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Effect of Dividing Low Dose Aspirin on Platelet Reactivity and the Correlation with Patient-related Factors

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ABSTRACT

Aims: The optimal dosing regimen of aspirin for primary and secondary prevention of ischemic events is a topic of debate. Therefore, the aim of this study is to evaluate whether administering 100 mg aspirin in two divided dose, rather than a single daily dose, is associated with a greater degree of inhibition of platelet aggregation.

Methods : Forty-eight patients compliant to once daily 100 mg of aspirin were recruited into this interventional before-after study. Patients were instructed to split the 100 mg aspirin tablet into two halves using a pill splitter and then to administer half tablet of aspirin twice daily for a duration of one to three months. Assessment of platelet aggregation was performed using Multiplate analyzer system with arachidonic acid as an agonist. Furthermore, assessment of the factors associated with platelet aggregation response was also conducted.

Results : There was no statistically significant difference in platelet aggregation parameters- including the area under the aggregation curve AUC- between once daily 100 mg and twice daily 50 mg aspirin regimens **(**20.3 ±11.3 vs. 20.7±15.6, *p*-value 0.626).There was no significant correlation between the AUC of both dosing regimens and many patients-related factors.

Conclusion : The administration of 50 mg twice daily aspirin regimen was not associated with a greater degree of platelets inhibition compared to the once daily 100 mg regimen.

Keywords: Aspirin regimen, Platelets, Divided doses, Twice daily, Multiplate, Whole blood aggregometry.

INTRODUCTION

Aspirin use is recommended in the management of cardiovascular diseases to prevent future thrombotic complications.[1]However, the extent of benefit from aspirin use is variable among patients. The question is therefore, whether or not patients who suffer events, despite using aspirin, do so because of insufficient antiplatelet effect of aspirin. Aspirin prevents about 25% only of coronary events and ischemic strokes when used for secondary prevention.[2] Much of this can be accounted for by the heterogeneous etiology of these diseases, especially in the case of ischemic stroke, where the mechanisms of stroke may be non-atherothromboembolic and non-platelet mediated.[3] However, it is estimated that between 5 to 60% of patients on aspirin therapy for secondary prevention do not respond appropriately to aspirin, a heterogeneous phenomenon which has come to be known as aspirin resistance. [4] Therefore, in this study we studied the approach of splitting the 100 mg daily dose into two divided doses as a way of decreasing aspirin resistance in patients with cardiovascular risk factors.

The use of antiplatelet agents is recommended in the management of a wide range of cardiovascular diseases.[2] In primary prevention for patients with no previous cardiovascular disease events, aspirin decreases the risk

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of nonfatal myocardial infarction (22% reduction) and likely results in small decreases in overall mortality (6% reduction),[5] therefore it might be recommended for patients at high risk of thrombotic events, such as patients with multiple risk factors for coronary artery disease (CAD) or diabetes.[6]

In secondary prevention, antiplatelet agents, including aspirin, are recommended to be given either acutely in patients with acute coronary syndromes (ACSs), following per-cutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), or chronically in patients with stable CAD, in patients with a history of transient ischemic attacks (TIAs) or strokes and patients with peripheral arterial disease (PAD)[6]. The benefit of aspirin therapy in each of these pathologies is related to the underlying thrombotic risk, and is usually greatest in high-risk individuals and lowest in individuals with no overt atherosclerotic disease.

The term "aspirin resistance" has been used to describe the occurrence of occlusive cardiovascular events despite regular intake of this agent at the recommended dose. [7-11]The optimal daily dose of aspirin required for primary and secondary prevention of ischemic events is a topic of debate. In fact, the need for different dosing regimens customized according to the thrombotic risk of the patient has been suggested before.[7] The suggested approaches in literature to overcome resistance include increasing the total daily dose of aspirin, [12] using a non-enteric extended-release formulation of aspirin, [13] adding another antiplatelet agent, [12,14] or adding omega-3 fatty acids. [15-17]

Evidence suggests that increasing the frequency of aspirin administration reduces platelet reactivity, while using 'high dose' aspirin (>100 mg daily) increases the bleeding risk without enhancing antiplatelet efficacy.[18,19] Therefore, in this study we studied the approach of splitting the 100 mg daily dose into two divided doses.

