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SHORT COMMUNICATION

EFFECT OF VARIABLE LOW DOSES OF ASPIRIN ON PLATELET FUNCTIONS

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Abstract : The effect of chronic administration of variable low doses of Aspirin was studied on platelet adhesiveness, platelet count, bleeding time and clotting time to find out as to how low the dose of aspirin needs to be in order to have an effective antiplatelet effect in patients who require such therapy. A statistically significant reduction in the platelet adhesiveness was observed in all the groups, but the best effect was exhibited by 50 mgm of aspirin dose. Bleeding time was also increased in all the groups but statistically significant difference was observed with 50, 75 and 100 mgm doses. There was no change in platelet count and clotting time.

Key worrds : platelet functions aspirin

INTRODUCTION

Steering Committee of Physician's Health Study Research Group (1) studied a large number of apparently healthy volunteers to find out the effect of 325 mgm of aspirin given on alternate days. They concluded that the benefit they have found in preventing myocardial ischaemia must be weighed against the hazzards of gastrointestinal disorders and bleeding. Peto et al (2) did not find any significant difference in the reduction of frequency of myocardial infarction in the aspirin treated group (500 mgm daily) as compared to the control group. Large scale long term clinical studies to assess the role of aspirin as an antiplatelet agent for the secondary prevention of myocardial infarction or stroke have not used doses of less than 300 mgm daily (3). Equal antiplatelet effects of aspirin 50 or 324 mgm/day in patients after acute myocardial infarction have been observed by some workers (4). Studies by other workers (5,6) have revealed that single dose of 40 to 80 mgm and 50 mgm of aspirin daily can significantly prevent generation of thromboxane as was indicated by Patrignani et al (7). It is apparent from the above studies that an appropriate dose of aspirin, which will prevent thrombotic myocardial and cerebral events without any serious side effects is still not certain.

The present study aims to find out the effect of chronic administration of low doses of aspirin on platelet functions and to find out the minimum daily dose of aspirin which should be most effective as an antithrombotic with least side effects for prevention of coronary and cerebral thromboembolic phenomenon.

METHODS

Screening and design of study : *A total number of 125* healthy volunteers of both sexes between the age group of 17-22 years were studied. They were students of Medical College and Dental College who gave their informed consent to participate in this study. Each student was carefully interviewed. Detailed personal and family history was taken regarding history of thrombocytopenia, coagulation disorders, hepatic and acid peptic disease, sensitivty to aspirin and intake of drugs known to affect platelet functions. After excluding all these factors, they were enrolled for the study. The study was ethically approved. The selected students were randomly divided into 5 groups of 25 students

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each. Out of 25 students, 20 received drug while 5 received placebo (Double blind technique was followed). The groups received aspirin/placebo in the dose of 50,75,100, 150 and 300 mgm per day respectively for 15 days, after meals. They were instructed not to take any other nonsteroidal anti-inflammatory drugs and extra aspirin and also to inform if he or she had forgotton to take the medicine or any one of them had any side effect of the drug.

Laboratory test : Platelet count, platelet adhesiveness, bleeding and clotting time were done before and after drug/placebo administration using standard techniques (8,9,10,11). The study was organised in a way that only 10 blood samples were collected for the investigations between 8-9 a.m. for each dosage/ placebo group before and after 15 days.

Statistical analysis : The results are reported as mean ± S.D. Each member of the study acted as his own control. Paired t test was used to find the statistical significance if any at 5% level.

RESULTS AND DISCUSSION

The present study has demonstrated that there was no significant change in bleeding time, clotting time, platelet count, and percentage platelet adhesiveness before and after administration of placebo in the subjects (Table I, II).

Bleeding time was increased in all the dosage groups of aspirin but 50, 75 and 100 mgm exhibited statistically significant increase in intra and inter group comparisons (Table I, III). There was no change in clotting time and platelet count after the administration

TABLE I : Comparison of differences of means between
(1) Before and after administration of drug/placebo
(2) Aspirin and Placebo groups.

