

# A prospective clinical study to compare between the role of Rosuvastatin against Nigella Sativa (N sativa) in protection of azithromycin toxicity in covid-19 patients in isolation centers, Minia Governorate, Egypt

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## Abstract

**Background:** Azithromycin is the most common antibiotic used nowadays. **Objectives:** To evaluate the cardio-toxicity of azithromycin and to assess the effect of Nigella Sativa (N Sativa) and Rosuvastatin in cardio-protection. **Patient & methods:** This clinical prospective study was carried out on adult patients diagnosed as positive COVID-19 and was admitted to isolation centers in Minia Governorate during the period from 1<sup>st</sup> of June 2021 to 30<sup>th</sup> of May 2022. It included 160 patients divided into 4 groups. Group I received 500 mg/ 24 hours (hrs) of azithromycin orally for five days, group II received 500 mg/ 24hrs of azithromycin + 20 mg/ day of Rosuvastatin orally for five days, group III also received 500 mg/ 24hrs of azithromycin + 4 mg/ kg/ 24hrs N Sativa orally for five days, group IV received the same previously mentioned doses and duration of azithromycin, Rosuvastatin and N Sativa. Full clinical examination was done, electrocardiogram (ECG) was performed and venous blood samples were drawn for estimation of CK-MB level from all patients before and after the treatment. **Result:** Patients aged 32- 59 years old, 62 were females and 98 were males. Significant elevation of CK-MB in group I after treatment with azithromycin comparing with before treatment in the same group ( $p<0.01$ ) was detected. There were significant differences in all groups between pre and post-treatment regards QT interval ( $p<0.01$ ). **Conclusion:** Azithromycin had toxic effect on the heart, Rosuvastatin was better than N Sativa in treating this toxic effect. Treatment with Rosuvastatin + N Sativa together leads to the best results. **Recommendation** of this study is taking of Rosuvastatin plus N Sativa during the treatment with azithromycin.

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## Key words

Azithromycin; Rosuvastatin; N Sativa; CK-MB, ECG

## Introduction

Azithromycin (AZ) is an antibiotic of the class of macrolides, it can act against anaerobic and aerobic bacteria (Gram negative and Gram positive) (NCBI, 2021). Also it has direct and indirect antiviral activity in bronchial epithelial cells and other host cells. This has been shown for influenza, rhinovirus, parainfluenza virus, zika virus and enterovirus (Zeng et al., 2019)

Coronavirus disease 2019 (COVID-19), the highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a catastrophic effect on the world's demographics resulting in more than 3.8 million deaths worldwide, emerging as the most consequential global health crisis since the era of the influenza pandemic of 1918 (Wang et al., 2020). Treatment with azithromycin leads to abnormalities in rhythm and duration of waves in ECG as side effects in different cases (Kim and Welch, 2014).

Rosuvastatin is a drug of statin class that has a role in lowering the lipid so it was given to decrease the incidence of cardiovascular diseases and decrease the lipid levels by preventing the liver from producing endogenous cholesterol (Luvai et al., 2019).

Nigella Sativa (N. Sativa) is a plant (Family Ranunculaceae) widely used in medicine worldwide. It is one of the popular drugs used in various traditional medicines like Ayurveda, Siddha, Unani, and Tibb. In history, oil and seeds from Nigella Sativa are used in many medical systems and food in folklore. The N. Sativa seeds had a role in the treatment of different diseases (Nemmar et al., 2011).

Many studies were conducted on N. Sativa and explored its pharmacological actions that may include immunomodulation, anti-inflammatory, anticancer, renal protective, spasmolytic, antidiabetic, gastro-protective, bronchodilator, analgesic, hepato-protective, antimicrobial, and antioxidant properties. N Sativa ranks among the top

evidence-based herbal treatments. The majority of the essential oil's medicinal qualities are explained by the presence of thymoquinone, which is the primary bioactive component in *N Sativa* (Fakchich and Elachouri., 2021).

