Abstract

**Purpose:** Bone and soft tissue infections are among the least desired complications after orthopaedic surgery. This study analysed the *in vivo* effects of the local application of nano-silver particles (AgNPs) [1nm = 1 billionth of a meter] in soft tissue infections.

**Materials-Method:** An experimental osteomyelitis model was formed by inoculating both tibias of 24 rats with methicillin-resistant *Staphylococcus aureus*. The rats were followed without treatment for 21 days. Blood samples and tibial x-rays at day 21 confirmed the development of infection. Then, the rats were divided randomly into two groups. One group (12 rats) underwent surgical debridement and received 21 days of teicoplanin therapy. The second group had the same treatment, with the addition of local nano-silver. All of the rats were sacrificed at day 42. Blood and wound swab samples were taken and the culture results were analysed.

**Results:** No differences were observed between the groups in healing values at pathological examination, or in changes in the number of colonies at days 21 and 42. No differences in white blood cell count (WBC) were observed between the groups before and after the treatment.

**Conclusion:** Although *in vitro* studies suggest the effectiveness of AgNPs on pathogens, we found that the application of nano-silver did not make any difference when used in addition to the classical osteomyelitis treatment with antibiotics and local surgical debridement. We believe that additional *in vivo* studies using repeated nano-silver application could be beneficial.

Key words: Nano-silver, Osteomyelitis, Soft Tissue Infection

Introduction

The treatment of osteomyelitis is expensive and the increasing prevalence of antibiotic-resistant bacteria is resulting in longer hospital stays. The rate of osteomyelitis has increased with advances in technology due to the increased use of orthopaedic implants in surgical procedures (1). The reported rates
of deep tissue infection after intramedullary nailing and joint replacement surgery are 0.5–17% (2).

Several modalities have been described for the treatment of osteomyelitis, each with different advantages and side effects. The basis of treatment is intravenous antibiotic therapy and surgical debridement, including local antibiotic therapy, antibiotic-containing cement, bone grafts, antibiotic-soaked sponges, polymethylmethacrylate (PMMA) beads, and antibiotic-coated implants (3).

Silver ions exhibit antimicrobial activity, having both bactericidal and bacteriostatic effects. The role of silver in the treatment of burns, urinary tract infections, central venous catheter infections, and chronic osteomyelitis has been demonstrated (4).

The antifungal and antimicrobial effects of both micron- and nano-sized metal silver have been studied for years. Nano-sized silver particles can be used alone or can be coated or precipitated on a surface using various methods, such as biochemical reduction, ultrasonic spray pyrolysis, and anodic oxidation (5–8).

Silver ions protect against bacteria in various ways because they affect bacterial cell membranes and the intracellular transport of essential molecules by integrating into the thiol groups of the enzymes and proteins essential for bacterial survival (9–11). These interactions inactivate the bacteria.

In this study, we investigated whether nano-silver particles (AgNPs) are a potential new alternative for the treatment of osteomyelitis using an in vivo rat model to determine the effectiveness of the local application of AgNPs in the treatment of osteomyelitis and infected soft tissue.

Materials and Methods

Ethics approval was obtained from the Bezmi-alem University Animal Subjects Ethics Committee. The study used 24 male and female Sprague-Dawley rats weighing 200–300 g. All surgical procedures were performed under anaesthesia induced with ketamine and xylazine. Four rats died during the study, so a total of 20 rats were included in the analyses.

Preparation of the inoculum

Bacteria were inoculated on sheep blood agar supplemented with 2% NaCl (sodium chloride), incubated at 35°C for 16 h, suspended in 0.85% NaCl, and centrifuged at 5000 rpm for 15 min. Then, the upper part was discarded and 10 mL of 0.85% NaCl was added to the solution. This was repeated twice. Finally, 0.85% NaCl was added to obtain a bacterial suspension (1×10⁷ CFU/mL) equal to 0.5 McFarland.

Preparation of AgNPs

AgNPs with a mean size of 15 nm were prepared from a silver nitrate solution, using sodium borohydride (NaBH₄) as the hydrogen donor (reductant), sodium lauryl sulphate as the surface modification agent, and oleic acid (Figure 1).

