Effect of Ciprofloxacin versus Levofloxacin on QTc-interval and Dysglycemia in Diabetic and Non-Diabetic Patients.

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Short Title: Safety of Ciprofloxacin versus Levofloxacin on QTc-interval and dysglycemia

Abstract

Background:

Levofloxacin and ciprofloxacin are more commonly used among fluoroquinolone class and the question of cardiac safety and glucose hemostasis of this class has been raised.

Objective:

To compare intravenous levofloxacin and ciprofloxacin regarding their risk on QTc prolongation and dysglycemia in diabetic and non-diabetic patients.

Methods:

A randomized prospective study at Beni-Suef university hospital was conducted on 200 adult patients over 6 months. The patients received intravenous levofloxacin 750mg once daily or ciprofloxacin 400mg twice daily. Electrocardiogram and fasting blood glucose were obtained from each patient before starting antibiotic, 24 hours, 72 hours after the first dose and 72 hours after antibiotics cessation.

Results:

The results of the current study showed the relative risk for QTc prolongation with levofloxacin was more than ciprofloxacin by about 4 and 1.5 in diabetic and non-diabetic patients, respectively. The relative risk for dysglycemia with levofloxacin was

2.28 and 1.39 times more than ciprofloxacin in diabetic and non-diabetic patients, respectively.

Conclusion:

The present study showed that the risk for QTc prolongation and hyperglycemia was greater with levofloxacin than ciprofloxacin in diabetic and non-diabetic patients. In addition, the risk for hypoglycemia was greater with levofloxacin than ciprofloxacin in non-diabetic patients.

What's already known about this topic?

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What does this article add?

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Take home message for clinician

The risk for QTc prolongation and hyperglycemia was greater with levofloxacin than ciprofloxacin in diabetic and non-diabetic patients. In addition, the risk for hypoglycemia was greater with levofloxacin than ciprofloxacin in non-diabetic patients.

Keywords: Ciprofloxacin, Levofloxacin, QTc-interval, Dysglycemia, Diabetic patients

ClinicalTrials.gov Identifier: NCT04456712

1. Introduction:

Fluoroquinolones represent an important class of antibacterial drug and they are used worldwide because they have many advantages as a broad spectrum of activity, oral and intravenous formulations, high potency, high serum levels, large distribution volume and good bioavailability [1, 2].

Fluoroquinolones are classified into generations according to the spectrum of antimicrobial activities that targeted them [3]. Fluoroquinolones may cause several side effects as tendon rupture, central nervous toxicity, cardiovascular toxicity, gastrointestinal toxicity, phototoxicity, disrupted glucose metabolism, skin disorders and hypersensitivity [4].

Ciprofloxacin, a second generation fluoroquinolone, is one of the most successful and widely used compounds of fluoroquinolone [5, 6]. Ciprofloxacin is the most potent fluoroquinolone, active against a wide range of bacteria especially, aerobic gram-negative bacilli [7]. On the other hand, levofloxacin is a third generation

fluoroquinolone [8]. It is a broad-spectrum antibiotic that has good activity against gram-positive and gram-negative aerobes and atypical bacteria [9].

Diabetes mellitus (DM) is chronic disease and a serious of metabolic disorder associated with the presence of hyperglycemia due to partial or complete insulin deficiency [10]. Diabetic patients are at high risk for infections due to poor metabolic control, decrease immune system and diabetic neuropathy. Sepsis occurs more in diabetic patients than other individuals, so costs of treatment in diabetics are 2.3-fold more than non-diabetic patients [11]. DM is a major risk factor for cardiovascular diseases [12].

Fluoroquinolone class is associated with cardiac side effects as QTc prolongation and torsade de pointes (Tdp). Some agents of fluoroquinolones were withdrawn from market. However, cardiac adverse effects has been developed with fluoroquinolones still in market [13]. The QT interval represents both the depolarization and repolarization phase of the action potential of the ventricle [14]. Normally QT intervals are shortened with tachycardia and lengthened with bradycardia, so QTc interval should be calculated [15].

Prolongation for QT interval has been induced by fluoroquinolones because this class blocks voltage gated K+ channels, especially the rapid component of the delayed rectifier K+ current (IKr). This channel has an important role in regulating ventricular electrical repolarization. All fluoroquinolone members antagonize this current which leads to QT prolongation [16]. Members of fluoroquinolones class have different effects on QT interval [17]. In Denmark and Sweden, Cho and Park (2018) found that there was no association between fluoroquinolones and serious arrhythmia in general population [18]. Controversy, the US FDA suggested that the risk and benefits ratio of fluoroquinolones should be taken into consideration [19].

In addition to hyperglycemia events are more common with fluoroquinolones than with other classes of antibiotics [20]. The food and drug administration (FDA) confirmed the current warning that fluoroquinolones may cause decrease in blood sugar especially in diabetic patients [21]. However, other study proved that fluoroquinolones may cause dysglycemic events in diabetic and non-diabetic patients [22].

So, the current study aimed to compare ciprofloxacin and levofloxacin regarding their risk on QTc prolongation and glucose hemostasis in diabetic and non-diabetic patients.

