ORIGINAL ARTICLE

The effect of ezetimibe monotheraphy on mean platelet volume in patients with hyperlipidaemia: a retrospective study of 45 patients

Yasar Sertbas,[1] Meltem Sertbas,[2] Ugur Ersoy,[3] Bulent Bilir,[4] Seracettin Gunaydin,[5] Ali Ozdemir[6]

Abstract

Objective: To investigate the effect of ezetimibe on platelet functions as a drug which increases mevalonate levels.
Methods: This retrospective study was conducted in Istanbul, Turkey, and comprised record of normolipidaemic and hyperlipidaemic patients taken from the outpatient clinic from October 2004 to February 2015,. The results were taken from the baseline and third-month data of ezetimibe treatment. SPSS 22 was used for statistical analysis.
Results: Of the total, there were 50(53%) normolipidaemic patients and 45(47%) hyperlipidaemic ones. Pre- and post-treatment values of mean platelet volume were significantly higher in the hyperlipidaemic group than controls ($p<0.001$). In the hyperlipidaemic group there was no significant difference between pre- and post-treatment values of mean platelet volume (8.96±0.93 vs. 8.92±0.84; $p>0.05$).
Conclusion: The use of ezetimibe alone should not be the first choice in hyperlipidaemia treatment.
Keywords: Ezetimibe, Mean platelet volume, Platelet activation. (JPMA 66: 1559; 2016)

Introduction

Hyperlipidaemia is an important risk factor for the cardiovascular diseases (CVD).[1,2] Ezetimibe is a lipid-lowering drug, which acts by inhibiting the absorption of cholesterol from the jejunum.[3] In many studies showing the pleitrophic effects of statins, another lipid-lowering drug, ezetimibe have been used as a placebo to decrease the serum cholesterol levels. In these studies ezetimibe decreased the low-density lipoprotein (LDL) levels, but unlike statins it also increased the mevalonate levels.[4,5] Although statins have some pleitrophic effects, such as improvement of endothelial function, an increase in nitric oxide (NO) levels, anti-oxidant and anti-thrombotic functions, ezetimibe is not known to have any pleitrophic effect.[6-9]

Platelet activity plays a role in the development and progression of atherosclerosis, and reduction of platelet activity is another pleitrophic effect of statins.[10,11] There are many methods to show the platelet activation but they are expensive and time-consuming with the requirement of special experience.[12-14] Mean platelet volume (MPV) is a simple marker for the platelet activity that is determined with routine automated haemograms as a part of the whole blood count (WBC).[15] The current study was planned to investigate the effect of ezetimibe on platelet activity as a drug which increases mevalonate levels.

[1,2,6]Department of Internal Medicine, [5]Department of Biochemistry, Fatih Sultan Mehmet Education and Research Hospital, Istanbul, [3]Department of Internal Medicine, Elazig Medical Park Hospital, Elazig, [4]Department of Internal Medicine, Namik Kemal University Medical Faculty, Tekirdag, Turkey.
Correspondence: Yasar Sertbas. Email: yserzincan24@gmail.com

Patients and Methods

This retrospective study was conducted in Istanbul, Turkey, and comprised data of hyperlipidaemic patients from October 2004 to February 2015 that was compared with gender- and age-matched normolipidemic subjects. Data was collected from the internal medicine outpatient clinical records of Fatih Sultan Mehmet Education and Research Hospital. Patients who had been treated only with ezetimibe were included. Moreover, as we usually control the lipid parameters at the third month of treatment for the hyperlipidaemic patients, we preferred to include patients examined in outpatient clinics for at least 3 months period with full laboratory parameters of lipid profiles and whole blood counts.

Patients who had any infection, thrombotic or haematologic disorders, any medication effecting platelet function, haemoglobin (Hb) < 12.5 g/dl in men and <11.5 g/dl in women were excluded. Lipid parameters and MPV values at baseline and 3 months after ezetimibe treatment were used for statistical analysis. Approval for this study was obtained from the ethical committee of the Fatih Sultan Mehmet Education and Research Hospital.

SPSS 22 was used for statistical analysis. Data was expressed as mean standard deviation (SD). One-sample Kolmogorov-Smirnov test was performed to assess the distribution of data. Numerical variables in different subjects were compared by t-test or Mann-Whitney U test. Variables calculated before and after the treatment were compared by paired t-test or Wilcoxon test. Bivariate correlation analyses were made by Pearson's correlation test. Probability values were two-tailed, and a $p<0.05$ was considered significant.

