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Original Article

Pharmacology Section

Antiplatelet Efficacy of 75 mg Aspirin Once a Day versus Twice a Day Dosing in Type 2 Diabetes Mellitus Patients- A Longitudinal Open Label Study

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ABSTRACT

Introduction: Patients of Type 2 Diabetes Mellitus (T2DM) characteristically have platelets hyper-reactivity and accelerated turnover rates leading increased adhesion, aggregation and procoagulant activity. Half-life of aspirin is only 20 minutes and it, therefore, irreversibly inactivates limited number of platelets over this short duration, when given as a once-daily dose. Newly generated-active platelets enter circulation, thereafter, and weaken antiplatelet effect of aspirin. Therefore, single daily dose of 75 mg aspirin may be insufficient to provide 24 hours protection against cardiovascular events, in these patients.

Aim: To study and compare antiplatelet efficacy of 75 mg aspirin twice a day (75 mg BD) versus 75 mg aspirin once a day (75 mg OD) in patients of T2DM and to study the effect of variation in glycated haemoglobin (HbA1c) levels on antiplatelet efficacy.

Materials and Methods: This was a longitudinal, open label, comparative trial conducted at tertiary care hospital for a period of nine months. A total of 129 subjects, diagnosed with T2DM according to American Diabetes Association (ADA) criteria 2018 (N=129) were enrolled in the study, of which nine were lost to follow-up and antiplatelet efficacy of aspirin dosing was examined at baseline and three-monthly intervals thereafter, till nine months, using colorimetric method.

Results: Mean age of enrolled patients was 62 years (Interquartile Range (IQR) 57-66). HbA1c levels of both the groups were comparable (p=0.77) at baseline. At the end of nine months, percentage platelet aggregability of the 75 mg B.D. group (29.30±10.39) was significantly lower (p<0.00001) than that of 75 mg OD (38.20±10.36). There was no correlation observed between HbA1c variation and percentage platelet aggregability for entire study population.

Conclusion: Present study concludes that, 75 mg OD aspirin as a strategy for secondary cardiovascular disease prevention is advocated, but not adequate in T2DM patients. Splitting a dose of 150 mg/day aspirin as 75 mg twice is more effective, due to increased platelet turnover in diabetic patients.

Keywords: Aspirin prophylaxis, Non insulin dependent diabetes mellitus, Split dosing

INTRODUCTION

Diabetes is a complex lifestyle disorder characterised by additional long-term effects like-"prothrombotic state" [1]. In T2DM patients platelet physiology is modestly different. Platelets in these patients are hyper reactive and have reduced life span and increased turnover rates leading to enhanced regeneration of platelets [2,3]. Hyperglycaemia also increases platelet reactivity by various mechanisms [4]. Other factors that contribute abnormal platelet activity is dysregulation of several signaling pathways with intensified adhesion, activation and aggregation [5]. Only modest reductions in cardiovascular events and mortality have been observed with once-daily low dose aspirin treatment in patients with diabetes (including patients with a previous cardiovascular event); perhaps because of disparity between aspirin pharmacokinetics and diabetes-related platelet abnormalities [6].

Aspirin irreversibly acetylates and inactivates Cyclooxygenase-1 (COX-1) in circulating platelets and has only a 20 minute half-life. This short duration of action, therefore, does not allow newly generated platelets entering the circulation to be sufficiently exposed to aspirin especially when there is accelerated thrombopoiesis in these T2DM patients. This may lead to a considerable proportion of circulating platelets with uninhibited COX-1 activity that continue to generate high levels of thromboxane and therefore, promote activation of circulating platelets and contributes to their increased risk of adverse cardiovascular events [7]. This may be attributed to raise platelet turnover rates resulting in an increased proportion of non aspirin-inhibited platelets during daily dosing interval. Therefore, there is theoretical possibility that a single daily dose could not be sufficient to exert a full inhibitory effect on the new platelets generated and released by bone marrow during the course of 24 hours after aspirin intake [8].

In this background, the study aimed to compare that increasing the frequency of aspirin administration might be effective in inhibiting the newly generated platelets and thus, improving aspirin-induced pharmacodynamic effects. The secondary outcome measures were to study the effect of variation in HbA1c levels on the antiplatelet efficacy of above mentioned doses of aspirin in the same set of T2DM patients.