2. Patients and Methods:

2.1.Setting and design:

A prospective randomized clinical study at Beni-Suef University hospital was conducted over six-month period from June 2018 to November 2018. The method of randomization was sealed envelope technique. The study was approved by the Ethics Committee, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt (# FWA00015574). The patients provided their written informed consent to participate in the current study.

2.2. Patients and methods:

The study population included two hundred adult patients, male and female between the ages of 18 to 70 years who admitted to the intermediate care unit in the study period after excluding 5 patients who were newly diagnosed with cardiac diseases and 5 patients who were de-escalated to another class of antibiotics as shown in (Figure 1). The sample size was calculated using Raosoft formula [23] .The patients were divided into two equal groups which are matched regarding gender and age. The first group included one hundred patients who received intravenous levofloxacin 750 mg/24 hours [24] and the second group included one hundred patients who received intravenous ciprofloxacin 400mg/12 hours [25]. Both groups were subdivided into two sub groups (fifty diabetic patients and fifty non-diabetic patients).Twelve lead Nihon Kohden's Cardiofax C electrocardiogram (Rosbach, Germany) and fasting blood glucose tests were obtained from each patient before starting antibiotic, after twenty four hours, seventy two hours from the first dose and after seventy two hours from antibiotic cessation [26] [27].

QTc was automatically calculated by ECG device using Bazett's formula where is QTc = QT / √ (RR) [28]. Borderline QTc range is 430–450 msec in males and 450–470 msec in females [29]. QTc intervals >450 msec in men and >470 msec in women were considered to be abnormal [30].

Hypoglycemic events in diabetic and non-diabetic patients defined as fasting plasma glucose levels <70 mg/dl [31] [32]. Hyperglycemic events in non-diabetic patients (presymptomatic dysglycemia) defined as fasting plasma glucose levels >100 mg/dl [33]. Hyperglycemic events in diabetic patients defined as fasting plasma glucose levels >130 mg/dl [34] [35] [36].

Patients were excluded if:

(i) Younger than 18 years or older than 70 years.
(ii) Has prolonged QTc before receiving therapy.
(iii) With a history of heart diseases.
(iv) Received class IA or III antiarrhythmic agents.
(v) Received macrolide antibiotics.
(vi) With a history of quinolone allergy.
(vii) Pregnant and lactating women.

Sample collection:

5 ml venous blood were withdrawn from all patients after fasting 8-12 hours then samples were collected in plain tubes, left for 10 minutes to clot and centrifuged at 5000 rpm for 15 minutes to separate the serum [37]. Serum was used for routine laboratory investigations.

Serum potassium (K) and sodium (Na) were indicated by Roche Diagnostics AVL 9180 Series Electrolyte Analyzers (Germany) [38].

Alanine transaminase (ALT), aspartate transaminase (AST), serum magnesium, blood glucose and the serum creatinine were determined by automated analyzer (Beckman Coulter AU480, Kraemer Blvd., Brea, CA 92821 USA) [39] [40] [41] .

Creatinine clearance (CrCl) was measured from Cockcroft and Gault formula (CG) using serum creatinine values on all patients [42].

CrCl (ml/min) = [(140 − age) × weight in kg]/72×serum creatinine × (0.85 if female).