Results

Of the 95 participants, there were 45(47%) cases and 50(53%) controls. There were 20(21.05%) men and 75(78.95%) women. There was no significant difference between the distribution of gender among the two groups as there were 10(22.22%) men and 35(77.78%) women in the case group compared to 10(20%) and 40(80%), respectively, among the controls (p>0.005). There was no statistically significant difference for age in hyperlipidaemic patients and the controls (53.40 9.35 vs. 49.44 10.07 years; p>0.05). LDL cholesterol levels were significantly higher in the hyperlipidaemic group than the controls (190.16±39.91 vs.116.46±26.43 mg/d;, p<0.001). Among the cases, the mean LDL cholesterol level decreased from 190.16±39.91 before ezetimibe treatment to 148.21±30.10 mg/dL after the treatment (p<0.001), whereas the mean total cholesterol levels fell from 271.28±48.83 to 219.26 36.18 mg/dL (p<0.001). Among controls, the mean LDL was 116.46±26.43 while total cholesterol was 190.58±34.6 mg/dL, both before and after the treatment (Table-1).

Table-1: Baseline and post-treatment cholesterol values of case and control groups.

	Case group	Control group	P value
Tot.chol.before treatment	271.28±48.83	190.58±34.6	<0.001
Tot.chol.after treatment	219.26 36.18	190.58±34.6	<0.001
p value btw. case groups	<0.001		
HDL chol.before treatment	48.80±14.74	44.70±10.91	0.178
HDL chol. after treatment	44.33±13.15	44.70±10.91	0.883
p value btw. case groups	0.013		
Triglyceride before treatment	148.00±64.68	145.60±65.35	0.884
Triglyceride after treatment	132.32±53.49	145.60±65.35	0.292
p value btw. case groups	0.841		
LDL chol.before treatment	190.16±39.91	116.46±26.43	<0.001
LDL chol. after treatment	148.21±30.10	116.46±26.23	<0.001
p value btw. case groups	<0.001		

All values are in mg/dL.
Tot: Total
Chol: Cholesterol
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
Btw: Between.

Table-2: Baseline and post-treatment haematological values of case and control groups.

	Case group	Control group	P value
WBC before treatment	6957.55±1553.24	7055.60±1354.84	0.740
WBC after treatment	6298.19 2510.88	7055.60±1354.84	0.07
p value btw. case groups	0.095		
Hb. before treatment	14.27±1.30	13.95±0.72	0.141
Hb.after treatment	14.02±1.28	13.95±0.72	0.748
p value btw. case groups	0.168		
Plt. before treatment	277.68±71.06	256.08±52.91	0.096
Plt. after treatment	261.73±68.61	256.08±52.91	0.658
p value btw. case groups	0.017		
MPV before treatment	8.96±0.93	7.56±0.69	<0.001
MPV after treatment	8.92±0.84	7.56±0.69	<0.001
p value btw. case groups	0.616		

WBC: Whole blood count 10^9/L
Hb: Haemoglobin - Gm/dL
Plt: Platelets 10^9/L
Btw: Between.

Although there was no significant difference between WBC, haemoglobin and platelet levels, the MPV values were significantly higher in the hyperlipidaemic patients than the controls (8.96±0.93 and 7.56±0.69 pre-treatment and 8.92±0.84 and 7.56±0.69 post-treatment; p<0.001). In the hyperlipidaemic group, there was no significant difference between pre- and post-treatment values of MPV (8.96±0.93 vs. 8.92±0.8; p> 0.05) (Table-2).

Discussion

The results of this study show that ezetimibe treatment does not affect the platelet activity, which plays an important role in development and progression of atherosclerosis.

Besides their lipid lowering effects, statins being major anti-hyerlipidaemic agents have some pleitrophic effects, such as improving endothelial function, decreasing oxidative stress and inflammation, improving the stability of atherosclerotic plaques, and decreasing thrombotic activity. Pleitrophic effects of ezetimibe, if any, are not as prominent as statins. Grioge et al. and Maki-Petaja et al. reported that both statins and ezetimibe themselves improve endothelial functions.[6,16] Another study has shown that neither ezetimibe alone nor ezetimibe /simvastatin combination has any effect on endothelial function while high-dose atorvastatin improves these functions.[17]

Superoxide dismutase and high-sensitivity C-reactive protein (hs-CRP) are the commonly used inflammatory markers among these studies. For inflammatory markers, studies have shown contradictory results for both ezetimibe and statins. In some of these studies, both simvastatin and ezetimibe decreased the CRP levels.[16,18] Landmesser et al. reported that ezetimibe had no effect on flow dependent dilatation and superoxide dismutases, while simvastatin treatment improved endothelial function and increased superoxide dismutase activity.[19] Sager et al. demonstrated that ezetimibe co-administration with simvastatin provides incremental decreases in hs-CRP, compared with simvastatin monotheraphy.[20] Piorkowski et al. reported that statins were more effective in decreasing platelet functions than

ezetimibe.

Most pleiotropic effects of statins are thought to be related to inhibition of the mevalonate-dependent isoprenylation of small guanosine triphosphate (GTP)-binding proteins, such as Rho, Ras, and Rac 1. The inhibition of RhoA and Rac 1 may cause a decrease of plasminogen activator inhibitor-1 (PAI-1), endothelin-1 (ET-1), oxidative stress and vascular smooth muscle proliferation with an increase of endothelial nitric oxide synthase (eNOS) and tissue plasminogen activator (t-PA).[21]

The opposite effect on the mevalonate of statins and ezetimibe may be a mechanism behind different pleitrophic effects. Hyperlipidaemia, particularly high LDL-cholesterol, is an important risk factor in atherogenesis. In our study, although ezetimibe treatment provided a 20% decrease in LDL cholesterol levels, post-treatment LDL-cholesterol levels were significantly higher than the controls. This insufficient reduction of LDL-cholesterol with ezetimibe treatment may be another mechanism behind no altered platelet activity. There is a need to verify these results with prospective, randomised, large-scale studies.

