

# Cochlear effects of intraoperative use of Mesna in cholesteatoma surgery

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**Abstract.** *Background and aim of the work:* Mesna is thiol compound proposed as chemical dissector in otolaryngologic surgery. The aim of this study was to address the issue of possible ototoxicity from topical administration of MESNA into the middle ear during otologic surgery. *Methods:* Audiological findings of patients (n=55) who underwent canal wall up tympanomastoidectomy with the ancillary use of Mesna in 1-year period were retrospectively reviewed. We identified another set of 51 patients who had undergone otologic surgery without the use of Mesna to serve as a control group. Preoperative and postoperative mean bone conduction thresholds were calculated and compared between the two groups for the frequencies of 500,1000,2000, and 3000; 4000 and 8000 Hz were further analyzed to search for high-frequency sensorineural hearing loss. *Results:* Fifty-five patients were operated on with the ancillary use of Mesna and 51 underwent surgery with traditional mechanical dissection alone. When mean preoperative bone conduction values were compared with postoperative values, no significant differences were found for any of the frequencies tested in both groups. Analyzing changes in bone conduction at 4000 and 8000 Hz a slight worsening was observed in both groups. *Conclusions:* We found no difference in hearing thresholds between the treatment and control groups. Thus, the results of this study confirmed data obtained in laboratory animal models demonstrating that intraoperative use of Mesna in middle ear surgery is safe and does not lead to ototoxic effects. (www.actabiomedica.it)

**Key words:** Mesna, ototoxicity, cholesteatoma, middle ear surgery

## Introduction

Cholesteatoma is a benign keratinizing hyperproliferative epithelial lesion that can affect middle and inner ear structures with possible hearing loss, vestibular dysfunction, facial paralysis, and even intracranial complications (1). The only effective treatment is complete surgical extirpation of the disease, but residual and recurrent cholesteatoma are unfortunately common (2-3). Residual cholesteatoma develops from epidermal debris left inadvertently behind from

surgery with an incidence ranging from 10 to 43% (4). Over the years, various technological innovations and surgical approaches have been proposed in order to reduce the incidence of residual cholesteatoma (5-7); for instance, different chemical agents have been utilized to make easier the removal of cholesteatoma, but, unfortunately, severe irritation to living tissues have limited their intraoperative use. (8-9).

Our group developed a research project entitled “Chemically Assisted Dissection” (CADISS) with the aim to search for a substance able to facilitate dissection

in cholesteatoma surgery without toxic effects on middle and inner ear structures. Since adhesions between pathological and healthy tissues as well as cholesteatomatous matrix are rich in disulfide bonds, we chose Mesna (sodium-2-mercapto-ethane-sulphonate), a synthetic sulfur compound widely utilized in medicine as a mucolytic agent, able to break the disulfide bonds of the polypeptide chains of mucus (10). Furthermore, Mesna is also used as protective agent against the toxicity of chemotherapy (11) and as antioxidant drug by virtue of its ability to scavenge reactive oxygen metabolites produced by oxidative stress (12). Before using Mesna in humans, we studied the effects on cochlear function of topical administration of Mesna into the middle ear of guinea pig model: transmission electron microscopy, scanning electron microscopy, and auditory brainstem response testing did not show any toxic effect on cochlear morphology (13).

The primary aim of this study was to verify the safety of topical administration of Mesna into the middle ear during otologic surgery in humans.

## Materials and methods

This study was a retrospective chart review of all adult patients (n=55) with middle ear cholesteatoma operated on by planned staged canal wall up tympanomastoidectomy with the ancillary use of Mesna from January 2008 and December 2008. The control group consisted of all patients (n=51) with middle ear cholesteatoma operated on in the previous year using the traditional mechanical technique alone. All patient were operated on by the two senior surgeons (CZ and JM) using the same surgical technique.

Chemically assisted dissection consisted of an injection of a 10% Mesna solution into the middle ear and mastoid; this solution was left in the surgical cavity for 3 minutes before starting cholesteatoma removal in order to allow Mesna to dissolve adhesions and disulfide bonds. Successively, Mesna was topically administered with continuous instillation by means of microdissector opportunely modified to deliver the chemical product directly from their tips.

Air- and bone-conduction thresholds were determined using a clinical audiometer calibrated according

to ISO standards. Bone conduction testing was performed with appropriate masking of the opposite ear. Pure tone averages (PTAs) were calculated using 500, 1000, 2000 and 3000 Hz according to guidelines set forth by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology and Neck Surgery (14). We defined postoperative sensorineural hearing loss (SNHL) as a fall in bone conduction of more than 10 dB. Furthermore, bone conduction was calculated also at 4000 and 8000 Hz to search for high-frequency SNHL. Audiograms were obtained the day before and the day after surgery. Bone conduction changes between pre- and post-operative tests were calculated to compare results obtained in the two study groups. The *t* test was performed for statistical comparisons. Statistical significance was defined as  $p < 0.05$ .

The study complies with the declaration of Helsinki and a written informed consent was obtained from all patients.

## Results

Of the total 106 patients studied, 55 were operated on with the ancillary use of Mesna (Mesna group) and 51 underwent surgery with traditional mechanical dissection alone (no Mesna group).

The Mesna group included 32 women and 23 men with a mean age of 44 years (range 18-67); the no Mesna group included 30 women and 21 men with a mean age of 43 years (range 18-72).

Mean bone conduction threshold shifted from 17.2 dB to 17.4 dB in the Mesna group and from 16 dB to 16.3 dB in the control group. No cases of SNHL were observed in both groups. Average preoperative and postoperative bone conduction thresholds for all patients can be seen in Table 1. These changes in hearing levels were statistically insignificant.

