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A Comparative Study of the Varying Effects of Acetylsalicylic Acid on Thromboxane B2

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ABSTRACT

Objectives: In this study, we evaluated the antiaggregant efficacy of the standard dose ASA and very low doses of ASA, which we use in the clinic, by looking at the serum thrombocyte B2 level and investigated the difference between the two groups.
Method: The study was built on 20 mg (1/4), 40 mg (1/2), 80mg 1/1 of Babypirin and 150 mg (1/2) of Dispril doses. 10 patients were grouped for each one of the four prescribed doses. Those patients with a history of gastrointestinal bleeding, peptic ulcer, hematological disorders, bronchial asthma, chronic obstructive pulmonary disease and allergy to ASA were excluded from the study. ASA doses were administered once a day. Before ASA, blood was collected from all patients for serum thromboxane (Tx) B2 analysis. Then, after 14 days of ASA use, blood was drawn from the patients again for the second time to detect TxB2 decrease.
Results: There was no significant difference between the groups in terms of age and gender ($p>0.05$). There was a significant difference between the groups in terms of % decrease in TxB2 after treatment ($p=0001$). In the post hoc test, it was concluded that the % decrease in the 20mg group was significantly lower than the other three groups ($p=0.002$), and the % decrease between the 40,80 and 150mg groups was higher in all three groups compared to the 20mg group. On the other hand, there was no difference in % reduction in the 40,80 and 150 mg groups ($p>0.05$).
Conclusion: The use of low-dose ASA seems to be more beneficial when considered in all aspects. Our results are that there is no difference in doses up to 40mg when considered from the antithrombotic point of view.

Acetylsalicylic acid (ASA) is arguably one of the most important pharmaceutical agents based on its widespread use and employment in various disorders. Besides its classic anti-inflammatory efficacy, it has a positive selective and proven effect on cardiovascular mortality via its anti-aggregating ability. The most prevalent usage avoidance is due to dose dependent gastrointestinal side effects and inhibition of prostacyclin.

In this study, we evaluated the antiaggregant efficacy of the standard dose ASA and very low doses of ASA, which we use in the clinic, by looking at the serum thrombocyte B2 level and investigated the difference between the two groups.

METHODS

The study was conducted on outpatients who had come to the general internal

medicine and diabetes clinic due to complaints of coronary artery disease and hospitalized at the second internal medicine clinic of Şişli Etfal Hospital. Babypin® 80 mg (Pfizer) and Dispril ® 300 mg pharmaceutical products were used as ASA. The study was built on 20 mg (1/4), 40 mg (1/2), 80mg 1/1 of Babypirin and 150 mg (1/2) of Dispril doses. 10 patients were grouped for each one of the four prescribed doses.

Those patients with a history of gastrointestinal bleeding, peptic ulcer, hematological disorders, bronchial asthma, chronic obstructive pulmonary disease and allergy to ASA were excluded from the study. ASA doses were administered once a day.

Measurement of serum thromboxane B2:

Blood samples were drawn from all patients in order to assess serum thromboxane B2 levels prior to administering ASA. Following 14 days of ASA usage, blood samples were drawn once again to determine whether thromboxane B2 levels had fallen. Blood samples were centrifuged right away and after serum was obtained specimens were kept at -24C. All serum samples were analyzed together at the end of the study. TBX2 levels were determined by ELİSA using acetylcholinesterase and ELİMAN reactive. This particular test functions on free and bound (bound to acetylcholinesterase) TXB2 competing. Eliman reactive (contains acetylcholinesterase substrate) which was added into the medium after the administration of rabbit antiserum; rendered a yellow tinge whose optical density was measured at 412 manometers by using spectrophotometry to assess each individual level.

Statistical Analysis

Statistical analysis were executed by using the SPSS (Statistical package for social sciences) programme. Deviation level was taken as 0.005 in intergroup comparisons. ANOVA (single direction variation analysis) was employed in normally dispersed variables; single Kruskal-Wallis's test was employed in non-normally dispersed variables. When a difference was detected, meaningfulness level border was moved to 0.0008. Mean-Whitney U test was applied as a post-hoc test. ki square test was employed to evaluate groups sexually.

RESULTS

There was no meaningful difference amongst groups related to age or sex ($p>0.005$). It can be summed up that with reference to the decrease in TbX2 in terms of percentage; meaningful differences were detected amongst groups. Based on the post hoc test, the decrease in terms of percentage in the group that received 20 mg. was meaningfully low compared with the other 3 groups ($p=0.002$). The decrease in terms of percentage with reference to the groups that received doses of 40 mg., 80 mg., 150 mg., was higher compared with the group that received the 20 mg. dose. It was also assessed that there was no difference in the decrease amongst the 40 mg., 80 mg., 150 mg. dose group (Table 1, 2, 3 and 4).

Table 1. TxA2 change in the group using 20 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
40	FEMALE	16,6	277-231
64	FEMALE	13,2	347-301
64	FEMALE	14,9	401-341
54	FEMALE	12,8	311-271
43	MALE	14,7	306-261
50	MALE	11,8	296-261
67	MALE	20,6	402-319
51	MALE	18,2	296-242
55	MALE	12,6	309-270
70	FEMALE	12,7	321-280

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

DISCUSSION

ASA is a selective antithrombotic agent in stopping thrombus formation in coronary artery disease and cerebrovascular diseases both in acute and in chronic cases. Data obtained from antiplatelet remedial studies have shown that daily doses <160 mg; 160mg to 325 mg., 500 mg to 1500 mg. of ASA have similar benefits [1]. Latest guidelines recommend 30 mg to 100 mg of ASA to avoid non cardioembolic secondary ischemia based on similar benefits no matter how high the dose is and to avoid GİS complications with increasing dose. According to American College of chest Physicians` 2012 guideline, the recommended dose of ASA is 75-100 mg /day [2] :according to the American Heart Association/American Stroke Association's 2021 guideline the recommended dose of ASA is 50-325 mg/day.[3]

The optimal daily dose of ASA to avoid long duration secondary cardiovascular incidents is indeterminate. The prevalently prescribed doses are 81 mg. and 100 mg. Many studies and their meta-analyses have evaluated 75 mg. t0 1300 mg./day of ASA. The Union of Anti Thrombus Studies has shown through meta-analyses of the above-mentioned studies that ASA doses of 76 mg. to 1300 mg. render similar benefits [4]. Nevertheless, it has been proven that GİS bleeding risk increases with doses exceeding 325 mg/day.

