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Promising Hypotensive Effect of Hawthorn Extract: A Randomized Double-blind Pilot Study of Mild, Essential Hypertension

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This pilot study was aimed at investigating the hypotensive potential of hawthorn extract and magnesium dietary supplements individually and in combination, compared with a placebo. Thirty-six mildly hypertensive subjects completed the study. At baseline, anthropometric and dietary assessment, as well as blood pressure measurements were taken at rest, after exercise and after a computer 'stress' test. Volunteers were then randomly assigned to a daily supplement for 10 weeks of either: (a) 600 mg Mg, (b) 500 mg hawthorn extract, (c) a combination of (a) and (b), (d) placebo. Measurements were repeated at 5 and 10 weeks of intervention. There was a decline in both systolic and diastolic blood pressure in all treatment groups, including placebo, but ANOVA provided no evidence of difference between treatments. However, factorial contrast analysis in ANOVA showed a promising reduction ($p = 0.081$) in the resting diastolic blood pressure at week 10 in the 19 subjects who were assigned to the hawthorn extract, compared with the other groups. Furthermore, a trend towards a reduction in anxiety ($p = 0.094$) was also observed in those taking hawthorn compared with the other groups. These findings warrant further study, particularly in view of the low dose of hawthorn extract used.

Keywords: magnesium; hawthorn; *Crataegus*; hypertension; phytotherapy; herbal extract.

INTRODUCTION

Control of blood pressure in patients with hypertension is necessary for cardiovascular morbidity and mortality risk reduction. For many mildly hypertensive subjects, lifestyle modification is chosen as first-line treatment, with emphasis on exercise and dietary modification. Current dietary recommendations advocate a low-salt, low-fat diet, high in fruit and vegetables and wholegrains (Harsha *et al.*, 1999). As well as modifying macro-nutrients such as total fat, adherence to such a diet also enhances micronutrient intake, including the intake of Magnesium and flavonoids. Both of these nutrients have established muscle-relaxant properties, which potentially extend to hypotensive effects.

Of all nutrients studied, dietary Mg showed the strongest negative association with blood pressure in the Honolulu Heart Study (Joffres *et al.*, 1987). This observation has been shown in several, but not all, subsequent epidemiological studies. Moreover, the epidemiological evidence is substantiated by a number of observational studies, which suggest depleted Mg body status in hypertensive patients. While many authors report decreased serum and erythrocyte Mg levels in hypertensive patients (and their first-degree relatives) (e.g. Sudhakar *et al.*, 1999), others speak of higher intra-erythrocyte Mg concentrations compared with healthy controls (Sasaki *et al.*, 2000). Nevertheless, neither serum nor erythrocyte Mg levels accurately reflect body Mg stores, despite being routinely used in clinical practice, because they do not always correlate with the Mg content of other types of cell. Therefore, the evidence of altered Mg homeostasis in hypertension remains unclear.

Although the majority of epidemiological and animal studies support a pathological role for low Mg status in the aetiology and development of hypertension, the evidence from intervention clinical trials has been less convincing. The response of hypertensive patients to Mg therapy is inconsistent and heterogeneous. Therefore, even if a role for decreased Mg levels in the pathophysiology of hypertension appears likely, a consistent, reproducible effect of Mg supplementation on blood pressure has yet to be confirmed.

Flavonoids, including oligomeric procyanidins, are a diverse group of highly antioxidant phytochemicals with a broad spectrum of biological activity ranging from those with antiinflammatory, immune modulatory, diuretic, antimicrobial and oestrogenic-like action to those having muscle-relaxant properties. These compounds are high in fruit and vegetables, and may contribute to the hypotensive nature of healthy diets (Conlin *et al.*, 2000). Flavonoids also account for much of the physiological activity of traditional herbal medicines, including the

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hypotensive effects of hawthorn (*Crataegus laevigata* (Poiret) DC and *C. monogyna* Jacq). Pharmacological studies have confirmed cardiotonic and antiarrhythmic, as well as hypotensive properties for hawthorn extracts of leaves, flowers and berries (Leung and Foster, 1996; Newall *et al.*, 1996). Flavonoids contribute to the vasodilatory action of hawthorn extracts, which are thought to lower raised blood pressure through reduced peripheral vascular resistance.

