

Treatment of Necrobiosis lipoidica with Low-dose Acetylsalicylic Acid

A Randomized Double-blind Trial

HANS-IVER BECK,¹ PETER BJERRING,¹ IDA RASMUSSEN,¹
HUGH ZACHARIAE¹ and STENER STENBJERG²

¹Department of Dermatology and Venereology, Marselisborg Hospital, Århus and

²Department of Clinical Immunology, Århus Kommunehospital, Århus, Denmark

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16 patients with clinically and histologically verified necrobiosis lipoidica lesions were treated with either 40 mg acetylsalicylic acid or placebo daily for 24 weeks in a double-blind controlled study. The lesions became statistically significantly larger in both groups in spite of inhibition of the aggregation of the platelets in the acetylsalicylic group. *Key words:* Necrobiosis lipoidica; Acetylsalicylic acid; Platelet aggregation. (Received September 18, 1984.)

H.-I. Beck, Department of Dermatology and Venereology, Marselisborg Hospital, DK-8000 Århus C, Denmark.

Recently, several investigations have been made treating necrobiosis lipoidica (NL) with acetylsalicylic acid (ASA) and dipyridamole, either alone (1, 2) or in combination (3-5). The rationale of this treatment is based upon the observation that NL probably is caused by vasculitis and vascular occlusion in the small vessels (6) as often seen at histological examinations. Besides the platelets in diabetic persons show increased tendency to spontaneous aggregation.

ASA inhibits the cyclo-oxygenase converting arachidonic acid into prostaglandins in the vessel walls (7) and thromboxanes in the platelets (8, 9) (Fig. 1). Thromboxane is considered to be prothrombotic as acting as a vasoconstrictor (10) and is able to induce aggregation of the platelets (9). In contrast, prostacycline inhibits platelet aggregation (PA) (11) and is a vasodilatator (12, 13) too.

In previous controlled and uncontrolled reports 1 000-4 500 mg ASA was given daily (1, 2, 4), sometimes in combination with 225 mg dipyridamole (3, 5). An improvement was shown in some cases (1, 2, 4) but later controlled investigations (3, 5) could not confirm these beneficial results. It was concluded that the missing effect probably was due to the high dose of ASA which then acted at the cyclo-oxygenase in both the platelets and the endothelial cells.

In the literature, different dosage schedules have been discussed at which ASA selectively inhibits platelets thereby preventing the prothrombotic effect of thromboxane (14). The latest investigations have shown that a dose of ASA at 40 mg/24 h or better 40 mg/48 h acts selectively at the enzymes of the platelets (15-17).

In order to confirm or refute the claims of the earlier reports and to investigate this new observation we designed a double-blind study with 40 mg ASA daily.

MATERIAL AND METHODS

Eighteen patients of both sexes aged between 17-75 (mean 41) years suffering from clinical and histological NL for 4-37 (mean 13) years were studied. 11 patients were suffering from diabetes

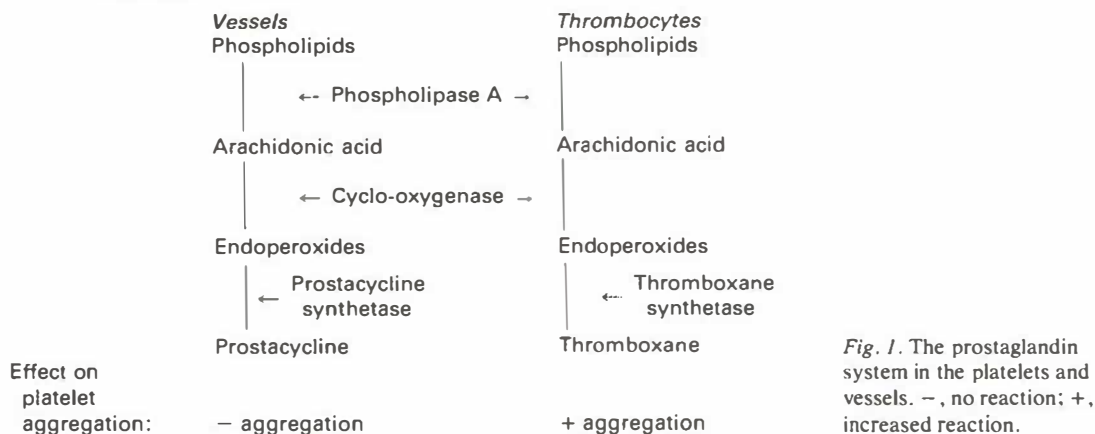


Fig. 1. The prostaglandin system in the platelets and vessels. -, no reaction; +, increased reaction.

mellitus (Table I). After withdrawal of all non-steroid anti-inflammatory drugs for one month the 18 patients were assigned to a 24-week randomized double-blind treatment with either 40 mg ASA daily or placebo. The placebo and ASA tablets had an identical appearance. During treatment no ASA-containing drugs and local steroids were allowed.