MATERIALS AND METHODS

This study was a prospective, open-labelled, parallel group, longitudinal study, conducted at B.J. Government Medical College and Sassoon General Hospital Pune, Maharashtra, India from November 2018 to June 2020. Approval from the Institutional Ethics Committee (IEC) was obtained prior to the commencement of the trial (IEC/Pharmac/D-0918135-135). A total of 129 subjects with T2DM were enrolled in the study, from those that attended the diabetic out-patient and of which nine were lost to follow-up. Written informed consent (in the vernacular language Marathi/ English) was taken from patients prior to inclusion in the study.

Inclusion criteria: Patients in the age group 35 to 70 years with previously diagnosed T2DM according to ADA criteria 2018 [9]. Above mentioned patients receiving oral antidiabetic (Metformin 0.5-2g/day sulfonylurea-Glimepiride 1-2 mg/day) and/or Antihypertensive drugs (Amlodipine, Enalapril). Patients receiving aspirin as antiplatelet (75 or 150 mg/day) as single dose.

Exclusion criteria: Patient who were smokers, those with uncontrolled diabetes mellitus (Fasting Plasma Glucose Level >300 mg/dL despite therapy), requiring insulin, uncontrolled hypertension, abnormal liver function tests and/or renal function tests, deranged bleeding and/or clotting time at baseline, patients on-analgesic antiinflammatory dose of aspirin therapy for >7 days and/or other non steroidal antiinflammatory drugs and/or any other antithrombotic or anticoagulant therapy were excluded from study.

Sample size calculation: [10]

$$n = \frac{Z^2(1-a/2)\,V}{d^2} \quad \text{.....(formula-1)}$$

Where

V=P1(1-P1)+P2(1-P2) ..... (formula-2) (**Calculated as below)

Z(1-a/2)=1.96

d=13%

(Prevalence of high on-treatment platelet reactivity in patients with diabetes).

**60-100 mg {23 Studies (n=1,689)}=23.6%

Platelet inhibition (Aspirin 60-100 mg) Prevalence P1=(100-23.6)=76.4%=0.764

101-162 mg {10 Studies (n=271)}=8.9%

Platelet inhibition (Aspirin 101-162 mg) Prevalence P2=(100-8.9)=91.1%=0.911

Substituting values in formula-2

V=0.764(1-0.764)+0. 911(1-0.911)

=(0.764*0.236)+(0.911*0.089)

=0.1803+0.0811

V=0.2614

Substituting values in formula-1

$$n=\frac{(1.96)^2*0.2614}{(0.13)^2}=\frac{3.8416*0.2614}{0.0169}=\frac{1.0042}{0.0169}$$

=59.42 patients per group

Detail Research Plan

Screening/Visit 1: Total 129 patients were screened for clinical inclusion/exclusion criteria, underwent physical examination and biochemical tests viz fasting plasma glucose level, clotting time, prothrombin time, liver function tests, renal function test and lipid profile and previous data of HbA1c levels were recorded.

Visit 2-Patients were selected as per the inclusion/exclusion criteria and written informed consent was obtained from eligible diabetic patients. Patients taking 75 mg aspirin once a day were assigned to Group A and those taking 150 mg aspirin once a day assigned to Group B.

Baseline platelet aggregability study was done by colorimetric method.

Group A: Patients taking 75 mg aspirin OD. were instructed to take daily dose of drug every day before breakfast (8 am).

Group B: Patients taking 75 mg aspirin B.D. were instructed to take one tablet every day before breakfast (8 am) and second 75 mg aspirin tablet every night before dinner (8 pm). Thus the total 150 mg dose was split in 75 mg twice.

After one month: Every patient was examined for any adverse effects (nausea, vomiting, epigastric pain, increased occult blood loss in stools, dyspepsia, acute gastritis, gastrointestinal bleeding) and enquired about compliance every month, till the completion of study.

After 3,6,9 months: Every patient was examined for adverse effects, if any, and blood sample were collected for determining platelet aggregability, Fasting Plasma Glucose Level (FPGL), Postprandial Glucose level (PPGL) and HbA1c.

