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Two case reports

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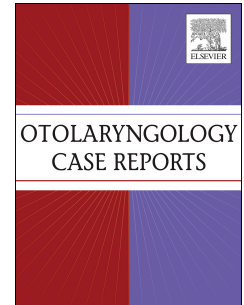
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Tympanic membrane perforation treated with Adelmidrol and Trans-traumatic acid: Two case reports.

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Conflict of Interest

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Abstract

Tympanic membrane perforation is a very common clinical condition encountered in otological practice; it can result from a large variety of causes such as trauma or infections. Ear buzzing, earache, and hearing loss are the major symptoms of tympanic membrane perforation, but it may also result into middle ear infection (*otitis media*) and transmissive hearing loss, if not treated in time. Various nonsurgical treatments have been offered in order to improve membrane re-epithelization, but to date, there are no efficient topical therapy to restore the membrane integrity. There are reported two case of tympanic perforation treated with a sterile medical device consisting of Adelmidrol and Trans-traumatic acid.

1. Introduction

Tympanic membrane (TM) is a thin semitranslucent, pearly white membrane that protects middle ear cleft, separating it from external. TM is a key component of the tympano-ossicular system with its main function of sounds amplification and transmission [1,2].

Tympanic membrane consists in *pars tensa*, a largest part below the malleolar folds, made of three layers: outer cuticular, middle fibrous and inner mucosal, and *pars flaccida*, a triangular area above, thin and devoid of fibrous tissue; usually *pars tensa* is the common site of rupture [3].

Tympanic membrane perforation (TMP) is a very common clinical condition encountered in otological practice; it can result from a large variety of causes such as trauma, infections or even malignant tumours. Common causes of traumatic TMP include rapid change in ear pressure due to slapping, blast, travelling in a non-pressurized air craft or sudden fluid compression while diving, but also faulty technique of ear cleaning with either a cotton swab (so called “Q-tip injury”) or other sharp objects [2-4].

Ear buzzing, earache, hearing impairment, bleeding, tinnitus, dizziness, are the major symptoms of TMP, but it may also result into middle ear infection (*otitis media*) and transmissive hearing loss, if not treated in time [1,5].

Up to 80% of all perforated TMs heal spontaneously, with relatively few requiring operative intervention. If perforation fails to close spontaneously after 6 months, myringoplasty or tympanoplasty are indicated [6,7].

Various nonsurgical treatments have been offered in order to improve spontaneous healing rate, but there are no efficient therapy to enhance re-epithelization of large or total tympanic perforation, in order to restore membrane integrity and sound transmission [8].

In this article there are described two case of TMP treated with a sterile medical device consisting of 2% Adelmidrol and 1% Trans-traumatic acid (Nevamast[®] gel - Epitech Group SpA, Saccolongo, Italy).

2. Case Presentation

2.1. Subject 1

In December 2020 a 30-year-old healthy woman came to MEDICA.IT Centre suffering from persistent symptoms lasting from three months, characterized by otodinia, otorrhea, hypoacusia and right ear itching, occurred after being in a swimming pool. Previous therapy with antibiotics and corticosteroids had failed.

Otomicroscopy showed an external auditory duct completely occupied by a purulent and malodorous discharge. Tragus digitopression and auricular pavilion traction evoked severe pain. After cleaning the external auditory duct, it showed hyperemia and edema, characterized by the presence of an abundant bluish purulent discharge. The tympanic membrane showed a perforation in the antero-inferior quadrant, between *pars tensa* and *pars flaccida*. Ear swab examination revealed a *Pseudomonas Aeruginosa* infection.

After seven weeks of topical and systemic therapy and three times a week medications, symptoms were resolved, but with the persistence of membrane perforation.

After seven days without medical therapy, under the guide of an otomicroscope, Nevamast[®] gel was applied with a sterile curette directly on the edges of perforation put to blood with a medical tip, in order to avoid gel instillation and spreading into tympanic cavity.

Perforation was observed after five days revealing a significant reduction of its diameter (Fig. 1), therefore it was decided to proceed with a second application of the medical device.

At the visit five days further, the perforation resulted totally healed (Fig. 2A) with a complete restoration of sound conduction, confirmed by the audiometry and impedance tests (Fig. 2B).

