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Comparison of Fenofibrate versus Gemfibrozil in the Management of Hypertriglyceridemia in Patients with Coronary Heart Disease

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ABSTRACT

Objectives: To compare the mean triglyceride (TG) level with fenofibrate versus gemfibrozil in patients presenting with acute coronary syndrome. **Design:** Randomized controlled trial (RCT) **Setting:** Department of Medicine Allied Hospital, Faisalabad. Period: From August 2014 to June 2015. **Methodology:** A total of 100 cases (50 in each group) were included in the study. Patients were randomly divided in tow groups by using lottery method. In group-F, patients were prescribed fenofibrate capsule of 201mg/day and in group-G, patients prescribed gemfibrozil 600mg twice/day. Patients were followed for 12 weeks. **Results:** Mean age of the patients was 59.40±10.93 and 59.04±10.77 years in group-A and B, respectively. In group-F, 30 patients (60.0%) were male and 20 patients (40.0%) were female while in group-G, 27 patients (54.0%) were male and 23 patients (46.0%) were female. In group-F, 25 patients (50.0%) were obese and in group-G, 27 patients (54.0%) were obese. Unstable angina was observed in 27 patients (54.0%) of group-F and in 17 patients (34.0%) of group-G. NSTEMI (non ST segment elevated MI) noted in 10 patients (20.0%) of group-F and 20 patients (40.0%) of group-G while STEMI (ST segment elevated MI) was present in 13 patients (26.0%) in both groups. When comparison of triglyceride level was made, mean triglyceride level in group-F was 172.76±21.52 mg/dl and in group-G 214.12±44.09 mg/dl. Statistically significant difference was observed between two groups ($p<0.001$). **Conclusion:** Mean triglyceride level at 12 weeks was lower in fenofibrate group as compared to gemfibrozil group. This study favorably supports the use of fenofibrate in the treatment of hypertriglyceridemia in patients presenting with acute coronary syndrome.

Keywords: Hypertriglyceridemia, Coronary heart disease, Fenofibrate, Gemfibrozil

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INTRODUCTION

Acute coronary syndrome (ACS) is a spectrum of clinical conditions ranging from ST elevation MI (STEMI) to NSTEMI and unstable angina.[1] On-treatment TG <150 mg/dl was independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG may be an additional consideration beyond low LDL-C in patients after ACS.[2] NHANES 1976-1980, data from survey between 1999 and 2006 indicated that the proportion of individuals with previously suboptimal TG (<150mg/dl) increased 5-fold in people at ages 60-74 years. Serum level of >150mg/dl is used as a cut point for hypertriglyceridemia in about a third of adults and the increase in mean TG level in the US most likely reflects the increasing prevalence of obesity.[3]

Patients with ACS are at an increased risk of developing recurrent cardiovascular events. And he patients with such events need an additional triglyceride-lowering therapy, beyond the level that achieved with statins.[4] The relationship between long-term outcomes and TG levels has not been established in patients with ACS.[5]

Significantly lower levels of TG by the use of fenofibrate are reported in a study. The values are (1211.7±1418.2mg/dl for gemfibrozil vs 534.4±524.6 mg/dl for fenofibrate, p=0.003).[6] But

another study reported that levels of TG (0.5±0.2 mmol for gemfibrozil vs 0.4±0.1 mmol for fenofibrate, p=0.1984.[7]

The objective of our study is to compare the mean triglyceride level with fenofibrate versus gemfibrozil in patients presenting with acute coronary syndrome. Higher levels of TG in patients complicated by severe cardiovascular events are reported in the literature. So lowering of TG level is pretty important to prevent the patients from the injurious and hazardous events, this will aid in decreasing the mortality and morbidity as well. And the rationale of this study is to get the local magnitude which will be helpful for the physicians to predict better management drug in local population with ACS to prevent the lethal complications such as any cardiovascular event or even death.

