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Title of article:

Pneumococcal meningitis post cochlear implantation: preventative measures

Short running head: Pneumococcal meningitis post cochlear implantation

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Running Heads:
Pneumococcal meningitis post cochlear implantation

Abstract:

Objectives

Both clinical data and laboratory studies demonstrated the risk of pneumococcal meningitis post cochlear implantation. This review examines strategies to prevent post implant meningitis.

Data Sources Medline search on topics related to pneumococcal meningitis post cochlear implantation

Review Methods Comprehensive analysis of the published clinical and scientific laboratory research data

Results The presence of inner ear trauma as a result of surgical technique or cochlear implant electrode array design was associated with a higher risk of post implant meningitis. Laboratory data demonstrated the effectiveness of pneumococcal vaccination in preventing meningitis induced via the haematogenous route of infection. Fibrous sealing around the electrode array at the cochleostomy site and the use of antibiotic coated electrode array reduced the risk of meningitis induced via an otogenic route.

Conclusion The recent scientific data supports the FDA recommendation of pneumococcal vaccination for the prevention of meningitis in implant recipients. Non-traumatic cochlear implant design, surgical technique and an adequate fibrous seal around the cochleostomy site further reduce the risk of meningitis.

Introduction

A previous review describes the current concept of pneumococcal meningitis in cochlear implant recipients based on recent laboratory studies. It examines possible routes of spread of *S. pneumoniae* infection to the meninges in cochlear implant recipients. It also provides insights into fundamental questions concerning the pathophysiology of pneumococcal meningitis in implant recipients. This review is the second part of a series and it examines methods to minimize the risk of post cochlear implant meningitis based on the current clinical data and the most recent scientific laboratory evidence.

Implant design and inner ear trauma and infection

Children receiving an implant with a positioner had 4.5 times the risk of developing meningitis compared to those who had other cochlear implant types [1,2] . It is possible that the dual component electrode array may induce increased levels of inner ear trauma and/or cause necrosis and absorption of the modiolus and osseous spiral lamina over time from constant pressure of the electrode on the bony structures [3,4] . Moreover, human temporal bone studies have demonstrated increased levels of insertion trauma associated with an electrode array with positioner, including damage to the OSL and/or the modiolus close to the cochleostomy[5-10]. The effects of inner ear trauma on risk of pneumococcal meningitis was studied in the animal model [11]. Severe trauma to the osseous spiral lamina and modiolus increased the risk of pneumoccal menigitis via the otogenic route[11] and this supports the clinical data.

Minimal trauma or atraumatic surgical technique and implant designs should be implemented in clinical practice to reduce the risk of meningitis. Implants with a positioner were withdrawn from the market in 2002 due to the higher incidence of meningitis in patients with this implant design[1]. Manufacturers have been recommended to avoid using potentially traumatic electrode arrays [12].

Fibrous tissue seal

The integrity of the fibrous tissue seal around the electrode array at the cochleostomy site has been considered to be very important in preventing infection spread from the middle ear to the inner ear and thence to the CNS [13-16].

Nadol and Eddington [14] have examined the tissue seal and biological response in 21 temporal bones from 20 individuals who had undergone cochlear implantation previously and died from other causes. A robust fibrous and bony tissue response was observed at the cochleostomy site, and no recognizable open communication or potential communication between the middle ear and the inner ear was seen in any specimen. The authors concluded that a late haematogenous contamination and colonization of the implant is a possible cause of late onset post-implant meningitis. This proposal was based on the observation of an inflammatory cellular response, including mononuclear leukocytes, histocytes and foreign body giant cells around the electrode array and the cochleostomy site. Other temporal bones studies of cochlear

implantation recipients who did not acquired meningitis also showed a well formed fibrous tissue and bony response around the electrode both at the site of cochleostomy and within the scala tympani. Accumulation of lymphocytes, plasma cells and giant cells was also found within the fibrous sheath. An alternative explanation for the presence of cellular inflammatory response around the electrode array is that it is a common immune reaction to the foreign body [17] and not necessarily a sign of chronic bacterial contamination.

Animal studies have demonstrated that a two week old fibrous seal around the implant was mature enough to prevent horseradish peroxidase from entering the inner ear from the middle earn [18]. Nevertheless, the appearance of inflammatory cells and bacteria within the fibrous seal around the electrode array suggested that the fibrous seal, which macro and microscopically appeared mature at four weeks, was not entirely effective in preventing bacteria from entering the inner ear from the middle ear [19-21].