Conclusion

In order to provide a beneficial effect on platelet activity during hyperlipidaemia treatment, the use of ezetimibe alone should not be the first choice of treatment. If there is low or no risk of myopathy, it may be better to use high doses of statins or combination treatment, suhc as ezetimibe plus statins.

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References

1. Gordon T, Kannel WB. Premature mortality from coronary heart disease. The Framingham Study. JAMA. 1971; 215:1617-25.
2. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. Ann Intern Med. 1971;74:1-12.
3. Sertbas Y, Ersoy U, Ayter M, Gultekin Tirtil F, Kucukkaya B.Ezetimibe effect on bone mineral density and markers of bone formation and resorption.J Investig Med. 2010; 58:295-7.
4. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S, et al. Simvastatin versus ezetimibe pleitropic and lipid lowering effects on endothelial function in humans.Circulation. 2005; 111:2356-63.
5. Pesaro AE, Serrano CV Jr, Fernandes JL, Cavalcanti AB, Campos AH, Martins HS, et al.Pleiotropiceffects of ezetimibe/ simvastatin vs. high dose simvastatin.Int J Cardiol. 2012; 158:400-4.
6. Grigore L, Raselli S, Garlaschelli K, Redaelli L, Norata GD, Pirillo A, et al.Effect of treatment with pravastatin or ezetimibe on endothelial function in patients with moderate hypercholesterolemia.Eur J Clin Pharmacol.2013; 69:341-6.
7. Hashimoto M, Akita H. Cerivastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, improves endothelial function in elderly diabetic patients within 3 days response. Circulation. 2002; 105:e30 -e1.
8. Ichiki K, Ikeda H, Haramaki N, Ueno T, Imaizumi T. Long-term smoking impairs platelet-derived nitric oxide release. Circulation. 1996; 94:3109-114.
9. Koh KK. Effects of HMG-CoA reductase inhibitor on hemostasis. Int J Cardiol. 2000; 76:23-32.
10. Huhle G, Abletshauser C, Mayer N, Weidinger G, Harenberg J, Heene DL. Reduction of platelet activity markers in type II hypercholesterolemic patients by a HMG-CoA-reductase inhibitor. Thromb Res. 1999; 95:229-34.
11. Hale LP, Craver KT, Berrier AM, Sheffield MV, Case LD, Owen J. The combination of Fosinopril and pravastatin decreases platelet response to thrombin receptor agonist in monkeys. ArteriosclerThromb.Vasc Biol. 1998;18:1643-6.
12. Michelson AD.Methods for the measurement of platelet function.Am J Cardiol. 2009;103:20A-6A.
13. Nicholson NS, Panzer-Knodle SG, Haas NF, Taite BB, Szalony JA, Page JD, et al.Assessment of platelet function assays.Am Heart J1998;135:S170-S178.
14. Colwell JA, Nesto RW. The platelet in diabetes: focus on prevention of ischemic events.Diabetes Care.2003;26:2181-8.
15. Dindar S, Cinemre H, Sengul E, Annakkaya AN.Mean platelet volume is associated with glycaemic control and retinopathy in patients with type 2 diabetes mellitus. West Indian Med J. 2013; 62:519-23.
16. Maki-Petaja KM, Booth AD, Hall FC, Wallace SM, Brown J, Mc Eniery CM, et al. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. J Am Coll Cardiol. 2007; 50:852-8.
17. Fichtlscherer S, Schmidt-Lucke C, Bojunga S, Rössig L, Heeschen C, Dimmeler S, et al. Differential effects of short-term lipid lowering with ezetimibe and statins on endothelial function in patients with CAD:clinical evidence for 'pleitropic' functions of statin theraphy. Eur Heart J. 2006; 27:1182-90.
18. Kostakou P, Kolovou G, Anagnostopoulou K, Theodoridis T, Galea V, Mihas C, et al.Efficacy of simvastatin or ezetimibe on tissue factor, von Willebrand's factor and C-reactive protein in patients with hypercholesterolaemia. Arch Cardiovasc. Dis. 2010; 103:26-32.
19. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchoff N, Schulz S, et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. Circulation. 2005; 111:2356-63.
20. Sager PT, Melani L, Lipka L, Strony J, Yang B, Suresh R, et al. Effect of coadministration of ezetimibe and simvastatin onhigh-sensitivity C-reactive protein. Am J Cardiol. 2003; 92:1414-8.
21. Weitz-Schmidt G, Welzenbach K, Brinkmann V, Kamata T, Kallen J, Bruns C, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med. 2001; 7:687-92.