Platelet Aggregability Method

Platelet aggregability was estimated by the colorimetric method as given by O'Brien J [11,12]. Blood was centrifuge using Centrifuge Machine of model type P-23 manufactured by REMI Group, Mumbai. Optical density was determined by Photochem-5 Colorimeter manufactured by AIMIL Instrumentation, India. Adenosine-5-diphosphate obtained from Sisco Research Laboratories Pvt. Ltd. Mumbai), Trisodium Citrate (3.8%) obtained from Chem Laboratory, Pune, Maharashtra, India.

Methodology: To avoid diurnal variation in platelet aggregation, time for collection of blood sample was kept constant between 10 am-12 noon. Blood sample was collected from the antecubital vein under all aseptic and antiseptic precautions using disposable syringes with 21-gauge needles.

About 9 mL of blood was collected in plastic centrifuge tubes by syringes already flushed with trisodium citrate (3.8%) (to minimise chances of blood coagulation in syringe) and mixed with 1 mL 3.8% of trisodium citrate. Clear Platelet Rich Plasma (PRP) obtained by centrifuging the blood at 1200 rpm for 15 minutes, 2 mL of which was used for determining platelet aggregability.

About 2 mL of PRP obtained as above, was taken in a plastic tube and kept in a preset colorimeter and absorbance reading was obtained. Colorimeter was adjusted for an operative wavelength of 540 nm in such a way that the absorbance for the dark is infinite and for distilled water, at 0. It was kept constant for each test.

Then, 0.1 mL of 200 µg/mL of Adenosine diphosphate (ADP) solution was added to it and mixed by manual stirring (gently shaking the tube) and absorbance reading was again noted at the end of 15 seconds. Thus, change in the absorbance (optical density-OD) of PRP at the end of 15 seconds was taken as measure of platelet aggregability. Greater the decrease in the absorbance, more is the platelet aggregability.

$$\text{\% Platelet Aggregability (PA)} = \frac{\text{(OD of PRP at 0 time-OD of PRP at 15 sec after ADP)}}{\text{(OD of PRP at 0 time-OD of PPP)}} \times 100$$

Hence, change in % Platelet Aggregability (ΔPA)=PA (x months)-PA (Baseline)

STATISTICAL ANALYSIS

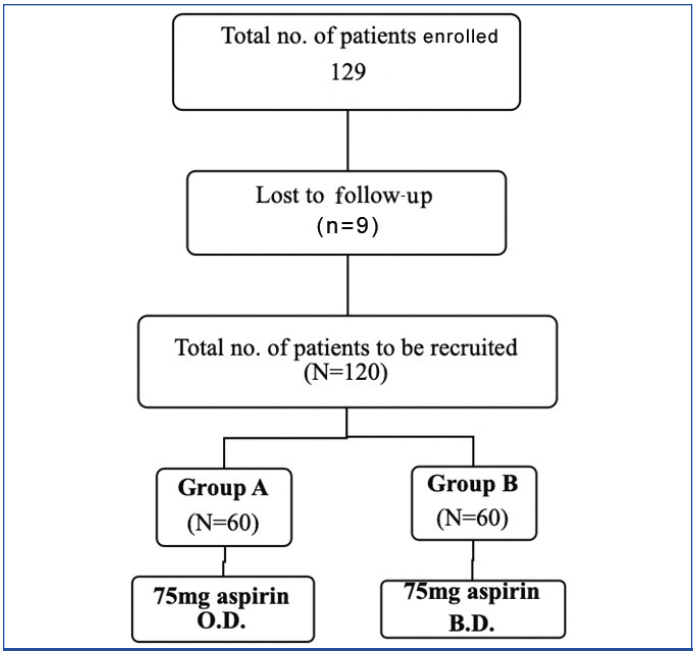
Data was analysed using Microsoft excel 2017 and OpenEpi (www.openepi.com) [13]. Repeated measure one-way Analysis of Variance (ANOVA) was used to assess efficacy of 75 mg aspirin once a day vs twice a day dosing. All p-values were two-sided with statistical significance evaluated at 0.05 α level.

