Improving Clinical Outcomes in Cochlear Implantation Using Glucocorticoid Therapy: A Review

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Cochlear implant surgery is a successful procedure for auditory rehabilitation of patients with severe to profound hearing loss. However, cochlear implantation may lead to damage to the inner ear, which decreases residual hearing and alters vestibular function. It is now of increasing interest to preserve residual hearing during this surgery because this is related to better speech, music perception, and hearing in complex listening environments. Thus, different efforts have been tried to reduce cochlear implantation-related injury, including periprocedural glucocorticoids because of their anti-inflammatory properties. Different routes of administration have been tried to deliver glucocorticoids. However, several drawbacks still remain, including their systemic side effects, unknown pharmacokinetic profiles, and complex delivery methods. In the present review, we discuss the role of periprocedural glucocorticoid therapy to decrease cochlear implantation-related injury, thus preserving inner ear function after surgery. Moreover, we highlight the pharmacokinetic evidence and clinical outcomes which would sustain further interventions.

Key words: Cochlear implantation, Drug delivery, Glucocorticoids, Hearing preservation, Inner ear pharmacokinetics.

(Ear & Hearing 2020;41;17–24)

INTRODUCTION

Hearing impairment is a leading cause of disease burden worldwide. It has been estimated that up to 466 million people have disabling hearing impairment and that this will increase to over 900 million by 2050 (Olusanya et al. 2014; World Health Organization 2019). Cochlear implantation (CI) is broadly considered one of the most successful procedures for auditory rehabilitation of patients with severe to profound hearing loss (Wilson & Dorman 2008), with more than 300,000 cochlear implant recipients in 2012 (Yawn et al. 2015). The indications for CI have broadened to include children with congenital profound hearing loss, patients with acquired bilateral sensory hearing loss, single-sided deafness, and high-frequency hearing loss (Lenarz 2017). Cochlear implant surgery can cause an inner ear injury which is related to the physical trauma of electrode insertion (Nadol & Eddington 2006; Roland & Wright 2006). Therefore, "soft" surgery techniques are generally considered important for all CI recipients to preserve the neural elements within the cochlea that are the target for electric stimulation (Cosetti & Waltzman 2012; Skarzynski et al. 2013). For patients that still have functional residual hearing before CI, soft surgery increases the chance of sparing some of that hearing, which may contribute to better speech and music perception, sound localization, and hearing in noise or complex listening environments (Gantz & Turner 2003; Von Ilberg et al. 2011; Helms Tillery et al. 2012; Büchner et al. 2017; Park et al. 2018).

The injury induced by cochlear implant surgery may trigger an acute inflammatory cascade leading to hair cell death (Eshraghi et al. 2006; Dinh & Van De Water 2009; Haake et al. 2009; Van De Water et al. 2010; Dinh et al. 2011), as well as delayed effects leading to chronic inflammation, cell degeneration, fibrosis, and new bone formation (O'Leary et al. 2013; Quesnel et al. 2016). Thus, these alterations may result in a decreased preservation of residual hearing that frequently worsens over time (Zanetti et al. 2015; Eshraghi et al. 2017; Moteki et al. 2017). Furthermore, inner ear damage resulting from CI may also lead to alteration in vestibular tests (Ibrahim et al. 2017) and significant postoperative dizziness and balance problems which can be transient or become permanent (Hänsel et al. 2018). This has been linked to histological changes in vestibular structures following CI (Tien & Linthicum 2002; Nadol & Eddington 2006). Thus, efforts have focused on reducing inner ear injury and have included less traumatic surgery techniques, different electrode designs, and pharmacologic methods such as glucocorticoids (GC) (Kontorinis et al. 2011; Santa Maria et al. 2014; Nguyen et al. 2016; Büchner et al. 2017). GC have well-documented effects on inflammatory-related pathways, and GC therapy has been explored to potentially manage several inner ear conditions including Meniere's disease, sudden-sensorineural hearing loss, among others (Hu & Parnes 2009; Casani et al. 2012; Garavello et al. 2012). This represents a potential pharmacologic treatment for decreasing inner ear damage during CI.

