Systemic steroid protects residual hearing in a guinea pig model of cochlear implantation

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Abstract

Background: The protection of residual hearing is an important goal of cochlear implant surgery. Local application of steroids to the round window membrane (RWM) of the guinea pig prior to cochleostomy has been shown to protect hearing, but requires a period of pre-treatment for at least one hour. To determine whether this waiting period can be avoided, the efficacy of administering systemic steroids prior to cochlear implantation is investigated.

Methods: Seventeen normal hearing guinea pigs were randomly assigned to receive a single preoperative intravenous injection of: 1) normal saline, 2) dexamethasone 0.2 mg/kg or 3) dexamethasone 2 mg/kg, 60 minutes before cochlear implantation. Implantation was completed with a silastic/platinum dummy electrode. Prior to surgery pure tone auditory brainstem response (ABR) thresholds were estimated from both ears separately in response to tone-pips from 2-32 kHz. This was again completed at 1 and 4 weeks postoperatively. The primary outcome measure was threshold shift at 1 and 4 weeks. Histology was examined for evidence of insertion trauma and foreign body reaction.

Results: Preoperative injection of 2 mg/kg dexamethasone prevented an elevation in ABR thresholds at all frequencies compared with the control group (8 - 32 kHz) at 1 and 4 weeks post implantation. This protection was not seen with a lower dose (0.2mg/kg) of dexamethasone. There was a foreign body reaction observed in control and low-dose treated animals, however this was suppressed in all but one of the high-dose dexamethasone-treated animals.
Conclusions: Intravenous high dose dexamethasone protects hearing during cochlear implantation and prevents the development of an inflammatory histological response. The prolonged intra-operative delay required for local delivery is avoided in this model. Furthermore, it may provide better protection of low frequency hearing than locally administered steroid.
Declaration

This is to certify that

• the thesis comprises only my original work towards a Master of Surgery degree
• due acknowledgement has been made in the text to all other material used,
• the thesis is less than 30,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signature: .................................................................

This work has been accepted for publication within the journal *Audiology and Neurotology* and can be referenced as:


Research data and records collected, used and maintained in the conduct of this research will be retained and accessible for five years from the point of thesis submission, unless publication or public release of the work of research subsequently occurs, in which case the research data and records will then be retained for five years after publication, or public release, of the work of research.
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The author also wishes to acknowledge the support of his wife, Pia and daughter, Ava.
# Table of Contents

**ABSTRACT**

**DECLARATION**

**ACKNOWLEDGEMENTS**

**INTRODUCTION**

**BACKGROUND**

- Cochlear Implantation Candidacy and Residual Hearing
- Table 1
- Table 1 (continued)
- Table 1 (continued)

**Cochlea Anatomy and Physiology**

- Human
- Guinea Pig

**Aetiology and Pathogenesis of Hearing Loss Following Cochlear Implantation**

**Hearing Protection**

**Surgical Technique**

**Electrode Design**

**Pharmacotherapy**

**HYPOTHESIS**

**METHODS**

- Animals
- Experimental Design
- Brainstem Auditory Evoked Potential Recordings
- Delivery of Intravenous Agent
- Silicone Cochlear Implant Electrode
- Cochlear Implantation
- Cochlear Histology
- Statistical Analysis

**RESULTS**

- Figure 1
- Figure 2
- Table 2
- Figure 3
- Figure 4
- Figure 5
- Figure 6
- Figure 7
- Figure 8
- Figure 9
Introduction

The established success of cochlear implantation in patients with total and profound hearing loss has seen candidacy criteria relaxed to include patients with greater residual hearing [1-5]. Protection of this residual acoustic hearing is desirable as significant portions of implant recipients are children and restorative strategies may become available in their lifetime. Furthermore, human trials of the utility of synchronous amplification of residual acoustic hearing alongside electrical stimulation in adult hybrid recipients are underway with encouraging results [6].

The benefit of acoustic hearing to implant recipients has motivated the development of strategies to protect this hearing including soft surgical technique [7-11] and altered electrode design [12-14]. However, there remains a complete loss of residual hearing in approximately 15% of cochlear implant recipients [8,9,11,15], with deep insertion beyond 400 degrees causing further low frequency loss [11]. As a profession, otologists are loath to accept an incidence of complete sensorineural hearing loss of only 2% with stapedectomy [16], so any improvements that can be achieved with cochlear implantation are likely to have a significant impact on patients, and perhaps broaden criteria for implantation.

More recent hearing protection strategies employ pharmacotherapy. The principal choice of pharmacotherapy has been glucocorticosteroids due to their enduring role in conditions such as sudden hearing loss [17] and vestibular neuritis [18]. The ideal route of application of glucocorticosteroids in cochlear
implantation has been subject to investigation. Local delivery has been considered for its capacity to provide higher concentrations of drug to the inner ear, whilst avoiding systemic complications [19-22]. Eshragi et al [23] and Vivero et al [24] have demonstrated that infusion of dexamethasone in artificial perilymph prevented a hearing loss in a guinea pig model that involved cochlear implant insertion and immediate withdrawal. James et al [25] provided evidence that a single dose pre-treatment with dexamethasone impregnated beads applied to the round window membrane (RWM) protected high frequency hearing in a guinea pig model of cochlear implantation (implant left in situ). This work was followed by Chang et al [26] who found that increasing the concentration or duration that steroid was applied to the RWM resulted in greater protection of hearing.

The clinical limitation of an approach using a single, locally applied, pre-cochleostomy dose of steroid is the intra-operative waiting time necessary to allow sufficient drug to diffuse across the RWM. The time it takes for steroid to distribute throughout the cochlea following RWM application is also pertinent for protection of low frequency hearing located at the apex of the cochlea. Plontke et al [27] modelled the distribution of dexamethasone throughout the cochlea after RWM application and showed a large concentration gradient between the basal and apical regions. This suggests optimal protection for low frequency hearing using local steroid may not be possible or will require prohibitively long application times.

The cause of hearing loss following cochlear implantation could relate to acoustic or direct mechanical trauma, altered cochlear homeostasis, infection or fibrosis
There is an immediate loss of hearing, perhaps due to altered basilar membrane biomechanics [28], followed by a delayed hearing loss [29] due to inflammation. Acoustic trauma has been shown to result in an inflammatory response initiated by resident inner ear immune cells, followed by recruitment of systemic immune cells in the days after injury [30]. Corticosteroids act upon inner ear cellular signalling pathways, including inflammation, to protect hearing following cochlear stress [31]. Intravenous delivery of steroid prior to cochlear implantation may protect hearing by achieving sufficient concentration within the cochlea to directly inhibit a local inflammatory response or it may act systemically to suppress the recruitment of circulating immune cells.

Herein a level of hearing protection is demonstrated and prevention of the histological manifestations of an inflammatory response is achieved following the systemic delivery of dexamethasone in a guinea pig model of cochlear implantation. The use of preoperative intravenous steroid may become an important option for hearing prophylaxis in cochlear implantation, and it will obviate the need to wait for distribution of steroid following RWM application, making better use of operating time. It may also be more favourably distributed throughout the cochlear compared to local delivery, resulting in better protection of low frequency hearing.
Background

Cochlear implantation candidacy and residual hearing

Since 1985, when the US FDA approved the first multiple electrode cochlear implant, speech recognition following cochlear implantation in profoundly deaf patients has progressively improved. Clark has outlined the evolution of the speech processing strategies that have contributed to this improved speech perception, from origins using fixed filters to more recent strategies including Multipeak and SPEAK [32]. Using these strategies the average profoundly deaf cochlear implant recipient can now communicate over the telephone [32]. This is considerable progress from early results with single channel electrodes where average patients could only perceive the prosodic elements of speech, with no discrimination in open sets [33].

Severely deaf patients with some residual hearing, but who experience only minor benefit from amplification, were previously excluded from selection for cochlear implantation due to concerns about potential damage to the cochlea with a prospect for only modest benefit [34]. However, the impressive speech perception enjoyed by profoundly deaf cochlear implant recipients with multichannel electrodes has led to the consideration of patients with residual hearing for implantation where there is a reasonable expectation that their speech perception with an implant will surpass performance with a hearing aid alone [1-5].

These patients with residual hearing are candidates for electric-acoustic stimulation, which involves synchronous acoustic amplification of auditory
stimulus to the low frequencies of the implanted ear alongside electrical stimulation of the high frequencies. It has been advocated by a number of groups who have reported that the presence of preserved residual hearing correlates with superior speech perception results following cochlear implantation. Electric-acoustic stimulation was first achieved by von Ilberg et al [6] and demonstrated to be useful by Kiefer et al [10]. The latter reported hearing outcomes with electric-acoustic stimulation superior to electric stimulation alone in 7/13 recipients with residual hearing. Using a 10 mm electrode, a group from Iowa further supported the benefit of electric-acoustic hearing in the special hearing situations of understanding speech in noise [35] and for the appreciation of music [36].

As patients with residual hearing are now candidates for cochlear implantation and the presence of residual hearing has been demonstrated to provide advantage through electric-acoustic stimulation, efforts have been directed at measuring the loss of residual acoustic hearing following cochlear implantation and understanding the cause of this loss in an attempt to develop hearing protection strategies.

Several investigators have measured the fate of residual hearing following cochlear implantation, and this is summarised in table 1.
### Table 1.

Summary of the literature: residual hearing after cochlear implantation.

