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REVIEW ARTICLE

Is gentamycin delivery via sustained-release vehicles a safe and effective treatment for refractory Meniere's disease? A critical analysis of published interventional studies

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Abstract The aim of this study is to review the literature on sustained-release vehicles delivering gentamycin in the inner ear of patients suffering from Meniere's disease (MD), and critically assess their respective clinical effectiveness and safety. A systematic literature review was conducted in Medline and other database sources until January 2016, along with critical analysis of pooled data. Overall, six prospective and four retrospective studies were systematically analyzed. The total number of treated patients was 320. A 2 year patient follow up was only reported in 40 % of studies. Inner ear gentamycin delivery using sustained-release vehicles is associated with improved vertigo control (strength of recommendation B), and quality of life (strength of recommendation B) in MD sufferers. In addition, dynamic-release devices seem to achieve high rates of improvement in the appearance of tinnitus (65.4 %) and aural pressure (76.2 %). By contrast, percentages of complete and partial hearing loss appear unacceptably high (31.08 and 23.38 % of patients, respectively), compared to historical data involving simple intratympanic gentamycin injections. Sustained-release vehicles for gentamycin delivery may have a role in the management of MD patients who have previously failed intratympanic gentamycin injections, or those who have already lost serviceable hearing. Their use as first line treatment over single intratympanic injections for all MD patients, who do not respond to conservative treatment should be discouraged.

Keywords Meniere's disease · Refractory · Gentamycin · Vertigo · Tinnitus · Perfusion · Micro-catheter · Micro-wick

Introduction

Meniere's disease is characterized by the clinical triad of recurrent vertigo, fluctuating sensorineural hearing loss, and tinnitus [1]. Aural fullness may also be present during the attacks. The relapsing nature of the disease may significantly affect the patients' quality of life, especially during periods of acute symptomatology [2, 3]. Vertigo mainly influences the physical dimension, while tinnitus and hearing loss influence the psychosocial dimension of patients' lives [1, 4], while the appearance of imbalance and unsteadiness between the attacks in some cases, either due to the disease, or the complications related to its management, may also have a negative effect in patients' quality of life.

The direct administration of gentamycin into the middle ear has become a very popular modality for the treatment of Meniere's disease over the last 2 decades [5–8]. And although the efficacy of intratympanic injections is proven [7, 9], there is still no consensus either on the appropriate gentamycin dose, or on the delivery method.

Part of the ambiguity lies upon the uncertainty involving the permeability of the round window membrane [10], as

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the round window niche has been found to be partially or completely obstructed by adhesions, fibrosis or fat plug in as many as 12–33 % of cases [11, 12]. In addition, the niche itself may be inaccessible [13], trapped air bubbles at the time of administration may result in impaired contact of the drug with the round window [13], while there can also be uncertainty regarding the length of time that the solution remains in the middle ear, or escapes through the Eustachian tube, or even how much of it remains in the middle ear without contacting the round window [14]. To further perplex the situation, there can possibly even be different rates of drug clearance or drug absorption from the inner ear itself [15, 16].

In an attempt to overcome these problems, some authors have described gentamycin delivery methods, other than intratympanic injection [16–29]. Sustained-release vehicles have the advantage of delivering a precise and consistent amount of medicine to the round window. This involves, in large part, dynamic-release devices, which allow the user to control the administration of the drug. In contrast, passive-release devices give the user little or no control over the activity of the device once it is placed in the middle ear. Hence, the medication cannot be accurately added, removed, or changed after treatment outset.

The aim of this study is to review the literature on sustained-release vehicles delivering gentamycin in the inner ear of patients suffering from Meniere's disease, and critically assess their respective clinical effectiveness and safety.

Materials and methods

An extensive search of the literature was performed in Medline and other available database sources until January 2016, having as primary end-point the assessment of the clinical effectiveness of sustained-release vehicles, which are used to deliver gentamycin in the inner ear as primary surgical treatment, in patients who suffer from Meniere's disease. This was approached (a) by evaluating the effect that this treatment modality had on the frequency and severity of vertigo, tinnitus, and aural pressure, and (b) by assessing the respective changes in the patients' quality of life.

Using this framework of results, the retrieved studies were critically appraised, according to evidence-based guidelines for the categorization of medical studies (Tables 1, 2). A secondary end-point included the effect that the gentamycin delivery had regarding the hearing of the treated ear.