Upon admission, a detailed history was obtained. This was subsequently supplemented by a laboratory screening (SR, Hb, leukocytes, differential count, thrombocytes, s-electrolytes, s-creatinine, s-thyroxine, blood sugar, urine for sugar and albumen). Besides we examined spontaneous and collagen-induced PA on a Payton aggregometer one week before and immediately before the treatment was started and again after 4, 12 and 24 weeks of treatment (Table I). The effect of the treatment

Table I. Patient data and the results of the platelet aggregation

F = female, M = male, A = active, P = placebo, NL = necrobiosis lipoidica, NT = not tested. 1 = start, 2 = 1 week, 3 = 4 weeks, 4 = 12 weeks, 5 = 24 weeks, + = positive, - = negative

Pat. no.	Yrs./sex	Dia- betes +/- A/P	NL (yrs.)	Overall assessment	Platelet aggregation										
					Collagen induced ($\mu\text{g/ml}$)					Spontaneous					
					1	2	3	4	5	1	2	3	4	5	
1	57/F	A	-	37	Unchanged	0.4	0.4	1	2	>2	+	+	+	+	+
2	32/M	A	+(20)	14	Unchanged	2	2	2	>2	>2	+	+	+++	+	+
3	27/F	A	-	14	Better	1	1	2	2	>2	+	+	++	+	+
4	52/F	A	-	10	Worse	0.4	1	0.2	>2	>2	+	+	+	+	+
5	75/F	A	-	20	Unchanged	1	1	0.4	2	1	+	+	++	++	+
6	35/F	A	-	10	Unchanged	0.05	0.05	0.4	2	2	++	++	++	+	+
7	37/F	A	+(27)	18	Better	0.1	0.1	2	2	>2	++	++	++	++	++
8	38/F	A	-	15	Better	0.4	0.4	0.2	2	>2	+	+	+	+	+
9	18/F	A	+(15)	9	Better	0.4	0.4	0.4	2	0.4	+	+	+	+	+
10	73/F	P	+(11)	10	Unchanged	0.2	0.2	2	1	2	+++	+++	+++	+	++
11	46/F	P	+(12)	27	Worse	0.4	0.4	2	1	NT	++	++	+	++	NT
12	30/F	P	+(8)	9	Better	1	1	2	1	1	+	+	+	+	+
13	52/F	P	-	4	Unchanged	0.4	1	0.4	0.4	0.4	++	++	++	++	++
14	17/F	P	+(9)	6	Unchanged	0.4	0.4	1	0.4	2	+	+	+	+	+
15	50/F	P	+(29)	16	Unchanged	1	1	1	0.4	0.4	+	+	+	+	+
16	35/M	P	+(7)	7	Unchanged	>2	>2	0.4	1	0.4	+++	+++	+++	+	+
17	22/M	P	+(8)	5	Unchanged	0.2	0.2	0.03	0.4	0.4	+	+	+	+	+
18	34/F	P	+(17)	11	Unchanged	0.4	0.4	0.4	0.4	0.4	+	+	+	+	+

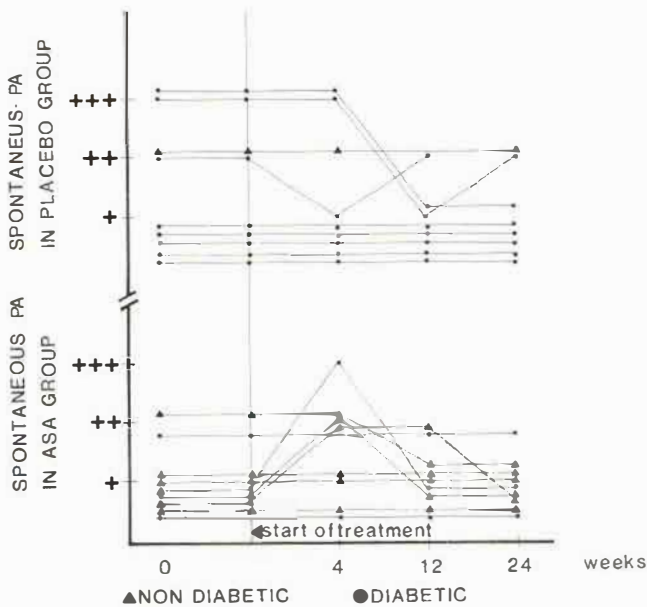


Fig. 2. Spontaneous platelet reaction (PA). ASA = acetylsalicylic acid.

was followed by recording the necrobiotic lesions by tracing around the outline of the lesions and a scabalone was made. The weight of this scabalone was then determined. The lesions were photographed and punch biopsies were performed.