In the present review, we discuss the role of periprocedural GC therapy to preserve inner ear function following CI. We highlight the pharmacokinetic basis as well as clinical evidence which would sustain further interventions.

METHODS

A literature review was conducted since April to June of 2018 using electronic databases such as PubMed, MEDLINE, and Google Scholar. Title selection and revision of the articles were performed by the first author and discussed with the other authors. The search included a combination of the following terms: "ear," "cochlea," "pharmacokinetics," "drug delivery," "systemic delivery," "local delivery," "hearing preservation," "cochlear implants," "cochlear implantation outcomes," "cochlear implantation performance," "glucocorticoid," "corticoid," and "steroid." Only articles in English were considered. No meta-analysis was performed. About 156 articles of interest were identified. The total number of publications for full review was also reduced as follows: We only considered articles which included experimental data about GC concentrations, delivery method, and timing of administration in humans during CI. For the case of studies including clinical outcomes related to GC

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<zdoi; 10.1097/AUD.0000000000000740>

usage during CI, we only considered articles that were specifically designed to evaluate GC usage, included data about GC administration and measured clinical endpoints during the follow-up. A total of 14 articles were reviewed in full and provided the basis for this article.

PHARMACOKINETICS OF GC THERAPY IN HUMANS DURING CI

The GC may be delivered systemically or locally to exert their effects on the inner ear. However, all administration routes have their own potential advantages and limitations (Table 1). Systemic administration is a common and simple way to deliver drugs, that in the case of GC, it can be limited by their systemic side effects. Local delivery includes transtympanic, intratympanic (IT), or intracochlear. Transtympanic and IT delivery aim to use the middle ear as a reservoir for drugs that can diffuse to the cochlea through an injection across the tympanic membrane or by direct placement of the drug in the middle ear during surgery, respectively. The drug concentration in perilymph is mainly influenced by the time of exposure of the middle ear to the drug (Salt & Plontke 2009). Intracochlear delivery consists in introducing the drug directly into the cochlea during a surgery, thus avoiding middle ear anatomic barriers.

Pharmacokinetic data on GC therapy in humans are still limited. Bird et al (2007) carried out a prospective nonrandomized study where they compared IT versus intravenous (IV) delivery of methylprednisolone (40 mg/mL) in 39 patients that received CI. There were three treatment groups: IT bolus administration of approximately 1 mL (median dose 20 mg), IV injection of 1 mg/kg (median dose 67.5 mg) over 30 seconds, and IV infusion of 10 mg/kg (median dose 770 mg) over 30 minutes. A single approximately 20 µL perilymph sample was taken through the round window membrane (RWM) from 0.5 to 3 hours after dosing. The median perilymph concentration was 126-fold higher after the IT administration than after the 1 mg/kg IV injection and 33-fold higher than after the 10 mg/kg IV infusion. Moreover, IT administration resulted in lower systemic concentrations than IV delivery. Also, a re-analysis of the data reported a perilymph clearance half-time of 27 minutes for methylprednisolone, suggesting a rapid elimination (Plontke et al. 2008b). A similar prospective, nonrandomized study by Bird et al (2011) was performed in 22 patients to compare IT and IV delivery of dexamethasone-sodium phosphate (-SP) (4 mg/mL) 0.5 to 2 hours before CI. Dexamethasone-SP corresponds to the water-soluble prodrug of dexamethasone available for human administration which is converted to dexamethasone within the inner ear. Two treatment groups were compared; IT administration of 0.4 to 1.8 mL (median dose 3.2 mg) and IV injection of 0.17 mg/kg (median dose 10.7 mg) over 30 seconds. Perilymph concentrations were approximately 88-fold higher after the IT administration than after the IV delivery. It is interesting that the concentration of dexamethasone-SP was considerably higher than those of the free dexamethasone, suggesting that the conversion process could be slow, extending the period of action of the drug (Salt et al. 2012). These studies represent the first trials to measure GC pharmacokinetics in humans. A large variability in concentration after IT delivery was observed. This variability could be explained by several factors including: time before sampling, air bubbles over the RWM, insufficient sample for analysis, rapid decline in drug concentration within the middle ear, and reduced drug availability due to leakage of the solution through Eustachian tube or back spillage into the external auditory canal (Salt & Plontke 2018). It was not reported if a method was applied to prevent contamination of the perilymph samples with the remaining solution in the middle ear or to prevent perilymph leakage after sampling. Although they measured GC concentration in the perilymph and blood, correlation analysis with clinical outcomes was not performed. Therefore, it was not possible to assess if those very low concentrations reached in the blood following IV delivery was enough to result in a clinical effect and, conversely, if IT delivery effectively could achieve better clinical outcomes than IV doses. As hearing preservation (HP) typically aims to preserve the apical areas of the cochlea related to low frequencies, the arrival of drugs to that area would depend on diffusion processes (Salt & Plontke 2009, 2018), and probably, delivering the steroid preoperatively does give more time for diffusion throughout the cochlea. However, most of the current knowledge about how drugs diffuse in the cochlea are based on experimental animal data (Liebau et al. 2017), which differs from the conditions for the human cochlea. These

