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# A new device for efficient preparation of standard antibiotic bead chains and customized antibiotic delivery

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Antibiotic-loaded polymethylmethacrylate (PMMA) beads are widely used in orthopedic practice for the prevention of infections after open fractures and in the management of osteomyelitis. The use of commercial beads is limited by insufficient flexibility, lack of provision for selection of specific antibiotic, and short drug-release time. Further, the manual procedure for the preparation of PMMA beads is slow, and the products are not uniform in size. Uniformity of the bead size is crucial because the placement of oversized beads place at sites with limited space (e.g., narrow medullary canal) is difficult, and their retrieval from such sites is painful to the patient. To overcome the limitations of commercial beads and manually prepared beads, we developed a simple device for the efficient preparation of antibiotic-loaded PMMA beads of uniform sizes. We describe the device, bead preparation, and the characteristics of the beads prepared using our device, and the preliminary clinical results. The beads obtained using this device were relatively small, had excellent flexibility, and were suitable for implantation in small spaces. The device permits the selection of the antibiotic to be loaded on to the beads. The results of preliminary studies of the beads prepared using our device have been positive, highlighting the need for more large-scale and longitudinal investigations.

## 1. Introduction

Postoperative infections occurring after the internal fixation of bone fractures are difficult to manage (Schmidt and Swiontkowski 2000). Although such infections can be treated to some extent by sustained irrigation–drainage, the process involves complex procedures, risk of treatment interruption (e.g., tube obstruction, fluid leakage at the wound), and the possibility of secondary infection. Therefore, there is a need for the development of effective strategies to control infection without impeding fracture healing.

Klemm (1974) reported a success rate of 91.4% in 129 chronic osteomyelitis patients managed with the temporary placement of gentamicin-loaded polymethylmethacrylate (PMMA) beads in the dead space formed after the debridement of infected bone tissue. The report of this high success rate prompted the development of antibiotic-loaded PMMA beads for commercial use (e.g., Septopal®; Merck, Darmstadt, Germany). Currently, these beads are being extensively used as effective tools in the prevention and treatment of bone and soft-tissue infections. Studies (Elson 1993) have shown that the local antibiotic concentration in bones achieved with the use of PMMA beads is greater than that safely achievable with the systemic administration of antibiotics. Moreover, the local concentration reached with antibiotic-loaded PMMA beads can be maintained at levels above the minimal inhibition concentration (MIC) for a prolonged period (Buchholz and Engelbrecht 1970). Clinical studies have shown that patients treated with PMMA beads have a significantly lower infection rate than those not receiving the treatment. Importantly, the incidence of adverse effects (e.g., immune response) in patients treated with PMMA beads has been reported to be significantly lower than that in patients treated with systemic antibiotics (Chohfi et al. 1998).

However, the PMMA beads currently available in the market also have some limitations. Firstly, they are expensive. Secondly, Septopal® chains of beads have a relatively small inter-bead distance, which compromises the flexibility of the chains and makes it difficult to implant the chains in small spaces, such as the narrow medullary canal. Thirdly, commercial Septopal® beads contain only gentamicin (Elson 1993) and are, therefore, unsuitable in cases of infection with gentamicin-resistant bacteria (Evans and Nelson 1993; Patzakis et al. 1993). More importantly, the *in vivo* release of gentamicin from Septopal® beads reaches a plateau within one day, which is a relatively short period in orthopedic surgery settings. Therefore, many surgeons prefer to manually prepare the antibiotic-loaded PMMA beads before or during the surgery. However, the manual preparation of PMMA beads has some drawbacks. First, since PMMA solidifies within 10–15 min, only small batches of beads can be prepared at a time. Second, manual preparation by the conventional methods does not ensure uniformity in bead size, which makes it difficult to implant the beads in narrow spaces and retrieve them if they are ill-fitting.

