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Evaluation of CPK (Creatinine Phosphokinase) in Hypertensive Patients used either Statin and/or Ezetimibe

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ABSTRACT

Background: The effectiveness of cholesterol in the improvement of cardiovascular disorder used to be proven in the 2d half of of the twentieth century. Cholesterol researcher Daniel Steinberg writes that whilst the 1984 Primary Coronary Prevention Study confirmed that reducing ldl cholesterol substantially reduces the chance of coronary heart assault and angina, clinicians, consisting of cardiologists, mostly disagree. Not convinced. In the 1990s, after a public marketing campaign in the United States to instruct human beings about ldl cholesterol ranges and the distinction between HDL and LDL cholesterol, countless pharmaceutical businesses started out producing their personal statins. Ezetimibe is a drug used to deal with excessive blood ldl cholesterol and some different lipid disorders. It is frequently used with dietary adjustments and statins. It's now not as famous as statins.

Aim: To reflect the serous side effect of combination of both Ezetimibe and Statin in elevation of CPK.

Patients and Methods: In this study, patients (50-75) will be divided into three organizations:

1-The first group which were treated only by Statin which were (145) patients

2-Second group which were treated by Ezetimibe were (140) Patients.

3-The third group who treated by both Statin and Ezetimibe were (142) Patients.

4- The total number were (427).

All the patients which were investigated regularly by each of their visit and, lab measurement of serum PCK in each visit. And all the patients were followed and also each patient received Statin, Ezetimibe or both of these drugs for 3 months and during these three months they followed and investigated completely.

Results: We found 145 patients (33.94%) responded to simvastatin 40mg/day when compared to those patients who treated by Ezetimibe 10mg/day which were 140(32.75%), While 142(33.25%) patients had good response when treated by combination of both Simvastatin and Ezetimibe Simvastatin10mg/ day, and statin 10mg/day. And 67(15.70%), complained from Rhabdomyolysis, in those patients treated by Ezetimibe 10mg/day. While 105(24.60%), were complained from Rhabdomyolysis, in those patients treated by a combination of both Ezetimibe 10mg/ day, and statin 10mg/day. We conclude from this study that; although there is significant effect of Statin and Ezetimibe in lowering Serum Lipids in general, but there is a serious increase of CPK which lead to Rhabdomyolysis, especially when moderately high doses of combination were used.

Keywords: *CPK (Creatinine Phosphokinase), Rhabdomyolysis, Statin, Ezetimibe, Hypertension*.

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INTRODUCTION

In the latter half of the 20th century, it was determined how important cholesterol was in the emergence of cardiovascular disease. (Goldstein JL et al). Programs targeted at reducing the burden of cardiovascular disease by lowering cholesterol levels have been developed as a result of this lipid theory. A low-fat diet and poorly tolerated drugs like Clofibrate, Cholestyramine, and niacin make up the majority of the treatment. While the 1984 Coronary Primary Prevention Trial found that reducing cholesterol lowered the incidence of heart attack and angina, doctors, especially cardiologists, disagreed. Believe (Steinberg D -2007). Scientists from academia and the pharmaceutical sector decided to create more effective cholesterol-lowering medications. The production of cholesterol from acetyl-CoA (Endo A -2010) involves 30 stages and multiple possible targets.

In 1971, Akira Endo, a Japanese biochemist working at the pharmaceutical business enterprise Sankyo, started out working on this question. Previous research have proven that the physique produces ldl cholesterol in the liver chiefly via HMG-CoA reductase (Simons J - January 2003).

In 1976, a British group isolated the same molecule from Penicillium brevis and termed it compactin(Brown AG et al).

In the 1990s, public education campaigns taught Americans about cholesterol levels and the distinction between HDL and LDL cholesterol, while pharmaceutical companies such as Sankyo Pravachol and Bristol-Myers Squibb began creating their own statins. The findings of the Merck-sponsored Scandinavian Simvastatin Survival Study were published in April 1994. Simvastatin (later marketed as Zocor by Merck) was tested in 4,444 patients with high cholesterol and cardiac disease. According to the study's findings, the patients had 35% lower cholesterol levels and a 42% lower risk of dying from a heart attack five years later.

