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Alternative Materials to Acrylic Bone Cement for Delivery of Depot Antibiotics in Orthopaedic Infections

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Acrylic bone cement has considerable laboratory and clinical data validating it as a delivery material for depot administration of antibiotics. However, an alternate material that does not require a secondary procedure for removal is desired. Many biodegradable materials have been evaluated as alternatives including protein-based materials (collagen, fibrin, thrombin, clotted blood), bone-graft, bone-graft substitutes and extenders (hydroxyapatite, beta-tricalcium phosphate, calcium sulfate, bioglass), and synthetic polymers (polyhanhydride, polylactide, polyglycolide, polyhydroxybutyrate-co-hydroxyvalerate, polyhydroxyalkanoate). Various forms and combinations of these materials have been investigated worldwide, characterizing their elution properties and performance in treating osteomyelitis in animal models. Many of these have had limited clinical evaluation. Outside the United States, some of these materials are used clinically. In the United States, none have been approved. None are commercially available for clinical use. Morselized cancellous bone and calcium sulfate are the two materials that have been used clinically in the United States on a physician-prescribed, hand-mixed, basis. Considering the limited clinical data that currently are available, the use of these materials still is experimental. Clinical application should be cautious, limiting the total antibiotic load. Until definitive data are available, a prudent dose would be no higher than one that would have acceptable toxicity risk if administered intravenously over 24 hours.

In a symposium held at the Thirteenth Annual Scientific Meeting of the Musculoskeletal Infection Society (August 2003), depot delivery of antibiotics for the treatment of orthopaedic infections was discussed in detail. The current report reviews the main points presented on possible alternative materials to acrylic bone cement for the delivery vehicle.

Polymethylmethacrylate (PMMA) is the standard material used as the delivery vehicle for depot antibiotics in orthopaedic surgery.[14,20,37] However, there are concerns about the use of PMMA that have led to the search for alternate materials to be used as the delivery vehicle. The greatest concerns are related to the retained PMMA acting as a foreign body after release of the antibiotic has fallen below therapeutic levels.

Polymethylmethacrylate is surface friendly to biofilm-forming bacteria.[4,18,34,38,43] This presents a potential risk of retained PMMA acting as a surface for the reestablishment of the original bacteria or for the initiation of an infection by new bacteria. This concern has not been realized in clinical practice,[9,17] although bacteria may be present without overt clinical manifestation.[35] As with all delivery vehicle materials, the antibiotic levels in the wound decrease over time. Prolonged subtherapeutic levels are possible, increasing the risk of bacteria developing resistance to the antibiotic. The release characteristics of antibiotic-laden PMMA can lead to low-level release for many months or years.[35] A material that has a faster, more complete release of the contained antibiotic theoretically would be associated with a lower risk. Removal of the PMMA depot after the infection is controlled commonly is thought to be required. A biodegradable vehicle would eliminate the need for the secondary procedure to remove the PMMA.

In some clinical situations it may be desirable to deliver antibiotics to a local site where the physical characteristics of antibiotic laden PMMA are not needed. These clinical situations include cases in which structural stability does not need to be provided by a spacer, cases in which a potential space to accommodate a reconstructive prosthesis does not need to be maintained, or cases in which the bone or soft tissue deficit is insignificant. In cases in which uncemented prosthetic components are used, delivery of antibiotics in PMMA is not an option.

Other undesirable qualities of PMMA include generation of heat during polymerization and systemic toxicity to absorbed monomer. The heat generated during polymerization is capable of substantial thermal injury, especially when making spacers in situ. To my knowledge and from

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my experience, the systemic response to monomer from antibiotic laden PMMA depot has not lead the catastrophic hypotension associated with arthroplasty fixation. Nevertheless, that concern remains valid. Avoiding these issues would be a further benefit of an alternate delivery material.

The alternate materials that have been investigated and used clinically can be divided into three main groups; proteins, bone graft materials, and synthetic polymers. They either are biodegradable or are capable of being incorporated in regenerating bone.

Protein Materials

The protein materials are derived from biologic tissues ranging from autograft to allograft to xenograft. Microfibrillar Type 1 collagen (bovine or porcine), lyophilized collagen sponge, gelatin, human fibrinogen and thrombin, albumin, and autologous blood clot have all been used clinically, both individually and in combination.[1,7,10,13,21,32,44] These materials function as delivery vehicles by providing a physical scaffold around the antibiotic mechanically limiting fluid flow, or by providing a protein to bind the antibiotic. Some data on release properties are published for all of these materials determined by either elution studies or by animal studies. Elution rates tend to be rapid, leading to release of essentially all of the contained antibiotic in the range of hours to a few days. Antibiotic release in animal models is slower. Time to release the majority of the contained antibiotic ranges from many days to several weeks. The investigations generating these data are limited, using a wide spectrum of methods, making a comparison of performance of the materials invalid. Clinical guidelines for the amount of the material to be used and for the dose of the contained antibiotic are not possible.

