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THE USE OF MAGNETIC NANOPARTICLES IN POSTOPERATIVE ANTIBIOTHERAPY

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Abstract. Despite the sterilisation of instruments used in operations, the development of infections after surgical interventions is the leading complication encountered in surgery today. As a result of postoperative complications and the many side-effects of the drugs used for the treatment of these, alternative treatment methods have been developed and trialled. With the development of various nanoparticles, as products of nanotechnology, studies on drug administration methods and their effects have shown a great development in this field. These are used to a great extent in pharmacology and the medical industry, in areas such as disease diagnosis, tissue engineering, and controlled drug release systems. Controlled drug release is the release of an active agent at a predetermined rate within a specific time. One of the most common methods used in controlled drug release is magnetic controlled systems, which provide control beyond the localisation of the drug. Together with the developments in drug technology, these systems, known as smart drug systems, which provide localisation of the drug in the infection region, have attracted great interest recently. As a result of the research into the methods of drug delivery and associated effects, magnetic nanoparticles are considered an alternative method in various treatments.

Keywords: *Antibiotherapy, magnetic nanoparticles, nanotechnology, operation.*

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1. Introduction

Infections formed in the organs and tissues in an operation wound or surgical entry site within the first 30 days postoperatively are known as "surgical site infections". Infections encountered after surgical interventions, despite the application of asepsis and antisepsis before, during, and after the operation, and the sterilisation of surgical instruments, are the leading complication seen in current surgery (Uzunköy, 2005). According to clinical research in hospitals, this type of surgical site infection is the second most common cause (15%-18%) of all nosocomial infections, and the most encountered infection when only surgical patients are evaluated (Lizan-Garcia *et al.*, 1997; Ok, 2007).

Especially in recent years, the formation of resistance in micro-organisms as a result of irrational antibiotic use, the presence of elderly and immunosuppressed patients, and the more common use of biomaterials in operations, has caused an increase in surgical site infections. According to the data of the National Nosocomial Infections Surveillance System (NNIS), the microorganisms causing the most surgical site infections are coagulase positive and negative staphylococci, which are normally present in the skin microflora (Mangram *et al.*, 1999; Nathens & Dellinger, 2000;

Uzunköy, 2005). Microorganisms found in the skin are usually the cause of operation wound infections. Therefore, the presence of an infection which encompasses the incision region in the skin, and especially not following the disinfection rules for the operation site when preparing the patient for the operation, increase the risk of surgical site infection (Uzunköy, 2005).

It is known that in addition to the negative effects on wound healing, secondary infections developing in the operation region can cause a general infection status through microorganisms entering the systemic circulation. When reasons such as these are considered, secondary infections in the operation region are significant complications requiring treatment. In cases such as these, treatment is applied with systemic and local broad spectrum antibiotics. The disadvantage of local application is that the drug administered is absorbed by surrounding tissues and expelled from the body within a short time. In such situations, antibiotics are required again. In systemic treatments, side-effects such as kidney and liver toxicity are frequently encountered problems (Grace & Pandian, 2007).

Alternative treatment methods have been developed and trialled by many researchers because of these treatment complications and the many side-effects of the drugs used. Together with the developments in drug technology, systems known as smart drug systems, which provide localisation of the drug in the infection region, have attracted great interest recently. With the development of various nanoparticles, as products of nanotechnology, studies on drug delivery methods and their effects have shown a great development in this field (Grace & Pandian, 2007).

Nanoparticles are known as solid bodies typically smaller than 100nm in size in all three dimensions. In these length scales, the positioning of a large part of the particle atoms on the surface or close to the surface provides the specific properties of nanoparticles. With a decrease in nanoscale particle size, quantum effects become apparent (Bayrak, 2012).

Science and engineering at the nano scale provides unique understanding and control at the atomic and molecular level. Nanoparticles have attracted particular attention because of their extraordinary electronic, optic and magnetic properties (Mahmoudi *et al.,* 2011). These are used to a great extent in pharmacology and the medical industry, in areas such as disease diagnosis, controlled drug administration, as biosensors, and in tissue engineering (Chomoucka *et al.,* 2010). The size and surfaces of nanoparticles make them ideal candidates for nanotechnology engineering and functional nanostructures. These types of modifications of nanoparticles facilitate their use as contrast agents for targeted drug delivery in biomedical applications, such as magnetic resonance imaging (MRI) and tumor therapy (Mahmoudi *et al.,* 2011).