Ezetimibe is a drug that lowers ldl cholesterol and is used to deal with excessive blood ldl cholesterol and different lipid issues. Statins and dietary adjustments are generally mixed with it. It is less well-known than statins. It is administered orally. Fixed Ezetimibe/Simvastatin, Ezetimibe/Atorvastatin, and Ezetimibe/Rosuvastatin combinations are also available ("Ezetimibe Monograph for Professionals". 2019). A history of allergic reactions, including rash, angioedema, and anaphylactic symptoms, as well as significant liver disease, particularly when paired with statins, are two contraindications to using ezetimibe. (U.S. National Library of Medicine).

Statins, additionally regarded as HMG-CoA reductase inhibitors, are cholesterol-lowering tablets that decrease morbidity and mortality in these who are at excessive hazard of cardiovascular disease. It is the most oftentimes prescribed cholesterol-lowering medicine. ("Cholesterol Drugs". American Heart Association. Retrieved 24 December 2019).

Statins have been linked to muscle pain, an increased risk of diabetes, and abnormal blood enzyme levels. Furthermore, they have uncommon but significant side effects, the most dangerous of which being muscular injury. (ABD TT,and Jacobson TA). Muscle problems, an increased risk of diabetes, and raised blood levels of liver enzymes due to liver damage are all major side effects. (Naci H et al , Bellosta S et al).

Creatine kinase (CK; EC 2.7.3.2) is an enzyme that kinases guanidino (or phosphagen). It catalyzes the reversible phosphate switch method between ATP and creatine, ensuing in ADP and phosphocreatine manufacturing. (S.D. Lahiri et al).

Normal creatine kinase (CK) activity is independent of elevated levels in blood tests. CK's job is to add phosphate groups, a class of natural chemicals, to creatine, a molecule found in muscle cells that aids in the production of energy. When creatine is combined with phosphate, it is converted into the high-energy molecule phosphocreatine, which your body uses for energy. (R. Grosse et al).

Although the definitive analysis of Rhabdomyolysis is primarily based totally on laboratory tests, we need to pay greater interest to the scientific manifestations. The signs and symptoms of Rhabdomyolysis vary depending

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on the severity of the condition and the extent of renal loss. Mild Rhabdomyolysis may also no longer causes muscle complaints, and the prognosis is entirely dependent on unusual blood test outcomes and distinct issues. Pain, soreness, weakness, and swelling of the afflicted muscular tissues characterize severe Rhabdomyolysis. Fluid from the broken muscular circulatory machine can motive hypotension and shock when swelling takes place quickly, such as when rescuing a man or woman from a collapsing structure. Other signs and symptoms are standard in nature and are related with muscle losing or ailments that motive muscle wasting. The launch of muscle tissue elements into the bloodstream can produce electrolyte imbalances, which can purpose nausea, vomiting, confusion, coma, or extraordinary coronary heart charge and rhythm. Because myoglobin is present, kidney harm can also end result in confined or no urine manufacturing 12 to 24 hours after the preliminary muscle damage. (P. Sauret JM et al).

Baseline CK is not associated with prognosis or acute renal failure unless CK > 40,000 units (Baeza-Trinidad -2015 , McMahon -2013).

Muscle damage is frequently caused by injury, intense activity, or a drug or substance use issue. Other causes include infection, electrocution, heat stroke, extended immobility, insufficient blood flow to the extremity, or snakebite (Sauret JM, et al). Statins (prescription medications used to decrease cholesterol) are considered low-risk (Sathasivam S, et al).

Recreational drugs including: ethanol (alcohol), amphetamines, heroin, cocaine, and ketamine can cause Rhabdomyolysis (Huerta-Alardín AL et al, Warren JD et al).

