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A PROSPECTIVE STUDY TO EVALUATE THE EFFECTIVENESS OF ORAL HYPOGLYCEMIC AGENTS COMBINED WITH STATINS VERSUS ORAL HYPOGLYCEMIC AGENTS COMBINED WITH BOTH STATINS AND ASPIRIN ON MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTER

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ABSTRACT

Introduction: In this study, we compared the mean platelet volume (MPV) in the two groups of diabetic patients aged 50–59 years with an HbA1C between 7 and 9, in order to examine the effects of statins and the combination of statins and aspirin with oral hypoglycemic medications.

Methodology: Patients who met the study's inclusion requirements were admitted. The baseline MPV of those with an Atherosclerotic cardiovascular risk estimate (ASCVD) of 10% will be noted for both groups. Group A received hypoglycemic drugs with statins, while Group B received hypoglycemic drugs with aspirin and statins. After three months, both groups were checked on, and MPV was assessed in each.

Results: **IN STATINS GROUP:-** Following a three-month course of treatment, the mean difference in MPV was 0.84 in the group with a HbA1c of 1.5%, a statistically significant difference ($p < 0.0001$), and an MPV mean difference of 1.55.

IN ASPIRIN WITH STATINS GROUP:- After 3 months of treatment, in the group with HbA1c $< 1.5\%$, MPV mean difference was 1.22, which was statistically significant ($p < 0.0001$). Whereas in the group with HbA1c $> 1.5\%$, MPV mean difference was 1.31, which was statistically significant ($p < 0.0001$).

Conclusion: Though there is significant reduction in both the groups, the mean reduction of MPV was more in the group treated with statins and aspirin. In both the groups, the reduction in MPV was found to be more in the subgroup where HbA1c was reduced more than 1.5 %. Our study concludes that along with Aspirin, HbA1c also plays a vital role in reduction of mean platelet volume in poorly controlled diabetic individuals.

Keywords: Aspirin, Diabetes Mellitus, Statin, Mean Platelet Volume (MPV), HbA_{1c}.

INTRODUCTION

Platelets are disc-shaped, non-nucleated, flattened organisms with a diameter of 1-4 μ m. They are made from the cytoplasm of megakaryocytes and are very dependent on the general health and nutritional status of the patient. Platelets consist of 65 percent inactive, smooth, disc-shaped cells and 10 to 35 percent spherically-shaped, less well-defined cells.¹ Normal mean platelet volume ranges from 7.5 fl to 10.5 fl, and average platelet count ranges from 150,000 to 400,000/l. The size of the platelets is determined by the granules density. With electron microscopy, platelet masses and glycogen are evident.⁴ Plasma is the primary energy source for platelets, and they use it to absorb glucose. Normally, 40–50% of the glucose that is consumed is converted to glycogen. Platelet size (MPV) is a crucial haemostatic characteristic and a measure—possibly even a determinant—of platelet function.²

Diabetes mellitus is a complex metabolic disease that causes issues with almost every organ in the body. It is characterized by persistent hyperglycemia. Diabetes is fast turning into a possible epidemic, with over 62 million people living with the disease in India.³ In India, 79.4 million people are predicted to have diabetes by 2030. Chronic type-2 diabetes lowers quality of life and raises morbidity and mortality rates. By preventing platelet activation, statins can lower MPV and regulate platelet function.⁴⁻⁵

Statins inhibit CD36 directly or alter CD36's intracellular signal transduction pathways to reduce platelet activation. Therefore, the study was carried out to evaluate the impact of aspirin and statins on mean

platelet volume and to compare the effectiveness of each group in reducing MPV in diabetic patients with inadequate glycaemic control, ultimately resulting in fewer problems.

MATERIAL AND METHODS

Study design and Setting:

The present prospective observational study was conducted in the Department of General Medicine & Diabetic clinic at Chettinad Hospital, and Research Institute, Kelambakkam, over a period of 1 year i.e. from April 2024 to June 2024 after the approval from Institutional Human Ethics Committee (IHEC).

