Clinical Trial Using A Silver-Coated Screw-Rod System and One-Year Follow-Up of The First 50 Patients

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Aim: The occurrence of implant-related infection in all surgical branches is one of the challenges for which a definitive solution has yet to be found. One way to reduce the incidence of implant-related infection is to use implants which are coated with antibacterial materials such as silver. The aim of this study is to investigate if the nanoparticle silver coated spinal implants reduce the implant related infection rates and safe for human use.

Method: In this clinical trial performed with 50 patients, we investigated whether or not silver-coated titanium implants alter renal and/or hepatic functions and increase serum silver levels at one year postoperatively. The required stabilization procedure was performed using the “nanoparticle silver coated transpedicular stabilisation system”. Blood and urine samples were taken from each patient at six different time points for detection of any alteration in silver concentration. Silver levels of all samples were investigated spectrophotometrically. Additional serum samples were taken for monitoring liver and kidney functions.

Results: All measured values were regarded as safe since they were lower than 5 μg/L. There was no alteration in renal and/or hepatic function, and the amount of silver in urine and serum was at undetectable levels using atomic absorption spectrophotometer. Neither complication was related to silver nor any implant infection was detected in one year follow-up period.

Conclusions: This study showed that, nanoparticulate silver coated spinal implants are capable to reduce implant-related infection rates and these type of implants are safe for human use.

Keywords: Silver, implant, infection, coating

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Gümüş Kaplı Vida-Rod Sistemi Kullanılan İlk Elli Hastanın Bir Yıllık Takip Sonuçları

Amaç: İmplant ilişkili infeksiyonların oluşması tüm cerrahi branşlar için hâlâ kesin olarak çözülememiş bir sorundur. Bu sorunun çözümünün yollarından birisi de implantlari gümüş gibi anti bakteriyel özelliğe sahip madde ile kaplamaktır. Bu çalışma amacını, nano partiküler gümüş ile kaplanmış implantların implant ilişkili infeksiyonları azaltıp azaltmadığını ve insanlardaki kullanımın güvenli olup olmadığını araştırmaktır.

Yöntem: Elli günlük hasta ile yapılan bu klinik çalışmada, gümüş kaplı implantların, bir yıllık takip sürecinde, boyunca, deneklerin karaciğer ve böbrek fonksiyonlarını etkileyip etkilemediği ve serum gümüş seviyelerinde artış olup olmadığını araştırıldı. Hastalara uygulan transpediküler vida rod sistemi ile stabilizasyon işlemi, nano partiküler gümüş ile kaplanmış implantlar kullanılarak yapıldı. Hastalardan altı ayağı alınan noktalarında, kan ve idrarlardaki gümüş miktarının belirlenilme adıma kan ve idrar örnekleri alınmıştı. Örnekler spectrofotometrik olarak incelemeli, hastaların karaciğer ve böbrek fonksiyonlarını değerlendirilmesi için aynı zaman noktalarında ayrıca serum örnekleri alınmıştı.

Bulgular: Gümüş seviyeleri adına yapılan tüm ölçüm değerleri, 5 mikrog/L’den düşük çıktığı için genelinde aralıkta olduğuna karar verildi. Hiçbir hastanın karaciğer ve böbrek fonksiyonlarında bozulma sanatlandı. Serum ve iadrardaki gümüş seviyelerinin, atomik absorbtion spectrofotometresinin ölçülmesi imkanını altında kaldı ve belirlendi. Bir yıllık takip süresi boyunca hiçbir hastada gümüşe bağlı bir komplikasyon veya implant ilişkili infeksiyon saptanmadı.

Sonuç: Bu çalışma, nano partiküler gümüş kaplı spinal implantlarının implant ilişkili infeksiyon oranını düşürme kapasitesine sahip olduğunu ve bu tür implantların insanlarda kullanılmasını güvenli olduğunu göstermiştir.

Anahtar kelimeler: Gümüş, implant, enfeksiyon, kaplama

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INTRODUCTION

The onset of implant-related infections in vertebral and orthopedic implant surgery is one of the challenges for which a definitive solution has not yet to be found. Infection rates in routine vertebral surgery applications such as discectomy and laminectomy, in which no implant is used, is around one percent (1,2). However, this rate rises to 2.1-8.5% in cases of implant use (3,4). The rate of primary infection for joint replacement is between .86% and 2.52% according to the National Nosocomial Infections Surveillance System (5) which demonstrates increase in the incidence of implant surgery. Antibiotic treatment alone is insufficient in nearly half of the patients, and inevitably the implant must be surgically removed, and in some cases, a new implant system must be inserted. This situation necessitates conduction of studies aimed at the development of an implant that will “decrease the risk of infection”.