Drug/Placebo dose		*Mean bleeding time ± S.D. (min)*			*Mean clotting time ± S.D. (min)*		
		Aspirin		*Placebo*	*Aspirin*		*Placebo*
50 mgm.	B	3.5 ± 1.1		2.7 ± 0.9	5.25 ± 1.60		4.90 ± 1.60
	A	4.3 ± 1.2		2.9 ± 1.0	5.00 ± 1.20		5.10 ± 1.30
	D	0.80 ± 0.20	P <.001	0.20 ± 0.13	0.25 ± 0.13	NS	0.20 ± 0.14
		P< 0.05		NS	NS		NS
75 mgm	B	4.3 ± 0.5		3.5 ± 0.50	5.20 ± 0.90		5.60 ± 0.90
	A	4.9 ± 1.0		3.2 ± 0.30	5.40 ± 1.60		5.30 ± 0.90
	D	0.60 ± 0.13	P <.001	0.30 ± 0.14	0.20 ± 0.14	NS	0.30 ± 0.16
		P<0.05		NS	NS		NS
100 mgm	B	3.9 ± 1.1		3.6 ± 0.60	6.30 ± 1.90		5.60 ± 1.20
	A	4.4 ± 1.2		3.8 ± 0.90	6.00 ± 1.00		5.40 ± 1.30
	D	0.50 ± 0.24	P <.001	0.20 ± 0.15	0.30 ± 0.19	NS	0.20 ± 0.12
		P<0.05		NS	NS		NS
150 mgm	B	3.7 ± 1.0		4.5 ± 0.80	5.80 ± 1.40		4.30 ± 1.20
	A	4.1 ± 1.6		4.8 ± 0.20	6.00 ± 0.90		3.90 ± 0.40
	D	0.40 ± 0.18	NS	0.30 ± 0.14	0.20 ± 0.16	NS	0.40 ± 0.23
		NS		NS	NS		NS
300 mgm	B	2.4 ± 1.7		3.0 ± 1.2	6.20 ± 1.30		5.90 ± 1.50
	A	3.2 ± 1.2		3.2 ± 0.90	5.90 ± 1.30		5.70 ± 1.20
	D	0.30 ± 0.14	NS	0.20 ± 0.13	0.30 ± 0.18	NS	0.20 ± 0.12
		NS		NS	NS		NS

B: Before A : After D : Difference

TABLE II : Comparison of differences of means between
(1) Before and after administration of drug/placebo
(2) Aspirin and Placebo groups.

Drug/Placebo dose		*Mean platelet count in 10^5/mm³ ± S.D.*			*Mean % adhesive platelet ± S.D.*		
		Aspirin		*Placebo*	*Aspirin*		*Placebo*
50 mgm	B	3.26 ± 1.50		3.42 ± 1.50	27.4 ± 6.8		30.3 ± 2.8
	A	2.98 ± 1..30		3.20 ± 1.40	15.0 ± 4.6		29.6 ± 3.2
	D	0.28 ± 0.12	NS	0.22 ± 0.16	12.4 ± 2.8	P < 0.001	0.70 ± 0.28
		NS		NS	P < 0.001		NS
75 mgm	B	3.61 ± 0.80		2.84 ± 0.30	22.2 ± 6.0		23.80 ± 1.2
	A	3.34 ± 1.50		3.04 ± 0.80	14.8 ± 3.8		24.02 ± 2.3
	D	0.27 ± 0.19	NS	0.20 ± 0.14	7.4 ± 2.4	P < 0.001	0.22 ± 0.18
		NS		NS	P < 0.001		NS
100 mgm	B	3.20 ± 1.20		3.92 ± 1.00	22.3 ± 7.2		25.0 ± 2.3
	A	2.97 ± 0.90		3.66 ± 1./30	14.7 ± 3.6		23.8 ± 2.6
	D	0.23 ± 0.16	NS	0.26± 0.14	7.6 ± 2.8	P < 0.001	1.2 ± 0.5
		NS		NS	P < 0.001		NS
150 mgm	B	3.62 ± 0.60		4.32 ± 0.60	24.1 ± 8.5		26.2 ± 1.4
	A	3.36 ± 0.20		4.02 ± 0.90	15.9 ± 6.7		27.0 ± 1.6
	D	0.26 ± 0.13	NS	0.30 ± 0.16	8.2 ± 2.5	P < 0.001	0.8 ± 0.38
		NS		NS	P < 0.001		NS
300 mgm	B	3.04 ± 1.20		3.92 ± 0.80	23.0 ± 7.0		25.2 ± 1.6
	A	2.79 ± 1.30		3.64 ± 1.30	14.8 ± 5.7		24.8 ± 1.9
	D	0.25 ± 0.14	NS	0.28 ± 0.13	8.2 ± 2.2	P < 0.001	0.40 ± 0.28
		NS		NS	P < 0.001		NS

B : Before A : After D : Difference

of aspirin. These observations are similar to the reports of the earlier workers (12,13,14).

There was a significant reduction in platelet adhesiveness in all the dosage groups after the administration of aspirin (Table II). It was also observed that 50 mgm dose of aspirin had shown statistically significant reduction of platelet adhesiveness as compared to 75, 100, 150 and 300 mgm doses (Table IV). This probably might be due to most effective inhibitionof thromboxane and least inhibition of endogenous prostacyclin by this low dose as earlier suggested by Fitzgerald et al (15) with their observations of chronic administration of aspirin at 20 mgm dose. According to them aspirin in excess of 80 mgm per day resulted in substantial inhibition of endogenous prostacyclin.