TABLE 1. Comparison of routes of administration of glucocorticoids: Potential advantages and limitations

Route of Administration		Advantages	Limitations
Systemic		Simple delivery method	Systemic side effects of GC
		More control of the amount, concentration, and timing of delivered GC	Not-well known concentration achieved in cochlea
		Do not interfere with the surgical procedure	
Local	**Transtympanic**	Lower systemic exposure	Require diffusion from the middle ear to the cochlea
	Intratympanic	Usually outpatient procedure (Transtympanic)	High variability of achieved concentrations (anatomic differences and potential obstructions of the round and oval window)
		Short- and middle-term local drug delivery	Drug clearance through Eustachian tube
		It can be associated to hydrogels and medical devices	Risk of infection or tympanic membrane perforation
	Intracochlear	Minimal systemic exposure	Invasive
		Longer exposure to the drug	Requires hospitalization
		Direct access to the cochlea avoiding anatomic variability	Risk of inner ear infection
		Potential delivery along with the cochlear implant	

GC, glucorticoids.

studies represent important efforts for understanding cochlear pharmacokinetics. However, to optimize drug delivery, maximize their effects on tissues, and decrease side effects, further pharmacokinetic data of GC in cochlea are needed. This is especially important for the cases where systemic side effects of GC should be avoided, and local delivery can account for positive effects without undesired effects.

CLINICAL OUTCOMES

Studies on humans are varied in their diverse use of types of GC, dosages, time of administration, measured outcomes, and surgical conditions, which altogether makes it difficult to compare and to draw conclusions about GC effectiveness. Herein, we discuss clinical studies designed to test GC for improving clinical outcomes in CI (Table 2). Other studies that have been designed to test other interventions and not to assess GC influence directly on clinical outcomes (Kuthubutheen et al. 2016) are beyond the scope of this review.

Systemic Delivery

A meta-analysis was performed on 24 studies to identify factors associated with better HP after CI (Santa Maria et al. 2014). This meta-analysis included heterogenous studies with different designs, inclusion criteria and three definitions of HP and few of them were designed to directly test the effects of GC. They reported that postoperative oral GC could lead to better HP rates compared with patients who did not receive postoperative oral GC. Also, topical GC placed into the middle ear during surgery showed a potential benefit at the 2000 Hz frequency alone. No benefits were reported using intraoperative IV or transtympanic GC before surgery. However, some of the studies included in this analysis did not describe the oral treatment in detail, such as type of GC, doses, and schedules (Skarzynski et al. 2007; Garcia-Ibanez et al. 2009; Skarzynski & Lorens 2010). Furthermore, it was not clear what was considered better and worse outcome according to the definitions provided in the study. Just one study reported postoperative oral dexamethasone for six days (Usami et al. 2011). Therefore, it is very difficult to draw any valid conclusion.

