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Application of Ionomer Cement Onto The Stapedial Footplate: Impact on the Perilymphatic Aluminum Level

Gábor Ráth, MD, PhD; Gábor Katona, MD, PhD; Péter Bakó, MD; László Török, MD; Péter Révész, MD; Edit Tóth, MSc; Imre Gerlinger, MD, PhD

Objectives/Hypothesis: From an acoustic aspect, fixation of the medial end of an ossicular replacement prosthesis to the stapedial footplate would be desirable. Technically, ionomer cement seems an ideal material for this purpose. The objective was to determine the aluminum level of the perilymph after the application of ionomer cement on the stapedial footplate.

Study Design: An experimental study on rabbits.

Methods: A total of 25 Pannon White rabbits were divided into three groups. Five rabbits (group I) underwent sham operation; in 15 animals (group II) ionomer cement was applied onto the stapedial footplate; and in 5 cases (group III) the application of the cement onto the footplate was followed by opening of the vestibulum. In groups of 5, the animals were killed on day 1, 7, 30, 180, or 365 postoperatively. Fluid samples were taken from the vestibulum and their aluminum levels were determined.

Results: The average aluminum level in the fluid was insignificantly lower in group II than in group I, but significantly lower in groups I and II than in group III.

Conclusion: As a glue, ionomer cement safely can be applied directly onto the footplate without the threat of raising the perilymphatic aluminum level, provided that there is no perilymph leakage. However, in the event of an open vestibulum, the application of cement onto the footplate is to be strongly discouraged due to the danger of a consequent increase in the aluminum level in the perilymph and the cerebrospinal fluid.

Key Words: Ionomer cement, rabbit, aluminum.

Level of Evidence: NA.

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INTRODUCTION

The tympanic membrane and the ossicular chain transmit sound energy biphasically into the inner ear. In the compression phase of sound, the eardrum and the ossicles are both pushed medially and then pulled laterally during rarefaction. The two phases alternate in rapid continuous succession. In the absence of the stapes superstructure (SSS), a prosthesis can be placed on the mobile stapedial footplate (SFP) to connect it with either the tympanic membrane or the remnants of the ossicular chain. Unfortunately, no prostheses, and not even bone grafts replacing the SSS, show any tendency to grow together with the SFP. In the lack of a fixed connection between the medial end of the prosthesis and the SFP, the chain cannot pull the SFP laterally during rarefaction. This phenomenon can lead to an energy loss, which may be responsible for a suboptimal hearing result after ear surgery. From an acoustic standpoint, the bony bonding of a prosthesis to the SFP would be desirable.[1]

Glass ionomer cement (GIC), originally developed as a fixing material for dentistry purposes, was first introduced into the armory of ossiculoplasty by Hehl.[2] Since that time, many ear surgeons have used the material for ossicular reconstruction. GIC hardens following a mildly exothermic acid-base neutralization reaction between an aqueous solution of a polymeric acid and calcium fluoroaluminosilicate glass powder. The hardening reaction of the cement is based on the gelation of the polymeric acid through the cross-linking of the carboxyl groups in the acid with aluminum (A1) and calcium ions released from the cement powder.[3] With a paste-like consistency, the material is easily workable, binds well to bare bone surfaces, and sets within a few minutes, leaving time for manipulation in the tympanic cavity before it hardens to a bony-like structure that exhibits excellent mechanical properties and biocompatibily.[4]

The closure of large skull base defects with significant amounts of GIC that came into contact with the cerebrospinal fluid (CSF) was earlier reported to result in Al-induced encephalopathy.[5–7] This unfortunate event was followed by restrictions on the usage of GIC in otoneurosurgery. Although GIC seems to be an ideal fixing material for the bonding of a prosthesis to the stapedial

From the Department of Pediatric Otorhinolaryngology (G.R.); the Department of Otorhinolaryngology & Head and Neck Surgery (P.B., L.T., P.R., I.G.), Pécs University, Pécs; the Department of Pediatric Otorhinolaryngology and Bronchology (G.K.), Heim Pál Hospital; and the Klebelsberg Institution Maintenance Center, Hungary (E.T.), Budapest, Hungary.