During the search the keywords ''Meniere's disease'', ''gentamycin'', ''round window", "micro-catheter", "micro-wick" and "gelfoam" were utilized. The keywords Meniere's disease and gentamycin were considered primary and were combined to each of the other keywords individually. In addition, reference lists from the retrieved articles were manually searched. Language restrictions limited the search to English-language articles only.

Results

Fourteen studies met the defined criteria and were initially included in study selection. Among these studies, two included results which were partially incorporated at later studies by the same senior investigator, and were hence excluded from the analysis of pooled data to avoid double-counting [16, 27]. Another study had used gentamycin-soaked Gelfoam both as primary, and salvage surgical treatment of Meniere's disease. In the absence of clear-cut data about the clinical effectiveness of intratympanic therapy as primary surgical treatment of Meniere's disease, this study was also not used in the analysis of pooled data [17]. Finally, one study was lacking clear-cut data regarding the method of gentamycin application [28]. This study was also excluded from the analysis of pooled data.

Overall, six prospective and four retrospective studies, which utilized sustained-release vehicles for delivering gentamycin as primary surgical treatment in patients with Meniere's disease, were systematically analyzed (Tables 3, 4). All studies represented Level 2b evidence. The total number of treated patients was 320; 94 of them were males, 144 females, whereas the gender was not reported in 82 patients. Patient follow up reached 2 years or more in four, at least 1 year in another four, and less than 1 year in two studies.

Six studies had assessed the use of dynamic-release devices for gentamycin delivery [23–27, 29]. The total number of treated patients was 200. Satisfactory vertigo control was achieved in 89.28 % of patients (175/196), with 139 (70.92 %) reportedly achieving complete remission. Tinnitus improvement was reported in 65.4 % of patients for whom relevant data was available (104/159). In addition, there was an improvement in aural pressure in 76.2 % (96/126) of treated patients. The treatment also seemed to improve the quality of life in 43 out of 58 patients for whom this parameter was reported (74.1 %).

Four studies had assessed the use of passive-release devices for delivering gentamycin in the inner ear of patients suffering from Meniere's disease [18–21]. The total number of treated patients was 120. Satisfactory vertigo control was achieved in 82.2 % of patients (97/118), with 75 % of them (69/92) reportedly achieving complete remission. Tinnitus changes were only reported in one study with 4 out of 15 treated patients demonstrating improvement in this symptom. Improved quality of life was

Table 1 Levels of evidence regarding the primary research question in studies that investigate the results of a treatment (http://www.cebm.net/index.aspx?o=1025)

Category of evidence	Study design
Level I	• High quality randomized trial with statistically significant difference, or no statistically significant difference but narrow confidence intervals
	• Systematic review of Level I randomized control trials (and study results were homogenous)
Level II	• Lesser quality randomized control trial (e.g., <80 % follow up, no blinding, or improper randomization)
	• Individual cohort study
	• Systematic review of Level II studies or Level 1 studies with inconsistent results
Level III	• Case control study
	• Systematic review of Level III studies
Level IV	• Case series
	• Lesser quality cohort or case control study
Level V	• Expert opinion

Table 2 Strength of recommendation by category of evidence for guideline development (http://www.cebm.net/index.aspx?o=1025)

Strength of recommendation	Category of evidence
A	Consistent level I studies
B	Consistent level II or III studies or extrapolations from level I studies
C	Level IV studies or extrapolations from level II or III studies
D	Level V evidence or troublingly inconsistent or inconclusive studies of any level

reported in 77.38 % of patients for whom this parameter was reported (65/84).

Complete and partial hearing loss represented the most important complications associated with the use of sustained-release vehicles for the intratympanic delivery of gentamycin in patients with Meniere's disease. The respective percentages reached 31.08 and 23.38 % of patients for whom relevant data was available (23/74 and 47/201, respectively).

Discussion

The topical delivery of medication to the inner ear for the treatment of Meniere's disease has entered its eighth decade of practice. Barany in the 1930s, Schuknecht in the 1950s, and Sakata in the 1980s used different agents for the treatment of patients with active Meniere's disease, refractory to maximal conservative and medical management. [30–32] The theoretical advantages associated with this direct route of administration included an organ-specific treatment, increased medication uptake through the round window membrane resulting in higher perilymph levels, and lesser to none systemic absorption and toxicity [23, 33, 34].

Intratympanic gentamycin therapy has gained popularity in the treatment of tenacious active disease, due to its proven control on vertiginous bouts, its minimal invasiveness compared to the traditional surgical procedures, and its improved cost-effectiveness [21]. This popularity has been associated with the predilection of gentamycin to damage the vestibular organs rather than the cochlea [18, 31]. The vestibulotoxic effect of gentamycin on the inner ear seems to be realized through the damage of the vestibular dark cells, which are thought to produce endolymph. Inhibiting the secretory function of the dark cells may reduce the endolymph volume, thereby improving the symptoms of Meniere's disease [23].

