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Full Length Research Paper

A comparison of fucidic acid and cefazoline released from cancellous human bone

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This study was designed to determine the antibacterial activity of fucidic acid or cefazoline in cancellous bone obtained from patients undergoing total knee replacement. Thirty samples of cancellous bone were obtained from patients undergoing total joint arthroplasty for primary osteoarthritis of knee joints. The prophylactic antibiotics were infused to the subjects an hour before the operation. In the first group (15 samples) fucidic acid (500 mg intravenous) was used as a prophylactic antibiotics and 1st generation of cephalosporin were used in the second group (15 samples) as the prophylaxis. Same strains of *Staphyloccocus aureus* were used to assess the antibiotic activity using the disc diffusion technique after 1, 3, 7, 10, 14, 18, 21 and 28 days. The antibiotic efficacy was defined as an inhibition zone diameter of 10 mm. Inhibition zone diameters were significantly higher in fusidic acid than cefazoline specimens on the first, third and 14th day after the incubation (P<0.05). No statistically significant difference was found in the inhibition zone diameter at the seventh, 18th and 21st days. Evaluation of inhibition zone diameters showed that samples obtained from the first group (fucidic acid) had a longer duration of antibiotic release than that of second group (cefazolin). Fucidic acid shows a higher release and a longer antibacterial activity when used as a prophylactic antibiotic compared to cefazolin.

Key words: Human cancellous bone, preoperative prophylaxis, fucidic acid, cefazoline.

INTRODUCTION

Despite the numerous studies about the prophylactic use of antibiotics to prevent the joint infections after total joint replacement procedures, there is little information in regard to the release of the antibiotics from the cancellous bones. The antibiotic elution from bone cement has been studied thoroughly (Masri et al., 1994; Holtom, 1998). Isiklar et al. (1999) studied the concen-trations of vancomycin from the drainage fluid after the use of the vancomycin-impregnated spacers in the treatment of orthopaedic implant–related *Staphylococcus epidermidis* infections. Diffusion of the antibiotics through cement films has been tested previously by Baystone and Milner (1982). The antibiotic impregnated cement was seeded in the agar and the inhibition zone was measured in millimeters. Kazımoğlu et al. (2008) has assessed the *in vitro* antibacterial activity of gentamicin- or teicoplanin-impregnated human cancellous bone as a local antibiotic carrier. They used the disc diffusion technique and measured the antibiotic efficacy as an inhibition zone diameter. The result of their study has showed that human cancellous bone incorporates a considerable amount of antibiotics and exhibits effective antibiotic release for approximately two weeks.

The aim of our study was to measure the antibiotic release from the fresh cancellous bone resected during the operation for total joint replacement as well as the bacteria growth inhibition *in vitro*. The antibiotics used

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were selected due to their affinity to the bone spectrum and effectiveness. The selected bacteria were recommended to us from the Department of Bacteriology.

MATERIALS AND METHODS

A total of 30 patients undergoing total knee replacement were included in the study. Patients who had a history of previous infection and patients to whom antibiotics had been administered within 1 week before surgery were excluded from the study. Two groups each of 15 subjects were selected according to the antibiotics received preoperatively. In the first group (allergic to the cephalosporines) fucidic acid (Stafine ® 500 mg ampul Kocak İlaç) and in the second group cefazolin (Cezolin® 1.0 g/vial steril toz Abdi brahim) was used as prophylactic antibiotic.

A sample of cancellous bone was obtained from the femoral bone resected during the operation of total knee replacement in patients with a diagnosis of primary osteoarthritis of the knee joint. All total joint arthroplasties were performed under identical conditions. Under fully sterile conditions and after thorough cleaning, washing and drying of the bone, the specimens were cut with a bone cutter to produce a standard piece of bone disc of 1 mm thickness and 10 mm in diameter. The bone discs were planted on the diagnostic sensitivity test agar which had previously been seeded with a strain of *Staphylococcus aureus*. The inhibition zone diameters of bone discs were measured with a caliper. Zone diameters ≥10 mm were evaluated as sensitive. The patients were followed for any sign of infection in the postoperative period of 6 months. Statistical differences were analyzed by Mann-Whitney U test. Significance was set at $p< 0.05$. SPSS software 11.5 was used for statistical analysis.

