GENTAMICIN-IMPREGNATED POLYMETHYLMETHACRYLATE BEADS: AN EXPOSITION AND EXPLANATION OF THEIR USE

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INTRODUCTION

The efficacy of any antibiotic is dependent upon maintaining an adequate concentration of the agent at the site of infection. Reduced vascularity as well as possible toxic side effects of the antibiotic can make this difficult to achieve with conventional parenteral administration. When attempting to control infection in these cases, the local application of an antibiotic would seem to represent a logical alternative. In the past, a primary shortcoming with local application has been the lack of protracted release. The use of a carrier substance to deliver the antibiotic is one method used to provide a long-term effect. The most successfully documented combination of antibiotic and a carrier has proven to be gentamicin in beads of polymethylmethacrylate (PMMA), an artificial resin which is commonly used as a bone cement in joint prosthetic surgery.

HISTORICAL OVERVIEW

An antiseptic delivered locally via a carrier substance was reported as early as 1928. Petrova mixed plaster of Paris with the antiseptics Kaolin and Rivanol and packed surgical defects in the bones of dogs, with reportedly excellent results.[1,2,3] In 1953, plaster of Paris containing penicillin and sulfonamide powder was successfully used by Kovacevic in three patients with hematogenous osteomyelitis of the tibia.[1,2,4] The first reported use of PMMA was in 1960 by Charnley, who used it to cement total hip joint replacements.[5,8] Subsequently, in 1969, Vidal and Allieu reported 17 cases of healing achieved by packing infected bone cavities with ordinary cement.[5,6]

The origin and development of Gentamicin-PMMA took place in Germany. It was Buchholz and Engelbrecht who, in 1970, were the first to mix gentamicin with the acrylic cement when replacing infected total hip prostheses.[5,7] After several successful cases they, subsequently, used their antibiotic cement in a variety of cases with the aim of prophylaxis in all instances of arthroplasty. Jenny, et.al., used solid plugs of Gentamicin-PMMA to fill osteomyelitic cavities, with little success.[5,9,22] Finally, in 1974, Klemm presented the gentamicin-impregnated PMMA bead which he later affixed to multi-stranded surgical wire in order to facilitate their removal.[5,9,10] In 1976, E. Merck Laboratories began marketing the bead under the trade name of "Septopal".[11] Today, the beads are used throughout the world although they are still not commercially available here in the United States. They are, however, being used in investigational studies here in the United States.

Klemm's innovation of the Gentamicin-PMMA bead was a critical improvement over the previously used solid plug for several reasons. Although the method of elution of gentamicin from PMMA is disputed by several authors, all agree that the surface area of the cement is directly proportional to the amount of antibiotic released. Therefore, beads have the potential to release greater amounts of gentamicin.[11,23,24,25] Other advantages of the beads include their lack of inhibition of the drainage of wound secretions and the fact that they do not impede consolidating osteogenesis. Instead, they actually serve as a temporary scaffold for the development of granulation tissue.[15] They more effectively fill the dead space, thus, reducing the potential for postoperative hematoma, and so discourage regrowth of infecting micro-organisms. The beads, also, allow short-term local antibiotic treatment to be given without another operation for the removal of the beads.[9]

Of the various types of bone cement available, one commercial brand "Palacos", appears to be the most effective in releasing antibiotics.[13,26,31] Many antibiotics have been used experimentally and have been shown to retain and exhibit

their normal activities in combination with PMMA. Satisfactory results have been reported with aminoglycosides, cephalosporins, penicillin, lincomycin and fusidic acid.[27, 30] Gentamicin was chosen on the basis of its broad spectrum, bactericidal action and a low incidence of hypersensitivity, side reactions, and toxicity when used locally.

PROPERTIES OF GENTAMICIN-PMMA COMPONENTS

PMMA (POLYMETHYLMETHACRYLATE)

PMMA is a high density acrylic material that is formed by combining a powdered polymer with the liquid monomer. Polymerization is an exothermic reaction which produces a strong network of interlinking spherules. PMMA itself has no apparent antimicrobial activity. It functions as the carrier agent for the antibiotic.

GENTAMICIN

Gentamicin belongs to the aminoglycoside family of antibiotics. It has a very broad spectrum of coverage, especially at the high local concentrations achievable by implantation of the Gentamicin-PMMA beads. It is effective against both gram-negative organisms (approximately 80 - 90%) and most gram-positive bacteria.[50, 51] Anaerobic species, however, are not affected by gentamicin.