RESULTS

A total of 129 subjects with T2DM were enrolled in the study, of which nine were lost to follow-up. Thus, total number of 120 of them completed the study and were included for analysis [Table/Fig-1].

Both the study groups were comparable as regards to demographic characteristics [Table/Fig-2] and laboratory baseline parameters [Table/Fig-3], except for median Serum Glutamic-oxaloacetic Transaminase (SGOT), median serum cholesterol and percentage platelet aggregability that differed significantly in the two groups. The percentage platelet aggregability was higher in group B as compared to that of group A, even at month 3, but not at month 6 of the study (p-value=0.61). Interestingly at month 9, it was significantly lower in group B. Percentage platelet aggregability at three, six and nine months, when compared with that at baseline; was statistically lower (p-value <0.0001), in group B. This was not seen in group A (p-value=0.36) [Table/Fig-4].

The baseline values of "change in percentage platelet" when compared with that of three monthly each, there was significant decrease of the values over three months in group A and group B (p-value <0.0001).



[Table/Fig-1]: Flow diagram.

Characteristic	Overall N=120	Group A 75 mg OD (n=60)	Group B 75 mg BD (n=60)	p-value (Fisher's-Exact test)
Male	69 (57.5%)	37 (61.7%)	32 (53.3%)	0.46
Female	51 (42.5%)	23 (38.3%)	28 (46.7%)	0.46
Age (years) Median (IQR)	62 (57-66)	62.5 (56.5-66)	62 (57-66)	0.85
HbA1c levels	----------	7.55±1.05	7.61±1.19	0.77

[Table/Fig-2]: Demographic distribution.
A p-value <0.05 is considered to be statistically significant

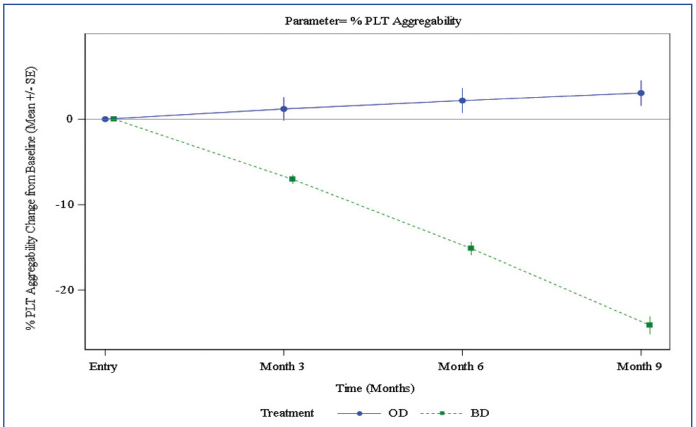
Blood parameters	Mean (range)		p-value (Wilcoxon's Rank Sum test)
	Group A 75 mg OD (n=60)	Group B 75 mg BD (n=60)	
Clotting time	0.16 (0.13-0.18)	0.15 (0.12-0.17)	0.19
Bleeding time	0.13 (0.11-0.15)	0.12 (0.11-0.15)	0.20
****Renal function test**			
Serum sodium (mg/dL)	139.5 (137-142.3)	141 (138-143)	0.11
Serum potassium (meq/L)	4.25 (3.8-4.65)	4.1 (3.7-4.5)	0.33
Serum chlorine (meq/L)	100.5 (98-103)	100 (98-103)	0.77
Serum creatinine (mg/dL)	1.1 (0.8-1.3)	1.15 (0.8-1.3)	>0.95
Blood urea (mg/dL)	20 (12.5-30)	22.5 (15-30)	0.27
Serum uric acid (mg/dL)	5.4 (4.7-6.6)	5.7 (4.85-6.95)	0.43
Liver function test			
SGPT (IU/L)	24.5 (19-33)	22.5 (16-30)	0.15
SGOT (IU/L)	29.5 (23-36)	26 (19.5-30.5)	**0.04**
Serum alkaline phosphatase (U/L)	84 (61-110.5)	87 (67-106.5)	0.68
Serum total protein (mg/dL)	6.85 (6.5-7.3)	6.95 (6.4-7.7)	0.35
Serum albumin (mg/dL)	4.3 (4-4.6)	4.2 (3.8-4.55)	0.25
Lipid profile			
Serum cholesterol (mg/dL)	184.5 (163-198)	196 (178.5-216)	**0.02**
Serum triglyceride (mg/dL)	119.5 (102-137)	114.5 (94.5-135.5)	0.54
Serum high density lipoprotein (mg/dL)	45.5 (35-53)	46.5 (37-54)	0.41
Serum low density lipoprotein (mg/dL)	117 (98.5-136.5)	112 (99-125)	0.21