METHODOLOGY

This was a Randomized control trial study undertaken in Department of Medicine, Allied Hospital Faisalabad. Study was carried out over a period of twelve months from August 2014 to June 2015. 100 patients with age range of 40-80 years of either gender presented with Acute Cornary syndrome (with unstable angina (i.e chest pain, palpitations, sweating with flattening T-wave but normal CK-MB (0-25 U/L), NSTEMI (i.e chest pain, palpitations, sweating, ST-segment depression but CK-MB may or may not be elevated CK-MB enzymes) with raised triglyceride as compared to normal level (i.e. >150mg/dl) were collected from medical OPD of Allied Hospital, Faisalabad. Sample size of 100 cases, 50 in each group is calculated with 95% confidence level, 80% power of test and taking magnitude of mean TG level i.e. 0.5±0.2mmol with gemfibrozil and 0.4±0.1 mmol with fenofibrate in patients presented with acute coronary syndrome. The patients excluded from the study are those with deranged LFTs (ALT>40IU, AST >40IU), deranged RFTs (serum creatinine >1.2 gm/dl) or on haemodialysis and having history of alcohol drinking and smoking and the patients already on lipid lowering drugs (through medical record).

Demographic information (name, age, gender and contact) was also be recorded. Blood samples was drawn from each patient was sent to pathology lab of the hospital and reports were assessed to determine the triglyceride level at baseline. Then patients were randomly divided in two groups by using lottery method. In group-F: patients were prescribed fenofibrate capsule of 201mg/dal and in group-G; patients were prescribed gemfibrozil 600mg twice/day. Then patients were followed for 12 weeks. And the blood was drawn and sent to hospital pathology lab and the level of triglycerides was measured in mg/dl 12 weeks after start of therapy in terms of mean triglyceride level.

Data was collected and was analyzed on SPSS version 17. Numerical data i.e. age, BMI (body mass index) and TG value were presented by calculating mean and standard deviation, whereas qualitative data like gender, type of acute coronary syndromes (unstable angina, NSTEMI and STEMI) and BMI status (obese, non-obese) was presented in form of frequency and percentage. Both groups were compared by using t-test for mean TG level taking p value <0.05 as significant. Data was stratified for effect modifiers like age, gender and obesity (BMI>30). Post-stratification chi-square test was applied.

RESULTS

A total of 100 patients (50 in each group) were including in this study.

In group-F (50 patients), patients were prescribed fenofibrate capsule of 201mg/day and in group-G (50 patients), patients prescribed gemfibrozil 600mg twice/day and were followed for 12 weeks.

Mean age of the patients was 59.40±10.93 and 59.04±10.77 years in group-A and B, respectively (Table-1).

Table 1: Distribution of cases by age

Age (Year)	Group-F (Fenofibrate)		Group-G (Gemfibrozil)	
40-50	13	26.0	14	28.0
51-60	15	30.0	13	26.0
≥ 61	22	44.0	23	46.0
Total	**50**	**100.0**	**50**	**100.0**
Mean±SD	**59.40±10.93**		**59.04±10.77**	

In group-F, 30 patients (60.0%) were male and 20 patients (40.0%) were female while in group-G, 27 patients (54.0%) were male and 23 patients (46.0%) were female (Table-2).

Table 2: Distribution of cases by gender

Gender	Group-F (Fenofibrate)		Group-G (Gemfibrozil)	
Male	30	60.0	27	54.0
Female	20	40.0	23	46.0
Total	**50**	**100.0**	**50**	**100.0**

In group-F, 25 patients (50.0%) were obese and in group-G, 27 patients (54.0%) were obese. Mean BMI in group-F was 29.44±4.96 and in group-G was 30.06±5.34 (Table-3).

Table 3: Distribution of cases by obesity

Obesity	Group-F (Fenofibrate)		Group-G (Gemfibrozil)	
Obese (BMI ≥ 30)	25	50.0	27	54.0
Non-obese (BMI < 30)	25	50.0	23	46.0
Total	**50**	**100.0**	**50**	**100.0**
Mean±SD	**29.44±4.96**		**30.06±5.34**	

Unstable angina was observed in 27 patients (54.0%) of group-F and in 17 patients (34.0%) of group-G. NSTEMI noted in 10 patients (20.0%) of group-F and 20 patients (40.0%) of group-G while STEMI was present in 13 patients (26.0%) in both groups (Table-4).