Till now, there is no large-scale outcome trials that have examined twice-daily 50 mg dosing to assess cardiovascular disease (CVD) prevention or bleeding risks. Most of literature examined doubling the dose of aspirin by twice daily administration. [19-22] However, only small-scale studies have compared the administration of the same total daily dose of aspirin as single daily dose or as two divided doses, and have suggested that splitting the total daily dose had no significant difference on platelet reactivity compared to the single daily administration. [19,20]

In the current study, we aimed to investigate the effect of splitting the total daily dose of aspirin into two halves (once daily 100 mg aspirin vs twice daily 50 mg aspirin) on platelet aggregation using aggregometry by electrical impedance method. This method is different from the methods used previously. [18-20] Furthermore, assessment of the factors associated with platelet aggregation response was also conducted.

METHODS

Study design and patient recruitment

This interventional study employed a before-after design to assess platelet aggregation prior to and after switching patients into twice daily 50 mg aspirin regimen. This study was conducted in Amman, Jordan. Patients were recruited through the cardiology department at Jordan University hospital over the period from June 2013 to April 2015. Patients were considered eligible if they were compliant to once daily 100 mg aspirin regimen for at least one month, and provided a written informed consent. Patients compliance to aspirin treatment was evaluated using an 8-item validated Arabic translated Morisky questionnaire. The participant was considered compliant if his/her score was ≤ 2.

Participants were excluded if they had blood disorders; oral anticoagulation therapy with a coumadin derivative; recent antiplatelet treatment (< 30 days) with a glycoprotein IIb/IIIa antagonist, history of gastrointestinal bleeding within the last 6 months; history of cerebro-vascular accident within the last 3

months; active bleeding or hemodynamic instability; any active malignancy; severe renal insufficiency (creatinine > 4 mg/ dL), recent surgery (within one month) including central nervous system (CNS) surgeries like lumbar puncture; pregnant women; and use of non-steroidal anti-inflammatory drugs in the past 10 days; platelet count <100 x 10^6/mL , baseline ALT >2.5 times the upper limit of normal, aspirin non-compliance (Morisky score >2).

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board at the Jordan University hospital.

Patient Data collection

Patient demographic data and relevant characteristics such as weight, past medical history, medications and laboratory data were obtained from medical records and through patient interview.

Intervention

Eligible consenting subjects were instructed to split the 100 mg aspirin tablet into two halves using the provided pill splitter, and to take half tablet twice daily for a duration of one to three months.

Blood collection

Blood samples were collected from eligible consenting subjects at baseline and at the end of the intervention period.Post-switching blood samples were collected from participants who were complaint to the twice daily 50 mg aspirin regimen. Participants' compliance was assessed as described under study design.

On the day of blood collection, patients were instructed to withhold aspirin until blood sample was taken. Blood was collected into a hirudin-anticoagulant containing test tube. Platelet aggregation response was then measured within 3 hours of blood collection.

Platelet aggregation assay

Platelet aggregation response was measured using whole blood aggregometry that measures platelet aggregation within whole blood by electrical impedance.

Arachidonic acid was the agonist used in this assay. A multichannel (5 channels) impedance-based analyzer (Multiplate system: VerumDiagnostica GmbH, Munich, Germany) was used in this study. The cut-off point for aspirin response was an AUC of 40 U. Patients were considered responders to aspirin at values ≤40 U; otherwise, patients were considered aspirin non-responders according to manufacturer recommendations. High bleeding risk in PCI was assessed using an AUC cut off of less than 20 U as per manufacturer.

Three parameters were calculated: The area under the aggregation curve (AUC) which is the best parameter to express the overall platelet activity. The other two more parameters were the aggregation which is the height of the aggregation curve and the velocity of aggregation which is the maximum slope of the curve.