All physicians used azithromycin in covid 19 treatment, so this study will assess the cardiac changes in patients treated with Azithromycin orally due to COVID-19 and compare between the protective roles of Rosuvastatin against *N Sativa*.

## Patients and Methods

The current study is a clinical prospective study that was conducted on adult patients of both sex diagnosed with (COVID-19) who were admitted to isolation centers in Minia Governorate during the period of one year from 1st of June 2021 to 30th of May 2022. Written consent was taken from each patient for participation in this study and the confidentiality of the patients' information was maintained. We have obtained approval from Scientific Committee for Research Ethics, Faculty of Medicine, Minia university (number: 41:2021).

### Inclusion criteria

- Adult patients aged (18 years up to 59 years old) of both sex

### Exclusion criteria

1. Patients with an electrolytes disturbance.
2. Patients with history of any abnormalities in rhythm or waves of ECG.
3. Patients with uncompensated stage of congestive heart failure.
4. Patient with history of complicated coronary artery disease.
5. Patients treated with antiarrhythmic drugs.
6. Patients treated with chloroquine, haloperidol, ciprofloxacin, terfenadine, methadone, droperidol, or chlorpromazine as all these drugs affect QT interval.
7. Elderly patients above 60 years (because they are more liable to azithromycin' effects in prolonging of QT).

The included COVID-19 patients divided into 4 groups.

Group I received azithromycin 500 mg/ 24hrs orally for five days (Gautret et al., 2020)

Group II received azithromycin 500 mg/ 24hrs, and 20 mg/ day of rosuvastatin orally (Rositor tablets contain 20mg of rosuvastatin) for five days (Di Napoli et al., 2005)

Group III received azithromycin 500 mg/ 24hrs, and 4 ml/ kg/ day of *N Sativa* orally for five days (Baraka capsules contain 450 mg of *N sativa* oil) (Al-Ghamdi, 2003).

Group IV was given the same previously mentioned doses of Azithromycin beside Rosuvastatin, and *N Sativa* for five days.

We took complete personal & medical history and did full clinical general examination to all patients. ECG was performed (details of time and method of interpretation of intervals especially QT) and venous blood samples were drawn for electrolytes level estimation and CK-MB level from all patients before and after treatment.

On ECG we commented on heart rate, rhythm, QT interval and ST segment. QT interval is the distance between beginning of QRS to end of T wave which = number of small square  $\times$  40msec.

Correction of QT for heart rate occurred by Bazett's formula (Bazett 1920).

### Statistical analyses

Statistical Package for Social Science (SPSS) version 21 under windows 10 operating system was used for data entry and all statistical analyses. Quantitative data are expressed as means  $\pm$  SD for and qualitative data as number and percentage (%). Analyses were performed for quantitative data between four groups by One Way ANOVA test which was preceded by Post Hoc Tukey's analysis between each two groups. The nonparametric quantitative variables analyzed by the same tests after logarithmic transformation. However, Chi square test was used for comparing qualitative data between groups. Probability level (P-value) was assumed significant if less than 0.05.

## Results

The isolation centers of Minia governorate received 2172 patients diagnosed with (COVID-19). 2012 patients were excluded, 1534 patients were > 60 years old; 64 patients had history of abnormal ECG and treated with anti-arrhythmic drugs, 13 patients presented with congestive heart failure, 153 patients had electrolytes disturbance and 248 patients were on mechanical ventilation and we cannot treat them with protective treatments (Rosuvastatin and *N Sativa*).

The total number of patients included in the present study was 160 COVID-19 patients treated by Azithromycin by oral route. Their ages ranged between 32- 59 years old, 98 were males and 62 were females. There was no significant differences were noticed among studied groups regarding age ( $p=0.27$ ), sex ( $p=0.53$ ) (Table 1).

Table (2) showed the comparison among groups regarding electrolyte elements. No significant differences were observed among groups as regards serum Potassium, Sodium, Calcium and Magnesium levels. All patients had normal electrolytes values.