[Table/Fig-3]: Baseline parameters.
SGPT (IU/L): Serum glutamate pyruvate transaminase; SGOT (IU/L): Serum glutamic oxaloacetic transaminase; A p-value <0.05 is considered to be statistically significant

Negative change in percentage platelet aggregability indicated there is increase in inhibition of platelet aggregation from baseline at three monthly visits in Group B [Table/Fig-5,6].

Months	Group A 75 OD (n=60)	Group B 75 BD (n=60)	p-value (Repeated measure ANOVA)
0	35.15±8.70	53.41±9.42	<0.00001
3	36.34±10.28	46.38±9.87	<0.00001
6	37.33±1.96	38.28±28	0.61
9	38.20±10.36	29.30±10.39	<0.00001
p-value	0.36	<0.0001	

[Table/Fig-4]: Percentage platelet aggregability.
A p-value <0.01 is considered to be highly statistically significant



[Table/Fig-5]: Three monthly change in percentage platelet aggregability from baseline upto nine months.

Months	Group A 75 OD (n=60)	Group B 75 BD (n=60)	p-value (Repeated measure ANOVA)
0-3	1.19±10.43	-7.04±1.16	<0.00001
0-6	2.18±11.07	-15.13±5.91	<0.00001
0-9	3.05±11.38	-24.11±7.98	<0.00001

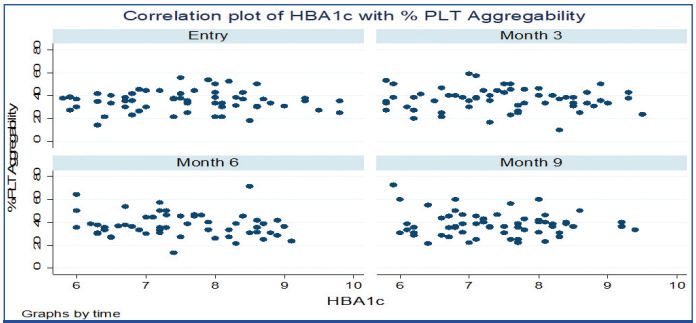
[Table/Fig-6]: Change in percentage platelet aggregability.
A p-value <0.01 is considered to be highly statistically significant

Both the groups were comparable as regards to fasting and post-prandial blood glucose levels. These readings had no statistically significant difference at the subsequent three monthly readings, with the respective baseline values within the groups. HbA1c Levels were comparable in two groups and did not show statistically significant difference [Table/Fig-7].

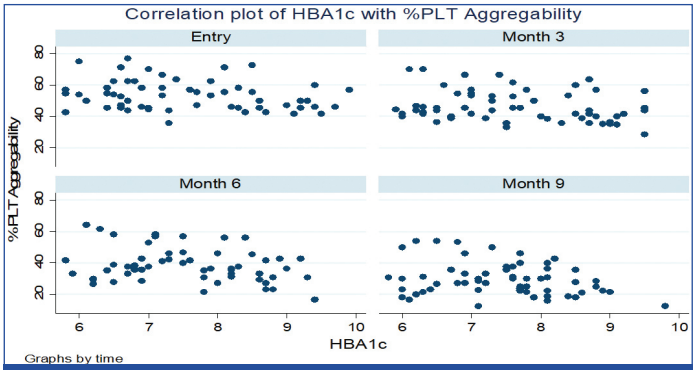
Visit	Parameters	Group A 75 OD (n=60)	Group B 75 BD (n=60)	p-value (Wilcoxon's Rank Sum test)
0 months	FPGL	129.94±22.21	131.28±22.07	0.79
	PPGL	210.23±41.78	210.67±47.38	0.95
	HbA1c	7.55±1.05	7.61±1.19	0.77
3 months	FPGL	129.32±20.81	130±19.64	0.87
	PPGL	207.12±41.25	210.62±42.37	0.65
	HbA1c	7.49±1.02	7.62±1.10	0.49
6 months	FPGL	130.53±15.57	128.30±17.13	0.46
	PPGL	205.17±36.75	210.42±37.92	0.44
	HbA1c	7.41±0.91	7.58±0.96	0.32
9 months	FPGL	126.70±16.47	124.81±16.09	0.53
	PPGL	197.87±33.78	202.58±34.84	0.45
	HbA1c	7.37±0.85	7.45±0.91	0.60