Most of the clinical studies on hawthorn extracts have been carried out in Germany and have been conducted on subjects in various stages of heart failure. These studies show overall improvement of cardiac function, including evidence of hypotensive effects. Hence one RCT (randomized controlled trial) involving 78 patients with heart failure showed, in addition to improvements in heart performance, a significant lowering of systolic blood pressure (Schmidt *et al.*, 1994). Despite this late-20th-century research focus on cardiac failure, phytotherapists have, for decades, regularly used hawthorn extract as a general cardiovascular tonic for the treatment of mild, essential hypertension in patients with otherwise good health (Mills and Bone, 2000).

Numerous mechanisms have been suggested to account for the development of primary hypertension. These include increased sensitivity of peripheral blood vessels to adrenalin, angiotensin II or vasopressin, and decreased sensitivity to antiinflammatory eicosanoids (Altura and Altura, 1984). Low Mg status may increase blood pressure by a number of mechanisms, including: sympathetic nervous system activation, renin–angiotensin system stimulation and, perhaps most importantly, by intracellular calcium accumulation in vascular smooth muscle, linked with electrolyte imbalance. Mg supplementation has the potential to ameliorate these adverse changes. The hypotensive effects of hawthorn extracts are ascribed to a combination of decreased vascular resistance through relaxation of vascular smooth muscle, inhibition of eicosanoid synthesis, inhibition of angiotensin-converting enzyme and mild diuresis (Murray and Pizzorno, 1999). Hence, both supplements appear to have multiple, overlapping and complementary mechanisms, which would be mutually supportive in the treatment of hypertension. Thus, the objective of this pilot study was to investigate the hypotensive potential of magnesium and hawthorn extract both singly and in combination, to investigate possible synergy between them.

SUBJECTS AND METHODS

Volunteers with mild hypertension (diastolic blood pressure 85–100 mm Hg) were recruited locally through posters and an article in the University Bulletin. Thirty-six, middle-aged patients (18 males, 18 females) completed the study. Subjects with any form of heart disease, with existing pathology of major organs (e.g. renal insufficiency), taking prescribed drugs for hypertension or magnesium supplements, as well as pregnant women, were excluded from the study. All subjects gave written informed consent to participate. The study was approved by The University of Reading Ethics and Research Committee. Information on lifestyle of the participants was collected, as well as a medical history. Subjects were asked to keep to their customary diet and avoid changes in their lifestyle (e.g. exercise levels) during their participation to the study.

Subjects were randomly assigned (by sequential blind selection from a container of previously well-mixed, folded pieces of paper, on which treatment options had been written on the inside of the fold) to one of the four following treatments for a period of 10 weeks: (a) placebo (cellulose); (b) Mg (magnesium amino acid chelate, providing 600 mg elemental Mg/day); (c) 500 mg/day of dried, full-spectrum aqueous-alcoholic extract of hawthorn leaves and flowers, standardized to $\geq$1.8% vitexin-2-rhamnosides; (d) a combination of (b) and (c). The hawthorn extract was supplied by Indena (Milan, Italy). Lamberts Healthcare Ltd, (Tunbridge Wells, Kent, UK) encapsulated the hawthorn extract and provided the Mg tablets. Hawthorn and Mg were administered as separate tablets using a double placebo. Compliance with intervention was assessed by counting the tablets returned at each visit.

Design of the study and analyses. The study was double-blind, placebo-controlled and parallel. Hence the volunteers and the investigator were unaware of the intervention allocation. Volunteers were invited to the Hugh Sinclair Unit of Human Nutrition on three occasions after screening: at baseline and after 5 and 10 weeks of intervention. On each occasion three readings of systolic and diastolic blood pressure (BP) and heart rate were performed at rest using an by Omron 703CP automatic BP monitor (Omron Terminals Ltd, Chessington, UK). Similar readings were taken after stress induced by a 5 min computer-based test of mental arithmetic, and again after 5 min on an exercise bicycle. For each set of three blood pressure readings the first value was discarded and the mean of the last two used for the analyses.

