The effect of levofloxacin combinations on CRP decrease in SARS CoV-2 pneumonia

ABSTRACT

Objective: Covid 19 pneumonia, caused by the SARS-CoV-2 virus, is a disease with severe damage to the lung. It was reported that in Covid 19, rate of 74% antibiotics were used, and secondary bacterial infections were detected in at least 17.6% of the patients who used antibiotics. In this study, the effects of antibiotics in Covid 19 patients who do not use the steroid on CRP decrease were aimed.

Materials and Methods: It was done in Ersin Arslan Training and Research Hospital Covid Wards between January 1, 2020, and December 31, 2020. The study included with positive PCR test (SARS-CoV-2), 18 age and more than, with pneumonia in CT, but users of steroid were excluded. Ages, genders, comorbidities, WBC values, neutrophil values, CRP values (in the first 24 hours and the 3rd day), lung involvements in CT and antibiotics of the patients were analyzed retrospectively. Accordingly, a total of 202 patients who compatible criteria were included in the study. Chi Square Test was used in the statistical analysis of the data.

Results: The mean age was 60.2±2.57 (19-89). 53.9% of the patients were males and 46.1% females. There was a history of chronic disease in 54.9% of the patients. Findings of pneumonia in CT were 67.8% multifocal, and 32.2% unifocal. Covid 19 pneumonia was more often in males, in over 60 ages and in have a history of chronic disease. Antibiotics used were levofloxacin (L) and combined levofloxacin with piperacillin/tazobactam (LT) and meropenem (LM) and ceftriaxone (LC). When the 1st and 3rd day CRP values were compared; as L<LT<LM<LC rate of decrease were calculated. It was determined that LM and LC were preferred more often in patients with comorbidities. There was no statistically significant difference between the rates of decrease on CRP values of levofloxacin and its combinations in patients with normal WBC values.

Conclusion: According to this study, in SARS-CoV-2 pneumonia; there is no significant difference between the rates of decrease on CRP values of levofloxacin and its combinations. Antibiotics should be preferred if bacterial infection is suspected when the patient's clinic and infection parameters are evaluated. It should be taken into account that secondary coinfection rates are not high in the selection of antibiotics in Covid 19. Further studies are needed to detect bacterial coinfections early in patients.

Keywords: antibiotic, Covid-19, CRP, effect, pneumonia

1.INTRODUCTION

Covid 19 pneumonia, caused by the SARS-CoV-2 virus is a disease with severe damage to the lung. It is known that most of the deaths caused by Influenza are related to secondary bacterial infections [1]. For this reason, antibiotic use is preferred in fatal Covid 19 pneumonia. It has been reported that the detection of bacterial products in the blood in Covid 19 pneumonia is related with severity of the disease [2]. As it is known, the use of antibiotics in viral infections is not recommended. However, antibiotic use is preferred in Covid 19 due to weakening of the patient's immune system, comorbidity, severe lung damage, and the risk of secondary bacterial infection. According to the findings obtained in a study; those have been suggested to used azithromycin, doxycycline, clarithromycin, ceftriaxone, erythromycin,

amoxicillin, amoxicillin-clavulanic acid, ampicillin, gentamicin, benzylpenicillin, piperacillin/tazobactam, ciprofloxacin, ciprofloxacin, ceftamycin in the management of Covid 19 [3]. When examined retrospectively, it was determined that levofloxacin and its combinations were used more frequently as prophylactic or empirical antibiotics by physicians during the Covid 19 management process. It was observed that broad-spectrum antibiotics were used due to the aggressive course of pneumonia caused by Covid 19. It was seen that physicians preferred antibiotics by paying attention to the patient's age, comorbidity, WBC (white blood cell) and CRP (C-reaktif protein) values, and involvement rates in lung tomography. For this reason, it was aimed to investigate the effects on WBC and CRP values of antibiotics used in this study.