One way to reduce the rate of implant-related infection is to use implants which have antimicrobial properties. Various antibacterial coatings, such as vancomycin (6), gentamicin (7), carbonated hydroxyapatite (HA) (8), nitric oxide-releasing xerogel (9), iodine (10,11) and silver (22) have been developed for use on implant surfaces.

We aimed to investigate whether or not a silver-coated transpedicular screw-rod system alters renal and hepatic functions, reduces the implant-related infection rate during postoperative period and to determine the resultant silver levels in body fluids.

Our previous in vitro studies have shown that silver-coated titanium implants have antibacterial characteristics as effective as pure silver metal (12). In another study, we have also made the following assertions: silver does not accumulate in vital organs, it has not any toxic effect on these tissues; serum silver values did not increase when silver-coated implants are used. All of these findings indicate that nanoparticle silver is not excreted at an undetectable level (unpublished data). We also demonstrated that silver coated screws inhibit biofilm formation in rabbits (13). Results derived from these studies encouraged us to perform a clinical trial on 50 patients participating on a voluntary basis, based upon an approval letter obtained from the Human Ethics Committee of ……… University, Faculty of Medicine (Approval number: 146-4612).

MATERIAL and METHOD

a) Silver-coated implants

The standard transpedicular screw-rod system routinely used in the clinic was coated with nanoparticle silver using the dip coating technique, in a quantity sufficient for approximately 50 patients (29 female [58%] and 21 [42%] male, respectively). All elements of the system were autoclaved and taken into the operating room on the morning of the operation.

b) Patient selection

The trial included a total of 50 ASA class I-II patients (median age, 56.8; range: 28-80 years of) with indications for posterior lumbar stabilization who stated in writing that they were participating in the trial on a voluntary basis. It was preferred that the patients included in the trial were particularly high-risk in terms of implant-related infection. For this purpose, patients who underwent previous surgery in our clinic or another center, and whose implants had been removed due to infection, in addition patients with suspect infection detected by preoperative magnetic resonance imaging (MRI) or clinical evidence of infection, diabetes, history of CSF leakage were especially included in the trial. Patients who did not belong to any of the above-mentioned risk groups were also included in the trial. Patient
demographics and statistics are given in Table 1 and 2.

c) Approaches and methods applied

On the morning of the trial, 5 cc blood and 5 cc urine were obtained from the patients admitted to the laboratory who provided signed informed consents. Samples were stored in biochemistry tubes in order to detect the basal silver level in the blood. Blood, and urine samples were taken from all patients and sent to the laboratory to detect erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for the follow-up and detection of any infection that might develop during the postoperative period. Leukocytes and platelet counts investigated for any hematopoietic harmful effect of silver on kidney and liver functions, and any alteration in the functions of these organs due to silver accumulation was evaluated.

The required stabilization procedure was performed using the “transpedicular screw-rod system” made of titanium alloy and coated with nanoparticle silver ion using dip coating technique. All patients were discharged from the hospital within an average of 5 days. Oral ceftriaxone (2 x 750 mg) was recommended to all patients in the postoperative period. This application was not different from the routine protocol that was used for several years in our clinic.

Blood and urine (5 cc from each) samples were taken from each patient on the postoperative 10th day, 1st, 3rd, 6th, and 12th months for the detection of silver concentration in blood and urine to be sent to Ankara University, Faculty of Medicine, Physiopathology Department Laboratory, where the silver quantity in these fluids was detected on atomic absorption spectrophotometer. Samples were also taken for complete blood count, blood biochemistry, ESR, and CRP on the same dates as stated above for detecting silver levels.

d) Detection of silver in blood and urine samples

For this purpose, 0.250 ml serum and 0.250 ml urine samples of the patients was taken and diluted with 5 ml of 2% nitric acid in the proportion of 1/5. The samples prepared were compared with the standards of 2.5, 5.0, 7.5, and 10 μg /L on Perkin-Elmer Analyst 800 Atomic Absorption Spectrophotometer to determine their silver concentrations.

e) Statistical analysis

The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine (Crea), leukocyte (Leu), platelet (Plt), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transaminase (GGT) and silver (in blood and urine) va-
lues which were measured at six different time points compared with the use of Repeated Measures ANOVA test, and Greenhouse-Geisser correction was made if sphericity could not be assumed. Bonferroni test was used as post-hoc test. Statistical analysis was made using computerized SPSS 11.5 programme.