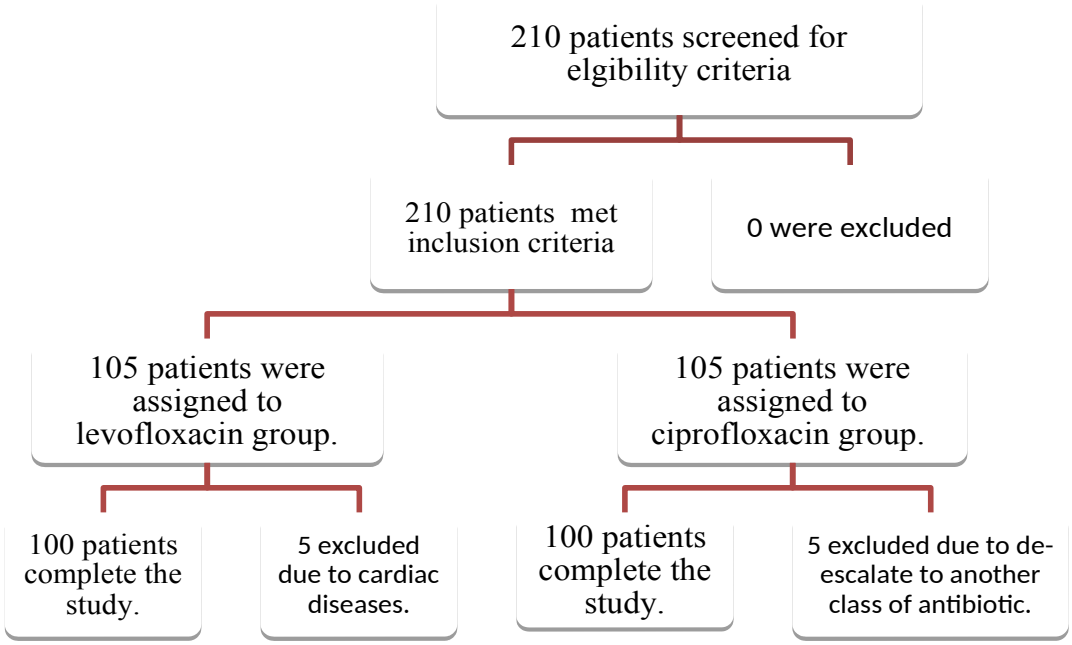

Figure 1: Follow-up of the study patients

3. Statistical Analysis:

All statistical analysis was performed by using SPSS version 23. The demographic and clinical characteristics of patients were expressed as mean ± standard deviation (SD). A chi-square test was used to examine the difference in QTc prolongation and dysglycemia between ciprofloxacin and levofloxacin in diabetic and non-diabetic patients. The difference in QTc prolongation and dysglycemia in ciprofloxacin and levofloxacin group regarding hours was examined by one-way analysis of variance (ANOVA) test followed by Wilcoxon signed-rank test. The difference between laboratory data was analyzed by Wilcoxon signed-rank test and paired sample t-test. Statistically significant was considered at a P-value <0.05. Relative risk (RR) and 95% confidence interval (CI) were determined for QTc prolongation and dysglycemia among ciprofloxacin and levofloxacin users.

4. Results:

The current study showed no significant difference between the four subgroups regarding their demographics and baseline laboratory data as illustrated in (Table 1).

The present study showed that levofloxacin administration produced a significant prolongation of QTc interval compared to the ciprofloxacin group after 72 hours of starting treatment in diabetic as presented in (Figure 2), while figure 3 shows that levofloxacin administration produced non-significant prolongation of QTc compared to ciprofloxacin in non-diabetic patients. Levofloxacin was associated with 4 times higher risk of QTc prolongation than ciprofloxacin in diabetic patients and (95% CI; 0.89-17.9) as indicated in (Figure 4). Levofloxacin administration resulted in more risk by about 1.5 times than ciprofloxacin on QTc prolongation in non-diabetic patients and (95% CI; 0.67-3.35) as shown in (Figure 5). The present study revealed that ciprofloxacin administration produced a significant prolongation of QTc, 24 hours and 72 hours after the first dose in addition to 72 hours after cessation compared to baseline values in diabetic patients, while non-diabetic patients produced a significant prolongation of QTc, 72 hours after the first dose and 72 hours after cessation compared to baseline values. On the other hand, levofloxacin administration produced a significant prolongation of QTc, 24 hours and 72 hours after the first dose in addition to 72 hours after cessation compared to baseline values in both diabetic and non-diabetic patients as illustrated in (Table 2).

In addition, ciprofloxacin administration produced a significant elevation of AST compared to baseline values in both diabetic and non-diabetic patients. Also, the results assured that levofloxacin administration produced significant elevation of ALT and AST compared to baseline values in diabetic patients. On the other hand, levofloxacin administration revealed a significant decrease in Na and K compared to the baseline values in diabetic patient, while non-diabetic patients showed a significant decrease only in K as presented in (Table 3).

Levofloxacin administration produced a significant hyperglycemia, 72 hours after the first dose compared to ciprofloxacin in diabetic patients, while levofloxacin administration produced a significant hyperglycemia, 24 hours after the first dose compared to ciprofloxacin in non-diabetic patients as shown in (Table 4). Levofloxacin administration was associated with 2.5times greater risk than ciprofloxacin on hyperglycemia in diabetic patients and (95% CI; 1.056-5.9) as indicated in (figure 4). Figure 5 shows that levofloxacin administration caused higher risk by about 1.29 than ciprofloxacin on hyperglycemia in non-diabetic patients and (95% CI; 0.947-1.77). The present study revealed that Ciprofloxacin administration produced a significant hyperglycemia, 24 hours after the first dose compared to the baseline values in diabetic patients as reported in (Figure 6). On the other hand, Figure 7 shows that levofloxacin administration produced a significant hyperglycemia, 24 hours, 72 hours after the first dose compared to the baseline values in diabetic patients. Ciprofloxacin and levofloxacin administration produced a significant hyperglycemia, 24 hours and 72 hours after the first dose in addition to 72 hours after cessation compared to the baseline values in non-diabetic patients as illustrated in (figure 6 and 7).

Levofloxacin administration produced a significant hypoglycemia, 72 hours after the first dose compared to ciprofloxacin in non-diabetic patients as reported in (table 4). Levofloxacin administration caused more risk by about 8 times than ciprofloxacin on hypoglycemia and (95% CI; 1- 61.6) in non-diabetic patients. Figure 7 shows that levofloxacin administration produced significant hypoglycemia, 72 hours after the first dose compared to baseline value in non-diabetic patients.

Table 1: Baseline characteristics of ciprofloxacin and levofloxacin groups regarding demographics, and laboratory data.

