Antibacterial and Antifungal Effects of Weak Direct Current and Silver Ions

Zayıf Elektrik Akımının ve Gümüş İyonlarının Antibakteriyel ve Antifungal Etkileri

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ABSTRACT Objective: The aim of this study was to demonstrate the antimicrobial effects of silver anode and to discuss its clinical use. **Material and Methods:** Silver containing dressing materials were cut tobe used as anodic and cathodic electrodes; on the other hand, for the assesment of the natural response of microorganisms to silver ions or silver containing formulations, sham electrodes, which were not connected with any electrical current source, were cut and placed in Petri dishes. Microorganism containing media were poured into the dishes. *Escherichia coli, Staphylococcus aureus, Candida albicans, Staphylococcus epidermidis, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter baumannii* were selected among the clinical isolates of our hospital. The outer ends of the electrodes were connected to a direct current (DC) source, except sham electrodes (if used). Different current levels and different durations were examined on different microorganisms for achieving a general overview about silver anode application. On the other hand, *E. coli, S. aureus* and *C. albicans* containing 3 Petri dishes were abreast connected abreast and a 2.5 microampere (μA) direct current was applied for 8 hours, while plates were incubated at 37°C for 24 hours. Inhibition zones around anode, cathode and sham electrodes were assessed. **Results:** Inhibition zones were seen around all anodic electrodes. In some cases additional inhibition zones were seen around cathode and/or sham electrodes. In our second study, which was run with abreast connected Petri dishes, there was no inhibition zone around cathode with *E. coli*, but marked inhibition zones were present with *S. aureus* and *C. albicans.* Zones around sham electrodes were variable and results were attributed to the natural response or resistance of organism to silver ions. **Conclusion:** Our study suggested the antimicrobial effect of silver ions, and showed that electrical current application could change this effect. Anodic current increases silver ion liberation from silver containing dressings, thus antimicrobial effect increases. On the other hand, cathodic current decreases this liberation and the effect of silver ions decreases. The results obtained from sham electrodes were considered the natural response of the organism to silver ions. Our results showed that silver containing dressings could be used to prevent pressure ulcers. While the addition of anodic current increased the antimicrobial effect, the cathodic current did not have such an effect.

