In Vitro Antifungal Activities of Antimicrobial Coated/Impregnated Central Venous Catheters Against Candida Albicans

Antimikrobiyal Kaplı Santral Venöz Kateterlerin Candida Albicansa Karşı In Vitro Antifungal Aktiviteleri

Sibel Gelecek Geyik[2], Barış Gürsoy[3], Banu Sancak[1], Sevtap Arıkan[4], Kaya Yorgancı[1]

[1]Hacettepe University Faculty of Medicine, Department of General Surgery, Sıhhiye, Ankara, Turkey
[2]Ankara Keçiören Research and Education Hospital, Division of General Surgery, Keçiören, Ankara, Turkey
[3]Vehbi Koç Foundation, İstanbul American Hospital, İstanbul, Turkey
[4]Hacettepe University Faculty of Medicine, Department of Clinical Microbiology and Infectious Disease, Sıhhiye, Ankara, Turkey

Abstract

Introduction: Antimicrobial coated catheters have variable activities against micro-organisms and little is known about their antifungal effect. The aim of the present study was to determine and compare the antifungal activities of silver sulfadiazine-chlorhexidine impregnated, minocycline and rifampicin bonded and rifampicin-miconazole coated catheters against *Candida albicans*.

Material and Methods: A non-antiseptic Hickman catheter was used as a control group. All catheter segments were trisected in one-centimeter pieces and were immersed in phosphate-buffered saline (0.01 mol/l) with 0.25% dextrose and incubated at 37 oC. This solution was replaced daily. On days 1, 3, 14 and 21, a 1 ml standardized inoculum *Candida albicans* was added for 30 min and then replaced with phosphate-buffered saline with 0.25% dextrose. One-third of the samples were sonicated and plated to determine fungal adherence immediately at 30 min. The remaining segments were plated in sabora-dextrose agar after 4 and 24 h incubation time to determine the further formation of fungal colonies.

Results: Rifampicin-miconazole impregnated catheters significantly prevented initial fungal adherence and 4th hour colonization for the entire study period. At 24 hours, although the rifampicin-miconazole catheter colonization was lower, this did not reach statistical significance. Silver sulfadiazine-chlorhexidine impregnated and minocycline-rifampin coated catheters prevented neither initial candidial adherence nor colonization.

Conclusions: Central venous catheters coated with rifampicin-miconazole were found to be effective against initial candidial adherence. These catheters are also effective against *Candida albicans* colonization for a limited time period.
(Yoğun Bakım Derg 2010; 1: 10-3)

Key words: Blood-stream infections, *Candida albicans*, central venous cateter

Received: 30.09.2009 **Accepted:** 05.01.2010

Özet

Giriş: Antimikrobial ajanlarla kaplı kateterlerin değişik mikroorganizmalara karşı etkinlikleri farklıdır ve antifungal etkinlikleri pek bilinmemektedir. Bu çalışmanın amacı gümüş sulfadiazine-klorheksidin, minosiklin-rifampin ve rifampisin-mikonazol kaplı kateterlerin *Candida albicans*'a karşı antifungal etkinliklerini belirlemek ve karşılaştırmakdır.

Yöntemler: Çalışmada antiseptik kaplı olmayan Hickman kateterler kontrol grubu olarak kullanılmıştır. Tüm kateter parçaları bir santimetre uzunluğunda bölünmüş ve bu segmetler üçe ayrılmıştır. Kateter segmentleri fosfat tamponlu salin (0.01 mol/l) ve %0.25 dekstroz çözeltisinde 37 °C'de inkübe edilmiştir. Çözelti günlük olarak değiştirilmiştir. Bir, 3, 14 ve 21. Günlerde 1 ml standart *Candida albicans* özeltisi 30 dakika süre ile eklenmiş ve ardından fosfat tamponlu salin (0.01 mol/l) ve %0.25 dekstroz ile tekrar inkübe edilmiştir. Örneklerin üçte birinden 30 dakika sonra sonikasyon işlemini takiben ekim yapılmış ve ilk fungal yapışma değerlendirilmiştir. Kalan kateter segmentlerden 4 ve 24 saat sonra fungal çoğalmayı değerlendirmek için sabora-dekstroz agar vasatına ekim yapılmıştır.

Bulgular: Rifampisin-mikonazol kaplı kateterler tüm çalışma boyunca başlangıç ve 4. saat fungal yapışmayı anlamlı olarak azalttı. Yirmidördüncü saatte, bu kateterlerde kolonizasyon daha az olsa da istatistiksel olarak anlamlı değildi. Gümüş sulfadiazine ve minosiklin-rifampin kaplı kateterler başlangıç fungal yapışmayı ve sonra gelişen kolonizasyonu önlemedi.

