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Efficacy/Role of Combination Therapy Versus Mono Therapy in Improving Triglycerides and Low Density Lipoprotein Cholesterol in Patients Uncontrolled on Monotherapy

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Abstract

Objectives: To compare the efficacy of combination therapy and mono therapy in improving triglycerides and low density lipoprotein cholesterol in patients uncontrolled on mono therapy.

Study design: Randomized controlled trial

Place and Duration of study: Department of cardiology, PAEC General Hospital, Islamabad, from 1st of December 2023 to 29th of February 2024 over a period of 3 months.

Methods: A total of 142 patients taking statin monotherapy and reported with uncontrolled levels of triglycerides and LDL Cholesterol were enrolled in this study and divided in to 2 equal groups. In combination therapy group, patients were added fenofibrate (200mg once daily) to their existing treatment while in monotherapy group patients were continued with their existing statin treatment.

The primary outcome was set as the change in the levels of triglycerides and LDL Cholesterol from the baseline after 2 months study period. The secondary outcome was the number of patients achieving the treatment goals at completion of study.

Results: The Mean±SD of age in this study was 55.90±8.10 years. The results of primary outcomes of the study show statistically significant difference in triglycerides levels in combination group compared to monotherapy group (233.4±36.74 Vs 260.50±37.39, respectively, p=0.00), however, no statistically significant difference was present in the levels of LDL Cholesterol between the 2 groups (161.73±10.27 Vs 163.5±5.3 respectively, p=0.19). There was significant difference in the levels of total cholesterol, HDL cholesterol and the number of patients achieving their targeted levels of both these parameters in combination therapy group compared to monotherapy group (5.63% Vs 0%, respectively, p=0.04).

Conclusion: Combination therapy in patients uncontrolled on mono therapy significantly improves the triglycerides levels, total cholesterol and HDL cholesterol levels. However there is no significant improvement in the LDL cholesterol levels.

Keywords: Combination therapy, Low density lipoprotein, Monotherapy, Triglycerides.

Introduction:

Dyslipidemia is characterized by disturbed plasma cholesterol levels which includes increased low density lipoprotein cholesterol (LDL C) and/or triglyceride (TG) levels and a low high density lipoprotein cholesterol (HDL C) levels. The statics shows that dyslipidemia increases the risk of cardiovascular disease (CVD) by 2 folds; it is therefore among the most prevalent risk factors for CVD and globally ranked 3rd in this list just after hypertension and dietary intake. [1,2] The data of majority of European countries in fact shows hypercholesterolemia as most prevalent CV risk factor.[3] Similarly, the data collected from African population shows the incidence of dyslipidemia as high as 25.5% with increased levels of low LDL C by 21.4% and triglycerides by 17%.[4]

An alarming global report mentions that 3.8 Million CV deaths were related to the high level of serum LDL C.[5] The elevated level of LDL C is thereby taken as a major risk factor of atherosclerotic CVD that can be modified by adopting appropriate starategies.[6]

The raised level of triglycerides (TG) is another abnormality found in patients with dyslipidemia. TG can primarily be result of some genetic dysfunction but more often they are synthesized as a result of disturbed TG related lipoprotein metabolism due to secondary etiologies like obesity, metabolic syndrome (Mets) and type-II diabetes mellitus. Studies have proven that the genes related to increase in TG levels are also involved in the atherosclerotic process in CVD. This is backed by the fact that patients with CV risk factors like diabetes and hypertension are also reported to have dyslipidemia. A recent meta analysis has shown that the CV risk with the elevated levels of TGs is as high as observed with elevated LDL C.[4,7]

Due to the above mentioned findings, interest in the treatment strategies that can help to treat hypercholesterolemia by reducing both LDL C and TG and improve HDL C become the subject of interest. Statin is a class of drug that has shown its efficacy in lowering the levels of LDL C. The American guidelines for the management of cholesterol mention statins as the main treatment strategy for improving lipid profile. [8] Despite having the status of 1st line recommendations, there is an increased risk of atherogenic dyslipidemia when TGs are not adequately controlled and HDL C is lowered with statin therapy. Hence the researchers have worked on strategies to find the recommended control of dyslipidemia in high risk patients. In a study conducted by Párraga-Martínez I, a group of patients with hypercholesterolemia despite of taking treatment, was put on intervention with patient' s education, dietary control and exercise. The objective of the study was to determine the proportion of patients achieving adequate lipid profile in 2 years follow up. At the follow up visit of 1 year time, proportion of patients achieving adequate control of dyslipidemia was higher in combination group compared to the control group. Similarly at the 2 years follow up, the levels of LDL C were significantly reduced in the combination group as compared to monotherapy group (a 13% 13.1% to 28.6%. decrease in LDL C levels, p=0.034) .[9] The findings of this study were encouraging but very few patients are able to follow the above interventions over this long period of time.