Key Words: Silver; electrodes; pressure ulcer

ÖZET Amaç: Gümüş anot uygulamasının antibakteriyel ve antifungal etkilerinin gösterilmesi ve klinikte kullanılabilirliğinin tartışılması. **Gereç ve Yöntemler:** Ticari olarak temin edilen gümüş fiber içerikli pansuman materyalleri anot ve katot elektrodu olarak kullanılmak üzere uygun ebatlarda kesildi; mikroorganizmaların gümüş iyonlarına veya gümüşlü preparatlara verdiği doğal cevabı değerlendirmek için ise elektrik akımının uygulanmayacağı sham elektrotlar hazırlandı. Tüm elektrotlar ilgili literatürlerde belirtildiği şekilde Petri kutularına yerleştirildi. Önce genel bir bakış açısı sağlayabilmek için klinik izolatlardan elde edilen *Escherichia coli, Staphylococcus aureus* ve *Candida albicans, Staphylococcus epidermidis, Pseudomonas aeruginosa, Klebsiella pneumonia* ve *Acinetobacter baumannii* içeren besiyerleri Petri kutularına döküldü; elektrotların dışarıda kalan uçlarına değişen sürelerle ve değişen değerlerde doğru akım uygulanarak 37°C'de inkübe edildi. Bu çalışmayı takiben aynı şartlar altında farklı mikroorganizmaların gümüş anot uygulamasına verdiği cevabı değerlendirmek için, ilk çalışmadan farklı klinik izolatlardan elde edilen *E. coli, S. aureus* ve *C. albicans* birbirine paralel bağlanmış petri kutularında, 8 saat boyunca 2.5 mikroamper doğru akım uygulanarak 37°C'de 24 saat enkübe edildi. Enkübasyondan sonra anot, katot ve sham elektrotlar çevresinde gözlenen inhibisyon zonları değerlendirildi. **Bulgular:** Tüm anodik elektrotların etrafında mikroorganizma üremesinin olmadığı bir inhibisyon zonu gözlemlendi. Bazı bakterilerde sham ve/veya katot etrafında da inhibisyon zonu olduğu ancak bunun bakteriye veya uygulanan akım değerine özgül bir sonuç olmadığı görüldü. Aynı şartların sağlanması için birbirine paralel bağlanarak aynı akımın aynı süreyle uygulandığı 2. çalışmamızda ise katodik elektrotta, *E. coli* içeren besiyerinde inhibisyon zonu gözlemlenmezken *S. aureus* ve *C. albicans* içeren besiyerlerinde belirgin inhibisyon zonu saptandı. Mikroorganizmaların sham elektrotlara verdiği cevap ise oldukça değişkendi ve muhtemelen mikroorganizmanın gümüş iyonlarına karşı olan duyarlılığının gerçek göstergesiydi. **Sonuç:** Çalışmamız, gümüş iyonlarının bilinen antibakteriyel ve antifungal etkilerini doğrularken elektrik akımı uygulaması ile bu cevabın nasıl değiştirilebileceğini göstermiştir. Anodik uygulama gümüş iyonlarının salınımını artırarak antimikrobiyal etkiyi artırmakta, katodik uygulama, doğal iyon emisyonunu da azaltarak gümüş iyonlarının etkinliğini azaltmaktadır. Sham elektrotlara verilen cevaplar ise mikroorganizmanın gümüşe karşı verdiği doğal cevabı yansıtmaktadır. Bulgularımız, gümüş iyonu içeren yara bakımı ürünlerinin elektrik akımı olmaksızın klinikte bası yaralarına karşı kullanılabileceğini, anodik akımla kombine edilerek bu etkinin artırılabileceğini, ancak katodik akımın uygun bir seçim olmadığını göstermiştir.

Anahtar Kelimeler: Gümüş; elektrot; bası yarası

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Antibacterial properties of the silver ion have been familiar to many physicians since BC and it has been widely used, particularly by *Avicenna* since 900s AC for its antibacterial effects.[1] Today, silver preparations in compounds such as silver nitrate, silver sulphate and silver sulphadiazine are still used for burns and dermal ulcers in particular.[2,3] Application of electric current to biological tissue has started to attract attention since 1960s. On the other hand, the use of "silver anode application" which can be summarized as "combination of silver ions with electric current" decreased due to the increasing use of the use of antibiotics. Moreover, increased use of the antibiotics brings itself the problem of developing resistance to the agents. However, no microorganism has been reported yet which showed resistance to the silver anode application. Furthermore, the microorganisms which are resistant to silver containing drugs can be eradicated with this application.

The antimicrobial effect of the silver anode application under both in vitro and in vivo circumstances and reports suggested that when applied properly it did not bear any damaging effect against eukaryote cells (except for fungi).[4-7] Yet this application has antifungal, antibacterial, antitumoral, and epithelium repairing properties.[3-6,8-13] Spadaro et al reported that silver anode treatment was effective on *Clostridia* species. This was the uniqe report that declared its anti-anaerobic effect.[6] Earlier, in vitro studies conducted with the metalic silver electrodes and treatment of chronic osteomyelitis proved the effectiveness of the silver anode treatment.[5,6,9,14-16] Silver containing fibers (Silverlon™) developed in the course of time were used to treat the chronic dermal ulcers and decubitus ulcers and brought a new dimension to the application.[5,6,11-13]

Decubitus ulcers continue to be a problem for the immobile and unconscious patients and sometimes account for the mortality. We conducted a series of in vitro applications which proved the effectiveness of the silver anode applications for both surgical infections and decubitus ulcers in our neurosurgery clinic.

MATERIAL AND METHODS

In this study, *Candida albicans, Staphylococcus aureus, Escherichia coli, Staphylococcus epidermidis, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter baumannii* were selected due to their frequency as pathogens involved in nosocomial infections. The microorganisms were isolated from samples obtained from decubitus ulcers in various clinics of our hospital. Media for cultures (Sabouraud's agar and Muller-Hinton agar) were supplied from the Laboratory of Infectious Diseases.

