Coagulation abnormalities (D.dimer) induced by Beta-Lactam antibiotics among Sudanese's patients in Khartoum state-2019

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Abstract

Back ground Cephalosporins, along with penicillin, belong to the beta-lactam group of bactericidal antibiotics. Based on the timeline of drug discovery and their antimicrobial properties, these antibiotic agents are grouped into different generations, first through fifth. In general, as we move from first to third, the microbicidal activity of cephalosporins decreases against gram-positive organisms but increase against gram-negative bacilli. Furthermore, the resistance against beta-lactamases increases from first to fifth generations.Cefuroxime / Ceftin is an antibiotic ending for the second generation of cephalosporins.Sforioroxime is used for their medical studies of infection after the spectacular surgeries. **Objective:** The aim of this study was to assess the presence of d.dimer coagulation or decomposition in the blood of Sudanese patients who are treated with cerfouxime / ceftin. **Method:** 100 samples of blood were collected 50, samples of patients using the antibiotic cefroxime \ ceftinas the case, 50 sample of health personnel as control. 2.5 ml of blood collected in a sodium citrate vessel and subsequently measured to deny or prove the presence of blood clotting. **Results:** The results showed that the mean of D.dimer was increased when compare case group (2108) with control group (304) with statistically significant (p.value=0.00)and when associated with the concentration of antibiotics and time taken and there was a significant rise.**Conclusion:** The present study showed that there were an insignificant difference in the clotting or decomposition of d.dimer in the blood of patients who treated with

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antibiotic cefoxime / ceftin when compared with the control and no relationship between blood clotting when associated with sex and age.

Keywords: Beta –lactam antibiotic, D.dimer- Sudan

1. Introduction

Large doses of the antibiotics can cause a bleeding diathesis in patients, these drugs presumably do so by impairing platelet function because they prolong the bleeding time of human volunteers. Moreover, platelets from individuals taking these antibiotics aggregate poorly in response to several aggregating agents and they agglutinate poorly in response to ristocetin. Platelets incubated with β-lactam antibiotics in vitro also respond poorly to a variety of platelet agonists, although larger concentrations of antibiotic are required to demonstrate this effect the mechanism by which these antibiotics impair platelet function is unknown, Platelet adhesion, aggregation and secretion are initiated by the binding ofagonists to their specific receptors on the platelet membrane. (Sanford J. shattil, *et al*)

The β-lactam antibiotics are a large class of diverse compounds used clinically in both the oral and parenteral forms. The β-lactam antibiotic agents have become the most widely used therapeutic class of antimicrobials because of their broad antibacterial spectrum and excellent safety profile. Reports of drug–drug interactions with the β-lactam antimicrobials are a relatively rare phenomenon, and when interactions do occur, they are generally minor. This chapter describes the drug–drug interactions of the β-lactam antibiotics: penicillins, cephalosporins, carbapenems, and monobactams. As an overview, each β-lactam drug interaction has been categorized as major, moderate or minor and is presented in Table 1. Interactions classified as major are considered well documented and have the potential to be life threatening or dangerous. Moderate interactions are those for which more documentation is needed or potential harm to the patient is less. Minor interactions are poorly documented, present minimal potential harm to the patient, or occur with a low incidence. The clinical significance of drug–drug interactions associated with the β-lactam antibiotics and understanding of the management of these drug–drug interactions are presented. Melinda M-*etal* 1980.

β-lactamase inhibitor has been isolated from Streptomyces clavuligerus ATCC 27064 and given the name clavulanic acid. Conditions for the cultivation of the organism and detection and isolation of clavulanic acid are described. This compound resembles the nucleus of a penicillin but differs in

having no acylamino side chain, having oxygen instead of sulfur, and containing a (3hydroxyethylidine substituent in the oxazolidine ring. Clavulanic acid is a potent inhibitor ofmany 8-lactamases; include ingthose found in Escherichia coli (plasmid mediated), Klebsiellaaerogenes, Proteus mirabilis, and Staphylococcus aureus, the inhibition being ofa progressive type. The cephalosporinase type of /8-lactamase found in Pseudomonas aeruginosa and E.coli are less well inhibited. The minimum inhibitory concentrations of ampicillin and cephaloridine against, 8-lactamase-producing, penicillin-resistant strains of S.aureus, K.aerogenes, P. mirabilis, and E. coli have been shown to be considerably reduced by the addition of low concentrations of clavulanic acid. C.Reading-*etal* 1996.

2. MATERIAL AND METHODS

This case-control study was conducted in Sharqealneilhospital in Khartoum state, during June to oct 2019. Included one hindered blood samples, fifty of these samples were collected from patients treated with beta-lactomantibioticsas a case group fifty samples were collected from apparently normal individuals as a control group. , Blood samples were taken from patientstreated with beta-lactom antibiotics. A total of 2.5 ml blood samples were collected in container containing 3.8 % of tri-sodium citrate to obtain platelets poor plasma that used to measure d dimer using ichromaTM. , Data was analyzed using SPSS version 14 for windows 7 ultimate to obtain mean, standard deviation and P value. P value less than 0.05 consider clinically significant and more than 0.05 considered clinically insignificant.