The general systemic distribution of therapeutic drugs, the lack of drug specificity to the region where the lesion is located, the need to use a high dose to reach the desired local concentration, non-specific toxicity, and other side-effects of the agent used are the main problems associated with systemic drug administration. To resolve these problems, it has been attempted to target the nanoparticles to the related region or lesion. If these types of agents can be directed to a restricted area for therapeutic purposes, it may be possible to keep strong drugs continuously in a specified region (Mahmoudi *et al.,* 2011).

Controlled drug release systems are modified release systems. Controlled release is the release of an active agent at a predetermined rate within a specified time. Release

of the active agent continues for a longer period compared to conventional dosage forms. The active agent is released at a controlled rate from a reserve (Lin *et al*., 2008).

One of the most common methods used in controlled drug release is magnetic controlled systems, which allow the possibility of control of the drug outside the localisation (Bayrak, 2012).

Magnetic nanoparticles designed with a surface which is used with the help of an external magnetic field are defined as a modern technology used to introduce particles to the desired area of drug delivery. Such a system allows the administration of the required drug dose and has the potential to minimise side-effects (Bayrak, 2012).

Nanoparticles have become extremely attractive because of several advantages such as the use in transport and/or targeting of drugs because of the properties such as the ability to release and control drug release systems, that both hydrophobic and hydrophilic drugs can be combined appropriate to combination therapy allowing two or more drugs to be transported together, and increasing the biobenefits of drugs (Uyanıkgil & Salmanoğlu, 2020). The main outcomes of studies related to magnetic nanoparticles can be grouped under three main headings of the synthesis of new magnetic nanoparticles, the synthesis of appropriately sized particles, and preventing the agglomeration that forms during synthesis (Bayrak, 2012).

The targeting of drug release systems can be passive or active. In passive targeting, no ligand is used as the target mediator and targeting is achieved with the inclusion of the therapeutic agent in a macromolecule or nanoparticle which passively reaches the target organ. These complexes in passive targeting accumulate and diffuse in regions such as a tumour or purulent tissue. In active targeting, using a ligand, the therapeutic agent or carrier system is conjugated to the tissue or cell-specific receptors which are over-expressed in tissue (Uyanıkgil & Salmanoğlu, 2020)

The purposes of nano-scale drug carrier systems are to increase the drug concentration in targeted regions, reduce systemic levels of the drug and toxic effects in healthy tissue, increase solubility to facilitate parenteral drug delivery, reduce degradation, and increase the effects and stability of the drug (Uyanıkgil & Salmanoğlu, 2020).

The importance of targeted drug delivery and treatment with target drugs is to transport the drug under various conditions directly to the centre of the disease and thus knowingly provide treatment without adverse effects on the body. Treatment is provided by the structure of these particles which are formed of an amagnetic nucleus, a recognition layer and a section loaded with the therapeutic agent. However, the development of approprate recognition layers is a difficult stage in the synthesis of magnetic nanoparticles (Chomoucka *et al.*, 2010). Nevertheless, drug delivery systems based on the use of nano and microparticles have significant advantages such as the ability to target certain locations in the body, the reduction of the amount of drug needed to reach a certain concentration around the target, and the minimising of serious side-effects of the concentration of the drug in regions outside the target (Chomoucka *et al.*, 2010; Mahmoudi *et al.*, 2011).

The greatest problem encountered in the use of nanoparticles is maintaining the particles at a certain concentration in the target tissue. As magnetic nanoparticles can be held at the desired concentration in the target tissue, by being localised to a specific region of the body they can be held in this region until treatment is completed, and can then be removed from the region at the end of treatment (Berry & Curtis, 2003).

Magnetic nanoparticles are formed of nuclei that can be targeted to the desired area by externally applied magnetism. These are I) a magnetic particle coated with biocompatible polymer, or II) a double structured configuration of biocompatible polymer dissolved within the pores of magnetic nanoparticles. The coating protects the magnetic nanoparticle from the surrounding environment and it can be made functional to increase targeteddelivery by combining carboxyl groups, biotin, avidin, carbodiimide and other molecules. These molecules then function as connection points for the binding of cytotoxic drugs or for the target antibodies to bind to the carrier complex (Mahmoudi *et al.*, 2011).

