Is A Combination of Antibiotics and Non-Steroidal Anti-Inflammatory Drugs More Beneficial Than Antibiotic Monotherapy For The Treatment of Female Acute Uncomplicated Cystitis? A Randomized Controlled Pilot Study

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Purpose: To compare the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) combination therapy to single-agent antibiotic therapy for the resolution of symptoms during two restricted activity days in patients with acute uncomplicated cystitis (AUC)

Materials and Methods: We performed a prospective, randomized control pilot study. A total of 55 patients were enrolled. Group I (n=28) was treated with cepodoxime (100 mg twice per day), and Group II (n=27) was treated with cepodoxime (100 mg) and aceclofenac (100 mg) twice per day; both groups were treated for three days. Upon dysuria after each administration, the participants entered a value on a numerical pain scale. The primary outcome was whether there were any differences in the decrease rate in pain scale between the two groups.

Result: The average age of the 55 patients was 49.9 ± 13.5 years, and prior to the clinical visit, the patients experienced an average of 2.4 ± 2.2 days of dysuria symptoms. The average numerical pain scale score for dysuria was 4.98 ± 2.18. Thirty-four patients (61.8%) showed positive culture results, and E. coli was the most commonly found bacteria, cultured in 32 patients.
Fifty-one patients visited the clinic on day 7, and 42 (76.4%) reported symptom improvement, while nine patients (16.3%) had persistent symptoms. The follow-up numerical pain score was 0.39 ± 1.02 points. The pain score was dramatically decreased after medication. No difference was observed in the magnitude of the pain scale reduction between the two groups ($P = 0.134$). However, group II showed faster symptom resolution ($P = 0.035$) at the third administration (day 1.5).

Conclusion: Combination therapy with NSAIDs and antibiotics for AUC patients can improve symptoms faster during two restricted activity days when patients have difficulty performing daily living activities.

Keywords: acute uncomplicated cystitis; antibiotic resistance; symptoms; antibiotics; NSAIDs

INTRODUCTION

Acute uncomplicated cystitis (AUC) is a simple disease that is treatable with three days of empirical antibiotic treatment in 90% of patients[1]. However, several symptoms bother patients during the treatment period. Dysuria is the most common symptom of cystitis and is accompanied by frequency, urgency, and gross hematuria. Lower abdominal pain is also present in some cases[2]. Due to these symptoms, 54% of women report difficulty in work-related or other daily activities and a decline in their quality of life[3]. It has been known that cystitis causes six symptomatic days and two restricted activity days on average[4].
Therefore, it must be worthwhile to control dysuria for cystitis management. In this sense, non-steroidal anti-inflammatory drugs (NSAIDs) are expected to reduce the dysuria, which may enhance the quality of life during the treatment period. However, the vast majority of clinical researches about acute bacterial cystitis have focused on bacterial isolation, antimicrobial sensitivities, their risk factors, the emergence of extended spectrum beta-lactamase (ESBL), and the management of resistant strains[5-7]. Because cystitis exhibits a fast response to antibiotic treatment, researchers have not examined the pain and decline in the quality of life that patients face during the acute phase of the disease[8-10]. Futhermore, most studies treating cystitis with NSAIDs have been conducted to evaluate the possibility of using NSAIDs as a substitute for antibiotic treatment to prevent development of antibiotic resistance[11,12].
Hence, we aimed to compare the efficacy of NSAID combination therapy (antibiotics + NSAIDs) to antibiotic single therapy for the resolution of symptoms during two restricted activity days in which the patients experienced the most discomfort.

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Table 1. Demographics

	Group I (n = 27)	Group II (n = 28)	*p*-value
Age, years; mean ± SD	50.26 ± 14.8	49.61 ± 12.3	.860
BMI, Kg; mean ± SD	22.62 ± 3.04	21.70 ± 2.67	.237
coitus Hx. within 2 weeks	11 (40.7%)	15 (53.6%)	.422
Culture positive	19 (70.4%)	17 (60.7%)	.537
Onset, day; mean ± SD	1.93 ± 1.54	2.89 ± 2.06	.055
OABSS total, points; mean ± SD	7.81 ± 2.99	8.07 ± 3.41	.507
Initial pain scale, points; mean ± SD	4.52 ±2.13	5.45 ± 2.18	.154
Symptom improvement	18 (66.7%)	24 (85.7%)	.075