Gentamicin is poorly absorbed from the gastrointestinal tract. Generally, it is administered parenterally to produce adequate systemic effects. Therapeutic serum levels are on the order of 1-10 ug/ml. It has a narrow therapeutic margin with toxic serum level occurring at greater than 12 ug/ml. Potential side effects include ototoxicity and nephrotoxicity, both of which are thought to be dose-related. With systemic application of gentamicin, tissue concentration may only reach 1 - 2 ug/ml, and this may be further reduced as vascularity to the infected site may be compromised. In general, bacteria with MIC/MBC of less than 1 ug/ml are regarded as sensitive. Those with an MIC/MBC of greater than 4 ug/ml are considered resistant. Anaerobic organisms are such an example.

Mechanism of Action

There are conflicting theories on the mechanism of release of antibiotics from bone cement. Some authors state that the antibiotic is merely removed from the cement surface.[49, 52] Others state that it is released through voids and cracks in the resin,[23, 53] while still others feel that the antibiotic diffuses through the matrix.[49, 54, 55]

Recent investigations show that the release of antibiotic into the surrounding tissues is bimodal.[8, 31, 57, 58] The elution from bone cement appears to decrease exponentially with time. The first phase appears to be an external surface phenomenon with the highest diffusion occurring rapidly over the first 24 hours, followed by a sustained release from within the matrix.[17, 56, 57, 58]

The diffusion rate and quantity of an antibiotic eluted from the cement is largely determined by certain variables: the type of bone cement, the type of antibiotic including the relative diffusion coefficients, the concentration of antibiotic used, and the surface area of the carrier agent.[8, 59] Furthermore, the particular types of cement and antibiotic are selected to provide an efficient sustained release of the agent.[5, 50, 53, 60]

Researchers have found that the Palacos (R) brand of PMMA beads released the largest amounts of antibiotic and for longer periods than any other commercially available bone cement.[5, 9, 31, 53]

There have been numerous in vitro studies using a wide range of antibiotics with PMMA to determine criteria for the ideal mixing agent. According to Wahlig and Buchholz, and Welch (1973, 1978), the following properties should be present:

1. Good water solubility, to allow diffusion into the surrounding tissues.
2. Heat stability to avoid denaturing of the antibiotic during the polymerization process which releases heat (50 - 150 C).[43]
3. Protracted stability at 37 C.
4. Exert little influence on the mechanical properties of the cement.[38]
5. Lack of chemical reaction with cement molecules.

Furthermore, the antibiotic should possess the following inherent properties:

1. Low allergenicity and toxicity.
2. Maximally broad spectrum of activity.
3. Bactericidal.
4. Low primary resistance.
5. Activity at small doses (i.e., low MIC/MBC)

Studies show that the aminoglycosides, gentamicin and tobramycin, appear to meet the above criteria. Additionally, gentamicin is the antibiotic that maintained its full activity after being exposed to the extremely high curing temperature of PMMA.[17] Most investigators have found that gentamicin diffused best from the Palacos (R) PMMA in comparison to other antibiotics.

Once again, the elution of antibiotic is also proportional to the surface area of bone cement in contact with surrounding tissues. This surface is, evidently, much increased by incorporating the antibiotic into cement in the form of spheres.[28, 39] The contact surface area may be further increased by the introduction of defects in the cement, including a rough surface to allow antibiotics contained within the interstices to escape.[23] Smaller beads have a greater surface area to volume ratio, and this implies a faster release.

Pharmacokinetics

Pharmacokinetic studies have been conducted by various investigators and confirmed that the extremely high localized concentration of gentamicin at the site of infections do not correspond to similar serum levels. Therefore, the risk of toxic side effects is significantly reduced[40]. The following details relate to research performed with the G-PMMA beads.

In vitro studies by Wahlig et. al. showed between 400 - 600 ug/ml gentamicin released per bead on the first day, 120 ug/ml on the 10th day, 50 ug/ml on the 20th day, and 10 ug/ml on the 80th day.[39] Even this small amount is still considered bactericidal for most of the pathogens commonly encountered. This is considered between 10 - 100 times higher than the MIC of the majority of relevant organisms, which lies between 0.5 - 4 ug/ml, and even a MBC of up to 10 ug/ml of gentamicin.[5, 16] Such concentration can never be reached with parenteral administration.

Walenkamp et. al. carried out comparison studies between parenteral and local application of gentamicin, as related to serum levels. Following the parenteral injection of 80 mg of gentamicin, concentrations of 3 - 5 ug/ml were measured in the serum and 80 - 200 ug/ml in the urine. The implantation of 80 - 180 G-PMMA beads yielded only 0.5 ug/ml in the serum and 7 ug/ml in the urine;[12, 36, 45] a peak concentration of 80 ug/ml was detected in the wound secretion at the site of infection. This is approximately 150 - 200 times higher than the local levels following a parenteral administration of the same antibiotic.