Subjects were weighed at each visit wearing indoor clothing and no shoes. Their height was also taken, in order to calculate Body Mass Index (BMI). Dietary intake was estimated at baseline by means of a validated food frequency questionnaire (DietQ Version 3, TINUVIEL Software, Warrington, UK). The subjects were also asked to fill out a validated well-being questionnaire (Bradley and Gamsu, 1994) on each visit. The subjective feelings of well-being were among the secondary aims of this study and included sections on vitality, anxiety and depression.

On three occasions, (baseline, week 5 and week 10) each subject provided a specimen of urine (the first voided after rising in the morning). Estimated 24-h urinary Mg excretion was expressed in terms of creatinine excretion based on the formula below:

$$\text{Estimated 24 h urinary Mg excretion} = \frac{\text{Mg concentration in mmol/L}}{\text{Creatinine conc. in mmol/L}} \times \text{ideal weight (kg)} \times 3.869 \quad (1)$$

where ideal weight was (Height in m)$^2 \times 21$ (21 was taken as the ideal BMI).

Urinary creatinine was analysed at the Pathology Laboratory of the Royal Berkshire Hospital using a colorimetric method (Ektachen Clinical Products Division, Eastman Kodak Co., Rochester, New York 14650). Urinary Mg was analysed using the Monarch auto-

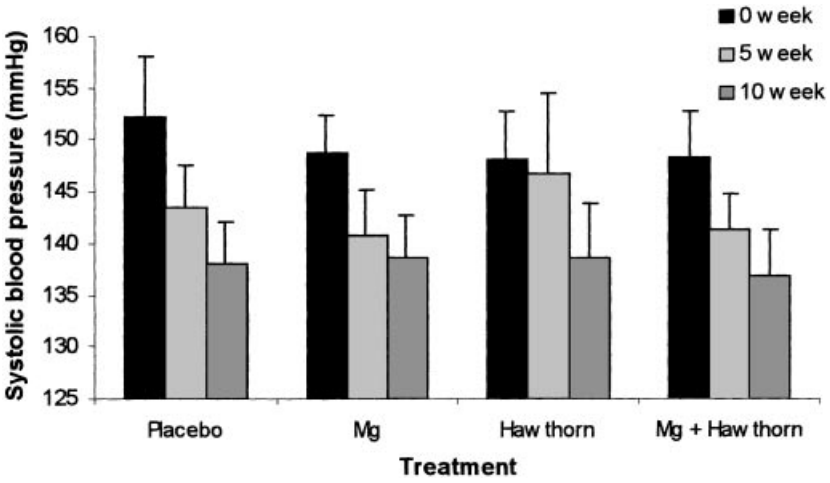

Figure 1. Mean resting systolic blood pressure (bars) and standard error of the mean (upper limit) of 36 mildly hypertensive subjects at baseline and 5 and 10 weeks after randomization to the following daily supplements: (a) placebo (b) 600 mg magnesium; (c) 500 mg extract of hawthorn leaves and flowers or (d) a combination of (b) and (c).

analyser (Instrumentation Laboratories UK, Ltd) which was equipped with an appropriate IL magnesium kit.

Statistical analysis. The number of subjects required for this pilot study was based on practical considerations. Data analysis was carried out in a blinded fashion until completed, when the treatment codes were revealed. ANOVA of treatment effect was undertaken on each dataset (e.g. diastolic resting BP, systolic resting BP) using the general linear models (GLM) procedure of the Statistical Analysis Software (SAS) package. The responses entered into ANOVA were differences of outcome from baseline at 5 and 10 weeks, and were adjusted for the effect of baseline BMI and Mg intake. ANOVA was extended to factor analysis for the main effects of magnesium and hawthorn extract intervention, as well as interaction. Baseline values were compared using Student's *t*-test for unpaired values.