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Send correspondence to Gábor Ráth, MD, PhD, Department of Pediatric Otorhinolaryngology, Pécs University, 7 József Attila út, Pécs, H-7634. Hungary. E-mail: gaborrath@freemail.hu

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footplate, the fear of Al toxicity led otosurgeons to refrain from the procedure, even though animal experiments did not demonstrate any damage to the cochlear function when it was applied onto the cochlear wall.[8]

Bauer recently reported on three cases in which a missing SSS was restored with an autogenous cortical bone columella fixed with GIC to the mobile SFP. No toxic effects or deterioration in bone conduction in comparison with the contralateral ear were detected during a 13-year observation period.[9]

The absorption of metallic elements from the middle ear into the perilymph can occur through the round window, the oval window, or the bony otic capsule. Although it has not been clearly demonstrated yet, it is speculated that in the oval window region Al can pass through the very thin SFP, the annular ligament, or the bony walls of the oval window niche. Our goal was to utilize an animal model to establish whether GIC placed on the stapedial footplate has any influence on the Al level in the perilymphatic space fluid.

MATERIALS AND METHODS

A total of 25 3- to 6-month-old Pannon White rabbits of either sex, weighing 1,340 g to 2,520 g, were used in the study. The left ears were left intact. The animals were sedated with an intramuscular (IM) injection of 20 mg of xylazine (Sedaxylan, Eurovet Animal Health BV, Bladel, The Netherlands), and were anesthetized with an IM injection of a mixture of ketamine (Calypsol, Richter Gedeon Rt., Budapest, Hungary) at a dose of 35 mg per 1000 g of body weight and 20 mg of xylazine. The animals were stabilized on a surgical table. The preauricular skin was shaved and disinfected with 5% iodine in 95% alcohol. Under aseptic conditions, a small horizontal skin incision was made over the right external auditory meatus under an operating microscope, and the canal was entered at the junction of the bony and the cartilagenous parts. The lateral wall of the bony meatus was partially removed with a strong pair of pliers to afford a better view of the eardrum. The tympanic bulla was opened through the pars flaccida, the lateral attic wall was partially removed, and the ossicles were identified. The pars tensa was maintained intact. Both incudo-stapedial and incudo-malleolar joints were divided with a fine needle and a hook, and the incus was removed. The lateral surface of the SFP was very gently denuded by scratching with a microknife. The malleus was left in place, and the tympanic membrane and the chorda tympani remained continuous.

The rabbits were divided into three groups: Groups I, II, and III consisted of five, 15, and five animals, respectively. The cement (GC Fuji I, GC Corporation, Tokyo, Japan, lot 1008101) was prepared according to the manufacturer's instructions using the commercial liquid provided. A total of 1.8 mg of powder was mixed with 1 ml of liquid on a plastic plate at room temperature until the mixture acquired a paste-like consistency. The paste was then transferred with a fine, blunt curved pick onto the lateral surface of the right SFP in groups II and III. No cement was used in the sham operations in group I. By means of suction, the operative field was maintained absolutely dry while the GIC was setting. Any GIC accidentally applied to an unwanted area in the tympanic bulla was immediately removed by suction. Only in group III was the SSS gently pushed posteroinferiorly with a fine hook until the first droplet of perilymph appeared in the oval window. No suction was applied in the vicinity of the oval window. The middle ear was closed by replacing the Shrapnel's membrane with a piece of fascia taken from the muscles laterally covering the meatus. Finally, the skin was closed with interrupted sutures with Mononylont 3-0 (Ethicon Ltd., Sao Jose dos Campos, Brazil).

After surgery the rabbits were maintained in cages with free access to food and water. In groups of five, all 25 animals were killed by the intravenous injection of 1 g of thiopental sodium (Thiopental, Sandoz GmbH, Kundl, Austria) on days 1, 7, 30, 180, or 365 postoperatively. After sacrifice, the surgical field was reexplored, similarly as previously. The tendon of the stapedial muscle was cut and the stapes was tipped out gently from its original position with a fine, curved oval window pick, until the first droplet of fluid emerged between the SFP and the annular ligament. The sample was obtained with a blunt-tipped calibrated capillary (VWR-53432-740 20 μL, Batavia, IL) held by hand against the oval window. Care was taken to position and insert the collection pipet quickly to prevent a significant outflow of perilymph. The fluid was collected for 2 minutes into a polystyrene tube. No glassware was used. The catheter and the tube were washed in 10% HCl and rinsed thoroughly with ultrapure water. The perilymph-CSF samples (5 μl–16 μl) were immediately transferred to a refrigerator at -40°C.