Sonuç: Rifampisin-mikonazol kaplı kateterler başlangıç fungal yapışmayı önlemede etkindirler. Bu kateterlerin *Candida albicans* kolonizasyonunu engellemede ise sınırlı bir süre etkinlikleri vardır. (Yoğun Bakım Derg 2010; 1: 10-3)

Anahtar sözcükler: Kan akım enfeksiyonları, *Candida albicans*, santral venöz kateter

Geliş Tarihi: 30.09.2009 **Kabul Tarihi:** 05.01.2010

Introduction

Catheter-related bloodstream infections (CR-BSI) are associated with a significant morbidity in critically ill hospitalized patients (1, 2). To reduce these infections, various guidelines and recommendations are published (3, 4). In these recommendations, the use of catheters coated with chlorhexidine/silver sulfadiazine or minocycline/rifampicin are recommended, especially when the risk of CR-BSI is high (5-8). However, in our previous studies we have shown that these catheters have considerable differences in their antibacterial effects against gram positive and gram negative bacteria (9, 10). In addition, their anti-fungal effects are not well established.

On the other hand, invasive candidiasis is an increasing problem in intensive care units. Besides several risk factors, the presence or even previous use of a central venous catheter is an independent risk factor for nosocomial candidemia (11). Therefore, although not frequently seen, fungal micro-organisms should be considered in CR-BSI, especially if the catheter is left in place for a long time.

The aim of the present study was to determine and compare the antifungal activities of silver sulfadiazine-chlorhexidine impregnated (SS-C),

Address for Correspondence/Yazışma Adresi: Kaya Yorgancı M.D., Hacettepe University, Faculty of Medicine Department of General Surgery, 06601 Sıhhıye, Ankara, Turkey
Phone: +90 312 305 16 76 Fax: +90 312 310 40 71 e.mail: yorganci@hacettepe.edu.tr

minocycline and rifampicin bonded (M-R) and a novel antifungal coated [rifampicin-miconazole (R-Mic)] catheters against *Candida albicans*.

Material and Methods

Catheters and their preparation

Antimicrobial treated catheters were silver sulfadiazine-chlorhexidine impregnated (Arrowguard Blue Plus, Arrow International, Reading, PA), minocycline-and rifampicin-bonded (Cook Spectrum, Cook Critical Care, Bloomington, IN) and rifampicin-miconazole impregnated (Laboratoires Pharmaceutiques, Vygon, France). They were triple-lumen, 20-gauge (7 French), 20 cm long and coated/impregnated on both inner and outer surfaces. A single lumen, 7Fr Hickman central venous catheter (Bard Access Systems, Salt Lake City, Utah) was used as a non-antiseptic-impregnated control group. Catheters were divided into 1cm segments above the first distal opening and below the catheter hub. Three lumen catheters were further divided longitudinally into three parts and the single lumen catheters were bisected longitudinally to expose intraluminal surfaces. These procedures were conducted under aseptic conditions.

Evaluation of initial candidal adherence and colonization

One-centimetre catheter segments were immersed separately into tubes containing 1 ml of phosphate-buffered saline (0.01 mol/l) with 0.25% dextrose (PBSD) and incubated at 37°C. The PBSD was replaced daily for a period of 21 days. On days 1, 3, 14 and 21, a 1 ml *Candida albicans ATCC* suspension adjusted to 0.5 McFarland was added to 72 tubes (18 tubes from each catheter). After 30 min, the suspension was discarded and replaced with PBSD. Twenty-four catheter segments (6 from each catheter type) were taken immediately, washed three times with PBS to remove non-adherent micro-organisms, sonicated at 20 kHz for 60 seconds (IKA Labor Tecknik, Germany), then vortexed and plated to determine initial candidial adherence. Fifty-four catheter segments were incubated for 4 and 24 h, after which they were processed as described to evaluate candidial adherence and further persistance on the catheter surface. Plates were read after 48 h of incubation.

Statistical analysis

The experimental data were recorded in a computerized statistical database (SPSS Statistics 16.0). Analysis of variance (ANOVA) was used to compare the occurrence of persistence and colonization between the catheter groups. Unless stated otherwise, the data are expressed as means±SEM. Probabilities less than or equal to 0.05 were considered as significant.

Results

Initial candidial adherence to the control group catheters were 62.9±3.8, 43.6±7.8, 54.9±6.9 and 53.7±5.7 cfu/ml on days 1, 3, 14 and 21 respectively (Figure 1). Rifampicin-Miconazole impregnated catheters significantly prevented initial bacterial adherence compared with the control group for the entire study period ($p< 0.001$). In addition, the antifungal activity of these catheters did not diminish throughout the study period. Silver sulfadiazine-chlorhexidine impregnated and MR catheters did not prevent the initial candidial adherence throughout the study period (Figure 1).