Drug	**Ciprofloxacin (n=100)**		**Levofloxacin (n=100)**	
Demographics and Laboratory data	**Diabetic (N=50)**	**Non-diabetic (N=50)**	**Diabetic (N=50)**	**Non-diabetic (N=50)**
Age (Yr)	48.7±14.7	44±15	53.5±11.5	51.4±12.4
Gender (males/ females)	27/23	30/20	26/24	28/22
Height(cm)	165±5.8	166.6±6.1	165.5±5.6	165±7.5
Body weight(Kg)	73.4±9.6	71.2±11.6	73.9±12.7	71.5±11.7
Serum Na (mEq/L)	139.7±2.7	138.8±2.6	139±3.2	138±2.6
Serum K (mEq/L)	4.3±0.6	4.2±0.45	4.6±0.57	4.1±0.44
Serum Mg(mg/dL)	1.8±0.11	1.8±0.95	1.8±0.097	1.8±0.1
Liver function:				
ALT(U/L)	25.8±9	24.2±12	31.4±10	24.6±8.6
AST(U/L)	32±11	28.8±9	33.4±9	28.3±10
Creatinine clearance(mL/min)	107±43	99±39	90±26.6	93±32.9

- Data are presented as mean ± SD.

Table 2: Comparison of QTc between each group regarding times.

Drug	Time / DM Or Non	Baseline	24 hours after the 1st dose	72 hours after the 1st dose	72 hours after cessation.
Ciprofloxacin	Diabetic	402±31.4	417±26.7*	416±26.4*	419.8±19.7*
	Non diabetic	404±52.6	417±32	428±31.9*	418.7±20.4*
Levofloxacin	Diabetic	414±29.5	427.4±38.3*	436±26*	425±21.7*
	Non diabetic	411±32.8	426±30.5*	434±35*	422±30.5*

- *considered significant $P < 0.05$ compared to baseline value.
- Data are presented as mean QTc (msec) ± SD.

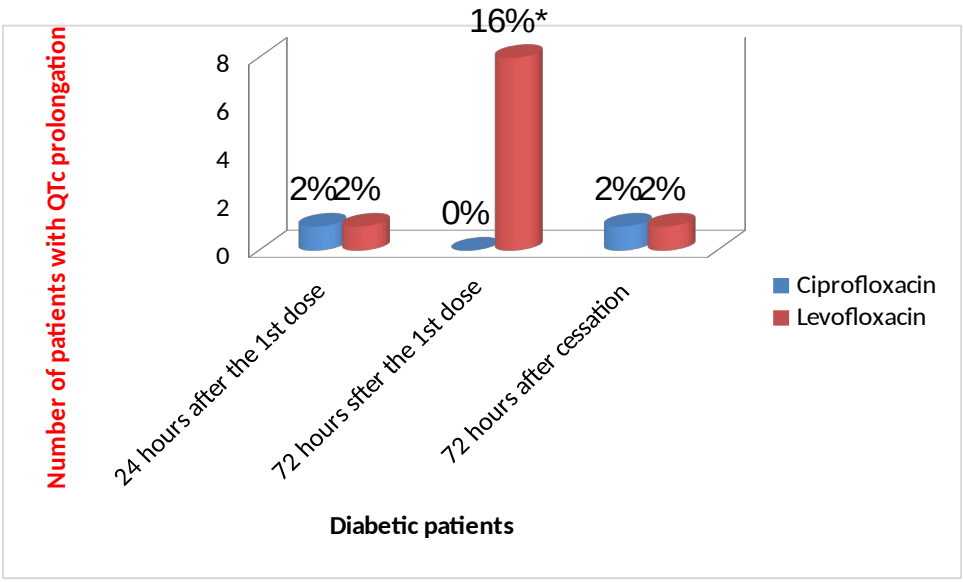

Figure. 2: Effect of administration of Ciprofloxacin and Levofloxacin on QTc prolongation in diabetic patients. * considered significant $p < 0.05$ compared to ciprofloxacin

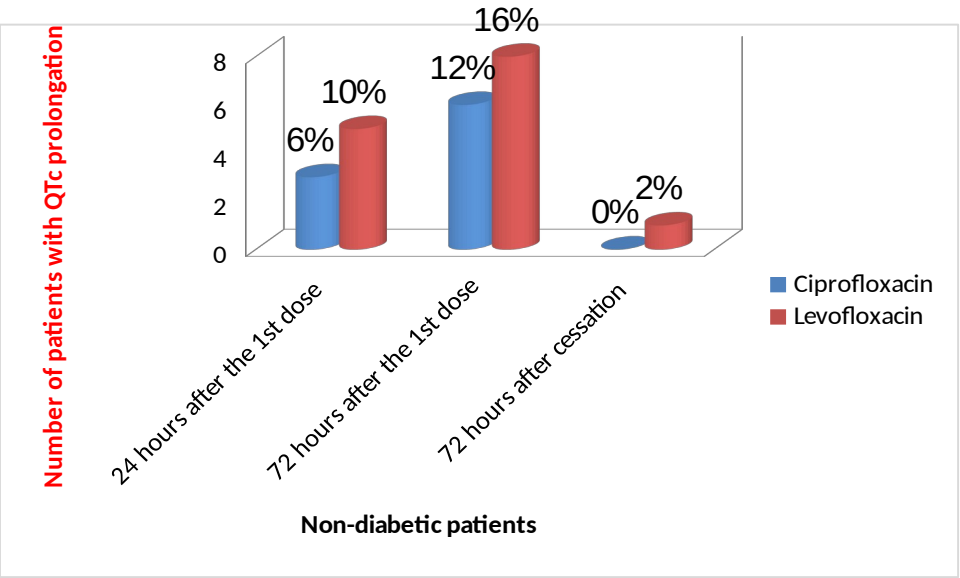

Figure 3: Effect of administrating Ciprofloxacin and Levofloxacin on QTc prolongation in non-diabetic patients

