RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2021.2021.10
Mediterr J Infect Microb Antimicrob 2022;11:10
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2021.2021.10

Comparison of the Efficacy of Cefazolin with and without Naproxen in Patients with Cellulitis Admitted to a Tertiary Hospital: 2019-2020

2019-2020 Yılları Arasında Üçüncü Basamak Bir Hastaneye Yatırılan Selülitli Hastalarda Naproksenli ve Naproksensiz Sefazolinin Etkinliğinin Karşılaştırılması

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Abstract

Introduction: It is pertinent to carefully monitor the clinical course of patients with cellulitis. If not treated properly, there is a possibility of its extension to other skin surfaces, recurrent infection, risk of systemic spreading, and incidence of worse complications, such as sepsis and severe abscesses. Various antibiotic regimens with or without anti-inflammatory drugs have been administered as a treatment against cellulitis. However, there is no proposed standard and selective line of treatment against cellulitis. This study aimed to compare the efficacy and outcome of two medications, cefazolin alone and cefazolin combined with naproxen as a non-steroidal anti-inflammatory drug.

Materials and Methods: This open-label randomized clinical trial was conducted on patients with cellulitis who were admitted to Labbafinejad Hospital (Tehran, Iran) from May 2019 to March 2020. The patients were randomly divided into group A (treated with 1-1.5 g of cefazolin alone intravenously every eight hours) and group B (treated with 1-1.5 g of cefazolin intravenously every eight hours combined with 500 mg of naproxen orally every 12 hours). The responses to these medications and the side effects were evaluated during hospitalizations.

Results: The mean age of the 64 patients included in the study was 50.52±2.10 years and 51.56% of the patients were male. There were no significant differences between the control (n=33) and intervention (n=31) groups in terms of history of diabetes mellitus (p=0.666), antibiotic use (p=0.594), trauma (p=0.722), cellulitis (p=0.529), and smoking (p=0.705). The mean body temperatures of the two groups were not different in any of the first (p=0.762), third (p=0.789), and fifth (p=0.893) days. The improvement of clinical symptoms on the third day was significantly (p=0.045) more in group B (90.3%) than in group A (51.5%). Also, the clinical improvement on the fifth day was significantly (p=0.036) higher in group B (100%) than in group A (69.7%). In addition, the mean hospitalization periods in the control (5.62±1.00) and intervention (4.04±1.00) groups were significantly different (p=0.012).

Conclusion: In patients diagnosed with cellulitis, the combination therapy with cefazolin and naproxen was far more effective than the monotherapy with cefazolin. Administration of the first regimen improves clinical manifestations and shortens hospitalization.

Keywords: Cellulitis, treatment outcome, cefazolin, naproxen

Cite this article as: Laktib A, Nayme K, El Hamdaoui A, Timinouni M, Hassi M, Ait Alla A, Msanda F, Bourouache M, El Yaagoubi M, Mimouni R, Bihadassen B, Hamadi F. Antibacterial Activity of *Lavandula mairei* Humbert Essential Oil Against a Carbapenem-resistant *Acinetobacter baumannii*. Mediterr J Infect Microb Antimicrob. 2022;11:3.

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Received/Geliş Tarihi: 15.09.2021 **Accepted/Kabul Tarihi:** 13.12.2021 **ORCID ID:** orcid.org/0000-0002-3467-763X

Published: 17 January 2022

Öz

Giriş: Selülitli hastaların klinik seyrini dikkatle izlemek gereklidir. Çünkü uygun şekilde tedavi edilmezse; diğer deri yüzeylerine yayılma, tekrarlayan enfeksiyon ve sistemik yayılma söz konusu olabilir ya da sepsis ve şiddetli apse gibi daha kötü komplikasyonların görülme riski vardır. Selülit tedavisi için anti-enflamatuvar ilaçlar içeren veya içermeyen çeşitli antibiyotik rejimleri uygulanmıştır. Ancak selülit için önerilen standart ve seçici bir tedavi bulunmamaktadır. Bu çalışmanın amacı, tek başına sefazolin ile non-steroid antienflamatuvar bir ilaç olan naproksen ve sefazolin kombinasyonunun etkinliğini ve sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Bu açık etiketli randomize klinik çalışma, Mayıs 2019 ile Mart 2020 arasında Labbafinejad Hastanesi'ne (Tahran, İran) başvuran selülitli hastalar üzerinde gerçekleştirildi. Hastalar rastgele; tek başına sefazolin (sekiz saatte bir intravenöz 1-1,5 g) ile tedavi edilen grup A'ya ve sefazolin (sekiz saatte bir intravenöz 1-1,5 g) ile kombine naproksen (12 saatte bir oral 500 mg) ile tedavi edilen grup B'ye dahil edildi. Daha sonra yatışlar sırasında ilaçlara yanıt ve yan etkiler değerlendirildi.