Sterile electrodes (Silverlon™, Argentum Medical, degree of purity 91%, 0.5 x 12 cm) and silver wire electrodes (degree of purity 98%, 1 mm diameter and 12 cm long) were inserted in 8 cm diameter sterile Petri dishes, last 5 cm of the electrodes were kept out in order to be able to apply electric current later. While the medium cooled (41°C), 2 mL of microorganism (ranging from 3 x 10^4 to 1 x 10^6 cfu, Table 1) containing stock solution was poured into the culture medium. Each microorganisms achieved different current values (ranging from 1.2 to 4.6 μA, Table 1) and different exposure periods (ranging from 15 minutes to 24 hours, Table 1). A second study was performed with *E. coli, S. aureus* and *C. albicans* with abreast connected Petri dishes to evaluate different microorganisms with the same electrical parameters. In the second study, sterile electrodes (Silverlon™, Argentum Medical, degree of purity 91%, 0.5 x 12 cm) were inserted in 8 cm diameter sterile Petri dishes; the last 5 cm of the electrodes were kept out in order to be able to apply electric current later. While the culture medium cooled (41°C), 2 mL of stock solution containing 1 x 10^5 cfu microorganism was poured into the culture medium and ten mililiters of this was poured in each Petri dish. One sham electrode was used for each microorganism. Then each Petri dish was connected with the same direct current (DC) generator, operating with a battery and a 2.5 μA DC current (total current) was applied for 8 hours (V: 1.5 volts, R: 200 ohms, A: 25. 10^{-6} ampere, distance between the electrodes was 40 mm).

TABLE 1: Different responses given by seven different microorganisms to different current values and different durations. Note that response was always given to the silver anode application. Zone diameter was independent from the type of the microorganism, duration of the application or current intensity. The fact that the zones were larger in the studies run with wire electrodes seems to be related to the degree of purity of the material (Silverlon™ has 91% purity and the anodic silver ion concentration released from its surface is probably lower than that of the wire electrodes).

Assay Number	Electrode Type	Microorganism (cfu)	Zone Width (mm) Anode	Cathode	Sham	Amount of Current (μA)	Duration of Current
1	Silverlon	*A. baumannii* (3 x 10^4)	5	2	3	2.8	24 hours
2	Silverlon	*C. albicans* (2 x 10^5)	3	0	0	2.0	24 hours
3	Silverlon	*E. coli* (1 x 10^6)	5	5	not used	1.6	3 hours
4	Silverlon	*E. coli* (5 x 10^5)	3	0	0	2.2	24 hours
5	Silver wire	*E. coli* * (2 x 10^5)	6	0	not used	2.6	24 hours
6	Silverlon	*E. coli* + *S. aureus* (2 x 10^5 cfu)	3	0	not used	2.0	24 hours
7	Silverlon	*K. pneumoniae* (4 x 10^4)	3	1	2	2.0	24 hours
8	Silverlon	*P. aeruginosa* (3 x 10^5)	3	1	3	2.5	24 hours
9	Silverlon	*S. aureus* (1 x 10^6)	4	0	not used	2.0	30 minutes
10	Silverlon	*S. aureus* (5 x 10^5)	3	0	5	2.0	24 hours
11	Silver wire	*S. epidermidis** (1 x 10^5)	4	0	0	4.6	1 hour
12	Silver wire	*S. epidermidis** (3 x 10^4)	4	0	0	4.6	24 hours
13	Silver wire	*S. epidermidis** (1 x 10^6)	5	0	not used	1.1	15 minutes

Culture medium resistance was measured as 400 ohms. Results obtained at the end of the application were shown in Table 2 and Figure 1-4.

The electrodes were kept in place for the next two weeks; no electric current was applied to the Petri dishes and samples obtained from the inhibition zones were cultivated at 5-day intervals.