These results tend to indicate that in no case was the serum gentamicin level higher than 0.5 - 1 ug/ml, and this essentially negates any ototoxic or nephrotoxic risk.[16, 46]

Walenkamp et. al. further propose that the blood-bone barrier that works, in a fashion, to prevent passage of systemic antibiotic to the peripheral tissues, provides a protective mechanism which allows for greater antibiotic levels to be achieved by the implanted beads without systemic toxicity.

Indications For Use

Indications for the use of Gentimicin-PMMA bead include any bone or soft tissue infection that can be sealed, ideally by cutaneous closure or, if necessary, through the use of an occlusive type dressing. Gentamicin-PMMA beads are used most frequently in cases where the blood-bone barrier inhibits bactericidal concentrations, as in osteomyelitis. Gentamicin-PMMA beads may prove to be the most practical successful treatment option. Diabetic patients or others suffering from peripheral vascular disease would also benefit from the local concentrated delivery of the antibiotic.

In soft tissue surgery, beads are often used for prophylaxis of wounds generally associated with a high incidence of infection due to their potential contamination with microorganisms at the time of surgery, (e.g., rectal or abdominal surgery). Gentamicin-PMMA beads have also been used in specialized areas such as vascular, plastic, and reimplantation surgery.

Advantages

Advantages provided by the Gentamicin-PMMA drug delivery system, as compared to conventional treatment modalities, (i.e., suction irrigation, or IV antibiotic administration) include:

1. Bactericidal concentrations are achieved at the site of implantation which can be maintained for many weeks.
2. The subsequent risk of toxic side effects are minimal or avoided altogether.
3. There is intimate contact between the entire area of the wound and the antibiotic with minimal fluctuations in concentrations.
4. Broad spectrum effectiveness against most primary pathogens.
5. No evidence of the development of bacterial resistance.
6. Significant allergic reactions have not been reported.
7. Reduction in instances of postoperative hematoma because the beads compress the residual cavity but without alterations of the mechanical characteristics of bone.
8. The physical structure of the beads stimulates the growth of granulation tissue.
9. Prompt pain relief and earlier mobilization enhance patient compliance.
10. Shorter hospitalization and therefore, reduced medical cost.

Contraindications

The relative contraindications to the use of Gentamicin-PMMA beads include wounds which cannot be closed or approximated, acute inflammation, or the presence of osteosynthesis materials.

Disadvantages

The disadvantages of Gentamicin-PMMA beads are minimal. The primary limitation is perhaps their minimal activity against streptococci, and lack of efficacy against anaerobic bacteria. The actual fabrication of the beads in the operating room is a potentially time-consuming process until one gains experience with the technique. Bead removal may be painful if implanted improperly or if they become anchored in the connective tissue. Other potential disadvantages include:

1. The possibility of localized toxic side effects or hypersensitivity reactions.
2. A chronic inflammatory response which may potentiate chronic osteosis, especially if implanted permanently.
3. Prolonged release of small amounts of gentamicin could theoretically lead to a selective growth of gentamicin-resistant to organisms.

DESCRIPTION OF COMMERCIALLY AVAILABLE GENTAMICIN-PMMA

The gentamicin-PMMA beads were first introduced in 1976 by Klemm. They are manufactured from Palacos(R) brand of PMMA and Refobacin(R) (gentamicin), and marketed under the trade name of Septopal(R) (Merck & Darmstadt). The classical beads are spherical. Each bead weighs 0.2g and has a diameter of 7mm. They consist of 7.5 mg of gentamicin sulphate, equivalent to 4.5 mg of gentamicin base, and 20 mg of Zirconium dioxide as a radiological contrast. The gentamicin compound is incorporated into the PMMA and pressed uniformly onto multi-filament stainless steel wire at intervals of 1 cm per bead. They are available individually or in strands of 10, 30 or 60 beads. An average of 400 ug of gentamicin per bead per day is released.

The application of Gentamicin-PMMA minibeads is indicated especially in the case where the classical bead cannot be used, due to anatomy and size of the wound. Such may prove to be the case in podiatric surgery. At the present time, these minichains are only hand-made by Ascher et. al. (1979).[47] The minibeads are oval with approximate dimensions of 3mm x 5mm. Each bead contains 2.8 mg of gentamicin sulphate (1.7 mg gentamicin base) and 3.9 mg of Zirconium dioxide. They are similarly prepared and affixed in stainless steel wire in chains of 10 and 20 beads.

Unfortunately, the Gentamicin-PMMA beads are not currently available for use in the United States. However, they are readily available in Europe. At present, beads containing tobramycin have been mixed in the operating room, due to the lack of availability of the powdered form of gentamicin in the United States.[48]

Fabrication of Beads

The ratio of gentamicin to PMMA affects the diffusion rate and amount of the antibiotic released. Additionally, the amount of antibiotic may affect the mechanical strength and structure of the bead. As more antibiotic is added to the PMMA, the surface becomes more porous and rougher so that the effective surface area is greatly increased and, proportionally, the elution of antibiotic is enhanced. If, however, too much antibiotic is added, the mechanical strength of the cement may be significantly reduced, rendering it ineffective as the carrier agent. The combination of an aqueous solution of antibiotic to the cement also interferes with polymerization and results in weakening. Various investigators have recommended specific limits on the antibiotic-PMMA ratio (1:5) to ensure hardening of the PMMA beads. Some researchers have found a retardation of curing when more than 1 - 2 g of antibiotic is added to 40 g of cement.