Bulgular: Çalışmaya alınan 64 hastanın yaş ortalaması 50,52±2,10 yıl olup hastaların %51,56'sı erkekti. Kontrol (n=33) ve müdahale (n=31) grupları arasında diyabetes mellitus (p=0,666), antibiyotik kullanımı (p=0,594), travma (p=0,722), selülit (p=0,529) ve sigara (p=0,705) öyküleri açısından fark yoktu. İki grubun ortalama vücut sıcaklıkları birinci (p=0,762), üçüncü (p=0,789) ve beşinci (p=0,893) günlerin hiçbirinde farklı değildi. Üçüncü günde klinik semptomlardaki iyileşme, grup B'de (%90,3) grup A'ya (%51,5) göre daha fazlaydı ve fark istatistiksel olarak anlamlıydı (p=0,045). Ayrıca, beşinci gündeki klinik iyileşme, grup B'de (%100), grup A'ya (%69,7) göre daha yüksekti ve fark istatistiksel olarak anlamlıydı (p=0,036). Ayrıca kontrol ve müdahale gruplarında ortalama yatış süreleri sırasıyla 5,62±1,00 ve 4,04±1,00 idi (p=0,012).

Sonuç: Selülit teşhisi konan hastalarda sefazolin ve naproksen ile kombinasyon tedavisi, sefazolin ile monoterapiden çok daha etkiliydi. Sefazolin ve naproksen rejimin uygulanması klinik belirtileri iyileştirir ve hastanede kalış süresini kısaltır.

Anahtar Kelimeler: Selülit, tedavi sonucu, sefazolin, naproksen

Introduction

Cellulitis results from the penetration of predominant bacterial infections from damaged skin barriers. It is a common condition with an annual incidence of about 2,500 per 100,000 cases in 2006 in the US. Lower limb involvement was reported in 70-80% of cases and is equal in men and women. Cellulitis is common in middle-aged and older adults[1,2]. Cellulitis mainly manifests as local warmth, edema, and erythema. The plaque in the affected area has an irregular margin and may invade healthy skin surfaces, creating an unexpected pattern[3]. The predisposing factors are classified into local and systemic. Among the local factors, interdigital intertrigo has taken the first place. Bacteria can accumulate in interdigital spaces where the colonization by *Streptococcus* or *Staphylococcus aureus* is common[4,5]. Impaired skin barrier due to wounds, trauma, edema, radiotherapy, or dermatosis is another risk factor[6]. Venous insufficiency caused by stasis dermatitis, venous ulcers, lymphedema, or lymphatic diseases constitutes another risk factor[7]. Another risk factor is the previous history of cellulitis, which has a recurrent rate of 8-20% over a period of 1-3 years[8]. Furthermore, smoking, diabetes mellitus, alcoholism, immunosuppression, and a history of cancer are all risk factors for cellulitis. Moreover, genetic susceptibility to cellulitis has been reported[9,10].

Evidence of recent streptococcal infection has also been reported in approximately 82% of patients with lower limb cellulitis, which has a diagnostic value[9].

In general, staphylococci and streptococci predominantly cause cellulitis. Thus, the first-line treatment includes first-generation cephalosporins or cloxacillin. If the clinical response is appropriate, clinical improvement will be seen within 24-48 hours. Oral antibiotics are sufficient for mild cellulitis. Using intravenous antibiotics, despite the oral treatment, is recommended in cases with systemic toxicity, immune deficiency, rapid and widespread progression of cellulitis, presence of progressive erythema, or exacerbation of symptoms within 48-72 hours. The duration of treatment also varies by individual. A 5-7 days course of treatment is sufficient for patients with uncomplicated cellulitis; however, continued treatment for up to 10-14 days will be necessary for severe episodes[11]. Clindamycin is recommended for patients with penicillin allergies. However, it should be noted that the treatment protocol is based on whether or not cellulitis is purulent[12]. In purulent cases and with evidence of abscess, treatment should be accompanied by coverage against methicillin-resistance *Staphylococcus aureus* (MRSA) strains. Monotherapy with cotrimoxazole or clindamycin is recommended in outpatient treatment; however, clindamycin, vancomycin, or linezolid in inpatient settings can be used in the treatment of cellulitis[11]. Non-steroidal anti-inflammatory drugs (NSAIDs) can potentially reduce inflammation, accelerate the healing process, and treat cellulitis along with antibiotics[13]. Due to the risks and effects of cellulitis, it is pertinent to treat patients with novel and effective drugs[14]. Previous studies have suggested that NSAIDs are more effective in treating cellulitis than antibiotics[15,16]. In addition, a study determining the effect of cephalexin and NSAIDs combination therapy compared with monotherapy in the treatment of cellulitis has shown that the combination therapy accelerates the recovery process and eliminates local inflammation[17]. Therefore, we decided to evaluate the efficacy of naproxen in combination with first-line antibiotic therapy in the treatment of cellulitis.