[Table/Fig-7]: Blood glucose levels (mg/dL).
FPGL: Fasting plasma glucose level; PPGL: Postprandial; glucose level; HbA1c: Glycated haemoglobin; A p-value <0.05 is considered to be statistically significant

There was no correlation between HbA1c and percentage platelet aggregability for entire the study duration in both the groups [Table/Fig-8-10]. Similarly, no correlation between serum cholesterol and percentage platelet aggregability was observed in the individual groups [Table/Fig-11].



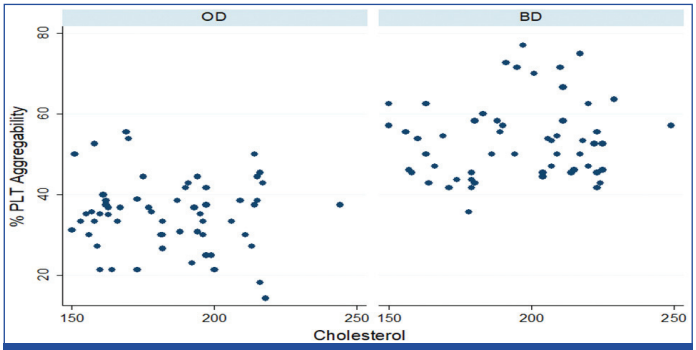
[Table/Fig-8]: Correlation between HbA1c and percentage platelet aggregability among group A.



[Table/Fig-9]: Correlation between HbA1c and percentage platelet aggregability among group B.

Months	Group A 75 OD (n=60)	Group B 75 BD (n=60)
Baseline	0.005	-0.23
3	-0.09	-0.22
6	-0.11	-0.27
9	-0.12	-0.26

[Table/Fig-10]: Coefficient correlation (r) of percentage platelet aggregability and HbA1c.



[Table/Fig-11]: Correlation between percentage platelet aggregability and serum cholesterol at baseline.

DISCUSSION

The aim of the present study was to find the potential benefit of BID dosing of 75 mg aspirin in effectively inhibiting the newly generated platelets and increased platelet turnover in T2DM patients. As per the study observations, total dose of aspirin 150 mg/day at baseline had significantly lower values of platelet aggregability as that compared to 75 mg/day. The main finding of the present study was that splitting a dose of 150 mg/day aspirin as 75 mg twice a day is more effective in inhibiting the platelet aggregability in T2DM patients.

Elevated levels of serum cholesterol in diabetic patients enhance platelet activation and platelet aggregability [14]. Although serum cholesterol median values were significantly higher in Group B of the present study, yet they were within standard normal cut-off for cholesterol and therefore, may not influence platelet aggregability at baseline. Further a statistical analysis was done, that, confirmed that there was no correlation between serum cholesterol and platelet aggregation values at baseline in both groups in the present study.

Additionally variability in antiplatelet response to aspirin has been documented in research previously and have attributed it to various patient related factors of which non compliance to aspirin therapy plays an important role [15]. The patients treated with aspirin 75 mg twice a day demonstrated a significantly effective and progressive inhibition of platelet aggregation estimated at three monthly intervals starting from the third month till the ninth month, when compared with baseline values. This phenomenon was not seen with 75 mg once a day dosing.

This is supported by fact that thromboxane A2 (TXA2) is the major arachidonic acid product generated by platelets and maximum inhibition of this phenomenon by aspirin occurs in portal circulation. The newly generated platelets are able to synthesise TXA2, and once this TXA2 reaches a certain concentration, it triggers aggregation of all platelets including the older acetylated ones (which remain sensitive to TXA2 even, if they do not produce it) [16].

