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Original Article

High Risk of Cardiovascular Events in Patients, Biosynthesis of Aspirin-Resistant Thromboxane and the Risk of Stroke, Myocardial Infarction or Death

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ABSTRACT

Objective: In a higher-risk group, we investigated if aspirin resistance, which is defined as inability to reduce production of thromboxane, enhanced the risk for cardiovascular disease. **Methods:** The Cardiac Outcome Preventive Assessment Study collected baseline urine samples from 5000 patients. A level of urinary 11-dehydro-thromboxane B2 was measured, which is a marker of within vitro cell generation of thromboxane, in 400 cured patients with aspirin having a cardiovascular death, stroke and infarction, stroke during a 5-year follow-up and in 400 age - and matching sex control subjects, which did not have an event, using a nested case-control design. **Result:** After accounting for baseline differences, the risks of infarction, strokes, or cardiac mortality rose with every fourth of 11-dihydro-thromboxane B2, with individuals in the top fourth section having a 1.9-fold greater threat than those from the lower portion ("OR, 1.9; 95% CI, 1.3 to 2.8; *p=0.009*). The upper quartile showed a 2-fold increased myocardial infarction risk ("OR, 2.1; 95% CI, 1.3 to 3.5; *p=0.07*) and a 3.6-fold elevated risk of cardiac death ("OR, 3.6; 95% CI, 1.78to 7.5; *p=0.01*) than the lower quartile. **Conclusions:** the 11-dehydro thromboxane B2 level in urine, better determine the risk of cardiovascular events or cardiovascular death in aspirin-treated patients. These findings also depicts that patients with elevated urine 11-dehydro thromboxane B2 concentrations are more impervious to aspirin, and could profit from greater antiplatelet medications or therapies that even more efficiently stop thromboxane generation in vivo or activities.

INTRODUCTION

In a broad population of therapeutic with arterial vascular disease, the threat events of cardiovascular are decreased by 25%, by using aspirin [1]. But, although 10 to 20% of patients who are suffering from venous thromboembolism are treated with repeated vascular episodes of aspirin, during long-term sequel, its effectiveness is limited [2]. Aspirin prevents thrombosis by irreversible acetylating platelets cyclooxygenase1 [3], which inhibits the thromboxane A2 production. Although it was also depicted that aspirin have other less defined functions which in result effects the platelet functionality, but their role to aspirin's antithrombotic effect is unknown. The poor efficacy of aspirin could be due to several factors [4]. To begin with, it is widely known because platelets can be triggered by mechanisms that are unaffected by aspirin. Secondly, it has been proposed that in some cases, greater dosages of aspirin (75–325 mg/d) could be necessary to get the optimum antithrombotic benefit of aspirin [5]. On the other hand, aspirin which is present in low-dose, stop the activity of platelet cyclooxygenase-1 by 95% [6] and having proof that the antithrombotic efficacy of this medicine is depended upon dosage [6, 7]. Third, certain patients might

have the ability to produce thromboxane A2, in spite of receiving standard aspirin dosages and hence fail to improve from aspirin therapy [8]. This third mechanism's clinical significance is unknown. Aspirin resistance has been labeled as all three probable reasons for aspirin failure. The word used by us, in order to depict the third putative process in this investigation: insufficient thromboxane suppression of production with the typical aspirin dosage. The 11-dehydro thromboxane B2 metabolite, which is a stable thromboxane A2 metabolite, present in urine with different concentrations is also measured, which can be recycled further to calculated the amount of thromboxane A2 inhibition [9]. As a result, the levels of baseline urine 11-dehydro thromboxane B2 was evaluated in 800 participants that were treated with aspirin, from tertiary care who were at higher risk of cardiovascular events. To see if insufficient inhibition of thromboxane production is related with the higher chances of getting cardiac events or diseases in future.