**RESULTS**

In all samples worked on, silver quantity was determined as <0.125 μg/L at 0.005 absorbance. No difference was detected between the preoperative samples and the samples taken 12 months after the operation. All other values measured were regarded as being safe since they were <5 micrograms/L (Table 3).

Complete blood counts, renal and liver functions, ESR, and CRP values of the patients included in the trial were periodically followed up for one year (Graphic 1-9). Any elevation in the white blood cell count which is an indicator of infection during postoperative period, was not determined in any patient. Reactive platelet elevation, which lasted for the first three months of the postoperative period and is known to be secondary to the operation, was detected in all patients, and a mild elevation in the white blood cell count that had normalized at the end of the first month was detected in some patients. All these values normalized during the 12-month follow-up period. No deterioration in renal and liver functions when compared to the preopera-

Table 3. Mean values of laboratory results in urine and blood of patients included in the trial at base level and during the follow-up period. (mo.: Month, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, BUN: Blood urea nitrogen, Cr: Creatinine, Leu: Leukocyte, Plt: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gamma-glutamyl transaminase)

| Time      | ESR   | CRP   | BUN   | Cr   | Leu  | Plt   | ALT   | AST   | GGT   | Silver (urine) | Silver (blood) | n   |
|-----------|-------|-------|-------|------|------|-------|-------|-------|-------|----------------|----------------|-----|
| 0 day     | 13.9  | 3.75  | 10.2  | 0.9  | 14.90| 380.00| 17.3  | 14.2  | 16.7  | <0.125         | <0.125         | 50  |
| 10th day  | 45.8  | 23.65 | 11.8  | 1.1  | 17.870| 893.000| 17.0  | 21.5  | 19.3  | <0.125         | <0.125         | 50  |
| 1st mo.   | 24.2  | 14.16 | 12.0  | 0.8  | 13.220| 568.000| 16.8  | 18.9  | 18.9  | <0.125         | <0.125         | 47  |
| 3rd mo.   | 19.1  | 9.08  | 11.9  | 1.0  | 11.300| 370.000| 17.2  | 13.2  | 22.8  | <0.125         | <0.125         | 49  |
| 6th mo.   | 21.3  | 3.80  | 9.3   | 1.2  | 11.450| 390.000| 19.5  | 17.6  | 19.3  | <0.125         | <0.125         | 45  |
| 12th mo.  | 10.9  | 2.57  | 8.9   | 0.9  | 9.700 | 345.000| 21.4  | 14.6  | 20.2  | <0.125         | <0.125         | 41  |

- **Graphic 1.** A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean sedimentation values differed statistically significantly between time points (F (2.737, 104)=440.6, p<0.001). According to the Bonferroni test, results at 10th day, 1th month, 3th month, and 6th month were statistically different set of values when compared to baseline (for all comparisons p <0.001) but were not different from baseline values at 12th months (p= 0.666).

- **Graphic 2.** A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean CRP values differed statistically significantly between time points (F (2.812, 106.862)=1527.741, p<0.001). According to the Bonferroni test, results at 10th day, 1th month, 3th month, and 6th month were statistically higher set of values when compared to baseline (for all comparisons p <0.001) but were not different from baseline values at 12th months (p= 0.666).
The postoperative period was determined in any of the patients in the trial. There was an increase in ESR and CRP values in the postoperative period as expected; however, these values had normalized in all patients within the first month. The summary of all these data is given in Table 3. Cerebrospinal fluid leakage occurred during the operation in only 3 patients, and the dural defects in these patients were primarily sutured and repaired using tissue adhesives. Lumbar external drainage was used for one of these 3 patients and these patients were followed up for 10 days. No surgical wound site problem was detected in the postoperative period in any other patient included in the trial.
Body temperature above 38°C was detected in only 2 patients on the postoperative 2nd day, and in 1 patient on the postoperative 3rd day, detected only in one measurement. No application other than cold compress was applied in these patients.

No clinical or laboratory infection was detected in any of these 50 patients included in the trial after one year, while it was 3% for our clinic, before we used silver coated system.