2. MATERİAL AND METHODS

The study done Ersin Arslan Training and Research Hospital Covid Wards between January 1, 2020 and December 31, 2020. The study included with positive PCR test (SARS-CoV-2), 18 age and more than, with pneumonia in CT. Those who negative PCR test results, younger than 18 years old, did not use of antibiotic and users of steroid were excluded. Ages, genders, comorbidities, WBC values, neutrophil values, CRP values (in the first 24 hours and the 3rd day), lung involvements in CT and antibiotics of the patients were analyzed retrospectively.. Patients who used steroids and their derivatives and inflammatory drugs were excluded from the study because they affected CRP values. It was determined that prophylactic antibiotics were preferred by physicians according to CRP elevation, age, comorbidity and radiological involvement in patients with normal WBC values. Accordingly, a total of 202 patients out of 1384 who compatible criteria were included in the study. The normal value range of C-reactive protein (CRP) 0-5 mg/L and WBC value 4-10 mL was accepted. In the study, dependent and independent variables were determined for statistical analysis. Chi Square Test was used in the statistical analysis of the data. Republic of Turkey Ministry of Health 2020-12-10T12_42_35 numbered and Gaziantep University Medical Ethics Committee 2021/75 numbered approval have been received.
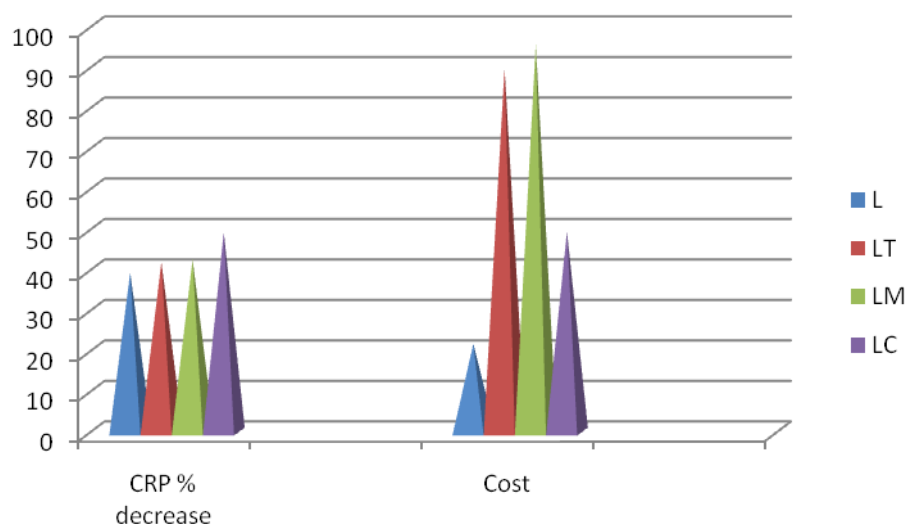
3. RESULTS

A total of 202 patients who were compatible with the study criteria were examined. The mean age was 60.2±2.57 (19-89). 53.9% of the patients were male and 46.1% female (table 1). There was a history of chronic disease in 54.9% of the patients. Findings of pneumonia in CT were 67.8% multifocal and 32.2% unifocal. Antibiotics used were levofloxacin (L), levofloxacin combined with piperacillin tazobactam (LT), levofloxacin combined with meropenem (LM), levofloxacin combined with ceftriaxone (LC). Usage doses of antibiotics were L: 500 mg/day, LT: 500 mg + 3x4.5 g / day, LM: 500 mg + 3x1 g / day, LC: 500 mg + 2x1 g /day. CRP values were decrease in all antibiotics used. When the 1st and 3rd day CRP values were compared; L 39.26%, LT 41.88%, LM 42.52%, LC 48.12% rate of decrease were calculated. According to CRP rates of decrease; the order from most to least was LC>LM>LT>L. The cost order of used antibiotics was LM>LT>LD>L (figure 1).