Aspirin is an inhibitor of the enzyme cyclooxygenase which is present in many other tissues where it leads to the formation of prostaglandins that may themselves inhibit platelet activation. Patrignani et al (7) observed inhibition of prostaglandins synthesis by chronic administration of aspirin. Cerlotti et al (16) have suggested that aspirin in doses of 100 mgm or less daily possesses an anti-thrombotic effect while doses more than this might have serious side effects versus usefulness. Jha et al (14) have suggested that for satisfactory antiplatelet action the dose of 600 mgm should be taken on every fourth day. What we feel that it will be better that if one takes the small dose without fear of side effects and also takes it daily without the tension of remembering the specific day to have the same satisfactory anti-thrombotic effect.

TABLE III : Intergroup comparison in mean differences of Aspirin groups.

Mean bleeding time differences (in min)

Doses (in mgm)

	50	75	100	150	300
50	0.80 ± 0.20	0.80 ± 0.20** 0.60 ± 0.13	0.80 ± 0.20* 0.50 ± 0.24	0.80 ± 0.20** 0.40 ± 0.18	0.80 ± 0.20** 0.30 ± 0.14
75	0.60 ± 0.13	-	0.60 ± 0.13* 0.50 ± 0.24	0.60 ± 0.13 ** 0.40 ± 0.18	0.60 ± 0.13** 0.30 ± 0.14
100	0.50 ± 0.24	-	-	0.50 ± 0.24* 0.40 ± 0.18	0.50 ± 0.24** 0.30 ± 0.14
150	0.40 ± 0.18	-	-	-	0.40 ± 0.18 NS 0.30 ± 0.14
300	0.30 ± 0.14	-	-	-	-

Mean clotting time differences (in min)

Doses (in mgm)

	50	75	100	150	300
50	0.25 ± 0.13	0.25 ± 0.13 NS 0.20 ± 0.14	0.25 ± 0.13 NS 0.30 ± 0.19	0.25 ± 0.13 NS 0.20 ± 0.16	0.25 ± 0.13 NS 0.30 ± 0.18
75	0.20 ± 0.14	-	0.20 ± 0.14 NS 0.30 ± 0.19	0.20 ± 0.14 NS 0.20 ± 0.16	0.20 ± 0.14 0.30 ± 0.18
100	0.30 ± 0.19	-	-	0.30 ± 0.19 NS 0.20 ± 0.16	0.30 ± 0.19 NS 0.30 ± 0.18
150	0.20 ± 0.16	-	-	-	0.20 ± 0.16 NS 0.30 ± 0.18
300	0.30 ± 0.18	-	-	-	-

* P < 0.05 ** P <0.001 NS = Not significant

TABLE IV : Intergroup comparison in mean differences of Aspirin groups.

Mean platelet count

Doses (in mgm)

	50	75	100	150	300
50	0.28 ± 0.12	0.28 ± 0.12 NS 0.27 ± 0.19	0.28 ± 0.12 NS 0.23 ± 0.16	0.28 ± 0.12 NS 0.26 ± 0.13	0.28 ± 0.12NS 0.25 ± 0.14
75	0.27 ± 0.19	-	0.27 ± 0.19 NS 0.23 ± 0.16	0.27 ± 0.19 NS 0.26 ± 0.13	0.27 ± 0.19 NS 0.25 ± 0.14
100	0.23 ± 0.16	-	-	0.23 ± 0.16 NS 0.26 ± 0.13	0.23 ± 0.16 NS 0.25 ± 0.14
150	0.26 ± 0.13	-	-	-	0.26 ± 0.13 NS 0.25 ± 0.14
300	0.28 ± 0.12	-	-	-	-

Mean platelet adhesiveness

Doses (in mgm)

	50	75	100	150	300
50	12.4 ± 2.8	12.4 ± 2.8** 7.4 ± 2.4	12.4 ± 2.8** 7.6 ± 2.8	12.4 ± 2.8** 8.2 ± 2.5	12.4 ± 2.8** 8.2 ± 2.2
75	7.4 ± 2.4	-	7.4 ± 2.4 NS 7.6 ± 2.8	7.4 ± 2.4 NS 8.2 ± 2.5	7.4 ± 2.4 NS 8.2 ± 2.2
100	7.6 ± 2.8	-	-	7.6 ± 2.8 NS 8.2 ± 2.5	7.6 ± 2.8 NS 8.2 ± 2.2
150	8.2 ± 2.5	-	-	-	8.2 ± 2.5 NS 8.2 ± 2.2
300	8.2 ± 2.2	-	-	-	-

** P <0.001 NS = Not significant

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