It is still unclear whether the fibrous tissue would become more mature over a longer period of time and therefore prevent inflammatory cells and bacteria traversing through the fibrous seal. However, bacteria were found to traverse through a thick fibro-muscular wall of stapedial artery [19] and inflammatory cells have been found to traverse the fibrous tract of temporal bone fractures sustained many years previously [22,23]. Fractures of the skull base is strongly association with recurrent community-acquired meningitis and the fracture sites tend to heal by fibrosis with a minimal amount of ossification [24-27]. It has been postulated that under these circumstances the bacteria enter the meninges via the fibro-osseous seal at the fracture site [28]. The presence of inflammatory cells in the fibrous tracts of temporal bone specimens following skull based fracture suggests a reduced immune surveillance of the fibrous tissue seal to the invasion of the bacteria [22,23]. These observations from both human and animal studies suggest that more mature fibrous tissue might not act as a complete physical barrier to the spread of infection.

The exact molecular mechanism by which the bacteria traverse the fibrous tissue is unknown. It is possible that scar tissues can potentially reduce immune surveillance. In the absence of the mucosa and basement membrane, the subreticular connective tissues appear to be less resistant to infection [29]. The presence of down-regulating immune factors within the newly formed scar may protect the tissue from the local immune response. One of the immunosuppressive molecules, glycoprotein α1-microglobulin, in healed tissues such as scars and peri-prosthetic membranes of hip and knee replacements, has been studied extensively [30-32]. The role of the immunosuppressive molecules within the fibrous seal of the cochlear implant remains unclear. The inhibitory effect of immunosuppressive molecules on immunocompetent cells, their presence in connective tissues [30,32] and their adsorption on the surface of a number of prosthetic materials [31,33] may play a major role in reducing the threshold for the direct spread of infection from the middle ear to the meninges via the inner ear in patients with a cochlear implant.

Although there was evidence to suggest that a peri-implant fibrous seal might not be adequate in preventing the spread of infection from the middle to the inner ear, an adequate packing around the cochleostomy site with fibrous tissue would still be considered to be a very important step in a cochlear implant procedure. A peri-implant fibrous tissue packing is preferable to a direct open communication between the middle and inner ear. Although, bacteria and inflammatory cells were able to traverse the fibrous tissue, the presence of a fibrous tissue seal might provide a pathway of greater resistance for bacterial movement. Furthermore, the presence of mucosa covering the seal may act as a defence against the invading organisms; the presence of respiratory epithelium lining the peri-implant fibrous seal[13].

Different sealing material for the prevention of post implant infection

The types of material used for sealing have also been investigated and are considered to be very important in prevention of infection after cochlear implantation. Fascia seal was found to be more effective and safer than muscle and Gelfoam (Pharmacia & Upjohn, Kalamazoo, MI, USA) seal [13]. The use of Dacron (polyethylene terephthalate) double velour (USCI, C.R. Bard, Inc, Billerica, MA , USA) has been shown to increase the incidence of infection of the inner ear [34]. Jackler and colleaugues [35] also demonstrated that an effective seal around the electrode entry point reduces the risk of labyrinthitis in the presence of otitis media. However, in that study a bioactive ceramic (Ceravital, Xomed, Jacksonville, FL, USA) appeared to be a better sealing material than autogenous fascia.

Attempts have been made to osseointegrate the electrode array within the cochleostomy to seal the potential gap between the electrode and the cochleostomy site. Although Purser and colleagues [16] were unable to achieve osseointegration with their titanium sealing device, the fibrous tissue generated within the gap between the titanium device and the edge of cochleostomy was sufficient to resist the transgression of bacteria from middle to inner ear. The problem with osseointegration of the electrode array at the entry site to the inner ear is the potential difficulty it creates for future re-implantation. This is an important issue as there are more deaf children and infants receiving cochlear implants, the device will undergo technological improvement throughout the subject's life span.