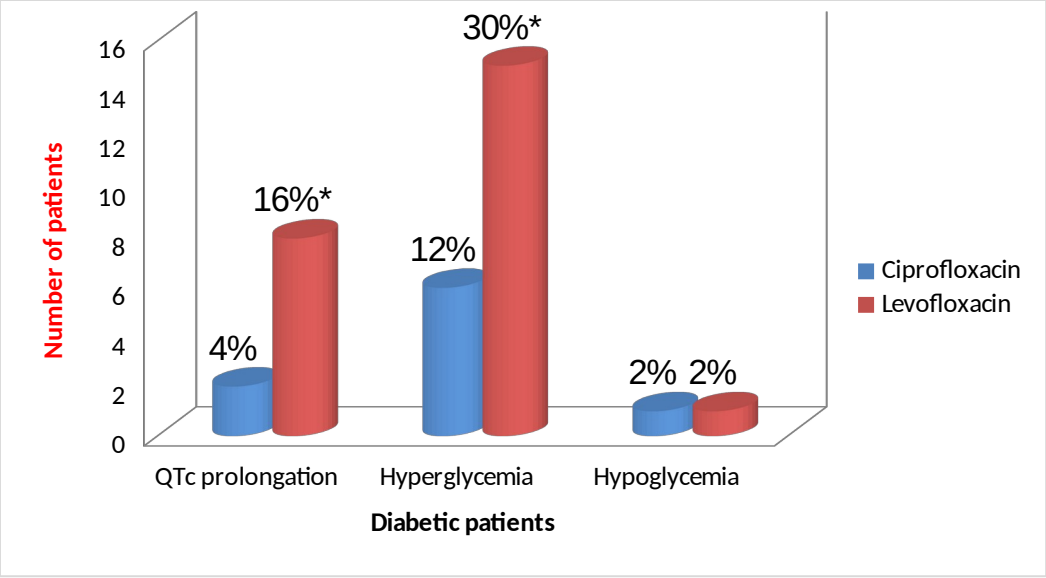

Figure 4: The relative risk for QTc prolongation, hyperglycemia and hypoglycemia in diabetic patients after the administration of Ciprofloxacin and Levofloxacin.

* considered significant $p < 0.05$ compared to ciprofloxacin

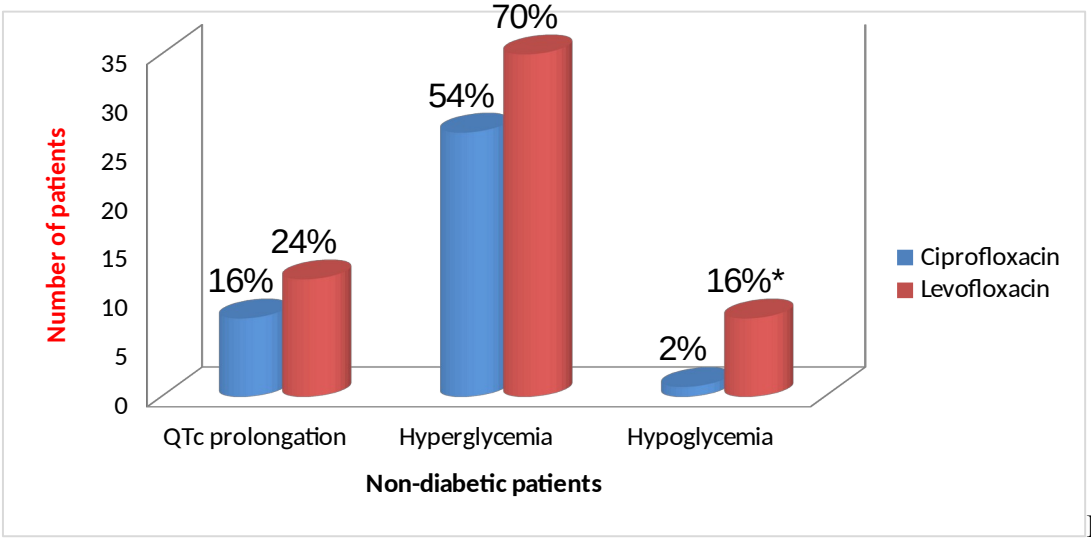

Figure 5: The relative risk for QTc prolongation, hyperglycemia and hypoglycemia in non-diabetic patients administrating Ciprofloxacin and Levofloxacin. * considered significant p <0.05 compared to ciprofloxacin

Table 3: Comparison between laboratories data before and after antibiotic administration.