Collagen sponge is the material in this group that has the best supporting data. There are laboratory studies[4,11,32,44] and it has been used clinically outside the US.[10,15,21] Collagen sponge is a preparation of Type 1 microfibrillar bovine collagen in a three-dimensional structure. Its use without an antibiotic load is contraindicated in infected wounds. Elution data have led to the conclusion that it is useful for the delivery of antibiotics for only 48 hours,[44] or that it is not satisfactory for clinical use in osteomyelitis.[4] Other authors conclude that it is an effective delivery vehicle for up to 28 days in a rabbit model[11] and that it is effective clinically.[10,15,21] Further characterization and technique refinement are required before it can be recommended as a delivery vehicle for antibiotics. In my opinion, collagen sponge has excellent potential to be validated on further investigation. Commercially prepared antibiotic-laden collagen sponge is not available for use in the United States.

Bone Graft Materials and Substitutes

The following materials have been chosen because they are compatible with or promote the regeneration of bone. They include calcium sulphate ($CaSO_4$), morselized cancellous bone, tricalcium phosphate (TCP), hydroxyapatite (HA), and bioactive glass. There are laboratory data characterizing release properties for all of them.[6,12,15,16,19,22,25,30,31,33,42,45] All these materials have been used clinically. None of these materials are FDA approved for use as an antibiotic delivery vehicle. None are available as commercially prepared antibiotic-laden products in the United States. Calcium sulphate and morselized cancellous bone have predictable release characteristics in the laboratory and have been used clinically in the United States.

Calcium sulfate is commercially available as a bone defect filler. Approximately 58% of contained antibiotic is released during the first 24 hours in elution studies.[25] Approximately 20% of contained antibiotic is released during the first 24 hours in a rabbit model.[33] Clinical data are limited with good control of infection in short-term studies[8,24]; Long-term outcome data collected after the use of antibiotic-laden calcium sulfate are insufficient. Clinical use of antibiotic-laden calcium sulfate in the United States is only possible on an off-label basis. Tobramycin and vancomycin are currently the only drugs with adequate elution data from calcium sulfate. Regeneration of bone at the site of calcium sulfate implantation is not necessarily assured, and there is a well-recognized problem of seroma formation and drainage associated with the use of calcium sulfate. Commercially prepared calcium sulfate mixed with tobramycin, is not available in the United States, although it is approved for use in Europe, Canada, and other countries.

Morselized cancellous bone has been used extensively as bone graft material. There are variations in the material that depend on the method of preparation. The data discussed here are from investigation done on morselized cancellous bone obtained by reaming fresh frozen cancellous allograft bone, typically femoral heads or distal femora, with an acetabular reamer. The marrow contents were not washed from the bone before morselization. There are more than 15 years of clinical experience with this material as a vehicle for antibiotics[27,28] Other investigators have used xenographic bone in laboratory investigations and clinically.[22,41,45]

The use of morselized cancellous bone as a delivery vehicle for antibiotics was developed in 1984 when there was limited choice in bone-grafting material and constraints related to biologic hazards were manageable.[30] The concept involved using a material that was already required for the reconstruction. Morselized cancellous

bone incorporates during bone regeneration and allows recruitment of host defenses to protect the reconstruction after the contained antibiotic has been depleted to sub therapeutic levels. In vitro elution studies[30] and in vivo studies in a rabbit model[26] have shown first-order kinetics for release of tobramycin during a period of over 3 weeks. Tobramycin levels exceeded usual bactericidal concentrations for 3 weeks in the graft material implanted in a rabbit. Maximum serum levels for tobramycin were approximately 6 to 8 μg/mL at 2 to 4 hours, decreasing to less than 1 μg/mL by 30 hours. Tobramycin and vancomycin levels were also studied in 26 patients treated with antibiotic-laden morselized cancellous bone grafts of 20 cc or more.[27,28] In serum, the levels were subtoxic (6 and 9 μg/mL, respectively, at 12 hours postoperatively). Levels present in urine showed continued release for at least 3 weeks. Drain fluid levels were high, 10 to 100 times the serum toxic levels (tobramycin, 185–1690 μg/mL; vancomycin, 230–2345 μg/mL). At the time of review, with 2 years minimum followup, there was no evidence of active infection in any patient. These data suggest clinical safety using this material and technique. They also validate the laboratory data in the clinical application but are insufficient to establish efficacy in treatment of osteomyelitis. I have used antibiotic laden morselized cancellous bone since 1986 for second-stage reconstruction of structurally stable defects.