Table 1. distribution of age and gender in the study

	n	SD	%95 CI
Gender			
Male	109	0.49	0.08
Female	93		
Age			
Mean	60.2	14.20	2.57

Figure 1. Rates of decrease on CRP and costs in antibiotics

As a result, admitted in wards in patients; Covid 19 pneumonia was more often in male, in over 60 ages and in have a history of chronic disease. LM and LC were preferred more often in the 19-40 age group and with comorbidity (p<0.0001). LT was preferred in multifocal patients according to the pneumonia focus (p<0.07). L and LT were related with a decrease of up to 20% on CRP in multifocal pneumonia (p<0.04). LM and LC were related with a 41-60% decrease on CRP in patients aged 19-40 ages with comorbidity (p<0.01). LC was related 61-80% decrease on CRP in patients with comorbidity (p<0.07). LT and LC were related with more than 80% decrease on CRP in unifocal pneumonia and more than 60 years old (p<0.0001) (table 2). When the 1st and 3rd day CRP values were compared; although there was a decrease on CRP with all antibiotics, there was no statistically significant difference between them (p<0.2, table 3).

Table 2. Statistical analysis of the study

	N:120	L		LT		LM		LC	
	n	p<	ODSS	p<	ODSS	p<	ODSS	p<	ODSS
Ages (range:19-89)									
19-40	42					0.0001	1.231	0.0001	0.798
41-60	66								
>60	94								
Comorbidity									
Yes	111					0.0001	1.096	0.0001	1.096

No	91							

Involvement of lung

Unifocal	65							
Multifocal	137	0.06	2.322	0.07	2.786			

CRP decrease (%)

↓20% and less	35	0.04	1.625	0.03	2.909			
↓21-40%	46							
↓41-60%	64					0.01	1.000	0.01	0.684
↓61-80%	36							0.07	0.982
↓81% and more	21			0.0001	1.000			0.0001	1.000

*L: Levofloxacin LT: Levofloxacin with Piperacillin/Tazobactam LM: Levofloxacin with Meropenem
LC: Levofloxacin with Ceftriaxone

Table 3. Statistical comparison of the decrease rates of antibiotics on CRP

	L	LT	LM	LC
1st day mean of CRP values	59.40	102.30	131.70	72.80
3st day mean of CRP values	36.08	59.46	75.71	37.77
% decrease of CRP values	**39.26**	**41.88**	**42.52**	**48.12**

*L: Levofloxacin LT: Levofloxacin with Piperacillin/Tazobactam LM: Levofloxacin with Meropenem
LC: Levofloxacin with Ceftriaxone ***p<0.2 Cramer's V:0.984 (Chi Square Test)

4. DISCUSSION

Due to the similarities between bacterial pneumonia and moderate or severe Covid 19 pneumonia, difficulties arise in choosing antibiotics. The choice of antibiotic is determined according as many factors such as inflammatory markers, age, comorbidity and clinical findings. In a large meta-analysis, it was reported that 71.9% of Covid 19 patients used antibiotics, although the bacterial coinfection rate was 3.5% [4]. Due to the fatal course of the disease during the Covid 19 pandemic process, physicians prefer antibiotics even if the patient's bacterial infection parameters are normal, because they cannot be sure of the exclusion of secondary infections and because Covid 19 is an aggressive disease. The severity of the disease cannot be attributed only to secondary bacterial infections. Because inflammatory cytokine storm is also important in the severity and process of the disease [2]. The high value of procalcitonin, which is used as a biochemical marker in bacterial infection, is related with the severity of the disease in Covid 19 [5]. High procalcitonin value is seen in many patients. Therefore, the necessity of using antibiotics occurred. However, as in this retrospective study, even if bacterial parameters such as procalcitonin, WBC and neutrophils are normal, sole or combined antibiotics were preferred. It was observed that physicians preferred combined antibiotics more frequently in elderly patients and with comorbidities. In addition, even if the WBC and procalcitonin values of the laboratory parameters were normal, it was determined that they mostly paid attention to the CRP values. Although it is known that only the CRP value alone does not prove bacterial infection, it was understood that it was preferred because of the anxiety of secondary coinfection and worse clinical course. For this reason, it was aimed to determine the effects of single and combined antibiotics used by physicians on CRP value together with other parameters. Bacterial pneumonias detected early can be effectively treated with antibiotics. Wide spectrum antibiotics are frequently used

