EXPERIMENTAL STUDY

The effects of oral antibiotics on infection prophylaxis in traumatic wounds

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ABSTRACT

BACKGROUND: The objective of this study is to examine the effectiveness of oral antibiotics in the prevention of infection development in traumatic wounds.

METHODS: Forty Wistar albino rats were divided into five groups of eight animals. After the crushed wound model was made on the back of the rats, wounds were closed with a simple suture and *Staphylococcus aureus* ATCC 29213 strain was used to create infection. All rats apart from the controls were given oral gavage with antibiotics, including cephalexin, amoxicillin-clavulanate, clarithromycin (CAM), or levofloxacin for 5 days. Wounds were evaluated qualitatively and quantitatively on 5th day approximately 18 h after the last treatment.

RESULTS: In the quantitative evaluation, no infection was observed in the treatment groups with amoxicillin-clavulanate, CAM, cephalexin, or levofloxacin. There was no significant difference on the numbers of bacteria found in the wounds among the groups. In terms of quantitative inflammation findings, no hyperemia or pus was detected in the groups that were given medication. Furthermore, no statistically significant difference was found among the groups in terms of induration.

CONCLUSION: Oral prophylactic antibiotics have been found to be effective in the prevention of wound infection in the traumatic crushed wound model infected with *S. aureus* in rats.

Key words: Antibiotic; prophylaxis; traumatic wound; wound infection.

INTRODUCTION

The purpose of wound care is to protect it from infection and allow for a functional esthetic-looking scar development. The factors affecting infection development are the localization of the wound, duration, depth, configuration and contamination characteristics.[1,2] The presence of a foreign body or visible contamination increases the risk of infection.[1,2] Since more devitalized tissue is created in crush wounds inflicted by blunt objects, the risk of infection increases compared to those in inflicted with sharp objects. Although bacterial inoculation development and its amount are related to the time that passes between injury and repair,[1,3] the relationship between wound closure duration and clinical infection is not clear.[4-6] The etiology, location, degree of contamination risk factors of the host and the importance of cosmetic look of the wound are important in determining primary or secondary closure. If the infection risk is high, 4 days later, late primary closure should be considered.[7]

Infection risk is determined by the interaction between the bacterial colonization and blood circulation. Therefore; anatomic localization is important to be able to estimate the clinical outcome of the infection.[1,2,4,8] The risk of infection is higher in lower extremities compared to the head and upper extremities. The number of bacterial colonization is high in

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Qucik Response Code

Ulus Travma Acil Cerrahi Derg
2014;20(4):231-235
doi: 10.5505/tjtes.2014.63993

damp areas. In wounds contaminated with human or animal excretion, infection risk is high despite treatment.[7]

Most of our knowledge concerning antibiotic prophylaxis was derived from experimental studies and surgical interventions.[9,10] What was learned from these studies is that before or right after wound contamination providing a fast antibiotic level determines the outcome and in most cases it is no use continuing the antibiotic after 24 hour. At the emergency department, antibiotic prophylaxis should be performed with effective agents against pathogens anticipated before obvious tissue manipulation. According to our knowledge, there are no studies comparing the initial dose taken intravenously or per-orally.[10]

For the wounds closed at the emergency department, the infection rate is approximately 3-5%.[1] There is no conclusive evidence showing that antibiotic prophylaxis prevents wound infection in patients whose wounds are closed at the emergency department.[1,10,11] Common practice is to start antibiotic prophylaxis after treatment at the emergency department on the traumatic wounds with suspected infection.

The aim of this study is to show and compare the effectiveness of oral cephalexin, amoxicillin-clavulanate, clarithromycin (CAM) and levofloxacin on the prevention of wound location infection development in traumatic crushed wounds inflicted on rats.

MATERIALS AND METHODS

Following the approval of Dokuz Eylül University Experimental Animal Research Ethics Committee (2004-24), 40 adult rats weighing 250-300 g whose sensitivity to microorganisms that cause infection in humans were proven in earlier research divided into five groups were used. In Group I: amoxicillin-clavulanate (Augmentin BID 400/57 forte oral suspension, SmithKline Beecham, Italy) In Group II: CAM (Klacid oral suspension 125 mg/5 ml, Abbott, Italy), In Group III: cephalexin (Maksipor oral suspension 250 mg/5 ml, Fako, Turkey), In Group IV: levofloxacin, (Avantis Pharma, Germany) and In Group V: normal saline (control group) were given, and animals were fed with standard fodder and water ad libitum. Since there is no oral suspension form of levofloxacin, 500 mg tablets (Avantis Pharma) were made as an oral suspension form with 1% Na-carboxy methyl cellulose and used.