Abbreviations: BMI; Body Mass Index, SD; standard deviation, OABSS; Overactive Bladder Symptom Scores

MATERIALS AND METHODS

Participants

This study was a prospective, open-labeled, and randomized control pilot study and was conducted at five academic medical centers between August 2014 and July 2015.Women who were 18 years or older with pyuria that was confirmed by a urinalysis that showed more than five white blood cells per high-power field were included in this study. The patients complained of more than two symptoms, including urination frequency, dysuria, urgency, and lower abdominal discomfort. Patients with interstitial cystitis, a history of cystitis within two weeks, suspected febrile urinary tract infection, and bladder outlet obstruction (residual urine more than 100 ml) were excluded. Patients taking antibiotics or analgesics due to other medical conditions were also excluded from the study. A flow diagram of the selection process is reported in **Figure 1**. All participants voluntarily provided written informed consent. A total of 55 patients were finally enrolled in this study. The study was ethically approved by the institutional review board committee of our hospital (IRB No.14-1-32) and was registered by Clinical Research Information Service (KCT0001876)

Study design and Outcome

Until now, there hasn't been any research on the effects of antibiotics and NSIADS combination therapy on AUC during the acute phase. Therefore, a pilot study was planned to estimate the effect size before planning a large study. It's rare to see AUC patients in resident training hospitals, so participating patients collected over a year were used as the sample size. To reduce the selection bias, patient were allocated to Group I (cefpodoxime 100 mg twice per day) or Group II (cefpodoxime 100 mg and aceclofenac 100 mg twice per day) by each hospital via randomization in blocks of six. Block randomization was performed by computer program, with created randomized assignments being concealed from the doctors who were examining the patients. If the doctor includes the patient into the study after examination, research nurses perform treatment assignment according to the randomized order. The primary outcome of this study was whether there were any differences in the decrease rate in pain scale between the two groups when six medications were administered in three days. In addition, the improvement rate of the symptom on the seventh day and the prevalence of antibiotic resistance were the point of focus.

Figure 1. Flow Chart

Intervention

A thorough patient history, questionnaire, physical examination, urinalysis, and urine culture were performed as an initial assessment. After randomization, the participants were assigned to either Group I or Group II. Both groups were medicated twice per day for three days. Upon each dysuria symptoms after medication administration, the participants rated their symptoms on a numerical pain scale by themselves. Seven days after their initial assessment, the participants revisited the clinic to check their symptoms and the results of cultures. The patients were then evaluated for the resolution of their symptoms and subjected to a follow-up urinalysis. The symptom improvement was defined that pain scale decreased to below one point. Positive urine culture was defined that bacteriuria (≥ 104 cfu/mL) in the mid stream urine.

Statistical analysis

All clinicopathological and clinical follow-up data were analyzed on an intention to treat basis. Descriptive statistics were used to summarize each patient's symptoms and resistance rate to antibiotics. Baseline clinicopathological data were analyzed using independent t-tests, Mann-Whitney U tests, and chi-square tests. Changes in the pain scale score were analyzed by generalized linear mixed model. The statistical analysis was performed with SPSS 19.0 (SPSS Inc. Chicago, IL, USA). All p-values were two-sided and were considered to be statistically significant when $p < .05$.

RESULTS

The average age of the 55 patients was 49.9 ± 13.5

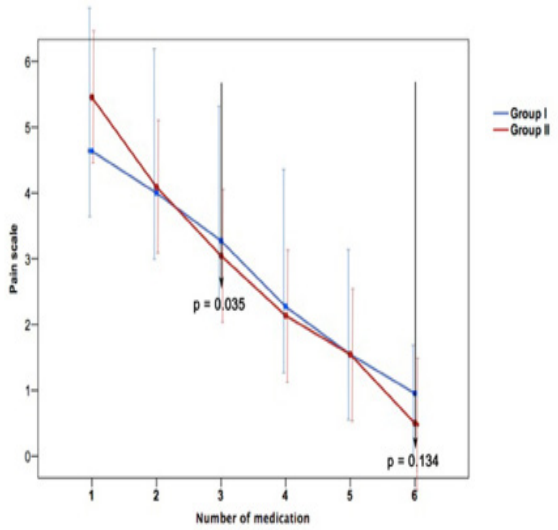

Figure 2. Combination therapy (Group II) produced faster symptom resolution than antibiotic monotherapy (Group I).