With a view to overcome these limitations, we developed a new device for the efficient preparation of antibiotic-loaded PMMA beads of uniform sizes. Compared to the use of commercial beads, the use of on-site preparation of PMMA beads with an appropriately designed molding device may ensure greater uni-

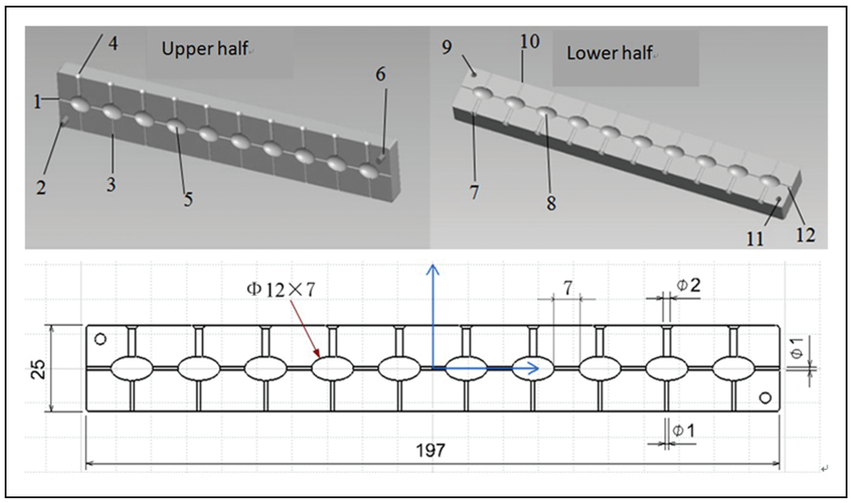


Fig. 1: Design of the bead preparation mold (2 and 6: locking pins; 3 and 10: venting channels to allow air flow and avoid bubble entrapment within the beads; 4 and 7: injection channels; 5 and 8: molding cavity; 9 and 11: locking aperture; 1 and 12: central channel for subsequent insertion of suture through the beads; dimensions labeled in lower panel, all numbers in millimeter).

formity in the size of the beads. In this report, we describe the device, the characteristics of the beads prepared using our device, and the preliminary clinical results obtained with their use at our hospital.

## 2. Investigations and results

Using the newly developed mold (Fig. 1), we prepared oval-shaped beads with uniform dimensions: long axis of 12 mm and short axis of 7 mm (10 beads in 12 min). The prepared beads were easily chained by inserting a Mersilk suture through the central aperture, with the inter-bead distance being 7 mm. This distance was maintained to allow for convenient placement of the bead chains in narrow spaces. Further, since this method involves the preparation of customized batches of beads according to the clinical requirements, the appropriate antibiotic can be selected in practice depending on the results of drug susceptibility tests for each individual patient.

Since July 2012, the chains have been used at our hospital in 20 cases for preventing postoperative infections after internal fixation of fractures. The outcomes in these cases have been positive. There are no ethical/legal conflicts involved in the article.

## 3. Discussion

This study was aimed at developing a strategy to overcome the disadvantages of commercially available and manually prepared PMMA bead chains, such as considerable inter-bead distance, reduced flexibility of chain, lack of provision for choice of antibiotics, and non-uniform bead size. Using the molding device developed by us, PMMA beads of uniform sizes were conveniently prepared before and during the operations. Unlike the case with commercial beads (Fig. 2E), the molded beads allow the clinician to adjust the inter-bead distance and select the antibiotic according to the requirements of each case. Further, compared with the manually prepared beads (Fig. 2F), the molded ones were smaller and more uniform in size, thereby facilitating their placement in smaller spaces and avoiding the subsequent difficulty in retrieval of the ones not fitting. Being smaller than the commercial Septopal® beads, the molded beads have a higher surface/volume ratio, which implies that a larger fraction of the drug is released. Additionally, our molds can be prepared in different sizes dimensions according to the requirement of the cases in order to generate beads of varying sizes within a short time.

The recognition of the disadvantages of the current methods used for the preparation of antibiotic-loaded PMMA beads has prompted studies on newer drug-release systems that can be used for the control of infections after orthopedic operations. Mendel et al. (2005) reported that collagen sponge was a more flexible alternative to PMMA beads in rats with osteomyelitis caused by *Staphylococcus aureus* and that the former was more effective than the latter in reducing the bacterial colony count in the bone. Similarly, Brin et al. (2008) studied the potential of injectable degradable polymer (poly-sebacic-co- ricinoleic-ester-anhydride) microspheres in the treatment of osteomyelitis. They found minimal or no intramedullary abscesses in rat tibiae treated by injection of microspheres containing gentamicin, but moderate abscesses in those treated by microspheres without gentamicin. Although these new polymer systems offer some advantages such as biodegradability (no need for retrieval), PMMA beads remain superior because they are inexpensive, do not produce acidic products (monomers) on degradation, and have already been approved for clinical use in many countries. Therefore, the improvement in the techniques for preparation of PMMA beads achieved by this study may have a direct positive impact on the control of postoperative infections.