METHODS

Participants were enrolled in a randomized, placebo-controlled, prospective study of ramipril plus vitamin E for subsequent cardiac preventing sickness. The institutional review committee approved the study at each participating center and gave informed consent in all subjects. Overall, 9652 patients, having a previous record of strokes, diabetes, coronary complications of heart and peripheral neuropathy, as well as at least one additional possible cardiac risk, were categorized randomly into 4 groups: Ramipril titrated to a maximum of 10 mg per day, 400 IU Vit E per day, both, or none. The trial began in 1993 and was prematurely ended in 1999, due to clear proof of ramipril's efficacy. Collection of Urine Samples at the time of randomization, each study participant was requested to produce a first-morning urine sample. The baseline urine samples were provided by 9393 patients (98%) out of a total of 9652 patients. The central laboratory at the city laboratory received 18 sample data (5638) from 139 study participants, which were held at 80°C until evaluation. Health Outcomes Monitoring and Assessment All participants were monitored for 30 days, 60 days, and 6 months till the trial was completed. Health consequences were documented and pharmaceutical use, particularly aspirin, was reported at each follow-up. Infarction, strokes, and mortality from CVD, as described earlier, were the primary outcomes. Cases & Control Subjects were chosen. Only patients who were taking aspirin at the start of the run-in phase (before randomization), at randomization (coinciding with the time of urine collection), and at each follow-up visit were included. Cases were classified such patients which are treated by aspirin who submitted a sufficient baseline urine sample and after the randomization it also had a verified stroke, myocardial infarction, or mortality of cardiovascular. After randomization, Some subjects which are under-control were chosen at random from those patients who gave an urine sample as an acceptable baseline but had no infarction, strokes, / cardiovascular mortality. Analytical Procedures Urine was collected and held at baseline for each case and the control subject was thawed and tested for 11-dehydro-TXB2 concentrations by an available commercially enzyme immunoassay with intraassay & intra-assay coefficients of variation in coefficients of intra-assay is 12.1% and 10%, accordingly. Assessments were carried out by laboratory personnel who were unaware of whether the patient was a case or a control participant. Furthermore, the control specimens and case were tested in a random order, limiting the risk of biases. Statistical Analysis: For cases and controls, we estimated means or percentages for baseline demographic and threat variables. The Student's 2-tailed for means and McNemar 2 test were used to determine the statistical importance of any alterations between cases and controls. The median levels were also estimated, and Wilcoxon's rank-sum test was used to compare values in case and control groups. After splitting the data into sections established by the division of the entire unit, trend tests were conducted to see if there was any link between rising baseline urine 11-dehydro-TXB2 levels and chance of infarction, strokes / cardiac mortality. A separate multivariable regression model was used to investigate the relationship between urinary 11-dehydro-TXB2 concentrations and baseline patient characteristics such as age, gender, heart rate, blood pressure, Mass index, history of vascular disease, conventional vascular risk factors, lipid-lowering therapy, blockers, diuretics, and randomized treatment allocation (ramipril or vitamin E). The intervals of confidence were determined at the 95% level and all probabilities are two-sided.

RESULTS

The general characteristics of the groups of case and control shown in Table 1.

Variables	Case total 400	Control total 400	p-value
Age	68.4 ±8.3	68.5 ±8.3	0.89
Gender female %	78(16.9)	78(16.9)	.
Mass index	28.9 ± 5.2	27.8 ± 4.8	Less than 0.001
Heartbeat rate	67.3 ± 11.4	66.7 ± 11.8	0.5
DBP	77.7 ± 8.9	76.7 ± 8.5	0.09
SBP	148.2 ± 21.7	144.6 ± 19.1	0.03