RESULTS

The silver containing dressing materials (Silverlon™) were effective. The results were shown in Table 1. Zone width was obtained by measuring only one side of the electrode (the distance from the electrode boundary to the zone boundary). Although the current was ceased after 8 hours (in the second study, Table 2) and not applied again, no changes wer seen in the diameters of the zones for the following 2 weeks. No bacterial growth was noted in the cultures of samples taken from the zones at the end of 24 hours for three cultivations made at 5-days intervals. No color change occurred in the agar plates at the end of the application; only a darkening was detected at the joint place of the electrodes and current source.

TABLE 2: Bacterial inhibition zones near silver containing fiber (Silverlon™) electrodes with 2.5 μA of direct currents.

Microorganism	Zone Width (mm) Anode	Cathode	Sham
Methyciline resistant *S. aureus*	2.5	2.5	2.5
E. coli	3.5	0	1
C. albicans	3	1.5	0

DISCUSSION

It has been well established since the time of Avicenna that Silver ions were antibacterial.[1] Inhibition of bacterial growth in response to weak electrical currents has been reported.[4–7] If a pure (>99.9%) silver wire is connected to a weak direct current (0.1-10 μA) in a semi-solid culture medium, a bacteria-free inhibition zone appears near the anode after an incubation period, but not near the cathode. This antibacterial effect persists for at least 10 weeks after the electric current is cut off.[7] This procedure is called silver anode treatment. In the relevant literature, electrically induced silver ions were shown to have antifungal, antibacterial

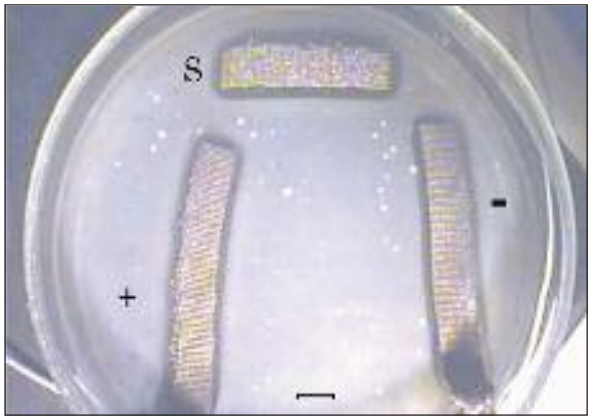

FIGURE 1: The inhibition zones are seen around anode and cathode at 2.5 microamperes and sham electrode (no current), for meticilline resistant *Staphylococcus aureus*. The zone in the sham electrode is equal to that in the anode, thus electrical stimulation may not be needed for in vivo applications. Interestingly, the cathodic current did not restrict the diameter of the inhibition zone. However, the anodic current did not increase the zone diameter (the scale is 5 mm long). (S: Sham, +: Anode, - : Cathode)

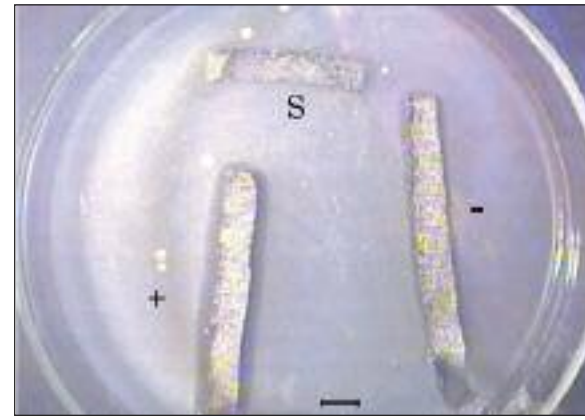

FIGURE 2: The inhibition zones are seen around anode and cathode at 2,5 μA on *C. albicans*. There is not any zone arround sham electrode (no current). Thus it can be speculated that this clinical isolate is resistant to silver. The zone diameter around the anode is larger than cathode as expected. Anodic current seems to be suitable for *C. albicans*, even if silver containg preparates are ineffective (the scale is in 5 mm long). (S: Sham, +: Anode, - : Cathode)

