, NY, USA), was used for statistical analyses. Descriptive statistical methods, including mean, standard deviation, frequency, ratio, minimum, and maximum, were employed to analyze the study data. Additionally, the Wilcoxon Signed Rank test was utilized to compare preoperative and postoperative measurements, while the Mann–Whitney *U*-test was used for group comparisons. Significance levels were evaluated at both $P < .01$ and $P < .05$.

RESULTS

Sodium 2-Mercaptoethane Sulfonate-Applied Group

Sodium 2-mercaptoethane sulfonate was applied during the operation to a total of 23 patients who accepted our invitation and came to the control examination. These patients were operated on between March 2009 and July 2014. These patients were followed up for a minimum of 8 years and a maximum of 13 years, with the mean follow-up period being 10.2 years. Of these patients, 11 were female and 12 were male. Seventeen of these patients underwent a CWD mastoidectomy, while 6 had a CWU mastoidectomy. Only 1 of the

patients who underwent CWD mastoidectomy had residual cholesteatoma on the control examination. No cholesteatoma recurrence was observed in any other patient. When the preoperative and long-term postoperative hearing results of the patients were compared, there was no significant difference between 500 and 4000 Hz air and bone conduction (Table 1).

Sodium 2-Mercaptoethane Sulfonate Nonapplied Group

Sodium 2-mercaptoethane sulfonate was not applied during the operation of 39 patients who came to the control examination. These patients were operated on between January 2009 and July 2014 and received follow-up evaluations for a period of 8 to 13 years. The mean follow-up timeframe was 10.5 years. Of these patients, 16 were female and 23 were male, and 36 patients underwent CWD mastoidectomy while 3 underwent CWU mastoidectomy. Residual cholesteatoma was seen in 3 of the patients who underwent CWD mastoidectomy. When considering the preoperative and postoperative hearing results, the increase in air conduction measurements at 500 and 4000 Hz was found to be statistically significant. No statistically significant difference was observed in bone and air conduction at other frequencies (Table 1).

When analyzing hearing evaluations, no significant difference was found between MESNA-applied and MESNA nonapplied groups in the measurements of the preoperative and postoperative 500, 1000, 2000, and 4000 Hz air and bone conduction ($P > .05$) (Table 2).

There was no statistically significant difference in recurrence rates between the MESNA-applied and MESNA nonapplied groups ($P > .05$) (Table 3).

No MESNA-related adverse events were observed in any of the patients who used MESNA during surgery.

Table 1. Evaluation of Preoperative and Postoperative Hearing Results

	500			1000			2000			4000		
	Pre-op	Post-op	P^a	Pre-op	Post-op	P^a	Pre-op	Post-op	P^a	Pre-op	Post-op	P^a
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
MESNA non-applied												
AC	53.08 ± 18.27	60.13 ± 22.46	.049*	49.87 ± 18.83	55.9 ± 24.19	.069	46.03 ± 20.46	53.56 ± 25.75	.070	53.46 ± 22.45	62.69 ± 29.31	.030*
BC	17.95 ± 10.24	22.56 ± 18.98	.205	15.77 ± 11.03	21.41 ± 19.4	.110	20.0 ± 15.39	26.03 ± 21.06	.234	23.08 ± 18.59	31.79 ± 22.84	.067
MESNA-Applied												
AC	57.83 ± 19.18	56.3 ± 25.1	.208	57.61 ± 21.1	56.96 ± 25.21	.958	53.91 ± 21.21	50.22 ± 30.13	.453	61.09 ± 24.63	60.22 ± 30.54	.917
BC	21.74 ± 19.11	26.65 ± 23.24	.641	22.39 ± 19.36	26.96 ± 23.49	.431	25.22 ± 21.02	28.91 ± 23.79	.442	26.52 ± 23.18	33.7 ± 24.78	.132

AC, air conduction; BC, bone conduction; MESNA, sodium 2-mercaptoethane sulfonate.
[a]Wilcoxon signed-rank test.
*$P < .05$.

DISCUSSION

Cholesteatoma is the presence of hyperplastic keratinized stratified squamous epithelium with a chronic inflammatory reaction in the middle ear and mastoid bone. Cholesteatoma can cause osteoclastic activity and bone resorption, resulting in hearing loss, facial paralysis, vestibular disorders, and fatal complications such as meningitis and brain abscess.[1-3] The only treatment for cholesteatoma is surgery. Research is carried out to facilitate the surgery of this pathology and to reduce this problem with medical treatment.

There are many studies in the literature on the efficacy of many substances to prevent the development of cholesteatoma or to facilitate dissection during surgery.[9-11] Sodium 2-mercaptoethane sulfonate is one of these substances that has been shown to be effective in many studies. Sodium 2-mercaptoethane sulfonate disrupts the disulfide bonds in the cholesteatoma matrix, allowing for easier dissection of the cholesteatoma and a reduction in the risk of residual disease.[4] In addition, the effect of MESNA on propylene glycol-induced experimental cholesteatoma formation has been investigated independently in various animal studies.[5-7] Ismi et al[5] reported that propylene glycol-induced cholesteatoma formation was inhibited by a single dose of 10% MESNA. MESNA was used at a concentration of 20% in the patients included in our study. Since the patients evaluated had undergone surgery approximately 10 years ago, the recommendations of the studies available at that time were

Table 2. Evaluation of Preoperative and Postoperative Hearing Results Between Groups