RESULTS AND DISCUSSION

In both group, clinical and radiological follow up has showed no infection in the 6 month postoperative period. On day 1, 3 and 10 fucidic acid demonstrated statistically higher inhibition zone diameter than cefazolin. No Statistically significant difference in the inhibition zone diameter was found on day 7, 14, 21 and 28. However fucidic acid inhibition zone diameter remained above the cefazolin through 28 days. Cefazolin inhibition zone dropped to below 10 mm by day 10. The fucidic acid inhibition zone remained above 10 mm on day 10 and this was statistically higher than cefazoline. The results are shown in Figures 1 and 2.

DISCUSSION

This study evaluated antibiotic release and inhibition zone diameter properties of two different antimicrobial agents. We demonstrated that parentral fucidic acid show a better bacterial growth inhibition than cefazoline do. The in vivo administration of antibiotics and in vitro testing by using the inhibition zone technique confirmed that a single dose of the antibiotics produced high local bone concentrations for 7 days in cefazoline and 14 days for fucidic acid without any significant systemic exposure. There was a time related decrease in the inhibition zone diameter, and the decrease was lower in the fucidic acid indicating a better property of incorporation into the cancellous bone.

The choice of antibiotic in this study was based on that it has excellent antibacterial activity against *S. aureus* and *S. epidermidis*, which are isolated at a high rate as primary causative bacteria in orthopedic infections (Boxma et al., 1996; De Lalla, 2001; Klekamp et al., 1999; Oishi et al., 1997).

Cefazolin was chosen because it is a first-generation cephalosporin, which has a strong antibacterial activity against gram-positive cocci (Fitzgerald and Thompson, 1983). It also has a longer half-life in both bone and serum than other first-generation cephalosporins and has been shown to be concentrated in postoperative hematomas (Jones et al., 1985). Cefazolin has been prophylactic antibiotic of choice for clean orthopedic surgery (Oishi et al., 1993).

Fusidic acid is an original agent with specific action against staphylococci. It acts by suspending protein synthesis and has superior binding affinity and high concentration levels on bone. A combination of oral rifampicin and fusidic acid has been used successfully after debridement and prosthesis retention for the management of early prosthetic joint infections (Barberan, 2006; Zimmerli et al., 2004). Contact with antibiotics in low concentration confers a risk of acquiring resistance (Ubukata et al., 1998), therefore in this study, parenteral fucidic acid prophylaxis was used instead of the oral dose which can be expected to provide superior antibacterial concentrations and reduce the risk of resistant.

This study has shown that Fucidic acid may be a useful alternative particularly in the case were MRSA infections, where cefazoline resistance is common, or where the patient shows intolerance to cefazoline. To our knowledge, the present study is the first to examine the efficacy of fucidic acid prophylactic protocol. Although further controlled and prospective studies that include larger number of patients are required, the present study suggests that fusidic acid is a good alternative for the prophylaxis against surgical wound infections.

Increased drug costs, the emergence of resistant organisms and appearance of the adverse effect of antimicrobial agents may occur secondary to excessive usage of antibiotics (Brunett et al., 1983; Manian et al., 2003; Oishi et al., 1993).

Reduction in usage of prophylactic antibiotics has been suggested by previous studies (Boxma et al., 1996; Engesaeter et al., 1996; Nelson et al., 1983; Williams and Gustilo, 1984). Engesaeter et al. (1996) has recommended the use of prophylactic antibiotics up to four times on the operative day only. This study has shown that inhibition zone remained above 10 mm on day 10 for the fucidic acid and day 7 for the cefazoline. Therefore, we believe that this study may provide objective evidence toward further reduction of the use of prophylactic antibiotics.