Rhabdomyolysis is a pathological circumstance in which skeletal muscle cells are damaged, inflicting toxic intracellular chemical substances to be launched into the bloodstream. The most frequent reasons consist of trauma, ischemia, medications, toxins, metabolic abnormalities, and infections. This syndrome's pathophysiological feature is an expand in intracellular free ionized calcium due to inadequate cell energy or direct rupture of the plasma membrane.. Increased intracellular calcium prompts countless proteases, improves skeletal muscle mobile contractility, induces mitochondrial dysfunction, and will increase reactive oxygen species production, eventually main to skeletal muscle telephone death.

Clinically, the syndrome is distinct by way of extreme muscle discomfort, weakness, and myoglobinuria. Elevated myoglobin and creatine phosphokinase stages induced with the aid of muscle phone demise are necessary laboratory findings that, when mixed with scientific data, enable clinicians to definitively perceive the illness. (Knochel JP 1982, Giannoglou GD et al).

PATIENTS AND METHODS

The patients are divided into three group:

1-The first group which were treated only by Statin which were (145) patients
2-Second group which were treated by Ezetimibe were (140) Patients.
3-The third group who treated by both Statin and Ezetimibe were (142) Patients.
4- The total number were (427).

All patients are being treated (examination and treatment) at the Al-Hussein Teaching Hospital in Thi-Qar Governorate. All patients complaining of hypertension and/or ischemic heart disease were evaluated and had regular blood pressure measurements at each visit and laboratory measurements of serum PCK at each visit. Follow-up of all patients (Table no.1). Some of those patients complained from painful muscles in different sites of their body after treatment especially muscles of the limbs, weakness and darkness of the urine (Knochel JP.1982, Giannoglou GD); which were diagnosed Rhabdomyolysis, as confirmed by their history, clinical examination and measurement of their serum PCK (Table No 2) which shows the distribution of Rhabdomyolysis in patients who were treated either by Statin, Ezetimibe or both drugs.

All the patients which were managed by this study were (50-75 years) old.

Also each patient received these agents for 3 months and during these three months they followed and investigated completely.

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Treatment dose and duration

We divided a total of (427) patients into 3 groups:-

1 - Group 1, (145) patients received simvastatin for 3 months, 40 mg simvastatin daily, with plenty of water in the evening.

2-The Second group which were (140) patients were treated by Ezetimibe, which given in a dose 10mg capsules per a day for three months also.

3-The Third Group which were (142) patients, treated by a combination of Simvastatin given 20mg per and Ezetimibe 10mg at night for three months.

All patients are being treated at Al-Hussein Teaching Hospital in Tikal Governorate.

RESULTS

In this study, a total of (427) hypertensive patients with hyperlipidemia received either statins (simvastatin 40 mg daily, nightly) or (Ezetimibe 10 mg daily, each late).

We found 145 patients (33.94%) responded to simvastatin 40mg/day when compared to those patients who treated by Ezetimibe 10mg/day which were 140(32.75%) patients reflect good lowering of serum lipid mainly achievement of low-density lipoprotein cholesterol.

While 142(33.25%) patients had good response when treated by combination of both Simvastatin and Ezetimibe Simvastatin10mg/ day, and statin 10mg/day. (Table N01).

Also we found in this study that all of these drugs causing Rhabdomyolysis, in which 65(15.22%) developed Rhabdomyolysis in those patients treated by Simvastatin 40mg/day.

And 67(15.70%), complained from Rhabdomyolysis, in those patients treated by Ezetimibe 10mg/day.

While 105(24.60%), were complained from Rhabdomyolysis, in those patients treated by a combination of both Ezetimibe 10mg/ day, and statin 10mg/day. Table No2.

DISCUSSION

The current study examined and evaluated the extent of CPK (Creatinine Phosphokinase) level in patients used Statin, or Ezetimibe, or both Statin and Ezetimibe.