years, and the average BMI was 22.2 ± 2.87 (**Table 1**). Before the clinical visit, the patients experienced an average of 2.4 ± 2.2 days of dysuria symptoms. The average initial OABSS score was 7.95 ± 3.18 points and the numerical pain score for dysuria was 4.98 ± 2.18 points. Twenty-six (47.3%) of the patients had a history of coitus within two weeks, and 21 (38.2%) patients experienced gross hematuria. Dysuria was the most irritating symptom (29 patients, 52.7%), which was followed by frequency (12 patients, 21.8%), lower abdominal discomfort (eight patients, 14.5%), and residual sensation (five patients, 9.1%). In the previous five years, 68% of patients had cystitis more than once, 34% more than twice, and 6% more than five times.

Of the 55 patients, 34 (61.8%) showed positive culture results, and Escherichia coli was the most common bacterium that was cultured (32 patients). Aside from E. coli, Enterococcus Faecalis and Streptococcus were also cultured in one patient. The resistance rates of E. coli were 64% to ampicillin, 22% to ampicillin/clavulanic acid, 46.4% to trimethoprim/sulfamethoxazole, 14.8% to third generation cephalosporin, and 25.9% to ciprofloxacin. All strains were susceptible to ertapenem (**Table 2**).

Fifty-one patients visited the clinic on day 7, and 42 (76.4%) reported symptom improvement, while nine patients (16.3%) had persistent symptoms. No correlation was found between a positive urine culture and symptom improvement (P = .607, data not shown). The follow-up OABSS score was 5.0 ± 2.85 points, and the numerical pain score was 0.39 ± 1.02 points (Group I: 0.68 ± 1.38 vs. Group II: 0.115 ± 0.33, P = .105). Pyuria with 1~4 WBC/HPF was observed in 45 patients in follow-up urinalysis, but pyuria with more than 5 WBC/HPF was still observed in six patients. Among these six patients, only two patients whose initial urine culture revealed E. coli resistant to cepodoxime had symptoms. No patient reported adverse drug effects in Group I, but four patients had adverse effects in Group II (epigastric pain in three patients, epigastric pain and face edema in one patient).

The pain scale score was dramatically decreased after medication. After the sixth administration, the pain score was decreased to 0.98 ± 1.00 in Group I and to 0.5 ± 0.74 in Group II. No difference was observed in the magnitude of the pain score decrease between the two groups at the time of the sixth administration when the therapy was completed (P = .134, **Figure 2**). However, analysis of the third administration cycle, which occurred on day 1.5, revealed faster symptom resolution in the Group II patients treated with NSAID combination therapy than in Group I patients who were treated with antibiotic single therapy (P = .035).

DISCUSSION

In general, cystitis that occurs in healthy, premenopausal, non-pregnant women with no anatomical abnormality in the urinary tract is defined as AUC. When such healthy patients have only one voiding symptom, the probability of AUC is 50%. When patients have two symptoms (i.e., dysuria and frequency) without vaginal discharge, the probability is 90%[13]. Although symptoms are very important in the diagnosis and treatment of AUC, little interest has been focused on the pain and quality of life that hyper-acute patients experience[8-10]. Cystitis symptoms improve after a single dose of antibiotics. Symptom improvement was observed after 500 mg of ciprofloxacin was taken once daily in 50% of patients at six hours, 87% of patients at 24 hours, and 91% of patients at 48 hours after the first dose. The average duration for symptom improvement was 2.4 days. According to a previous study, twenty-two percent of patients reported complete resolution of symptoms within 24 hours, and 63% of patients reported resolution after the third dose of antibiotics[4]. Thus, cystitis causes an average of two restrictive activity days when daily work is limited and six symptomatic days when basic daily living activities are possible. Therefore, 78% of patients on day 1 and 37% of patients on day 3 still have symptoms that restrict their daily life, and their symptoms could be relieved if NSAIDs are added during this early phase. In fact, other researchers have reported that the empirical use of phenazopyridine, which is an over-the-counter urinary analgesic, in combination with antibiotics until the voiding symptoms are resolved helped to improve the symptoms[14]