D-dimer concentration was investigated by quantitative determination of cross-linked fibrin degradation product containing D-dimer using ichromaTM. The method comprise of four processes. Firstly apply 50µl of washing solution to the Test device, Avoid touching the membrane with the pipette and allow the washing solution to soak into the membrane, and then added 50µl of undiluted platelet-free citrated plasma or control to the Test device. The sample should be absorbed into the membrane in less than 50 seconds by Apply 50µl of conjugate to the Test device. The conjugate should be absorbed into the membrane in less than 50 seconds, finally apply 50µl of washing solution in the Test Device and read the result.

3. Results

One hundred blood samples were collected, 50 from patients used antibiotic as case and 50 from healthy person as control, the mean result of D.dimer was increased when compare case group

(2108) with control group (304) with statistically significant (p.value=0.00)

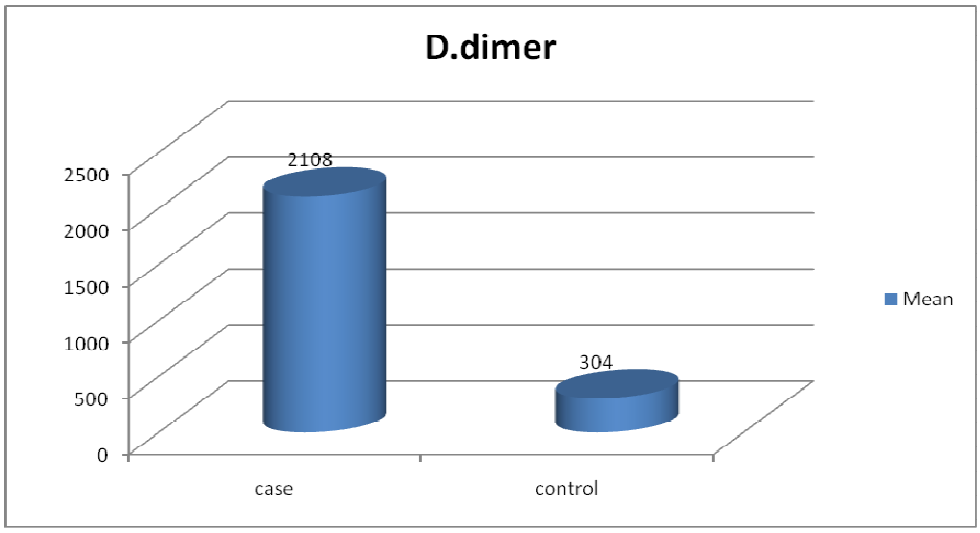

Figure 3.1: Mean of D. dimer among study group

There were no significant differences in D.dimerin study population when correlated to gender [male (1809) and female (2742)] (p.value=0.2)**.**

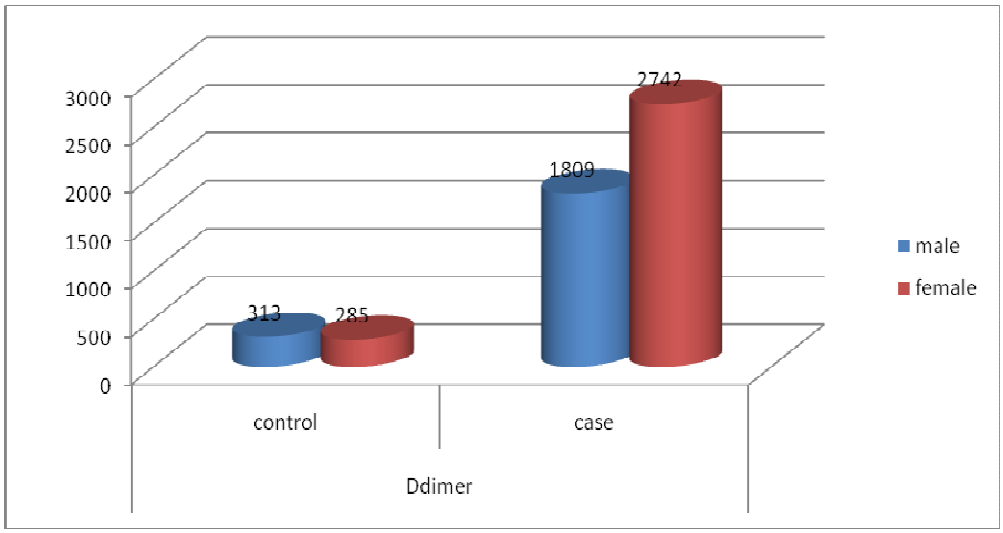

figure3.2: Mean of D. dimer among gender in study group

There were no significant differences in D.dimerin study population when correlated to age group [20-40y (2003), 41-60y (2001), 61-80y (1189) and >80y (5348), respectively] when compared to control group with p.value=0.4 and 0.5, respectively.