Statistical analysis

Data analysis was carried out using the statistical package for social studies SPSS version 23 (Inc, Chicago, IL). Continuous variables are presented as mean values ± SD, and categorical variables are expressed as percentages and frequencies. Kolmogorov–Smirnov test was used to test for normality. Parametric tests like independent sample t test were used if their conditions were fulfilled (normal or at least symmetrical distribution and equality of variance). Independent sample t test was used to compare means between groups (AUC of males and females for once daily dose aspirin or twice daily dose aspirin). Nonparametric tests were used if the conditions required for parametric tests were violated. Related sample Wilcoxon signed rank test (AUC of both once daily and twice daily regimens) was used to compare means of before and after intervention groups. Pearson's chi square test and Fisher exact test were used to examine the significance of association between two categorical parameters (such as aspirin resistance and dosage regimen of once or twice daily dosing of aspirin). *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient demographics

A hundred and twenty-six patients met the inclusion criteria at the first visit and were recruited to assess platelet aggregation response to the once daily 100 mg aspirin regimen. However, only 48 patients complied with the study protocol and were compliant with the twice daily 50 mg aspirin regimen through the study period, and from whom blood samples were collected. Dropout reasons were mainly attributed to non-compliance with the twice daily dosing regimen, failure to attend hospital appointment for blood sample withdrawal, emergence of new exclusion criteria that were not identified at recruitment (for example performing surgery within one month including CNS surgeries like lumbar puncture; use of non-steroidal anti-inflammatory drugs in the past 10 days and aspirin non-compliance (Morisky score >2)). Patients' demographics and clinical parameters are illustrated in Table 1.

Table 1. Baseline demographic and clinical characteristics (N=48)

Age ±SD	60.5 ±8.4
Male, n (%)	28 (58.3)
BMI, kg/m^2 ±SD	27.6 ±3.3
Risk factors, n (%)*	
Smoking	12 (25.0)
Hypertension	32 (66.7)
Diabetes	20 (41.7)
Medical history n (%)*	
Prior MI	17 (35.4)
Prior CABG	4 (8.3)
Prior stroke	1 (2.1)
Medications n (%)*	
ACE inhibitors	15 (31.3)
Beta blockers	43 (89.6)
Statins	37 (77.1)
Insulin	4 (8.3)
Clopidogrel	7 (14.6)
Proton pump inhibitors	19 (39.6)
Laboratory data	
Platelets ($1000/ mm^3$) ±SD	282 ± 92
Hematocrit, %, ±SD	39.5 ± 4.4
HbA1c ,%, ± SD	6.4 ±1.3
Creatinine, mg/dL , ±SD	0.8 ± 0.3

**valid percent*

Table 2. Descriptive statistics of platelet aggregation in the whole study population at recruitment (before conversion to twice daily dosing of 50 mg) (N=126)

	100 mg once daily
AUC ± SD	26.1 ± 21.3
Velocity ± SD	8.7 ± 6.9
Aspirin resistance* [N (%)]	18 (14.5)
High bleeding risk in PCI¥ [N (%)]	60 (48.4)

*Patients with AUC values > 40 were considered aspirin resistant according to manufacturer recommendations.

¥ Defined as AUC< 20 unit as per manufacturer

Platelet aggregation response in the whole study population

Platelet aggregation parameters in the blood samples in the whole study population are presented in table 2. There was no significant difference in platelet aggregation parameters in the blood samples before and after switching into the twice daily 50 mg aspirin regimen. The average AUC of platelet aggregation of once daily regimen was 20.3 vs. 20.7 of twice daily 50mg regimen (p value 0.641). Neither the rate of aspirin resistance nor the bleeding risk was different between the two regimens of aspirin. Platelet aggregation parameters in the blood samples before and after switching into the twice daily 50 mg aspirin regimen are presented in Table 3.

Platelet aggregation response in patients with diabetes

Patients with diabetes accounted for 40% of the study population. Platelets in patients with diabetes have altered pharmacodynamics properties. [20, 21] However, our results showed that there was no significant difference in platelet aggregation parameters between the two regimens. The median AUC of the 100 mg once daily regimen was 20, while the median AUC of 50 mg twice-daily regimen was 13.0 (p value 0.314, Related Samples Wilcoxon Signed Rank Test).

