

PREPARATION OF GENTAMYCIN AIPMMA (ANTIBIOTIC IMPREGNATED POLYMETHYL METHACRYLATE) BEADS FROM BONE CEMENT.

The contents of the pack are sealed in sterile containers. Provided that the materials are maintained in sterile conditions, re-sterilisation of the beads is unnecessary.

1. Prepare a sterile surface using a sterile drape in a well-ventilated area.
2. Unpack the contents of the box, identifying the liquid component and the powder component of the cement.
3. Turn out the two parts onto the drape. When turning out the powder keep the outer pouch. The inner surface is sterile and will act as a non-stick surface for making the beads.
4. Lay the powder pack out onto the drape with the sterile surface uppermost.
5. Scrub up and put on sterile gloves.
6. Take a catheter mount syringe and remove the plunger. Place on drape.
7. Mix the liquid to the powder in a sterile container (Autoclavable pot provided) Mix thoroughly with a wooden spatula or sterile spoon.
8. Pour into syringe barrel keeping sterile finger over end of nozzle the cement is quite viscous and may need help with the spoon to get it into the syringe.
9. Place plunger in barrel, invert and express air.
10. In the manner of an icing bag squeeze out small blobs approx 5mm diameter onto the surface. The mixture will start to stiffen in the syringe after 1-2 minutes depending on ambient temperature. Quickly squirt out a column of bone cement up and down onto the sterile surface as a long worm. The mix will start to thicken quite quickly so express all the cement as soon as possible.
11. Once all the cement is out start cutting the worm into bead size portions using a sterile blade.
12. Before the cement fully hardens it can be moulded to a degree. Using a sterile dental scraper it is possible to create miniature 'polo' mints through which sutures may be passed if the bead requires stitching in place.
13. Once set the cement beads may be stored sterile in either sterile urine sample bottles or small blood sample bottles.
14. The shelf life of the beads is unknown but probably similar to the expiry date on the bone cement. Presumably shelf life is maximised by refrigeration.

****** Bone cement is not designed for use in the rabbit nor does it have a product licence for this species. Veterinary Instrumentation accepts no responsibility for any use of the product other than as orthopaedic bone cement. Veterinary surgeons using bone cement in the rabbit would be well advised to explain this to clients and have them sign a disclaimer******

The following article may be of interest to surgeons treating rabbit abscesses.

(text in bold in italics has been added by ourselves to reflect U.K. sources of PMMA)

MANAGEMENT OF ABSCESES OF THE HEAD IN RABBITS

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Abscesses in rabbits are often caused by *Pasteurella multocida*; however, a variety of other organisms including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus* sp, *Bacteroides* sp or a combination have been cultured. Abscesses are considered to occur as a result of bacteremia though often no source or predisposing cause is identified. Abscesses of the head may be secondary to dental disease, food packed between the tooth and gingiva, tooth fracture, tooth root abscess, or a foreign body. They occur in rabbits of all ages and frequently develop rapidly (in a matter of a few days). The abscess is usually nonpainful and the rabbit appears clinically unaffected. When teeth are involved the rabbit may become completely or partially anorectic. The abscess may be soft or firm but frequently they have a soft center. They are usually not moveable and when bone is involved there may be bony swelling as well. The wall of the abscess is very thick and usually contains bacteria. The pus is caseous, thick, and creamy white in appearance. Of all abscesses occurring in rabbits, retrobulbar and skull abscesses are considered to be the most difficult to treat.

The clinical work up includes a CBC, serum biochemistry panel, urinalysis, and chest radiographs especially in rabbits with chronic or recurrent abscesses. Skull radiographs under anesthesia are essential to evaluate the presence and extent of infection associated with tooth root abscess and osteomyelitis. With the rabbit under anesthesia a complete oral and dental exam are conducted. An aspirate is obtained using a large bore needle to confirm that the mass is an abscess and for evaluation cytologically and microbiologically. The pus is usually thick and a sample cannot be obtained through a fine gauge needle. The aspirate is submitted for culture and sensitivity, but a Gram's stain is also evaluated as many aspirates yield no bacterial growth and the Gram's stain may help direct preoperative antibiotic therapy. The rabbit is placed on antibiotic therapy prior to surgery based on the culture results or Gram's stain cytology.