On the first day of the study, the haemograms of each rat were recorded. Then, both hind limbs were shaved, povidone iodine solution was applied, and an approximately 1.5-cm longitudinal incision was made on the anteromedial side of the anterior tibia under sterile conditions. Anterior to both proximal metaphyseal regions, the tibia was opened with a 2-mm dental burr and a 4–6-mm diameter cortical lid was formed. Using this method, mechanical trauma was created in the metaphyseal region and the intramedullary area was carved using various sized Kirchner wires and a burr. Methicillin-resistant Staphylococcus aureus (MRSA; 1×10⁷ CFU; ATCC 43300) was inoculated through the cortical lid on the tibia into the intramedullary area.

Figure 1: Distribution of particles by size in the 15 nm nano-silver solution. (Before beginning our study, in vitro tests performed at the Turkish Centre for Disease Control revealed that nano-silver (used in our study) produced at the Istanbul Technical University Faculty of Metallurgy was effective against Escherichia coli (ATCC 259922), Staphylococcus aureus (ATCC 25923), and Salmonella spp. (RS) with no bacterial growth in the cultures.)
The incision was closed using 4.0 polypropylene, followed by routine wound dressing, and both legs were bandaged with Tensoplast. The mobility of the rats was not restricted. The rats were fed a standard regular pellet diet and water, and food intake was measured for 21 days before any treatment was given.

At day 21 post-surgery, blood samples were obtained from the carotid arteries and haemograms were obtained. Anteroposterior (AP) and lateral x-rays of the tibias were obtained. The x-rays were analysed by four different orthopaedic surgeons and evaluated according to the criteria of Aktekin et al. Chronic osteomyelitis formation was observed. The presence of bone deformation, joint effusions, soft tissue swelling, osteolysis, metaphyseal widening, and periosteal reaction were recorded. A diagnosis of osteomyelitis was made when three of these factors were present. Infectious parameters (number of leukocytes) were higher after the operation compared with preoperatively.

The rats were randomised into two groups consisting of 12 rats each. Wound swab and tissue culture samples were obtained from the proximal tibia where the surgery was performed, and MRSA colonies were counted. Soft tissue abscesses and purulent discharge were observed in the majority of rats. Hyperaemia, fistula formation, discharge, and knee joint effusions were observed in some rats. Partial cortical defects and the formation of soft fibrous cortical bone were also observed.

The rats were divided into two groups (A and B). In group A, local wound and infectious bone debridement were performed. The area was then irrigated with 100 mL of 0.09% NaCl isotonic solution, and systemic 6 mg/kg/day teicoplanin was administered for 21 days. In group B, after wound and bone debridement, the area was irrigated with 100 mL 0.09% NaCl isotonic solution. A total of 0.0002 mg AgNPs (20 mL nanoparticle AgNPs) soaked in 3 mmL of 0.09% NaCl isotonic solution, was placed in the tibial defect. Then, systemic 6 mg/kg/day teicoplanin was administered for 21 days.

Debridement was performed only once for each group. Blood was drawn from the carotid arteries and haemograms were obtained on postoperative day 42. Both of the lower extremities were shaved. The proximal tibial metaphysis was reached by dissecting through the previous incision line with a number 15 scalpel. Wound swab and tissue cultures were obtained from the tibial wound areas using sterile swabs. Bacterial colony numbers were studied by inoculating samples on blood agar. After the rats were sacrificed, both of their tibias were fixed in formaldehyde and examined histopathologically. Osteomyelitis and healing scores were calculated separately. The incidence of acute and chronic inflammation, the number of necrotic centres, number of micro-abscess foci, percentage of fibroblastic proliferation areas, and degree of vascularisation (number of lumens forming vessels) were investigated (Figure 2a,b). Fibroblast proliferation and vascularisation were considered as indications of healing, and inflammation, necrosis, and micro-abscess foci were considered as osteomyelitis (Figure 3a,b). The degree of osteomyelitis was scored on a scale of 1–3, ranging from mild to severe, while healing levels were scored as 1–3, ranging from low to high.