Recently, a prospective, nonrandomized study was performed in 36 patients to compare the effects of different regimens of systemic dexamethasone-SP on HP after CI through the RWM (Skarżyńska et al. 2018). There were three groups: a control group without GC administration, a standard schedule of 0.1 mg/kg IV of dexamethasone-SP 30 minutes before surgery and every 12 hours for three days, a prolonged GC schedule of 1 mg/kg oral prednisone for three days before surgery, and then the standard GC schedule, and last, 1 mg/kg oral prednisone for three days and then decreasing 10 mg per day. They reported that both GC groups had significantly better pure-tone average (PTA; 125 to 8000 Hz) than the control group at 1 and 6 months after implant activation, without significant differences between the GC groups. Six months after implant activation, patients who received the combined oral and IV treatment had higher overall HP than the other groups. Some limitations of this study include lack of randomization, uneven number of patients between the groups, lack of long-term follow-up, and lack of inclusion of other clinical outcomes such as vestibular tests or speech discrimination outcomes.

Local Delivery

Intratympanic • A nonrandomized prospective study was performed in 34 patients to test the effects of IT perioperative methylprednisolone (Rajan et al. 2012). The researchers divided the patients according to whether they met the criteria for electroacoustic stimulation (EAS) or not, receiving different types of electrodes. However, the control group was a historic cohort who did not meet the criteria for EAS. All patients received dexamethasone 4 mg IV according to anaesthetic protocol, and the electrode was installed through the RWM. The IT treatment consisted of transtympanic delivery of 0.6 mL methylprednisolone (40 mg/mL, depot form) in the middle ear. Furthermore, the GC was delivered repeatedly throughout the surgery to keep the middle ear filled with the drug. The non-EAS patients who received IT methylprednisolone resulted in a higher HP rate than the control group measured by the change of PTA at 125 to 750 Hz. However, it is not clear when this measurement was performed during follow-up. Similarly, a prospective randomized study was carried out in 18 patients to compare the effects of IT dexamethasone alone or combined with hyaluronic acid on HP (Ramos et al. 2015). In the GC groups, the middle ear was filled with dexamethasone (4 mg/mL) for 15 min before electrode insertion through the RWM and also after sealing the electrode insertion site. Hyaluronic acid was placed over the RWM and used to coat the electrode array. The control group did not receive these drugs. All patients received hydrocortisone 4 mg/kg IV by the anaesthesiologist. Patients treated with dexamethasone and hyaluronic acid showed lower mean changes in PTA (125 to 500 Hz) at six months after surgery than the other groups. Possible explanations are a less traumatic electrode insertion through the use of hyaluronic acid to coat the electrode (Chandrasekhar et al. 2000; Laszig et al. 2002), or that the hyaluronic acid placed on the RWM can retain dexamethasone in the middle ear, increasing exposure time and diffusion of GC into the cochlea (Chandrasekhar et al. 2000). Individual effects of hyaluronic acid were not measured since there was no control group only treated with this substance. We highlight that the authors tried to maintain constant drug concentrations during surgery, which could exert a positive effect as it prolongs the exposure time to GC and potentially reaches the cochlear apex (Salt & Plontke 2009, 2018). However, in these studies, other clinical outcomes such as speech discrimination rates were not explored. Furthermore, some methodologic limitations include the following: a lack of consistency in the time of follow-up between groups, no reported audiometric data during follow-up, a lack of comparison between patients with different inclusion criteria, and no clear randomization methods were used which allows the possibility of potential selection bias.

