

The use of *Ginkgo biloba* in Raynaud's disease: a double-blind placebo-controlled trial

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Abstract: Raynaud's phenomenon (RP) is a common and painful condition characterized by episodic digital ischaemia produced by emotion and cold. Treatment of RP is notoriously difficult because of the high incidence of side effects. The aim of our study was to investigate the clinical efficacy of a standardized *Ginkgo biloba* extract (Seredrin) in the treatment of RP in patients with no apparent, associated condition such as systemic sclerosis.

A two-week assessment period was done during which patients were asked to record frequency, severity and duration of attacks in diaries. Subjects were then randomized independently of the study centre to receive either active or placebo treatment for 10 weeks, during which time the same data were recorded in their diaries. Patients were seen after two and four weeks of treatment and at the end of the 10-week treatment phase. Blood samples pre- and post-treatment were taken for haemorrhology.

Only in the number of attacks per day was there a significant effect of treatment over placebo. The number of attacks per week prior to treatment with Seredrin was 13.2 ± 16.5 reducing to 5.8 ± 8.3 , a reduction of 56%, whereas placebo reduced the number by only 27% ($p \leq 0.00001$). There were no significant differences in haemorrhology between the two groups.

Ginkgo biloba phytosome may be effective in reducing the number of Raynaud's attacks per week in patients suffering from Raynaud's disease.

Key words: alternative medicine; *Ginkgo biloba*; Raynaud's disease

Introduction

It is now over 130 years ago that Maurice Raynaud first described the symptoms of Raynaud's phenomenon (RP). Classically it is manifest by blanching caused by digital artery vasospasm, cyanosis as the remaining blood becomes deoxygenated and rubor, which is the reactive hyperaemic phase following the ischaemia. RP occurs in two forms: Raynaud's syndrome where there is an associated disorder (often a connective tissue disease) and primary Raynaud's disease (RD) where there is not. The latter is a common condition affecting as many as 10-20% of young women.¹ Whilst RD is benign in terms of ulceration and gangrene, it can be troublesome, interfering with both work and social activities by producing pain and reduction in manual dexterity. Vasodilator treatments for RD exist.^{2,3} In particular, calcium channel antagonists such as nifedipine have proven useful.³ Nevertheless, there is an unacceptably high level of side effects with calcium channel blockade⁴ in some patients. A product with fewer side effects but effective against the symptoms of RD would be useful in this disorder.

Chinese medicine has used extracts from the *Ginkgo biloba* tree at least since the fourteenth century. It was held to be sacred by the Japanese and Chinese, being grown in their temple gardens, with the leaf being made into an

infusion. It is reputed anecdotally to be potent in circulatory and other disorders and has become one of the top 10 purchased herbs in northern America. Because of the interest in its use, a number of clinical studies have been carried out evaluating cognitive functions, such as memory disturbances and dementia, and classical disorders of the circulation such as intermittent claudication. Double-blind placebo-controlled studies of *Ginkgo* have shown improvement in aspects of memory in healthy middle-aged volunteers⁵ but, despite a number of encouraging reports in dementia, a large randomized double-blind placebo-controlled trial from The Netherlands proved negative.⁶ Similar negative results in tinnitus were reported by Drew and Davies⁷ despite previously positive uncontrolled studies in this area.

Trial results in conventional circulatory disorders, however, appear more encouraging. There have been eight randomized placebo-controlled double-blind trials where *Ginkgo biloba* extract was used as a treatment for intermittent claudication. A recent meta-analysis⁸ of these trials found *Ginkgo biloba* extract to be superior to placebo in its symptomatic treatment.

The Raynaud's and Scleroderma Association (Alsager, UK) is a patient self-help group that has regular contact with sufferers of RP. Two years ago the Association carried out a questionnaire study after 250 of their members had tried a four-month course of Seredrin, a high-potency *Ginkgo biloba* phytosome. A total of 72% of the 250 respondents commented that the preparation improved the symptoms of RP. In questionnaire studies such as these, responder bias is well recognized, where people who have appeared to benefit take the time to write in with a positive response whereas those who have had no benefit do not

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reply. In the light of this we felt it was appropriate to carry out a double-blind placebo-controlled pilot study of a standardized *Ginkgo biloba* extract (Seredrin; Health Perception (UK) Ltd, Sandhurst, Berkshire, UK) in patients with primary RD.

Patients and methods

Patients

A total of 22 patients with RD were enrolled into the study. Ethical approval for the study was obtained from the local ethics committee and all patients recruited gave informed consent. All study procedures were in accordance with institutional guidelines. Patients were enrolled from the out-patient clinics and all lived in the same geographic area and therefore experienced the same climatic conditions.

After enrolment, all patients were given a pocket-sized diary in which they were requested to record the frequency and duration of any vasospastic attack (blanching). An overall severity score was recorded on a 10-cm visual analogue scale. Severity was defined as the patient's overall perception of their Raynaud's attack and included numbness, pain, burning, paraesthesiae and the effect of the attack on activities of daily living. There was a two-week baseline assessment period prior to the beginning of the treatment period. Patients who were already receiving treatment for their RD were asked to discontinue their medication during the first week. During the second week they were asked to note each vasospastic attack in the diary card. At the end of the baseline two-week period patients entered the treatment phase. Half of the patients were randomized to receive *Ginkgo biloba* extract 120 mg three times a day (total 360 mg per day) and the other half received a matching placebo. Neither patients nor investigators were aware of the treatment group allocation. Patients were reviewed after two, four and 10 weeks of treatment.