The patients then returned for control after 1, 4, 12, and 24 weeks of treatment. At each time the patients were asked whether the lesions were better, unchanged or worse. At the end of the trial an overall assessment was made by photographing and tracing the lesions.

RESULTS

At the end of the trial 2 patients, one in the ASA group (no. 5) and one in the placebo group (no. 11) were excluded from the study because of wrong administration of the tablets (Table I). The overall assessment of the 16 patients (8 in the ASA group and 8 in the placebo group) showed that the scabalones of the necrobiotic lesions in both groups grew statistically significantly larger (Wilcoxon, $p < 0.02$ for the ASA group, $p < 0.05$ for the placebo group). No difference in the course of the NL between ASA group and placebo groups was recorded ($p < 0.1$).

From the patients' comments we recorded, that 44% in the ASA group felt that the lesions improved, while only 11% in the placebo group did so. The improvements were: 1) lesser sensitivity of the lesions, 2) changing of the colours, 3) disappearance of ulcerations (one patient in both groups) and 4) impression of the lesions became smaller.

There was no obvious relationship between clinical response and the presence or absence of diabetes mellitus, but unfortunately only 3 diabetes patients were in the ASA group (Table I). The laboratory screening showed no side effects of the treatment. The determination of PA revealed that the spontaneous aggregation in the ASA group was more constant than in the placebo group (Fig. 2). At the determination of the minimal dose of collagen, which induced irreversible aggregation, we found increasing values in the ASA group with a maximum at 12 weeks (Fig. 3). The values in the placebo group were constant and they were not increasing after treatment was started, as was seen in the ASA group (Fig. 3).

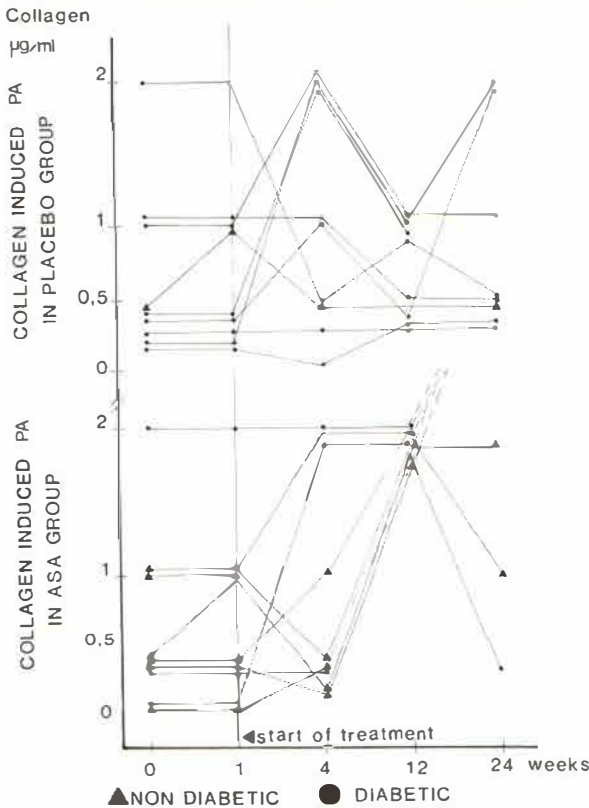


Fig. 3. Collagen-induced platelet aggregation (PA). ASA = acetylsalicylic acid.

DISCUSSION

The treatment with 40 mg ASA daily in 24 weeks showed an inhibition of PA in the ASA group against the placebo group. In the ASA group the minimal dose of collagen which induced irreversible PA showed increasing values with a maximum at 12 weeks of treatment, probably because of the cumulative inhibitory effect of ASA at the cyclooxygenase in the platelets (8, 14, 15). The test for spontaneous aggregation did not show consistent differences between the two groups. In spite of the fact that PA was inhibited and that 44% of the patients in the ASA group felt better, the treatment of NL failed as the lesions in both groups became statistically significantly larger.

We must therefore conclude that 40 mg ASA daily for 24 weeks cannot prevent progression of old NL or development of new NL and therefore does not seem in any larger degree to benefit patients with this disease. The pathogenesis is still poorly understood, but this trial demonstrates that PA does not play as important a role in the development of NL as previously suggested.

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