Table 4: Distribution of cases by acute coronary syndrome

Type of ACS	Group-F (Fenofibrate)		Group-G (Gemfibrozil)	
Unstable angina	27	54.0	17	34.0
NSTEMI	10	20.0	20	40.0
STEMI	13	26.0	13	26.0
Total	**50**	**100.0**	**50**	**100.0**

When comparison of triglyceride level was made, mean triglyceride level in group-F was 172.76±21.52 mg/dl and in group-G 214.12±44.09 mg/dl. Statistically significant difference was observed between two groups (p<0.001) (Table-5). Stratification with regard to age, gender and BMI presented in Tables 6-8.

Table 5: Comparison of triglyceride level

Group	Mean (mg/dl)	Standard deviation
Group-F (Fenofibrate)	172.76	21.52
Group-G (Gemfibrozil)	214.12	44.09
P value	**p < 0.001**	

Table 6: Stratification with regard to age

Group	Age	Hypertriglyceridemia		Total
		Yes	**No**	
Group-F (Fenofibrate)	40-50	12	1	13
	51-60	12	3	15
	≥ 61	18	4	22
	Total	**42**	**08**	**50**
	χ^2 = 0.92		**P = 0.629**	
Group-G (Gemfibrozil)	40-50	14	0	14
	51-60	13	0	13
	≥ 61	22	1	23
	Total	**49**	**1**	**50**
	χ^2 = 1.2		**P = 0.549**	

Table 7: Stratification with regard to gender

Group	Gender	Hypertriglyceridemia		Total
		Yes	**No**	
Group-F (Fenofibrate)	Male	27	3	30
	Female	15	5	20
	Total	**42**	**08**	**50**
	χ^2 = 2.01		**P = 0.156**	
Group-G (Gemfibrozil)	Male	26	1	
	Female	23	0	
	Total	**49**	**1**	**50**
	χ^2 = 0.87		**P = 0.351**	

Table 8: Stratification with regard to BMI status (Obese >30, Non-obese < 30)

Group	BMI	Hypertrigly-ceridemia		Total
		Yes	No	
Group-F (Fenofibrate)	Obese	25	0	25
	Non-obese	17	8	25
	Total	**42**	**08**	**50**
	χ^2 = 9.52		**P = 0.002**	
Group-G (Gemfibrozil)	Obese	27	0	27
	Non-obese	22	1	23
	Total	**49**	**1**	**50**
	χ^2 = 1.20		**P = 0.273**	

DISCUSSION

Increased levels of Plasma triglyceride is a common biochemical finding, but the evidence have shown that the benefit of treating this altering lipid level remains less robust as compared to treating the elevated low-density lipoprotein–cholesterol. Regarding specific recommendations in such patients, there exist some difficulty as the frequently elevated triglyceride levels are associated with other conditions that affect cardiovascular disease risk, such as obesity, metabolic syndrome, decreased high-density lipoprotein, proinflammatory and prothrombotic biomarkers, and type 2 diabetes. Recent investigations have showed that the outcomes of cardiovascular accidents with the use of medications to reduce triglyceride levels suggest that, although a net benefit probably exists, both relative and absolute risk reductions seem underwhelming when compared with the benefit of reducing low-density lipoprotein–cholesterol levels with treatment. However, the totality of evidence inferes that elevated triglyceride levels are likely the sole contributor in the development of cardiovascular disease. Furthermore, severe hypertriglyceridemia is also associated with other conditions such as an increased risk of acute pancreatitis, irrespective of its effect on risk of cardiovascular disease. We review the causes and classification of elevated triglyceride levels, the clinical manifestations in patients with primary hypertriglyceridemia and the management of such patients.[8]

As far as the pathogenesis of hypertriglyceridemia is concerned, some authors suggest that patients with insulin deficiency shows an increased production of VLDL (by increasing the flow of hepatic fatty acids which, in addition tempts the ketogenesis, can be secreted as VLDL) and decreased clearance of VLDL (by decreasing the activity of lipoprotein lipase).[9]