Yet, when gentamycin is administered with a single intratympanic injection, the dose delivered into the middle ear may on one hand be known, however, the amount of drug actually in contact with the round window is practically unknown [25, 27]. Sustained-release vehicles have the theoretical advantage of delivering a more consistent amount of medication to the round window.

With regard to dynamic-release devices for gentamycin delivery, this study reveals a remarkably high percentage of vertigo control in treated patients (89.28 %). Based on the quality of studies and the uniform nature of the reported results, the clinical effectiveness of dynamic-release devices for gentamycin delivery in controlling the vertiginous bouts of patients with Meniere's disease can be graded as B. This result is quite important since the functional level of each individual patient with Meniere's disease, according to the criteria set by the American Academy of Otolaryngology, is associated with the effect of dizziness on his/her activities [35]. In addition, to the beneficial effects of this treatment modality on vertigo in patients with Meniere's disease, gentamycin delivery via dynamic-release devices seems to achieve high rates of improvement in the appearance of tinnitus (65.4 %) and aural pressure (76.2 %) in patients receiving local therapy.

Nevertheless, the relapsing nature of the disease and its effect on the patients' everyday activities inevitably affect their physical and emotional well-being, and thus their quality of life. Although quality of life issues are often very complicated, the administration of gentamycin using dynamic-release devices seems to be associated with improved quality of life in a significant percentage of treated patients (74.1 %), although this parameter has

Table 3 Studies assessing the use of dynamic-release devices for gentamycin delivery in refractory Meniere's disease

Authors	Study type	Evidence level	Number of patients	Follow up†	Administration method	Vertigo control (%)≠	Hearing complications	Tinnitus	Remarks
Suryanarayanan et al. [23]	Prospective	II	22	34	Round window micro-catheter	95	(a) Complete HL: 2 ears (b) Partial HL: 3 ears	(a) Unchanged: 50 % (b) Improved: 36 % (c) Deteriorated: 14 %	(a) Aural fullness improved in 68 % of patients (b) Post-treatment DHI scores were significantly reduced in 71.4 % of patients
Seidman [24]	Retrospective	II	86	10	Round window micro-catheter	89.1	Partial HL in 23 ears	(a) Improved: 71.1 % (b) Deteriorated: 2.4 %	CGT for 10 days at low flow rate is safe and effective for vertigo/tinnitus/aural pressure associated with MD refractive to conservative treatment
Hoffer et al. [25]	Prospective	II	36	>12±	Round window micro-catheter	89	Partial HL in 4 ears	Improved: 62 %	Vestibular function improved in 79 % of treated patients
Schoendorf et al. [26]	Prospective	II	11	<12	Round window micro-catheter	80	(a) Complete HL: 8 ears (b) Partial HL: 1 ear	n.r.	CGT does not seem advantageous over other applications in terms of effect on hearing and hospitalization time
Thomsen et al. [14]	Prospective	II	27	9–12	Round window micro-catheter	81.5	Complete HL in 6 ears	n.r.	(a) Aural fullness improved in 50 % of patients (b) Drop attacks stopped completely in 66 % of patients (c) Anacusis occurred within the first 24 h after catheter placement and treatment start in all patients experiencing this complication
DeCicco et al. [29]	Prospective	II	18	12	Round window micro-catheter	100	Partial HL in 1 ear	(a) Unchanged: 11.1 % (b) Improved: 83 %	Aural fullness improved in 94 % of patients, which was a significantly better result compared to IT injections

HL hearing loss, *DHI* dizziness handicap inventory, *CGT* continuous gentamicin therapy, *n.r.* not reported, *IT* intratympanic

† mean value in months

≠ complete and partial

± median value in months

Table 4 Studies assessing the use of passive-release devices for gentamycin delivery in refractory Meniere's disease