Creation of Wounds

Following the ether anesthesia on rats, the hair on their back was shaved off. The surface was cleaned with 70% ethyl-alcohol and 10% povidone-iodine solution. A 2 cm incision was made with no. 15 scalpel from the fourth thoracic vertebra (regio interscapularis) to caudal with paravertebral longitudinal extension reaching fascia, but not including fascia. In order to devitalize wound lips, 1.5 cm wound edges that covered dermoepidermal intersection were clamped for 5 minute with hemostatic clamp.[12,13]

Creation of Wound Infection and Closure

In order to create wound infection, *Staphylococcus aureus* ATCC 29213 strain was used. It was vitalized by being incubated in a bloody agar overnight at microbiology laboratory. Bacterial suspension was prepared from reproducing colonies by saline with 108 colony/ml. Devitalized incision line was sutured using three interrupted suture using 4/0 polypropylene. The blood residue on the incision line was cleaned and dried with sterile wet sponge. 0.2 ml bacterial suspension was injected and inoculated into sutured incision line and deep fascia.[1,12-14] In order to provide analgesia, rats were given pethidine hydrochloride (Dolantin, Hoechst Marion Roussel, Germany) 20 mg/kg intramuscularly.[15] The entire wound then was closed with sterile sponge and plastered.

Treatment

Four hours after the wound closure, oral antibiotic or placebo treatment was started, and previously-grouped rats were given antibiotics with oral gavage for 5 days.[13] Medication dosage for rats were as follow: cephalexin 60 mg/kg per oral (po) twice a day, amoxicillin-clavulanate 350/50 mg/kg po twice a day, CAM 5 mg/kg po twice a day, levofloxacin 125 mg/kg po once a day.[15,16] Placebo group was given normal saline 1.5 cc with oral gavage twice a day.

Evaluation

At the end of day 5, an average of 16-18 hours after the last treatment, rats were evaluated macroscopically and microscopically in terms of wound infection under ether anesthesia. Macroscopic evaluation was conducted in an observational manner by an emergency physician uninformed of the treatment protocol. Incision scars were evaluated with a view to infection findings such as swelling, erythema, induration, purulent flow, and the findings were noted down. For the microscopic evaluation, the scar surface off the suture line was cleaned with 70% ethyl-alcohol and 10% povidone-iodine. After the sutures were removed, wounds were opened with no. 15 scalpel. From every wound, standardized rectangular tissue samples were taken 0.5 cm far from the wound edges containing epidermis, dermis, and subcutaneous tissue. Tissue samples were sent to the microbiology laboratory within 15 minute in petri containers. Each piece was homogenized immediately, and serial dilutions were prepared. By seeding culture into blood agar, bacteria count per gram tissue was calculated, and ≥105 bacteria count per gram tissue was regarded as wound infection.[12]

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA), version 11.0, was used for all statistical analyses. For quantitative bacteria colony counts, first log10 transformation was performed. Chi-square test was used in order to evaluate the effectiveness in the prevention of infection. In all groups, Kruskal–Wallis variance analysis was used in the simultaneous evaluation of measurements, Mann–Whitney U-test in the evaluation of dual groups. Significance level was determined as p<0.05.

RESULTS

No sign of infection was observed in any of the animals, and no rat was excluded from the experiment. During the macroscopic evaluation performed to detect local findings of the infection, hyperemia in found in two wounds in the placebo group (25%), induration in eight wounds (100%), pus in five wounds (62.5%) were detected. Induration was detected in two wounds in the groups given amoxicillin-clavulanate (25%), in four wounds in the groups given CAM (50%), in six wounds in the groups given cephalexin (75%), in two wounds in the groups given levofloxacin (25%) (Table 1). No difference was observed among the four groups that were treated (Chi-square=5.587, p=0.134). No hyperemia or pus was detected in the groups other than the placebo group (Table 1).

The Effect of Oral Antibiotic Treatment on Groups

When the bacteria count of the wounds in amoxicillin-clavulanate, CAM, cephalexin and levofloxacin groups was examined, no difference was observed among the mean bacteria counts of four groups (Kruskal-Wallis p=0.07). No infection was detected in the four groups treated with antibiotics (Table 2). When the wounds were evaluated in terms of suture areas, hyperemia, induration and pus presence, no significant difference was observed among the groups treated with antibiotics (Chi-square=5.587, p=0.134) (Table 1).