Study population, Inclusion and Exclusion criteria:

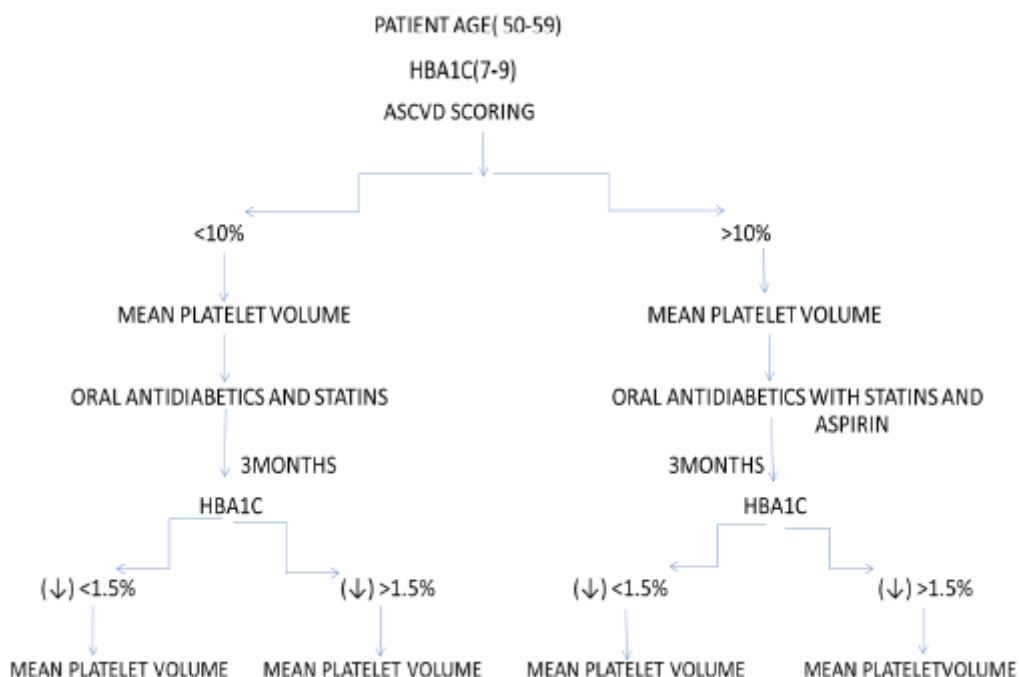
The study population included in the study were patients of either sex who are already diagnosed with diabetes mellitus but with poor glycaemic control (HbA_{1c} : 7-9) between the age range of 50-59 years and willing to give informed consent. Patients with $HbA_{1c} > 9$, taking aspirin or other drugs which alter MPV, who are all on insulin treatment and patients with good glycemic control, hypertension, inflammatory bowel disease, idiopathic thrombocytopenic purpura, myelo-proliferative disorders, bernard -souliers syndrome, thrombocytosis and thrombocytopenia were excluded from the study.

Sample size and sampling method:

Based on the results of proportion of variations in the Diabetes Mellitus among patients who had aspirin and statin variations observed in an earlier publication[1] and with 80% power and 95% confidence the minimum sample size comes to 40. Study participants were recruited consecutively by convenient sampling, till the sample size is reached.

Study Procedure:

Patient satisfying the inclusion criteria was taken into the study. Those with Atherosclerotic cardiovascular risk estimator (ASCVD) $< 10\%$ was taken as group –A and those with ASCVD $> 10\%$ was considered as group—B. Baseline MPV was recorded for both the groups. Further study was be conducted as mention in the flow chart below.



Study tools:

Mean platelet volume was measured with automated blood counter (Beckman coulter). Atherosclerotic Cardiovascular Disease (ASCVD) Risk was calculated to divide the sample into two groups. Those with ASCVD score less than 10% was categorised as group A and those with ASCVD score more than 10 % was categorised into group B.

Statistical analysis:

For quantitative variables, mean and standard deviation were used, whereas for categorical variables, frequency and proportion were used. The Chi square test was used to determine the statistical significance of two qualitative variables, whereas the paired t Test was used to determine the statistical significance of two quantitative variables. Statistical significance was defined as a p value of less than .05. For statistical analysis, IBM SPSS version 22 was employed.

RESULTS

The study included a total of 40 patients with males were 45% and females were 55% of the total sample.. In the present study, the mean age of the study participants was 54.75 ± 3.19 years The baseline parameters were recorded and is shown in Table 1. 25% of the sample had a positive history of smoking cigarette.

Table 1:- Descriptive statistics showing baseline parameter

	MEAN $\pm$ S.D.	MINIMUM	MAXIMUM
HbA1c	7.94 $\pm$ 0.62	7	9
Systolic BP	146.92 $\pm$ 14.95	118	164
Diastolic BP	92.56 $\pm$ 8.56	74	108
Total Cholesterol	192.45 $\pm$ 24.65	160	260

HDL	48.23±4.76	43	54
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The patients were categorized into two groups, based on ASCVD score, where score less than 10% was observed in 52.5% and more than 10% was observed in 47.5%. Mean platelet volume in the present study was 9.62 ± 0.98 .