RESULTS AND DISCUSSION

Resting BP: Mg supplementation

Baseline mean BP values were not significantly different between the treatment groups. There were no significant changes ($p<0.05$) in resting systolic or diastolic blood pressure and cardiac output after chronic supplementation with Mg, either alone or in combination with hawthorn extract, in this group of untreated, mildly hypertensive patients. There was a strong placebo effect which confounded the interpretation of results (Fig 1 and 2). The moderately short duration of the study (10 weeks) may also have contributed to the non-significance found in this study, as long-term studies have, mostly, reported significant hypotensive effects for Mg (Lind *et al.*, 1991; Witteman *et al.*, 1994). Interestingly, in the latter study,

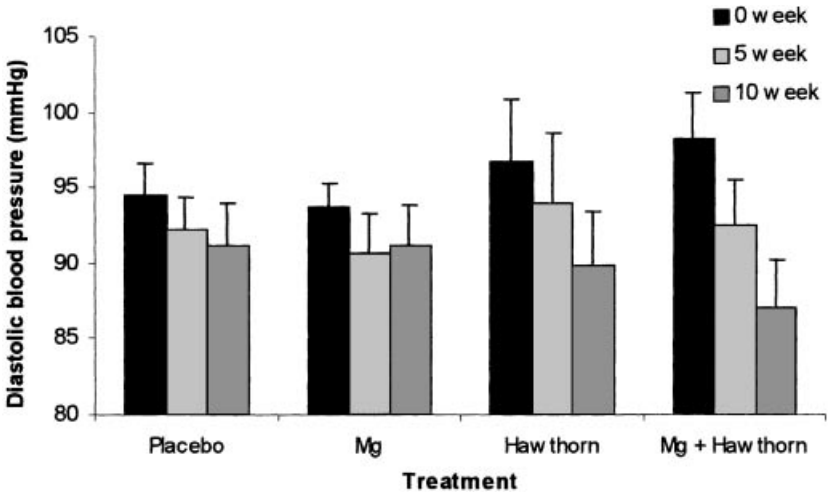

Figure 2. Mean resting diastolic blood pressure (bars) and standard error of the mean (upper limit) of 36 mildly hypertensive subjects at baseline and 5 and 10 weeks after randomization to the following daily supplements: (a) placebo (b) 600 mg magnesium; (c) 500 mg extract of hawthorn leaves and flowers or (d) a combination of (b) and (c).

Table 1. Personal characteristics of the volunteers in the four treatment groups

	Treatment group			
	Placebo	Magnesium	Hawthorn	Hawthorn and Mg
Gender, M/F	4/6	7/2	3/4	4/6
Age, years	49.4 ± 4.1	53.2 ± 3.8	53.3 ± 2.4	48.8 ± 2.9
Waist/hip ratio	0.82 ± 0.03	0.86 ± 0.03	0.87 ± 0.02	0.84 ± 0.03
BMI (Wt/Ht^2)	27.5 ± 0.7	25.5 ± 1.6	29.1 ± 1.3	28.9 ± 2.0
Smoking, Y/N	1/9	1/8	1/6	1/9
Dietary Mg (mg/day)	346.2 ± 27.3	485.0 ± 79.5	355.7 ± 32.3	339.3 ± 26.2
Dietary Ca (mg/day)	918.8 ± 55.9	1119.6 ± 128.8	1040.3 ± 82.2	1035.3 ± 117.6

Age, waist/hip ratio, BMI and dietary intakes of Mg and Ca are expressed as mean ± SE.

no significant effects of Mg were noted after 3 months, but after 6 months there was a significant drop in diastolic BP.