Percentage of non acetylated platelets necessary to start a significant global response to arachidonic acid is estimated at about 20-30% platelet turnover. This recovery could be reached in 24 hours in patients whose platelet turnover is accelerated as for patients with DM. Therefore, a second dose of aspirin 75 mg may inhibit the newly generated platelets [17]. In particular, lower than expected inhibition of platelet-derived TXA2 has been reported in approximately 1/3rd of T2DM patients on a once daily, low-dose aspirin regimen compared to that in non-DM patients [18].

Several studies have concluded that the antiplatelet dose of aspirin (150-200 mg/day) when spilt as twice daily dose as compared to single total dose shows benefit in terms of decreasing the platelet reactivity. These studies were done in patients in the western diabetic population and they had smaller sample size, as compared to present study [19,20].

A crossover trial by Spectre G et al., but with smaller effect sizes compared aspirin 75 mg once daily, 75 mg twice daily in 25 people with T2DM and macrovascular or microvascular complications, and demonstrated that, aspirin 75 mg twice daily significantly reduced whole blood platelet aggregation compared with once daily [21]. Di Minno G et al., first suggested that entry of new platelets into circulation can allow thromboxane formation as early as four hours after aspirin ingestion [22]. Plasma level peak is about 30 to 45 minutes after aspirin ingestion, and aspirin half-life in plasma is 15 to 20 minutes [23]. The time aspirin is present within plasma to acetlytate platelets in blood is very less, around two hours. In normal conditions, approximately 10-15% of circulating platelets are replaced daily, and near normal aggregation due to non acetylated platelet replacement has been found 48 to 72 hours after last aspirin intake [24].

Studies suggest that patients with suboptimal or ineffective response to aspirin may benefit from this split-dosing regimen (e.g. twice- versus once-daily) as a result of greater platelet inhibition [25]. Patients with T2DM have specific abnormalities in platelet function. Thus, this group of patients are suitable population to assess if modified dosing regimens of aspirin may impact pharmacodynamic response [26,27]. Hyperglycaemia, independently enhances platelet activation despite aspirin treatment [28]. The present study also explored the blood glucose variation at three monthly intervals from baseline and its effect on platelet aggregability; but no statistical significant variation found. Similarly, there was no correlation between HbA1c levels and percentage platelet aggregability for entire study population as well as individual groups at all time. This may be attributed to sample size effect or control diabetes in the study population. In a similar study by Neergaard-Petersen S et al., found that levels of HbA1c did not correlate with platelet aggregation and platelet turnover in coronary artery disease patients with known T2DM [29].

The ongoing Aspirin Twice a Day in Patients with Diabetes and Acute Coronary Syndrome (ANDAMAN) trial is comparing a standard 100 mg vs BD regimen (100 mg in morning and 100 mg in evening) of low dose aspirin in treatment of DM patients with ACS, and will provide the required clinical evidence for the efficacy and safety of this approach [30].

Limitation(s)

Patients already receiving 150 mg/day were allocated to 75 mg twice a day group and split dosing was done. A third group of 150 mg/day as single daily dose would have added more value in terms of minimising bias due to dose dependent effect on platelet aggregation. Certain baseline parameters were not comparable, but, did not show statistically significant impact on study parameters. Colorimetric method for determination of platelet aggregability has its own limitations.

CONCLUSION(S)

Despite recent progress, there is still an unmet therapeutic need for primary prevention of serious vascular events in DM. The present study concludes that, 75 mg OD as a strategy for secondary cardiovascular disease prevention is advocated but not adequate in T2DM patients. Addressing to the additional needs of diabetic patients, as regards to platelet turnover, it is advisable to use a higher dose of aspirin i.e.150 mg once a day in these patients. The use of 150 mg/day dose is more effective, if splitted, into 75 mg twice a day. The study showed a statistically significant effect on inhibition of platelet aggregation and appropriate utilisation of the drug by the body. Further, well-planned randomised control trials are needed to assess clinical efficacy in order to validate this approach for prevention of cardiovascular events and cardiovascular mortality in clinical practice.

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