Control of Bacterial Infections after Knee Joint Replacement Therapy

Abstract

Background: Knee joint replacement is an effective method to decrease pain and improve knee function in patients with advanced knee joint arthritis. However, there are some factors leading to the failure of the treatment, such as infection, mechanical failure of the replaced joint, and destruction or loosening of the implant, which may lead to the need for revision surgery. The aim of this study was to assess new methods to improve the longevity of the knee arthroplasty, as well as finding measures to decrease infection-related failures.

Methods: Databases such as PubMed and Science Direct as well as the Material Journal were searched to find articles about infections of bone implant surgeries. 76 articles were retrieved; of them 41 articles were used for this review.

Results: Of the 41 articles, 33 were about non-antibiotic treatment of bone implant infections, five articles had evaluated in vivo non-antibiotic treatment and its effect on bone tissue, and four other articles were related to combination of these agents with antibiotics and their increased effects after surgery.

Conclusion: Using non-antibiotic agents to prevent post total knee surgery infections and biofilm formation is recommended to prevent antibiotic resistance. Currently polymethyl meta-acrylate cement mixed with antibiotics such as vancomycin and gentamycin is used in such operations but biofilm formation and microbial resistance can occur, which may lead to acute infection. In this review we evaluated technologies that can enhance the functions of orthopedic implants so that total knee joint surgery infections can be decreased. Reports show that combined various technologies can enhance preventing microbial infections.

Keywords: implants, infections; Antimicrobial therapy; Knee joint surgery, Anti-adhesion biomaterial, Antibiofilm, Antimicrobial biomaterial

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Introduction

Having considered the increased rate of infection after knee joint arthroplasty, it is recommended to use implants with approved antimicrobial properties. Such infections are not limited to patients with immunodeficiency or those at risk of infections because they can occur in all patients. So preventive measures cover all patients undergoing such treatments. Although it is more reasonable to use antimicrobial measures for patients at higher risk of infection, as antimicrobial implants are used to decrease the costs and increase the efficiency, all patients undergoing knee joint arthroplasty can use them(1). Reports published since 2010 show that infection is the most prevalent cause of re-do surgery in the next two years after the primary surgery. After that period non-infectious causes are responsible for re-do surgeries, which have been shown in National Joint Registry(2). Various measures have been considered to prevent such resistance, such as restricting bacteria at the site of adhesion to the implant in order to prevent the primary infection(3). Antibacterial plates are another solution to actively destroy bacteria contacted to the implant. Many antibacterial strategies have been assessed and reported but some of them have had limited efficacy and some others are not suitable to be located in osseous tissue(4).
Factors to cause infections in bone implants include contamination at the site of the implant, transfer of the contamination from the surgeon’s or the staff’s hands, transfer from the skin or mucus membrane of the patient, or transfer from the other patients, which by controlling them infections can be decreased\(^5\).

“Primary microbial adhesion” as the main cause of infection
The process of bacterial adhesion can be divided into two basic phases; reversible and irreversible. The reversible phase has less stability compared with the second phase and is caused by the non-specific cellular and molecular reactions of the bacteria with the surface of the implant\(^6\). Bacteria attached to the implant sometimes express biofilm gene, which leads to secret a preventive sluggish material (biofilm) that leads to resistance of the bacteria and enhances its dissemination\(^7\). Bacteria use various ways for pathogenesis. So there are many parameters for biofilm formation by them. Preventing bacteria from primary adhesion to the surface (for example using anti-adhesion surfaces) can be one of the measures to control infection\(^8,9\).

