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Biocompatible implantable antimicrobial release for necrotizing external otitis

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Abstract

The efficacy of a biocompatible, surgically implantable, antimicrobial release system (IARS) as the exclusive antimicrobial therapy of necrotizing external otitis (NEO) was evaluated in six NEO patients. Gentamicin incorporated polymethyl-methacrylate beads were implanted, following surgical debridement and were removed two months later. Post-implantation alleviation of clinical symptoms: pain, periauricular tissue swelling, otorrhoea, eradication of pseudomonal infection (100 per cent) and substantially shortened hospitalization (4–15 days) were the salient results of this therapeutic modality. Three patients recovered. Two patients who died, one of sudden cardiac arrest and the other of paralytic ileus, 15 and 60 days postoperatively while the beads were still implanted, were symptomless. Recurrence was seen in one patient with early bead extrusion. Ipsilateral sensorineural hearing loss (one patient) and external meatal stenosis were the main complications. IARS appears to offer an effective alternative to long-term systemic antibiotic administration for the eradication of NEO-pseudomonal infection in patients who are sensitive, develop resistance, or when quinolone medical treatment has failed or is contra-indicated.

Introduction

The eradication of pseudomonal necrotizing external otitis (NEO) has been attempted during the last two decades by long-term systemic administration of a combination of semisynthetic penicillins and aminoglycosides. These drugs had to be administered intravenously necessitating costly hospitalization for weeks and even months. Besides being expensive, this therapeutic regimen has a relatively high rate of relapse and recurrence, and exposes the patient to ototoxic and nephrotoxic side-effects. Even more important, the delivery of systemically administered antimicrobial drugs to diseased tissues in NEO is severely limited by the development during the early stage of the disease of a thick, nearly acellular, partly devitalized, amorphous collagen layer extending from the cartilage into the dermis. (Ostfeld *et al.*, 1981*b*; Ostfeld, 1989).

The treatment of first choice in NEO is medical (Kimmelman and Lucente, 1989). Promising cure rates with oral (Leggett and Predergast, 1988; Morrison and Bailey, 1988; Rubin *et al.*, 1989; Sadé *et al.*, 1989) or intravenous ciprofloxacin (Joachims *et al.*, 1988; Sabater *et al.*, 1988), oral ofloxacin (Levy *et al.*, 1990) and with third generation of cephalosporins (Kimmelman and Lucente, 1989) were recently reported. Experience gained in the treatment of large series of skeletal bone osteomyelitis caused by aerobic gram-negative bacilli indicates cure rate of 50–80 per cent (Greenburg *et al.*, 1987; Slama *et al.*, 1987; Gilbert *et al.*, 1987; Nix *et al.*, 1987; Norrby, 1989). Emergence of resistant strains (Norry, 1989) and drug-induced adverse reactions, in rare instances requiring cessation of treatment (Nix *et al.*, 1987; Rahm and Schacht, 1989) spurred the search for improved methods of antimicrobial drug delivery to hypovascular tissues by surgical implantation of controlled antimicrobial release systems (Perry et al., 1986).

The characteristics of surgically implantable, biocompatible, controlled drug-releasing systems, and their success in the treatment of severe osteomyelitic and soft tissue infections (Muller, 1980; Grieben, 1980; Perry *et al.*, 1986) pointed to the possible efficacy of this approach in NEO (Couldery and Sharma, 1988).

We describe here the experience of the Otolaryngologic Department at Hillel Yaffe Medical Center with a surgically implantable, antibiotic release system (IARS) as the exclusive antimicrobial therapy administered to NEO patients.

Patients and methods

A surgically implantable, biocompatible, controlled antimicrobial release system of gentamicin incorporated into beads of polymethyl-methacrylate (PMMA-G) was used in the study. The beads (diameter 7 mm) were threaded on a multistranded stainless steel wire (Fig. 1). The single-bead (Septopal®, E. Merck Darmstadt, Fed. Rep. Germany) composition is: Gentamicin sulphate, 7.5 mg and methylmethacrylate as matrix.