After initial adherence to the catheter surface, micro-organisms tend to persist and colonize. Candidial colonization was evaluated after 4 and 24 h of *Candida albicans* exposure. At 4h, there was a significant reduction in *Candida albicans* colonization with R-Mic catheters compared with the control group on all days ($p<0.001$) (Figure 2). At 24 hours, although R-Mic catheter colonization was lower than the control group catheters, this did not reach statistical significance. Silver sulfadiazine-chlorhexidine impregnated and MR catheters did not prevent colonization either at 4 h or at 24 h. (Figure 2 and 3).

Discussion

Modern medicine, through newer, extensive and aggressive treatment modalities, necessitates the liberal use of catheters in intensive care units. On the other hand, infections caused by these catheters may be a great threat to the treatment success. Although there is still some controversy regarding attributable mortality, CR-BSI's significantly prolong the length of hospitalization, increase hospital costs, and expose the patient to the additional risks of broad spectrum antibiotic use, catheter removal and new central catheter insertion (12-16).

Recent surveys from different countries have revealed that candidemia is now the fourth most common nosocomial blood stream infection (17-21). In the past two decades, this increase has reached as high as 48.7% in some hospitals (22). It is also known that intensive care units have a ten fold higher incidence of candidemia compared to medical and surgical wards (16, 23-26).

Several studies have showed that present or even previous use of central venous catheter is a significant risk factor for nosocomial candidemia (11, 27-29). In addition, more liberal use of central venous catheters and concomitant increase in incidence of candidemia made

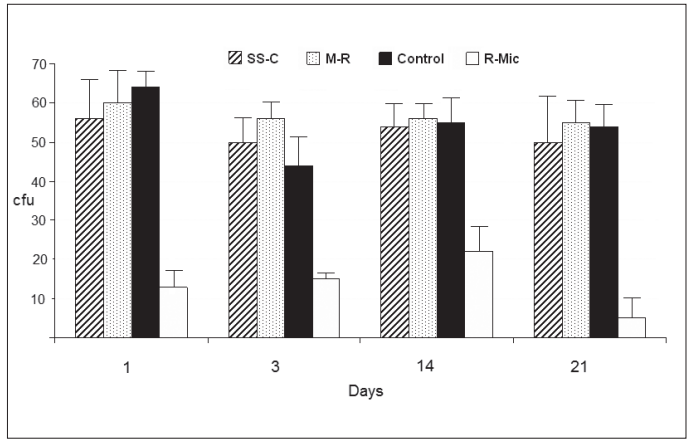

Figure 1. Initial candidial adherence

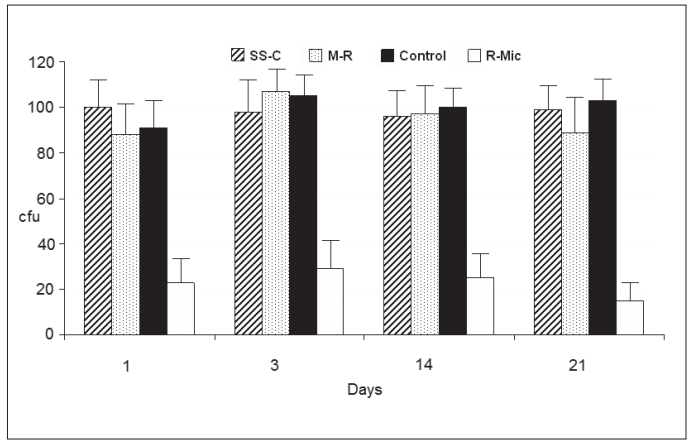

Figure 2. *Candida albicans* colonization at 4 hours

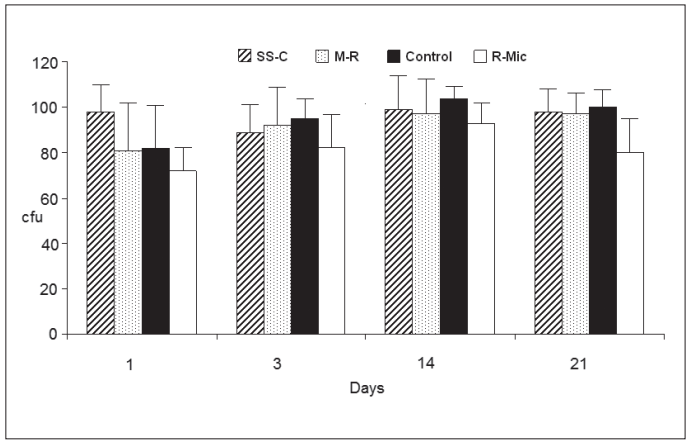

Figure 3. *Candida albicans* colonization at 24 hours

the CR-BSI with *Candida spp*. a more significant and challenging problem (12, 22, 30).