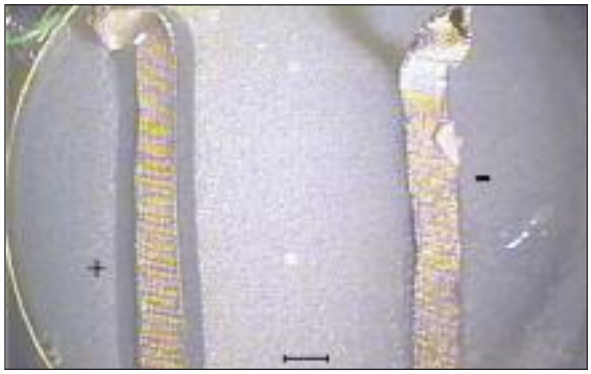

FIGURE 3, 4: The inhibition zones are seen around anode and cathode at 2.5 μA on *E. coli*. The best respons was achieved in anodic application on *E. coli* (3.5 mm diameter), however there is not any inhibition arround cathode (Figure 3), but 1 mm of inhibition zone was seen arround sham electrode (Figure 4). The lack of inhibition zone around the cathode may be due to restricted liberation of silver ions (Ag^{++}) from the electrode surface, because of possitive load of silver ions and negative load of cathode. Opposite poles or loads will attract each other as expected (the scale is in 5 mm long). (S: Sham, +: Anode, - : Cathode)

and antiviral properties, and were found to be nonallergenic and nontoxic to mammalian cells.[7,14] Minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) of electrically induced silver ions in nutrient broth (GIBCO) are approximately 100 times lower than they are for silver sulfadiazine.[7] This study was run with both clinical isolates and commercially provided strains. This shows that electrical polarization confers extensive bactericidal specificity on silver. No other metal has as strong an antimicrobial effect as anodized silver.[10] The specificity of silver suggests that electricity is not the key factor in silver anode antisepsis. The mechanism of anodic silver antisepsis may originate either from free silver ions scattering from the anode surface to the medium or from the electrical current. It is known that the antibacterial effect does not occur via silver iontophoresis.[7]

The idea of inserting silver electrodes into living tissue is not new in orthopedics and dentistry. Becker et al treated infected non-union fractures with silver anodes. Similarly, Aydın et al treated infected teeth with inserted silver anodes. In such cases the actual current passes through the tissue and the total charge is based on tissue changes. In the

literature, the threshold for living eucaryotic cells is given as 20 μA for actual current and 2 C/day for total charge.[4] In the present study, these electrical parameters were maintained to avoid irreversible tissue damage even if it is used in mammalians.

Bio-implants in the human body act as passive surfaces that are prone to bacterial adhesion and thus, may cause implant-associated infections.[17] In 2008, Secinti et al reported that silver coated titanium implants had significant bactericidal effect on meticilline resistant *S. aureus* when used as vertebral implants in rabbits if anodized.[18] Antibiotic treatment of infected implants is not satisfactory because the biofilm architecture protects the adhering organisms. The MIC of antibiotic needed to inhibit free-floating bacteria was reported to be approximately 50-500 times lower than that required for bacteria in a biofilm.[19]

Biofilms may cause antibiotic resistance by harboring pathogenic microorganisms.[20] Electricity has been used to remove biofilms from medical surfaces.[21] Poortinga et al stated that it was possible to stimulate bacterial detachment from conducting indium tin oxide-coated glass by using a 10 $\mu A/cm^2$ electrical current.[22] Similarly, van der Borden et al reported electrical current-induced detachment of *S. epidermidis* and detachment of biofilm formations from surgical implants.[20,23,24] However all these studies were done under in vitro conditions. Thus, higher current values were used but they were not suitable for living tissues. This results demonstrate that electrical current antisepsis is not useful for in vivo applications if silver electrodes are not in use. Aydin et al studied antibiotic sensitivity after exposure of bacteria to a silver anode.[25] The results of their study provided the opportunity to speculate that when the silver containing dressing materials were anodized, the antibiotics became more effective.