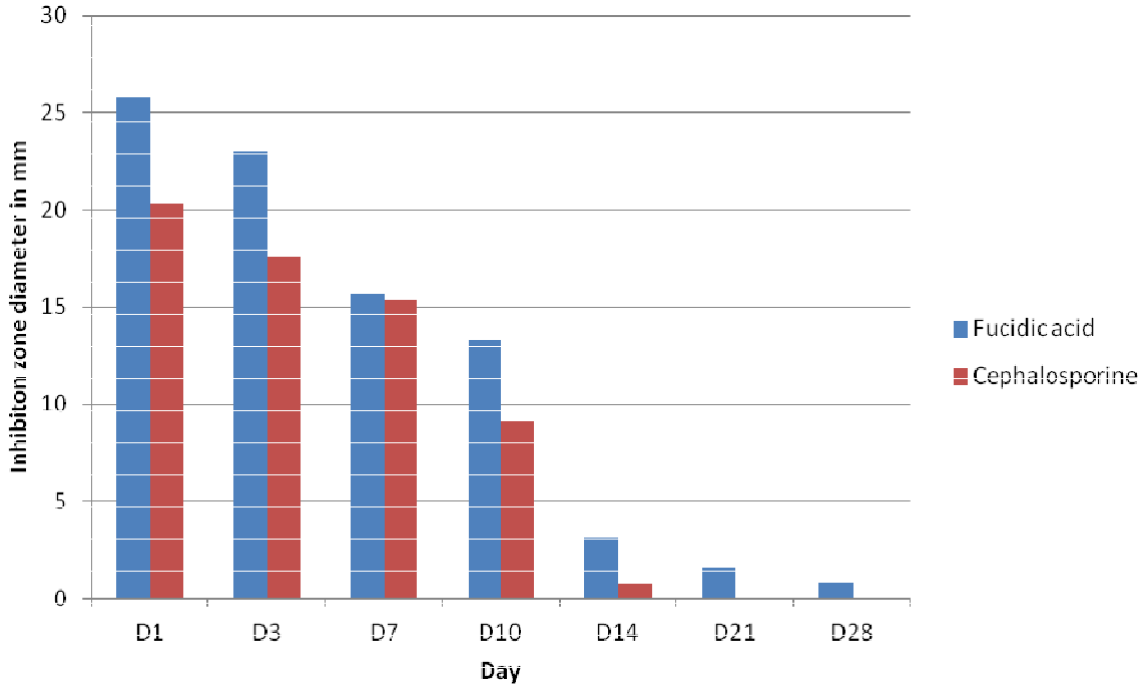

Figure 1. Inhibition zone diameters of fucidic acid and cefazoline. The sensitive inhibition zone diameter for both agents was 10 mm diameter.

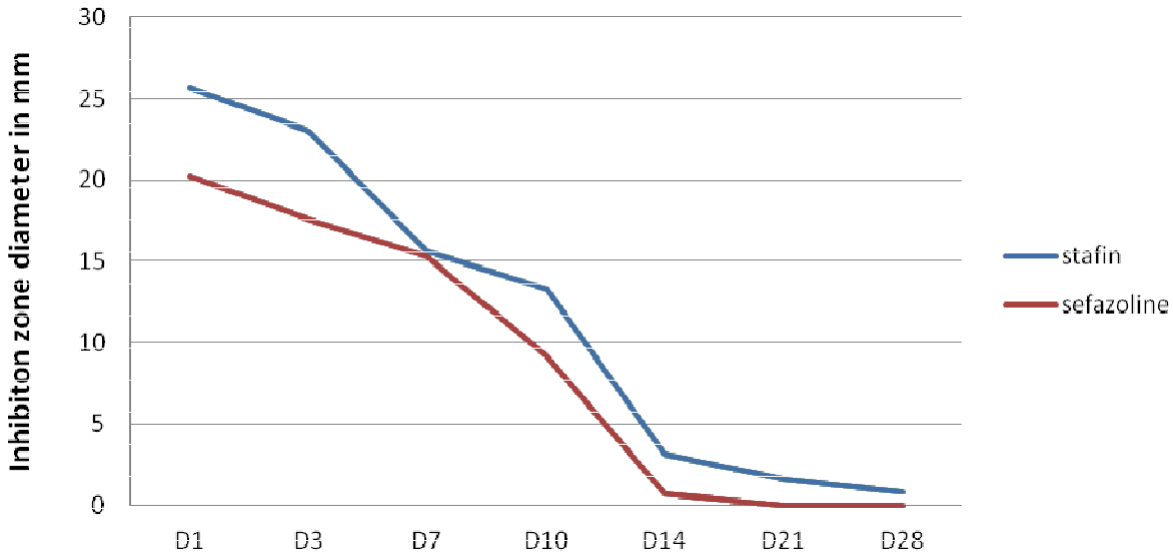

Figure 2. Comparison of fucidic acid and cefazoline inhibition zone diameter.

The limitation of this study is the small number of patients, and that the survey was performed in a single ward in one institution and for 1 year only. However, it is valuable for showing that reducing the isolation rate of MRSA in a ward was possible with less antibiotic usage than was previously the case without increasing in the incidence of SSI caused by any organisms, including MRSA.

In conclusion, the results of this study suggest that fusidic acid offers an alternative to the cefazoline for the

prophylaxis of the orthopaedic prosthetic infection either when the patient is intolerant to cefazoline or when the cefazoline resistant *Staphylococcus* spp. is frequently detected in the cultures.

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