During the mid 1980s and late 1980s, extensive elution studies were done on antibiotic-laden morselized cancellous bone using different compaction densities, drug concentrations, surface areas, and combinations with fibrin and clotted blood. The effect of density, drug concentration, and surface area had the expected proportional effect on the rate of elution, but adding fibrin or clotted blood had the unexpected effect of increasing the elution rate.[30] Storing the antibiotic-laden morselized cancellous bone frozen at −70° C for 2 weeks decreased the elution rate to nearly 1/5 of the rate of the unstored mixture.[30]

Elution studies comparing morselized cancellous bone with beta-TCP ceramics[29] showed release rate for TCP double that for the morselized cancellous bone. Further studies on HA and TCP with varying degrees of porosity found rapid rates of elution that were not meaningfully effected by changing porosity, adsorption time, or frozen storage. All the ceramics released 80% or more of the antibiotic during the first 24 hours. More recently, slower elution rates have been shown to occur from HA and HA-TCP-PLA combination in animal models.[6,12,40,42]

Synthetic Polymers

Synthetic polymers have been selected for their bioresorbable properties to be used in wounds that do not require a secondary reconstruction. Many synthetic polymers have been investigated worldwide. The list of studied polymers includes polyanhydride P(FAD-SA), polylactide (PLA) and polyglycolide (PGA), poly-DL-lactide-co-glycolide, polyhydroxybutyrate-co-hydroxyvalerate (PHB-HV), polyhydroxyalkanoate (PHA), and polypropylene fumarate-methylmethacrylate. These polymers have been studied individually in various chemical forms and in combination. Polylactide and PGA encapsulation techniques, including formation of microspheres, have been investigated.[2,5,15,23,36]

Any of these materials could function as a delivery vehicle for antibiotics with further evaluation and development. Manipulation of the material properties and combinations of one or more of these materials can lead to any clinically desirable release rate. Investigations have been done exploring these variables.[2] However, no one material has shown dominance with confirmatory investigations and progression in development towards a usable clinical preparation. These materials require commercial manufacturing.. There are none available for clinical use as a depot antibiotic delivery vehicle. This may be related in part to the economics of bringing these products to market premixed with antibiotic. Currently, there is no polymer available that can be hand mixed with antibiotics in the operating room.

Other materials have been suggested. Some, including monocarboxycellulose, alginic acid, glyceryl-monostearate, and calcium phosphate/PLA combination, have been studied in preliminary laboratory investigations.[1,32,39,43]

DISCUSSION

These materials are not available in the United States because the data defining their performance are inadequate, not because they don't work. The lack of validating data is due to many issues largely involving experimental design. First, the available data are the product of experimental methods that are so varied that the results cannot be quantitatively compared. Important parameters such as type of elution fluid, volume of elution fluid, temperature, agitation of the fluid, exchange interval, percent of fluid exchanged, antibiotic concentration, surface area of the material, and the volume of the material vary considerably from laboratory to laboratory, from material to material, and even from date to date in the same laboratories. To effectively discriminate between these materials on an in vitro basis, standard protocols need to be established, controlling all of these parameters.

The second issue is the lack of correlation between in vitro and in vivo parameters. Even with standardization of in vitro parameters, the data can only be useful to define clinical protocols if they represent parameters that repro-

duce the clinical wound environment. The data from studies evaluating collagen,[4,11,45] calcium sulfate[25,33] and PLA-PGA[2] microspheres show considerably longer release duration in animal models than in elution studies. This suggests that fluid dynamics in the animal model are more restricted than in the elution bath and that the elution parameters do not accurately reproduce the environment in a wound.

If there was consistency in the parameters used in elution studies and consistency in the parameters used in animal models, some conversion relationship may be possible. Unfortunately, the animal models are completely unstandardized as well. Important variables including site of implantation, implant size, concentration of contained antibiotic, and antibiotic load/body weight vary considerably from study to study. In some studies the same material/implant is used for in vitro and in vivo studies,[2,25,33] but these studies are not controlled for antibiotic dose, fluid volume, or implant size between the elution bath and the animal size or wound size. Also, they are not proportioned to the parameters that could be expected in clinical practice. To be fair, experimental parameters for in vitro or in vivo studies cannot reproduce the clinical wound environment because the clinical parameters are unknown. Even if best-guess assumptions were made for the clinical parameters, accuracy cannot be assessed. Application of the current data to clinical protocols is simply not possible. It should be no surprise that some controlling agencies have not approved antibiotic-laden preparations using these materials for clinical use.

