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Chronic osteomyelitis treatment with PerOssal®: a literature review



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ABSTRACT

Chronic osteomyelitis is an inflammatory process in the bone followed by bone destruction caused by microorganism infection. The annual incidence of osteomyelitis is approximately 21.8 cases per 100,000 person-years in the general population. Implanting antibiotic-loaded carriers directly at the site of infection becomes a promising treatment approach. PerOssal® is an osteoconductive synthetic bone substitute for restoring and filling bone defects. PerOssal® pellets contain 51.1% nanocrystalline hydroxyapatite and 48.5% calcium sulfate. It has a role as bone material

to fill bone defects caused by dead bone in chronic osteomyelitis. The porosity of PerOssal® allows a high initial antibiotic release, then decreases to ensure a local concentration of the antibiotic. PerOssal® did not show any *in vitro* cytotoxicity and fatal adverse event as bone material. PerOssal® is a promising antibiotic-loaded carrier for the management of chronic osteomyelitis. It demonstrates good biocompatibility with initial high antibiotic release without *in vitro* cytotoxicity and fatal adverse event.

Keywords: Antibiotic, Bone Graft, Carrier, Chronic Osteomyelitis, PerOssal®.

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INTRODUCTION

Chronic osteomyelitis still becomes a health burden, especially in developing countries, including Indonesia. Chronic osteomyelitis is an inflammatory process in the bone followed by bone destruction caused by microorganism infection.¹ The annual incidence of osteomyelitis is approximately 21.8 cases per 100,000 person-years in the general population. Up to 40% of cases are associated with *Staphylococcus aureus* infection.^{1,2} Chronic osteomyelitis is more common in men and the most common sites of infection are the femur, tibiofibular and hip joints.² Research at Hasan Sadikin Hospital showed that most osteomyelitis patients had experienced chronic onset (94.4%).³ Antimicrobial therapy and surgical debridement are the main modalities for managing chronic osteomyelitis.⁴ Local vasculature damages hinder achieving local concentrations with parenteral administration. Implanting antibiotic-loaded carriers directly at the site of infection becomes a promising approach. The advantage is attaining optimum

local antimicrobials without generating systemic toxicity.⁵

Calcium sulphate (CaSO₄) is a bone substitute that acts as an antibiotic carrier material or growth factor delivery.^{5,6} The first success of calcium sulphate as a bone substitute was reported in 1892 and has been used as an antibiotic carrier material since 1928. Although several studies have reported successful calcium sulfate, there are some disadvantages, such as rapid resorption, causing a cytotoxic effect that triggers redness and swelling of the wound. Usually, the loaded of antibiotics is carried out before the hardening and sterilization process; therefore, it may reduce the activity of the active substance. This process also makes a limited choice of antibiotics in treating bone infection.^{6,7} To overcome these disadvantages, a carrier material (PerOssal® s; Coripharm, Dieburg, Germany) was developed consisting of a combination of calcium sulfate and nanocrystalline hydroxyapatite (HA) (Osteotim; aap Biomaterials). The addition of nanocrystalline degradable hydroxyapatite can improve biocompatibility, as shown by several *in*

vitro and *in vivo* studies. PerOssal® can also be loaded with several specific antibiotics according to the local epidemiology.⁸

Based on those mentioned above, this literature study aims to determine further the PerOssal® as a treatment for chronic osteomyelitis.

CHRONIC OSTEOMYELITIS

Chronic osteomyelitis is a long-term infection of the bone caused by microbes such as bacteria, mycobacteria or fungi. The time threshold of chronic infection is undetermined, but the infection usually persists for months to years.^{9,10} A bacterial infection causes most chronic osteomyelitis. Gram-positive microorganisms were the most common type isolated from chronic osteomyelitis cases (approximately 60%), with the predominance of *Staphylococcus aureus*.⁹ Necrotic bone, new bone formation, and polymorphonuclear leukocyte exudate with other blood components were found in bone with chronic osteomyelitis pathologically. The viable fragments of the periosteum and endosteum at the site of

infection form new bone (involucrum), an encasing sheath of the living bone surrounding the dead bone beneath the periosteum.^{10,11}