A double-blinded, placebo-controlled randomized trial was performed to assess the effects of local methylprednisolone on vestibular function in 43 patients (Enticott et al. 2011). Adult recipients were allocated to receive either 125 mg/mL methylprednisolone or saline solution. The drug was used to soak a polymeric sponge of carboxymethylcellulose and hyaluronic acid which was then applied to the RWM for 30 minutes during CI. All patients received dexamethasone 0.1 mg/kg IV by the anaesthesiologist. Postoperative vestibular symptoms were significantly lower in the GC group (5%) than that in the control group (29%) at three months after surgery. The GC group also showed decreased electrode impedances from the middle

TABLE 2. Studies designed to use corticosteroids for improving clinical outcomes in cochlear implantation

Reference	Methodology	Corticosteroid	Dose/Delivery	Inclusion Criteria	Groups	Primary Endpoint	Results
Cho et al. (2016)	Prospective interventional	Dexamethasone-SP	5 mg/mL IV 24 hr and 1 hr before surgery 0.5 mL IT repeatedly during surgery	Not specified	GC group (n = 19) Control group: No GC treatment (n = 10)	Change between post and preoperative PTA at 250, 500, 1000, and 2000 Hz Caloric response	Decrease change in PTA in the GC group
De Ceulaer et al. (2003)	Retrospective cohort	Triamcinolone-acetonide	Intracochlear 1 mL of 40 mg/mL before electrode insertion	Children without ear anatomy alterations receiving the first implant	Group 1: Straight electrode (n = 30) Group 2: Straight electrode + GC (n = 24) Group 3: Contour electrode (n = 18) Group 4: Contour electrode + GC (n = 20)	Change of intracochlear impedances over time	Decreased impedance in GC groups at two months. The reduction was sustained up to 12 months except for contour electrode groups
Enticott et al. (2011)	Double-blinded, placebo-controlled randomized controlled trial	Methylprednisolone Dexamethasone	125 mg/mL IT applied in the RWM using a polymer sponge for 30 min 0.1 mg/kg for induction in all patients	Patients ≥18 years with evidence of vestibular function in the ear to be implanted before surgery, no bilateral implant surgery, no radical mastoid obliteration	Control group: Saline solution (n = 21) GC group: Methylprednisolone (n = 22) exposure	Vestibular function: Postoperative symptoms, caloric tests, and electrode impedances	Decreased postoperative vestibular in the GC group (5%) than the control group (29%) ($p = 0.04$) Decreased electrode impedances from the middle portion of the electrode array in GC group compared with controls No differences in caloric function
Kuthubuthen et al. (2017)	Randomized controlled trial	Prednisolone Dexamethasone-SP Dexamethasone	1 mg/kg/PO for six days before surgery 0.5 mL of 10 mg/mL IT/24 hr before surgery 10 mg/IV during induction	Patients aged 18–85 with preoperative thresholds ≤80 dB at 125 and 250 Hz, and ≤90 dB at 500 and 1000 Hz	Control group (n = 11): IV + IT dose during surgery IT group (n = 9): IT dose 24 hr before surgery + IT during surgery Oral group (n = 9): Prednisolone + IT during surgery	HP rate by PTA at 125–8000 Hz	IT group showed decrease in the all-frequencies PTA at 3 months and 12 months compared with other groups ($p < 0.05$)
Paasche et al. (2006,2009)*	Prospective interventional cohort	Triamcinolone-acetonide	40 mg/mL intracochlear (unknow amount) before electrode insertion	Older than 18 years with postlingual severe to profound SNHL without criteria for EAS	Group 1: Standard electrode (n = 7) Group 2: Standard electrode control plus GC (n = 6) Group 3: Iridium-coated electrode (n = 8) Group 4: Iridium-coated electrode plus GC (n = 5)	Change of intracochlear impedances over time	Decreased impedance in GC groups at short- and long term* mainly in the basal area of cochlea

(*Continued*)

TABLE 2. Continued.