A variety of surgical therapies have been used in treating abscesses of the head in rabbit with variable results. In general, the prognosis for complete recovery without recurrence is guarded to poor. Client education prior to surgery is vital. Often, multiple surgical procedures are required because of the tendency to recur. Depending on the procedure used, postoperative care may involve intense nursing care and wound management. Frequent visit to the veterinarian and often a significant financial commitment are required as well.

Regardless of the treatment method selected, it is important to remove any teeth that are involved either from tooth root infection or as a result of osteomyelitis. Long term antibiotic therapy is also essential. It is best to culture the tissue of the wall of the abscess intraoperatively. The bacteria within the pus are frequently dead but when the wall is cultured the chances of obtaining a positive culture are greater. Two weeks of antibiotics is usually inadequate because of the great potential for recurrence and many recommend low dose, life-long antibiotic therapy to prevent recurrence.

The traditional treatment of abscesses in mammals (lancing and draining) is not effective in rabbits. The pus is too thick to drain adequately and recurrence is common. When approaching abscesses of the head it is important not to drain the abscess into the oral cavity. A stoma or fistula into the oral cavity will result in poor and delayed wound healing.

Another technique used to treat rabbit abscesses involves lancing the abscess, curetting the wall, and leaving the defect open to heal by second intention along with wound irrigation. The wound is irrigated with an antiseptic solution such as dilute chlorhexidine or dilute povidone iodine. Irrigation is performed 2-3 times daily until a healthy bed of granulation tissue is present. Once the wound bed appears healthy, topical treatment with an antibiotic cream or ointment is continued until the wound is well epithelialized. Proteolytic enzymes (spray or ointment) such as trypsin may be used in the wound to help with wound debridement and removal of infected, devitalized tissues.

Recently, packing the abscess cavity with calcium hydroxide has been recommended. In one report of 14 cases, 10 resolved without recurrence. Once the pus is removed from the abscess and it is debrided, the cavity is filled with dental calcium hydroxide. This material has a pH of 12.0 which kills bacteria but is supposed to be nontoxic to tissue. The material is left in place for 1 week, removed, the wound evaluated, and new calcium hydroxide placed. This procedure is repeated until there is no evidence of infection. Then the wound is allowed to close by second intention. The author has used this technique but it has caused serious tissue damage and necrosis. It appears that the high pH is damaging to the tissues. When bone must be debrided, the defect may be filled with bioglass (Consil; Nutrimax Laboratories). This material also creates an environment in which bacteria cannot live and stimulates bone growth. It has shown promising results in treating abscesses of the head of rabbits with bone involvement.

Because of the high recurrence rate of these abscesses, it appears that excising the abscess en bloc as one would remove cancer is more likely to result in a cure without recurrence. The abscess mass is excised with wide margins attempting to remove the abscess without rupturing it. Most abscesses of the head involve bone or teeth making it very difficult to remove them without rupturing them. It is best to dissect the abscess out down to bone, quickly remove the abscess at the level of the bone, curette the bone and remove any teeth that are involved in the abscess, and irrigate copiously to decrease the effects of contamination from the ruptured abscess. It may not be possible to completely excise abscesses associated with osteomyelitis or tooth abscesses; however, it is vital to remove all abnormal tissues - soft and hard. After the abscess is excised, the wound is left open to heal by second intention. Wound irrigation is also a part of this therapy and must be performed 2-3 times daily.