Factors associated with platelet aggregation response

There was no significant correlation between the AUC for any of the tested regimens and the age, BMI, hemoglobin, serum creatinine or the presence of diabetes (Table 4).

Table 3. Descriptive statistics of platelet aggregation in the once daily 100 mg aspirin regimen samples and in the twice daily 50 mg aspirin regimen samples (N=48)

	100 mg once	50 mg twice	*P*-value
AUC [median (25^{th}-75^{th} percentile)]	18 (13-24)	18 (10-26)	0.641€
Velocity [median ((25^{th}-75^{th} percentile)]	5.1 (4.5-6.6)	5.5 (4.0-8.2)	0.285 €
Aspirin resistance [N (%)]	3 (6.3%)	6 (12.6%)	0.486 £
High bleeding risk in PCI¥ [N (%)]	25 (52.1%)	28 (58.3%)	0.538 #

€ related sample Wilcoxon signed rank test, £ Fisher exact test, # Pearson Chi square, ¥ Defined as AUC< 20 unit as per manufacturer

Table 4. Factors associated with platelet aggregation response

	AUC once daily	*P* value*	AUC twice daily	*P* value *
Gender				
Males	21.4±11.6	0.149	21.8±12.7	0.170
Females	18.6±10.9		19.3±19.3	
Diabetes				
Yes	17.6 ±5.6	0.426	18.9±18.3	0.180
No	22.2±13.8		22.0±13.5	
Smoking				
Smoker	21.2±12.5	0.575	22.3±17.4	0.446
Non-smoker	17.3±6.3		15.8±6.8	
Prior MI				
Yes	16.2±5.8	0.103	13.2±8.9	0.005
No	22.5±13		24.8±17	
ACE inhibitors				
Yes	23.9±13.4	0.123	21.7±13.9	0.470
No	18.5±10.3		19.8±17.1	
Statins				
Yes	19.3±9.8	0.625	18.6±15.2	0.123
No	24.4±17.3		27.8±17.7	
Insulin				
Yes	30.3±17.5	0.139	9±6.8	0.069
No	19.3±10.7		21.5±16.2	
Clopidogrel				
Yes	18.3±9.6	0.725	26.3±29	0.988
No	20.7±12		19.3±12.6	
Proton pump inhibitors				
Yes	19.7±8.1	0.685	16.5±11.1	0.251
No	20.7±13.6		23.0±18.3	

*independent sample t-test

DISCUSSION

This study was the first to investigate the effect of 50 mg twice daily aspirin on platelet reactivity and aggregation. Furthermore, the allocation of treatment amongpatients was concealed as same patients were used for both doses.

Till now, there is no large-scale outcome trials that have examined twice-daily 50 mg dosing to assess cardiovascular disease prevention or bleeding risks. Most of literature examined doubling the dose of aspirin by twice daily administration. [16-19] However, only small-scale studies have compared the administration of the same total daily dose of aspirin as single daily dose or as two divided doses, and have suggested that splitting the total daily dose had no significant difference on platelet reactivity compared to the single daily administration. [19,20]

Aspirin use is recommended in the management of cardiovascular diseases to prevent future thrombotic complications.[1]However, the extent of benefit from aspirin use is variable among patients. The question is therefore, whether or not patients who suffer events, despite using aspirin, do so because of insufficient antiplatelet effect of aspirin. Aspirin prevents about 25%

only of coronary events and ischemic strokes when used for secondary prevention.[2] Much of this can be accounted for by the heterogeneous etiology of these diseases, especially in the case of ischemic stroke, where the mechanisms of stroke may be non-atherothromboembolic and non-platelet mediated.[3] However, it is estimated that between 5 to 60% of may have aspirin resistance. [4] Therefore, in this study we studied the approach of splitting the 100 mg daily dose into two divided dose as a way of decreasing aspirin resistance in patients with cardiovascular risk factors.