Education, hand hygiene, maximal barrier precautions for catheter insertion, chlorhexidine skin antisepsis and optimal site care are the principle approaches for reducing the incidence of CR-BSI (31). The use of antiseptic or antimicrobial impregnated catheters is another and important intervention for reducing CR-BSI (31, 32). Various well organized prospective randomized trials have clearly revealed that SS-C and R-M coated/impregnated central venous catheters can effectively prevent CR-BSI (33-35). Their impact may be greater in prolonged catheterization (36). Interestingly, Wright et al, in their prospective study, found no benefit with the use of antibiotic coated central catheters. In addition, increased candidial colonization was observed with antibiotic treated catheters (37).

Catheter contamination and further microbial colonization is the first step for CR-BSI (22). Without colonization there can be no catheter related infections. The main idea for the use of antibiotic/antibacterial catheters is their ability to reduce initial bacterial adherence and further colonization. In our previous studies we have shown that these catheters can prevent bacterial adherence and colonization effectively. Like other studies, these catheters showed substantially different activities against different bacteria in our experiments (9, 10, 38). In this study, we evaluated the effectiveness of two different antibiotic/antibacterial treated catheters and one antifungal impregnated catheter against the initial adhesion and further colonization of *Candida albicans*. To our knowledge, this is the first report that *in vitro* compares these three catheters against a fungal organism within the same experimental protocol.

In this study initial candidial adherence and further colonization was evaluated on days 1, 3, 14 and 21. In previous studies, including ours, it was demonstrated that SS-C and M-R treated catheters can show their antibacterial effect for at least 10 days (10, 39). Similarly, R-Mic loaded catheters showed long-term activity (38, 40). It is generally known that candidial CR-BSIs tend to occur after several days of insertion and extended stay in the intensive care unit (22). For these reasons, in this study, we had the opportunity to observe the long term antifungal effects of the study catheters. Rifampicin-miconazole treated catheters prevented initial bacterial adherence and colonization at the 4th hour throughout the study period and their antifungal activity did not diminish in this period.

In this study, only R-Mic catheters significantly reduced initial candidial adhesion throughout the study period. Silver sulfadiazine-chlorhexidine impregnated and M-R catheters showed no effect. This finding is supported by the results of Schierholz JM et al. in which they found a significantly higher zone of inhibition by the R-Mic catheters compared with CC-S treated catheters against *C. albicans* (38). In their study SS-C catheters showed the lowest activity against *P. aeruginosa*, *Enterobacter spp*. and *C. albicans*. Raad I et al, in their prospective randomized clinical trial, demonstrated the antistaphylococcal efficacy of M-R catheters. However, these catheters did not reduce catheter colonization and further infection by *Candida albicans* (33). These findings, including ours, clearly demonstrate that antibacterial treated catheters had different activities against different organisms, and SS-C and M-R catheters have little or no effect on *Candida albicans* colonization. So, while using an antimicrobial treated catheter, duration of catheterization, microbial flora and antibiotic susceptibility profile of that unit/hospital should be kept in mind, as these parameters determine the type of micro-organism responsible for CR-BSI.

Candida albicans colonization is effectively prevented by R-Mic catheters at the 4th hour. However, at 24 hours, they did not prevent colonization significantly. This finding is mainly related with the release kinetics of rifampicin and micanazole out of the catheter matrix. Rump et al showed that antimicrobial releases from these catheters are not constant and may be slower after some time. In their study, miconazole showed much higher decay than rifampicin (41). These findings may explain the insufficient prevention of colonization by R-Mic catheters, at 24 hours.

Our study had some limitations. We evaluated the effectiveness of antimicrobial treated catheters in an *in vitro* model. As in all experimental studies, our results may not correlate well with the real clinical environment. However, antibacterial/antiseptic coated catheters are studied extensively in many *in vitro* studies, and generally good correlations are obtained when compared with *in vivo* experimental and clinical studies (42, 43). The last point that we should mention is we used only one strain of *Candida albicans*. Therefore our results may or may not be applicable to other types of fungal spp.

Conclusion

Central venous catheters coated with rifampicin - miconazole were found to be effective against initial candidial adherence. These catheters are also effective against *Candida albicans* colonization. These findings, including previous studies, clearly demonstrate that antibacterial treated catheters had different activities against different organisms and SS-C and M-R catheters have little or no effect on *Candida albicans* colonization. So, while using an antimicrobial treated catheter, duration of catheterization, microbial flora and antibiotic susceptibility profile of that unit/hospital should be kept in mind as these parameters determine the type of micro-organism responsible for CR-BSI.

Acknowledgements

This study was supported by Hacettepe University Research Council HUTF 06D0210100.

Conflict of Interest

The authors of this manuscript confirm that there are no competing interests or financial disclosures to declare.

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