Even though intracellular or serum Mg concentrations were not measured in this study, it is likely that most volunteers were Mg replete. Dietary assessment revealed that mean dietary Mg intake was higher than the RNI (Reference Nutrient Intake; Department of Health, 1991) – particularly for the Mg group (Table 1). Mg supplementation may benefit only hypertensive patients with clinical or induced Mg deficiency, for example, those with prolonged diuretic treatment or with alcohol dependency. Hence, a positive response of Mg supplementation may depend on the pre-intervention Mg status. Indeed, a number of studies have provided data to support this notion (Plum-Wirell *et al.*, 1994). In our study, baseline differences in Mg urinary excretion (e.g. 130.7 ± 47.6 mg/day for the Mg group and 89.6 ± 16.1 mg/day for the combination group) were also shown, reflecting the differences in Mg intake. Hence, differences in Mg status between the groups might, at least partly, have accounted for the variable diastolic BP response to the treatments, observed at the end of the study.

There is debate as to whether there is a critical dose of Mg that can significantly lower blood pressure, or whether the dose required varies depending on the body status of other nutrients. The BP-lowering effect of Mg is believed to be mediated partly through a direct effect of Mg on the free concentration of intracellular calcium and/or other minerals, such as sodium. If the concentration of these intracellular minerals is high, higher amounts of Mg may be required for a hypotensive effect.

As far as the dose is concerned, Mg in high doses may have a true pharmacological effect on blood pressure. Intravenous Mg administration in pregnancy—a routine procedure for the prevention and treatment of eclampsia—shows a marked hypotensive effect in many pregnant women suffering from hypertension (Rudnicki *et al.*, 2000). However, the amount of Mg entering the body through the oral route is normally smaller than that via the intravenous route, and hence any effect of oral Mg supplementation may be less apparent. Nevertheless, Widman *et al.* (1993) have clearly demonstrated a dose-dependent effect of oral administration of Mg on blood pressure, with doses greater than 600 mg per day leading to a significant reduction in diastolic BP. However, even though the dose administered in this study (600 mg/day) was high enough to have the same effect without causing serious gastrointestinal discomfort, Mg was no better than placebo in its hypotensive potential.

As already mentioned, despite positive results from some studies, a number of intervention studies have failed to show any significant effect of Mg in hypertension. However, we ought to bear in mind that some of the negative studies reported in the literature were not carried out under strict control. For example, in a study by Plum-Wirell and co-workers (1994), who reported no effects of Mg supplementation on blood pressure, subjects were advised to lose weight at the commencement of the study. Weight loss can have a profound effect on blood pressure and may mask any effects of the active treatment. In addition, protein intake, fat intake, stress, physical activity and alcohol ingestion all appear to modulate the BP response. In our study, there were no changes in weight, in any of the treatment groups. Unfortunately though, one volunteer in the Mg plus hawthorn group increased his alcohol intake and reduced his exercise level during the study. In the same group, three other volunteers experienced unusually stressful events and one of them also stopped exercising. On the other hand, in the placebo group one volunteer improved her dietary habits (avoided sweets and alcohol) following baseline measurements, despite our request to avoid dietary or lifestyle changes.

Resting BP: hawthorn extract supplementation

Baseline BP values were not significantly different between the treatment groups. There was no statistically significant change in BP after administration of hawthorn extract, either alone or in combination with Mg (Fig 1 and 2). However, factorial analysis in ANOVA revealed a tendency towards a lowering of diastolic BP after 10 weeks among those 19 subjects assigned to hawthorn extract ($p = 0.081$). Lack of statistical significance could be attributed to the relatively small number of volunteers and the low dose of the hawthorn extract. A daily dose of 500 mg of full-spectrum extract is equivalent to approximately 2.5 g of dried herb per day. In a publication not available to use at the time of the study, Mills and Bone (2000) indicate that higher doses (up to equivalent of 3.5 of dried herb per day) may be necessary for effective control of hypertension. These authors also report hawthorn to be a safe herb with no restrictions on its long-term use. It is clear from the literature that, as for Mg supplementation, the clinical efficacy of hawthorn extract depends on adequate dose and duration of administration. Placebo-controlled studies of hawthorn extracts, focused on the working capacity of the heart, have shown that BP differences between active treatment

Table 2. Changes in systolic and diastolic blood pressure after stress during the course of the study