Management of chronic osteomyelitis requires surgery and medication, including adequate drainage, extensive debridement of all necrotic tissue, obliteration of dead spaces, and adequate soft tissue coverage, followed by antibiotic therapy. Bone defects can be formed after debridement, which is called dead space. Treatment of this dead space aims to replace dead bone and scar tissue with viable vascularized tissue, generally with bone graft. Antibiotic-impregnated acrylic beads can be used to maintain and sterilize the dead space. Commonly used antibiotics in beads include vancomycin, tobramycin, and gentamicin.^{4,11,12}

The Overview of PerOssal[®]

PerOssal[®] (Coripharm, Dieburg, Germany) is an osteoconductive synthetic bone substitute for restoring and filling bone defects. PerOssal[®] pellets contain 51.1% nanocrystalline hydroxyapatite and 48.5% calcium sulfate. It may be implanted in infected or contaminated areas after thorough surgical debridement. PerOssal[®] has a unique porous structure that allows the safe uptake of aqueous solution (0.5 ml per 6 pellets and 4 ml per 50 pellets) and liquid substances (such as antibiotics).⁷ Unlike other antibiotic-loaded bone grafts where the antibiotic is impregnated directly into the antibiotic powder mixture, PerOssal[®] is a soaking bone graft in an antibiotic solution before implanting in a defect area.¹³

PerOssal[®] is an alternative to cancellous bone and can be used alone or combined with cancellous bone. The indication of using PerOssal[®] is to fill the bone void. It is also useful to promote cancellous bone growth and as an antibiotic carrier material in areas of infected bone. PerOssal[®] can only be integrated into the viable bone; therefore, careful debridement of the infected area must be carried out before implanting PerOssal[®]. The wound must be completely closed to avoid contamination after filling the defect with PerOssal[®].⁸

PerOssal[®] as Bone Graft

Bone grafting is a surgical procedure that aims to replace the missing bone

with natural or artificial substitute material.¹⁴ The graft is used as a skeleton to provide bone formation and support wound healing and a reservoir to aid in the formation of new bone. As the bone grows, it replaces the graft material completely and creates a new bone area. Different sources of bone graft and bone material are available, including autograft, allogenic bone, xenogeneic bone or bone substitute.^{6,14}

Autograft is a gold standard of bone grafting. Autograft transfers a number of tissues from the same individual without a vein, thus allowing continuous bleeding from one place to another. Autogenous bone graft has osteogenic, osteoinductive and osteoconductive capacities and avoids immunological rejection. Allograft is a transfer of tissue from another person or bone bank, which is a porous structure containing progenitor cells and endothelial cells as well as growth factors in the bone matrix that are released when resorbed by osteoclasts. Xenograft bone is obtained from the tissue of another species. Unfortunately, this technique has been abandoned because of the high immune response, poor biomechanical quality and foreign body reactions in the body.¹⁴

Bone substitutes can be classified into two main categories, bone substitutes derived from biological products and synthetic bone substitutes. The ideal bone substitutes should provide three attributes for bone healing: osteoconduction, osteoinduction and osteogenesis. Osteoconduction is to provide a biocompatible scaffold that acts as a framework for osteogenic cell adhesion and new blood vessel growth. Osteoinduction is a process that supports mitogenesis and undifferentiated mesenchymal cells lead to the formation of osteoprogenitor cells with the ability to form new bone. Osteogenesis occurs when the graft material contains cells capable of producing new bone.⁵

In orthopedic practice, calcium sulfate and nanocrystalline hydroxyapatite (HA) are common bone substitutes. Calcium sulfate is an inorganic mixture having the formula CaSO₄. Calcium sulfate has a compressive strength equivalent to the cancellous bone but is brittle and loses strength rapidly due to hydrolysis.