Gentamicin was chosen as the antibiotic because: (1) it acts against gram positive and negative microorganisms at low minimal inhibitory and bactericidal concentrations (anti-pseudomonal MIC 4 microg/ml); (2) has a low incidence of allergic reactions; (3) is freely soluble in water; (4) is stable at relatively high temperatures; and (5) has few resistant strains (Wahling *et al.*, 1978).

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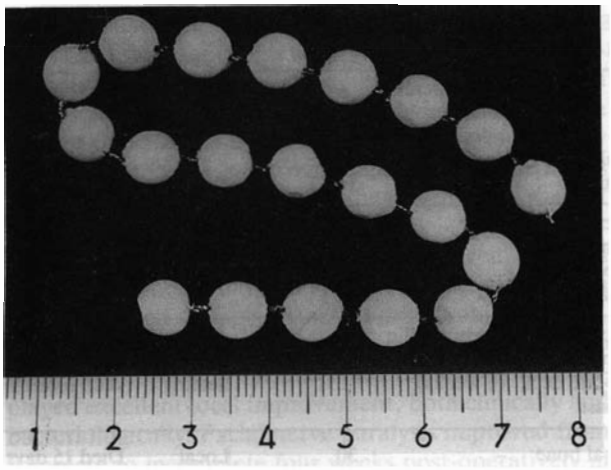

FIG. 1

Chain of beads of PMMA-G: biocompatible-implantable controlled antimicrobial releasing system.

The diagnosis of NEO was based on a decision algorithm integrating clinical symptoms (stubborn attack of external otitis and retro-, infra- or preauricular painful non-pitting inflammatory oedema), suggestive otoscopic findings (granulation tissue protruding from an ulcer of the inferior aspect of medial part of the EAC and purulent otorrhoea), bacteriological cultures of external ear discharge (aerobic gram negative enteric rods), and radioisotopic Tc99 MDP bone scan (Ostfeld *et al.*, 1981*a*).

Six patients who fulfilled the diagnostic criteria for NEO were included in the study. The clinical data on the five adults and one infant are summarized in Table I. Duration of the symptoms before hospitalization ranged from three to six weeks. Two patients had failed long-term systemic intravenous anti-pseudomonal therapy.

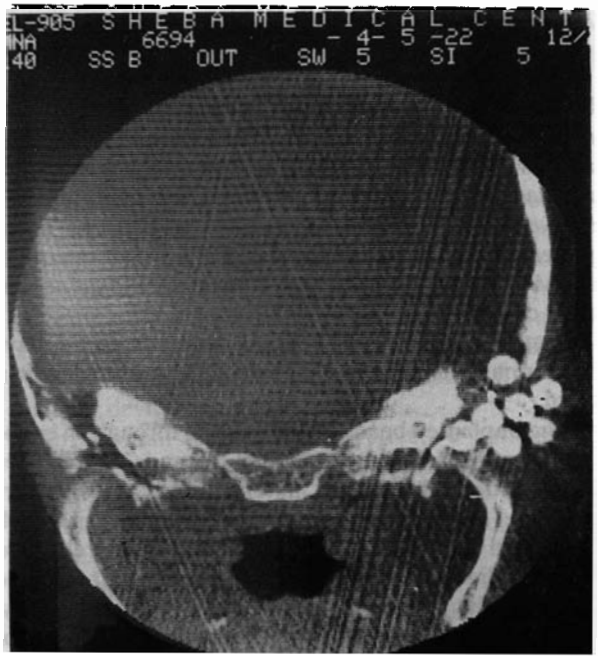

FIG. 2

Coronal computerized axial tomography scan of temporal bone showing PMMA-G beads implanted into the middle ear-mastoid-external ear cavity.

Four patients received insulin for maturity onset diabetes; one patient received oral hypoglycaemics and one was not diabetic. *Pseudomonas aeruginosa* grew in five patients (in two patients associated with *Proteus species*). *Candida* was cultured from one patient. The mastoid Tc99 MDP bone scan showed pathological concentration in three out of four patients. All the patients belong to the period before the introduction into clinical use of the quinolone anti-pseudomonal agents.