Results

Histopathological scoring was performed. White blood cell (WBC) counts were compared using the Mann-Whitney U-test. The osteomyelitis scores of groups A and B did not differ statistically (p = 1). Moreover, there were no significant differences in the soft tissue healing scores of the pathological specimens from the two groups (p = 0.244). At the beginning of the treatment phase, there were no significant differences in the colony numbers on the wound sites between the two groups (p = 0.693). However, on day 42 of treatment, the colony counts for groups A (mean, 10.5) and B (mean, 11.6) differed significantly (p = 0.041). There were no significant differences in the change of the number of colonies between the two groups from day 21 to 42 (Tables 1 and 2).

| Table 1: Statistical comparison of healing and the number of colonies between the two groups. |
|---------------------------------|----------|-----------------|-----------------|-----------------|-----------------|
| Osteomyelitis        | Healing 21 | Colony Day 42 | Colony Day 42 | Colony Day 42 |
| Z                  | 0.000    | -1.165          | -0.395         | -2.042         | -0.978          |
| p                  | 1.000    | 0.244           | 0.693          | 0.041          | 0.328           |

| Table 2: Comparison of the healing scores and number of colonies between the two groups. |
|---------------------------------|----------|-----------------|-----------------|-----------------|-----------------|
| Groups             | Osteomyelitis | Healing 21 | Colony Day 42 | Colony Day 42 | Colony Day 42 |
| AN                | 20        | 20             | 20             | 20             | 20             |
| Mean              | 1.350     | 2.600          | 68.500         | 11.650         | -56.8500       |
| Standard deviation | 0.4894   | 0.5026         | 35.6673        | 21.7795        | 37.90747       |
| Median            | 1.000     | 3.000          | 92.500         | 6.000          | -61.0000       |
| BN                | 20        | 20             | 20             | 20             | 20             |
| Mean              | 1.350     | 2.350          | 70.650         | 10.500         | -60.1500       |
| Standard deviation | 0.4894   | 0.6708         | 37.0082        | 18.4890        | 42.12172       |
| Median            | 1.000     | 2.000          | 100.000        | 0.000          | -67.5000       |

At the beginning of the study, the WBC counts of all rats were similar (p = 0.880). Moreover, there were no differences in osteomyelitis formation between the groups on treatment day 21 (p = 0.096); however, WBC counts were higher compared with the
preoperative values. At the end of the treatment period, no significant differences were found in treated rats between the groups \((p = 0.880)\), and there were no differences in changes to WBC counts between days 21 and 42 \((p = 0.076)\) (Tables 3 and 4).

**Discussion**

Coagulase (-) staphylococci are frequent etiologic agents of osteomyelitis. *S. aureus* is the organism isolated most commonly, particularly in acute haematogenous osteomyelitis, and it is the most common cause of osteomyelitis (13). Non-collagen components of bone, including osteonectin, osteocalcin, proteoglycan, and sialoprotein, are targets for *S. aureus*. Indeed, a specific connection has been found between sialoprotein and a specific osteomyelitis-causing subspecies of *S. aureus* (14). *S. aureus* is an intracellular microorganism that lives inside osteoblasts (15); it triggers inflammation and inhibits the reproduction of T lymphocytes. This bacterium can invade neutrophils and monocytes drawn into areas of inflammation, continuing its existence intracellularly (16,17).

Despite recent advances in antibiotic treatment, osteomyelitis remains difficult to treat. Low antibiotic concentrations, bone necrosis, and the low vascularity of bone render treatment even more difficult (18). Additionally, extracellular glycocalyx and necrotic bone tissue can lead to the development of biofilms, a major complication of chronic osteomyelitis.

Teicoplanin is a broad-spectrum bactericidal antibiotic that is effective against most Gram-positive and anaerobic bacteria, including MRSA and methicillin-resistant coagulase-negative *S. aureus* (19). It is an ideal antibiotic with a long half-life, high absorption capacity from bone, high protein-binding capacity, and low nephrotoxic side effects compared with vancomycin, which makes it an ideal antibiotic for the treatment of MRSA-induced osteomyelitis. However, it is never adequate when used alone.