After calibration with ultrapure water, the Al contents of the centrifuged samples were determined with an inductively coupled quadrupole plasma mass spectrometer (Agilent 7500ce) according to the manufacturer's instructions, in the Chemical Laboratory of the Hungarian Institute of Occupational Health in Budapest.

The Kruskal-Wallis test and the Mann-Whitney U test were chosen as statistical analyses with which to determine the level of significance between the Al contents in the three groups of animals. All experiments were carried out in full accordance with internationally accepted rules and regulations regarding the use of animals in medical research, and the study was approved in advance and monitored by the local Animal Health and Food Control Station (BA02/2000–6/2008).

RESULTS

Exploration following sacrifice revealed a dry middle ear and an inflammation-free mucosa in all 25 ears. No scarring and no evidence of a foreign body reaction or perilymph leakage was found in the bulla. On removal of the stapes, fragmentation or displacement of the GIC was not detected on the SFP in any of the 20 ears where it was applied. No severe disease, unintended death, behavioral change, balance disorder, seizure, or hair loss was observed throughout the study.

The Al levels detected in the perilymph samples are presented in Table I. The Kruskal-Wallis test indicated a significant difference ($P = 0.003$, $P < 0.005$ was considered to be significant). This means that the result on at least one of the samples was different from those for the other samples. The test does not identify where such differences occur or how many differences actually occur. With the paired Mann-Whitney test, a statistically significant difference was demonstrated both between group III and group I and between group III and group II ($P = 0.008$ and $P = 0.000$, respectively; $P < 0.001$ was considered to be significant). The values did not differ significantly between groups I and II ($P = 0.8$) and were mildly higher in group I.

In group III the Al level was highest on day 7 and second highest on day 1. Between day 7 and day 365 the level gradually decreased as time passed.

TABLE I.
The Level of Aluminum (μg/L) in the Perilymph at Different Times After Surgery, Together With the Average Values in Groups I, II, and III. In Group II, Standard Deviation (SD) and the Average of the Three Values at Different Time Intervals Are Also Shown.

	Group I (n = 5)	Group II (n = 15)	Group III (n = 5)
Day 1	0.174	0.130, 0.128, 0.581 (average = 0.2797) SD = 0.26096	2.712
Day 7	0.145	0.232, 0.269, 0.454 (average = 0.3183) SD = 0.11894	3.612
Day 30	0.754	0.212, 0.177, 0.731 (average = 0.3733) SD = 0.31024	2.364
Day 180	0.125	0.163, 0.601, 0.416 (average = 0.3933) SD = 0.21988	1.945
Day 365	0.545	0.128, 0.410, 0.473 (average = 0.3370) SD = 0.18372	1.119
Average	0.3486	0.3403	2.3504

SD = standard deviation.

DISCUSSION

Originating from the labyrinthine capsule, the SFP is highly inert and displays no tendency to grow together with any graft, not even with bone autografts. If it suffers a fracture, it never heals. In the absence of the SSS, the substituting prosthesis exerts some pressure on the SFP, the annular ligament is distended, and lateral movement can take place at the expense of the elasticity of the annular ligament.[10] It is difficult to create and maintain this optimal, though sligh, tension in the long run, which results in the degree of contact necessary for the best possible transmission throughout the frequency range.[11] Thus, sound conduction can be achieved only at the expense of the elasticity of the annular ligament, even a slight distension of which (10 μm) causes a 10-dB conductive hearing loss.[1] The normal ossicular chain works as a push-pull system, that is, the compression phase of the sound moves the eardrum and the ossicles medially and the rarefaction phase laterally. As a total ossicular replacement prosthesis cannot transmit a pulling force, better sound conduction could be expected from the fixation of the medial end of the prosthesis to the SFP.[10] However, caution is recommended in view of the Al content of certain materials.