Debridement of diseased soft tissue of the external auditory meatus (EAM) and osteitic foci of the tympanic bone was performed in all patients (Ostfeld, 1989). Extended radical mastoidectomy and partial temporal bone resection with infratemporal fossa abscess drainage was performed in two patients (Table I).

The PMMA-G beads were implanted into the mastoid-middle ear cavity if a mastoidectomy had been performed, or in the enlarged EAM (Fig. 3).

Fewer than five beads were implanted in two patients; 13–17 beads in three patients; and 30 beads in one patient following partial temporal bone resection and infratemporal fossa abscess drainage.

To prevent premature bead extrusion, the bead chain was sutured to the surrounding soft tissue and meatoplasty avoided. Closure of the tympanic membrane, and isolation of the oval and round windows by gel-film, were performed to reduce the risk of sensorineural damage. The last bead of a chain was fitted into the EAM as a 'lumen keeper'.

The beads were removed through an endaural approach under general anesthesia two months after implantation and biopsies taken from the tissue surrounding the implanted beads.

Pre-, intra- and daily post-operative bacterial cultures and sensitivity tests were performed by culturette swabs: pre- and post-operatively from the deep aspect of the EAM and intra-operatively from the EAM and the damaged areas of external ear soft tissue and the mastoid if a mastoidectomy had been performed.

The swabs were plated on blood agar and incubated aerobically and anaerobically at 35°C. The aerobic gram negative rods were inoculated on a MacConkey agar plate and defined on indole, urea and triple sugar agar

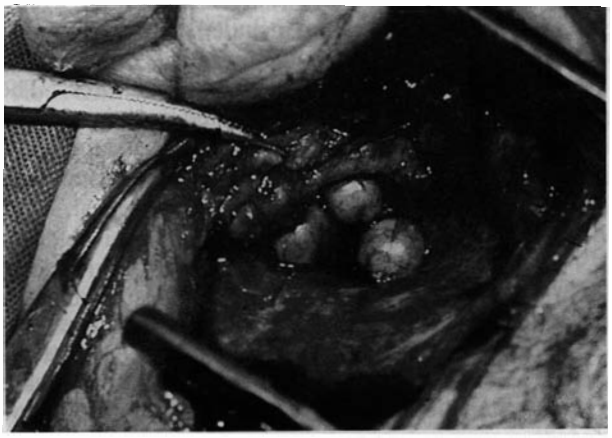

FIG. 3

Beads implanted in the enlarged EAM following surgical debridement of necrotic soft tissue.

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TABLE I
MANAGEMENT OF SIX PATIENTS WITH IMPLANTED PMMA-G BEADS

Pat. no.	Age (years)	Sex	Prior systemic antimicrobial therapy (weeks)	Cranial nerve palsy	Preoperative EAM bacterial culture	Surgical procedure	Post-operative antimicrobial administration (weeks) systemic	PMMA-G beads (no.)	Outcome	Remarks
1.	60	F	Ampicillin (2)	None	Ps.aerug.	*En bloc* excision Tymp.bone expl. Rad.Mast.	–	15	Healed	–
2.	81	M	Cloxacillin (6)	VII	Ps.aerug. Proteus vulgaris	*En bloc* excision Tymp.bone expl. Rad. mast.	Carbenicillin Tobramycin (6 weeks)	–	Apparent local healing	Two month later base of skull osteitis
			Mezlocillin (2)	IX,X	Ps. aerug.	Temporal bone res. Drainage of infra temporal abscess Tracheostomy	–	30	Local improvement	Died 15 days post surgery (of sudden cardiac arrest)
3.	70	F	Ampicillin Cloxacillin (3)	None	Ps. aerug.	*En bloc* excision Tymp.bone expl. Rad. mast.	–	3	Local recurrence	Cured by Azlocillin Gentamicin (10 days)
4.	83	F	Amoxycillin Gentamicin (IM) (6)	VII	Ps. aerug. Proteus vulgaris	*En bloc* excision Tymp.bone expl. Rad. mast.	–	17	Healed	Died 2 months later (of ileus)
5.	50	M	Ampicillin Cloxacillin (4)	None	Ps. aerug.	*En bloc* excision Tymp. bone expl. Rad. mast.	–	13	Healed	
6.	1			None	Candida	*En bloc* excision	Cefalexim	–	Local recurrence	
				None	Candida	Rev.excision: EAM stenosis and granulations	–	2	Healed	

Legend: Ps. aerug. = Pseudomonas aeruginosa.
Tymp.bone expl. = Tympanic bone exploration.
Rad.mast. = Radical mastoidectomy.

media. *Staphylococcus epidermis* and *aureus* were indentified by use of Veristaph.