In the author's experience, the best method for treating abscesses of the head of rabbits involves complete (or as nearly complete as possible) excision of the abscess and filling the defect with antibiotic impregnated polymethyl methacrylate (AIPMMA) beads. The abscess is removed as completely as possible and the defect is filled with AIPMMA beads which release relatively high concentration of antibiotic locally with little systemic absorption. The rabbit is still placed on systemic antibiotics for 2 weeks but long term therapy is not necessary as the beads release antibiotic for many months. The antibiotic chosen is based on culture and sensitivity results. Where there is no growth, a broad spectrum antibiotic with activity against *P. multocida* is selected. The beads are left in place a minimum of 2 months at which time they may be removed assuming there is no recurrence of abscessation. If the beads are not removed, they do not cause clinical problems as they are biologically inert. Indications for removal are the presence of a fistulous tract, poor cosmetic results, and interference with normal function. If they are placed within a mucosal lined cavity such as the nasal cavity, their presence will stimulate production of a serous exudate and removal is indicated. For purposes of removal, it is ideal to place the beads on an orthopedic wire when making them, forming a string of beads. In this manner when the beads are to be removed the surgeon need only locate one bead and the remainder can be removed by pulling the string. Unfortunately, when used in rabbit head abscesses, the beads are often too small to string on an orthopedic wire making bead removal more challenging.

Antibiotic Impregnated Polymethyl Methacrylate Beads AIPMMA has been used in human medicine since the early 1970's for the treatment and prevention of infection. Since that time it has been used for a variety of soft tissue and orthopedic problems. In veterinary medicine, it has most commonly been used for total hip arthroplasty to decrease the incidence of osteomyelitis associated with the procedure; however it has also been used to treat cellulitis in a bear, chronic sinusitis in cats, and open fractures and septic arthritis in horses. The author has also had positive results with it in treating septic arthritis and osteomyelitis in reptiles and birds. The rationale behind the use of AIPMMA is to provide high local concentration of antibiotic with low systemic absorption and, therefore, less toxicity. It is useful in infections where long-term use or the systemic use of the antibiotic of choice would be contraindicated. This is often the case with rabbit abscesses. It is useful in intractable patients where it is difficult to administer systemic antibiotic with the required frequency. And it is useful when an expensive antibiotic is indicated as repeated administration is not required. It is NOT indicated for treatment of systemic infections.

The ideal antibiotic for use in AIPMMA beads is one that is bacteriocidal, broad spectrum, effective in low concentration, heat stable (up to 100o C), and has high water solubility and low tissue toxicity. Gentamicin has been studied extensively and has been shown to elute concentrations above the break point susceptibility concentration for over 80 days with levels detectable for over 5 yrs. The average serum concentration (1 g gentamicin/20 g PMMA) was only 0.5 mcg/ml and the wound fluid concentration was 80 mcg/ml. These studies were conducted using powdered gentamicin which is not available in medical grade. Many use tobramycin at the same concentration as it is available in a powder. Recent research conducted by the author indicates there is no difference in elution between the powdered gentamicin and the liquid form used clinically. The formulation and amount of antibiotic can affect the strength of the PMMA but that is not of concern when making beads as they are not under stress.

Antibiotics commonly used where elution information is available include the following: gentamicin or tobramycin (1g/20g PMMA) and cephalothin or cefazolin (2g/20g PMMA). The author has recently conducted studies with amikacin and ceftiofur. It appears that amikacin (1.25g/20g PMMA) and ceftiofur (2g/20g PMMA) also elute at effective rates and concentrations. This data has not been fully analyzed at this point, however. In our work, there was no difference in elution between powdered and liquid gentamicin; however, there was a difference in the elution rate between liquid and powdered amikacin. The liquid form eluted slower than the powder.