<table>
<thead>
<tr>
<th>Paper (Year)</th>
<th>Patients’ residual hearing prior to surgery</th>
<th>Definition of loss or preservation of hearing</th>
<th>Type of implant and stated insertion depth</th>
<th>Implantation route</th>
<th>Atraumatic surgery</th>
<th>Steroids</th>
<th>Fate of residual hearing</th>
</tr>
</thead>
</table>
| Riker (1988)  
[34] n=7 | Severe to profound hearing loss. | Loss, defined as any threshold shift (magnitude not stated). | Nucleus 22  
(n=6), House  
3M single channel device (n=1). Insertion depth not stated. | Not stated | Not stated | Not stated | 7/7 had permanent threshold shift. Average hearing loss of 27 dB at 500 Hz, 34 dB at 1 kHz, 23 dB at 2 kHz. |
| Bogess (1989)  
[37] n=12 | Measurable response to limit of audiometer in any one frequency (0.25 – 4 kHz). Severe to profound hearing loss range. | Loss of hearing was >5 dB shift in any one frequency. | Nucleus 22,  
25mm. | Not stated | Not stated | Not stated | 12/12 had threshold shift. Range 5 – 35 dB loss. 11/12 had partial preservation hearing in at least one frequency, 6/12 (50%) complete preservation in single frequency (<10 dB shift in freq 500 Hz and over) |
| Hodges (1997)  
[38] n=40 | Residual bilateral responses in profound hearing loss range. Excluded tactile responses. | Preserved hearing was measurable response in at least one speech frequency (0.5, 1 or 2 kHz) | Nucleus  
(n=33) inserted 22 electrodes, Clarion (n=7) inserted 16 electrodes | Not stated | Not stated | Not stated | 21/40 had preserved hearing in 1 or more speech frequencies. |
| Kiefer (1998)  
[5] n=21 | Adults / children: Average thresholds 106/114 dB HL in implanted ear, 109 / 110 dB in contra-lateral ear. Severe to profound hearing loss. | Preserved hearing for adults / children was threshold <110 / 100 dB in 2 or more / 1 or more frequency from 250 / 500 – 4000 Hz. | Nucleus 22/ 
24: average insertion depth 20.7 mm, MED-EL 
Combi 40-/: average insertion depth 25.9 mm | Not stated | Not stated | Not stated | Adults: 4/17, 24% preservation  
Children: 13/17, 77% preservation |
| Von Ilberg (1999)  
[6] n=1 | Downsloping moderate to severe HL <1 kHz, severe to profound HL >1 kHz | Hearing loss was pre to post operative change in pure tone audiogram frequencies 125, 250, 500 and 1000 Hz. | MED-EL 
Combi-40+. Insertion depth 20 mm | Not stated | Not stated | Local triamcinolone (Volon A, 0.03 mks) | Partial preservation (15 – 20 dB loss) |
| Gostteitner (2004)  
[9] n=21 | Well preserved low frequency hearing of 20 – 60 dB HL <1 kHz, whilst severe-to-profound hearing loss for frequencies >1 kHz | Complete hearing preservation was an average of <10 dB difference between pre and post operative levels | MED-EL 
Combi-40+ (or 40+ medium). Insertion depth average 20.3 mm (range 16 – 24 mm) | Cochleostomy  
(caudal) | Yes. Partial insertion | Corticosteroids topically and systemically (dose not stated) | 18/21 hearing preservation: complete in 13/21 (62%), partial in 5/21 (24%) and total loss in 3/21 (14.3%) |
<table>
<thead>
<tr>
<th>Paper (Year)</th>
<th>Patients’ residual hearing prior to surgery</th>
<th>Definition of loss or preservation of hearing</th>
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<th>Fate of residual hearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gantz 2005 [12] n=24</td>
<td>Well preserved low frequency (125 – 1000 Hz) mild-to-severe HL, mid to high (&gt;1kHz) severe to profound HL</td>
<td>Not defined.</td>
<td>Iowa/Nucleus Hybrid 6mm (n=3) and 10mm (n=21)</td>
<td>Cochleostomy anteroinferior</td>
<td>Yes</td>
<td>Not stated</td>
<td>23/24 (96%) hearing preservation. Pure tone drop 9.5 dB over range 125 – 1000 Hz.</td>
</tr>
<tr>
<td>James (2005) [11] n=12</td>
<td>Minimum 10% open word set recognition</td>
<td>Hearing loss was measured as difference between pre and post operative thresholds. Median calculated.</td>
<td>Nucleus Contour Advance perimodiolar electrode array, inserted 17 mm</td>
<td>Cochleostomy anteroinferior</td>
<td>Yes Advance off stylet and partial insertion</td>
<td>Systemic corticosteroids (dose not stated)</td>
<td>Median threshold increase was 23, 27 and 33 dB at 125, 250 and 500 Hz.</td>
</tr>
<tr>
<td>Kiefer (2005) [10] n=13</td>
<td>Well preserved low frequencies (125 – 1000 Hz) thresholds 20 – 60 dB Severe to profound HL &gt; 1 kHz.</td>
<td>Hearing loss was measured as difference between pre and post-operative thresholds. Mean calculated.</td>
<td>MED-EL Combi 40+ Insertion depth limited to 19 – 24 mm</td>
<td>Cochleostomy</td>
<td>Yes Partial insertion</td>
<td>Local triamcinolone (40mg/ml) and preoperative prednisolone 500mg (time not stated)</td>
<td>11/13 hearing partially preserved. Mean shift ~20 dB &lt;1 kHz and &lt;5 dB shift &gt;1 kHz.</td>
</tr>
<tr>
<td>Balkany (2006) [15] n=28</td>
<td>Severe to profound HL</td>
<td>Hearing loss was PTA threshold shift (dB)</td>
<td>Nucleus Freedom Contour Advance. Insertion depth 19 mm (450 – 540 degrees)</td>
<td>Cochleostomy anteroinferior (n=21), round window membrane (n=7).</td>
<td>Yes Advance off stylet</td>
<td>Dexamethasone 8mg</td>
<td>32% complete preservation (&lt;10 dB PTA threshold shift). 57% partial preservation (&gt;10 dB shift with some measurable hearing)</td>
</tr>
<tr>
<td>James (2006) [39] n=10</td>
<td>&lt;60 dBHL at 250 and 500 Hz.</td>
<td>Hearing loss was</td>
<td>Nucleus 24 Contour Advance perimodiolar electrode array Insertion depth 1.2 mm.</td>
<td>Cochleostomy anteroinferior. Size limited to 1.2 mm.</td>
<td>Yes Advance off stylet Partial insertion</td>
<td>Not stated</td>
<td>70% preservation</td>
</tr>
<tr>
<td>Adunka (2008) [40] n=50</td>
<td>Cohort: residual hearing. Controls: no residual hearing</td>
<td>Substantial residual hearing defined by CUNY &gt;60%, HINT &gt;50%, or CNC&gt;20%</td>
<td>MED-EL Combi 40 (27), Pulsar CI 100 (6), Nucleus CI24 (7), Nucleus Freedom (5), Clarion 1.2 (5)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>post operative acoustic hearing not measured. No difference between groups final speech perception. Significantly greater improvement from pre op levels for controls c.f. cohorts.</td>
</tr>
</tbody>
</table>
### Table 1 (continued).
Summary of the literature: residual hearing after cochlear implantation

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</tr>
</thead>
<tbody>
<tr>
<td>Lenarz (2009) [41] n=32</td>
<td>Hybrid patients (n=24), high freq loss. Expanded patients (n=8), substantial residual hearing across frequencies.</td>
<td>Threshold shift: &lt;1kHz (hybrid) 125 – 4000 Hz (expanded) Freiburg monosyllabic word test</td>
<td>Hybrid L (16mm straight electrode, oval profile, 22 half band electrodes)</td>
<td>Round window membrane</td>
<td>Yes</td>
<td>Cortisone 500mg iv</td>
<td>Median change across all frequencies was 10dB</td>
</tr>
<tr>
<td>Gantz (2009) [42] n=87</td>
<td>Severe to profound HL &gt;2kHz CNC word scores 10 – 60%</td>
<td>Change in mean low frequency threshold (125 – 1000 Hz) Useful hearing was frequencies better than 90 dB HL</td>
<td>10-mm Iowa/Nucleus Hybrid electrode cochleostomy 0.5 mm anteroinferior</td>
<td>Yes</td>
<td>Not stated</td>
<td>1 month: Partial preservation 85/87 &gt;3 months: 79/87 (91%) &gt;30 dB low freq threshold shift in 30%</td>
<td></td>
</tr>
<tr>
<td>Skarzynsky (2009) [43] n=28</td>
<td>Partial deafness: mild to mod &lt;1kHz, severe to profound &gt;1kHz</td>
<td>Complete preservation was post op thresholds within 10 dB of preop thresholds</td>
<td>MED-EL Combi 40+ standard (15), M (3) or flex (1), Pulsar M (7) or flex (2).</td>
<td>Round window membrane</td>
<td>Yes</td>
<td>Not stated</td>
<td>Complete preservation (within 10 dB of preop thresholds) in 13/28 (46%)</td>
</tr>
</tbody>
</table>

Widespread loss of residual hearing was reported in early papers. Rizer et al [34] documented the outcome of residual hearing in 7 patients undergoing cochlear implantation with short, 6 mm (n=1) and long, 20 mm (n=6) electrode arrays. The preoperative selection criteria for these patients were that they had some residual acoustic hearing, but obtained limited benefit and no speech discrimination from conventional amplification. All patients demonstrated an immediate, sustained decline in audiometric thresholds following implantation. Average pure tone losses were 17dB at 500 Hz, 34 dB at 1 kHz and 23 dB at 2 kHz. Further evidence that cochlear implantation damaged residual hearing was provided by Boggess et al [37]. This group reported that 12/40 (30%) of cochlear implant candidates in their series had some measurable acoustic
hearing prior to implantation, although like the study of Rizer et al, none were able to understand speech. The characteristics of those with residual preoperative hearing typically saw the low frequencies preserved with all 12 retaining hearing at 500 Hz, whilst only 2/12 had any measureable hearing at 4000 Hz. Following insertion of a 25 mm multichannel electrode, pure tone thresholds in the implanted ear were significantly reduced (defined as greater than 5 dB shift in at least one frequency) in all recipients. However, 11/12 did retain some measurable hearing in at least one frequency. This observation was used by subsequent authors to describe partial hearing preservation [38]. Thus, the series of Boggess et al [37] confirmed widespread loss of residual hearing following cochlear implantation, but also provided evidence that hearing can be preserved at least partially, most of the time.

Later papers apply this more optimistic approach and generally reported preservation of hearing, rather than loss. In a retrospective review of cochlear implant recipients, Hodges et al [38] reported that 21 of 40 patients with preoperative residual hearing retained measurable hearing in at least one speech frequency following implantation with a full-length electrode. Since then, many groups have reported that hearing preservation is possible with cochlear implantation (Table 1).

There is considerable variability in the method of reporting hearing preservation data, making comparison between series difficult. James et al [11] and Balkany et al [15] provided insights upon the group analysis of hearing preservation outcomes. They highlighted a reporting bias in cases with post-operative hearing thresholds that are beyond the limits of the audiometer and therefore
cannot have “true” threshold shift calculated. They observe that some investigators calculated threshold shift to the limit of the audiometer [8]. Such results may have been less than the true shift. Therefore, papers that calculated average threshold shift including such cases potentially underestimated the true average. James et al [11] suggested that difficulty in presenting the central tendency for group statistics that include ‘not measurable’ values can be overcome with the use of median reporting, which has been used by several others since [41]. Balkany et al [15] opted for a different approach: adding 5 dB to the post-operative threshold when the limit of the audiometer was reached. They acknowledged that this may still have underestimated the true average, but claimed it would be more accurate than previous methods.

Regardless of the method of reporting hearing outcome data, the best results on hearing preservation following cochlear implantation using soft surgical technique and improved standard length electrode design still saw approximately 15% of individuals lose all residual hearing (table 1). This was reduced to 9% with short (10mm) electrodes [42].