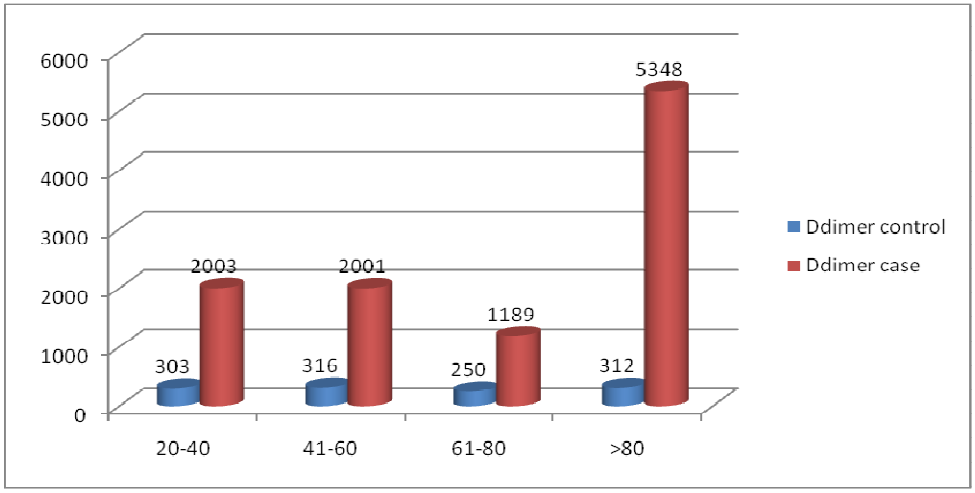

Figure 3.3: Mean of D. dimer among age with study group

Out of 50 patients that used antibiotic , the most frequent duration used wasless than 1week 32 patients (64%), followed by 16 (32%) of total patients used antibiotic in duration between 1-2 weeks and lastly 2 (4%) patients were used antibiotic for 1month. The most frequent antibiotic used was cefuroxime 750 (26 patients) followed by cefuroxime 1g (10patients), cefuroxime 500 (8 patients) and 6 patients used cefuroxime 1.5g

Table 3.4: Frequency result of duration and antibiotic

		Frequency	Percent
Duration	<1 week	32	64%
	1-2 week	16	32%
	1 month	2	4%
Antibiotic	cefuroxime 500	8	16%

	cefuroxime 750	26	52%
	cefuroxime 1G	10	20%
	cefuroxime 1.5G	6	12%

The mean result of D.dimer was increased in correlated to duration of administration was more increased in those patients used antibiotic for 1-2 weeks (3496) and with statistically significant (p.value=0.05). The mean result of D.dimer when correlated to type of antibiotic used was more increased in those patients used cefuroxime 1g (2742), followed by cefuroxime 750 (2682) and in those patients used cefuroxime 500 and cefuroxime 1.5 were (591 and 585, respectively) with statistically significant (p.value=0.04).

Table 3.5: D. dimer among duration and antibiotic

		D. dimer		p.value
		N	Mean	
Duration	<1 week	32	1540	0.05
	1-2 week	16	3496	
	1 month	2	77	
Antibiotic	cefuroxime 500	8	591	0.04
	cefuroxime 750	26	2682	
	cefuroxime 1G	10	2742	
	cefuroxime 1.5G	6	585	

4. Discussion

Defects in hemostasis may occur after the administration of many beta-lactam antibiotics. One hundred blood samples were collected, 50 from patients used antibiotic as case and 50 from healthy person as control.

In our study, the mean result of D.dimer was increased when compare case group (2108) with control group (304) with statistically significant (p.value=0.00). That agrees with previous study done by Teresa, *et al*. A total of fifty subjects treated with cefuroxime antibiotic as case group and 50 healthy volunteers as control group were recruited for the study. Two groups were matched in terms of the age and sexuality, the D.dimer was increased among case group when compared to controls with statistically significant changes was shown between two groups (p.value=0.02) [**TERESA**, *et al,* 1986].

Also agrees with another study done by Ulrych*et al*. Two hundred sixteen patients that used antibiotics after surgery were enrolled, in this study. A statistically significant increase in coagulation D-dimer levels ($p < 0.001$) [Ulrych et al, 2016]. But disagree with previous study done by Dinev, *et al*. A total of 100 patients treated with cefuroxime antibiotic as case group and 100 healthy person as control group were included in this study, the D.dimer was within normal range among case group when compared to controls with statistically insignificant (p.value=0.1) [**Dinev***et al*, 2006]

Conclusions

According to the present result there is a relation between d.dimer level and uses of antibiotics , due to increased result of d.dimer when copmpair with control (p.value=0.00)which agreement with most previous study.

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