2.2. Subject 2

In March 2021 a 71-year-old healthy woman came to MEDICA.IT Centre suffering from persistent symptoms lasting from three months, characterized by right ear itching and bilateral otorrhea. Bilateral hypoacusia was also present for some years, but gotten worse over the past three months and was now accompanied by right ear muffling. Previous different pharmacological therapies had failed.

Otomicroscopy showed an external auditory duct completely occupied by a whitish cottony discharge, surmounted by small blackish spheres. Tragus digitopression and auricular pavilion traction evoked mild pain.

After cleaning the external auditory duct it appeared hyperemic and desquamated. TM showed a perforation in the antero-inferior quadrant. Otomicroscopy and patient symptoms was also suggesting the presence of an *Aspergillus Niger* mycotic infection complicated, but not related, to the tympanic perforation.

After about ten days of appropriate pharmacological therapy, infection get resolved but with the persistence of membrane perforation (Fig. 3).

Nevamast[®] gel was applied under the guide of an otomicroscope with the same methodic and precautions of the previous case. Perforation was observed after five days, revealing a significant reduction of its diameter (Fig. 4A); it was so decided to proceed with a second application of the medical device.

After five days, the audiometry and impedance tests showed a mild improving for the right ear, while membrane perforation resulted completely restored (Fig. 4B).

3. Discussion

TM is a thin trilaminar tissue sheet (outer, intermediate and inner layer) responsible for maintaining tympanic homeostasis and ear health [9]. TM epidermis is mainly populated by keratinocytes that constantly proliferate and migrate centrifugally throughout the membrane to preserve and renew its integrity [10,11]. The loss of its integrity may cause a perforation in the thin tissue that separates the ear canal from the middle ear. TMP may be caused by different reasons such as trauma, barotrauma, insertion of objects into the ear and acute or chronic middle ear infection [12]. This condition can cause pain, accompanied by hearing loss, otodinia, otorrhea, vertigo and tinnitus [13].

Unlike skin wound healing is characterized by the presence of fibroblasts, the regeneration of TM occurs with keratinocytes migrating from the edge to bridge the perforation [14,15]. To accelerate the wound healing, it is therefore essential to identify efficacious treatments able not only to reduce inflammation, but also to stimulate keratinocytes proliferation.

For the first time to our knowledge, two TMPs was treated using a sterile medical device (Nevamast[®] gel) applied after pharmacological treatment, to stimulate perforation healing.

The device is a isosmotic hydrophilic gel consisting of 2% Adelmidrol and 1% Trans-traumatic acid able to support the natural re-epithelialization process of skin lesions. An experimental study showed that this association accelerated the healing process in diabetic mice as early as 6 days after wound induction and that the re-epithelialization was approximately complete after 12 days of treatment [16]. Furthermore the results obtained in a clinical study on diabetic foot ulcers, showed the ability of the combination of Adelmidrol and Trans-traumatic acid to promote re-epithelialization and wound healing process [17].

Adelmidrol is the diethanolamide derivative of azelaic acid with both hydrophilic and hydrophobic properties, mainly used in topical formulations to normalize skin inflammatory processes [16].

Adelmidrol, belonging to the ALIAmide family (*Autacoid Local Injury Antagonist Amides*) is able to increase the physiological endogenous levels of palmitoylethanolamide (PEA), whose mechanism of action is the down-modulation of mast cell degranulation through the so-called ALIA mechanism (*Autacoid Local Injury Antagonism*) [18,19]. Through this “*entourage effect*” exerted by Adelmidrol

on PEA concentrations, it is able to modulate the inflammatory process, as shown in canine keratinocytes [19].

Trans-traumatic acid is a monounsaturated dicarboxylic acid naturally biosynthesized by non-enzymatic oxidation of traumatin and secreted to encourage wound healing in plants (also called *wound hormone*) [20,21]. Furthermore, Trans-traumatic acid is able to stimulate the convergence of keratinocytes in wound edges, accelerating epithelial integrity recovery in animal tissue [22].

The association of Adelmidrol and Trans-traumatic acid therefore determines a synergistic effect that favors the natural process of re-epithelialization [16,17].

The ability of Adelmidrol to increase endogenous PEA level, modulating mast cells degranulation [19] and the capacity of Trans-traumatic acid to stimulate keratinocytes convergence from the edges to the core lesion [22], allow a rapid healing process.