Later sections of this thesis will examine the advances in surgical technique and electrode design that have contributed to improvement in outcomes for implant recipients. The following section details the basic science that is pertinent to developing an understanding of the processes that lead to loss of hearing during cochlear implantation, and thus assists in understanding the development of strategies to protect this hearing.
Cochlea anatomy and physiology

Knowledge of the surgical anatomy and physiology of the normal human cochlea is requisite for understanding the process of cochlear implantation and the various types of trauma that can occur during implantation surgery. Standard textbooks [44,45] and reviews [46] agree broadly upon aspects of anatomy and physiology that have been established for many years, however there are emerging areas such as cochlea blood supply that have required newer technologies including scanning electron microscopy to fully elucidate them [47]. Recent reviews have concentrated on establishing the relevance of cochlear anatomy to implantation surgery, in particular to determine if there are regions of the cochlea that owing to anatomical factors are more vulnerable to damage during insertion of an electrode array [48].

Human

The human cochlea is situated in the anterior aspect of the inner ear and is comprised internally of a spiral-shaped membranous labyrinth that is surrounded by an additional fluid space containing perilymph all within an otic capsule. The osseous structure of the cochlea has generally been accepted to have an average of 2 ½ turns around a central column, the modiolus. However, a histological evaluation of human temporal bones from Biedron et al demonstrated that 65% have more than 2 ½ and 11% have up to 3 turns [49], so others describe an average of 2 ¾ turns [44]. West [50] proposes that the hearing advantage provided by the spiral form of the cochlea is to increase the audible octave range.
The modiolus contains Rosenthal’s canal, through which passes the cochlear
erve from the internal auditory meatus. Spiralling around the modiolus is a
bony shelf called the spiral lamina. This bony structure is porous due to
numerous branches of the cochlear nerve passing through it to supply the
sensory cells of the inner ear. The spiral lamina partly divides the cochlea into
upper and lower compartments called the scala vestibuli and scala tympani,
respectively. These two compartments communicate at the apex of the cochlea
at a region known as the helicotrema. The spiral lamina approaches a structure
on the lateral wall of the cochlea called the spiral ligament. The basilar
membrane is a malleable layer of tissue that bridges the gap between these two
shelves. The width of the basilar membrane changes along the length of the
cochlea and varies inversely with the spiral lamina. At the base of the cochlea
the spiral lamina projects a long way across the cochlea and the basilar
membrane is narrow, whilst towards the apex the spiral lamina shelf is small and
the basilar membrane is wider. This has important functional implications for
tone specificity along the basilar membrane. The length of the human basilar
membrane ranges between 33.5 to 35 mm [50].

The vestibule is a part of the osseous labyrinth found posterior to the cochlea
and it contains the utricle and saccule, which are continuous with the
membranous cochlea's scala media. The vestibule features an opening on its
lateral aspect between the saccule and utricle named the oval window where the
ossicles of the middle ear terminate, transmitting sound from the tympanic
membrane to the fluid of the scala vestibuli. The round window opens into the
basal turn of the cochlea within the scala tympani compartment where it acts as a release valve for sound transmitted via the oval window [45].

The membranous labyrinth is an enclosed system within the osseous labyrinth. Within the cochlea it forms the central compartment, called the scala media. This is sandwiched between the scala vestibuli above and scala tympani below. The scala media is bounded inferiorly by the basilar membrane and superiorly by Reissner's membrane. It is filled with endolymph that has an ionic composition similar to intracellular fluid, with a high concentration of potassium. In contrast, the scala tympani and vestibuli are filled with sodium rich perilymph that resembles extracellular fluid and CSF. Thus, a potential differential is constructed between perilymph and endolymph that is important for the function of the inner ear. This distribution of ions is maintained in part through active transport of ions through abundant Na-K-ATPase located within the striae vascularis, a three layered structure on the outer wall of the scala media, opposite the spiral lamina [51].

The scala media contains the organ of Corti, which features inner and outer hair cells nestled amongst a number of supporting cells. The organ of Corti is integrated with the basilar membrane, upon which it rests. Thus, hair cells have perilymph within the scala tympani on their basal surfaces and endolymph of the scala media bathing their apex. Tight junctions between organ of Corti cells ensure separation of these compartments.

Acoustic energy entering the cochlea via the oval window forms a travelling wave of displacement along the basilar membrane. The point of maximal displacement is called the characteristic frequency and it varies tonotopically.
High frequencies cause maximal displacement basally, whilst low frequencies will locate towards the apex. These displacement characteristics of the basilar membrane are termed passive properties as they result from properties intrinsic to the physical structure of the basilar membrane. Active properties of displacement of the basilar membrane are achieved through the action of outer hair cells. At characteristic frequency outer hair cells detect movement of the basilar membrane and actively participate in amplifying this displacement, an effect greatly exaggerated at the point of characteristic frequency.

Greenwood has developed an equation to provide a convenient expression of the relationship between cochlear position and frequency. This function was based upon observations in human cadaveric temporal bones, but has since been validated with physiological data from animals [52] and can be used to predict the place frequency relationship in several species, including the guinea pig. The function is:

\[ F = A \left(10^{ax} - k\right) \]

where \( F \) = frequency (kHz) and for the guinea pig \( A = 0.35 \), \( a = 2.1/18.5 \), \( k = 0.85 \) and \( x \) = distance (mm) along the basilar membrane.

The equation describes an exponential relationship between the position upon the basilar membrane and its characteristic frequency. It is essentially the same between species, except for a constant that relates to the length of the basilar membrane. This constant must be changed according to species. The value of this equation in the study of cochlear implantation is that it can be used to relate
the length of the electrode array to the basilar membrane and hence, the frequencies predicted to be affected by the adjacent electrode.

The role of inner hair cells of the organ of Corti, which also rest upon and are integrated with the basilar membrane, is to transduce the mechanical energy of basilar membrane displacement into an electrochemical signal carried by the cochlear nerve as an action potential. These action potentials then travel within central pathways were they are perceived as sound.

The anatomy of the blood supply of the cochlea has been described by a number of researchers. This knowledge has been obtained through studies of macroscopic, microscopic and more recently injection techniques (coupled with scanning electron microscopy). It is the last approach that has gleaned the greatest knowledge of cochlear blood supply. In a historical review, Mudry [47] provided commentary on the ingenuity of various researchers in achieving our current understanding of cochlear anatomy. Briefly, the cochlea blood supply depends upon the internal labyrinthine (or auditory) artery, which is a branch of the anterior inferior cerebellar artery. The labyrinthine artery divides into two branches upon entering the internal auditory canal. The first branch is the common cochlear artery, which branches subsequently into the vessels that supply the cochlea: the proper cochlear and vestibulocochlear arteries. The former enters the central canal of the modiolus and gives several branches supplying 80% of the cochlea. The latter gives a cochlear branch that follows the spiral course of the modiolus and ends by anastomosing with the cochlear artery and supplying the remaining 20%. Important note is made by several investigators regarding the separate blood supply of the membranous and
osseous labyrinth. This is relevant for systemically administered medication, as to reach the cochlea it must travel down the above arterial network where it is then distributed to inner ear cellular structures including the organ of Corti, stria vascularis and spiral ganglion cells.

In histological studies of implantation of the human cochlea there are regions that are regularly reported as suffering from direct mechanical trauma. These at risk positions are at the base of the scala tympani, at 180 degrees along the basal turn and in deep insertions beyond 400 degrees around the human cochlea. Verbist et al [48] have provided a study of cochlear dimensions to determine if there are anatomical factors that predispose trauma to occur at these locations. They have speculated that the steepness of the cochlea may rise and fall in constant positions and reason that at places of rapid rising slope the implant will tend to impact the floor, whilst in regions of rapid down-sloping the implant will cause damage to the roof, which in the scala tympani is the basilar membrane. The authors confirmed that the steepness of the cochlea is variable and that at certain areas it rises or falls considerably. They demonstrated a correlation between the degree of steepness of the cochlear turn and the regions reported by others to be sites of implantation trauma including the base, at 180 degrees and at 405 to 450 degrees.

**Guinea Pig**

The guinea pig has become a widely used model for ear research in the past decade, including for study of cochlear implantation [23,25]. In order to design an electrode array for insertion into a guinea pig cochlea, it is important to know its dimensions. Lee et al [53] have studied the dimensions of the guinea pig
Cochlea using a technique that combines measurements derived from histological analysis with micro CT. This data was used to create a model with highly accurate measurements of cochlear compartments and structures. They reported that the length of the basilar membrane is 18 mm from the base to the apex. Their work on the dimensions of the scala tympani is of most relevance for the study of cochlear implantation as this is the compartment that the electrode array is inserted within. The cross sectional area of the guinea pig scala tympani can be followed along the course an inserted electrode will take. This area was reported to initially increase in size, before rapidly diminishing 5mm from the round window membrane to 0.49 mm². This has important implications for the size of an implant that will be able to pass beyond this point. Additional factors that may limit insertion depth of a model electrode array include the diameter of the cochlear turn and the flexibility of the electrode. It would be reasonable to anticipate that the much smaller dimensions of the guinea pig cochlea will limit the insertion depth of an experimental electrode compared to the depths of insertion that are achievable in humans.
Aetiology and pathogenesis of hearing loss following cochlear implantation

Research has continued to investigate the reasons for the frequent loss of residual hearing following cochlear implantation with the expectation that this knowledge may help to develop strategies for greater protection. The proffered aetiology and pathogenesis includes: direct mechanical trauma from the implanted electrode to the basilar membrane, spiral ligament or osseous spiral lamina [54-57]; noise injury [58] and vibration trauma [59,60] from the proximity of the high speed cutting drill; and hydraulic damage [61] following the insertion of the volume displacing cochlear implant within the relatively closed scala tympani. These mechanisms lead to inflammatory, oxidative and pro-apoptotic stress [58], with loss of normal cochlear homeostasis and reduction of the endocochlear potential [62].

A number of investigators have examined these processes by measuring the consequences of cochlear implantation in studies of: cadaveric temporal bones [57,63-68]; post mortem human cochlear implant recipients [55,56,69-72]; and animal studies that emulate cochlear implantation [23,25,61,73-76].

The study of cochlear tissue for gross morphological changes and the use of specific stains to identify cell types at various times following implantation trauma helps to delineate the pathogenesis of implantation hearing loss. For the purpose of researching cochlear trauma following implantation, Eshraghi et al [54] proposed a grading system, ranking macroscopic damage to intracochlear structures from grade 1 to 4. In Eshraghi’s modified system, grade 1 represents no observable macroscopic trauma but may include molecular damage that can lead to apoptosis; grade 2 describes elevation of the basilar membrane; grade 3
sees the dislocation of the electrode into the scala vestibuli; whilst in grade 4
gross damage occurs with fracture of the osseous spiral lamina/modiolus or a
tear occurs in tissues of the stria vascularis/spiral ligament complex. This
system has been used by others for comparison of cochlear implantation
insertion techniques [63].