Drug	Ciprofloxacin (n=100)				Levofloxacin (n=100)			
	Diabetic (n=50)		Non-diabetic (N=50)		Diabetic (N=50)		Non-diabetic (N=50)	
Laboratory data	**before**	**after**	**before**	**after**	**before**	**after**	**before**	**after**
Serum Na (mEq/L)	139.7±2.7	139±2	138.8±2.6	138.7±2.9	139±3.2	138±4*	138±3.3	138±2.4
Serum K (mEq/ L)	4.3±0.6	4.2±0.5	4.2±0.45	4.3±0.5	4.6±0.57	4.1±0.4*	4.1±0.44	3.9±0.2*
Serum Mg(mg/ dL)	1.8±0.11	1.9±0.1	1.8±0.95	1.8±0.1	1.8±0.097	1.8±0.08	1.82±0.1	1.79±0.07
Liver function:								
ALT(U/L)	25.8±9	27±10	24.2±12	26±11	31.4±10	38±6*	24.6±10	23.7±8
AST(U/L)	32±11	35.3±4*	28.8±9	33±5*	33.4±9	37.2±3*	28.3±10	25.8±9

Creatinine clearance(mL/ min)	107±43	110±35	99±39	105±34	90±26.6	88±19	93±32.9	94.5±28

- * considered significant $P < 0.05$ compared to baseline value.
- Data are presented as mean ± SD.

Table 4: Comparison between ciprofloxacin and levofloxacin regarding their risk on dysglycemia.

Time	**After 24 hours from 1st dose Number of patients (%)**		**After 72 hours from 1st dose Number of patients (%)**		**After 72 hours from antibiotics cessation. Number of patients (%)**	
Drug	ciprofloxacin	levofloxacin	ciprofloxacin	levofloxacin	Ciprofloxacin	levofloxacin
All patient	(n=100)	(n=100)	(n=100)	(n=100)	(n=100)	(n=100)
Hyperglycemia	21(21%)	38(38%)*	19(19%)	32(32%)*	7(7%)	11(11%)
Hypoglycemia	2(2%)	3(3%)	0(0%)	8(8%)*	0(0%)	0(0%)
Diabetic Patients	(n=50)	(n=50)	(n=50)	(n=50)	(n=50)	(n=50)
Hyperglycemia	5(10%)	10(20%)	2(4%)	10(20%)*	0(0%)	1(2%)
Hypoglycemia	1(2%)	0(0%)	0(0%)	1(2%)	0(0%)	0(0%)
Non-diabetic patients	(n=50)	(n=50)	(n=50)	(n=50)	(n=50)	(n=50)
Hyperglycemia	16(32%)	28(56%)*	17(34%)	22(44%)	7(14%)	10(20%)
Hypoglycemia	1(2%)	3(6%)	0(0%)	7(14%)*	0(0%)	0(0%)

* Considered significant $P < 0.05$ compared to ciprofloxacin group.

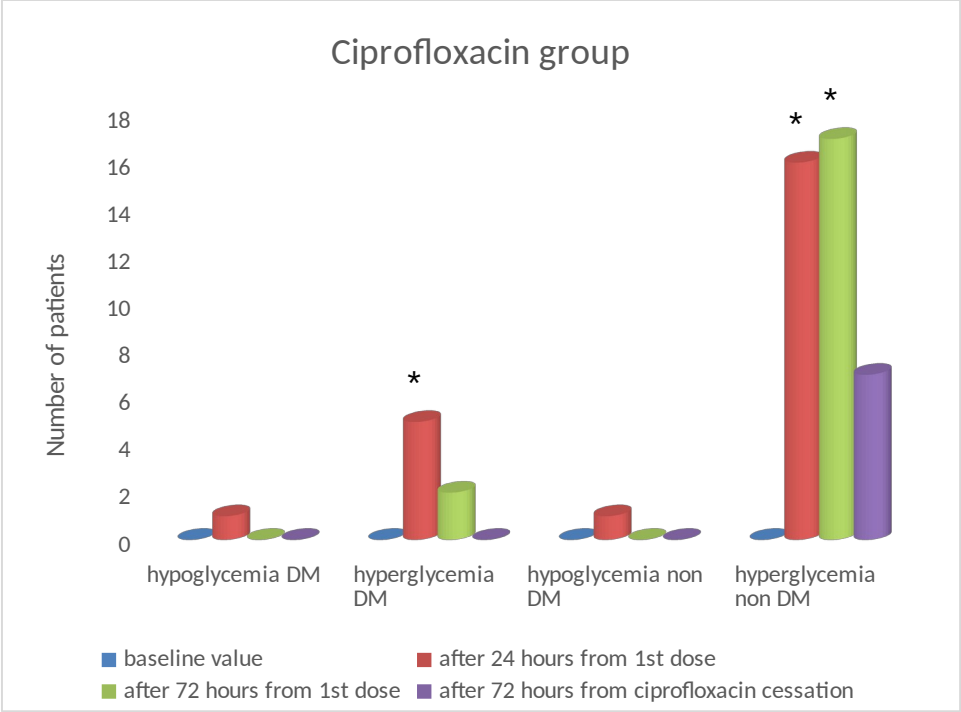

Figure 6 : The effect of ciprofloxacin on dysglycemia in diabetic and non-diabetic patients regarding hours.*considered significant $P < 0.05$ compared to baseline value