The Comparison of Oral Treatment Options with Placebo

When amoxicillin-clavulanate, CAM, cephalexin and levofloxacin groups were compared with the control group in terms of bacterial count, the number of microorganisms in the control group was significantly higher (Mann–Whitney U-test p=0.001) (Table 2). Evaluation in terms of infection rates according to microorganism count per gram tissue, while no infection was detected in amoxicillin-clavulanate, CAM, cephalexin and levofloxacin groups, infection was detected in the seven wounds in control animals (Tables 1 and 2).

DISCUSSION

In wound care, applications such as irrigation, debridement, saturation and antibiotics aim to protect the wound from infection and provide functional, esthetic-looking scar.[17] Another method to be used in the prevention of wound infection is prophylactic antibiotics. However, there is no evidence suggesting that prophylactic antibiotics decrease wound in-

Table 1. The distribution of qualitative evaluation parameters according to oral treatment groups

	Hyperemia		Enduration		Pus	
	n	%	n	%	n	%
Amoxicillin-clavulanate	0	0.0	2	25.0	0	0.0
Clarithromycin	0	0.0	4	50.0	0	0.0
Cephalexin	0	0.0	6	75.0	0	0.0
Levofloxacin	0	0.0	2	25.0	0	0.0
Placebo	2	25.0	8	100.0	5	62.5

Chi-square, (p=0.134).

Table 2. The distribution of quantitative evaluation parameters according to oral treatment groups

	Quantitative bacterial count $\log_{10}$±SD	The presence of microbiological infection	
		n	%
Amoxicillin-clavulanate	0.7963±1.48	0	0.0
Clarithromycin	2.3668±1.66	0	0.0
Cephalexin	2.39±1.52	0	0.0
Levofloxacin	0.7813±1.45	0	0.0
Placebo	5.2813±0.77	7	87.5

Kruskal-Wallis variance analysis (p=0.07), Mann-Whitney U-test (p=0.001).

fection development in patients with traumatic wounds diagnosed at emergency departments.[1,10,11] There is always a long time gap between the initiation of oral prophylactic antibiotics and the occurrence of injury. Therefore, in order to resemble routine applications, treatment was started 4 hours after the inoculation of active organisms into the wound in the present study.[12]

In order to prevent wound infection during surgical interventions, application of intravenous prophylactic antibiotics is recommended immediately before or during the procedure. In this way, before the surgical incision is made, high antibiotic concentration will be created in the tissue near the wound.[18,19] However; in traumatic wounds, until the wound evaluation is performed, there is no chance of antibiotic application. Deterioration of perfusion on the incision and occurrence of clot prevent the penetration of antibiotics to the wound rim.[20]

As it has been demonstrated in previous animal studies, the effectiveness of prophylactic antibiotics depends on the initiation phase, the earlier is better. However, the effectiveness of oral treatment hasn't been proven yet.[21] Although *S. aureus* and group A *Streptococcus* are responsible for most wound infection, antibiotics to be selected in the atypical wounds, should also be effective on rare pathogens.[20] Since they have antibacterial effectiveness against *S. aureus*, group A *Streptococcus* and atypical pathogens depending on the type of the wound, amoxicillin-clavulanate, CAM, cephalexin and levofloxacin are recommended agents.[10,20,22]

In this traumatic crushed wound model created on rats infected with *S. aureus* oral amoxicillin-clavulanate, CAM, cephalexin and levofloxacin application has been proven to be 100% effective in the prevention of wound infection.

Berry et al. created a saturated wound model infected with *Streptococcus* pyogenes and *S. aureus* in an experimental study on rats in order to compare the effectiveness of gemifloxacin. They demonstrated that gemifloxacin, grepafloxacin, levofloxacin, amoxicillin-clavulanate, cefuroxime and azithromycin given per-orally caused a significant decrease in the number of bacteria compared to the control group.[23]