As cochlear implantation involves a number of distinct simultaneous
mechanisms of trauma, described previously, it is helpful to examine the role
that each of these factors may play in isolation in order to explore their
significance.

Direct Mechanical Trauma:

Nadol et al [56] reported the post mortem findings of 8 human cochlear implant
recipient’s temporal bones that were implanted in life with Nucleus (n=4),
Ineraid (n=4) or House single channel (n=2) electrode arrays. They reported
universal but variable damage to the spiral ligament and stria vascularis. The
implant traversed the basilar membrane in 3 of the 8 cases. New bone formation
was seen throughout the basal turn and at the cochleostomy site in all instances.
These findings appear to represent sequelae of direct mechanical trauma to
intracochlear structures.

The histological assessment of the changes that occur with cochlear implant
insertion in animal studies has been described by Clark et al [77] and Xu et al
[76]. They reported: characteristic damage to the basilar membrane, spiral
ligament and osseous spiral lamina; inflammatory cell infiltrate; inner and outer
hair cell loss; and new bone growth.
The University of Melbourne subsequently investigated the chronic histological changes of cochlear implantation in a guinea pig. This study demonstrated in addition to the above macroscopic changes, that there was reduced spiral ganglion cell density within Rosenthal’s canal. This finding was seen only after 3 months had elapsed post implantation [78], illustrating the importance of evaluation at longer time intervals to fully explore cellular responses to injury.

**Noise Injury and Vibration Trauma:**

Acoustic trauma results in characteristic changes within the organ of Corti and other inner ear structures [79]. There is a gradient of cellular damage progressing from the most vulnerable outer hair cells to more resilient inner hair cells, and from sensitive cells at the base of the cochlea to their more robust counterparts located at the apex [80]. Changes in the vascularity and cellularity of the spiral ligament and stria vascularis are also seen following noise injury [81,82], and result in a reduction in endocochlear potential in a dose dependent manner [62]. The pathogenesis of noise induced cellular death is typically via apoptosis [58]. This may be due in part to an inflammatory response initiated by resident inner ear immune cells, followed by the recruitment of systemic immune cells [30,83]. Immune cells staining for CD 45 are derived from bone marrow, and are not normally found in the cochlea. However, following acoustic trauma they are recruited to the inner ear [30,83] where they may initiate repair or propagate further damage through inflammatory mediators such as TNF alpha that can directly induce apoptosis [31].
Cochlear implantation may result in trauma to the inner ear through exposure to noise through air conduction of sound from surgical drilling [84], the direct transmission of vibrations through bone [59,60] or vibrations amplified along the ossicular chain after accidental contact [85].

**Hydraulic Trauma:**

Hydraulic trauma may occur as a consequence of displacement of perilymph upon the introduction of the electrode array into the relatively closed cochlea. The damage this process may cause to intracochlear structures and to hearing has been simulated by Do et al [61] in an experiment involving the injection of phosphate buffered saline into a mouse cochlea through a cochleostomy. Small volumes were well tolerated, but larger volumes resulted in significant hearing loss. These findings suggest implants with a smaller volume, or which allow leakage of perilymph equal to (but not greater than) their own volume, may be better tolerated.

Further insights into the aetiology and pathogenesis of hearing loss following cochlear implantation can be attained through eliciting the temporal sequence of hearing loss during and after implantation. The cochlear microphonic and otoacoustic emissions are indicators of outer hair cell function and have been measured during cochlear implantation in a patient with auditory neuropathy [29]. Such patients are useful for the investigation of the impact of implantation on residual hearing, as they typically have preserved outer hair cells. Intraoperative monitoring of this patient confirmed that the cochlear microphonic remained intact until electrode insertion, following which it was
reduced, but still present. Ten minutes after implantation there was no further reduction in the microphonic. However, 2 weeks post-operatively, this patient had lost all residual hearing. These findings indicate that the greatest loss of hearing is delayed following implantation, and that factors other than immediate insertion mechanical disruption or altered basilar membrane biomechanics are responsible for the majority of hearing loss. Candidate processes for this ongoing loss are inflammation, apoptosis and oxidative stress.

There are 3 cellular signalling pathways that are implicated in the progression of auditory cells to death following cellular injury: 1) Inflammation with release of pro-inflammatory cytokines, including TNF alpha; 2) activation of pro-apoptotic signal cascades; and 3) oxidative stress [31]. These processes must occur in the hours and days after the initial surgical trauma to result in progression of hearing loss following implantation.

The effect of fibrosis (resulting from inflammation) within the cochlea on acoustic hearing has only been subject to limited investigation that has demonstrated some correlations between audiology and histology in animal studies [86]. This relationship has been more precisely modelled mathematically. Choi and Oghalai [87] used a one dimensional model to calculate the effect that increasing the dampening from scala tympani fibrosis in the basal one half of the cochlea will have on basilar membrane vibration. They demonstrated a substantial reduction in basilar membrane velocity at the apex of the cochlea with increased dampening due to fibrosis associated with cochlear implantation. This suggests that the protection of low frequency acoustic hearing could be assisted through prevention of scala tympani fibrosis. Animal
studies support the accuracy of this model by demonstrating that the degree of fibrosis within the basal scala tympani correlated with increased ABR threshold, particularly in cases where the basal fibrosis was adjacent to the basilar membrane. In such circumstances it was found that ABR threshold to click stimulus was increased [86]. The authors of this study speculated this is because of altered basilar membrane biomechanics with impaired propagation of sound energy along the basilar membrane [86]. Even in the absence of fibrosis the electrode itself will abut the basilar membrane in sections causing a degree of dampening. This has also been investigated through the use of another mathematical model based on histological observations of cadavers and hearing outcomes in human recipients [28]. This three dimensional model predicts that stiffening of the basal portion of the basilar membrane from an adjacent electrode will affect basilar membrane biomechanics, but will not affect low frequency hearing. There is a tendency to focus acoustic energy in regions adjacent to the section of the basilar membrane fixed through contact with the implanted electrode, but more distal apical regions are not affected. This latter study therefore provides evidence that if fibrosis can be avoided then low frequency hearing can be preserved, as the direct effects of the electrode will not dampen hearing in this region.
Hearing protection

An understanding of the processes implicated in the development of hearing loss following cochlear implantation has directed research to hearing protection strategies. This has seen changes in the surgical technique used to implant the electrode within the cochlea to minimise trauma. Further advances have been achieved though alterations in the design of the implantable electrode array to cause less injury by avoiding vulnerable structures [13,88,89] or presenting a shorter array to spare the apical regions from direct mechanical damage [12,13,88]. The evolution of these hearing protection strategies has seen an improvement in hearing outcomes for cochlear implant recipients, however these methods alone still result in a complete loss of residual hearing in approximately 15% [8,9,11,15]. This has motivated the introduction of pharmacotherapy for prophylaxis. The delivery of various agents has been attempted via local and systemic routes to enable hearing preservation.
**Surgical technique**

As the first candidates for cochlear implantation did not have residual hearing, there was no requirement to protect their remaining hair cells. The focus of implantation surgery was simply to insert the electrode array within the cochlea, close to the spiral ganglion. This was typically achieved by placing the electrode within the scala tympani [33], which Clark et al [73] demonstrated was associated with less damage to the organ of Corti than insertion via the scala vestibuli, and resulted in greater stimulation of spiral ganglion cells. However, electrodes may traverse the basilar membrane to lie within the scala vestibuli after attempted scala tympani insertion [90]. Curiously, the final position of the electrode was not seen to correlate with cochlear implant performance with electrical stimulation alone [56], although it would be expected that a scala vestibuli position or disruption of the basilar membrane would limit acoustic stimulation.

A special ‘soft’ surgical technique was the first attempt made by surgeons to limit trauma to the inner ear during implantation. First reported by Lenhardt et al [7], soft surgery required a cochleostomy drilled anterior to the round window niche until the blue lined endosteum was visualised. A small incision was then made and the electrode inserted. However, the size and position of the small, relatively anterior cochleostomy described by Lenhardt did not allow adequate visualisation of the osseous spiral lamina, basilar membrane or modiolar wall and placed these structures at risk of damage whilst also increasing the occurrence of scala vestibuli or scala media insertions [90]. Briggs et al [90] therefore recommend the site of cochleostomy be inferior to the RW. Soft
surgery has since been elaborated by Kiefer et al [8] and Gstoettner et al [9], who use the term atraumatic insertion. The principles of atraumatic insertion are to place the cochleostomy caudal to the RW (caudal appears to correlate with the inferior position suggested by Briggs et al [90]); carefully remove all bone dust; avoid suction over the open cochleostomy; place steroid and hyaluronic acid over the open cochleostomy; and plug the cochleostomy with a fascial graft that has been placed as a cuff over the electrode prior to insertion to limit perilymph leakage.

Further hearing preservation is considered possible by inserting the electrode array via the RW approach as this will reduce perilymph leakage and avoid the introduction of bone dust or blood into the cochlea [88]. Earlier temporal bone studies support this by demonstrating a reduction in the histological grade of basal turn trauma in an approach via the round window compared to a cochleostomy inferior to the round window [63]. RW insertion has since been adopted by many groups for the purpose of hearing preservation in cochlear implantation [13,41,43].

As deeper insertion of a cochlear implant contributes to the loss of low frequency residual hearing [11], some groups have limited the insertion depth of the electrode, termed partial insertion, to avoid trauma to the apical cochlea where the low frequencies reside. Limiting insertion depth to 19 – 24 mm has resulted in preservation of residual hearing to within 20 dB of preoperative levels in 12/14 (86%) of implant recipients [8]. Others have limited insertion depth to 19 mm [15] or 17 mm [39], with improved hearing outcomes (table 1).
**Electrode design**

A partially inserted electrode will have redundant electrodes in an extracochlear position. To experience the benefit of a shorter depth of insertion and avoid this redundancy, shorter electrodes have been designed [88,91]. These provide the additional benefit of allowing the correct fitting of the base of the electrode to the site of the cochleostomy, which facilitates closure of the cochleostomy in arrays that have a platinum band placed proximally [88]. In addition to shortening electrodes, other design modifications for the purpose of hearing preservation include reducing the array diameter [12,13,88]; increasing the vertical stiffness of the electrode whilst maintaining horizontal flexibility [13]; advance off stylet insertion [11]; and half band modiolus facing electrodes to limit damage to the lateral wall [88,89].