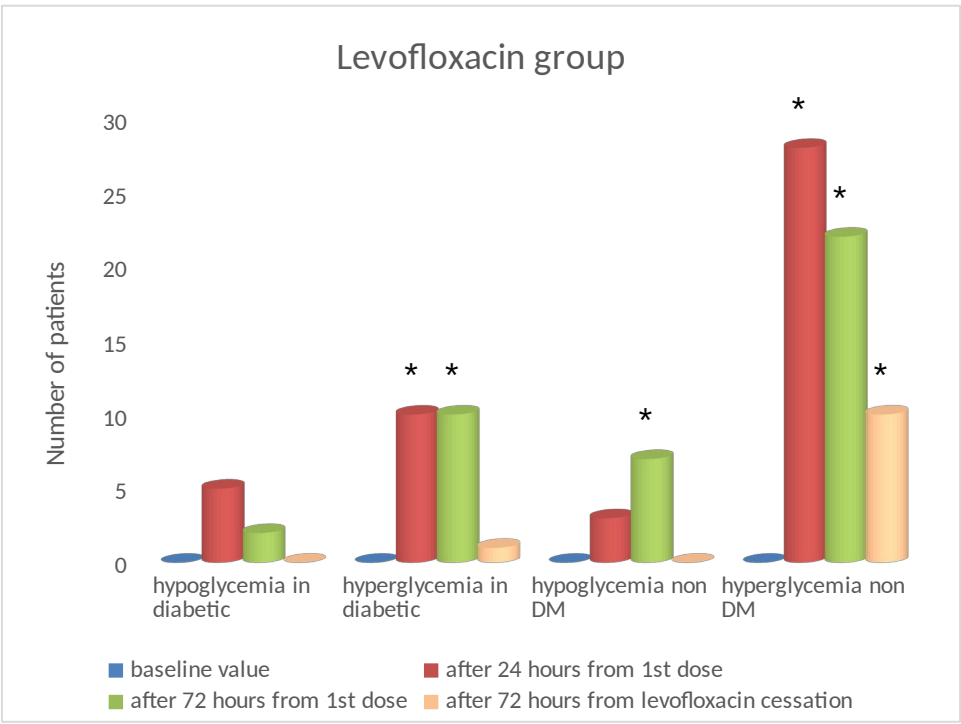

Figure 7: The effect of levofloxacin on dysglycemia in diabetic and non-diabetic patients regarding hours.* considered significant $P < 0.05$ compared to baseline value

5. Discussion:

The current study showed that levofloxacin was associated with a higher risk for QTc prolongation than ciprofloxacin in both diabetic and non-diabetic patients. This is in accordance with the results of Mehrzad and Barza (2015) [43]. The mechanism of fluoroquinolones induced QT interval prolongation is that this class blocks voltage-gated K+ channels, especially IKr. This channel has an important role in regulating ventricular electrical repolarization. All fluoroquinolone members antagonize this current which leads to QT prolongation [16]. Consistent with the current study, Abo-Salem et al. (2014) study revealed that serum concentration required for inhibition I_{kr} with ciprofloxacin is 2 times more than levofloxacin [44]. Moreover, in the present study, levofloxacin administration increased significantly the QTc interval compared to the baseline values in both diabetic and non-diabetic patients. In contrast, another study showed that no statically significant difference existed between pre and post levofloxacin administration [45]. This contrast may be explained by the criteria of patient selection, as the previous study didn't exclude patients with QTc prolongation before receiving levofloxacin, while the current study excluded these patients before receiving therapy. In the current study, levofloxacin administration produced a significant decrease in Na and K compared to the baseline values in diabetic patients. Levofloxacin administration was associated with a significant elevation in ALT and AST in diabetic patients compared to the baseline values. Also, ciprofloxacin administration resulted in a significant elevation in AST in diabetic and non-diabetic patients. This significant changes in electrolytes and liver enzymes may be the risk factor for developing QTc prolongation after fluoroquinolone administration in this study. Although fluoroquinolones are safe, clinicians should be careful with electrolyte imbalance or any cardiac disease to avoid any cardiovascular problem [46]. Fluoroquinolones induced QTc prolongation was more likely with risk factors as electrolyte disturbance and hepatic dysfunction [47] [43]. Electrolyte imbalance is common risk factor in drug induced QTc prolongation. Low extracellular potassium may block IK_r by enhanced inactivation and sodium pump [48]. In addition, fluoroquinolone can cross the blood brain barrier, leading to stimulate γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors, resulting in the synthesis and releasing antidiuretic hormone, causing water retention then prompting a sodium reduction [46]. Also, liver dysfunction may associate cardiac autonomic disturbance that is risk factor for QTc prolongation [49]. Fluroquinolone can cause mild elevation in liver enzymes [9]. Liver dysfunction is rare adverse effect of fluoroquinolone, but serious. Although the mechanish of fluoroquinolone induced liver dysfunction is still unknown, many reports said that this adverse effect may be due to immunoallergic reaction [50]. DM is one of diseases that is associated with electrolyte abnormalties [51]. This metabolic disease may affect vital organ system in the body. So, DM can lead to hepatopthy and cardiovascular diseases [52].