Comparative studies indicate that assessing platelet aggregation within whole blood by electrical impedance method gives results similar to those obtained via classical turbidimetricaggregometry, and outperformsturbidometric methods when monitoring anti-platelet therapy. [25, 26]This method is proving to be useful for diagnosing platelet defects and monitoringaspirinandclopidogrel, and is in widespread use in Europe. [27]

The results of our study showed that the rate of aspirin resistance in the group of once daily 100 mg aspirin was found to be 6.3% while in the group of twice daily 50 mg aspirin, it was found to be 12.6%. However, this difference was not statistically significant, most probably due to the small sample size. In a previous study conducted in Jordan using the same method for platelet aggregation assessment (Multiplate analyzer using arachidonic acid), the rate of aspirin resistance was found to be 18.7% in a sample of 418 adult patients who were taking aspirin.[28]

Our study demonstrated that in patients compliant to the tested regimens, the two tested regimens had similar degree of inhibition on platelet reactivity as shown in AUC and velocity values. These results are in parallel with the results of previous reports. [18, 19] The study of Capodanno et al. has not shown a difference in platelet reactivity between aspirin 81 mg twice and 162 mg once daily or 162 mg twice and 325 mg once daily.[19]In addition, Bethel et al [18] showed that platelet reactivity was more effectively reduced with aspirin 100 mg twice daily vs. 100 mg once daily, but not vs. 200 mg once daily. Aspirin 200 mg once daily did not differ from 100 mg once daily. Despite the fact that 100 mg twice daily was more effective than 100 mg once daily, the higher dose is associated with an increased risk of bleeding. Noteworthy, these reports have used different methods for the assessment of platelet reactivity other than Multiplate analyzer method employed in this study. Aspirin-induced platelet inhibition depends largely on the method used for the assessment of platelet reactivity as has been shown before by Rocca *et a*l [20] and Capodanno*et al* [2011].[19] Rocca *et al.* [2012] investigated the response to aspirin in 100 patients with Type 2 diabetes with (46%) or without (64%) CVD. Rocca *et al*. showed that when compared with 100 mg once daily ,100 mg twice daily, or 200 mg once daily, only 100 mg twice-daily aspirin dosing completely reversed the abnormally fast recovery of thromboxane B2 (TXB2). However, no difference was seen between treatment groups in the inhibition of platelet aggregation measured by the VerifyNow ASA assay. [20] Similarly, in the study of Capodanno *et al.* [19] the effect of twice daily aspirin was assessed in patients with diabetes and stable CAD. When aspirin was administered as 81 mg once daily, there was no significant effect on platelet reactivity by increasing the once-daily dosing to 162 mg or 325 mg using aspirin-sensitive assays (collagen-induced aggregation and VerifyNow-Aspirin assays). However, twice daily administration (81 mg once daily vs 81 mg twice daily and 81 mg once daily vs 162 mg twice daily) was associated with a significant reduction in platelet reactivity as assessed by collagen-induced aggregation and VerifyNow-Aspirin assay. However, such difference between the above regimens was not reflected on adenosine diphosphate–induced aggregation.[19] Therefore, the difference in platelet reactivity is dependent on the test used to detect platelet reactivity.

Previous studies have demonstrated associations between age, poor glycemic control, hyper-lipidemia and

smoking with increased platelet turnover.[29] In Jordan, aspirin resistance was associated with female gender and diabetes.[28]

In this study, however, platelet reactivity in the samples of the tested regimen was not significantly associated with patient gender, the presence of diabetes, smoking or the prescription of certain medications including statins, angiotensin converting enzyme (ACE) inhibitors, clopidogrel or proton pump inhibitors (PPIs).

A subgroup of the study population was patients with diabetes (n=20, 41.7%). Aspirin resistance can occur in patients with/without diabetes.[30]However, patients with diabetes are at increased risk of recurrent athero-thrombotic events despite using the recommended aspirin regimen. This might be attributed to the enhanced platelet reactivity and the reduced response to aspirin in patients with diabetes compared to those without diabetes. [23, 24] Possible mechanisms for aspirin resistance in diabetes include the following: increased platelet reactivity in patients with diabetes by decreased endothelial nitric oxide production, increased platelet turnover, dyslipidemia- induced alteration of platelet structure and an increase in intra-platelet calcium concentration.[30] Another possible mechanism is that diabetes is associated with an increased level and activity of prothrombotic clotting factors, associated with a tight clot structure and impairment in fibrinolysis. This effect is attributed to insulin resistance, dyslipidemia and low-grade inflammation. One more possible mechanism for aspirin resistance may be related to hyperglycemia that would interfere by glycation of platelets and clotting factor proteins thus inhibiting acetylation by aspirin.[30]