The use of a short multiple electrode array for hearing preservation began with a 6 mm device that was introduced by a group from Iowa [12,91]. The aim of this electrode was to enable electric-acoustic stimulation in patients selected with high frequency deficits to which the electrode length would correspond. As predicted by the place frequency perception experiments by Blamey et al [92] and James et al [93] this resulted in an unpleasant high frequency percept that limited its use. A 10 mm array was subsequently preferred by these same investigators [12], the tip of which will correspond with approximately 2500 to 3000 Hz according to the Greenwood place-frequency map. The occurrence of iatrogenic loss of residual hearing in this group was at first less than 5% (table 1). However, when hearing loss occurs, either as a consequence of implantation trauma or due to progression of underlying pathology, the implant may need to
be replaced due to the limited range of the electrode. This is a significant limitation of this electrode and may reduce its applicability, particularly to younger patients who are more likely to suffer further hearing loss and therefore require a longer region of electrical stimulation to offset further acoustic hearing loss.

A medium-length electrode array inserted via a round window approach has been introduced by a cooperative research team from The University of Melbourne [88] and The Medical University of Hannover [13], which has since been called the Hybrid L. In similar fashion to the Hybrid S from Iowa, this device aims to preserve low frequency hearing for acoustic stimulation, but is distinguished by providing the recipient 22 electrodes over 16 mm that are inserted through 240 degrees to facilitate optimal electrical stimulation to more apical regions of the cochlea. In the event of progressive or implantation related hearing loss, the Hybrid L will provide additional electrical stimulation to the middle frequencies. The device has half band modiolus facing electrodes, which present a smooth surface to the lateral wall and have been shown in other devices to limit damage to the lateral wall [89]. The Hybrid L has been demonstrated to preserve residual hearing in clinical trials where the median post operative shift across all frequencies was 10 dB [41].

Perimodiolar arrays have been designed to bring the electrode closer to neural elements than straight arrays that will lie in a lateral position within the cochlea. This is undertaken with the expectation that the closer proximity will use less current thus providing improved battery life, a wider dynamic range and greater channel separation [94]. Temporal bone insertion studies of free form pre
curved arrays have demonstrated that they will penetrate the basilar membrane 20% of the time, but this is equivalent to straight electrodes [54,89,94].

Advance off stylet insertion has been used to avoid the problem of damage to osseous spiral lamina and basilar membrane damage seen in the ascending turn of the basal cochlea with perimodiolar arrays. This insertion aid guides the electrode for the first 8.5 mm of insertion, allowing it to take a more inferior and medial position within the scala tympani. Temporal bone studies by Stover et al [95] have demonstrated the safety of this device, and clinical studies by James et al [39] and Balkany et al [15] confirm it can be employed with full length electrodes to achieve hearing preservation. Advance off stylet has also been incorporated to shorter electrodes [13].

The cross sectional shape of the electrode will also influence its flexibility characteristics. The electrode is required to follow the curve of the cochlear turn, and so will need horizontal flexibility. At regions of rapid rise or fall of cochlear turn dimensions there is risk of damage to the floor or basilar membrane [48]. Increasing the vertical stiffness of the electrode will reduce the tendency of the electrode towards upward excursion and so limit injury to these regions. The combination of horizontal flexibility and vertical stiffness of the electrode can be achieved through the use of an oval shaped cross sectional design [13].

As the above modifications in surgical technique and electrode design still result in the unacceptably high incidence of hearing loss of 15% of recipients losing all residual acoustic hearing (table 1), research has followed to provide additional protection of hearing through the use of prophylactic pharmacotherapy.
Pharmacotherapy

A number of agents have been used to attenuate hearing loss during cochlear implantation. Glucocorticosteroids have been the principal candidate, based on their role in conditions such as sudden hearing loss [96] and vestibular neuritis [18]. The rationale for their use is as a potent inhibitor of inflammation, which can protect organ of Corti explants exposed to the inflammatory cytokine TNF alpha [31]. In addition to an anti-inflammatory effect, glucocorticosteroids are thought to act upon the MAPK/JNK signalling pathway to limit apoptosis, and to downregulate the production of nitric oxide synthase, attenuating oxidative damage [23].

The route of delivery of steroids for the prevention of cochlear implantation hearing loss has typically involved local application. Local delivery aims to provide a high concentration of steroid in close proximity to the inner ear to protect the organ of Corti and stria vascularis, whilst avoiding systemic dosing and hence, complications. Studies of local delivery utilise a variety of innovative techniques including: intratympanic injection of solution containing steroid; a drug soaked bead placed directly upon the RWM [25,26]; an implantable mini osmotic pump [23]; or direct placement upon an open cochleostomy [10]. Most of these methods rely upon the drug diffusing across the RWM into the perilymph where it is able to affect cochlear tissues.

The mechanism of action of locally delivered steroid relies upon its aforementioned anti-inflammatory, anti-apoptotic and anti-oxidative qualities, but for local delivery to be effective the drug needs to penetrate into the inner ear. Parnes et al [20], Chandrasekhar et al [97] and Bird et al [19] confirm in the
guinea pig and human that intratympanic delivery of steroid will achieve 
perilymph concentrations of steroid to an order of magnitude larger than those 
measured simultaneously in plasma. These pharmacokinetic studies appear to 
provide good evidence that a local delivery approach will achieve the aim of high 
levels of drug delivery to the inner ear, whilst avoiding the complications that 
result from high plasma steroid levels.

However, confirmation of steroid entering the perilymph does not offer 
sufficient detail of the final anatomical distribution to account for an effect on 
hearing preservation. Consideration of the sites within the inner ear that are 
known to be important for hearing and proof that locally administered steroid 
distributes to these sites in particular is needed. This knowledge of inner ear 
distribution of dexamethasone is provided by Hargunani et al [98], who also 
investigated the pharmacokinetics of dexamethasone following intratympanic 
delivery. At various post injection time points ranging from 5 minutes to 7 days 
the mice used in this study were sacrificed and their cochleae prepared for 
histological analysis using an immunohistochemical stain that identified 
dexamethasone. They demonstrated maximum staining intensity one-hour post 
injection, with complete clearance by 24 hours. The use of an 
immunohistochemical staining technique allowed these authors to determine 
that dexamethasone distributed most avidly to the organ of Corti, spiral 
ligament, spiral ganglion and vestibular sensory epithelia. It appeared to spare 
the marginal cells of the stria vascularis, which may be a potential shortcoming 
of local delivery, as these cells are important for the maintenance of the 
endocochlear potential, critical for acoustic hearing.
Locally administered corticosteroids have been demonstrated to prevent hearing loss from cochlear implant electrode insertion in a number of animal studies [23-26]. James et al [25] and Chang et al [26] have demonstrated that the intraoperative placement of a dissolving bead soaked in dexamethasone and placed against the RWM prevents threshold shift in a guinea pig model of cochlear implantation, but it requires prolonged intraoperative waiting from thirty minutes [25] to 2 hours [26], which markedly reduces the efficiency of the operating theatre and prolongs the period of anaesthesia. This represents the key clinical limitation of local delivery: the time it takes for steroid to diffuse through the round window membrane to ensure optimal cochlear tissue levels prior to implantation and protect hearing.

The protection of apical regions of the cochlea will require an even longer application time, as drug will need to travel along the length of the scala tympani and achieve sufficient concentrations to be effective. Chang et al [26] provided support for the existence of a clinically significant limitation due to the inherent nature of diffusion that is relied upon for local delivery. They demonstrated that increasing the concentration or duration of steroid applied to the RWM in a guinea pig model of cochlear implantation will improve hearing protection, but that periods of up to 2 hours are required. Plontke et al have demonstrated in a study of guinea pigs that dexamethasone administered intratympanically will achieve perilymph concentrations sampled from the apex of the cochlea many times smaller than those found at the base [27]. The limited capacity of diffusion to overcome the concentration gradient described by Plontke raises doubts
about the ability for local delivery to achieve adequate protection of the apically
located low frequencies.

Enticott et al [99] have completed a randomised controlled trial of locally applied
methylprednisolone in a series of 43 human cochlear implant recipients that
directly followed the work of James [25] and Chang [26]. Participants in this
study had a bead impregnated with dexamethasone or methylprednisolone
applied directly to the RWM for 30 minutes intraoperatively. Postoperative
subjective vestibular dysfunction was significantly reduced in the treatment
group (5%) compared to controls (29%), but no significant difference was
demonstrated in hearing outcomes. The vestibular protection may be afforded
by the relative close proximity of the vestibule to the RWM, so the study drug did
not have to overcome the concentration gradient seen along the length of the
scala tympani. The failure of this study to demonstrate a protective effect on
hearing may be because it was underpowered, but may also be due inadequate
distribution of steroid throughout the cochlea as a consequence of limited
diffusion. It is possible that local delivery does not provide adequate levels of
steroid to the apex where the preserved low frequencies reside.

The timing of delivery of pharmacotherapy in relation to when trauma is
sustained is also important. Consideration of the mechanisms of cochlear
implantation trauma indicate that hearing damage may begin as early as the
moment of cortical mastoidectomy, prior to the more significant insult of
cochleostomy and electrode insertion. It is reasonable to anticipate that having
peak levels of steroid prophylaxis at the time trauma takes place will result in
maximum protection. The delivery of pharmacotherapy after drilling a
cochleostomy has been advocated either through direct application upon the cochleostomy [10] or via an implantable miniosmotic pump [23,24], but such approaches will result in peak levels of steroid after trauma has already occurred. It follows that pre-treatment will enable peak cochlear tissue levels before electrode insertion trauma occurs, and will logically be better placed to offer protection.

This paper therefore examines the role of systemic delivery of dexamethasone in protection of hearing during cochlear implantation as a means of overcoming several of the shortcomings seen with local delivery. Systemic steroid has not been investigated previously as a candidate for hearing prophylaxis in cochlear implantation.

As systemic delivery can easily be administered via an intravenous injection it can be given on induction of anaesthesia and avoid the intraoperative delay endured with local delivery. This will achieve the aim of ensuring maximum cochlear levels prior to the time that trauma takes place, without requiring a period of surgical down time.

For systemic delivery of dexamethasone to be effective in preventing hearing loss during cochlear implantation (if it is to be assumed that it will act upon the same sites as locally administered steroid) then it must be capable of entering the inner ear. Tobita et al [100] provide evidence that steroid when administered intravenously does reach cochlear tissue. These investigators measured tissue concentration of prednisolone in guinea pig cochlear homogenate at various time points following intravenous delivery. They found that prednisolone levels peak within the inner ear following systemic delivery at
60 minutes, and then slowly reduce over 8 hours. This was in contrast to hepatic and plasma levels, which diminished rapidly. It was concluded that prednisolone is transported to the inner ear, where it remains for a relatively long time. The experiments of Parnes [20], Chandrasekhar [21] and Bird [19] provide further pharmacokinetic information in the guinea pig and human that intravenously administered steroid will reach the inner ear in measurable quantities. In these similar experiments, perilymph samples were taken at various time points after intravenous administration of a corticosteroid (hydrocortisone, methylprednisolone or dexamethasone). It was demonstrated across these studies that steroid was detectable within the perilymph and endolymph in levels that peaked at about 1 – 2 hours following administration.