Reference	Methodology	Corticosteroid	Dose/Delivery	Inclusion Criteria	Groups	Primary Endpoint	Results
Rajan et al. (2012)	Prospective interventional	Dexamethasone Methylprednisolone	4 mg/IV during induction 40 mg/mL IT depot form repeatedly	Patients with "measurable preoperative thresholds" (not specified) EAS patients: ≤60 dB at 125, 250 and ≤100 at 500 Hz	Control group: Dexamethasone IV (n = 12) EAS adult group (n = 4), EAS children group (n = 5), non-EAS group (n = 13): Dexamethasone + methylprednisolone IT	HP rate assessed by change between post- and preoperative PTA at 125–4000 Hz	IT groups showed higher HP rate than control group In the PTA 125–750 Hz ($p = 0.05$)
Ramos et al. (2015)	Randomized prospective study	Hydrocortisone Dexamethasone	4 mg/kg IV during induction 4 mg/mL IT to fill the middle ear for 15 min (twice)	Older than 18 years with preoperative thresholds ≤80 dB at 125, ≤90 at 250, and ≤100 at 500 Hz	Control group (n = 6): No local treatment Group 2: Dexamethasone IT Group 3: Dexamethasone IT Hyaluronic acid on the RWM and for coating the electrode	Change between post- and preoperative in PTA at low frequency (125, 250, and 500 Hz)	Decreased postoperative change in PTA for Group 3 at six months
Skarżyńska et al. (2018)	Prospective interventional	Dexamethasone-SP Prednisone	0.1 mg/kg/IV 30 min before surgery and every 12 hr for three days after surgery 1 mg/kg PO for three days before and after IV GC treatment, then decreasing doses	Patients ≥18 years Cochlear duct length ≥ 27.1 mm Preoperative Thresholds 10–120 dB at 125–250 Hz, 35–120 dB at 500–1000 Hz, 75–120 dB at 2000–8000 Hz	Control group (n = 22): No GC treatment Standard GC (n = 9): Dexamethasone-SP IV Prolonged GC (n = 5): Dexamethasone IV + Prednisone PO	HP rate by change between post- and preoperative PTA at 125–8000 Hz	Higher overall HP rate in prolonged GC group than the other groups Lower PTA in both GC groups than controls
Sweeney et al. (2015)	Retrospective cohort	Prednisone Dexamethasone	Up to 60 mg/PO for two weeks 10 mg/IV prior surgery 4 mg/mL IT twice	Preoperative thresholds ≤90 dB at 125 Hz, ≤105 at 250, ≤110 at 500, ≤120 at 750, and ≤120 at 1000 Hz	Oral prednisone + Standard treatment (dexamethasone IV and IT) (n = 20) vs. standard treatment (n = 7)	Preservation of LF PTA at 125–1000 Hz	Greater degree of HP in GC group compared with standard treatment ($p < 0.05$)

HP, hearing preservation; IV, intravenous; IT, intratympanic; PO, per oral; dexamethasone-SP, dexamethasone-sodium phosphate; EAS, electroacoustic stimulation; GC, glucorticoids; SNHL, sensorineural hearing loss; LF, low frequency; PTA, pure-tone average.

portion of the electrode array compared with controls over time, especially between two and nine months after surgery. No differences were observed in caloric test and in hearing thresholds. In 19 patients, the follow-up period was longer than eight months compared with the majority of patients, which could introduce a follow-up bias. Most of the patients did not receive "soft" surgery due to technical difficulties. Thus, it is possible that trauma from surgery could have overshadowed hearing improvements from GC administration in terms of residual hearing. As other clinical outcomes such as discrimination rates were not evaluated, it is not possible to discard other potential effects of GC. It has been reported that an increased impedance is related to the degree of new tissue growth around the electrode after CI (Bas et al. 2016; Wilk et al. 2016). A decreased electrode impedance seen in the middle turn may suggest some influence of the drug in this zone. However, time of exposure to GC was 30 minutes, which would limit the possibility to reach distal areas (Chang et al. 2009; van der Laan & Meijer 2008). Regrettably, the trial had to finish early which could have contributed to an inability to detect any change in outcomes.