Materials and Methods

This randomized clinical trial was an open-label study without blinding. The study was conducted with patients with cellulitis who were admitted to Labbafinejad hospital (Tehran, Iran). Patients were recruited from May 2019 to March 2020. The inclusion criteria were hospitalization with a diagnosis of cellulitis, patients' age of over 18 years, and patients' willingness to participate in the clinical trial. On the other hand, the exclusion criteria of the study were allergy to penicillin, cefazolin or naproxen, immunodeficiency, mucocutaneous diseases, kidney diseases, venous catheter, history of infected diabetic foot ulcer, bite or presence of a foreign body the wound, perianal cellulitis, recent hospitalization history, chronic hemodialysis, pregnant women, injection drug abusers, suspected septic arthritis, or osteomyelitis.

Study Procedure

Eligible patients were divided into control (A) and intervention (B) groups with the aid of a random number table. First, the baseline characteristics (medical history, signs, and symptoms) were evaluated. Group A was treated with cefazolin alone (intravenous 1-1.5 g every eight hours) and group B was treated with cefazolin (intravenous 1-1.5 g every eight hours) in combination with naproxen (oral 500 mg every 12 hours).

Outcomes Assessment

On the third, fifth, and seventh day of treatment, a trained physician evaluated the patients' clinical improvement.

Signs of clinical improvement included cessation of fever and reduction in the extent of cellulitis. Also, side effects (epigastric pain, mild diarrhea, mild itching, and mild rash) were monitored after the medications. Moreover, on the third day of treatment, based on the response to treatment, we decided whether to continue the current antibiotic treatment or change it.

Statistical Analysis

The results were expressed as mean and standard deviation for quantitative variables and percentage for qualitative variables. The independent samples t-test was performed to compare the quantitative variables. The qualitative variables were also compared by the chi-square test or Fisher's exact test. We analyzed the data using IBM Statistical Package for the Social Sciences Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA) at a significance level of 0.05 or less.

Ethical Considerations

Written informed consent was obtained from patients who were given sufficient information about the study before the intervention. The patients were assured of the confidentiality of their information and access to the research results if they wished.

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran (approval ID: IR.SBMU.RETECH.REC.1398.86, date: 07.05.2019).

Results

In this study, 33 patients were assigned to the control group (A) and 31 patients were assigned to the intervention group (B). Table 1 shows the baseline characteristics of patients. The mean age of patients was 50.52±2.10 years and 51.56% of the patients were male. There were no significant differences between the two groups in terms of age (p=0.889) and gender (p=0.780). Also, there were no significant differences between the two groups in terms of history of diabetes mellitus (p=0.666), antibiotic use (p=0.594), trauma (p=0.722), cellulitis (p=0.529), and smoking (p=0.705). In addition, none of the patients in the two groups had venous insufficiency, lymphatic drainage disorder, and pre-existing skin infections.

Table 1. Comparison of baseline characteristics of patients in the two groups

Characteristics		Groups		p value
		Control (cefazolin alone)	Intervention (cefazolin+naproxen)	
Gender	Male	18 (60.0)	15 (44.1)	0.780
	Female	15 (40.0)	16 (55.9)	
Age		51.4±2.2	49.6±2.1	0.889
History of diabetes mellitus		7 (21.2)	5 (16.1)	0.666
History of antibiotic use		10 (30.3)	7 (22.6)	0.594
History of trauma		6 (18.2)	7 (22.6)	0.722
Previous cellulitis		5 (15.2)	7 (22.6)	0.529
History of smoking		8 (24.2)	6 (19.4)	0.705

Values are expressed as no. (%) or mean±SD unless otherwise indicated.