The elution of the antibiotic is bimodal with a rapid release in the first few days followed by a slow, long term release of antibiotic over weeks to months. The beads become encapsulated with fibrous tissue within a few weeks and then only tissues within about 3 mm receive the high concentration of antibiotic. Because of this it is essential to remove the abscess as completely as possible before placing the beads. They should not be placed within the abscess capsule. The rate of elution is affected by various factors. The amount of fluid flowing past the beads influences the rate such that highly vascular areas elute the antibiotic more rapidly with more systemic absorption and more rapid depletion of the antibiotic within the beads. When placing beads in vascular tissues a higher concentration of antibiotic may be necessary than when placing beads in less vascular tissue such as bone. The head of rabbits tends to be made up of relatively well vascularized tissue, but the author has not increased the concentration of antibiotics. The diffusion properties of the antibiotic and its heat stability also affect elution rates. The exothermic polymerization reaction can denature antibiotics such as penicillins making them less effective. These drugs can be used but in higher concentrations. The previously mentioned antibiotics are heat stable. Enrofloxacin is not heat stable. Until elution studies have been conducted it is not recommended that new antibiotics be used clinically. Combining antibiotics also may change elution rates in unexpected ways and is not recommended.

Another factor influencing elution rates is the shape of the beads. These are not commercially available and must be made by the veterinarian. They may be made at the time of surgery aseptically and implanted immediately or made preoperative, sterilized with ethylene oxide, and stored for future use. The shelf life for these beads is unknown but assumed to be the normal expiration date of the antibiotic. Because the fumes are annoying and potentially damaging to contact lenses, many prefer to make the beads in a hood prior to surgery. The cement comes in 20 and 40 g packets (Surgical Simplex; Howmedica, Rutherford, NJ or Bone Cement; Zimmer, Patient Care Division, Charlotte, NC) which is enough to treat several rabbit abscess. **(VETERINARY INSTRUMENTATION is able to supply the following versions of PMMA. BC1G already contains appropriate levels of Gentamycin. BC1 is a bone cement containing no antibiotics. Both types come as 40g packs. By mixing half quantities or quarter quantities in appropriate ratios it is possible to make a range of different AIPMMA beads. ORDER CODES for combination of bone cement, catheter mount syringe and instructions: BCGKIT and BCKIT)** Any unused beads are gas sterilized and used in future patients. **(provided that the beads are made in sterile conditions and kept in sterile urine sample bottles, it is our view that further gas sterilization is not necessary. These beads are not going into sterile areas. Care should, however, be taken to avoid cross contamination.)** The antibiotic is mixed THOROUGHLY with the copolymer powder prior to adding the liquid monomer. With some antibiotics this takes several minutes. Once the polymerization begins, the cement hardens within 10

minutes. Refrigerating the reagents prior to use will extend this time. It can be challenging to make all the beads that quickly and the aid of an assistant is very helpful. Beads may be rolled into spheres and strung on a fine gauge wire. A sphere has the most surface area which increases elution. A rough surface also has more surface area. Unfortunately, the size of bead that can physically be made with the fingers is often too large for use in rabbit abscesses. As an alternative, the mixture is placed in a syringe (catheter tip for larger beads and regular tip for small beads) and squirted out onto a paper surface (such as a table drape intraoperative). A scalpel is then used to cut the tube of cement into small pieces. In this manner, a group of small cylinders will be created to function as beads. These beads will be too small to string on a wire. When placing the beads, count the number implanted and record it in the patient record.

Complications associated with the beads are few. Superinfections due to long term antibiotic use have not been reported. There are no reports of allergic reactions to the antibiotics eluted from the beads. There have been no reports of systemic toxicity from the antibiotics either. Elution, however, can vary and with potentially toxic antibiotics such as gentamicin and penicillin (in rabbits) care is taken to make sure that an excess dose is not delivered systemically by placing too many beads with a high concentration of antibiotic.

Suggested Reading

Tobias KMS, Schneider RK, Besser TE. Use of antimicrobial-impregnated polymethyl methacrylate. *JAVMA* 208(6):841-844, 1996.

Hillyer EV. Dermatologic diseases. In, Hillyer EV and Quesenberry KE. *Rabbits, Rodents, and Ferrets*. WB Saunders, Philadelphia, pp 212-214, 1997.