No systemic or topical antimicrobial agents were administered during or following PMMA-G implantation. Indomethacin was given to adult patients as an analgesic and non-steroidal anti-inflammatory agent. Post-implantation follow-up included daily examination of the external ear, testing for facial and other cranial nerves paralysis and bacteriological cultures. The weekly ambulatory follow-up included investigations of the healing process, EAM lumen, and the state of the implanted beads. Audiograms were performed in a soundproof room.

Results

Early post-implantation follow-up showed lessening of the periauricular swelling in all cases. All patients were pain-free. Otorrhoea was minimal in three patients, and the EAM was dry in three patients. *Staphylococcus aureus* grew post-implantation from the EAM of one patient at two weeks, and of two patients at two months. In one of these patients, the cultures turned negative and the EAM dried up following removal of the beads and eventually healed. Isolated colonies of *Proteus vulgaris* (gentamicin resistant) were found associated with *Staph. aureus* in one case; the gentamicin resistance was noted pre-operatively and attributed to a six-week course of this drug prior to surgery. Three patients showed consistently sterile post-operative EAM cultures. In no instance was *Pseudomonas aeruginosa* cultured.

Post-operative hospitalization ranged from 4–5 days in four patients, ten days in one patient, and 15 days in a third.

The implanted beads were removed through an endomeatal approach in two patients, 55 and 75 days after implantation. The biopsy material from the tissue surrounding the removed beads showed fibrous tissue with incidental finding of a multinucleated giant cell. Two patients died, one from sudden cardiac arrest and one from paralytic ileus, 15 and 60 days post-operatively, and the beads could not be removed. Early extrusion of the beads from an apparently healed EAM occurred in one patient, 14 days after implantation, resulting in recurrence treated by systemic administration of azlocillin and tobramycin for 10 days. It was evident that the beads had become loose and dropped out because of

subsiding tissue oedema. Following this case, to prevent early extrusion, the chains were sutured to the surrounding soft tissue with chromic catgut in three patients and this prolonged the bead retention to 30–60 days. One patient rejected the beads after 30 days, evidenced by the appearance of a retroauricular fistula; the beads were removed surgically and the healing process was not impaired.

Three patients have been followed for three, four and eight years, and all of them are cured. The patient with recurrence and salvage systemic antimicrobial therapy, was not available for long-term follow-up. The two patients who died from unrelated conditions had displayed excellent local improvement, both clinically and bacteriologically. Facial nerve paralysis improved from complete to incomplete four weeks post-operatively in the patient who subsequently died from paralytic ileus and was unchanged in another (who had developed jugular foramen syndrome before implantation, and subsequently died from sudden cardiac arrest).

Severe sensorineural hearing loss (dead ear) occurred in the first patient operated on, in whom 15 beads were implanted; this was probably due to surgical damage during removal of the beads. In two patients in whom audiological evaluation was feasible, the unchanged post- versus pre-operative BC and AC (adult) and 25 dB hearing threshold measured in free field (two-year-old child) indicate that the closure of tympanic membrane and gel-film isolation of oval and round windows are effective in prevention of gentamicin ototoxicity.

Middle ear and mastoid obliteration was noted in one patient, and severe stenosis of EAM in another. Prevention of EAM stenosis was attempted in three patients. One adult had a fair lumen; a second adult died before the beads could be removed. The infant underwent this procedure following secondary excision of a fibrous, granulomatous, nearly obliterated EAM; the beads remained in place for approximately 30 days, the EAM healed, but its external opening did not exceed 2 mm in diameter.

