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Polymers as Carriers of Gentamicin in Traumatology and Orthopedic Surgery – Current State Of Knowledge

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Osteomyelitis in patients undergoing surgery because of injuries and diseases of the musculoskeletal system is a serious clinical, economic and social problem. It is one of the greatest therapeutic challenges in traumatology and orthopedic surgery. To achieve the best results in the treatment of osteomyelitis, surgical debridement and intravenous antibiotic therapy is supported by local antibiotic delivery. Many different substances can be used as drug carriers. In this study we present and compare some polymers used as carriers of gentamicin. Some of them, such as poly(methyl methacrylate), are well known and have been used for 30 years, and others, such as polycaprolactone, polyacrylic acid, polyanhydrides, poly-trimethylene carbonate, polylactide, polyglycolide and poly(trimethylene carbonate), are perspectives for the future. In this study, we have tried to briefly present all of these polymers and compare some of their features. We have concentrated on the pharmacokinetics and bioactivity of such implants, which are important aspects for their potential practical use (**Polim. Med. 2016, 46, 1, 101–104**).

Key words: polymers, gentamicin, osteomyelitis, drug carriers.

Bacterial infections are a serious problem in musculoskeletal system surgery [1–3]. The complication rate is significantly higher in patients undergoing surgery because of acute injuries than in scheduled surgery [4]. In traumatology, the highest rate of infection is in patients with open fractures [5], and in orthopedic surgery in patients with implants such as an endoprosthesis [6]. In both cases, the problem is due to the antibiotic's poor penetration into the operation site [7–10]. The kind of bacterial strains that we deal with also play a significant role in osteomyelitis. Very often these are strains resistant to the most commonly available antibiotics such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacter*, *Pseudomonas* or *Streptococcus ssp.* [11]. Treatment of osteomyelitis depends on its clinical grade, which is estimated with the use of certain classifications, such as those created by Cierny and Mader or by Lew and Waldvogel [12–14]. Surgical debridement and blood supply restoration associated with general and local antibiotic therapy seem to be the best course in the treatment of osteomyelitis [15–17]. A lot of substances are used as drug carriers in local antibiotic ther-

apy, but not all antibiotics may be used to create such medicines. The main problem is the antibiotic's activity after combination with such carriers [18]. Gentamicin is one of the most commonly used antibiotics in local treatment because of its thermal stability and resistance to the sterilization process. In clinical practice, an implant made of poly(methyl methacrylate) (PMMA) and gentamicin has been in use for over 30 years [19, 20]. It is well known in Europe as a commercial product such as SeptopalTM [21] (Fig. 1). PMMA is a biocompatible but not bioabsorbable biomaterial. The positive results obtained in osteomyelitis treatment using PMMA beads with gentamicin application have inspired studies on new kinds of polymeric drug carriers such as polycaprolactone (PCL) [23], polyacrylic acid [24], polyanhydrides [25], poly-trimethylene carbonate [26], polylactide (PLA) [27], polyglycolide (PGA) [28] and poly(trimethylene carbonate) (PTMC) [26]. Their main common feature in contrast to PMMA is their biodegradation. PMMA beads need to be removed during a secondary surgery [22], which is their main disadvantage. PMMA, as a non-absorbable polymer, can also be

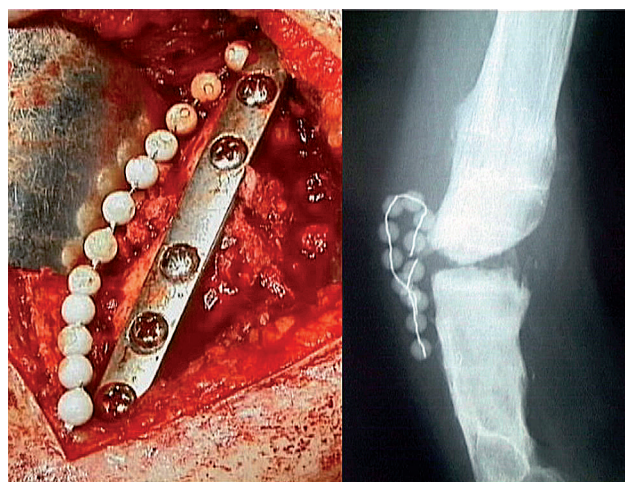


Fig. 1. Clinical examples of PMMA bead usage in osteomyelitis treatment in own material

Conclusions

The aim of this study was to present the polymeric materials used as a gentamicin carriers for local treatment in osteomyelitis. We also wanted to compare some of their pharmacokinetic features and bioactivity, which are important for potential clinical use. One problem was that we do not have enough data available in a few cases because a lot of the published studies have an introductory character and a lot of others have only been done on *in vitro* models. There is no possibility of a proper comparison in the case of data achieved on *in vivo* and *in vitro* models. Some side effects, such as the increased fibrotic tissue creation or decreased bone regeneration described in PGA, PLA and PCL use or the risk of secondary biofilm creation on PMMA beads, are generally known and proven in multiple stud-

Table 1. Comparison of pharmacokinetic features and bioactivity of polymeric implants with gentamicin

Name of substance	Biodegradation ability	Time of biodegradation (in months) or necessity of removal	Time of gentamicin release (in weeks)	Amount of gentamicin released	Side effects
PMMA (poly(methyl methacrylate))	no	needs to be removed	up to 16 [29]	20–70%	secondary bacterial biofilm creation
PCL (polycaprolactone)	yes	up to 30 [30]	up to 2	up to 80% [31]	uncontrolled growth of fibrotic tissue
Polyacrylic acid	yes	no <i>in vivo</i> tests available	no information	up to 100%	no serious side effects
Polyanhydrides	yes	up to a few (depending on the type and ratio of the monomers)	up to 4	up to 100%	no side effects
PLA (polylactide)	yes	72–84 [32]	up to 1.5	up to 100%	acidic degradation products and a subsequent decrease in local pH are the cause of decreased bone regeneration [33]
PGA (polyglycolide)	yes	12 [34]	up to 1.5	up to 100%	acidic degradation products and a subsequent decrease in local pH are the cause of decreased bone regeneration [33]
PTMC (poly-trimethylene carbonate)	yes	2	up to 2	up to 60% [26]	no side effects

a localization for secondary bacterial biofilm creation after gentamicin release. Although the new, bioabsorbable materials seem to be better than PMMA because of the lack of necessity to remove them after their implantation, they have some serious disadvantages in comparison to PMMA beads.

In the Table 1 above, some of the main features of these polymers are presented.

We found a lot of data about the rest of the polymers, i.e. PTMC, polyacrylic or polyanhydrides, but we don't know much about the potential side effects after implantation of such products as gentamicin carriers in a human body. All these polymers were described only as a potential carriers of gentamicin and, in many studies, a comparison with non-absorbable PMMA beads only had an experimental character. In the current state of knowledge, we can say that PMMA beads with genta-

micin are the only polymer carrier which is widely used in clinical practice and has a well-documented antibacterial effect. The potential use of absorbable polymers as a gentamicin carrier in the treatment of osteomyelitis

necessitates many specific tests including *in vivo* experiments on animal models. At present, they are one of the potential prospects in local antibiotic therapy development in the future.

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