It has been stated in the literature that gray-blue skin discoloration at the site of the implant can occur after silver intoxication (14,15,16). We thus inspected the incision area for any such development when patients presented for their follow-up examination. No skin discoloration was observed in any patient. It was also reported in the literature that especially in strabismus operations to shorten the ocular muscles, silver metal was used for reattaching the muscles to the bone, and gray-blue discoloration in the sclera was detection in association with exposure to silver metal (17). Each patient that presented for follow-up was reinspected in this regard, even though discoloration develops due to the local rather than systemic impact of the implant. During further follow-up (at 3rd, 6th and 12th months), each patient was contacted by telephone or e-mail and queried regarding any discoloration on the skin or sclera. Patients were kept under follow-up for 12 months, during which period there was no
dermal or scleral color change that would suggest silver accumulation.

Some patients required a second lumbosacral MRI during their follow-up examinations. MRIs showed that the artifact level was no different from that of the classical titanium screws. It was detected that the silver coating was also useful in this respect and did not create any problems in postoperative follow-up imaging.

**DISCUSSION**

Clinical trials have shown that the presence of biomaterial in the surgical site renders the host tissue sensitive to infection in both the early and late periods (18). The bacterial biofilm layer formed on the surface of the implanted material is the most important factor in development of resistance (8,13). This layer forms a serious barrier against the effect of antibiotics on the bacteria. Thus, infections occurring in biomaterial respond hardly to antibiotics, and the infection generally cannot be controlled until removal of the implant (19,20,21). Infections that occur following implantation may require long-term treatment, including replacement of the infected implant, resection arthroplasty, or amputation, depending on the severity of symptoms (22). Implant-related infections occurring after instrumental spinal surgery are among the most difficult problems for which there remains no proven solution. Antibiotic treatment alone is not sufficient in nearly 50% of the patients, and a surgical procedure is inevitable. This is undesirable both in terms of patient comfort and financial burden. Increased usage of metal implants in vertebral surgery, especially within the last decade, has brought about an increase in postoperative infection rates. The infection rate reported after surgical operations in which routine antibiotic prophylaxis is performed is 1% in cases where a metal implant is not used, and increasing up to 2.1-8.5% in patients who underwent metal implantation (19,23,24). This demonstrates the presence of a strong correlation between instrument use and infection development.

Silver has been used for centuries due to its antibacterial properties and no evidence has been found thus far showing that it has any important function in animal or plant metabolism (25). Only small amounts of silver will be resorbed by the intestine and transported as a complex with plasma proteins. Most silver is then excreted by the liver. The rest of the silver is stored and accumulated intracellularly in organs and tissues without any use (22). However, silver binds not only to proteins but also to bacterial DNA and RNA. In a study conducted using radioactive silver, it was detected that silver formed covalent bonds with *Pseudomonas aeruginosa* DNA, but did not change the structure of the DNA (26). The same experiment showed that silver binds to the RNA and other components of bacteria at a much lower rate. Silver that penetrates the cell inhibits the energy metabolism of bacteria. It deactivates sulfhydryl enzymes and forms compounds with amino, imidazole, carboxyl, and phosphate groups (27). It disrupts DNA replication and prevents mitosis in prokaryotes and disrupts the selective permeability of the cell membrane, ultimately causing the cell to swell and die (28). It reacts with tissue proteins, which disrupt the medium required for the reproduction of proteolytic bacteria (27). It stops replication of *P. aeruginosa* by binding to its DNA in the logarithmic reproduction phase. It prevents the oxidation of glucose, glycerol, fumarate, succinate, D-lactate, and L-lactate in *Escherichia coli* and affects the oxidative phosphorylation of the cell, and therefore, ATP synthesis (28). It inhibits B-galactosidase enzyme thereby stopping the respiratory chain and causing cell death (27). Glucose, glycerol, fumarate, succinate, D-lactate, and L-lactate are oxidized, whereas the oxidation of free sulfhydryl groups and NADPH is inhibited (27,28).
The toxic activity of silver is often local. Its systemic effect tends to remain local since silver is absorbed very slowly. Silver ions bind to proteins and form sediments of silver chloride at the application site. A trace amount of silver is absorbed through mucous membranes or through the skin in burn patients in the form of silver nitrate. Absorbed silver finds itself a wide area of distribution in the body. It particularly accumulates in the subepithelial area of the skin. It causes blue-gray discoloration, also known as argyria, as a result of its subepithelial accumulation at greater amounts (14,15). This pigment consists of silver sulfide and metallic silver which causes only permanent cosmetic problem.