Surfaces with anti-adhesion properties
Polysaccharides with bacterial anti-adhesion properties (antibiofilm):
One of the most cost effective and simplest ways to prevent biofilm formation is to prevent the bacteria from adhesion to the surfaces by using anti-adhesion covers\(^10\). Bacterial adhesion is a complex process that can be influenced by many factors such as physical and biochemical properties of the materials’ surfaces, cellular characteristics of the bacteria including its hydrophobia, electrical charge of the cellular surface, environmental factors (ionic potential), and presence of organic material and electricity flow. Having considered that the electrical charge of the specified cellular wall of bacteria is negative in neutral PH, it is usually seen that hydrophilic materials have less bacterial adhesion compared with hydrophobic materials\(^11\). Although there are controversies in this regard, it is overall accepted that hydrophilic surfaces in contact with mediators with organic molecules such as proteins are against producing an anchor for the bacteria to start the bacterial adhesion process and biofilm formation. So anionic polysaccharides with hydrophilic properties are possible candidates to produce anti-adhesion surfaces\(^12\). Currently, hyaluronic acid has been studied as one of the polysaccharides to be used as antibiofilm cover. Recently antibacterial property of hyaluronic acid has been reported by finding the decreased adhesion of staphylococcus aureus to surfaces with titanium covered by hyaluronic acid compared with surfaces with titanium but without coverage with the acid\(^13\).
Heparin is another natural polysaccharide with anti-adhesion properties that has been studied recently. Heparin as an anticoagulant is used in implants with direct contact with the blood such as surgical catheters, and stents\(^14\). Reports show that staphylococcus aureus changes fibrinogen to fibrin by secretion of coagulase, and then fibrin works as a preservative network for bacteria and facilitates bacterial adhesion to the implant’s surface. By using tissue plasminogen activator as a molecular cover in bone implants, such proteins can transform the host’s plasminogen to active plasmin leading to direct fibrinolytic activity on the implant’s surface (where the fibrin contaminated with the bacteria exists) and destroy the contaminated fibrin by degrading the fibrin and consequently destroy the bacterial anchor for adhesion to the surface\(^15\).
In some strains of staphylococcus aureus, decreased biofilm formation by tissue plasminogen activator and its strong effect has been reported. It has also been mentioned in the report that coagulation inhibitors such as vit K, heparin, and hydroin may theoretically
prevent biofilm formation but they cannot prevent fibrin sediment formation by staphylococcus aureus and destroy fibrin contaminated with bacteria. It was also reported that heparin even increased biofilm formation in staphylococcus aureus\textsuperscript{(16)}. Staphylokinase existed in staphylococcus aureus functions similar to tissue plasminogen activator but it is not related to biofilm formation in this bacterium. It is sometimes secreted heavily in biofilm former strains\textsuperscript{(17)}.

**Polymer covers with anti-adhesion characteristics**

Some polymer covers such as hydrophilic poly meta-acrylic acid, polyethylene oxide, and protein resistant polyethylene glycol can be attached to titanium implants\textsuperscript{(18)}. They can significantly inhibit bacterial adhesion. Even if some of such covers disturb osseous tissue function, malfunction of the cells can be restored and alleviated by using active biomolecules such as sericin protein\textsuperscript{(19,20)}.

**Dextran**

There are other synthetic and biopolymers with anti-adhesion properties\textsuperscript{(21)}. Dextran is a polysaccharide that is widely used for biomedical applications because of its very high compatibility\textsuperscript{(22)}. It is reported that this polysaccharide has anti-adhesion as well as protein inhibiting properties similar to hydrophilic polyethylene glycol, for which it has been widely studied\textsuperscript{(23)}.

Dextran has some adhesion points to bacterial cell surface, along the polymeric chain, to inhibit the protein formation of micro-organisms. It is while polyethylene glycol has only one active terminal adhesion point. It does not have reactivity along the whole polymeric chain. That is why dextran is potentially a good alternative for polyethylene glycol to deactivate active biomolecules because more inactivated bacterial active biomolecules can be achieved by that compared with polyethylene glycol cover\textsuperscript{(24)}.

**Antimicrobial peptides**

Antimicrobial peptides can be good alternatives for antibiotics because of low toxicity and causing low bacterial resistance\textsuperscript{(25)}. They have hydrophilic and hydrophobic regions, are water soluble, and can pass the bacterial lipid rich membranes\textsuperscript{(26)}. Their residuals that have positive charge can disturb bacterial membrane processes by interacting with negative loaded microbial cell wall particles (lipopolysaccharides in gram negative and teichoic acid in gram positive bacteria)\textsuperscript{(27)}. This property is useful for designing antimicrobial surfaces, where primary adhesion and bacterial contact can occur\textsuperscript{(28)}.