ASA inhibits COX and thus causes a decrease in the formation of TxA2. It causes prostacyclin not to come into being by inhibiting the same enzyme. TxA2 is a strong vasoconstrictor that increases thrombocyte aggregation; whereas prostacyclin is a strong anti-

Table 2. TxA2 change in the group using 40 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
55	MALE	43,2	344-196
65	FEMALE	70,4	392-116
70	FEMALE	44,6	327-181
60	FEMALE	26,9	412-301
70	MALE	26,3	288-212
48	FEMALE	22,9	401-309
64	MALE	36	300-192
55	FEMALE	36,3	316-201
63	MALE	29	386-274
47	MALE	29,2	421-298

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

Table 3. TxA2 change in the group using 80 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
32	MALE	55,0	329-148
58	FEMALE	40,7	336-199
56	FEMALE	30,8	266-184
27	FEMALE	31,3	287-197
28	FEMALE	27,6	336-243
55	FEMALE	25,5	290-216
50	FEMALE	26,5	328-241
60	MALE	38,9	272-166
56	MALE	39,8	321-193
50	MALE	34,7	308-201

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

Table 4. TxA2 change in the group using 150 mg ASA

Age	Gender	% Reduction in TxB2	pg/dL
50	FEMALE	33,1	287-192
29	FEMALE	35,5	304-196
28	MALE	34,3	329-216
31	MALE	38,2	329-203
75	MALE	34,1	290-191
59	FEMALE	31,6	306-209
48	FEMALE	49,6	281-142
64	FEMALE	37,3	321-201
50	MALE	34,4	308-202
61	MALE	37,7	307-191

ASA: Acetylsalicylic acid, TxA2: Thromboxane A2

aggregating agent and vasodilator which means that it functions antagonistically.

Besides inhibiting platelets, ASA inhibits COX in vascular tissue which in turn causes prostacyclin to be inhibited.[5]. The important question that we should ask at this point is: whether ASA is more effective in inhibiting COX in thrombocytes or in vascular tissue. Are such effects dose dependent and variable? Do such effects alter the balance between TXA2 and prostacyclin. İn case ASA's inhibiting effect is more pronounced than its inhibiting effect on TXA2; ASA could actually cause more thrombus to come into being.

Once ASA inhibits COX in thrombocytes, it emerges as an irreversible effect and thrombocytes cannot synthesize COX anymore throughout their life span. Vascular tissue on the contrary has the ability to re-synthesize COX after being exposed to ASA. [6]

In a study conducted on coronary bypass patients; both arterial and venous prostacyclin &TxB2 levels were screened prior to ASA exposure and after 80mh to 325 mg of ASA exposure.

80 mg. of ASA rendered 83% decrease in venous prostacyclin; 40 mg. of ASA caused 35% decrease in arterial prostacyclin whereas the decrease was 71% with 325 mg. of ASA [7, 8].

It has been argued in some other studies that ASA doses lower than 100 mg. were not effective in inhibiting thrombocytes from aggregating and in prostacyclin being synthesized [9, 10]. In another study in comparison with a dose of 75 mg of ASA; as low as 20 mg of ASA was claimed to have inhibited thrombocyte TxA2 secretion and aggregation. [11]. We have found out that doses of 40 mg of ASA & over rendered 40% decrease in TxB2; 20 mg of ASA rendered less than 15% decrease in TxB2 in our study.

ASA's arguably most important clinical setback consists of GIS side effects: bleeding, gastric or duodenal ulcers [12]. Such GIS side effects are of paramount importance due to the fact that once a patient experiences any one of them; neither the doctor nor the patient wishes to continue using ASA. As a result, the employment of an effective anti-thrombus agent gets lost. It is also a possibility that catastrophic intracranial bleedings can happen. According to 2019 meta-analyses incorporating ASCEND, ARRİVE, ASPREE clinical studies; low dose ASA intake (<100 mg/day) increased the risk of intracranial bleeding compared with placebo. [13]. It yet has not been clearly delineated, which dose window renders ideal antithrombotic effect to zero GIS side effects and bleeding complications.

Results of our study have shown similar outcomes with most other studies related to the topic. Nevertheless, some studies have results pointing to significant decrease in TxB2 with relatively low doses of ASA. Those studies with very low doses were conducted on healthy volunteers who didn't use any other medicine. Patients who were enrolled in our study used a number of pharmaceuticals each and drug interactions might have caused absorption related issues.

CONCLUSION

In conclusion, approximately 24.4% of COVID-19 patThe base of our study was to outline the effects of

ASA (with varying doses) on thromboxane synthesis. Studies with low doses of ASA have proven that thromboxane synthesis inhibition was dose correlated. Lower dose usage of ASA seems to be more beneficial when all effects are taken into consideration. Our results have proven that antithrombotic effects of ASA are stable and remains constant up to 40 mg.

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