The mechanism of action of silver ions on bacteria can be summarized as inactivating sulfhydryl enzymes, combining with amino, imidazole, carboxyl and phosphate groups, influencing DNA replication and stopping mitosis in procaryotes, affecting selective permeability of cell membrane, combining with tissue proteins so proteolytic bacteria cannot replicate, stopping replication by binding to the DNA of log phase *P. aeruginosa*, inhibiting oxidation of glucose, glycerol, succinate, D-lactate and L-lactate and endogenous substrates of intact cell suspensions of *E. coli* thereby inhibiting the respiratory chain, and inhibiting the β-galactosidase enzyme, causing bactericidal effect on *E. coli*.[1,4,8,25-27]

In our study, *S. aureus* seems to be the most sensitive microorganism to silver in this application. The zone in the sham electrode is satisfying and electric stimulation may not be needed for the in vivo applications. *C. albicans* appears to be the most resistant microorganism. The fact that there is no zone in the sham applications makes the current application compulsory for in vivo studies. *E. coli* seems to show intermediate sensitivity.

The results to be drawn from this study are as follows: Silver anode application is bactericidal and fungicidal. If this application was only bacteriostatic or fungistatic, the cultures obtained from the inhibition zone after the cessation of electrical current, would not be negative. On the other hand, the diameters of inhibition zones did not reduce after 2 weeks in the second study; this situation suggests that the silver anode is bactericidal and fungicidal. Thus, it is clear that, this application is not bacteriostatic or fungistatic. The total current density applied to the culture media was calculated as 0.72 coulomb in the second study; this value is lower than the dose described as harmful for human tissues in the literature.[7]

Microorganisms that are not naturally sensitive (*C. albicans*, note that this microorganism was not responsive to cathodic current or sham electrodes in both study 1 and study 2) or semi-sensitive (*E. coli*) to silver under normal circumstances became sensitive after the current application. Therefore the effect cannot only be related to the silver. However the fact that there was no inhibition in the studies applied to different metals or that these metals required higher current degrees suggests that inhibition does not only depend on the electric current.[9] Thus, the effect seems to be related with the combined effect of silver and weak direct current applied.

In Table 1; the comparison of assays 3, 4 and 5 revealed that the diameter of the inhibition zone around the anode was not parallel to the increase in current value. Three hours of current application seemed to be better than 24 hours current application on *E. coli* in assay 3 versus assay 4, but not in assay 3 versus assay 5. If assay 9 and 10 were compared with each other, 30 minutes of application seemed to be better than 24 hours of application on *S. aureus* with the same (2.0 μA) current density. When assay 11, 12 and 13 were compared there was no difference between 1-hour or 24-hour long application with 4.6 μA current density on *S. epidermidis.* However, 15 minutes of 1.1 μA current application seemed to be a better choice for *S. epidermidis*. Assay 6 demonstrated that this application was effective even when used on mixed bacteria population.

P. aeruginosa is known as "silver sensitive", thus, silver sulfadiazine containing formulations are have been used for years on burn wounds. In assay 8, sham electrode seemed to be more effective than cathode. Cathodic current decreases the liberation of silver ions from the electrode surface, thus the silver ion concentration around the cathode may be less than that for the sham electrodes in some cases. This can explain the smaller inhibition zone diameter around the cathode than the sham. We think the same situation is present in assay 7 also for *K. pneumoniae.*

However our experiences showed that the zone width did not depend on applied current density or the kind of microorganism and could not be predicted. Furthermore, all the microorganisms used in our assays were always inhibited with the silver anode application (Table 1).

We believe that the application of current is the best approach in every case since the applied current is not harmful to normal tissue. Moreover, the conducted studies demonstrated that the silver ions, which were stimulated by electricity, had a higher penetration depth into the tissue.[4] This shall ensure a more effective and more permanent antimicrobial effect. No bacterial resistance to silver anode treatment (not silver alone) has not been reported up to date.

Because of its wide spectrum, low resistance rates and long duration periods, we suggest the use of silver anode treatment in appropriate clinical cases.

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