Cardiovascular accidents are considered to be the leading cause of morbidity and mortality in type 2 diabetics. Hypertriglyceridemia (HTG) and low levels of high-density lipoprotein-cholesterol (HDL-C) are seen in patients with type 2 diabetes mellitus. However, in the UKPDS, low-density lipoprotein-cholesterol (LDL-C) levels were significantly increased in women, but not in men. Thus, the major abnormalities with the respect to the dyslipidemia in T2DM include, increased number of LDL particles, increased number of triglyceride-rich particles, decreased HDL particle numbers, increased postprandial concentrations of triglyceride-rich particles, small dense LDL particles, and several changes in particle composition of HDL.[10]

Dyslipidemic disorders (mainly hypertriglyceridemia and low level of HDL cholesterol) have been treated by he use of fibrates for more than 30 years. Fibrates have shown an increased efficacy in reduction of cardiovascular events, particularly in individuals with significant elevations in plasma triglycerides.[11]

Although less clinical interventional studies have been performed with fibrates than with statins yet the therapeutic benefits using one of the three “major" fibrates (fenofibrate, bezafibrate and gemfibrozil) were significantly demonstrated among patients with high triglycerides and low HDL-cholesterol. In contrast, in patients without dyslipidemia the favorable effects of fibrates on the “hard" cardiovascular end points were absent and usually there were no significant difference between fibrate and placebo groups.[12] According to a meta-analysis there is appreciated a 35% RR reduction in cardiovascular events in a subgroup of dyslipidemic patients by the use of five main fibrates trials, as compared with a 6% RR reduction in those not meeting dyslipidemic criteria.[13] As expected, in a so called “general population" – reflecting a blend of effects in patients with and without atherogenic

dyslipidemia[14] the beneficial effect of fibrate therapy was diluted, producing only a modest 10% RR decrease in major cardiovascular events and a 13% RR reduction in coronary events in the other meta-analysis.[15]

The two fibrates Gemfibrozil and fenofibrate are extensively used in clinical practice, they raise HDL cholesterol (HDLc) and are thought to reduce the risk of atherosclerotic cardiovascular disease. These drugs act as PPARα agonists and upregulate the expression of genes crucial in reverse cholesterol transport (RCT).[7]

In present study mean triglyceride level was 172.76±21.52 (mg/dl) and 214.12±44.09 (mg/dl) in Fenofibrate group and Gemfibrozil group, respectively. Statistically significant difference was observed between two groups ($p<0.001$). Results of Rotllan et al[7] comparable with our findings. Therefore, in appropriate patients use of fibrates probably lead to cardiovascular risk reduction.

A randomized, double-blind, double-dummy, cross over study assessed the efficacy of gemfibrozil 900 mg/day and fenofibrate 200 mg/day in 21 patients with hyperlipidemia.[16] After 6 weeks of treatment, both fenofibrate and gemfibrozil significantly reduced total cholesterol, LDL, and triglycerides and increased HDL (all $p<0.01$). Reductions in total cholesterol and LDL were both significantly greater with fenofibrate than with gemfibrozil (-22% vs -15%, $p<0.02$; and -27% vs -16%, $p<0.02$, respectively). No significant differences observed between the two treatments with regard to triglycerides or HDL.

The impact of fibrates on cardiovascular events and in the reduction of triglyceride level following ACS hospitalization is unclear. Only one study suggested that bezafibrate was associated with a lower incidence of major cardiovascular events during hospitalization.[17] Therefore, our data offer essential insight on this gap of knowledge.

CONCLUSION

Mean triglyceride level at 12 weeks was lower in fenofibrate group as compared to gemfibrozil group. So the use of fenofibrate in the treatment of hypertriglyceridemia in patients presenting with acute coronary syndrome is avidly supported in this study. Apart from these results, other important parameters, such as drug cost and patients' susceptibility to elevations in serum creatinine and plasma homocysteine must be taken into consideration by the practitioners, when prescribing fibrate therapy.

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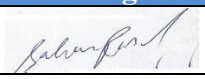
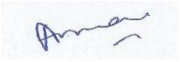
Dr. Sahar Rasool	Main Author	
Dr. Amna Siddique	Co-Author	
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