Other preventative strategies

In addition to atraumatic surgical technique and cochlear implant design and an adequate and robust peri-implant seal, the FDA has recommended immunisation against *S. pneumoniae* for implant recipients in the hope that this will reduce the incidence of pneumococcal meningitis [1]. The two most commonly available types of *S. pneumoniae* vaccine are the 7-valent pneumococcal conjugate vaccine (PCV7, Prevnar, Wyeth-Lederle Vaccines, Madison, NJ), and the 23-valent pneumococcal polysaccharide vaccine (PPV23, pneumovax 23, Merck & Co., Inc.,Whitehouse Station, NJ; and Pnu-Immune 23, Lederle Laboratories, Madison, NJ) [36]. However, there is no clinical data examining the effectiveness of pneumococcal vaccination in preventing pneumococcal meningitis in cochlear implant recipients. Assessment of the

protective role of pneumococcal vaccination was limited in the FDA/CDC study because only small numbers of implanted children were vaccinated prior to the year 2000. There were insufficient numbers of immunised children both in the implanted and control cohorts to make a statistically meaningful comparison [2].

The protective effect of PPV23 was examined for the first time in implanted animals [37]. When implanted animals mounted an immune response to PPV23, they were protected from pneumococcal meningitis if the bacteria were given via the haematogenous or middle ear route. This demonstrated that antibodies produced in the systemic circulation and the middle ear mucosa could protect the implanted animal from acquiring meningitis and raising the threshold of infection to levels comparable to the non-implanted controls. When bacteria were inoculated directly into the inner ear of implanted and vaccinated animals, the risk of the meningitis was not altered (the moderate risk reduction was not statistically significant) compared to the control cohort [37]. Previous studies have shown that antibody levels in the inner ear are lower than the systemic blood circulation due to the blood-cochlear barrier [38-40]. Therefore, the risk of pneumococcal meningitis remained high after immunisation if the bacteria reached the inner ear.

This study suggests that the vaccine could protect healthy implanted subjects from subsequent meningitis of the vaccine-covered serotypes. However, if *S. pneumoniae* passed from the middle ear to the inner ear, the risk of subsequent meningitis would remain high. Therefore, any open communication between the middle and inner ear should be repaired even if the subjects are fully vaccinated. This repair is important in reducing the number of bacteria entering the inner ear from the middle ear.

It is important to appreciate that there are more than 90 serotypes of *S. pneumoniae* and the maximum number of serotypes covered by the currently available vaccines is 23. Whether implant recipients acquired meningitis from non-vaccine covered serotypes remains to be determined. There is also a concern that the incidence of meningitis caused by non-vaccine covered serotypes may increase with the universal use of pneumococcal vaccine [41]. This concern was raised because the use of PCV7 has been shown to increase the frequency of acute otitis media caused by non-vaccine covered serotypes [42,43]. It remains unknown whether universal vaccination of cochlear implant recipients will change the frequency of meningitis caused by non-vaccine covered serotypes. However, a recent clinical study of PCV7 in the general population did not show an increase in the incidence of meningitis caused by cross-reacting serotypes or non-vaccine serotypes [44].

In addition to pneumococcal vaccination, another preventive strategy was examined. Antibiotic coating of the electrode array with a ciprofloxacin/Healon® mixture was shown to reduce the risk of pneumococcal meningitis when the bacteria were given via the haematogenous route [45]. This protective effect was observed at 4 weeks after implantation. However, when the bacteria were given via the middle or the inner

ear, the risk reduction was not statistically significant. The results suggested that the use of an antibiotic coated electrode array may have a role in preventing future cases of meningitis in human subjects. Further research in this field is required especially there is a concern of development of antimicrobial resistant strains of the bacteria from the extensive use of antimicrobial agents.

Conclusion:

An increase in the number of reported cases of implant-related meningitis has prompted action to evaluate implant designs and surgical techniques in order to reduce the risk of meningitis among cochlear implant subjects. An atraumatic insertion of the electrode array will prevent the creation of a more direct communication between the inner ear and subarachnoid space.

An intact seal around the cochlear implant is important to prevent the direct spread of infection from the middle ear to the inner ear and the meninges. The quality and the nature of the seal are important factors to consider in the prevention of implant related infections, and should take the nature of immune surveillance into account. The type and configuration of the prosthetic material used in cochlear implants also contribute to the biological safety in patients with cochlear implants. This is illustrated by a higher risk of meningitis associated with implants with a positioner and a higher risk of inner ear infection when Dacron is used as a peri-impant seal. The use of pneumococcal vaccination appeared to be very effective in preventing meningitis in implanted animals when the bacteria were inoculated via the haematogenous or the middle ear route. This finding supports the current FDA recommendation and all implant recipients should be given age appropriate vaccine.

Many of the lessons associated with cochlear implantation will be common to other implantable devices associated with the CNS and importantly recent studies examining this issue will lead to even safer application of the cochlear implant and other CNS associated devices.

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