Dissolution occurs rapidly around 6-12 weeks in bone.⁵ This resorption creates porosity while stimulating bone ingrowth and its resorption is faster than the rate of new bone deposition.⁶ A prospective study has shown pure calcium sulfate as a bone graft substitute for treating osseous bone defects, resorption, and new bone incorporation in 13 of the 15 samples studied.¹⁵

Hydroxyapatite (HA) has a chemical component [Ca₁₀(PO₄)₆(OH)₂]. It is also a ceramic with good biocompatibility properties because its mineral content is similar to human bones and teeth chemically and physically. Synthetic hydroxyapatite shows good affinity; it can chemically bond to the surrounding bone or hard tissue by forming an HA interfacial layer.¹⁶⁻¹⁸ The porosity of HA is very good as a bone graft because it improves osteoconductivity, the process of osteoblast cell colonization is faster, facilitates the penetration of osteoblast cells and becomes a medium for osteoblast cells to be attached. The porosity of HA is very important in linking the bond between the material and bone.¹⁶ PerOssal[®] is fully absorbed in the implantation site and surrounding bone, typically within 6 months, depending on defect size.⁸

PerOssal[®] as Antibiotic Carrier

Calcium sulfate, the constituent component of PerOssal[®], has been widely used to deliver local antibiotics because of its structural properties and ease of reabsorbing.¹³ Antibiotic uptake on PerOssal[®] was quite good, where the uptake for gentamicin was 2916 g/pellet on PerOssal[®] compared to 2198 g/pellet on pure calcium sulfate after loading 50 pellets each into 4 ml of 40 mg/ml gentamicin. For vancomycin, PerOssal[®] had an uptake of 3648 g/pellet and pure calcium sulfate of 2661 g/pellet after loading 50 pellets into 4 ml of vancomycin 50 mg/ml.⁷

PerOssal[®] can provide long-term protection of up to 10 days to protect bone replacement material against colonization with sensitive bacterial pathogens. The antibiotic release within 10 days from a single PerOssal[®] pellet was 2764 mg (94.7%), initially loaded with 2,916 mg of gentamicin and 3,513 mg (96.3%) often initially loaded 3,648 mg of vancomycin.⁷

The porosity of PerOssal[®] allows a high initial antibiotic release then decreases to ensure a local concentration of the antibiotic above the minimal inhibitory concentration (MIC) of bacteria (e.g., *S. aureus*) in the first 28 days in the rabbit model. The antibiotic concentration will last longer in the *in vivo* compared to *in vitro* model.⁸

PerOssal[®] as an antibiotic-loaded carrier, has advantages in the manufacturing process compared to previous carriers. Calcium sulphate pre-loaded with Tobramycin (OsteoSet-T[®]), the previous antibiotic-loaded carrier, loaded the antibiotic into the pellet before hardening the calcium sulphate, thus affecting the antibiotic activity after the hardening and sterilization process. On the other hand, the hardened PerOssal[®] pellets were sterilized by gamma-irradiation before being immersed in antibiotics, thus preventing the potential inactivation of antibiotics due to the sterilization and hardening process.^{7,8}

Efficacy of PerOssal[®] in Chronic Osteomyelitis

Several studies have carried out the use of PerOssal[®] as a bone substitute for bone defects and osteomyelitis therapy. Most studies show promising results. A study regarding the use of PerOssal[®] in 19 patients with spondylitis showed that bone formation was most rapidly detected after 6 weeks in one patient and the rest after 3 months. No signs of ongoing infection from blood examination and no bone loss in the vertebrae were visible on radiological examination. This study used PerOssal[®] while carrying gentamicin and vancomycin showed that after a follow-up of at least 1 year showed normalization of infection parameters, there was no bone loss in the affected region and bone fusion occurred 3-6 months postoperatively. There is no repair surgery associated with the use of PerOssal[®].⁸

A retrospective study assessed 52 cases of chronic osteomyelitis with curettage and PerOssal[®] showed a cure rate of 86.5%, significantly higher than the group treated with OsteoSet-T[®] and polymethyl methacrylate (PMMA), showing a cure rate of 50% and the group receiving curettage only had 80% cure rate. Antibiotics were

given in the form of vancomycin in all cases, gentamicin or imipenem was also shown in several cases.¹⁹