Authors	Study type	Evidence level	Number of patients	Follow up†	Administration method	Vertigo control (%)≠	Hearing complications	Tinnitus	Remarks
McKeith et al. [18]	Prospective	II	28	28	Hyalouronic acid pledgets	88.5	(a) Complete HL: 4 ears (b) Partial HL: 8 ears	n.r.	(a) Although the control of vertigo is comparable to IT injections, the rate of HL is significantly higher (b) This method may have a role in patients who have previously failed intratympanic injections
Crane et al. [19]	Retrospective	II	8	≥4	Gelfoam pledgets	75	Complete HL in 2 ears	n.r.	MEE-G is a viable treatment for MD, refractory to IT gentamicin therapy, before considering ablative surgery
Suryanarayanan et al. [20]	Retrospective	II	15	≥24	Silverstein micro-wick	100	(a) Complete HL: 1 ear (b) Partial HL: 3 ears	(a) Improved: 26.67 % (b) Deteriorated: 13.33 %	Patients with complete vertigo control demonstrated improved quality of life following the intervention
Hill et al. [21]	Retrospective	II	69	24	Silverstein micro-wick	76.8	n.r.	n.r.	(a) The application of gentamicin via the Silverstein micro-wick system has been consistently effective (b) Patients with complete vertigo control demonstrated improved quality of life following the intervention

HL hearing loss, *n.r.* not reported, *MEE-G* middle ear exploration with direct application of gentamicin to the round window, *IT* intratympanic

† mean value in months

≠ complete and partial

± median value in months

been rather underreported in the respective studies. Based on the quality of studies and the uniform nature of the reported results the positive effect of this mode of gentamycin administration on patients' quality of life can be graded as B.

With regard to the use of passive-release devices for delivering gentamycin in the inner ear of patients suffering from Meniere's disease, this study also reveals that vertigo is adequately controlled in most treated patients (82.2 %). Based on the quality of studies and the uniform nature of the reported results, the clinical effectiveness of this treatment modality in controlling the vertiginous bouts of patients with Meniere's disease can be graded as B. A similar strength of recommendation can be adopted regarding the positive effect of this mode of gentamycin delivery on patients' quality of life.

However, it should be mentioned that due to the fluctuant nature of Meniere's disease, there is a requirement of 2 years of follow up before a treatment outcome in Meniere's disease can be positively assessed [36]. This requirement was only met by 40 % of the studies included in the present systematic analysis, although the respective results did not differ from the ones deriving from the studies with lesser follow up. In addition, appropriate preoperative informed consent requires that the patient is aware of the potential risks which can be associated with this specific type of surgical intervention. Although the recurring nature of the disease ultimately results in some degree of hearing loss, often severe, the use of sustained-release vehicles has demonstrated alarmingly high percentages of post-treatment complete and partial hearing loss, affecting almost one in three, and one in four treated patients, respectively. Compared to historical data involving simple intratympanic gentamycin injections, this complication appears unacceptably high, taking into account that the respective percentages of vertigo control are similar [7, 9].

Indeed, in a recent meta-analysis regarding the outcomes of intratympanic gentamicin injection in the treatment of Ménière's disease, Huon et al. reported satisfactory vertigo control in 87.5 % of patients receiving intratympanic gentamycin injection, with a dead ear incidence of 1.8 % [9]. In the meta-analysis of Cohen-Cerem et al., the percentage of satisfying vertigo control reached 92.7 %, with reportedly no adverse effect on hearing level and word recognition [7]. Furthermore, the mean follow up period in the former study was extensive, reaching 49.8 months, which was corroborative for the sustainability of the observed positive outcomes.

Hence, although quality of life issues seem to be positively affected by the utilization of sustained-release vehicles for gentamycin delivery, it seems more prudent that the latter treatment modality is reserved for patients who have previously failed intratympanic gentamycin injections, or those who have already lost serviceable hearing. Round window lesions, mutations rendering the patient more susceptible to the cochleotoxic effect of gentamycin, specific enzyme disorders, and impaired patency of the cochlear aqueduct have been proposed to explain the adverse effect associated with the administration of gentamycin using sustained-release vehicles; however, there is still no clear evidence of the exact cause in the occurring cochlear toxicity.

Conclusion

Gentamycin delivery in the inner ear of patients suffering from Meniere's disease using sustained-release vehicles provides an organ-specific treatment associated with improved vertigo control (strength of recommendation B), and quality of life (strength of recommendation B). Nevertheless, the administration of gentamycin using sustained-release vehicles is also associated with unacceptably high percentages of complete and partial hearing loss in the treated ear. This detrimental effect on hearing, along with other possible complications associated with the more invasive nature of these procedures discourage their use as first line treatment over single intratympanic injections for all Meniere patients, who do not respond to conservative treatment. By contrast, sustained-release vehicles for gentamycin delivery may have a role in the management of patients who have previously failed intratympanic gentamycin injections, or those who have already lost serviceable hearing.

Compliance with ethical standards

Conflict of interest None declared. The authors have no financial interest, and have not received any financial support for this article.

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