The current treatment methods for osteomyelitis and infection by highly virulent bacteria such as MRSA remain inadequate, and the search for different treatments continues. A variety of treatment options have been explored, such as local antibiotic administration. The most important reason why local antibiotic administration is effective is that it results in higher tissue concentrations than systemic administration (20). Several studies have investigated this, and the use of antibiotic-loaded hydroxyapatite blocks to increase the concentration of antibiotics in bone tissue has become a treatment for osteomyelitis (18).

![Figure 2](http://www.jbji.net)

**Figure 2:** a: Wide osteomyelitis region showing high grade inflammation (grade 3). In the middle, intensive accumulation of polymorphonuclear leucocytes and mononuclear inflammatory cells and also wide necrosis and abscess foci seen. b: Wide destruction of bone lamellae in these foci. H&E, x400.

![Figure 3](http://www.jbji.net)

**Figure 3:** a: Healing signs in the foci of chronic osteomyelitis. b: Apparent neovascularization showing lumen formation in these foci. H&E, x2000.
Local antibiotic treatment has also been used to treat chronic osteomyelitis and infected prostheses, and has been described as an adjunct treatment method. Cements containing antibiotics have been shown to be effective; they continue to release antibiotics for up to 6 weeks and maintain the antibiotic concentrations. Buchholz and Engelbrecht first reported that antibiotics could be incorporated into bone cements to provide local, long-term, and high-dose treatment (21). However, Sener et al. demonstrated that the cement remaining at the end of the antibiotic release period can act as a foreign body and result in increased rates of infection (22). They also showed that combining surgical debridement with such cements is more effective than debridement alone. Garcia et al. used an antibiotic powder to reduce soft tissue infection and abscess development, but the results were not significant histologically, microbiologically, or radiologically (23).

Another way to administer local antibiotics is via implants. Schmidmaier et al. studied the use of antibiotic-covered implants for the treatment of osteomyelitis and observed significant results (24). PMMA containing antibiotics has been presented as an alternative treatment modality; successful results have been reported with aggressive debridement, repeated irrigations, and PMMA soaked with 500 mg gentamicin and 2.4 g tobramycin (25). Keeling et al. showed that PMMA soaked with vancomycin and daptomycin decreased biofilm formation (26).

The administration of antibiotics in biologically degradable materials has been used for the same purpose. This is an important procedure because the material does not require removal. The use of collagen sponges containing gentamicin, polymyxin B, chloramphenicol, tobramycin, clindamycin, vancomycin, fusidic acid, fluoroquinolones, moxifloxacin and rifampicin. Isefuku et al. found that the administration of gentamicin and rifampicin prevented fracture healing (27).

The local application of antibacterials has also been used to treat osteomyelitis effectively. However, due to the increasing prevalence of antibiotic resistance, it is necessary to develop other treatment modalities.

Biofilms can render the treatment of osteomyelitis very difficult. The potential for new technological developments to revolutionise the treatment of infections can be investigated by examining the direct effects of AgNPs on biofilms. AgNPs help treat biofilms by affecting the expression of genes (icaA and icaR for *Staphylococcus epidermidis*; fnbA and fnbB for MRSA) that decrease bacterial adhesion and inhibit biofilm formation (28).

Simone et al. found that using AgNP-covered silk sutures decreases the incidence of surgical site infections and bacterial colonisation and reduces hospitalisation costs and morbidity (29). Shameli et al. found that AgNPs in zeolite exhibits antibacterial activity against Gram-negative (*Escherichia coli* and *Shigella dysenteriae*) and Gram-positive bacteria (*S. aureus* and MRSA) (30).