Table (3) showed the comparison among groups regarding CK-MB level. A significant elevation of CK-MB level was observed in group I after treatment with azithromycin in comparison with before treatment (0.01\*), but the differences before and after treatment in the rest groups were not significant due to the protective effects of Rosuvastatin and *N Sativa*.

The results in Table (4) showed the ECG findings in the studied groups. On admission ECG, sinus rhythm (figure 1a) was found in all cases in the four groups with no significant differences but, there were highly significant differences in all groups between pre and post-treatment ECG ( $p<0.01$ ). After treatment, there were recorded ECG changes (Figure 1 b, c and d) where, cases with prolonged QT interval were 16 cases (40.0%) in group I, 6 cases (15.0%) in group II, 10 cases (25.0%) in group III compared to only 2 cases (5.0%) in group IV while, tachycardia recorded in 3 cases (7.5%) among group I, 1 case (2.5%) in group II and 4 cases (10.0%) in group IV.

Table (1): Relation between the studied groups regarding age and sex by ANOVA and Chi-square statistical analysis (no= 160).

Variable		Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	Group (III) AZ+NS (n = 40)	Group (IV) AZ+RS+NS (n = 40)	P. value (Sig.)
Age	Mean $\pm$ SD	49.1 $\pm$ 4.3	50.1 $\pm$ 4.9	48.9 $\pm$ 5.5	50.4 $\pm$ 4.4	0.27 <sup>NS</sup>
	Range	39-56	40-59	32-59	43-58	
Sex	Male	26 (65.0%)	21 (52.5%)	27 (67.5%)	24 (60.0%)	0.53 <sup>NS</sup>
	Female	14 (35.0%)	19 (47.5%)	13 (32.5%)	16 (40.0%)	

AZ: azithromycin, RS: Rousvastatin, NS: Nigella sativa, SD: standard deviation,  $p \geq 0.05 = NS$  (Non-significant).

Table (2): Relation between studied groups regarding electrolyte level by ANOVA test (no= 160).

Variable		Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	Group (III) AZ+NS (n = 40)	Group (IV) AZ+RS+NS (n = 40)	P. value (Sig.)
K (mmol/L)	Mean $\pm$ SD	4.17 $\pm$ 0.56	4.18 $\pm$ 0.47	4.26 $\pm$ 0.51	4.15 $\pm$ 0.49	0.79 <sup>NS</sup>
	Range	4.0-5.1	4.0-5.0	4.0-5.10	3.9-5.0	
Na (mmol/L)	Mean $\pm$ SD	137.4 $\pm$ 7.54	139.0 $\pm$ 8.74	138.1 $\pm$ 6.41	138.4 $\pm$ 6.87	0.81 <sup>NS</sup>
	Range	135.5-145	136-145	135-145	136-144	
Ca (mg/dl)	Mean $\pm$ SD	8.82 $\pm$ 0.38	8.91 $\pm$ 0.40	8.87 $\pm$ 0.42	8.95 $\pm$ 0.45	0.54 <sup>NS</sup>
	Range	8.5-9.3	8.5-9.4	8.5-9.1	8.5-9.7	
Mg (mmol/L)	Mean $\pm$ SD	2.0 $\pm$ 0.47	2.14 $\pm$ 0.33	2.11 $\pm$ 0.34	2.23 $\pm$ 0.47	0.21 <sup>NS</sup>
	Range	1.8-2.3	1.8-2.5	1.8-2.5	1.8-2.9	

AZ: azithromycin, RS: Rousvastatin, NS: Nigella sativa, SD: standard deviation, K: potassium, Na: sodium, Ca: calcium, Mg: magnesium, One way ANOVA test was used,  $p \geq 0.05 = NS$  (Non-significant).

Table (3): Relation between studied groups regarding CK-MB level before and after treatment by ANOVA test (no= 160).