**Chitosan**

Currently, chitosan is used as a practical material in antimicrobial compounds, as well as food, cosmetic, and water and sewage industries. That is why in recent years antimicrobial properties of chitosan and its derivatives against various types of microorganisms have been noticed\textsuperscript{(29)}. Chitosan has various advantages over other antiseptics such as high antimicrobial properties covering a wide range of organisms and low toxicity for mammalian cells. Its capability to destruct biofilms formed by bacteria has also been approved, although its antimicrobial properties tend to decrease because of its low water solubility. Nowadays antimicrobial and biological compatibility of chitosan can be enhanced by producing water soluble chitosan (hydroxypropyl trimethyl chloride chitosan)\textsuperscript{(30)}.

Surely there is always a concern that combining chitosan with bone cement may affect its mechanical properties\textsuperscript{(31)}. To solve this issue, nanoparticles of the chitosan or chitosan ammonium quaternary can be used. Such nanoparticles also enhance the antibacterial function of bone cements mixed with gentamycin (these particles present loaded surface density to interact with bacteria leading to destruction of bacterial cell
wall hence eliminating bacteria\(^{(32)}\). As chitosan nanoparticles can mix uniformly with bone cement, mechanical properties will not be seriously affected if the ratio of powder to weight is considered\(^{(30)}\).

Regardless of using antibiotics such as gentamycin mixed with bone cements, they are not much effective to prevent the infection. So in some studies chitosan in the form of propyl methyl ammonium chloride mixed with polymethyl meta-acrylate bone cements (which has been evaluated in vivo) could considerably inhibit infection caused by methicillin resistance staphylococcus epidermidis and this method had a promising role to control the infection\(^{(33)}\).

**Metallic nanoparticles with antimicrobial properties**

High area to volume ratio and ease of production has made nanoparticles an important treatment modality against bacterial biofilms\(^{(34)}\). There are various reports explaining multi-potentiality of nanoparticles as antimicrobial elements. Capability of metals to target different parts of organisms make them superior to routine antibiotics against infection so using metallic nanoparticles can be an important and practical measure to prevent infection\(^{(35)}\).

Although recent studies show safety of using nanoparticles in different treatments, these nanoparticles can affect human body according to their compositions. Factors such as volume of nanoparticles, size, shape, duration of exposure, and chemical surfaces can affect their functions\(^{(36)}\).

**Silver**

Recently, silver nanoparticles have been considered very much to design implant surfaces. This is important because such particles have antimicrobial properties and strong anti-biofilm potential with low toxicity for mammalian cells. Silver nanoparticles can effectively inhibit bacterial growth including highly resistant strains with very low densities, and do not show any acute cytotoxicity\(^{(34)}\).

Although bacterial resistance has been reported for silver ion, there is not such a report for silver nanoparticles. So having considered that bacterial resistance has been changed to an international crisis using such non-antibiotic measures can help to control such a crisis\(^{(35)}\). In a study, silver nanoparticles combined with vancomycin and titanium nanotubes showed high antibacterial properties against methicillin resistant staphylococcus aureus and bacterial adhesion was prevented for 28 days by the combination. The report concluded that using nanotechnology in implant surfaces and combining a non-organic bactericidal agent such as silver nanoparticle with an organic antibiotic such as vancomycin was an effective method to prevent the infection and injury to the soft tissue specifically when external implants are used in the body.

Titanium implants having silver nanoparticles can destroy floating bacteria as well as bacteria attached to the surfaces with the same mechanism during 1, 4, and 12 days. On the other hand, reports show that sensitivity of floating bacteria to silver nanoparticles can decrease bio-film formation\(^{(37)}\). Nowadays silver nanoparticles are used with the combination of other therapeutic measures but there are always concerns regarding its toxicity and blood transmission. Toxicity of silver nanoparticles is related to environmental and biological changes such as surface oxidation, silver ion dissemination, and reactions with biological macromolecules. And it is always a challenge to diagnose how much silver ion in the form of nanoparticles may cause toxicity because by decreasing the density the antimicrobial effect will also decrease. Silver nanoparticles can connect to membranous proteins and inhibit cellular replication by activation of messenger pathways. They can also enter the cells through endocytosis or dissemination and disturb mitochondrial function leading to
injury to intracellular proteins or nucleic acids\(^{(38)}\).