Coronary history %			
Any other	478(97%)	475 (96%)	0.65
Infraction	375(75.7)	310 (64%)	Less than 0.01
Angina stable	366 (73.80	347 (64.8)	0.19
Angina unstable	195 (38.8)	187 (37.2)	0.76
CABG	187 (37.2)	165 (32.7)	0.26
PCI	88 (18.9)	105 (22.4)	0.07
PVS %	250 (50.3)	174 (36.6)	Less than 0.01
HYPERTENSTION	120 (45.8)	155 (32.7)	Less than 0.01
Diabetic %	160 (33.7)	106 (22.6)	Less than 0.01
Total colterol level	280 (57.3)	311 (64.6)	0.49
Smoking habit	82 (17.7)	58 (12.8)	0.04
Medicine %			
Aspirin	400 (100)	400 (100)	.
Beta blocker	242 (50.5)	236 (49.3)	0.87
Lipid low agent	122 (25.9)	167 (35.1)	0.03
Direutics	74 (16.0)	35 (8.1)	Less than 0.01
Calcium blocker	290 (60.3)	249 (49.9)	0.03
Ramipril	238 (47.6)	285 (57.2)	0.03
Vitamin E	257 (51.5)	263 (53.7)	0.85

Table 1: Study Participants' Baseline Characteristics

"Values are mean±SD or n (%). CABG indicates coronary artery bypass graft surgery; CV, cardiovascular; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and TIA, transient ischemic attack"Patients who had cardiovascular death, stroke or myocardial infarction, stroke, had a mean BMI highly and baseline blood pressure and have a history of smoking, high blood pressure diabetes, infarction, or peripheral vascular disease than those who did not have these events. At the outset, cases were more likely to be given diuretic or blockers of calcium channel, and few likely to be given such drugs which were lipid-lowering or assigned to a therapy of ramipril. The gender and age of the patients and controls were similar as a result of the similarity. The result of myocardial infarction in patients who developed the composite, stroke, or mortality of cardiovascular had significantly greater median and mean of geometric urine quantity at baseline of 11-dehydro-TXB2 than those who did not experience these events, Table 2.

Concentration,11-Dehydro Thromboxane B2 ng/mmol Creatinine			
Result	Case	Control	P- value
CV death, stroke MI or (n=488)			
Geometric mean	25.6	22.6	.02
Median	23.8	22.1	.01
MI (n=388)			
Geometric mean	25.6	21.8	.04
Median	23.9	21.4	.02
Stroke (n=80)			
Geometric mean	26.1	28.5	0.58
Median	22.4	26.8	.51
death in CV (n=255)			
Geometric mean	26.7	21.5	<.01
Medain	25.1	18.8	<.01

Table 2: Concentratios of Urine (11 Dehydro Throboxane B2) In Case Control Group Baseline Myocardial infarction is referred to as MI, while cardiovascular disease is referred to as CVD

Those who had an infarction (25.6 vs 21.8 ng/mmol creatine, P0.04) or died of a cardiac reason (26.7 vs 21.5 ng/mmol creatinine, P0.02) exhibited the highest difference between cases and controls. In the urine of subjects, the quantities of 11-dehydro thromboxane B2 who went on to have a stroke and their comparison group (26.1 VS 28.5 mmol creatinine, P=0.58) were not substantially different. For each rising quartile of baseline urinary 11dehydro thromboxaneB2 concentrations (p for trend across quartiles, 0.02). The probable outcomes indicated that, the patients lies in the higher quartile have a greater probability of 1.8 folds of getting CV diseases, strokes and myocardial infarction and death as compared to the patients having lower quartile (p for trend across quartiles, 0.02). (1.9 95% of OR, CI, 1.3 to 2.8 P=0.09. Infarction (p-value= 0.005, for tendency across the quartiles) and cardiac mortality (p-value= 0.02, for trend across quartiles) showed a similar relationship, while stroke (value of p= 0.31, for tendency across quartiles) not in Table 3. Adjusting or non- adjusting for basis dissimilarities among the group of cases and controls, including traditional cointerventions, cardiovascular risk and randomized therapy allocation, the results were similar. Separate analyses was conducted on individuals that had an incident in one year of training enrollment and those who had an 12 months event later to see if elevated concentrations of baseline 11-dehydro-TXB2 were linked with initial CV events somewhat delay CV events. Using linear multivariable regression modeling, the adjusted odds for the composite outcome of myocardial infarction, stroke, or cardiovascular death that was associated with the highest quartile of urinary 11-dehydro-TXB2 as compared to the lowest quartile were 2.8 (95% CI, 0.8 to 9.2) for events occurring within the first 12 months and 1.8 (95% CI, 1.1 to 2.8) for events occurring after the first 12 months (p=0.05). These variables, however, were capable of predicting 5% of the difference in urine 11-dehydro-TXB2 levels when they were combined (R2 .056), Table 3.