SD: Standard deviation

Table 2 shows the outcome of the medication in the two groups. The body temperature of the patients in two groups was on the first, third, fifth day of the study. The mean body temperatures of the two groups were not different on the first (p=0.762), third (p=0.789), and fifth day (p=0.893). Figure 1 shows the trend of the patients' body temperature changes over time. The improvement of clinical symptoms on the third day was significantly (p=0.045) more in group B (90.3%) than in group A (51.5%). Also, the clinical improvement on the fifth day was significantly (p=0.036) higher in group B (100%) than in group A (69.7%). Figure 2 shows the improvement of clinical symptoms over time.

The mean hospitalization periods in the control (5.62±1.00) and intervention (4.04±1.00) groups were significantly different (p=0.012). Figure 3 shows the prevalence of side effects in the two groups. There was no significant difference between the two groups in terms of side effects.

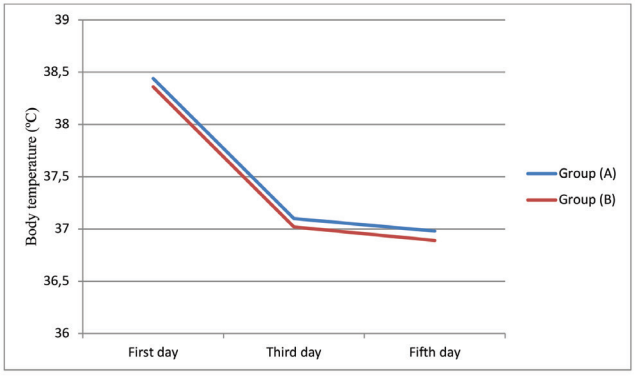

Figure 1. Trend of body temperature changes in the control (A) and intervention (B) groups

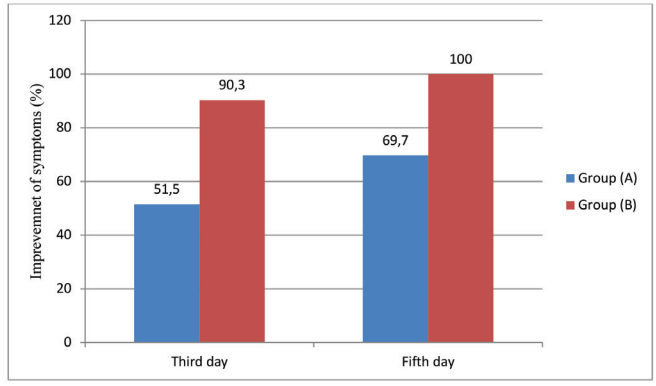

Figure 2. The improvement of clinical symptoms over the time in the control (A) and intervention (B) groups

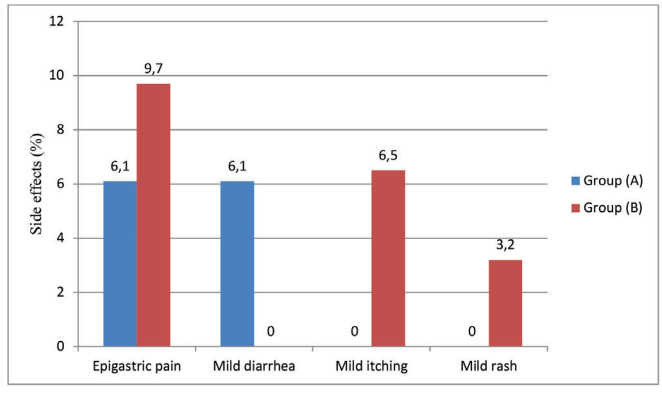

Figure 3. The prevalence of post-treatment side effects in the control (A) and intervention (B) groups

Table 2. Comparison of the outcomes of the medication in the two groups

Characteristics	Groups		p value
	Control (cefazolin alone)	Intervention (cefazolin+naproxen)	
Body temperature			
First day	38.44±0.26	38.36±0.22	0.762
Third day	37.10±0.12	37.02±0.10	0.789
Fifth day	36.98±0.09	36.89±0.07	0.893
Improvement of clinical symptoms			
Third day	17 (51.5)	28 (90.3)	0.045
Fifth day	23 (69.7)	31 (100)	0.036
Hospitalization period	5.62±1.00	4.04±1.00	0.012
Side effects after treatment			
Epigastric pain	2 (6.1)	3 (9.7)	0.673
Mild diarrhea	2 (6.1)	0 (0.0)	0.494
Mild itching	0 (0.0)	2 (6.5)	0.494
Mild rash	0 (0.0)	1 (3.2)	0.698

Values are expressed as no. (%) or mean±SD unless otherwise indicated.