From a physical perspective, magnetic targeting is obtained with a magnetic field gradient from magnetic force applied to the nanoparticles. The area of therapy efficacy depends on various physical parameters such as strength, gradient and the volumetric and magnetic properties of the particles. The process of drug localisation using magnetic nanoparticles is based on the competing forces of the force applied to the particles by blood vessels and the magnetic force produced from the magnetic field applied. In most cases, the magnetic field gradient is produced by strong permanent magnetism such as Nd^{---}, Fe^{---}, B fixed outside the body over the target area. Drug/carrier complexes are generally in the form of a biocompatible ferrofluid injected to the patient with a circulation system mediator. When magnetic forces exceed the rate of direct blood flow in arteries or capillaries, magnetic particles are held in high-gradient magnetic areas outside the target region. When the drug is directed to the target with carrier magnetic particles, it may remain free through changes in physiological conditions such as pH, osmolarity or heat, or enzymatic activity of the area where increased concentration is desired, and may be absorbed by endothelial cells of the target tissue. Theoretically, this system has great advantages compared to normal untargeted cytotoxic drug treatment methods (Mahmoudi *et al.*, 2011). In addition, when drugs modified with synthesised magnetic nanoparticles are administered through systemic, oral, pulmonary, transdermal or other routes, it has been found to be useful in respect of the drug reaching the target, increasing the bio-benefit capacity, and protecting stability (Grace & Pandian, 2007). As an alternative in several cases, if the treatment demands it, the particle suspension can be injected to the area in general. Discussions are still ongoing in respect of which of these routes is better (Berry & Curtis, 2003; Hajipour *et al.*, 2012).

Magnetic nanoparticles designed for biomedical applications have generally been made functional, as biocompatible ferrite powders coated with an organic molecular shell containing active pharmaceutical agents on its surface. Physiologically, magnetic nanoparticles are well tolerated. For example, the toxicity of dextran-magnetite cannot be measured according to the LD50 index. Iron oxides such as magnetic Fe_3O_4 are extremely resistant to oxidation, and are preferred in various applications as they have no toxic properties (Berry & Curtis, 2003; Ciurlica *et al.*, 2010; Hajipour *et al.*, 2012).

Previous studies have reported several procedures related to either coating iron oxide nanoparticles with double layers based on fatty acids or the dispersion of magnetic parts in a polar or non-polar carrier with a carboxylic acid shell such as oleic, lauric or myristic acid (Ciurlica *et al.*, 2010).

Magnetic particles loaded with drugs for targeting purposes can be injected to the subject by intravenous or intra-arterial injection (Dobson, 2006) and the drug reaches the target with the external application of magnetism. In a study of tumours, Widder et al used an intra-arterial injection close to the tumour region to increase the magnetic

targeted delivery and this was reported to have 200-fold greater targeted delivery than administration with an intravenous injection. In later studies using porcine, rabbit, and rat models, successful results were reported in drug dissemination and tumour remission. Kubo et al modified this technique in a hamster model, and placed permanent magnets in solid osteosarcoma regions, and cytotoxic components were then transmitted with magnetic liposomes. Compared to the normal intravenous efficacy, a 4-fold increase was observed in the delivery of cytotoxic drugs to the osteosarcoma regions (Mahmoudi *et al.,* 2011).

Şen et al (2020) simulated operation wounds in a rat model study using antibiotic-coated iron oxide nanoparticles. The interscapular region was selected for the incision to prevent the rats reaching the wound in the postoperative period, and a 15mm long skin incision was made. The region was then infected with S. aureus and sutured with 4/0 monofilament sutures. To be able to obtain maximum delivery in the magnetic targeting, iron oxide magnetic nanoparticles were injected subcutaneously to the region after the formation of infection, coated with 2.5mg/kg enrofloxacin in one group, coated with 5mg/kg enrofloxacin in the second group and with no antibiotic coating in the third group. Magnets were placed directly over the incision line, fixed in place with bands and the area was covered. On the postoperative 6th day, the suture line was observed to be completely closed in all the rats in the group applied with the 5mg/kg dose of enrofloxacin- ironoxide complex. It was also observed in this group that there was epithelial regeneration and the formation of connective tissue in the region and the wound had completely recovered. When histological evaluation and electron microscopy data were taken into consideration the magnetic targeting was reported to be successful. From those results it was claimed that the magnetism capturing the drug-nanoparticle complex applied to venous or arterial circulation reduced the rate and possibility of retention in the region compared to subcutaneous application, and that by applying external magnetism over the skin, subcutaneously applied antibiotic-coated nanoparticles could contribute more to the healing process (Şen *et al.,* 2020).