Among all (427) patients, 145 (33.94%) responded to statins and 140 (32.75%) responded to statins, with little difference in lipid-lowering efficacy between the two drugs. As reported in this study by Patel J et al. They discovered that they could reduce cholesterol levels. Total cholesterol, triglycerides, LDL cholesterol, and HDL ldl cholesterol degrees' upward jostle as a end result of absorption. Ezetimibe had no impact on fat-soluble nutritional vitamins such as A, D, and E. (Fadia Tohme Shaya , et al).

This is suggested by Fadia Tohme Shaya et al. They discovered that combining ezetimibe with statin medication reduced LDL cholesterol somewhat more than statin therapy alone. However, in some ASCVD patients with particularly high LDL-C levels, this may not be sufficient despite optimal statin therapy (27). This research was also carried out by Samia Mora and Paul M. Ridker. Statin medication reduced the risk of atherosclerosis in individuals with elevated hs-CRP levels, according to data from the Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Furthermore, there is emerging evidence that statins lower plasma hs-CRP levels in ways that are essentially independent of LDL-cholesterol reduction (Patel J, Sheehan V,et al).

The parameter of the study was an increase in CPK (creatinine phosphokinase), and we found a significant increase in CPK (33.95%) in patients treated with statin 145. Takamitsu Nakamura, Mitsumasa Hirano, and colleagues performed this investigation; the two-dose statin team exhibited a sizeable upward jostle in HDL-C levels, however no longer the statin-ezetimibe group. CRP levels were lower in the statin double-dose group by a greater percentage than in the statin-Ezetimibe group (30). Furthermore, Takamitsu Nakamura, Mitsumasa Hirano, and others. This finding was documented in individuals receiving Ezetimibe 140 (32, 75) as well as patients getting statins and Ezetimibe 142 concurrently (33, 25). a bit. In humans with excessive RLP-C levels, including Ezetimibe to persevering with statin remedy decreased RLP-C stages and aggravated endothelial dysfunction

extra than doubling the statin dose. (Takamitsu Nakamura et al).

The study showed that the concomitant use of dye and Ezetimibe had a significant effect on rabies incidence in patients receiving both drugs105 (24.60%), especially when both drugs were administered at high doses (40 mg statin) and 20 mg statins) when used. Noemie Chanson, Philippe Bossi, et al. reported 20 mg of statins and 20 mg of Ezetimibe). Of course; in their study, they found that neither Ezetimibe nor simvastatin alone caused the Rhabdomyolysis seen in their case, and they argue that physicians should exercise caution when choosing lipid-lowering drugs for HIV-infected patients. They have to pay cautious interest to doubtlessly hazardous drug interactions and renal failure. (Noemie Chanson et al). Although statin use alone resulted in rhabdomyopathies in 65 (15.22%) patients and 67 (15.70%) patients in this study, this is consistent with the findings of Newman C et al :) and statin-related self-Immune myopathy occurs in less than 0.1% of patients. (Newman CB et al) We also found in this study that Rhabdomyolysis improved in patients treated with Ezetimibe alone, but not in combination with Ezetimibe - National Library of Medicine HSDB Overdose of Ezetimibe. However, acute Ezetimibe overdose can result in an overdose of the usual effects, resulting in loose stools, abdominal pain, and fatigue (Ezetimibe - National Library of Medicine HSDB Database".2018).

CONCLUSION

We conclude from this study that; although there is significant effect of Statin and Ezetimibe in lowering Serum Lipids in general, but there is a serious increase of CPK which lead to Rhabdomyolysis, especially when moderately high doses of combination were used.

Declarations

Study Limitations

The study is limited to the sample analyzed, no additional limitations were known at the time of the study.

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CONFLICT OF INTEREST

There were no conflict interests in this study.

Informed Consent

Our purpose of this study is to explained the effect and side effect of both Statin and/or Ezetimibe.