Many studies of the role of NSAIDs in AUC have fo-

Table 2. Urine culture results. Resistance rates of E. coli were 14.8% to third generation cephalosporin

				E. Coli resistance (%)	
Culture (+)	34 (61.8%)	*E. Coli*	32 (94.1%)	Ampicillin	64%
		E. Faecalis	1 (2.9%)	Amp/clua	22.2%
		Streptococcus	1 (2.9%)	Trim/sul	46.4%
				Ciprofloxacin	25.9%
				Third cepha	14.8%
				Ertapenem	0%

cused on treatment efficacy rather than symptom improvement. Bleidorn et al. reported that single treatment ibuprofen showed similar symptom improvement to antibiotic treatment[11]. In this study, the ibuprofen group had significantly more culture-positive samples in the follow-up urine cultures after 7 days of treatment, but no difference in symptom improvement was observed between the two groups. However, that did not indicate a difference in symptom improvement during the first three days because symptom assessment was performed after the fourth day of treatment. To assess the efficacy of NSAIDs combination therapy during the acute phase of AUC, patients were told to record their symptoms on a numerical pain scale twice per day for three days to collect six numerical pain measurements, which was not performed in previous studies. We observed faster symptom improvement in the combination therapy group during the hyper-acute phase.

Various antibiotic therapies have been used as standard treatments for AUC for many years[1]. However, due to increasing resistance to antibiotics and the benign nature of AUC, physicians have evaluated several alternative treatments that avoid the use of antibiotics, including increased fluid intake, wait-and-see prescriptions, intravesical instillation and NSAIDs as single agent therapies[11-13,15-19]. These alternative treatments are supported for the following reasons. First, a placebo group that was not treated for AUC exhibited early resolution in 25 to 50% of patients. Second, NSAIDs have bactericidal effects in animal experiments and stabilize detrusor instability, which leads to the effective treatment of overactive bladders(20,21). Third, no benefit was observed in the occurrence of pyelonephritis and the emergence of resistant strains in the antibiotic group, although the antibiotic group had a higher clinical cure rate and microbiological success rate than the placebo group. Finally, the number of adverse events was higher in the antibiotic group[9]. In summary, the primary objective of AUC treatment is to relieve symptoms during two activity restricted days because AUC does not typically progress to a serious condition[14].

In actual practice, patients use many alternative treatments for AUC care aside from antibiotic therapy due to high medical costs and limited access to health care. One of the most common treatments is the use of uroanalgesics such as methenamine hippurate and phenazopyridine hydrochloride. These over-the-counter drugs are effective for symptom improvement compared to placebos, but no report has clearly demonstrated their efficacy[16-18].

According to a report of community-acquired urinary tract infections that was published in Korea in 2011, the most common strain in AUC is E. coli (72.7%), followed by E. faecalis (10.7%) and Klebsiella pneumoniae (3.5%)[12]. In our study, E. coli was isolated most frequently, and the resistance rate was similar to previous studies. One noteworthy point was that the resistance rate to third generation cephalosporin had more than doubled from 6.4% to 14.8%. This may be due to a recent increase in the use of cephalosporins to avoid quinolones. In general, antibiotics with a resistance rate greater than 20% are not appropriate as empirical antibiotics[1]. Therefore, the proper management of cephalosporin is necessary to prevent further increases in the rate of resistance.

Our study was a prospective, randomized study with several limitations. First, because it was a pilot study with a small number of participants, the sample size was not sufficient to prove statistical significance. Second, our study measured the numerical pain score with dysuria only to represent the overall symptom status of patients. Because patients differ in which symptoms they report most, a survey that is simple but measures more symptoms should be used in subsequent studies. Third, it would have been helpful to have an NSAID monotherapy group that could clearly demonstrate the role of NSAIDs, although this group could not be included due to ethical issues in Korea.

CONCLUSIONS

NSAIDs and antibiotic combination therapy for AUC cystitis can improve patient symptoms faster than antibiotic monotherapy and is useful when patients have difficulties performing daily living activities.

CONFLICT ON INTEREST

There is no conflict of interest.

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