Intracochlear • A retrospective cohort study was performed in 92 patients to test the effect of intracochlear triamcinolone-acetonide delivery on electrode impedance over time (De Ceulaer et al. 2003). Patients were divided into four groups according to the type of electrode and the use of GC or not. The GC schedule consisted of intracochlear delivery of a mixture of hyaluronic acid and 1 mL of triamcinolone-acetonide (40 mg/mL) before electrode insertion. The electrode itself was also immersed in this mixture before insertion. Control patients did not receive any substance. The authors reported a decreased impedance in both GC groups at two months. However, GC groups also received hyaluronic acid, which could exert an effect by reducing surgical trauma (Chandrasekhar et al. 2000; Laszig et al. 2002; Ramos et al. 2015), and patients were treated at different surgical units and by different surgeons which may also contribute to diverse degrees of surgical trauma. Similarly, Paasche et al (2006, 2009) performed a prospective cohort study in which they compared the influence of an iridium-coated electrode and intracochlear delivery of triamcinolone-acetonide on impedance at short- and long term in 26 patients. Both GC groups received a single unspecified amount of triamcinolone-acetonide (40 mg/mL) injected through the cochleostomy. In both GC groups, cochlear impedances were reduced over the first four weeks after CI where iridium-coating alone did not have an effect. The effect of GC was more pronounced at basal electrode contacts. Furthermore, impedances were significantly decreased in the GC groups throughout follow-up until four years after surgery, where the differences between the groups were mainly found at the basal and middle parts of the cochlea, which could indicate that postoperative fibrous tissue mainly appears in these regions. These studies showed that intracochlear delivery is feasible and could account for positive effects in the cochlea at both the short- and long term. This is likely related to the decreased inflammatory and profibrotic reaction that is reported in experimental models (Lyu et al. 2018; Jia et al. 2016). It is interesting that although intracochlear delivery can reach higher concentrations along the cochlea (Hahn et al. 2012), these effects were mainly reported in basal areas of cochlea. This could be related to an uneven distribution of the drug along the cochlea due to technical difficulties during the injection, anatomic variations, the degree of surgical trauma, partial washout by perilymph outflow and suction at the site of the cochleostomy.

Combined Delivery

In a retrospective cohort study with 27 patients, Sweeney et al (2015) compared patients who received decreasing oral prednisone beginning three days before surgery with patients who did not receive oral doses (controls). Pediatric patients received prednisone 1, 0.5, and 0.25 mg/kg for five, three, and three days, respectively (total dose: 7.25 mg/kg). Adults received prednisone 60 mg for six days and then decreasing 10 mg every two days (total dose: 660 mg). All patients received dexamethasone-SP 10 mg IV before the surgical incision, and the middle ear was bathed in dexamethasone-SP (4 mg/mL) upon exposure of the RWM, during electrode insertion and before surgical site closure. The authors reported that the rate and degree of HP were greater for patients who received oral treatment compared with nonoral treatment at three weeks after CI. This result can be explained considering that an extended oral regimen of GC achieved more sustained concentrations over time which could ameliorate the delayed inflammation after surgery. Some limitations of this study include the following: a retrospective study design, uneven number of patients between the groups, the use of different surgical approach, electrodes, and follow-up. The inclusion of pediatric patients in the analysis, whom received a different GC schedule, could influence the results since it has been reported that younger age is related to better HP rate (Anagiotos et al. 2014; Zanetti et al. 2015).