The nanocrystalline HA in combination with calcium sulfate showed higher porosity and water absorption than pure calcium sulfate, leading to higher antibiotic uptake and faster release of gentamicin and vancomycin in the first days after implantation. This antibiotic delivery system achieves local antibiotic concentrations for vancomycin and gentamicin well above the minimal inhibitory concentrations (MIC) for susceptible bacteria such as *Staphylococcus aureus* with an MIC90 value of 1 mg/ml for vancomycin and gentamicin. Released gentamicin and vancomycin concentrations exceeded 100-fold MIC90 of *Staphylococcus aureus* in the first 24 hours and 10-fold MIC90 for 3 and 4 days.⁷

Adverse Events of PerOssal[®]

Previous studies have reported foreign body-related adverse reactions to calcium sulfate alone and associated with longer secretion from wounds.^{8,19} The addition of nanocrystalline HA will increase the biocompatibility of the composite compared to pure calcium sulfate, reducing the risk of body rejection.⁸ The recurrence rate observed after the first operation in cases of chronic osteomyelitis treated with PerOssal[®] was 19.6%. The mean time to recurrence in the group receiving PerOssal[®] therapy was 314 days and the group receiving the other Bone Void Filler (BVF) system was 208 days. This difference is statistically significant.¹⁹

In vitro cell, cytotoxic test after administration of PerOssal[®] was also carried out quantitatively by looking at the number of viable cells, lactate dehydrogenase release and total protein content and qualitatively by assessing the ingrowth of human osteoblasts. The results showed no quantitative or qualitative differences between PerOssal[®] and the non-toxic control group. The results of quantitative toxicity tests on fibroblasts mouse also showed better results in PerOssal[®] compared to pure calcium sulphate. Qualitative assessment of osteoblast ingrowth also showed better biocompatibility for PerOssal[®].⁷

Advantages and Disadvantages of PerOssal[®]

PerOssal[®] has advantages and disadvantages as chronic osteomyelitis treatment compared with antibiotic bone cement. Polymethylmethacrylate (PMMA) is bone cement approved by US Food and Drug Administration (FDA) and is a gold standard of antibiotic delivery in treating infection in the orthopedic field. PMMA poses several disadvantages in the treatment of osteomyelitis. It needs a second surgical procedure for bead removal, has a probability of antibiotic resistance due to prolonged release of antibiotics at the subtherapeutic level, risk of systemic toxicity to absorbed monomer, and does not participate in the bone healing process.²⁰

Meanwhile, PerOssal[®] does not need a second surgical because it will be fully absorbed in the implantation site within six months.⁸ The risk of antibiotic resistance in implanted PerOssal[®] is lower due to the release of antibiotics in higher local concentrations than MIC of bacteria for a shorter duration.^{7,8} Nanocrystalline HA in PerOssal[®] produces biocompatibility of the composite material and reduces the risk of body rejection.⁸ Osteomyelitis treated with PerOssal[®] showed higher bone healing (86.5%) than cement (50%). It also can be loaded with a large choice of antibiotics intra-operatively.¹⁹ The lack of high-quality studies with randomized controlled trial (RCT) data is a limitation of PerOssal[®] for osteomyelitis. It questioned the mechanism of action and safety of PerOssal[®] in a larger population.²¹ Finally, there is no available data on the quality and quantity of new bone formation from defects treated with PerOssal[®].

CONCLUSION

PerOssal[®] is a promising antibiotic-loaded carrier for the management of chronic osteomyelitis. Calcium sulfate nanoparticulate HA composite material showed better biocompatibility with a high initial antibiotic release with subsequent decline, ensuring local concentration above MIC. PerOssal[®] did not show any *in vitro* cytotoxicity and fatal adverse event as a bone material, so that it can be a new treatment option in osteomyelitis.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this review. The authors also performed an objective and blind review of the selected journals in this review.

ETHICS CONSIDERATION

This literature study has followed the COPE and ICMJE protocol regarding publication ethics.

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AUTHOR CONTRIBUTION

All authors equally contribute to the study from the conceptual framework, data acquisition, and data analysis, until reporting the study results through publication.

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