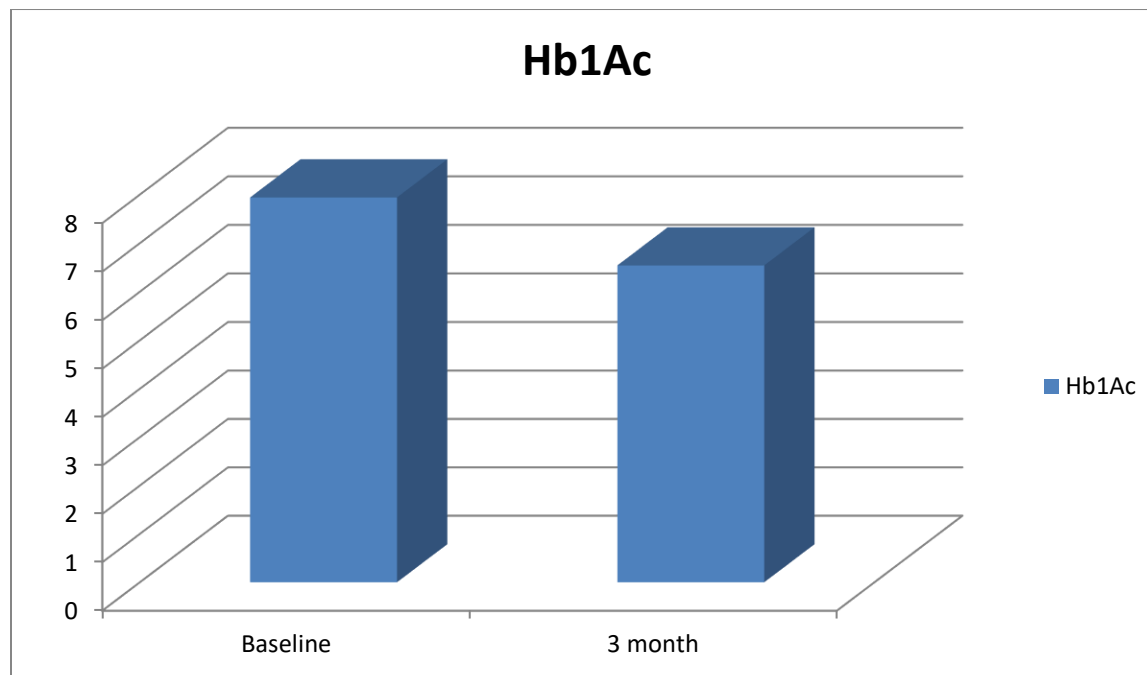


Fig 1: Values of HbA1c at baseline and 3 months post treatment

After three months of treatment the mean value in the statins group was observed to be 8.52 ± 0.84 and mean value of MPV in statins and aspirin group was 8.21 ± 0.93 . The P value found to be less than 0.05 indicated that there was a statistically significant difference between the two groups in terms of mean platelet volume. The t test was used to determine the significance in this situation.

In Group A, the mean difference of mean platelet volume with statins, in HbA1c group $<1.5\%$ The mean MPV before treatment was 9.56 and after treatment was 8.21 and the mean difference was statistically significant $p < 0.0001$. In the group where change in HbA1c $>1.5\%$, MPV before statin treatment was 9.71 and after treatment was 8.86. This finding was observed to be statistically significant $p < 0.0001$.

In Group B, in the HbA1c group with less than 1.5% change before statin and aspirin treatment, the mean MPV was observed to be 9.45 and after treatment it was 8.23. This finding was observed to be statistically significant as the P value calculated to be <0.0001 . In the group where change in HbA1c $>1.5\%$, MPV before statin treatment was 9.42 and after treatment was 8.11. This finding was observed to be statistically significant $p < 0.0001$.

Table 2:- Values of Hb1Ac and MPV at baseline and 3 months post treatment in both the groups

		Before Treatment	After Treatment	p-value
Hb1Ac	Statins (ASVCD $<10\%$)	8.23 ± 0.62	6.93 ± 0.75	$<0.001^*$
	Statins + Aspirin	7.94 ± 0.51	6.75 ± 0.82	$<0.001^*$

	(ASVCD >10%)			
Mean Platelet Volume	Statins (ASVCD <10%)	9.48 ± 0.87	8.70 ± 0.99	<0.001*
	Statins + Aspirin (ASVCD >10%)	9.41 ± 0.99	8.03 ± 0.99	<0.001*

DISCUSSION

The study investigated which diabetic group had a better effect in regulating mean platelet volume in this sample group with poor glycaemic control, which finally reduces the consequences. It also focused on changes in MPV caused by statins and aspirin.