Besides, aspirin has only a 20-minute half-life, therefore the accelerated platelet synthesis-a characteristic feature of platelets in diabetic patients- does not allow newly generated platelets entering the circulation to be sufficiently inhibited by aspirin.[31- 33] Hence, it may be postulated that the administration of the total daily dose of aspirin in two divided doses, rather than a single daily dose, might be an effective strategy to inhibit platelet reactivity in patients with diabetes. However, our results in patients with diabetes were similar to those obtained from the whole study population; the two tested regimen had similar extent of inhibition of platelet reactivity (AUC and velocity). Further studies with bigger sample size are required for conclusive results regarding patients with diabetes.

Study limitations

The present pilot study was conducted in a small sample size, which limited adjustment for multiple comparisons. However, given the precursory nature of our study, adjustment for multiple comparisons was not planned to avoid increasing the risk of type II error (e.g, accepting false-negative results), thereby missing importantpilot information of potential value to be replicated and confirmed in larger-scale studies.

CONCLUSION

The finding of this study suggested that splitting the total daily dose of aspirin into two had no additional benefit on the antiplatelet effect of aspirin. Besides, there was no significant association between platelet reactivity parameters, of both dosing regimens, and patients-related factors, including age, body mass index (BMI), hemoglobin and serum creatinine. Similar results were also obtained for the small subgroup of patients with diabetes in this study.

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تأثير تقسيم الجرعة المنخفضة من الأسبرين على تفاعل الصفائح الدموية وارتباطه بالعوامل المتعلقة بالمريض

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ملخص

أهداف

تعد الجرعة الأمثل للأسبرين للوقاية الأولية والثانوية من الأحداث الإقفارية موضوعاً للنقاش. ولذلك، كان الهدف من هذه الدراسة تقييم ما إذا كان تناول الأسبرين بجرعة 100ملغ على شكل جرعتين مقسمتين، بدلاً من جرعة يومية واحدة، يرتبط بدرجة أكبر من تثبيط تكدس الصفائح الدموية.

الطريقة

ضمت هذه الدراسة ثمانية وأربعين مريضاًكانوا يأخذون الأسبرين بجرعة 100 ملغ مرة واحدة يومياً وخلال الدراسة، تم توجيه المرضى لتقسيم قرص الأسبرين 100 ملغ إلى نصفين باستخدام أداة التقسيم وتناول نصف قرص من الأسبرين مرتين يومياً لمدة تتراوح من شهر إلى ثلاثة أشهر. تم إجراء تقييم تكدس الصفائح باستخدام حمض الأراكيدونيك كمحفز باستخدام جهاز تحليل Multiplate.

النتائج

لم تكن هناك فروق ذات دلالة إحصائية في معالمتكدس الصفائح الدموية بما في ذلك المساحة تحت منحنى تكدس الصفائح الدموية لكل من جرعة الاسبرين بمقدار 100 ملغ مرة يومياً و50 ملغ مرتين يومياً. القيمة الاحتمالية 0.625 (20.3 ±11.3 مقابل 20.7±15.6) كما لم يكن هناك ارتباط ذو دلالة إحصائية بين كل من الجرعتين المستخدمتين في الدراسة والعديد من العوامل المتعلقة بالمرضى.

الاستنتاج

لم يرتبط الأسبرين بجرعة 50 ملغ مرتين يومياً مع درجة أكبر من تثبيط الصفائح الدموية مقارنة مع جرعة 100 ملغ مرة واحدة يومياً.

الكلمات الدالة:نظام الأسبرين، الصفائح الدموية، الجرعات المقسمة، مرتين في اليوم، قياس تكدس الدم الكلي.

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