Recently, a randomized controlled trial was performed in 30 patients to assess the effects of different GC administration routes on hearing outcomes (Kuthubutheen et al. 2017). Patients were randomized to a control group, an oral GC group of prednisolone 1 mg/kg/day for six days before surgery, or a transtympanic group which received a single 0.5 mL dose of 10 mg/mL dexamethasone-SP 24 hours before surgery. All patients received an unspecified amount of topical dexamethasone-SP (10 mg/mL) before RWM opening and dexamethasone-SP 10 mg IV during anesthesia. Patients who received transtympanic GC had a better PTA (125 to 8000 Hz) over three months compared with the control and oral GC group, which persisted at 12 months. No differences were reported in speech discrimination. These findings support a small benefit in the short term with minimal effects in the longer term. Furthermore, in this study, hearing was preserved in all-frequency PTA with a greater effect in low frequencies, despite the known gradient of GC concentration along the cochlea after IT delivery in experimental models (Plontke & Salt 2006; Plontke et al. 2008a; Salt & Plontke 2018). A possible explanation is that although low amounts of GC reach more apical zones, a sustained exposure would be able to trigger genomic responses not completely related to the degree of concentration gradients.

In a nonrandomized prospective study with 19 patients, systemic and local dexamethasone-SP delivery was compared with no GC treatment (Cho et al. 2016). After CI, they reported a lower PTA (250 to 2000 Hz) in the GC group compared with controls obtained from a different cohort. Nonetheless, it is not clear when they did this measurement because the follow-up was different between the groups. In a pharmacologic point of view, we could highlight that dexamethasone was delivered IV 24 hours and 1 hour before surgery and 0.5 mL of

dexamethasone-SP (5 mg/mL) was repeatedly administrated in the middle ear during surgery. These practices would be feasible considering that when patients are admitted to the hospital the day before surgery, they could receive this GC dose to increase the time of exposure prior and during the surgery, which would contribute to increase the amount of drug that crosses into the cochlea. However, this study has several methodological limitations such as no randomization, different usage of cochlear implant devices and surgical techniques, different follow-up, small number of patients, and absence of demographic data of patients, which leads to a difficulty to draw valid conclusions.

CONCLUDING REMARKS AND PERSPECTIVES

In the present review, we discussed the role of periprocedural GC therapy to preserve inner ear function after CI based on pharmacokinetic and clinical data. It seems that periprocedural GC may exert positive effects on the inner ear after CI. However, clinical evidence of GC effectiveness is confusing as studies use a diverse range of drugs, doses, schedules, and have methodologic limitations. Furthermore, although many of the studies outcome measurements report improvement in a variable, some of these results have questionable clinical relevance or only short-term improvement with no difference over time.

Pharmacokinetics of GC in the inner ear is complex, and all administration routes have their own advantages and disadvantages. It is interesting that we could not identify studies which have related GC perilymph concentrations and clinical data for IV delivery alone, although this route represents the easiest way to provide GC. Pharmacokinetics studies of GC in humans are scarce, which limit the possibility of developing effective GC delivery schedules to reduce inner ear injury during CI.

For the case of periprocedural extended oral or IV GC schedules, it should be considered case to case, balancing systemic side effects with potential effects on inner ear. Especially for those patients in whom systemic GC administration is not recommended, the usage of local methods to deliver GC seems to be reasonable. In any case, future research should aim to develop clinical studies to compare different types of GC, routes of administration, and pharmacokinetic schedules with clinical outcomes to obtain the most effective, safe, and practical delivery schedule of GC.

Furthermore, future clinical trials should consider the existence of no-standard definitions of HP and different surgical techniques, methodologic issues like randomization and placebo usage, time of follow-up, and the inclusion of other parameters like speech discrimination outcomes, vestibular symptoms, or quality of life measurements, which could be clinically more representative of CI outcomes (McRackan et al. 2018; Moberly et al. 2018).

ACKNOWLEDGMENTS

The authors have no conflicts of interest to disclose.

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Received October 8, 2018; accepted March 14, 2019.

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