Fenofibrate is a drug that has been found effective in lowering the levels of TGs in cases where mono therapy with statins was not effective in controlling dyslipidemia. A decrease of 25% to 50% was observed in TGs levels in cases of hypertriglyceridemia and studies have proven a significant decrease in CV events when fenofibrate was given in patients with high levels of TGs.[10, 11]

There is lack of data on the benefits of combination therapy in patients uncontrolled on monotherapy with statins in our local population. This study was therefore planned to compare the efficacy of mono therapy with statin and combination therapy of statin+fenofibrate in improving TG and LDL C in patients uncontrolled on mono therapy with statins. The results of this study will help the physicians and cardiologists in setting up appropriate treatment plan to provide adequate control of mixed dyslipidemia.

Methodology:
This randomized controlled trial was conducted at the Department of cardiology, PAEC General Hospital, Islamabad from 1st of December 2023 to 29th of February 2024 over a period of 3 months.
Sample size was calculated with OpenEpi sample size calculator taking,
power=80% and α=5% (two-sided)
m1=145.5, m2=280.5
sd1=±53.6, sd2=±400.60
n2/n1= 1, sample size n1=71, n2=71.[12]

A total of 142 patients reported with uncontrolled levels of triglycerides (≥200-499 mg/dL) and LDL C (≥160 mg/dL) and taking statin monotherapy (Atorvastatin 10-20 mg once daily or rosuvastatin 10mg once daily for at least last one month) were enrolled in this study through consecutive sampling and divided in to 2 groups through computer generated randomization. In combination therapy group, patients were added fenofibrate (200mg once daily) to their existing statin treatment while in monotherapy group patients were continued with their existing statin therapy.
Exclusion criteria were set as co morbidities like secondary dyslipidemia (may be due to Nephritic or Cushing syndrome), patients with uncontrolled thyroid disorders, abnormally raised levels of ALT or AST. Moreover patients with uncontrolled diabetes (HbA1C ≥9%), renal impairment (GFR< 60 mL/min/1.73 m²) were also excluded.
All the demographic details, clinical findings and laboratory investigations of these study participants were performed and recorded .The patients were asked for follow up visits at the end of 1 month and 2 month (final visit). Blood samples were taken at these follow up visits for the assessments of study parameters.
The primary outcome was set as the change in the levels of TG and LDL C from the baseline at the end of treatment. The 2ndary outcome was the number of patients achieving the treatment goals at the end of treatment. (TG levels ≤199 mg/dL & LDL C levels≤159 mg/dL). Data was analyzed using SPSS version 25. Quantitative variables were expressed in form of Mean±SD while qualitative variables were expressed in form of frequency and percentage. Study outcomes were compared between the 2 groups by applying Chi-square test and independent t-test, where p ≤0.05 was considered statistically significant.

Results:
The Mean±SD of age in this study was 55.90±8.10 years with an age range of 42-68 years. The male gender was 57.75% of the total study population while female gender was 42.25%. The Group wise details of demographics and baseline clinical characteristics are shown in Table-I.
Table-I: Demographics and baseline clinical findings

n=142

Demographics & clinical characteristics		**Combination therapy Group (n=71)**	**Monotherapy Group (n=71)**
Age (Mean±SD) years		57.11±7.98	54.69±8.11
Gender	**Male n (%)**	41 (57.75)	43 (60.56)
	Female n (%)	30 (42.25)	28 (39.44)
Risk factors	**BMI (Mean±SD)**	30.94±4.64	29.98±4.23
	Smoking n (%)	19 (26.76)	22 (30.98)
Concomitant Disease	**Hypertension n (%)**	42 (59.15)	38 (53.52)
	Diabetes n (%)	36 (50.7)	31 (43.66)
	CV disease n (%)	15 (21.12)	19 (26.76)

The details of baseline lipid profile of patients in both groups show that these patients had uncontrolled total cholesterol, LDL C, TG and HDL as shown in Table-II.

Table-II: Baseline lipid profile

n=142

Baseline lipid profile	**Combination therapy Group (n=71)**	**Monotherapy Group (n=71)**
Total Cholesterol (Mean±SD) mg/dL	262.6±26.43	260.60±19.93
LDL C (Mean±SD) mg/dL	175.±9.56	173.87±9.5
TG (Mean±SD) mg/dL	275.43±39.02	271.52±35.85
HDL C (Mean±SD) mg/dL	39.39±7.57	38.98±7.10

The results of study outcomes show that the patients in the combination group had significantly decreased total cholesterol and triglycerides while increased levels of HDL C. Moreover, number of patients achieving their targets levels of TG and number of patients achieving targets of both TGs and LDL C were significantly higher in combination therapy group compared to monotherapy group after 2 months of treatment as shown in table III.

Table-III: Study outcomes

n=142

Lipid profile at 2 months	**Combination therapy Group (n=71)**	**Monotherapy Group (n=71)**	**p-value**
Total Cholesterol (Mean±SD) mg/dL	232.21±26.55	245.6±19.93	0.00
LDL C (Mean±SD) mg/dL	161.73±10.27	163.5±5.3	0.19
TG (Mean±SD) mg/dL	233.4±36.74	260.50±37.39	0.00
HDL C (Mean±SD) mg/dL	46.23±8.71	42.97±7.85	0.02
Patients achieving Target of TG n (%)	17 (23.94)	3 (4.22)	0.00
Patients achieving Target of LDL C n (%)	14 (19.72)	15 (21.72)	0.24
Patients achieving both Targets n (%)	4 (5.63)	0 (0)	0.04

Discussion:

The topic of controlling dyslipidemia has remained under discussion during last decade due to its importance in preventing the chances of future CV events. Statins are most commonly recommended treatment option for dyslipidemia; however, the treatment strategy in patients uncontrolled with statins is important subject for clinicians.