4. Conclusion

The topical application of Nevamast[®] gel directly on the bloody edge of tympanic perforation promoted membrane re-epithelization and its complete restoration in about 10 days. This study shows, to our knowledge for the first time, that the local application of the medical device in two patients suffering from TMP, stimulated perforation healing. The combination of Adelmidrol and Trans-traumatic acid could represent an innovative treatment in otological practice to promote recovery and *restitutio ad integrum* of damaged tympanic membranes.

Declarations of interest

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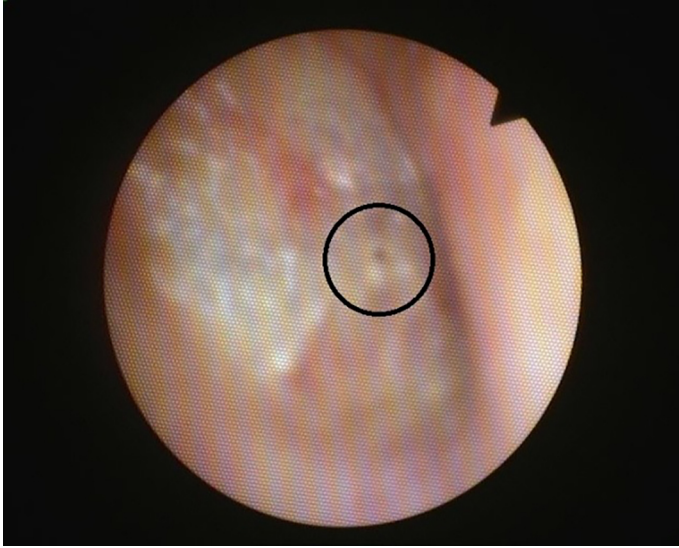
Figure legends

Fig. 1. TMP (black circle) in the antero-inferior quadrant five days after the first application of Adelmidrol and Trans-traumatic acid.

Fig. 2. (A) Complete healing of TMP five days after the second application of Adelmidrol and Trans-traumatic acid. (B) Pure-tone Audiometry showing bilateral normal hearing after treatment.

Fig. 3. Persistence of TMP in the antero-inferior quadrant after infection healing.

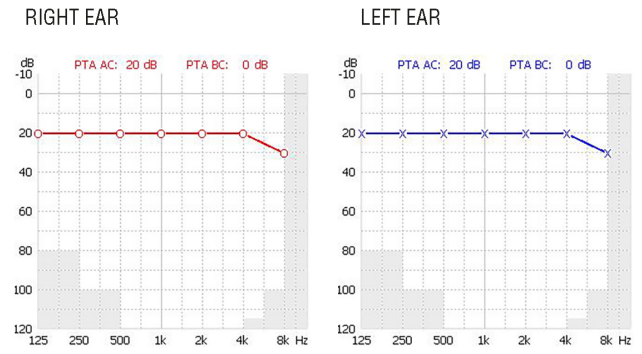
Fig. 4. (A) TMP (black circle) in the antero-inferior quadrant five days after the first application of Adelmidrol and Trans-traumatic acid. (B) Complete healing of TMP five days after the second application of Adelmidrol and Trans-traumatic acid.



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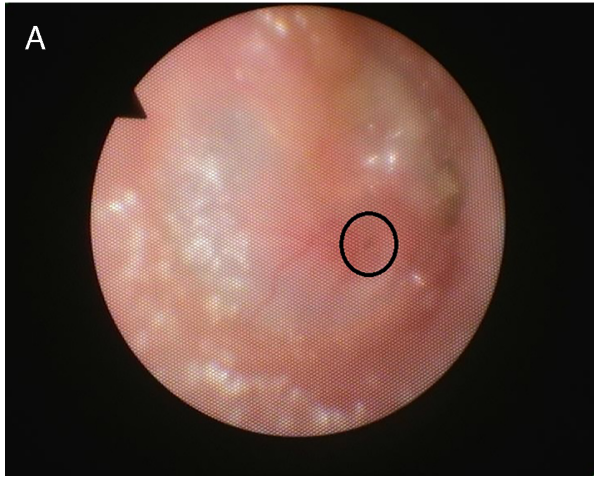


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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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