Dysglycemia is considered as one of the most clinically important side effects associated with fluoroquinolones [9]. In 2006, Manufacturing Tequin® (gatifloxacin) was stopped by Bristol-Myers Squibb due to associated dysglycemia [53]. Not only gatifloxacin associated with glucose homeostasis disturbance, but all fluoroquinolones can cause fluctuation in blood glucose [4].

Dysglycemia could occur with diabetic patients and non-diabetic patients [22]. This side effect may not be clinically significant with all patients receiving fluoroquinolones

because there were physiological mechanisms that regulate blood sugar levels in our body [1]. The current study proved that levofloxacin administration produced significant hyperglycemia compared to ciprofloxacin, 72 hours after the first dose in diabetic patients and 24 hours after the first in non-diabetic patients.

Moreover, 4% and 20% of diabetic patients had hyperglycemia events 72 hours after the first dose in ciprofloxacin and levofloxacin groups, respectively. Additionally, 32% and 56% of non-diabetic patients had hyperglycemic episodes 24 hours after the first dose in ciprofloxacin and levofloxacin, respectively. According to a retrospective study by Mathews and Thalody (2019), they observed that the use of fluoroquinolone in diabetic patients could develop hyperglycemia [46]. In addition, the results of the present study revealed that 34% and 44% of non-diabetic patients had hyperglycemia events 72 hours after the first dose in ciprofloxacin and levofloxacin, respectively. This is in accordance with another study reporting that the highest hyperglycemia event was found with levofloxacin (70%), followed by ciprofloxacin and moxifloxacin (39% and 33.3% respectively) [54]. The results of the current study was identical to the results of Kabbara and Ramadan study, which reported that ciprofloxacin was more safe than levofloxacin regarding their risk on hyperglycemia [22]. The mechanism of fluoroquinolones induced hyperglycemia may be associated with elevated level of epinephrine [55].

On the other hand, the event of hyperglycemia is more common than hypoglycemia [22]. The present study observed that levofloxacin administration was associated with eight times hypoglycemia risk more than ciprofloxacin in non-diabetic patients. Also, another study confirmed that levofloxacin had been associated with a higher risk of hypoglycemia than ciprofloxacin [56]. The current study reported that levofloxacin administration was associated with a significant hypoglycemia compared to ciprofloxacin 72 hours after the first dose in non-diabetic patients. In accordance to this result, Kabbara (2015) documented that the highest incidence for hypoglycemia was with moxifloxacin (11%), followed by levofloxacin (6%) and ciprofloxacin (0%) [22]. The present data was similar to the published work from FDA Adverse Event Reporting System (FAERS) and the Veteran Affairs system highlighting that levofloxacin was associated with higher risk for hypoglycemia than ciprofloxacin [57]. The mechanism of fluoroquinolones induced hypoglycemia is that fluoroquinolones block adenosine triphosphate (ATP) sensitive potassium channels in the pancreatic β-cells which lead to insulin secretion because of depolarization of the membrane of β-cells and calcium entering the cell through the voltage-dependent calcium channels [58].

In the present study, levofloxacin administration produced two times risk for dysglycemia more than ciprofloxacin in diabetic patients. Additionally, previous study determined according to FARES that rank order for dysglycemia with Fluoroquinolones was: gatifloxacin> moxifloxacin> levofloxacin> ciprofloxacin [59]. The dysglycemic effects of levofloxacin and ciprofloxacin may be due to disturbing the function of cellular glucose transport and Glucose transporter 1 (GLUT1) [22]. GLUT1 is a protein responsible for glucose transport into central nervous system and peripheral tissues [20].

6. Conclusion:

The current study showed that the risk for QTc prolongation was higher in levofloxacin than ciprofloxacin in diabetic and non-diabetic patients. Additionally, levofloxacin was associated with a greater risk for hyperglycemia than ciprofloxacin in diabetic and non-diabetic. Furthermore, the risk for hypoglycemia was greater with levofloxacin more than ciprofloxacin in non-diabetic.

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Author contributions

Nada A. Saad: Concept, data analysis, data entry, writing

Ahmed A Elberry: Concept, data entry, and critical revision of article

Hazem Samy Matar: Concept, data collection and critical revision of article

Raghda R.S. Hussein: Concept, data entry and critical revision of article

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8. List of Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
ATP	Adenosine triphosphate
CG	Cockcroft and Gault formula
CI	Confidence interval
CrCl	Creatinine clearance
DM	Diabetes mellitus
ECG	Electrocardiogram
FAERS	FDA Adverse Event Reporting System
FDA	The food and drug administration
GABA	γ-aminobutyric acid
GLUT 1	Glucose transporter 1
IK_r	The rapid component of the delayed rectifier potassium current
K	Potassium
Na	Sodium
NMDA	N-methyl-D-aspartate
QTc	The corrected QT interval
RR	Relative risk
SD	Standard deviation
Tdp	Torsade de pointes