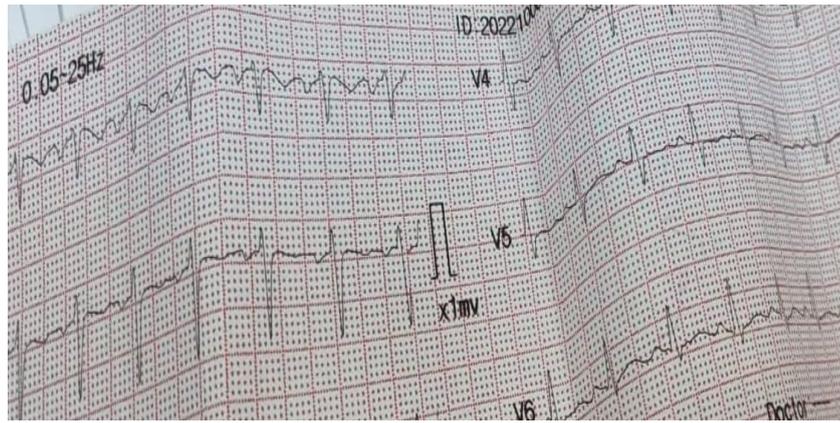
CKMB (U/L)		Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	Group (IV) AZ+RS+NS (n = 40)	Group (IV) AZ+RS+NS (n = 40)
On admission	Mean $\pm$ SD	19.3 $\pm$ 5.4	19.2 $\pm$ 4.0	19.9 $\pm$ 5.6	18.9 $\pm$ 4.8
	Range	10-29	12-27	11-30	9-28
After treatment	Mean $\pm$ SD	35.8a $\pm$ 8.9	20.1b $\pm$ 4.4	20.3b $\pm$ 5.5	19.2 b $\pm$ 5.0
	Range	12-54	13-29	11-29	10-29
P. value (Sig.)		<0.01**	0.06NS	0.17 NS	0.32NS

AZ: azithromycin, RS: Rousvastatin, NS: Nigella sativa, SD: standard deviation, CK-MB: Creatine Kinase MB, a, b Means in the same row (between groups) with different superscript letters are significantly different, \* P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS).

Table (4): Relation between studied groups regarding electrocardiogram (ECG) findings by Chi-square test (no= 160).

ECG		Group (I) AZ (n = 40)	Group (II) AZ+RS (n = 40)	Group (III) AZ+NS (n = 40)	Group (IV) AZ+RS+NS (n = 40)	P. value (Sig.)
On admission	Sinus rhythm	40 (100.0%)	40 (100.0%)	40 (100.0%)	40 (100.0%)	1.0 <sup>NS</sup>
After treatment	Sinus rhythm	20 (50.0%)	33 (82.5%)	30 (75.0%)	34 (85.0%)	<0.01*(S)
	Prolonged QT	16 (40.0%)	6 (15.0%)	10 (25.0%)	2 (5.0%)	
	ST elevation	1 (2.5%)	0	0	0	
	Tachycardia	3 (7.5%)	1 (2.5%)	0	4 (10.0%)	
P. value (Sig.)		<0.01**(S)	<0.01**(S)	<0.01**(S)	<0.01**(S)	

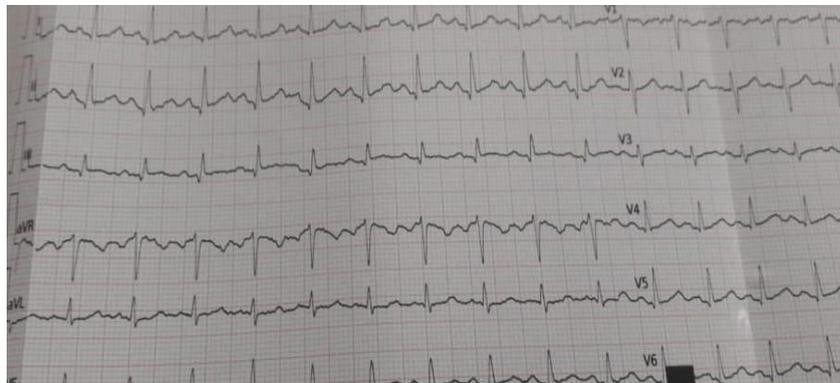
AZ: azithromycin, RS: Rousvastatin, NS: Nigella sativa, SD: standard deviation, ECG: electrocardiogram, \* P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS).