Although Al comprises a significant percentage of the contents of the Earth's crust, it is practically absent from the central nervous system. When Al was introduced experimentally into the central nervous system, numerous neurotoxic effects were observed: enzymatic and neurotransmitter changes, epileptic seizures, neurofibrillary changes, and behavioral and cognitive deficits.[12] No such symptoms were observed during the observation period in our study. In rats, neither the acute nor the chronic intraperitoneal administration of Al caused either clinical or histological ototoxicity.[13]

Reconstruction of large skull base defects with significant amounts of Ionocem (calcium fluoroaluminosilicate) that came into contact with the CSF was earlier found to result in Al-induced encephalopathy.[5,6,14] An increased mean bulk Al concentration in the cortex and subcortex up to 9.3 μg/g (normal range <2 μg/g) was revealed.[7] The Al level in the postauricular CSF accumulation was 176 μg/L,[14] and ranged between 495 and 1440 μg/L in the cerebrospinal fistula,[6] and between 63 and 185 μg/L in the CSF.[5,6] These levels are much higher than those we experienced (3.6 μg/L at maximum). Obviously, the amount of GIC that can be applied to the SFP is far smaller (less than 1 mg) than that used to repair large skull base defects.[7] Thus, as only a small amount is needed for ossicular reconstruction and there is no contact with any body fluid, this method may be regarded as safe.

Although the two fluid compartments interact with each other, it is not clear to what extent and with what dynamics perilymphatic Al would influence the Al level in the CSF in the rabbit. Reconstructions of 3-dimensional magnetic resonance images indicated that the total perilymph volume in the guinea pig was 15.94 μL,[15] and that the total perilymph volume in the human was 158.5 μL.[16] In the present study, the volumes of the vestibular samples from the rabbits ranged between 5 μL and 16 μL. A fluid sample taken from the vestibulum or the basal turn of the cochlea cannot be assumed to be pure perilymph. It is contaminated with CSF, as the cochlear aqueduct enters the perilymphatic space nearby. Once the vestibulum is opened, perilymph leaks through the oval window into the middle ear, driven by CSF entering the inner ear.[17] As Al has access to the brain parenchyma from the GIC via perilymph and CSF fluid leakage, the Al level of the mixture of these two fluid compartments is relevant in our case. A higher perilymph predominance can be achieved by rapid sampling, taking a smaller volume of sample or sampling through the cochlear apex.[18]

Nevertheless, the mild increase detected in the level of Al in the perilymph clearly demonstrates the need for caution. The application of GIC onto the SFP in the presence of an open vestibulum is to be strongly discouraged, and its application anywhere in the middle ear when the leakage of perilymph is noticed (e.g., during fixation of a prothesis with GIC to the incus during a stapedotomy procedure or during fixation of a cochlear implant with GIC in the presence of an opened inner ear) demands close consideration and may even be contraindicated.

Application of GIC onto the SFP resulted in a mildly lower Al level in the perilymph, relative to the samples from the sham-operated animals. This observation leads us to believe in the safety of the usage of GIC onto the SFP in the close vicinity of the inner ear, even if no hearing tests or hystological examination of the inner ear structures were carried on in the current study.

Of interest, the human round window is 6 times thicker and has a greater collagen density than the rodent membrane. This difference could afford a greater barrier to the passive diffusion of a drug from the middle to the inner ear, and also suggests that rodent models could serve as sensitive sentinel models for ototoxicity.[19]

Al release from different kinds of GICs are not equal. GICs contain a proportion of water, which allows ion interchange with a surrounding liquid. Initially, there is a rapid burst of ion release during the 150 seconds of the setting reaction under wet conditions.[20] Thereafter, the release is significantly reduced and it subsequently declines even further, so that by week 6 only traces are detected.[21] Lübben and Geyer concluded that GIC should be kept dry and protected from any fluid contact for at least 30 minutes after mixing, as in vitro cytotoxic effects were observed when ionomeric cement was not carefully protected from fluid contact.[22] The maintenance of dry conditions during surgery in the neighbourhood of the applied cement inhibits the release of Al from the material, as such release can only occur into surrounding liquids.

In vitro, compomers and resin-modified cements have been reported to release less Al than conventional GICs.[23,24] A GIC in which zinc substituted Al was recently developed. Unfortunately, despite its excellent mechanical properties, this material failed basic biocompatibility tests.[25] The introduction of new types of GICs into otosurgery that release less or no Al deserve serious consideration.

CONCLUSION

Our data tend to support the view that GIC can be used as a safe material in the close vicinity of the SFP, without the risk of increasing the perilymphatic Al level, provided that there is no perilymph leakage. However, in the event of an open vestibulum, the application of GIC onto the SFP is strongly contraindicated because of the otherwise consequent increase in the Al level in the perilymph.

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