In conclusion, we reported the development of a simple device for the efficient preparation of PMMA beads of uniform sizes with loading of specific antibiotics. The bead chains prepared using our device were flexible enough to allow for their implantation in small spaces. This device also allowed for the selection of the appropriate antibiotic based on the results of the antibiotic sensitivity tests. The results of preliminary outcome studies of the beads prepared using our device have been positive, highlighting the need for more large-scale and longitudinal investigations.

## 4. Experimental

The device is essentially a mold (Fig. 1) with two symmetrical components. Each component was formed by molding cavities, injection channels (diameter: 2 mm), venting channels, a central channel, and pins and openings for locking.

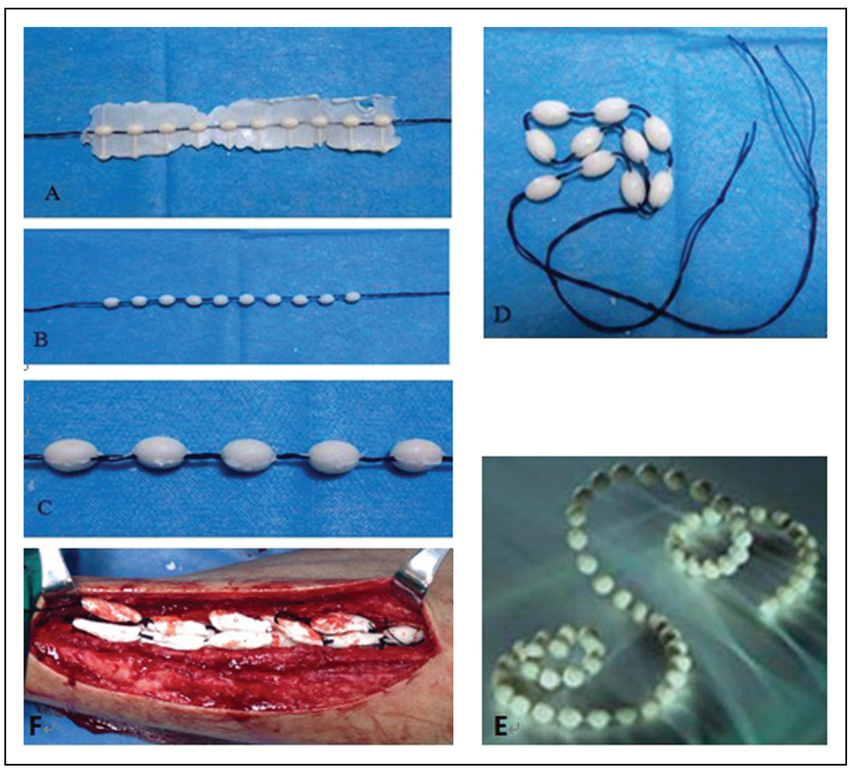


Fig. 2: Photographs of (A) PMMA beads prepared using our device and (B-D) chained beads. Photographs of (E) the commercial Septopal® chain (notice the small inter-bead distance) and (F) the manually prepared PMMA chain (notice the large and uniform bead size).

The beads were prepared with two different methods. In the first method, the two components were assembled, and a Mersilk suture (Ethicon, Somerville, NJ, USA) was inserted into the central channel. Then, PMMA bone cement powder (Depuy CMW, Blackpool, UK) was mixed with an appropriate amount of an antibiotic according to the severity of infection. Typically, up to 4 g of gentamicin was added to 40 g of the PMMA cement powder. In some cases, other antibiotics (e.g., vancomycin and meropenem) were used depending on the pathogens involved in the infection. The powder was mixed with the liquid component (i.e., methylmethacrylate monomer) following the manufacturer's instructions. Once the mixture was in the slurry stage, it was loaded onto a syringe and introduced into the mold *via* the injection channels. In the second method, the mixture was prepared as a dough and transferred into the cavities in both components of the mold by spreading into the cavities using a stainless steel spatula; a Mersilk suture was then fitted into the central channel, and the two components were assembled and the locking pins fastened. After the mold was prepared via either method, polymerization (end of temperature increase) was completed; the mold was opened and the PMMA product (Fig. 2A) was retrieved. After removing the excess material, beads of uniform sizes were obtained (Fig. 2 B-D).

Conflicts of interest: None declared

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