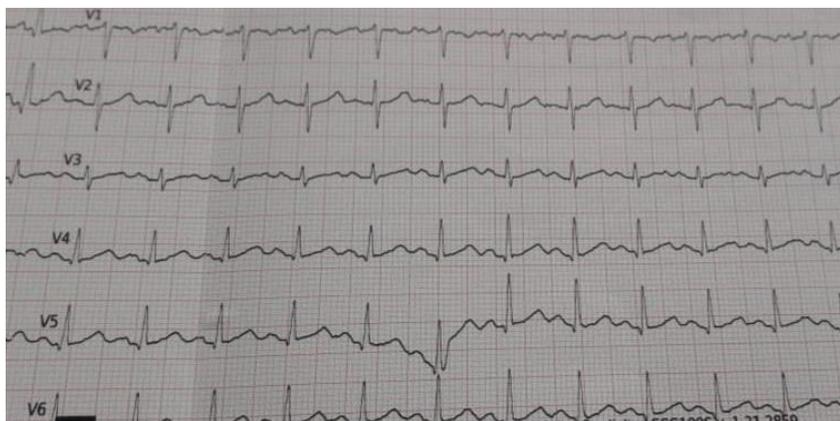
**Figure 1 (a): Sinus rhythm**



**Figure 1 (b): ST elevation**



**Figure 1 (c): Tachycardia**



**Figure 1 (d): Prolonged QT interval**

## Discussion

Coronavirus disease is viral illness caused by coronavirus-2. Its clinical manifestations vary from asymptomatic state up to multi organ dysfunction (Singhal, 2020).

Azithromycin is an antibiotic derived from erythromycin. It is used as an anti-inflammatory and antiviral and has allegedly proven active in combating SARS-CoV-2 (Oliver and Hinks, 2021). If it was given early, it can prevent the progression of tissue damage through its anti-inflammatory effects that reduce cytokine levels (Oldenburg et al., 2021).

Rosuvastatin is a drug of statin class that has a role in lowering the lipid so it used to decrease the incidence of cardiovascular diseases and control elevated levels of lipid by inhibiting the liver from the production of endogenous cholesterol (Luvai et al., 2019). Rosuvastatin can also used as antioxidant, anti-inflammatory, stabilizer for ion channel, and regulator for autonomic nervous system (Hasan and Kow, 2020). There is substantial evidence supporting the use of statins in COVID-19 patients. (Castiglione et al., 2020).

Nigella Sativa is a medicinal plant that known with its great medicinal value that known with its great medicinal value (Tiwari, 2018). Thymoquinone is identified as an active component in N. Sativa and its safety profile has been reported in many clinical trials like previous trial with asthmatic patients (Koshak et al., 2021).

The current results revealed that the difference among groups regarding electrolyte level was not significant. These results are in agreement with Yu et al., (2018) who reported that administration of Rosuvastatin did not affect significantly electrolyte elements and Koshak et al., (2021) demonstrated that the plant N. Sativa has no impact on electrolytes in their study.

Coinciding with results published by Atli et al., (2015) current results showed that CK-MB level after treatment with azithromycin was significantly increased in group (I) compared to group (II, III and IV). Administration of Rosuvastatin or N. Sativa (alone or combined) had significant effect on decreasing CK-MB level after treatment with azithromycin.

Wang et al (2018) reported that Rosuvastatin decreased LDH, CK-MB and induced cardio protective effects by suppressing ROS production and inhibiting mitochondria-mediated apoptosis.

In addition, Yu et al., (2018) revealed that Rosuvastatin prevents cardiac tissue damage due to its ability to improve the antioxidant activities and to decrease the lipid peroxidation.

Bocsan et al., (2021) studied the benefit of N Sativa in preventing acute myocardial ischemia in rats. They found that it reduced the level of proinflammatory cytokines and CK-MB level.