On average, bone conduction thresholds at 4000 and 8000 Hz slightly worsened (0.6 dB in the Mesna group and 5 dB in the control group). Changes in bone conduction at 4000 and 8000 Hz are provided in Table 2.

**Table 1.** Mean pre- and post-operative bone conduction thresholds for frequencies 500, 1000, 2000 and 3000 Hz

	500 Hz		1000 Hz		2000 Hz		3000 Hz	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
Mesna	14.1	14.1	15.7	15.9	18.2	18.5	20.9	21.2
No Mesna	13	13	14.9	15.2	17.1	17.5	19.3	19.7

**Table 2.** Mean pre-operative and post-operative hearing levels for frequencies 4000 and 8000 Hz

	4000 Hz		8000 Hz	
	Preop	Postop	Preop	Postop
Mesna	24.2	24.8	25.9	26.5
No Mesna	21.9	26.1	22.8	27.8

## Discussion

In cholesteatoma surgery, complete and accurate removal of the matrix is of paramount importance to minimize the likelihood of leaving in place epidermal debris that might grow to be a residual cholesteatoma. In most cases incomplete removal of squamous epithelium is due to a defective surgical view because of middle ear has anatomic areas that are difficult to access under otomicroscopy, such as retrotympanum and anterior epitympanum (15); inadequate exposure of cholesteatoma can also result from imperfect opening of the epitympanum or insufficient drilling into the facial ridge (7). Intraoperative use of otoendoscope, allowing surgeon to better inspect the blind pocket of the middle ear, has contributed to a decrease of residual cholesteatoma incidence but, unfortunately, cannot guarantee its elimination (16). In fact, residual disease is often observed also in areas directly controllable with the microscope. In these cases, incomplete cleaning of matrix is related to a dissection which may be challenging for several reasons. First, matrix can infiltrate the pneumatized mastoid cavity or replace middle ear mucosa (17); furthermore, in presence of intact ossicular chain, labyrinthine fistula, epidermization of the facial nerve or bony defects of middle cranial fossa, the gentleness of dissection needed to avoid iatrogenic lesions can expose to an higher risk of incomplete extirpation of the disease (6).

Traditionally, removal of cholesteatoma is based on mechanical forces alone by dissection or avulsion of

the soft tissue mass from the underlying bony structures. In order to make more complete the extirpation of the disease we have associated chemical dissection to mechanical technique. As chemical dissector we have utilized Mesna, a substance able to dissolve adhesions between pathological and normal tissues by breaking disulfide bonds.

It is well known that any chemical agent injected into the middle ear can enter the inner ear via the permeability of the round window membrane, where it may cause toxic effects to the cochlear structures (18). Considering the disparate toxicological, experimental and clinical studies, and the large clinical use of this compound, ototoxicity was not expected from application of Mesna into the middle ear. Nevertheless, we performed a study on the potential ototoxicity of Mesna in an experimental model of guinea pigs, in which the conditions of the surgical use of this compound were reproduced (13). Mesna solution was administered in one ear, while the opposite ear received a placebo (saline solution) and functional as well as morphologic evaluation of cochlear structures were performed. Functional study by means of auditory brainstem response (ABR) testing showed that there was no difference in ABR thresholds between ears injected with Mesna and those injected with saline solution. Observation of both Mesna-treated and placebo-treated cochleas by means of transmission electron microscopy and scanning electron microscopy demonstrated that Mesna application did not induce a hair cells loss greater than that caused by placebo. The same results were achieved by Van Spaendonck et al. (19) who did not observe any toxic effect of ototopical application of Mesna in a study on inner ear morphology performed using interference contrast microscopy and scanning electron microscopy.

No specific studies were reported in the literature on the potential ototoxicity of intraoperative use of Mesna in humans. Yilmaz et al. (20), reporting on the

ability of Mesna to facilitate surgery in atelectatic ears and adhesive otitis media, did not observe any SNHL in treating 41 patients, but no data on pre- and post-operative bone conduction were reported.

The absence of adverse effects of Mesna in laboratory animal models suggests that this chemical agent is not ototoxic in humans, but interspecies differences in the anatomy and physiology of the round window can confound the predictability of the response (21). For this reason, in this study we addressed specifically the issue of possible toxic effects of Mesna application into the middle ear during otologic surgery in humans. No cases of SNHL were observed neither in the patients treated with the support of Mesna nor in the patients operated without the use of Mesna. Changes in mean bone conduction thresholds after surgery for frequencies from 500 to 3000 Hz were negligible in both groups.

The analysis of hearing levels for frequencies 4000 and 8000 Hz showed a mean worsening of 0.6 dB in the Mesna group and of 5 dB in the no Mesna group. Furthermore, in patients treated with the support of Mesna the worsening of the high frequencies reached a maximum of 10 dB, while in patients operated on without the use of Mesna the maximum worsening was of 30 dB. There are 3 mechanism that could account for the observed high-frequency SNHL: direct contact with the ossicular chain that cause excessive vibration of the stapes footplate, direct injury to the membranous labyrinth, an acoustic trauma caused by high levels of drill noise (22). Probably, acoustic trauma could be responsible for the worsening of high frequencies observed in the present series since the portion of the cochlea most vulnerable to high levels of noise is the basal turn, which is associated with high-frequency sound. An interesting finding of this study was the stability of high frequencies bone conduction in patients treated with Mesna; since antioxidant drugs appear very promising for therapeutic use against noise-induced hearing loss (23), it could be hypothesized a protective role of Mesna in virtue of its antioxidant properties. Further studies are needed to confirm this hypothesis.

In conclusion, the results of this study confirmed data obtained in laboratory animal models demonstrating that intraoperative use of Mesna in middle ear surgery is safe and does not lead to ototoxic effects.

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