			MESNA Nonapplied		MESNA Applied		*P*[a]
			Mean ± SD	Minimum–Maximum (Median)	Mean ± SD	Minimum–Maximum (Median)	
Pre-op	AC	500	53.08 ± 18.27	15-100 (50)	57.83 ± 19.18	25-90 (60)	.239
		1000	49.87 ± 18.83	20-115 (45)	57.61 ± 21.1	30-105 (55)	.153
		2000	46.03 ± 20.46	15-95 (45)	53.91 ± 21.21	25-105 (50)	.171
		4000	53.46 ± 22.45	25-110 (55)	61.09 ± 24.63	25-120 (60)	.208
	BC	500	17.95 ± 10.24	0-50 (15)	21.74 ± 19.11	5-75 (15)	.900
		1000	15.77 ± 11,03	0-50 (10)	22.39 ± 19.36	0-75 (15)	.347
		2000	20 ± 15.39	0-55 (15)	25,22±21,02	0-70 (20)	.382
		4000	23.08 ± 18.59	0-75 (15)	26.52 ± 23.18	0-75 (20)	.706
Post-op	AC	500	60.13 ± 22.46	20-105 (65)	56.3 ± 25.1	15-100 (55)	.525
		1000	55.9 ± 24.19	15-100 (60)	56.96 ± 25.21	20-100 (55)	.855
		2000	53.56 ± 25.75	20-100 (50)	50.22 ± 30.13	5-100 (40)	.584
		4000	62.69 ± 29.31	15-120 (55)	60.22 ± 30.54	15-110 (70)	.683
	BC	500	22.56 ± 18.98	0-70 (20)	26.65 ± 23.24	0-70 (15)	.709
		1000	21.41 ± 19.4	0-70 (15)	26.96 ± 23.49	0-70 (15)	.491
		2000	26.03 ± 21.06	0-70 (15)	28.91 ± 23.79	5-70 (15)	.586
		4000	31.79 ± 22.84	5-75 (25)	33.7 ± 24.78	5-75 (20)	.753

AC, air conduction; BC, bone conduction; MESNA, sodium 2-mercaptoethane sulfonate.
[a]Mann–Whitney *U*-test.

taken into account.[12,13] However, more recent studies have shown that 100% concentrated MESNA without dilution is more effective in controlling cholesteatoma.[7,8] Kokten et al[6] used a 100% concentration of MESNA and reported that it inhibited the formation of cholesteatoma in their study investigating its effectiveness on cholesteatoma.

In addition to experimental studies, the effect of MESNA on cholesteatoma was investigated in some clinical studies. In the study by Kalcioglu et al[3], in which the effects of MESNA application on cholesteatoma surgery were examined, it was reported that MESNA application facilitated surgery and was found to be more effective in terms of residual disease. In the review by Moffa et al[16], the results of 607 patients across 27 studies were examined, and it was concluded that MESNA can be safely used in facilitating surgery. All studies in the literature cover the early postoperative follow-up period; however, the results of follow-up periods between 5 and 10 years in cholesteatoma surgery are extremely important.[8-16] The mean follow-up period in the current study was 10.3 years, and to the best of our knowledge, it was the first study in the literature on the long-term effects of MESNA.

Table 3. Comparison of Recurrence Rates by Sodium 2-Mercaptoethane Sulfonate Application Status

	MESNA Nonapplied		MESNA Applied		*P*[a]
	n	%	N	%	
No recurrence	36	92.3	22	95.7	.605
Recurrence	3	7.7	1	4.3	

MESNA, sodium 2-mercaptoethane sulfonate.
[a]Pearson's chi-square.

The study shows that dissection of the cholesteatoma matrix is easier when MESNA is used during surgery. When the 2 groups were compared for cholesteatoma recurrence, it was detected in only 1 patient within the MESNA-applied group and 3 patients in the MESNA non-applied group; revision surgery was planned for these 4 patients. Although there was no significant statistical difference during comparison, the resulting 3 recurrences in the MESNA non-applied group and 1 recurrence in the MESNA applied group indicate the possibility that the use of MESNA may be effective. The issue may be clarified through studies with a larger case series.

Although MESNA is highly effective in the treatment of cholesteatoma, the recurrence of cholesteatoma in 1 patient in the MESNA group suggests that complete eradication may not be achieved with MESNA. Recent studies have reported that the use of MESNA at 100% concentration is more effective in preventing cholesteatoma formation. Our study included patients for whom MESNA was used at a concentration of 20%. It can be assumed that the use of MESNA at a concentration of 20% may have been insufficient.

When the hearing results were evaluated, no significant difference was found between these 2 groups for preoperative and postoperative air and bone conduction at 500, 1000, 2000, and 4000 Hz. This result also supports studies that show that MESNA does not have ototoxic side effects.[3]

This study has several limitations. One is the retrospective nature of the study. Another important limitation of the study is that the randomization method was not used in the selection of patients with or without MESNA. If MESNA was available at the time of surgery, it was used in these patients, and if it was not available, it was not used. This

resulted in a lack of systematic randomization. In addition, because our study included patients operated on an average of 10 years ago, information that could be used to comment on the stage of cholesteatoma was not accessible in the archive search. The high number of patients who underwent CWD in both groups may also have influenced the results obtained.

As a result, the use of MESNA allows for more reliable surgery for cholesteatoma removal by breaking the disulfide bonds and decreases the possibility of recurrence.

Ethics Committee Approval: This study was approved by Ethics Committee of Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital (Approval number: 2021/0664; Date: December 22, 2021).

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

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