Gopinath et al. found that biogenic AgNPs are effective against endospores of *Bacillus* and *Clostridium* species (31). Wang et al. studied the antimicrobial effects of AgNP-coated titanium surfaces, which resulted in decreased expression of biofilm-related genes (icaA and icaR for *S. epidermidis*; fnbA and fnbB for MRSA), prevented bacterial adhesion, and inhibited biofilm formation (28). Albers et al. found that AgNPs have antimicrobial effects against *S. epidermidis*, but questioned their

### Table 3: WBC counts of rats on days 21 and 42.

| Groups | Preoperative WBC | Day 21 WBC | Day 42 WBC | Change Day 21 – Preoperative | Change Day 42 – Day 21 | Change Day 42 – Preoperative |
|--------|------------------|------------|------------|-----------------------------|------------------------|-----------------------------|
| AN     | 10               | 10         | 10         | 10                          | 10                     | 10                          |
| Mean   | 12.9170          | 13.7010    | 10.8720    | 7.840                       | -2.8290                | 2.0450                      |
| Standard deviation | 1.67203 | 3.30691 | 2.92038 | 3.34590 | 2.20561 | 2.30046 |
| Median | 12.8400          | 13.7050    | 10.4500    | -1.750                      | -3.5550                | -1.7250                     |
| BN     | 10               | 10         | 10         | 10                          | 10                     | 10                          |
| Mean   | 13.3260          | 16.5310    | 10.9010    | 3.2050                      | -5.6300                | -2.4250                     |
| Standard deviation | 3.77413 | 3.53991 | 1.87925 | 3.90455 | 4.11149 | 4.91005 |
| Median | 12.1700          | 15.7600    | 10.3550    | 2.8000                      | -5.1950                | -2.2100                     |

### Table 4: Statistical comparisons of WBC counts by time and between the two groups.

|          | Preoperative WBC | WBC Day 21 | WBC Day 42 | Change Day 21 – Preoperative | Change Day 42 – Preoperative | Change Day 42 – Preoperative |
|----------|------------------|------------|------------|-----------------------------|-----------------------------|-----------------------------|
| Z        | -0.151           | -1.663     | -0.151     | -1.209                      | -1.777                     | -0.227                      |
| p        | 0.880            | 0.096      | 0.880      | 0.226                       | 0.076                      | 0.821                       |
biocompatibility with implants that are directly exposed to bone, and recommended future in vivo studies (32).

Consistent with previous findings, the AgNPs applied in our study were effective against E. coli (ATCC 259922), S. aureus (ATCC 25923), and Salmonella spp. in vitro.

The inhibitory effects of AgNPs are greater than those of silver micro-particles (33). Accordingly, AgNPs have been shown to have cytotoxic effects against both osteoblasts and osteoclasts. Cytotoxicity decreases with increasing particle counts and surface area, and osteoblasts are more susceptible to AgNPs than are osteoclasts (32).

Gosheger et al. discovered that the incidence of deep tissue infections and need for revision surgery decreased with the use of silver-coated implants. In their study, the infection rate in operations performed with silver-coated endoprostheses was 7%, while it was 47% with titanium prostheses. Moreover, the C-reactive protein levels and WBC counts were significantly lower in a silver-coated implant group than in a titanium group (34). Qin et al. reported that AgNP-coated titanium implants decreased the transcription of biofilm-forming genes of S. epidermidis both in vitro and in vivo (35).

Another study reported that silver-coated endoprostheses decreased the rate of deep tissue infections to a greater degree than conventional endoprostheses (36). The short-term results of these studies revealed neither hepatotoxicity nor nephrotoxicity (37).

Although our results were not the same, we found that it was consistent with the literature. We found no significant differences between the groups according to the infectious parameters studied. No significant changes in WBC counts were observed with the application of AgNPs. In Gosheger et al., a silver-coated implant group had lower WBC counts than a titanium-coated implant group (34).

In our study, MRSA was grown in cultures obtained from the wound sites on postoperative day 21. No significant differences were observed between the two groups in terms of the bacterial colony count or decrease in bacterial load. The number of bacterial colonies in both groups decreased compared with pretreatment levels. Our histopathological examinations revealed no significant differences between the two groups in terms of osteomyelitis and healing scores. When performed in conjunction with debridement and systemic antibiotic administration, local AgNP application was found to have neither positive nor negative effects.

Conclusion

Although several in vitro studies have demonstrated the effects of AgNPs in combination with intravenous antibiotics, clinical practice and local surgical debridement, this combination did not have an effect on osteomyelitis in our in vivo setting. Future in vivo studies of AgNPs are warranted.

Competing Interests

The authors have declared that no competing interest exists.

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