Discussion

The most common infectious pathogen associated with NEO is *Pseudomonas aeruginosa,* and eradication of tissue infections caused by this agent depends on the antibacterial activity at the infection site. The serum concentration of the antibacterial agent does not always correlate with the antibacterial activity at the infection site, especially if there is vascular obliteration or much acellular devitalized tissue.

An essential requirement of effective anti-pseudomonal activity is adequate tissue concentration for sufficient periods of time. It is very difficult to obtain sustained long-term concentrations of these agents in ischaemic tissues by systemic administration. Moreover, patients given identical doses may show different serum concentrations at different times (Siegenthaler *et al.*, 1986). Klemm (1988) found the peak concentration of gentamicin in serum, wound secretions, connective tissue, cancelous bone and cortical bone following intramuscular administration of 80 mg to be 3.5, 0.4, zero, 0.6 and 0.25 mg/ml or kg/g, respectively; following implantation of 80–180 PMMA-G beads in bone cavities, the concentration reached 0.5, 8.0, 23, 4 and 2 mg/ml or kg/g. Our most recent measurements of gentamicin concentration following implantation of PMMA-G beads in the mastoid cavity indicate a high level in the wound secretion—up to over 100 mcg/ml—and a minimal detectable level in the serum ranging between less than 0.2 to 1 mcg/ml (Ostfeld, unpublished data). The high gentamicin bactericidal histo-concentration surrounding the implanted beads considerably exceeded the minimum bactericidal concentration (Wahling and Dingeldein, 1980), and made the need for additional systemic antibiotic therapy unnecessary (Klemm, 1988). Moreover, the increasing use of PMMA-G, in the treatment of osteomyelitis and infection protection of hip prostheses has not led to an increased incidence of gentamicin resistance (Dingeldein, 1981).

Clinical and experimental long-term follow-up following PMMA-G beads implantation showed continuous release of gentamicin for up to 69 months. The largest amounts of antibiotic release, however, were measured during the first two months post-implantation (Wahling and Dingeldein, 1980).

The IARS (PMMA-G) has proved effective in the treatment of chronic skeletal bone and soft tissue infections. Grieben (1980) summarized the results of a multicentre study on 1247 osteomyelitis patients treated by implantation of PMMA-G beads; infection was controlled in 91 per cent of cases. Analysis of the failures revealed remaining sequestra or osteosynthesis material, stressing the importance of adequate surgical debridement.

The Pseudomonal infection was eradicated in all our implanted patients. *Staphylococcus aureus* was cultured from the EAM in the post-operative period, with no effect on the healing process. Gentamicin-resistant *Proteus* was cultured in one patient who had had this drug administered intramuscularly for six weeks prior to entry to the study; this infection persisted post-operatively.

A remarkable result of surgical debridement followed by implantation of IARS in our patients was a substantial shortening of the post-operative hospitalization: from six weeks or more (Strauss *et al.*, 1982; Kraus *et al.*, 1988) to 4–5 days. Two patients were hospitalized for 10 and 15 days. One was the first implanted patient who was kept for observation until the outcome became clear, and the second remained in hospital because of a previous tracheostomy.

The most prominent symptom, pain, ceased. While this could be attributed in part to the use of non-steroidal anti-inflammatory agents (indomethacin), our clinical experience shows that the effects of such agents are negligible without adequate surgical debridement and control of infection.

Today, the primary therapy of NEO is medical (Kimmelman and Lucente, 1989) with the new generation of anti-Pseudomonal quinolone carboxylic acid derivatives such as ofloxacin (Levy *et al.*, 1990) and ciprofloxacin (Sadé *et al.*, 1989).

This study was neither randomized nor controlled. Its goal was to examine whether the implantation of a long-term antibiotic release system in the EAM and mastoid will be able to reproduce the favourable effects reported

in the treatment of skeletal bone osteomyelitis and soft tissue infections caused by aerobic gram negative bacillary infections.

The encouraging experience reported here with IARS (PMMA-G) in the treatment of NEO offers an effective alternative for eradication of severe otological aerobic gram negative bacillary infections in patients who are sensitive or developed resistance, or where quinolone medical treatment has failed or is contraindicated (*e.g.* in children).

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