in Covid 19 patients [6]. In the study, it was observed that levofloxacin and its combinations were frequently preferred as wide-spectrum antibiotics in patients in Covid 19 wards. Although the first WBC values were normal, it was detected levofloxacin combinations were preferred due to the patient's high ages (>60) , high CRP values, widespread involvement of lung in CT, and comorbidities. The increase in neutrophil values in the 3rd day may be related to the patient's susceptibility to secondary bacterial infection. Therefore, the related of L, LT, LM and LC with decrease CRP values can be explained by the prevention of secondary bacterial infection. Because the antibiotic used in patients with normal WBC values in Covid 19 is for prophylactic purposes. Effective and rational antibiotic to prefer is essential in pneumonia. Unnecessary use of antibiotics causes an increase in antimicrobial resistance. Resistance to antibiotic is cause for not responding to the treatment, and lack of access to antibiotics kills more people than resistance [7]. However, due to the poor clinical course of the disease and its fatal outcome, widespread use of antibiotics were observed during the pandemic process. In a multicenter study, it was reported that bacterial coinfection was detected at a rate of 9.5% clinically in Covid 19 [8]. In another study, it was reported that in Covid 19, rate of 74% antibiotics were used, and secondary infections were detected in at least 17.6% of the patients who used antibiotics [9]. In the study, it was observed that bacterial cultures were rarely studied due to the too many patients during the pandemic process. Therefore, the proven bacterial coinfection rate could not be calculated, but it was estimated to be 3-5%. If in a study; it has been reported that piperacillin/tazobactam, ciprofloxacin, ceftazidime, cefepime, vancomycin, meropenem and cefuroxime are recommended in the treatment of Covid 19 [3]. In this study, levofloxacin, piperacillin tazobactam, meropenem and ceftriaxone were used. Although with the LC combination are decrease on CRP values more , it was not statistically significant. LM were related with less length of hospital stay, but that was no difference with other antibiotics in CRP decreases of rates. It has been reported that the use of empirical antibiotics in patients with Covid 19 pneumonia do not prevent clinical worsening or mortality [10]. Therefore, considering efficacy, cost, and antibiotic resistance, levofloxacin should be used alone as a prophylactic antibiotic. Considering the increase in WBC values in the 3rd day; LC or LM combination can be preferred as empirical antibiotics in patients with comorbidities between 19-40 years of age in Covid 19 pneumonia. In multifocal Covid 19 pneumonia, the LT combination empirically can be preferred. The combination of LT and LC is related with a more than decrease on CRP value. However, in this study, there were no statistically significant difference between the effects of levofloxacin and its combinations on the decrease on CRP values, considering the patient's age and comorbidity. In the guidelines recommend empirical antibiotics only if bacterial infections are suspected in moderate Covid 19, empirical antibiotics are routinely recommended for severe Covid 19 [11,12]. Therefore, effective and rational antibiotic prefer is required in Covid 19 pneumonia. Widespread unnecessary use of antibiotics will expose patients to risks of adverse effects and the spread of antimicrobial resistance globally. It may be difficult to distinguish between progressive COVID-19 disease and bacterial coinfection or superinfection, but antibiotic selection should be made by carefully evaluating bacterial coinfection rates, the patient's clinic, and infection parameters. Further studies are needed to detect bacterial coinfections early in Covid 19 patients.

4. CONCLUSİON

According to this study, in SARS-CoV-2 pneumonia; there is no significant difference between the rates of decrease on CRP values of levofloxacin and its combinations. Antibiotics should be preferred if bacterial infection is suspected when the patient's clinic and infection parameters are evaluated. It should be taken into account that secondary coinfection rates are not high in the selection of antibiotics in Covid 19. Further studies are needed to detect bacterial coinfections early in patients.

ETHICAL APPROVAL

Republic of Turkey Ministry of Health 2020-12-10T12_42_35 numbered and Gaziantep University Medical Ethics Committee 2021/75 numbered approval have been received.

CONSENT
As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Author declared that is no conflict of interest.

FUNDING

No financial support has been received

DATA AVAILABILITY

The data are available in the article.

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