A further potential advantage to systemic delivery is that it is unlikely to suffer the limitations due to a diffusion concentration gradient along the scala tympani that occurs following local delivery, and may therefore provide better protection to the apically located low frequencies. Evidence of an advantage of systemic delivery in distributing drug to apical regions of the cochlea in preference to the base has been demonstrated by Zou et al [101], who examined the cochlear distribution of gadolinium-diethylenetriaminepentaacetate-bismethamine (Gd-DTPA-BMP) following intravenous injection into a guinea pig. These investigators found greater MRI signal of the Gd-DTPA-BMP in the second and third cochlear turns compared to the basal turn following intravenous administration.
Hypothesis

The aim of this paper is to demonstrate that intravenous dexamethasone can be administered prior to cochlear implantation of a silastic/platinum dummy electrode in a guinea pig to prevent auditory threshold shift, especially in the lower frequencies, and protect against the inflammatory histological consequences associated with the trauma of surgery and the insertion of a foreign body. The dose of dexamethasone required to achieve this protection will be determined. Protection using this approach will avoid the intraoperative waiting time necessary for prophylaxis using local delivery techniques.
Methods

Animals

All animal experimental procedures were approved by the Animal Ethics Committee of the Royal Victorian Eye and Ear Hospital (Ethics approval 07/146). Tricolour guinea pigs were bred in the Department of Otolaryngology, Biological Resource Centre, The University of Melbourne and weighed 300 g or more. The anaesthesia used for all ABR testing was an intramuscular injection of 4 mg/kg ketamine and 60 mg/kg xylazine. For surgical procedures inhalational anaesthesia was titrated against respiration with 0.5-1% isoflurane given with oxygen at a rate of 500 ml/min for up to 90 minutes.

Experimental design

Seventeen normal hearing, tricolour guinea pigs were randomly assigned to receive one of three intravenous agents. The three intravenous agents were: 1) normal saline (n=6); 2) low dose dexamethasone, 0.2 mg/kg (n=6); or 3) high dose dexamethasone, 2 mg/kg (n=5). The normal saline group thus served as a control group, whilst the high and low dose dexamethasone groups were included to accommodate investigation of dose-response relationship. All animals had pure tone ABR thresholds estimated from both ears separately in response to tone-pips from 2-32 kHz prior to surgery, followed by delivery of intravenous agent to the right internal jugular vein via a surgical cut down approach. After a 60 minute waiting period all animals underwent left sided soft surgical implantation of a silastic/platinum dummy cochlear electrode array. Animals were recovered and underwent further ABR threshold measurement at
1 week (T1) and 4 weeks (T4) postoperatively. Threshold shift was defined as the difference between T0 and either T1 or T4. A positive threshold shift indicated an elevation of auditory thresholds. Upon completion of the experiment animals were deeply anaesthetised and euthanized with an overdose of pentobarbitone (1.0g/kg) before transcardiac perfusion with phosphate buffered normal saline solution. Cochleae were harvested immediately, decalcified and paraffin embedded before mid-modiolar sections were cut with a thickness of 5 μm and stained with haematoxylin and eosin for histological analysis.

**Brainstem Auditory Evoked Potential Recordings**

ABR recordings were completed immediately prior to surgery (T0), then at T1 and T4. The ABR recording system used in this series of experiments has been described in a number of papers by investigators from the Department of Otolaryngology, University of Melbourne [25,26,102,103]. A loudspeaker (Richard Allen DT 20, UK) was placed 0.1 m from the pinna of the test ear of the anaesthetised, prone animal and used to deliver computer generated tone pips lasting 5 ms with 1 ms rise/fall times. The left (implanted) ear was delivered the frequencies 2, 8, 16, 24 and 32 kHz, whilst the right (non implanted) ear was delivered frequencies 2, 8 and 32 kHz only. The non-test (contralateral) ear was masked using an ear mould compound (Otoform K2, DLT, West Yorkshire) that was individually crafted for that ear to ensure a snug fit.

ABRs were recorded using subcutaneous needle electrodes placed upon the skull vertex and dorsal neck whilst a ground needle was placed subcutaneously at the dorsal aspect of the torso of the guinea pig. Responses were amplified by
100,000 (DAM-5A, W-P Instruments Inc, New Haven, Conn., USA) and band-pass filtered (Krohn-Hite 3750, Avon, Mass., USA) between 150 Hz and 3 kHz (6 dB/octave). This signal was fed to a 16-bit analogue-to-digital converter (Tucker Davis Technologies, USA) and sampled at 20 kHz for 10 ms after stimulus onset. This sample was then averaged over 250 stimulus repetitions. Stimulus intensity was reduced by 5 dB decrements to sub-threshold levels. The waveforms were analysed using a custom program (software written by Dr James Fallon and adapted by Prof Stephen O’Leary) in Igor Pro 5.02 (Wavemetrics Inc.) with the researcher blind to treatment group. Threshold was defined as the lowest stimulus intensity to evoke a wave III response greater than 0.4 µV.

**Delivery of Intravenous Agent**

A paramedian longitudinal incision was made over the course of the right Internal Jugular Vein (IJV) in the anterior neck in the supine, anaesthetised animal. The IJV was dissected from surrounding tissue and ligated distally using 4/0 silk. A 25G cannula was passed into the IJV immediately proximal to this ligature and a second ligature of 4/0 silk placed proximally, over the cannula. One ml/kg of intravenous agent was slowly injected over 30 seconds before the cannula was removed and the proximal ligature tied off.

**Silicone Cochlear Implant Electrode**

The cochlear implant electrode array has also been described previously in papers from the Department of Otolaryngology, The University of Melbourne [25,26]. Its total length was 15 mm, consisting from its tip of 3 platinum rings welded 0.75 mm apart upon an internal platinum wire 25µm in diameter on a
Silastic carrier (MDX4-4210 Dow Corning Products, USA). The platinum rings thus served as a depth gauge with insertion to the third ring indicative of 2.25 mm insertion. The maximum diameter was 0.45 mm, tapering to 0.41 mm towards the tip of the electrode. Sterility of the implant was achieved with ultrasonic cleaning and ethylene oxide.

**Cochlear Implantation**

A post-auricular incision was made and tissue dissected from the bulla after injection of local anaesthetic (lignocaine 1mg/ml with adrenaline 1:100000). Using an operating microscope a 3mm cutting burr was used to create a bullotomy. Under magnification, a 0.7mm cutting burr was used to place a cochleostomy approximately 2 burr widths (1.4mm) from the RWM into the basal turn of the scala tympani. Suction was not used throughout the case, including following cochleostomy as the operative field was reasonably bloodless. The silastic-platinum dummy electrode was handled with jewellers forceps and passed gently through the cochleostomy using soft surgical principles to the level of the third platinum ring (2.25 mm) and left in situ. A fascial graft of post auricular tissue (fascia or muscle) was used to seal the cochleostomy around the implant. The extracochlear portion of the implant was trimmed to fit within the bulla and so ensure it was not inadvertently removed during skin closure, which was achieved with interrupted sutures of 3/0 vicryl (polyglycolic acid suture manufactured by Ethicon Inc, Somerville, New Jersey).

**Cochlear Histology**

After transcardiac perfusion with phosphate buffered normal saline, both cochleae from all animals were removed and placed in 10% formalin. The
cochleae were then decalcified in 4% (w/v) ethylenediaminetetraacetic acid for 1 week. Cochleae were trimmed, dissected and oriented using agar and then paraffin embedded. Three sections of 5 μm thickness were mounted, coverslipped and stained with haematoxylin and eosin. Three sections were examined by light microscopy (Carl Zeiss, Göttingen, Germany) by an independent, blinded pathologist. Slides were examined for the presence of histiocytes, multinucleated giant cells, collagen, or ossification in response to electrode implantation. Quantification of the percentage of the lower basal turn scala tympani occupied by fibrosis was calculated as the cross-section fibrotic area divided by the cross-section area of the lower basal scala tympani of a mid-modiolar section using AxioVision 4.8 software (Carl Zeiss Imaging Solutions, Germany).

Spiral ganglion cell (SGC) densities were calculated at the upper, middle and basal turns by counting the number of type I SGC nucleoli within a calculated area of Rosenthal's canal for each turn. SGC densities were averaged across the upper and lower basal turns, and similarly for the second and third turns. Finally, the densities of the ipsilateral side were converted into a ratio by dividing the density estimates of the ipsilateral (implanted) by the contralateral (unimplanted) cochleae of the same animal. For each animal, spiral ganglion neuron (SGN) density ratios were calculated across 3 mid-modiolar cochlear sections and averaged.

**Statistical Analysis**

Statistical analysis was performed on SPSS version 16 implemented on Windows XP. The animals' tone-pip ABR thresholds prior to implantation were compared
between treatment groups using analysis of variance (ANOVA) implemented under the Univariate General Linear Model (GLM). Threshold shift was determined for each animal and correlated with treatment group and histological findings. Any significant main effects or interactions were further evaluated with multiple comparison tests of significance (Holm Sidak).
**Results**

All animals used in the study had normal hearing prior to implantation confirmed with preoperative ABR. On a univariate analysis of variance, preoperative tone-pip ABR thresholds differed between the groups (p=0.03). The only significant difference was found to be between the low-dose group and the controls (post-hoc analysis Bonferroni test, p=0.03), where the former had slightly worse hearing with a mean threshold that was 7 dB lower than controls. In view of this difference, further analyses were performed on threshold shift, defined as the difference in threshold between the ABRs recorded prior to implantation and those obtained 1 and 4-weeks later, as reported previously [25,26].

Figure 1 demonstrates the magnitude of threshold shift at 1 and 4 weeks postoperatively across the frequency range 2 – 32 kHz following implantation in control, low-dose (0.2 mg/kg) and high-dose (2 mg/kg) dexamethasone treatment groups. Cochlear implantation resulted in threshold shift in the control group across the range 8 – 32 kHz. This threshold shift was unchanged in the control group between the first and fourth post-operative weeks, but trended towards a modest improvement in both of the treatment groups (not significant). The low frequency (2 kHz) thresholds remained unaffected by implantation in all groups.