In a double-blind, randomized multi-centric study, Lipsky et al. compared the effectiveness of sparfloxacin and ciprofloxacin in complicated skin infections contracted in the community and 475 patients were given oral sparfloxacin (200 mg once a day following loading dose of 400 mg) and ciprofloxacin (750 g twice a day). In terms of cure and recovery, clinical success rate was found to be 90.1% with sparfloxacin (210/233) and was 87.2% with ciprofloxacin (211/242). Within the subgroups in the study the success rate with infected wounds with the most common complicated skin infection, clinical success rate was found to be 95.7% with sparfloxacin, 96.9% with ciprofloxacin, supporting our study. Bacteriological eradication rate was found to be 87% with sparfloxacin and 79.9% with ciprofloxacin.[24]

In another study on experimental skin infection by Gisby and Bryant, oral and topical mupirocin applications were compared on a wound model infected with *S. aureus* or *S. pyogenes* on rats similar to ours.[13] Mupirocin and fusidic acid were used in local treatment and erythromycin, cephalexin, floxacillin in systemic treatment. When all the groups treated actively were compared with the control group that wasn't treated, it was observed that there was an obvious decrease in the average bacteria count.

In a double-blind, placebo-controlled clinical study, in order to compare the effectiveness of topical mupirocin and oral cephalexin on secondary infected traumatic wounds (small lacerations, abrasions, or suture wounds), Kraus et al.,[25] gave three doses of topical mupirocin and four doses of oral cephalexin a day. The success rates in the prevention of clinical infection presence in secondary infected traumatic wounds were 95.3% for cephalexin, 95.1% for the groups given mupirocin and the success rate for the microbiological prevention of infection was 98.9% and 96.9%, suggesting similarity to our study on the effectiveness of oral treatment. Furthermore; *S. aureus* (41%) and *S. pyogenes* (7%) were the most common isolated microorganisms.[25]

Cummings[26] examined eight randomized studies in his meta-analysis on the prevention of infection by antibiotics on patients with dog bite and concluded that prophylactic antibiotic halve infection risk in patients with dog bite injury.

Limitations

In most cases, multi-organisms and patients' existing defense mechanisms play an important role in traumatic wounds infection. But in this study, traumatic wound infection model was created by a single organism.

Conclusion

In the traumatic crushed wound model infected with *S. aureus* in rats, oral prophylactic antibiotics have been found to be effective in the prevention of wound infection. Amoxicillin-clavulanate, CAM, cephalexin and levofloxacin given orally were all found to be 100% effective in the prevention of traumatic wound infection.

Acknowledgement

Authors thank to Hatice Giray MD and Bulent Sari MD for their support during the preparation of study.

Conflict of interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZET*

Travmatik yaralarda oral antibiyotiklerin enfeksiyon profilaksisindeki etkileri

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AMAÇ: Bu çalışmanın amacı, travmatik yaralarda enfeksiyon gelişiminin önlenmesinde oral antibiyotiklerin etkinliğini incelemektir.
GEREÇ VE YÖNTEM: Kırk adet Wistar albino sıçan sekizerli beş gruba ayrıldı. Sıçanların sırtında ezik yara modeli oluşturulduktan sonra, yaralar basit sütür ile kapatıldı. Staphylococcus aureus ATCC 29213 suşları enfeksiyon oluşturulmak için kullanıldı. Kontrol grubu dışındakilere oral gavaj ile beş gün sefaleksin, amoksisilin-klavulanat, klaritromisin ve levofloksasini içeren antibiyotikler verildi. Yaralar, son tedavi verildikten sonra 18. saatinde kalitatif ve kantitatif olarak değerlendirildi.
BULGULAR: Kantitatif değerlendirmede amoksisilin-klavulanat, klaritromisin, sefaleksin, levofloksasin ile tedavi edilen gruplarda enfeksiyon tespit edilmedi. Guruplar arasında yaralardaki bakteri sayısı açısından anlamlı fark bulunmadı. Kantitatif enflamasyon bulgularına göre değerlendirildiğinde, medikasyon uygulanan dört grubun hiçbirinde hiperemi ve püy belirlenmedi. Endürasyon açısından gruplar arasında anlamlı fark bulunmadı.
TARTIŞMA: Sıçanlarda Staphylococcus aureus ile oluşturduğumuz enfekte travmatik ezik yara modelinde; oral proflaktik antibiyotiklerin yara enfeksiyonunu önlemede etkin olduğu bulunmuştur.
Anahtar sözcükler: Antibiyotik; profilaksi; travmatik yara; yara enfeksiyonu.

Ulus Travma Acil Cerrahi Derg 2014;20(4):231-235 doi: 10.5505/tjtes.2014.63993