"11Dehydro Thromboxane B2 Concentration Quartiles, ng/mmol Creatinine"					
RESULT/ OUTCOME	<16.2	16-22.9	22.8-34.8	>34.9	P-VALUE
MI/stroke/CV death (n 400) P-value	1.1	1.4 (0.10T02.2) 14	1.5 (0.10T02.3) .010	1.9 (1.3T02.8) 0.010	C.02
MI (n 389) 95 CI P	1.1	1.4 (0.09T02.2) .27	1.6 (0.11TC2.6) .08	2.1 (1.3T02.4) .0.07	0.05
stroke 95 CI P	1.1	2.6 (0.7TC11.1) .19	0.7 (0.3T02.3) .45	0.7 (0.3T01.8) .35	0.30
CV death n 255 95 CI P	1.1	2.6 (1.1TC3.8) 0.07	0.7 (0.3T02.3) .46	2.6 (1.6-7.5) Less than 0.01	0.01

Table 3: Adjusted Odds* of Future Cardiovascular Death, myocardial Infarction, and Stroke Based on 11-Dehydro Thromboxane B2 Urinary Concentrations at Baseline

DISCUSSION

This study shows a link between, aspirin resistance, which is defined as the inability to decrease thromboxane production, and cardiovascular events. Elevated baseline urine levels of 11-dehydro thromboxane B2 (11-dehydro-TXB2) were linked with a higher chance of cardiovascular events (CV), notably cardiovascular death and infarction that is exactly define as treated group of aspirin who were at great threat of cardiovascular. This link was graded, strong and unaffected by traditional vascular risk factors such as increased BMI, BP, hypertension, diabetic, smoking, and previous vascular disease history. Furthermore, changes in the majority of individuals having lipid-lowering/ antihypertensive treatment between cases and controls, as well as those randomized to vitamin E or Angiotensin-converting enzyme inhibitors, did not affect the strength of the connection. The inadequate inhibition of thromboxane production by aspirin can be explained by several processes [10]. To begin, polymorphisms/mutations in the "cyclooxygenase-1 genes" (COX-1) that enable it resistant to the effect of aspirin inhibition could give a biological basis for aspirin resistance. Secondly, Nucleated cells like monocytes and vascular endothelial cells can either supply prostaglandin Hydrogen gas to platelet to pass platelets COX-1 or use prostaglandin H2 to generate its "thromboxane A2" because they have a lot of it [11, 12]. COX-1 or -2 catalyzes the conversion of arachidonate to prostaglandin H2. Although low-dose aspirin kills COX-1 in platelets permanently and fully, Nucleated cells can renew the enzyme [13,14]. Whereas COX-1 is inhibited with the concentration of 90 to 400 mg of aspirin, a dose that is comparable to that used in the city laboratory. The suppression of COX-1 necessitates daily dosages of aspirin above 500 mg [14,15]. Whereas, COX-1, which is stated continuously in nucleated cells, stimuli for inflammation increase the expression of COX-2 10 to 20-fold in nucleated cells. Because atherosclerosis is an inflammatory disease, increased COX-2 overexpression may lead to aspirin resistance in patients with ischemic heart disease [16].