Argyria is most commonly observed in humans exposed to silver (22). This pathological finding was seen more commonly in the 19th century in association with occupational exposure in silversmiths, miners, and photographers (15,16,22). Argyria can also appear from the use of colloidal silver products and/or silver containing medical agents (22). A research on silver accumulation in the tissue and blood tends to show that the level of this metal in a normal population not affected by industrial exposure should be only at a level of nanograms per gram of tissue (29). After the spectrophotometric examination they performed on a patient prediagnosed with lead poisoning because of his gray-blue skin color. A study detected that the blood silver quantity of the patient was 0.5 µg/ml; however, they stated the normal silver content in the blood should be at maximum 5 ng/ml (or 5 µg/L) (25,29). As the history of the patient was further investigated, it was learned that the patient had taken silver nitrate capsules of 16 mg x 3 times a day for his gastrointestinal symptoms.

In another resource, normal values of silver are given as follows (30):
Serum: 2.1±1.5 µg/L (19.5±13.9 nmol/L)
Plasma: 0.68±0.33 µg/L (6.3±5.8 nmol/L)

Pure platelet: 29±18 ng/gram (wet weight) (269±167 nmol/gram wet weight)
24-hour urine: <1 µg /day (<9.3 nmol/day)
Hair strand: 0.02-1.00 µg/gram (dry weight) (0.2-9.3 nmol/gram) (dry weight)

According to Wan et al. blood silver levels lower than 200 ppb must be considered as normal. Because regular human diets includes small amounts of silver and consumers take silver via their diets (31). Oral silver intake from a typical diet has been estimated to range between 27, and 88 ug/day but some other researchers estimated lesser intake of 10-20 ug/day (29,32,33). A concentration of silver in the blood of more than 300 ppb has been reported to cause argyria, and liver and kidney damage (34). Drake and Hazelwood found that acute symptoms of overexposure to silver nitrate include a decrease in blood pressure, diarrhea, irritation of the stomach, and decreased respiration (35). Chronic symptoms resulting from intake of a low dose of silver salts are fatty degeneration in the liver and kidneys (35). Long-term inhalation or ingestion of soluble silver salts or colloidal silver may cause argyria.

Usage of nanoparticle silver because of its antibacterial and antifungal properties is increasing in frequency with the result of development in nanoscience. Food, drug and cosmetic industry have begun to use nano silver in their products. Thus water, food, cosmetics, drugs, and drug delivery devices can be a route for ingesting silver nanoparticles (36). It has been also demonstrated that silver ions can liberate from ingested products into the blood. Thus they can be responsible for accumulating in visceral organs leading to liver and kidney toxicity (37). However, acute oral or transdermal intake of nanoparticle silver (2,000 mg/kg-body weight) has not caused any significant clinical signs, mortality, acute irritation, or corrosive reactions affecting the eyes and skin neither in rats nor in guinea pigs or in rabbits (38,39). Kawata et al. reported that nano-
particle silver may cause cytotoxicity in human hepatoma cells but only at high doses (>1 mg/L) (40). Other investigators (41,42) reported that silver is nonmutagenic.

Despite all these studies and increase in usage of nano silver, most of these studies are still restricted to in vitro experiments and conduction of a clinical trial is still needed. Our study is the unique study which focused on clinical usage of nanoparticle silver coated vertebral implants in human beings.

When we discuss and focus on our results; elevated levels in ESR-CRP and platelet-leukocytes levels during the first month after exposure were expected because acute phase reactants and reactive species respond to nano silver implant placement. All these values were normalized after 3th month of study. Sedimentation, CRP and leukocytes values were under baseline at the end of the 12th month. Decrease in the levels of these parameters suggested recovery of some preoperatively infected patients. Increased levels of BUN and creatinine at early period of trial (up to 1th month) may be misleading. All patients received intravenous saline therapy all night long preoperatively as a clinical routine and all blood samples were taken at the end of night, just before the operation. This condition decreased the baseline parameters of renal function. A mild elevation of these parameters may be due to anesthesia and/or analgesic and antibiotic therapy after operation or dehydration because of blood loss during surgery as expected. Only hepatic functions, especially ALT measurements were deteriorated. AST suddenly elevated at 3th month and returned to baseline at the end of 12th month. While GGT decreased at 3th month, a mild elevation was occurred at 6th month but it was close to baseline at the end. Despite all these fluctuations and alterations in hepatic functions, all parameters were still in normal ranges. Continuous elevation in ALT at all time points of trial may be the sign of long-term harmful hepatic effects of nano silver, even the measurements were still within the normal ranges. Although isolated ALT elevation has not any clinical value, ongoing elevation of ALT may be thought to be associated with exposure to nano silver, and it may cause hepatic dysfunction in the long run if serum or urine silver levels were elevated. But our spectrophotometric analysis clearly demonstrated that serum or urine silver levels did not elevate, thus all these results could not be associated with serum and urine levels of silver.