A study conducted by Foucher C et al, aimed to find the efficacy of fixed dose combinations in patients uncontrolled on monotherapy and having elevated TG and LDL C levels and low HDL C levels. The results of the study showed significant reduction in TG (32.2%, $P < 0.001$) and increase in HDL C levels (7.5%, $P < 0.001$) in patients receiving statin+fenofibrate combination therapy compared to monotherapy with statins. Similarly, significant reduction was observed in the levels of LDL C in patients on this combination therapy compared to monotherapy with fenofibrate. [13]

Tarantino N et al conducted a review on the role of combination therapy of statin and fenofibrate (Simavastatin+ fenofibrate) for achieving the required decrease in TG and non-HDL C in patients already taking statin treatment. The review concluded that addition of fenofibrate is significantly more effective and reliable in place of doubling the dose of statin in the patients uncontrolled on monotherapy.[14]

Zhao S et al studied the efficacy of adding fenofibrate in patients where targeted TG levels were not reached with statin monotherapy. The results of this study showed a 31% reduction in the levels of TG after 8 weeks of treatment with this combination therapy (1.77 mmol/l decrease, p= 0.01). The study also reported an increase in HDL C levels by 17.4% versus baseline (1.07mmol/l increase from baseline, p=0.01) after addition of fenofibrate to statin.[15]

In a study by IHM SH et al, efficacy and acceptability of statin+fenofibrate combination was assessed in comparison to monotherapy of statins in patients having mixed dyslipidemia and high CV risk. The results showed a significant 12.45% reduction in non-HDL C levels in combination group compared to statin monotherapy group after 8 weeks of treatment. This decrease in unhealthy lipids with combination therapy included decrease in overall lipid profile observed both at 4 and 8 weeks follow up visits and observed at a statistically significant rate of 88.30% Vs 77.98% (p=0.011).[16]

The efficacy of statin+fenofibrate Vs statin monotherapy was also studied in a phase IV trial with patients facing dyslipidemia on statins. The patients with uncontrolled levels of triglycerides despite of statin monotherapy were put on combination therapy of statin and fenofibrate. At the end of 8 weeks of treatment with combination therapy, there was significant reduction in the levels of triglycerides (269.8 mg/dL to 145.5 mg/dL, P < 0.0001) and increase in the levels of HDL C (45.0 mg/dL to 50.4 mg/dL ,p= 0.0004) while the patients continuing on monotherapy didn' t show any significant change in these important lipid parameters of TG and HDL C (271.1 to 280.5 mg/dL and 44.3 to 44.7 mg/dL respectively).[12]

A recent review by Ferri N discussed the efficacy of different possible combination of lipid lowering agents with respective mono therapies. The review concluded that these combinations are significantly more effective in bringing down the plasma lipids to normal range and reducing the atherosclerotic burden of CV disease. [17]

The Mean±SD of age in our study was 55.90±8.10 years with an age range of 42-68 years. The male gender was 57.75% of the total study population while female gender was 42.25%. The results of laboratory investigations showed disturbed lipid levels in these study patients. The results of primary outcomes of the study show statistically significant difference in triglycerides levels in combination group compared to monotherapy group (233.4±36.74 Vs 260.50±37.39, respectively, p=0.00), however, no statistically significant difference was present in the levels of LDL C between the 2 groups (161.73±10.27 Vs 163.5±5.3 respectively, p=0.19) after 2 months of treatment. There was significant difference in the levels of total cholesterol, HDL C and the number of patients achieving their targeted levels of both these parameters in combination therapy group compared to monotherapy group (5.63% Vs 0%, respectively, p=0.04). The results of our study are in line with studies discussed above and provide a clear evidence of effective control of dyslipidemia by lowering triglycerides and improving HDL C in patients shifted to combination therapy who were previously uncontrolled on monotherapy with statins.[12,13,14,15,16,17]

The findings of our study provide useful evidence for the control of dyslipidemia in our local population to limit their CV risk. Banach M et al in a recent review also mentioned that in presence of multiple drug choice and treatment strategies, patients with uncontrolled lipid profile is a concern and the health care providers must treat them to reach their treatment goals to avoid the incidence of future CV events.[18]

The major limitation of our study is small sample size and shorter follow up duration. Future studies covering these limitations will be helpful in providing more useful data for effective control of dyslipidemia.

Conclusion:

Combination therapy in patients uncontrolled on mono therapy significantly improves the triglycerides levels, total cholesterol and HDL C levels. However there is no significant improvement in the LDL C levels. Clinicians must opt for the evidence based strategies for effective control of lipid parameters to save patients from this major CV risk factor.

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Conflict of interest:
None
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