**Copper**
Low expense and easy use of copper on other metallic surfaces has led to its practical use\(^{(38)}\). Antibacterial effect of copper on titanium through decreasing the adhesion of bacteria such as staphylococcus aureus and epidermidis has been reported. Although such densities can make toxicity in mammalian cells, decreasing the amount and using nanoparticles can be the remedy for such a problem\(^{(39)}\). Copper nanoparticle is an effective factor against herbal and animal pathogenesis that is why it is used as pesticide and growth enhancer in agricultural industry. Copper nanoparticles are also used as antimicrobial cover on medical instruments to prevent bacterial contaminations\(^{(40)}\). There are some reports about biofilm prevention by copper nanoparticles against bacteria such as E. Coli, pseudomonas aeruginosa, and methicillin resistant staphylococcus aureus. High potential of these particles for absorption, penetration, and easy access has led to introducing them as antibiofilm material. But toxicity and blood transmission of copper is also a challenge similar to what exists for silver\(^{(41)}\).

**Gold**
Gold nanoparticles are considered as practical nanoparticles because of their high potential for strong absorption and high conductivity. Gold particles can easily penetrate to bacterial cells (because of their small size) and compress bacterial cell DNA. This process can prevent genome replication, so the cell loses its capability to replicate leading to bacterial death. In addition to this, penetration of gold nanoparticles into the cell wall inactivate enzymes and produce hydrogen peroxide, which its toxicity can kill the bacteria\(^{(41)}\). Gold metal shows weak antimicrobial properties against wide spectrum of microbes and can only kill bacteria in specific densities so using this metal is not practical.

**Methods**
This research is a general evaluation of studies that had been done about the effects of biological materials and other non-antibiotic treatments to be used as antimicrobial materials and bacterial antibiofilms in artificial knee joint surgeries. Data gathering was done by searching in both Persian and English language articles published from 2003 to 2016. Databases such as Scopus, google, PubMed, and google scholar were searched using related keywords to find articles that had required information about infection of artificial joints and the ways of prevention of such infections. New and practical methods mentioned in those articles were briefly reported in this review.

**Results**
In this paper, we have tried to find the various strategies regarding the prevention of deep infections around the implants. Among the factors introduced, biological materials naturally reliable, durable, non-toxic and safe and can prevent bacterial adhesion and biofilm formation at implant surface. Currently, Heparin is natural polysaccharide with anti-adhesion properties which is used as an anti-adhesion of the blood cells to implants such as surgical catheters and stents. Some polymer covers with anti-adhesion properties like Dextran that is widely used to inhibit the protein formation of microorganisms.
Antimicrobial peptides such as chitosan and nanoparticles of metal such as silver, copper and gold are coatings that can be used as antimicrobial agents. Recently, the use of heparin polysaccharide in stents is practically used as an anti-adhesive property, and then chitosan is considered as an anti-adhesive polymer coating and more attention has been
paid to the antimicrobial properties of silver nanoparticles for the design of implant surfaces.

**Conclusion**

In order to prevent infection, post knee joint surgery treatments should be in a way that by decreasing the infection rate, no limitation occurs in merging the osseous tissue in the region, no disorder happens in the bone tissue, biostability exists at the surgical site, and mechanical properties of the implant is not altered.

Basically, all materials used for producing bone implants can lead to bacterial biofilm formation; hence to inflammation and necrosis of the host’s tissue. High dose antibiotics are prescribed to prevent infection-related complications. Currently mixing antibiotics with bone cements that is used by orthopedic surgeons in knee arthroplasties is considered as a potentially effective method to dispense the drug at the site of surgery. But irregular distribution of the antibiotics, short life, and hydrophobicity of sub-inhibitory concentrations of netilmicin. International journal of antimicrobial agents. 2003;22(2):164-7.