Laboratory data limitations are magnified by lack of clear clinical requirements. What constitutes therapeutic tissue levels is undefined and varies with different bacteria and different antibiotics. Is it a level that will eliminate planktonic bacteria, or must levels be provided that will eliminate sessile colonies found in biofilms associated with biomaterials related infections? The later likely is necessary, but the former often is presented in the results of in vivo investigations. Antibiotic levels necessary to kill bacteria in sessile colonies may be extreme, 10 times to 100 times that required for killing planktonic bacteria. Although reports of adverse local tissue response are not in the clinical or laboratory literature, it is not known how high is too high for local tissue levels. In vivo levels in excess of 2000 μ/mL for tobramycin are possible when morselized cancellous bone is used as the vehicle clinically. At the very least, any material that releases the majority of the contained antibiotic during the first 24 hours in elution studies can be expected to have that capability as well. This is much less of an issue for antibiotic-laden PMMA, which retains antibiotic for years, and would only be expected to produce extremely high levels if altered to increase the release rate or if surrounded by an extremely small fluid volume that changes extremely slowly.

The antibacterial activity of the antibiotic after it has been released from the delivery vehicle must be confirmed. The antibacterial activity of vancomycin and tobramycin eluted from morselized cancellous bone has been assessed by comparing the zone of inhibition with known concentrations using the Kirby-Bauer diffusion disc technique. Most published studies on other materials have not addressed this concern.

Release characteristics of each preparation of antibiotic-laden material are specific to that preparation. If the material is altered, if components are added to or subtracted from the preparation, if the antibiotic altered, or if the preparation technique is changed in any way, the release characteristics cannot be assumed to remain the same. This is exemplified by the differing results seen with the different preparations of polymers.[2] Particularly important is when a material you are familiar with using is replaced with a new preparation. The old elution data are no longer valid. With respect to morselized cancellous bone, the preparation used in the 1980s is no longer the preferred bone graft material. Use of the original material is supported by elution, animal, and clinical data. Those data do not apply to preparations made with more contemporary grafting materials that have had all the marrow contents completely removed or that have been freeze dried or that have been demineralized. Past data and clinical experience with morselized cancellous bone serve to show that it is possible to develop a depot delivery protocol using these materials. It does not justify using previous protocols on new materials without determining the new release characteristics.

Many of these alternate materials release the contained antibiotic rapidly, following first-order kinetics (single exponential rate of release dependent on the concentration of the antibiotic being released as the only variable changing with time as apposed to zero order kinetics, which is not dependent on the concentration of the antibiotic being released). Rapid initial release leads to high initial concentrations. Short-duration high-concentration levels in the wound may be desirable for antibiotics such as aminoglycosides that increase effectiveness with increasing concentration. It may be undesirable for antibiotics such as vancomycin that do not do this. Specific release characteristics needed to optimize the efficacy of each antibiotic need to be determined. If longer durations are needed, a larger antibiotic load can increase the duration but will also increase the early wound concentration even if it is not needed clinically. A combination of materials with progressively longer release rates or a material with different release kinetics may be a more desirable solution. As already noted, the release performance in a clinical

wound may not be consistent with in vitro data. In vivo data may be closer to desired clinical performance; however, that needs to be confirmed. Fluid volume and flow in clinical wounds need to be determined. The site of the depot, intramedullary versus soft tissue, for example, may be extremely important in determining the required release characteristics. In vivo investigations that reproduce clinical wound environment need to be carried out.

The concept of delivering antibiotics locally to the site of orthopaedic infections is sound. There is considerable laboratory data defining the release characteristics of PMMA. Polymethylmethacrylate is widely used clinically with good results. In situations where PMMA is undesirable, an approved alternate material currently is not available in the United States. Collagen sponge, calcium sulfate, morselized bone, and PLA-PGA have considerable potential for successful development to clinically usable products.

Until good data are available, clinical use of these materials as delivery vehicles for antibiotics must be approached with caution. If a surgeon decides that the clinical need for depot delivery of antibiotics outweighs the risk of using a vehicle with uncertain release rates, it would be prudent to limit amount of antibiotic used. The total antibiotic load should not exceed the dose that would have an acceptable risk if it was administered intravenously over 24 hours.

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