SD: Standard deviation

Besides, none of the patients had complications, such as abscess, sepsis, or death. All patients recovered completely by the seventh day of hospitalization and none received oral medication after discharge.

Discussion

It is necessary to carefully monitor the clinical course of patients with cellulitis. If not treated properly, there is a possibility of its extension to other skin surfaces, recurrent infection, risk of systemic spreading, and incidence of worse complications, such as sepsis and severe abscesses[18]. In this regard, due to the high diversity of cellulitis-causing bacterial strains, broad-spectrum therapies with the dual goals of suppressing bacterial strains and inhibiting inflammatory responses induced by cytokines are recommended. Accordingly, special attention has been paid to the MRSA strains, which can have far more adverse consequences following the development of cellulitis. A variety of antibiotic regimens with or without anti-inflammatory drugs have been used in the treatment of cellulitis. However, so far, no selective and standard line of treatment has been provided to treat this condition[16,19]. Since non-purulent cellulitis is not mainly caused by *Streptococcus,* there is no need for the initial treatment to cover the MRSA strains. Most purulent cellulitis is caused by MRSA strains, which require appropriate antibiotics. Also, in patients with abscesses, incision and drainage are the main treatment modalities[20].

The present study aimed to compare the efficacy and outcome of two treatment regimens, including administration of cefazolin alone and cefazolin combined with naproxen as an NSAID. Based on our results, the body temperature of both groups within five days of treatment with both medications was completely normal. However, the combination therapy in our interventional study was superior to the monotherapy because, first, the improvement in clinical manifestations in the combination therapy was far more pronounced than in the monotherapy (cefazolin alone). Second, the combination therapy reduced the duration of hospitalization. Reducing the duration of hospitalization itself effectively decreases the risk of other opportunistic nosocomial infections and the likelihood of spreading cellulitis and other morbidities. Due to the safety of this combination therapy, in patients diagnosed with cellulitis, combination therapy with naproxen can be used as the first-line of treatment with high confidence.

Various studies have employed various regimens to treat cellulitis, although a study similar to ours was not found in the literature. The study by Zarezade et al.[21] reported a much higher efficacy of cefazolin compared to ceftriaxone in the treatment of cellulitis. Davis et al.[16] documented that co-administration of cephazolin with acetaminophen improved the condition of patients with cellulitis, with approximately 73% of the patients responding well to the treatment. Therefore, in the abovementioned studies, the effect of cefazolin as an effective antibiotic in the treatment of cellulitis can be far more favorable than different types of cephalosporins.

There are also several studies on the efficacy of various NSAIDs in the treatment of cellulitis, the efficacy of which has been confirmed particularly in the improvement of inflammatory and systemic symptoms of the disease. Ko et al.[15] indicated that naproxen use in patients with cellulitis is more efficacious than the antibiotic cephalexin. Zervos et al.[14] found that naproxen showed appropriate efficacy (85%), while the antibiotic alone showed relative efficacy (43%) in the treatment of cellulitis. Dall et al.[17] found that the addition of NSAIDs effectively accelerates recovery and that cellulitis-induced inflammation was relieved in 9.1% and 82.8% of the patients, respectively. In addition, perfect treatment of cellulitis took four days and more than eight days, respectively. Interestingly, the treatment with naproxen alone sometimes has even more acceptable therapeutic effects than some antibiotics. Based on our findings, the combination therapy of cefazolin with naproxen has high efficacy to cure cellulitis, even in short term. However, due to the small sample size of our study, it is essential to conduct more comprehensive studies with larger sample sizes.

Our study had some limitations. This study was an open-label study without blinding and placebo. To remove the placebo effect, it is necessary to design a blinded controlled study. We followed up with the patients for seven days. If we followed up with the patients for a longer period, we could have had a more complete judgment of the effect of the intervention, recurrence, and rehospitalization.

Conclusion

In cases of cellulitis, combination therapy with cefazolin and naproxen is far more effective than monotherapy with cefazolin. The administration of the first regimen was associated with further improvement of clinical manifestations and a shorter duration of hospitalization.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran (approval ID: IR.SBMU.RETECH.REC.1398.86, date: 07.05.2019).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., B.H., S.S., Concept: B.H., Design: S.T., Data Collection or Processing: S.T., S.S., A.K., Analysis or Interpretation: S.S., A.K., Literature Search: S.T., Writing: S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: Funding for this research was provided by the Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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