Authors' Contributions

All the process in which patients are given important information, including possible risks and benefits, about a medical procedure or treatment, had been done. In this study, i have made a substantial contribution to the concept or design of the article

Human And Animal-Related Studies

Ethical Approval

THI-QAR MEDICAL COLLEGE, Academic Promotions Committee, THI-QAR (IRAQ). According to the Instruction of the University of Thi-Qar N0. 6726 on the 2nd of Oct. 2020.

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TABLE 1: The distribution of increasing CPK in patients who were treated by Statin and/or Ezetimibe

Age(years	50-55	56-60	61-65	66-70	71-75	Total
No of the patients who treated with Statin*	23(15.86%)	24(16.55 %)	27(18.62 %)		33(21.75 %)	145(33.95%)
No of the patients who treated with Ezetimibe	18(12.85%)	27(19.28 %)	25 (17(85%)		32(22.85 %)	140(32.75)
No of the patients who treated by both Statin and Ezetimibe	21(14.79%)	21(14.79 %)	36(25.35 %)	27(19.01%)	38(26.20 %)	142(33.25)
Total					38(27.14 %)	427(100 %) *

*The total number of the patients are (427)

TABLE 2: The distribution of Rhabdomyolysis in patients who were treated either by Statin, Ezetimibe or both drugs

Age	50-55	56-60	61-65	66-70	71-75	Total
No of the Rhabdomyolysis in patients who treated with Statin*	11(16.92%)	20(30.76%)	10(15.38 %)	16(24.61%)	8(12.30 %)	65(15.22 %)
No of the Rhabdomyolysis in patients who treated with Ezetimibe	8(11.94%)	18(26.86%)	10(14.92 %)	13(19.40%)	18(26.86 %)	67(15.70 %)
No of the Rhabdomyolysis in patients who treated by combination of Statin and Ezetimibe	27(25.71%)	25(23.80%)	14(13.33 %)	22(20.95%)	17(16.19 %)	105(24.60%)
Total						237(55.50%) ***