Blood tests

A total of 60 ml of blood was taken from the antecubital fossa using a 19-gauge butterfly needle and minimal venostasis. The blood was processed to allow measurement of platelet aggregation in response to 1 μ mol ADP and for measurement of plasma fibrinogen. Platelet aggregation was carried out as follows: platelet aggregation was measured both in whole blood and platelet-rich plasma, i.e., with and without the influence of red and white blood cells. Platelet aggregation in whole blood was measured using a Clay Adams Ultra-Flo 100 whole blood platelet aggregometer.⁹ Aggregation in platelet-rich plasma was measured using a PAP 4 platelet aggregometer (Bio-Data) based on the method of Born. Plasma fibrinogen was measured using a coagulometer (method of Clauss).

Statistical considerations

Formal power calculations were not carried out for the study, which was considered to be a pilot study destined to show trends between groups. The distribution of the number of daily attacks per individual was highly non-normal and a Poisson distribution was assumed. The likelihood ratio test was employed to compare the change in daily attack rates between the two treatment groups. The likeli-

hood ratio test uses the difference in measured deviance between a model assuming no difference in effect between placebo and active treatment and a model expressing this difference.

Results

The demographic details of the two patient groups are shown in Table 1. The age range of the Seredrin group was 19–51 years compared with 18–52 years in the control group. A total of 22 patients were enrolled into the study. One patient went on holiday to southern Europe, another patient withdrew consent early in the study and another failed to fill out her diary card properly. It was inappropriate to analyse these three patients because there were no meaningful data. It was therefore decided to exclude them from the analysis prior to the code break. In total, 10 patients in the placebo group and nine in the active group remained for the analysis. The active group contained nine women and the control group contained nine women and one man. There were seven nonsmokers, one current smoker and one ex-smoker in the treatment group. There were nine nonsmokers and one smoker in the control group. All patients fulfilled standard criteria for diagnosis of RD.

There were no significant side effects in either group and no subject wished to withdraw due to side effects. Adverse events noted were thought to be due to normal winter conditions. Influenza (there was an epidemic at the time of the study), headache, chilblains, sinusitis and nausea were reported. Analysis of the diary cards showed that the mean (\pm standard deviation) number of attacks before treatment in the placebo group was 14.6 ± 10.7 attacks per week whereas the mean number of attacks after 10 weeks on placebo was 10.7 ± 12.3 , the increased number of attacks being explained by the reduction in the ambient temperature over the study period. The number of attacks per week prior to treatment with *Ginkgo biloba* was 13.2 ± 16.5 reducing to 5.8 ± 8.3 ($p = 0.00001$ for the *Ginkgo* group). This result is highly statistically significant when the change in daily attack rates of the two treatment arms is compared ($p = 0.0000048$, between-group comparison, likelihood ratio test). This reflects a reduction in the number of attacks by 56% in the active group compared to 27% in the placebo group. The mean duration of attacks was found to be 28 minutes (range 0–155) in the control group before placebo therapy and 17 minutes (range 0–252) after ther-

Table 1 Demographics and results.

Patient demographics	Placebo	Ginkgo
Sex	9 females/1 male	9 females
Median age (range)	42 (18–52)	36 (19–51)
Nonsmokers	9	7
Smokers	1	1
Ex-smokers	0	1
Median number of attacks/week [range]		
Before treatment	13 [1–30]	8 [3–63]
After treatment	9 [0–38]	4 [0–32]

apy, whereas the duration of attacks in the active group was 27.8 minutes (range 0–330) prior to Ginkgo therapy and 10.3 minutes after therapy (range 0–350, $p=0.48$ likelihood ratio test). The median number of attacks per week and ranges are expressed in Table 1. There was an 11% reduction in personal severity scores in the placebo group and a 25% reduction in the Ginkgo group ($p=0.11$, likelihood ratio test). Neither the reduction in duration or severity of attacks reached statistical significance.

Mean fibrinogen levels in the placebo group rose from 2.682 g/l to 2.718 g/l, an increase of 0.036 ± 0.549 (mean \pm SD), $p=0.84$. The mean fibrinogen levels in the Ginkgo group decreased from 2.984 g/l to 2.72 g/l, a decrease of 0.264 ± 0.549 (mean \pm SD), $p=0.111$. The difference in effect between the two groups was not significant ($p=0.21$). The platelet aggregant adenosine diphosphate (ADP) was used and the percentage change in aggregation after the treatment period was calculated. The percentage change (\pm SD) in the placebo group was -33.935 ± 57.349 . The percentage change (\pm SD) in the Ginkgo group was -35.435 ± 65.683 ($p=0.83$ for the difference between the placebo and active groups).

Discussion

This small pilot study documents the first double-blind placebo-controlled trial of *Ginkgo biloba* phytosome in RD. We used a reasonably large dosage (360 mg/day) in contrast to more recent negative studies such as tinnitus and dementia⁶ where lower doses were evaluated. In the majority of the positive intermittent claudication studies,⁸ in the positive cognitive function studies⁵ and in our own study a higher dosage regime was evaluated. This may have contributed to the detected benefit seen in these studies.

There are a number of reasons why one might see benefit from *Ginkgo biloba* treatment in patients with RD. *Ginkgo biloba* extract appears to have free radical scavenging properties¹⁰ and antiplatelet effects.¹¹ We have previously shown abnormalities in both these parameters in patients with RP.^{12,13} However, whilst these antiplatelet and radical scavenging effects may be beneficial in this group of patients, caution should be exercised by combining *Ginkgo biloba* with conventional anticoagulation therapy,¹⁴ in case interactions are seen.

This initial study is of interest as it showed a clear and highly statistically significant reduction in the number of Raynaud's attacks per day, as well as positive trends in the

other parameters. However, it contained only small numbers and should function as pilot work for a large multicentre study to evaluate the potential effect of *Ginkgo biloba* as a treatment for RD.

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