2. Conclusion

Magnetic nanoparticles are a relatively new subject. Together with the developments in drug technology, these systems, known as smart drug systems, which provide localisation of the drug in the infection region, have attracted great interest recently. As a result of the research into the methods of drug delivery and associated effects, magnetic nanoparticles are considered an alternative method in various treatments. These systems increase the therapeutic effect of the particle-dependent drug, improve drug localisation, and thus have the potential to reduce drug toxicity. Positive results have been seen to have been obtained in increasing the benefit of drugs together with the use of these systems. By benefitting from the optic, fluorescent, and magnetic properties of nanoparticles, the diagnosis of various diseases can be provided, and the early determination of tumour cells and the elimination of cytoxic agents by targeting tumoral tissue and cells, and local treatment of infected regions. Studies related to the use of nano particles for treatment purposes are still new. With the use of these drug carrier systems, most of the problems of conventional therapy, such as side-effects and the development of resistance will be able to be overcome.

References

Bayrak, A. (2012). Controlled synthesis of surface modified magnetic nanoparticles (MNP) and their use in polymerization. Inönü Universty Graduate School of Natural and Applied Sciences, Department of Chemistry, Master Thesis (in Turkish).

Berry Catherine, C., & Curtis Adam, S.G. (2003). Functionalisation of magnetic nanoparticles for applications in biomedicine. *Journal of Physics D: Applied Physics*, 36, R198–R206.

Chomoucka, J., Drbohlavova, J., Huska, D., Adam, V., Kizek, R., & Hubalek, J. (2010). Magnetic nanoparticles and targeted drug delivering. *Pharmacological Research*, 62, 144–149.

Ciurlicaa, E.F.N., Nadejdea, C., Creangaa, D.E., Carlescua, A., & Badescub, V. (2010). Antibiotic coated magnetite nanoparticles for biological applications. *Neuroscience Research*, 10-15.

Dobson, J. (2006). Magnetic Nanoparticles for Drug Delivery. *Drug Development Research*, 67, 55–60.

Grace, N., & Pandian, K. (2007). Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles—A brief study. *Colloids and Surfaces A: Physicochem. Eng. Aspects*, 297, 63–70.

Hajipour, M.J., Fromm, K.M., Ashkarran, A.A., de Aberasturi. D.J., de Larramendi, I.R., Rojo, T., Serpooshan, V., Parak, W.J., & Mahmoudi. M. (2012). Antibacterial properties of nanoparticles. *Trends in Biotechnology*, *30*(10), 499-511.

Lin, M.M., Kim, D.K., Haj. A.J., & Dobson, J. (2008). Development of sıperparamagnetic iron oxide nanoparticles (SPIONS) for translation to clinical applications,*IEEE Transactions on nanobioscience*, *7*(4), 298-305

Lizán-Garcia. M., Garcia-Caballero, J., & Asensio-Vegas, A. (1997). Risk factors for surgical-wound infection in general surgery. *Infection Control&Hospital Epidemiology*, *18*(5), 310-315.

Mahmoudi, M., Sant, S., Wang, B., Laurent, S., & Sen, T. (2011). Superparamagnetic iron oxide nanoparticles (SPIONs): Development, surface modification and applications in chemotherapy. *Advanced Drug Delivery Reviews*, 63, 24–46.

Mangram, A.J., Horan, T.C., Pearson, M.L., Silver L.C., & Jarvis, W.R. (1999). Guideline for Prevention of Surgical Site Infection. *American Journal of Infection Control*, 27, 97-134.

Nathens, A.B., & Dellinger, E.P. (2000). Surgical site infections. *Current Treatment Options in Infectious Diseases*, 2, 347-358.

Ok, E. (2007). Surgical Site Infections. *Journal of Turkish Intensive Care Association*, 5, 69-72 (in Turkish).

Şen. İ., Karayiğit, M.Ö., Kara, H., & Karataş, Ö. (2020). Treatment of Operation Wounds in Rats with Antibiotic-Coated Magnetic Nanoparticles. *International Journal of Academic Medicine and Pharmacy*, 1, 26-33.

Uyanıkgil, E.Ö., & Salmanoğlu, D.S. (2020). Targeting of metallic nanoparticles. *Ege Journal of Medicine*, *59*(1), 71-81.

Uzunköy, A. (2005). Surgical site infections: risk factors and methods of prevention. *Turkish Journal of Trauma & Emergency Surgery*, *11*(4), 269- 281.