Our result of an independent, albeit modest, the link between the disease history of peripheral vascular & urine 11-dehydro-TXB2 concentrations in the urine is reliable with previous research demonstrating that the intensity of atherosclerotic is a key predictor of production of thromboxane. Moreover, a very moderate dosages of aspirin effectively and irreversible block or stop platelet COX-1, changes in the degree or intensity of atherosclerotic are improbable to alter de novo platelet thromboxane generation in patients taking aspirin. Upregulation of COX-2 in atherosclerotic tissue 24 has been linked to increased prostaglandin H2 synthesis and transport to platelets, bypassing platelets COX-1 and resulting in these patients in aspirin-insensitive thromboxane manufacture. Since very modest dosages of aspirin effectively and irreversible block platelet COX-1, changes in the degree or intensity of atherosclerotic are unlikely to alter de novo generation of platelet thromboxane in patients taking aspirin. Up-regulation of COX-2 in atherosclerotic tissue24 has been linked to increased prostaglandin H2 synthesis and transport to Platelets, COX-1 platelet bypassing and resulting production of insensitive aspirin-thromboxane in the patients. The reason for the lack of an association between urinary 11-dehydro-TXB2 and risk of stroke is unclear. Increased concentrations of urine of 11-dehydro-TXB2 have been described to following aspirin failure, stroke in patients to decrease platelet reactivity or in response prevent platelet activation to different agonists of platelet has also been observed after stroke in these patients [17-19]. The mean 11-dehydro-TXB2 concentration of urine in stroke cases was comparable to that in all case scenarios (26.1 vs 25.6 ng /mmol, creatinine), but the relating matched concentration in urinary stroke was greater in control subjects than that in all subjects (28.5 vs 22.6 ng /mmol, creatinine). The figure of patients having stroke and matched control subjects, on the other hand, was small relatively (n80). Certain pure and ordered relationship among both urinary 11-dehydro-TXB2 concentration and also the complex results of stroke, infarction, or cardiac mortality, and also other discrete constituents of this outcome, the lack of a demonstrable relationship between stroke risk and urinary 11-dehydro-TXB2 concentration is most likely due to chance. There are various potential limitations to our research. First, there were important alterations between cases and controls in terms of potentially critical confounders such as BMI, systolic,

hypertensive, diabetes, smoking, and vascular disease history. Even after these differences were taken into account, a clear link was found between the concentration urine 11-dehydro-TXB2 and the threat of mortality, myocardial infarction, and stroke. The absence of a link among the concentrations urinary 11-dehydro-TXB2 and baseline patient characteristics adds to the evidence that confounding was not a factor in our findings. Secondly, a recently acute events of thrombotic like myocardial infarction or stroke, may have altered urine 11-dehydro-TXB2 concentrations, which are likely to be related to activation of platelet and increased the excretion of thromboxane metabolites in urinary. Patients that had an infarction or stroke during the past seven weeks were not included in the research, therefore this interpretation is less [20]. Thirdly, single baseline measurements of urine 11-dehydro-TXB2 levels may not adequately reflect the activation of platelet over time. However, the link between increased urine 11-dehydro-TXB2 levels at baseline with subsequent risk of cardiac events was visible both during the first 12 months following randomization and beyond that time, indicating a long-term relationship. Fourth, we could not use salicylate blood levels or urine to verify patient satisfaction with aspirin medication. Yet, at each follow-up visit, we particularly examined compliance with aspirin medication, and we only included patients who were using aspirin prior to randomization and at a six-month follow-up visit. At any point, patients who still taking aspirin throughout the research were excluded. Lastly, the variation magnitude in urine 11-dehydro-TXB2 levels is unidentified, which could restrict the use of this indicator in predicting the chance of potential CV cardiovascular events particularly in a patient.

CONCLUSIONS

It concludes that chronic thromboxane production, independently of certain other cardiovascular risk factors, expects the probability of composite results of aspirin-treated individuals in infarction, strokes, or death in cardiovascular at greater threat of cardiac events. These results suggest that higher urinary levels of 11-dehydro-TXB2 may be used to identify patients having resistance against a predictable dosage of aspirin antithrombotic and who might valuable from greater therapies or treatments of antiplatelet that more efficiently inhibit the activity or thromboxane generation.

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