Gaul and Staud estimated that a 50-year old man can store an average of 0.23-0.48 g of silver in his body (14). Literature has also revealed that total accumulated intravenous dose of 8 g silver arsphenamin (1.84 g silver) is enough to cause argyria (14,43). It has been also reported that ingesting 30 mg/day silver for 1 year, elevates serum silver levels to 0.5 mg/L and may cause argyria (44). Olcott reported that 89 mg/kg/day colloidal silver consumption resulted in ventricular hypertrophy in rats after 218 day, and upon autopsy, advanced pigmentation was seen in visceral organs, but the ventricular hypertrophy was not attributed to silver deposition (45). Furchner et al. studied absorption and retention of silver (as silver nitrate) in mice, rats, monkeys and dogs. In all species cumulative amount of silver nitrate excretion ranged from 90 to 99%, and only 1 to 10% of it was retained (46). Nanoparticle silver may have a higher retention rate because of its nano scale, but even so, approximately 90% of silver will be excreted after it is released from implant surface.

Another topic about silver toxicity or biosafety may focus on amalgam fillings. As is known, conventional amalgam is a powder of silver-tin alloy mixed with mercury. Silver proportion of an amalgam filling is 65% (approximately 2.6 g of silver). Despite most of the articles about amalgam fillings focused on its mercury content,
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a few studies about its silver content and tissue dispersion can be found.

Drasch et al. studied 173 cadavers that had more than 9 amalgam fillings (23 g silver, as calculated by us). They found that silver concentration was 5.41 ug/kg in cerebral cortex, 4.25 ug/kg in white matter, 5.02 ug/kg in cerebellum, 8.15 ug/kg in liver and 0.44 ug/kg in renal cortex (47).

The data about cadavers’ mental and health status could not be predicted while they were alive, and the authors did not note any skin coloration which could reveal argyria. Maybe one can claim that toxic metal accumulation in brain may cause mental disorders, but all other clinical trials have been claiming that amalgam fillings are safe enough and do not cause mental or neurological disorders (48,49,50). When the said study and the listed dental literature interpreted together, we can claim that even 23 g of silver implantation will not cause argyria or mental or neurological disorders.

Tsukamato et al. declared that 2% silver hydroxypatite coating of a femoral replacement prosthesis contains 1.14 mg of coating material (0.0228 mg silver, calculated by us). And they said that surface area of such a prosthesis is 76 cm². On the other hand, they claimed that this amount of silver would not cause argyria (22).

Our pedicle screws used in this study had 26 cm² surface area for a 6.5x45 mm sized implant (data provided from manufacturer, Mikron Makine, Ankara, Turkey). The sol-gel chemical which was used for dip coating of implants contained 100 ppm nano silver (100 mg/L). Estimated thickness of coating was 300 nanometer, calculated volume of chemical and amount of silver which coated on one screw were 0.00078 ml and 0.000078 mg, respectively. It means, that if 10 screws are used for one patient, total exposure to silver will be 0.78 ug for a whole body distribution. According to the literature listed above, a normal person intakes 10-20 ug/day silver with its diary diet (29,32,33). Even this literature alone proves that the silver-coated implants are sufficiently safe. On the other hand, according to Furchner et al (46), minimum 90% percentage of 0.78 ug silver must be excreted. This means that 0.078 ug of silver will be retained in the whole body of a patient for each screw. According to Kawata et al (40) 0.78 ug silver will not cause any cytotoxic effect.

Even a simple calculation indicates that our each screw has approximately 23 million-fold lower silver amount than toxic dose (14,43). With such implant it is impossible to cause argyria (14,31,34), mental or neurological disorders (48,49,50), hepatic and renal disfunction (29,31,32,33), cytotoxicity (40) or mutagenity (41,42). Our findings have shown that titanium implants coated with nanoparticle silver can be used safely for preventing implant-related infections.

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