The threshold shifts in the low-dose dexamethasone group were similar to controls where a significant hearing loss across the frequency range of 8 – 32 kHz was seen, with sparing of the apically based low frequency hearing (2 kHz).
The most significant finding of the study was found in the high-dose treatment group. The threshold shift observed at one and four weeks in the control and low dose treatment groups was not seen in the high dose treatment group. This reduction of threshold shift, and hence hearing protection, was seen across the frequency range 8–32 kHz, at one and four weeks post operatively. These data were subjected to analysis of variance, with T1 and T4 threshold shift as the dependent variables and treatment group and frequency as fixed factors. This analysis revealed significant main effects of both group and frequency, with comparison testing demonstrating that threshold shifts differed significantly between high-dose dexamethasone treatment and controls (P<0.01) and high and low-dose treatment groups (p<0.01). Threshold shifts were significantly different between controls and high-dose dexamethasone at both T1 and T4 for frequency 8, 16 and 24 kHz, and at T1 only for 32kHz (P<0.01).
Figure 1.

Threshold shift following cochlear implantation at T1 (shift from preoperative thresholds and those recorded at one week, black) and T4 (shift from preoperative thresholds and those recorded at four weeks, white). Error bars are standard errors of the mean. High dose dexamethasone (2mg/kg, squares) protects residual hearing at T1 in the frequency range 8 – 32 kHz and at T4 from 8 – 24 kHz, whilst low dose dexamethasone (0.2 mg/kg, triangles) is similar to controls (diamonds).
Hearing outcomes for the contralateral, unimplanted ears for both control and treatment groups are presented in figure 2. The averaged outcomes ranged from a 7dB gain to an 8dB loss. On an ANOVA there was no significant elevation of ABR thresholds in either treatment groups or controls, demonstrating that the high dose dexamethasone was not ototoxic.
Figure 2.

Threshold shift in the right, unoperated, control ear at T1 (shift from preoperative thresholds and those recorded at one week, black) and T4 (shift from preoperative thresholds and those recorded at four weeks, white). Error bars are standard errors of the mean.
Implanted ears demonstrated fibrosis and occasional ossification within the scala tympani of the lower basal turn. Histiocytes, foreign body multinucleated giant (MNG) cells and collagen was often seen adjacent to the electrode tract in control and low-dose treated animals. The foreign body reaction was generally present, in the control and low-dose treated animals, albeit considerably variable. However a foreign body reaction was generally absent in the high-dose treated animals where only 1 animal displayed histiocytes and none had MNG cells, ossification (table 2) or extensive fibrosis (figure 3).

The nature of the foreign body reaction is seen across a spectrum with some level of fibrosis seen in most animals, including those treated with high dose dexamethasone. Those with a greater level of fibrosis correlate with the presence of other cells indicative of a foreign body reaction, histiocytes and MNG cells (table 2).
Table 2.

Histology summary. Scala tympani fibrosis (cross sectional area of the scala tympani occupied by fibrosis), maximum thickness of histiocyte layer (number of cells), collagen (- absent, + present), MNG, multinucleated giant cells (- absent, + present), ossification (- absent, + present).

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Treatment group</th>
<th>Scala tympani fibrosis (%)</th>
<th>Maximum thickness of histiocyte layer</th>
<th>Multi-nucleated Giant Cells</th>
<th>Collagen</th>
<th>Ossification</th>
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<tr>
<td>1</td>
<td>Control</td>
<td>62</td>
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<tr>
<td>7</td>
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<td>49</td>
<td>3</td>
<td>+</td>
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</tr>
<tr>
<td>8</td>
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<td>22</td>
<td>3</td>
<td>+</td>
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</tr>
<tr>
<td>9</td>
<td>low-dose</td>
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<td>1</td>
<td>-</td>
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</tr>
<tr>
<td>10</td>
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<td>-</td>
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<td>48</td>
<td>3</td>
<td>+</td>
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<td>-</td>
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<tr>
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<td>24</td>
<td>2</td>
<td>-</td>
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</tr>
<tr>
<td>13</td>
<td>high-dose</td>
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</tr>
<tr>
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<td>2</td>
<td>-</td>
<td>+</td>
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</tr>
</tbody>
</table>
Figure 3 displays the high variability in the level of fibrotic reaction among control and low dose treated animals. Fibrosis was seen amongst all groups, however treatment with high dose dexamethasone resulted in a trend toward reduced variability and extent of the fibrotic reaction. There were no cases of extensive fibrosis (> 30%) in the high dose treatment group.

Figure 3.
Scala tympani fibrosis: variability in the level of fibrosis within the scala tympani of implanted ears in control, low dose dexamethasone (0.2 mg/kg) and high dose dexamethasone (2 mg/kg) treated animals. The horizontal bar represents mean fibrosis. Fibrosis is calculated as the percentage of the scala tympani with a fibrotic reaction.
There was no statistically significant difference in spiral ganglion cell densities between any groups at the end of one month, correlating with the findings of Maini et al, which indicated the changes in spiral ganglion densities do not become evident until 3 months after implantation [78]. However, individual cases displayed evidence that extensive fibrosis, particularly when the fibrosis was adjacent to the basilar membrane, was associated with flattening of the organ of Corti and loss of spiral ganglions (figure 4).

![Figure 4](image-url)

Figure 4.

The effect of fibrosis on the organ of Corti and spiral ganglion cells in 2 control animals: (a) animal C4 and (b) animal C1. Haematoxylin and eosin staining of lower basal turn scala tympani 4 weeks after cochlear implantation. Open arrows indicate the flattening of the organ of Corti and filled arrows the loss of spiral ganglion neurons in (b), which has significantly more fibrosis, a thicker histiocytic layer and presence of multinucleated giant cells compared to (a). Black bar is 100 µm.

The presence of MNG cells was seen to correlate with the extent of fibrosis, with MNG cells seen to be associated with higher percentage fibrosis of the lower
basal turn of the scala tympani. There was no significant association seen between the extent of histological evidence of a local inflammatory response (fibrosis, MNG cells, collagen or neoossification) and the magnitude of threshold shift. However, in the three animals where neoossification occurred, there was an associated hearing loss and there were examples where fibrosis adjacent to the basilar membrane was seen to be associated with poorer hearing outcomes.
Figure 5.
The relationship between multinucleated giant (MNG) cells and the amount of fibrosis in the lower basal turn.

The presence of MNG cells (1) in figure 5 was seen to correlate with a significantly greater degree of fibrosis compared with when there were no MNG cells (0), (p<0.05).
Figure 6.

The relationship between fibrosis and hearing outcomes (PTA8-32: average threshold shift from 8, 16, 24 and 32 kHz). Dose relates to either high or low concentrations of steroids, control is saline.

Figure 6 demonstrates that good hearing outcomes (PTA 8-32 <10) were only seen when minimal fibrosis (<30%) was present, but there was no statistically significant correlation found between degree of fibrosis and hearing outcomes (p>0.05).
Figure 7.

The effect that the presence of multinucleated giant (MNG) cells has on hearing outcomes, measured as pure tone average threshold shift at 8, 16, 24 and 32 kHz (PTA 8-32).

There was a trend towards superior hearing outcomes in animals without MNG cells as demonstrated in figure 7. However, this trend did not reach statistical significance (p>0.05).
Figure 8

The relationship between the presence of ossification and hearing outcomes (PTA8-32).

Figure 8 shows that there was a trend towards worse average hearing outcomes (horizontal bar) when ossification was present within the lower basal turn. However, this difference did not reach statistical significance (p>0.05).
Figure 9.

The relationship between hearing outcomes (PTA8-32) and the maximum thickness of histiocyte layer (1-5, cells thick).

The best hearing results were demonstrated where the histiocyte layer was absent (0). The presence of a histiocyte layer was associated with a worse hearing outcome, however this did not reach statistical significance (p>0.05). There was no greater hearing loss observed when a thicker histiocyte layer was present compared with a thin histiocyte layer.
Discussion

The present study is the first attempt to examine the effects of systemic dexamethasone for prophylaxis of acoustic hearing in cochlear implantation. As such, it is in an ideal position to demonstrate a number of novel attributes.

Principally, the present study finds that intravenous dexamethasone given sixty minutes prior to implantation provides hearing protection and prevention of an inflammatory response around an implanted electrode in a guinea pig model. This hearing and histological protection is dose dependent with only high doses providing protection. Hearing protection is achieved not only in the high frequency regions directly damaged by the electrode but also in the mid frequency range, in regions of the cochlea indirectly damaged during implantation. Importantly, protection is achieved without the prolonged intraoperative delay required for local delivery.

The means through which systemic dexamethasone achieves hearing protection and prevention of an inflammatory response in the scala tympani following cochlear implantation is not fully understood, but is likely due to its anti-inflammatory effects. It may achieve protection by acting directly and exclusively within the inner ear following distribution throughout the systemic circulation. The pharmacokinetic studies of Chandrasekhar [21], Parnes [20] and Bird [19] demonstrate that intravenous delivery of steroid will produce measureable levels within the perilymph and endolymph of the cochlea, confirming that steroid can at least arrive in the inner ear and thus is capable of exerting a direct effect here. However, these same investigators also demonstrated in the same study that intratympanic delivery of the same steroids
was able to achieve perilymph concentrations many times higher than the levels measured following intravenous delivery. This could lead one to assume that local delivery would provide better protection against hearing loss in cochlear implantation compared to systemic delivery through provision of higher perilymph concentration. Further evidence to support the importance of perilymph concentration of steroid in providing hearing protection is provided by Chang et al [26], who showed that increasing the time or concentration of locally applied steroid to the RWM (and thus increasing perilymph concentration) resulted in greater protection of the hearing in the guinea pigs in their study who underwent cochlear implantation.

If it is to be asserted that systemic dexamethasone acts exclusively within the inner ear and in the same anatomical locations as locally applied steroid then it may be expected that because systemic administration will provide much lower perilymph concentration of steroid that it will therefore provide reduced protection from auditory threshold shift in cochlear implantation. However, the present study demonstrates similar hearing protection with systemic delivery of dexamethasone as studies using local delivery [25,26]. The finding of similar hearing outcomes with different routes of delivery of the same drug challenges the notion that higher perilymph concentration is the principal determinate of hearing protection.

This apparent inconsistency can be explained through consideration of the anatomical locations of the dexamethasone receptor in the inner ear and the pathway that dexamethasone will take after local or systemic delivery to reach these receptors. Hargunani et al [98] mapped the distribution of the
dexamethasone receptor throughout the inner ear with the use of an immunohistochemical stain and showed that it was found upon the organ of Corti, stria vascularis, spiral ligament, spiral ganglion and vestibular epithelial cells. In order for systemic delivery to reach these receptors it must arrive directly to cochlear tissue via the supplying blood vessels with some downstream leakage to perilymph. Thus, perilymph levels will necessarily be smaller than levels achieved within the cochlear tissue. In contrast, local delivery requires the drug to traverse the perilymph prior to reaching cochlear tissue and these dexamethasone receptors, and so it logically follows that higher perilymph levels will correlate with improved protection with local delivery and that perilymph levels will be higher than those achieved within the cochlear tissue.

