New Concept For The Treatment Of Implant-related Infections Via Magnetizable Implant Materials Combined With Antibiotic Linkable Magnetic Nanoparticles

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Introduction: Regarding the broad field of implant-related infections in fracture fixation and arthroplasty a potent treatment is required which avoids development of antibiotic resistances. Therapeutics should be applied at the moment when infection occurs in contrast to prophylactically administered antibiotics via e.g. general postoperative treatment or coated implants. Several studies are investigating the potential of targeting drugs to a certain area of the body via the combination of magnetic nanoparticles and external magnetic field. The advantage is a higher concentration of medication at the desired region while decreasing the level in the rest of the body. The main problem which arises is the decrease of magnetic field strength in the depth of the tissue. Therefore several attempts were made to increase the magnetic effect using magnetizable devices like wires, stents and seeds. Our group is studying this approach from an orthopedic perspective as orthopedic implants with magnetic properties would enable a sufficient magnetic field at the bone or joint to increase the accumulation of magnetic nanoparticles (Fig. 1). Thus our hypothesis was that a martensitic steel platelet would increase the amount of accumulated magnetic nanoparticles within an in vitro experimental setup mimicking the in vivo situation within the body and may therefore introduce the idea for a new kind of implant material which could improve the management of postoperative infections.

Methods: Accumulation of magnetic nanoporous silica nanoparticles was investigated in an in vitro flow system (Fig.2). An infusion pump passed 5ml of a solution containing nanoparticles via a PVC tube through a custom designed chamber with a flow velocity \(v_{\text{flow}} = 25.44 \text{ml/h}\) corresponding to the natural blood flow velocity in human capillaries. The flow chamber served as mounting system for neodymium magnets as external magnetic field generator and martensitic steel platelets (Mat.No. 1.4122) as internal magnetic field intensifier. Magnetic flux density \(B\) was measured continuously via a teslameter. The nanoparticle concentration of the solution which was retrieved after passing the magnetic field (collected sample) and of the solution remaining in the tube between the magnets (tube sample) were colorimetrically quantified and computed. Ratios \(r\) were calculated between concentration of collected sample (ccs) and tube sample (cts). To examine the mode of action in a flow system like the organism in vivo blood flow was simulated in a set of transfer experiments by flushing the tube system with distilled water after nanoparticle accumulation corresponding to the basic experiments. Three different setups were examined. In a first trial (“only magnets”), only magnets were mounted for accumulation and then removed when flushing the system. In a second trial (“magnets and platelet”), both magnets and platelet were mounted for accumulation and removed from the flow chamber when flushing was performed. In a third trial (“platelet stays during flushing”), magnets and platelet were mounted for accumulation by subsequent removal of magnets during flushing. The ratio of transfer experiments included two collected samples, ccs1 after accumulation and ccs2 after flushing passage \(r_{\text{transfer}} = (\text{ccs1+ccs2})/\text{cts}\). Each experiment was repeated eight times. Results are given as mean ± standard deviation and tested for normal distribution. Either student’s t-tests or univariate ANOVA (significance level \(p = 0.05\)) were performed. In case of significant ANOVA, multiple comparisons were made via post-hoc tests (tukey and games-howell, respectively).

![Figure 1: Conceptual drawing of the system](image1.png)

Figure 1: Idea of magnetic drug targeting in orthopedics.

![Figure 2: Experimental set up.](image2.png)

Figure 2: Experimental set up.

![Figure 3: Accumulation of MNPs at the martensitic steel platelet.](image3.png)

Figure 3: Accumulation of magnetic nanoparticles in PVC tube.

![Figure 4: Magnetic flux density B and ratios of transfer experiments.](image4.png)

Figure 4: Magnetic flux density B and ratios of transfer experiments.

Results: The martensitic steel platelet (thickness 3mm) significantly increased the magnetic flux density (0.55T to 0.62T) and therewith the accumulation of nanoporous silica nanoparticles (Fig.3; \(r_{\text{basic}}\) decreases from 0.134 ± 0.027 to 0.11 ± 0.05, ANOVA...
Being placed between the magnets, the platelet was magnetized to saturation. After removing the magnets, a remaining magnetic flux density of 0.0012 T was measured. The magnetized platelet without mounted magnets was able to retain significantly higher amounts of nanoparticles ($r_{\text{basic}} 0.551 \pm 0.074$) in comparison to the setup without any devices mounted ($r_{\text{basic}} 0.736 \pm 0.049$, $p<0.05$; influence of tube only). During the three transfer experiments (Fig.4), the lowest concentration of MNPs was reached after accumulation with the magnets only and flushing without a magnetic field. After additionally mounting the platelet during the accumulation passage, higher amounts of MNPs could be retained during the flushing passage even with no magnetic field present. A further increase in retention capacity was seen when the martensitic platelet remains adjacent to the flow system during the flushing cycle. Nevertheless, differences were not statistically significant.

In general, higher amounts of nanoparticles were accumulated with higher quantity of magnets, lower distance between magnets, and lower $v_{\text{flow}}$ ($r_{\text{basic 200ml/h}} 0.43 \pm 0.06$; $r_{\text{basic 50,88ml/h}} 0.14 \pm 0.02$; $r_{\text{basic 12,72ml/h}} 0.08 \pm 0.01$, $p<0.05$). Thicker platelets reached higher concentration of accumulated nanoparticles albeit not statistically significant.

**Discussion:** The main difference between first and second trial of transfer experiments was the presence of the martensitic steel platelet during the accumulation passage. For both trials no magnetic field was present during flushing. Transferred to clinical use this would mean, that no permanent implant is located in the organism after the patient leaves the magnetic field. The values showed that the temporary presence of the platelet accumulates higher amounts of MNPs. The third trial evaluated the in vivo situation of an implanted osteosynthesis system which remains within the organism. Therefore, the martensitic platelet was left inside the flow chamber during flushing after removing the magnets. It was shown that a permanently present magnetizable implant is able to retain higher amounts of MNPs adjacent to it.

In conclusion the experimental setup demonstrated that the martensitic steel platelet increased the accumulation of magnetic nanoparticles and introduced the idea of magnetic drug targeting as a new treatment concept of implant-related infections. This approach seems to be a promising alternative to prophylactically administered antibiotics. It further provides numerous opportunities for the development of new implant materials as e.g. ferromagnetic materials with significant magnetic remanence would possibly enhance the effect shown here. Applications as plates, intramedullary nails or artificial joints are conceivable.

**Significance:** The present study showed that the application of magnetizable implants could improve treatment success of implant-related infection by enabling accumulation of antibiotic linked magnetic nanoparticles in the depth of the tissue.

**Acknowledgments:**

**References:**

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