HbA1c and Statins:

The mean HbA1c in the statin group was 8.23 before therapy and 6.93 after treatment; thus, there was a 1.20 mean difference between the two periods, which was found to be statistically significant. p is less than 0.0001. An RCT using two high-potency statins, rosuvastatin and atorvastatin, in adults without diabetes showed equal HbA1c values in both groups at baseline and three months into treatment.⁶ rosuvastatin increased HbA1c levels in non-diabetic subjects from 5.7 to 5.9% in another investigation.⁷ Simvastatin had a favorable impact on HbA1c, while atorvastatin had a significant negative impact, according to a meta-analysis⁸. In a different meta-analysis, Erquo et al.⁹ found that although the control group's pooled HbA1c concentration was 7.41% (95%CI: 7.11-7.72), statin-using patients had a concentration of 7.53% (95%CI: 7.20-7.86) at follow-up. According to the study, the overall 95 percent confidence interval (CI) for the pooled mean difference estimate was 1.3 mmol/mol.

MPV and Statins:

Following three months of therapy, the statins group's mean value was found to be 8.70 ± 0.99 . Mean platelet volume before and after therapy: in the statin group, the mean MPV was 9.48 before treatment and 8.70 after treatment. A statistically significant difference of 0.78 was found to be the primary difference. p is less than 0.0001. The fact that statins have anti-thrombotic properties is commonly known. However, in individuals with hypercholesteremia treated with statins, the lipid-lowering impact does not correlate with the suppression of platelet-dependent thrombus formation. This demonstrates that various factors contribute to the anti-aggregatory effects of statins.¹⁰ Statins are known to inhibit HMG-CoA reductase and produce mevalonate, which suppresses the formation of isoprenoid intermediates.¹¹ Posttranslational modifications occur to many proteins, and the intermediates that result from these modifications are essential lipid attachments. Furthermore, because of their pleiotropic effects, statins stimulate platelets in two different ways. One process involves the upregulation of platelet eNOS, whilst the other is dependent on thromboxane.¹²⁻¹³ The final point to keep in mind in this regard is the significance of MPV as a straightforward laboratory value, which considerably decreases following statin medication. This impact has nothing to do with the tendency to lower cholesterol. Moreover, rosuvastatin and atorvastatin both exhibited comparable effects on MPV, suggesting that a class effect rather than a specific molecule is at play. Recently, rosuvastatin's impact on MPV has been shown in a small number of people.¹⁴ According to Kucera et al. (2015)¹⁵, the largest lipid-lowering effect was observed in those whose MPV and RDW values were considerably reduced only after three months of atorvastatin therapy.

HbA1c, Aspirin, and Statins:

The mean HbA1c in the statin and aspirin group was 7.94 before therapy and 6.75 after treatment, both of which were statistically significant ($p < 0.0001$).

Aspirin with Statins and MPV:

Following a three-month course of therapy, the average MPV value in the statin group was 8.70 ± 0.99 , whereas the aspirin and statin group's average MPV value was 8 ± 0.98 . With regard to mean platelet volume, there was a statistically significant difference between the two groups, as indicated by the P value of less than 0.05. The student t test was the statistical method used in this case to determine significance. The mean platelet volume in the statin and aspirin group was 9.41 prior to treatment and 8.03 following treatment. The major difference was found to be statistically significant at 1.38. p is less than 0.0001.

In a study by Xinyang et al.¹⁶, it was found that people who had previously used aspirin or a statin had significantly lower levels of platelet aggregation and platelet-leukocyte aggregates when compared to people who had never used one. Individuals who combined their aspirin and statin use before to a stroke were less likely to experience neurological side effects. Mean platelet volume was characterized by Colkesen et al. (2017)¹⁷ as a predictive marker of platelet size, and they came to the conclusion that aspirin use had no bearing on its function in PAF patients.

CONCLUSION

There was significant reduction in mean HbA1c as well as mean MPV values in both the groups after 3 months of treatment (i.e., in group with statins and group with statins and aspirin. Though there is significant reduction in both the groups, the mean difference of MPV was more in the group treated with statins and aspirin. In both the groups, the reduction in mean platelet volume was observed to be more in the sub group where HbA1c was reduced more than 1.5 %.

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