A Randomized Double Blind Comparison of an Aspirin Dipyridamole Combination versus a Placebo in the Treatment of Necrobiosis Lipoidica

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Abstract. Fourteen patients with a clinical and histological diagnosis of necrobiosis lipoidica were treated in a double-blind control study with either an aspirin dipyridamole combination or a matching placebo for an 8-week period. None of the patients in the aspirin dipyridamole group showed a significant improvement.

Previous, uncontrolled reports (1, 2, 8) have suggested that a striking improvement may follow the treatment of necrobiosis lipoidica with aspirin and dipyridamole, either alone or in combination. Four out of five cases thus treated showed a complete resolution of the cutaneous lesions on this therapy.

The rationale of this treatment is based upon the histological appearance of vascular occlusion (7) reported to occur commonly within the lesions and the increased tendency for diabetic subjects to show platelet aggregation in response to various pharmacological stimuli (4).

Aspirin and dipyridamole exert a synergistic "anti-thrombotic action" by blocking Thromboxane A_2 generation and phosphodiesterase activity respectively (6).

There is much controversy covering the optimal dosage of aspirin which should be given in combination with dipyridamole. Masotti et al. (1979) (5) have shown that too high a dosage of aspirin will virtually abolish prostacyclin activity and thus the synergistic action of the dipyridamole, whereas Harker (1974) (3) has shown that aspirin/dipyridamole, in a dosage schedule very similar to that used in this study, increases platelet survival time in patients with recurrent arterial thrombosis. The dosage chosen for this study was designed to confirm or refute the claims of the earlier, uncontrolled reports.

METHODS

Fourteen patients, who had given their informed consent and who had lesions showing the typical clinical and histological features of necrobiosis lipoidica (7) were divided into pairs matched for the presence or absence of diabetes mellitus and ulcerated or non-ulcerated cutaneous lesions. The clinical details are shown in Table 1. All patients classified as non-diabetic had shown a normal oral 50 g glucose tolerance test within the previous 12 months.

Patients within each pair were then allocated in a double-blind manner to receive either a capsule containing 300 mg aspirin and 75 mg dipyridamole, or an identical placebo capsule, each to be taken three times daily.

Table 1. *Clinical details of patients and treatment groups*

Patient	Age	Sex	Diabetic	Duration of necrobiosis lipoidica (y.)	Ulceration	Treatment group
1 A	27	F	Yes	4	No	Active
2 A	49	F	No	2½	No	Active
2 B	25	F	No	10	No	Placebo
3 A	21	F	Yes	5	Yes (healed during trial)	Placebo
3 B	17	M	Yes	4	Yes	Active
4 A	47	F	No	1½	No	Placebo
4 B	63	F	No	3	No	Active
5 A	22	F	Yes	16	No	Active
6 A	49	M	No	14	No	Placebo
6 B	58	F	No	3½	No	Active
7 A	24	F	No	6	No	Placebo
7 B	54	F	No	2	No	Active

Prior to commencing therapy the following assessments were performed: (*a*) the area of the lesions was recorded by carefully tracing around the outline of the lesions, followed by measurement of the tracing with a planimeter, (*b*) the lesions were photographed under standardized conditions, and (*c*) a 4 mm punch biopsy was performed from the edge of a lesion and subsequently prepared for routine histological examination with haematoxylin and eosin stains.

The patients were then re-examined at 2, 4 and 6 weeks, when further tracings were performed. Finally, at 8 weeks a full assessment was made with tracings, photography and repeat biopsy of the same lesions. At 4 weeks and 8 weeks the patients were asked to comment if they felt the lesions were unchanged, better, or worse.

RESULTS

Two patients (1B and 5B) repeatedly defaulted from follow-up and were withdrawn from the study. Both of these patients belonged to the placebo group. Of the remaining patients 7 were taking the aspirin dipyridamole combination and 5 the placebo treatment. Only one patient (3A) showed any convincing improvement, the areas of ulceration which had been persistent for several months steadily improved and were completely healed at the end of 6 weeks. However, breaking the code showed this patient to be in the placebo group. The patient with whom she was matched (3B) in the aspirin dipyridamole group showed a slight extension of the ulcerated areas during the trial period.

Two patients each developed a new lesion whilst undergoing the trial; one belonged to the aspirin dipyridamole group, the other to the placebo group. Biopsies taken before and after the treatment period showed no significant differences with regard to the presence of necrobiotic change, inflammatory cell infiltration, or morphology of small blood vessels.

CONCLUSIONS

Treatment with an aspirin dipyridamole combination in this dosage for an 8-week period has failed to produce any improvement, either in ulcerated or non-ulcerated lesions of necrobiosis lipoidica.

Although only 12 patients completed this study, necrobiosis lipoidica is a condition which very rarely undergoes spontaneous resolution and if the claims of the uncontrolled reports had been substantiated, we would have expected 50–75% of the patients in the "active" group to have shown an improvement.

The 2 patients taking the aspirin dipyridamole combination who developed an extension of the ulcerated area, or a fresh area of active disease, strongly suggest that this drug combination has failed to influence the underlying pathogenesis of this poorly understood condition. We believe that this study underlines the need to accept with caution anecdotal and uncontrolled reports of improvement after the use of new treatments.

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