Technique: Powdered Form of Antibiotic

With the powdered form of antibiotic, it is necessary to first mix it with powdered polymer. 0.5 - 1.0 g of antibiotic powder is added to 40 g of the powdered polymer (usually 1.2 g tobramycin powder). 20 ml of the liquid monomer is added to initiate the polymerization process. The "paste" may be rolled into beads or placed in a 30cc syringe and pushed onto a double-twisted 28-gauge stainless steel wire and allowed to harden. 10 - 15 minutes may be required for the beads to harden completely.

Technique: Liquid Form of Antibiotic

With the liquid form of antibiotic, it is necessary to first mix the powdered polymer with the liquid monomer. 10 vials of 80 mg per 2 ml gentamicin sulphate are added to the PMMA cement. The paste is mixed well to homogeneity and then pushed through a 30cc syringe onto the 28-gauge twisted surgical stainless steel wire.

Guide to Implantation and Therapeutic Principles

The first and most critical step when preparing to implant the Gentamicin-PMMA chain is the radical debridement of the infected cavity. It cannot be over-emphasized that the use of G-PMMA beads is only an adjunct to the application of correct surgical principles. Any and all necrotic tissue, sequestrum, or osteosynthesis materials should be completely removed or excised. External fixation may be used to stabilize a fracture or osteotomy, if needed. The use of a tourniquet and the vital staining technique with disulphine blue are both options to assist in identifying the extent of non-viable tissue to be ablated. The infected area is then flushed thoroughly with copious amounts of sterile saline solution.[5, 9, 15] Pressure irrigation is often very effective and helpful to accomplish debridement.

The cavity is then completely filled with the G-PMMA chain. Thoughtful positioning of the beads will facilitate the trouble-free removal at a later date. This can best be accomplished by avoiding sharp bends in the wire while arranging the beads in a meandering pattern so that they do not become entangled. Particular care should be taken to avoid entrapment within the neurovascular structures and to ensure that they will not "catch" on projecting hooks of bone or fascial defects when they are withdrawn[9, 36]. The number of beads should be counted to confirm complete removal at a subsequent date.

The wound should then be closed, preferably through a cutaneous closure technique, or if necessary, through the use of an occlusive dressing. Coverage, and preferably, closure is mandatory; otherwise, secretions containing gentamicin may be lost from the wound resulting in decreased concentrations of the antibiotic at the site of infection. For this same reason, suction drainage systems are contraindicated with the use of Gentamicin-PMMA beads. Overflow or gravity drains with secretion bags are used and removed as soon as possible to minimize the loss of secretions. The period of implantation is variable and is commonly classified as short-term temporary, long-term temporary or permanent. Permanent implantation is rare and is used only when an osteomyelitic cavity cannot be filled by bone grafting, due to exhausted bone reserves as is usually seen in elderly patients. Long-term temporary implantation is used to provide an infection-free field for a future surgery. Examples would include the grafting of cancellous bone or re-implantation of a joint endoprotheses, that would still be necessary even if the Gentamicin-PMMA chain was not implanted. Short-term temporary implantation is most commonly used. One or two of the beads are left above the surface of the skin so that, by simply pulling on the exposed bead, the entire chain theoretically can be extracted. This should be done within seven days for soft tissue or ten days in bone implantation because of the rapid proliferation of connective tissue which encases the beads.

Removal of the beads may be carried out by either of two different techniques: through the gradual loosening and removal of one or two beads on a daily basis so as to remove the entire strand over two to three weeks, or removal of the total chain at one time. Due to the extreme discomfort caused by gradual removal, it may be necessary to remove the total chain under local or general anesthesia.

SUMMARY

The use of antibiotic impregnated PMMA beads appears to be a useful modality for the management of infections in the lower extremity. Their primary use is in those individuals in whom the normal parenteral administration of antibiotics is likely result in insufficient levels of antibiotic at the site of infection. Although not yet currently available in the United States, the beads can be easily fabricated in the operating room. Because systemic absorption is minimal, toxic side effects have not been reported. Finally, with the exception of anaerobic bacteria and streptococci, Gentamicin-PMMA beads appear effective in the treatment of most other gram-positive or gram-negative pathogens encountered in lower extremity infections. Their popularity and use is likely to increase over the next 10 years.

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