***The total number who developed Rhabdomyolysis after treatment

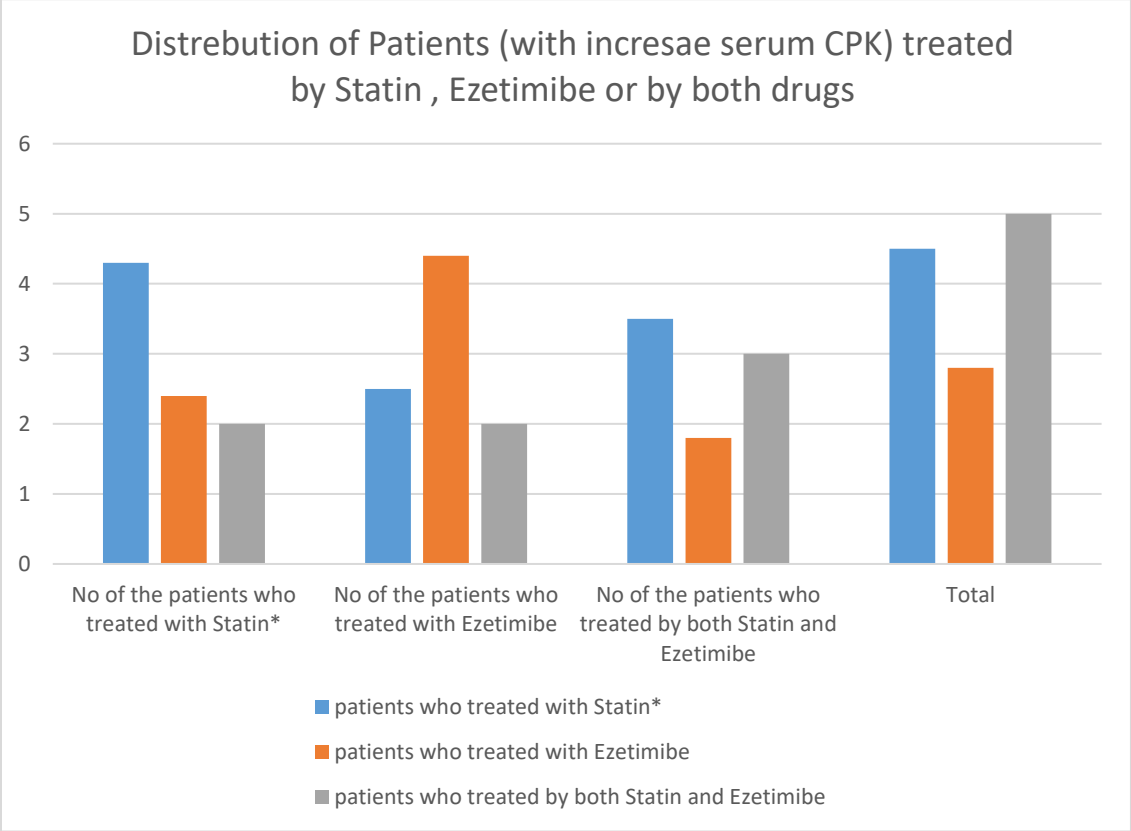

FIGURE 1: shows the distribution of Patients (with increases serum CPK), which treated by Statin, Ezetimibe or by both drugs

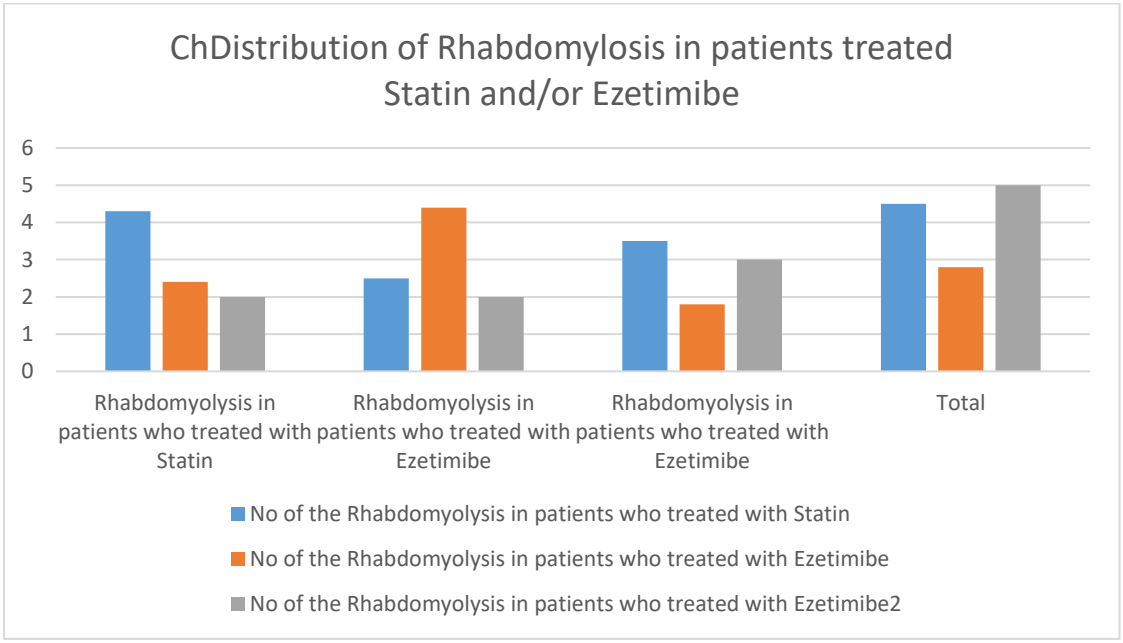

FIGURE 2: shows the distribution of Rhabdomyolysis in patients who were treated by Statin and/or Ezetimibe

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