The present results revealed that there were significant prolongation in QT interval between groups in ECG ( $p < 0.01$ ) after treatment with azithromycin this in agreement with (Kim and Welch, 2014) who

reported that treatment with azithromycin lead to prolongation of QT interval as a side effects.

Rosuvastatin and N Sativa have protective role against the effect of azithromycin on ECG and this was in agreement with Mansour et al., (2021) Who revealed that rosuvastatin has a protective effect against cardiotoxicity that caused by azithromycin in a rat model. They found that the ECG changes and alterations of oxidative stress markers that occurred with azithromycin can be improved by rosuvastatin.

## Conclusion

This study concluded that the main cardio toxic effect of azithromycin was prolonged QT interval, Rosuvastatin was better than N Sativa in treating this toxic effect, and treatment with Rosuvastatin + Nigella Sativa together leads to the best results.

## Recommendations

This study recommended taking Rosuvastatin plus N Sativa during the treatment with azithromycin.

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## دراسة سريرية مستقبلية للمقارنة بين دور روسفاستاتين ازاء زيت حبة البركة في الحماية من سمية الأيزثروميسين في مرضى كوفيد -١٩ بمراكز العزل بمحافظة المنيا ، مصر.

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### الملخص العربي

**الخلفية العلمية:** أيزثروميسين مضاد حيوي واسع النطاق واسع الاستخدام. الأهداف: تهدف هذه الدراسة إلى التعرف على التأثير السام للقلب للأيزثروميسين وتقييم التأثير الوقائي لروزوفاستاتين وحبّة البركة والمقارنة بينهما .

**طريقة البحث:** أجريت هذه الدراسة السريرية المستقبلية على المرضى البالغين الذين تم تشخيص إصابتهم بـ (كوفيد -١٩) والذين تم حجزهم بمراكز العزل بمحافظة المنيا خلال الفترة من ١ يونيو ٢٠٢١ إلى ٣٠ مايو ٢٠٢٢. وأشتملت الدراسة على ١٦٠ مريضا مقسمة إلى ٤ مجموعات. تلقت المجموعة الأولى ٥٠٠ ملغ / يوم من أيزثروميسين عن طريق الفم لمدة ٥ أيام ، تلقت المجموعة الثانية ٥٠٠ ملغ / يوم من أيزثروميسين + ٢٠ ملغ / يوم من روزوفاستاتين بالفم لمدة ٥ أيام ، المجموعة الثالثة تلقت ٥٠٠ ملغ / يوم من أيزثروميسين + ٤ ملغ / كغ / في اليوم من زيت حبة البركة شفويا لمدة ٥ أيام ، تلقت المجموعة الرابعة أيزثروميسين + روزوفاستاتين + زيت حبة البركة لمدة ٥ أيام بنفس الجرعات السابق ذكرها. تم إجراء الفحص الإكلينيكي الكامل ، وتم إجراء مخطط كهربية القلب (ECG) وسحب عينات الدم الوريدي من أجل تحديد مستوى انزيم كايبيز الكرياتينين(CK-MB) من جميع المرضى قبل العلاج وبعده.

**النتائج:** تراوحت أعمار المرضى بالدراسة الحالية ما بين ٣٢ و ٥٩ سنة ، ٦٢ من الإناث و ٩٨ من الذكور مع وجود ارتفاع كبير في مستوى CK-MB في المجموعة الأولى مقارنة بما بعد العلاج بالأيزثروميسين ( $p < 0.01$ ) كما كانت هناك فروق ذات دلالة إحصائية في جميع المجموعات بين قبل وبعد العلاج ( $P < 0.01$ ) في فترة QT.

**الخلاصة:** للأيزثروميسين تأثير سام على القلب، وكان للروزوفاستاتين وحبّة البركة دور وقائي ضده. كان الروزوفاستاتين أفضل من حبّة البركة في علاج هذا التأثير السام بينما يؤدي العلاج بروزوفاستاتين + حبّة البركة معًا إلى نتائج أفضل. توصيات هذا البحث هي ضرورة تناول زيت روزوفاستاتين + زيت حبة البركة أثناء العلاج بالأيزثروميسين.

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