Therefore, as both delivery techniques have been demonstrated to afford hearing protection, despite providing different perilymph concentrations, it may be that systemically delivered dexamethasone achieves equal or at least sufficient quantities of steroid within the cochlear tissue to saturate all dexamethasone receptors.

Tobita et al [100] provide a more relevant measure of the inner ear levels of steroid achieved following systemic delivery. In their experiments, they measured the concentration of prednisolone found within cochlear tissue, rather than cochlear perilymph. A very high dose of intravenous prednisolone was administered to guinea pigs and the concentration seen in cochlear tissue homogenate was measured at various time intervals following delivery. Their conclusion was that prednisolone was actively concentrated to the inner ear
after systemic delivery, in contrast to other organs. Thus, there may exist a transport mechanism that assists delivery of steroid into the inner ear from the systemic circulation. The study of Tobita et al provides an important observation and confirms levels within the cochlear tissue equivalent to plasma levels. It should be noted, however, that the dose required for detection of the steroid with the methods used in that study was exceedingly high at 100 mg/kg, with a dose of 30 mg/kg falling below detection levels. Even after application of an anti-inflammatory conversion factor [20], these doses are an order of magnitude greater than the equivalent dose of dexamethasone required to protect the inner ear in the present study, or doses used clinically. Whether the pharmacokinetic profile described by Tobita applies at lower, more clinically relevant doses, is yet to be determined. Employment of the immunohistochemical techniques of Hargunani et al [98] would provide further useful insights on the anatomic distribution of dexamethasone within the inner ear following systemic delivery, but these experiments have not been performed yet, and were beyond the scope of the present study.

The above discussion hinges upon the supposition that systemic dexamethasone exerts its effect directly upon inner ear dexamethasone receptors. However, systemic dexamethasone will also affect dexamethasone receptors found within the systemic circulation. Whilst activation of systemic dexamethasone receptors is well known to be responsible for a host of unwanted side effects, it is also possible for many therapeutic effects, which may include the protection seen in this study. If it can be demonstrated that cochlear implantation leads to a
systemic immune response, then it follows that suppression of this immune response may be beneficial.

Evidence that cochlear implantation may cause a systemic inflammatory response can be derived from investigations that follow the initiation of a local cochlear immune response resulting from the application of the intensely immunogenic keyhole limpet haemocyanin [104] or acoustic trauma [30,83]. In these experiments there is recruitment of systemic immune cells important for propagation of inflammation. These systemic immune cells migrate to the inner ear where further inflammation and tissue damage occurs. As acoustic trauma and foreign body reaction are likely components of the trauma that occurs during cochlear implantation, it is reasonable to assume that a systemic immune response characterised by the migration of systemic immune cells to the inner ear will occur following cochlear implantation. As intravenous steroid will achieve much higher plasma levels than those following local delivery, systemic delivery will be better placed to have an effect upon this recruitment and migration of systemic immune cells to the point of injury. This discussion remains speculative as suppression of the systemic immune response could not be demonstrated in the present study because the endpoint was at one month after surgery, well after the acute inflammatory response would be expected to have resolved. A histological examination of the cochlea at earlier post-operative time points may clarify the issue by documenting the nature of the inflammatory response at various time points soon after implantation in the presence or absence of systemic steroid.
One of the aims of the present study was to determine if systemic dexamethasone protects low frequency hearing. It is considered clinically relevant and achievable to protect low frequency acoustic hearing for several reasons. Firstly, cochlear implant candidates suitable for a hearing preservation approach typically have available residual hearing in the lower frequencies [6,10] and the little high frequency hearing they do have is generally lost during implantation due to direct trauma in the basal turn of the cochlea. Secondly, the benefit of preserved low frequency acoustic hearing for music appreciation and hearing in the presence of background noise, even in severe to profoundly deaf patients compared to cochlear implant listeners, has been established by Turner et al [105]. Finally, the apical hair cells are considered more robust than their basal counterparts to many types of trauma [79] and may therefore respond better to preservation techniques.

The present study demonstrates protection of mid frequency hearing, but as low frequencies were not damaged in the guinea pig model used, no assumptions can be made about the capacity of intravenous steroid to protect in these regions. The reason there was no loss of low frequency hearing probably relates to the limited insertion depth of the electrode array. The implant was placed via a cochleostomy 1.4 mm from the RWM and passed to a depth of 2.25 mm. Thus, the tip of the electrode array was 3.65 mm from the RWM, which relates directly to hearing at the frequencies 16 – 32 kHz according to the Greenwood equations in the guinea pig [52]. The auditory threshold shift that was seen adjacent to the electrode could be considered to be a direct consequence of insertion trauma and proximity of the implanted electrode array. The use of high dose
Dexamethasone was able to protect hearing in this region. In addition, threshold shifts were also apparent at lower frequencies, derived in more apical regions that were beyond the tip of the electrode array: at 8 kHz threshold shift of 30-40 dbHL was observed in control animals. This indirect trauma is also apparent in most other experimental studies of cochlear implantation [23,25,26] and its pathogenesis has been attributed to inflammation, oxidative stress and the activation of pro-apoptotic pathways [31]. The present study indicated that high dose intravenous dexamethasone prevented the loss of hearing at 8 kHz.

The mechanism of hearing protection with systemic dexamethasone in the mid frequencies may be due to suppression of a systemic immune response or via a direct effect upon the inner ear, as outlined in previous discussions. Furthermore, there may be an advantage to the apical regions of the cochlear following systemic delivery if the results of Zou et al are considered. These investigators demonstrated that systemically administered Gd-DTPA-BMP will perfuse to the apex of the cochlea to achieve levels that are greater than those seen at the base. This is in contrast to local delivery, which in the experiments of Plontke et al demonstrated a concentration gradient with higher basal levels and significantly less within the apex following intratympanic injection of dexamethasone. It is possible that the mid frequency hearing protection seen in the present study is achieved due to ease of distribution throughout the cochlea to apical regions following intravenous delivery.

The finding of hearing protection with systemic dexamethasone in regions distant to the electrode offers some support to the hypothesis that intravenous dexamethasone may protect hearing at low frequencies. This is again
speculative, but is based on the assumption that the pathogenesis of the mid
frequency hearing loss seen in the present study may be similar to the low
frequency hearing loss that complicates human cochlear implantation.

The models of Choi and Oghali implicate fibrosis surrounding the electrode
abutting the basilar membrane and causing dampening of the propagating wave
in the aetiology of hearing loss that follows cochlear implantation [87]. This
suggests that the prevention of such fibrosis may improve hearing outcomes.

The present study demonstrates that high dose dexamethasone protects hearing,
as discussed above, and that good hearing outcomes (<10dB PTA shift) are only
seen when minimal fibrosis (<30%) is present (figure 6). This appears to
correspond with the models of Choi and Oghali, and supports efforts to prevent
fibrosis within the lower basal turn to improve basilar membrane biomechanics
and therefore acoustic hearing. However, the relationship between fibrosis and
hearing outcomes was not statistically significant in the present study and
analysis of larger numbers may be required to investigate this further. Similarly,
high dose dexamethasone was seen to prevent excessive fibrosis (>30%), and
trend towards less fibrosis than control or low-dose treated animals, but high
dose dexamethasone was not sufficient to avoid fibrosis altogether (figure 3).
The prevention of MNG cells was significantly correlated with less fibrosis
(figure 5), which is not surprising as MNG cells are active mediators of
inflammation, including fibrosis. Avoiding MNG cells trended towards improved
hearing outcomes (presumably because there was also less fibrosis), however
this association did not reach statistical significance (figure 7).
It is important to assess the clinical safety of high dose glucocorticosteroids prior to use in human trials of cochlear implantation. A single dose of dexamethasone may in vulnerable human patients raise blood pressure and glucose, cause gastrointestinal bleeding, adrenal suppression or an altered mental state [96]. However, there are precedents of high dose steroids being used safely in the management of a variety of conditions in human subjects. Optic neuritis is treated with infusions of 1 g methylprednisolone daily [106] and sudden hearing loss clinical trials have used doses of 300 mg dexamethasone daily for 3 days, without major complications [107]. In the perioperative period, cardiac transplant teams are familiar with the use of high dose methylprednisolone (1 g) and dexamethasone (200 mg) intravenous infusions for the induction of immunosuppression of heart transplant recipients [108].

The clinical practice of using high doses of intravenous steroids for hearing protection during cochlear implantation is not routine, however several investigators report using high doses of steroids for this purpose. Kiefer et al [8] use 500 mg prednisolone, whilst Lenarz et al [13] use 500 mg cortisone and Balkany et al [15] use 8 mg dexamethasone.

To translate the steroid doses used in the present study to the equivalent human dose, the FDA recommends a conversion that accounts for differences in body surface area: the guinea pig drug concentrations should be divided by 4.6 to arrive at the equivalent human dose [109,110]. Based on this calculation, in a typical 70 kg adult the 2 mg/kg dexamethasone dose used in the present study would be equivalent to a single dose of approximately 30 mg dexamethasone, between 90-300 mg of methylprednisolone (depending upon the conversion
factor chosen) or 190mg Prednisolone [111]. While these levels are higher than the typical dose given during surgery to control nausea [112] they are lower than the examples referenced above, and within the range of doses used clinically, so it would be reasonable to anticipate such doses would be acceptable to most clinicians.

The greatest potential advantage of systemically delivered steroids is that they will provide a practical means of providing prophylaxis in the clinical environment, as their delivery can be easily administered via an intravenous cannula and timed with induction of anaesthesia to avoid the long waiting times required for effective protection with locally applied steroids [26].
Conclusion

This study demonstrates that the use of preoperative intravenous dexamethasone protects hearing and prevents an inflammatory histological response in a guinea pig model of cochlear implantation. Large doses are required to realise this protection. Systemic administration of dexamethasone can be achieved via an intravenous cannula and be timed with induction of anaesthesia to ensure there are maximal levels in the inner ear at the time trauma takes place. The optimal dose and timing in humans is yet to be determined. Preoperative intravenous delivery avoids the intra-operative delay required for local delivery and requires no modification to established surgical technique or electrode design. There is also a potential that systemic steroids will provide protection to low frequency hearing through distribution to the apex of the cochlea or via suppression of systemic recruitment of immune cells.

Residual acoustic hearing has been clearly established as useful to cochlear implant recipients via electric-acoustic stimulation. Current implantation strategies result in an unacceptable loss of this hearing. The positive results of the present study may motivate further investigation of prophylactic intravenous dexamethasone in human implant recipients. If protection can be achieved in human trials and significant reductions seen in the loss of residual hearing, this may further broaden eligibility for implantation. This in turn may afford improved hearing outcomes and quality of life to a greater number of people with hearing loss.
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