	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
Treatment	0 week	5 week	10 week	0 week	5 week	10 week
Placebo	154.5 ± 4.1	143.7 ± 4.5	139.6 ± 4.4	100.0 ± 4.5	92.7 ± 2.4	92.2 ± 3.7
Mg	150.0 ± 3.5	139.4 ± 3.8	141.0 ± 3.1	95.7 ± 2.2	91.7 ± 3.0	93.6 ± 2.4
Hawthorn	146.3 ± 6.0	145.6 ± 6.2	139.1 ± 5.5	93.1 ± 3.8	93.9 ± 4.4	91.4 ± 4.6
Mg and hawthorn	148.5 ± 4.4	144.2 ± 3.3	139.1 ± 3.9	96.7 ± 3.3	95.2 ± 4.1	90.8 ± 3.3

Figures are mean ± SE.

and placebo increases with both the dose of the administered extract and the duration of the supplementation (Schmidt *et al.*, 1994). While the dose of hawthorn used here was less than would normally be expected to have a hypotensive effect, the duration (10 weeks) may also have been too short. Clinical experience indicates that even at higher dosages, hawthorn extract supplementation requires at least 2 months to show a hypotensive effect (Mills and Bone, 2000).

Stress and blood pressure

Magnesium is known to act as an inhibitor of the sympathetic nervous system. Therefore, Mg deficiency may sensitize individuals to acute or prolonged stress. Whilst most people can adapt to suboptimal Mg intake in the short term, long-term imbalance in Mg homeostasis may aggravate stress reactions (Wirell *et al.*, 1994). While BP responses to mental stress may be influenced by dietary Mg intake, in our study, neither Mg nor hawthorn supplementation produced any significant reductions in the BP after stress induction (Table 2). Tests of mental arithmetic, even though they do not mimic perfectly the effect of real-life stress, are easily standardized and therefore represent a useful instrument for investigating cardiovascular variables (Deferne and Leads, 1996).

Exercise and blood pressure

Bicycle ergometer tests are usually conducted to assess changes in exercise capacity. Hellenbrecht *et al.* (1990) reported increased circulatory stress tolerance as assessed by exercise-induced stress after hawthorn supplementation in a small study (9 volunteers) of short duration (1 month). The authors attributed the effect to changes in adrenergic α- or β-receptor activity, since responsiveness to exogenous catecholamines was not altered. The site of action of this effect was suggested to be the myocardium or the peripheral blood vessels or both.

A randomized, double-blind, placebo-controlled, parallel study by Voneiff *et al.*, (1994) reported a significant decrease in heart rate at rest and mean diastolic BP during exercise after hawthorn supplementation in patients with dyspnoea (class II of the NYHA functional classification). Studies evaluating the effects of Mg on blood pressure after exercise in subjects without such severe pathology have not been conducted. In our study, no significant effects were demonstrated in any of the treatment groups (Table 3).

Effects of treatments on well-being

Few studies have examined the effects of Mg supplementation on well-being. However, in the study by Cox *et al.* (1991) on the use of Mg in the treatment of chronic fatigue syndrome, a significant improvement in vitality was seen after Mg treatment. This may be due to the role of Mg in energy transfer mechanisms mediated by phosphate bonds. In addition, depression and other psychiatric disorders, when associated with poor Mg status, usually respond promptly to Mg supplementation (Rasmussen *et al.*, 1989). Hence, Mg may play a role in general well-being, as assessed by various self-assessment scoring systems for depression, anxiety, vitality and positive well-being. In this pilot study, there were no significant differences between treatment groups at baseline. There was a small increase in vitality in the Mg group, but this did not reach statistical significance. In addition, there was no effect of any of the active treatments on general well-being or on other subscales. However, baseline scores of the volunteers showed that they did not suffer severely from any of the symptoms. Despite this, there was improvement in anxiety after 10 weeks in the 19 subjects randomized to hawthorn extract (Fig. 3), albeit that this benefit to health was not statistically significant ($p = 0.094$). This finding also

Table 3. Changes in systolic and diastolic blood pressure after exercise during the course of the study

	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
Treatment	0 week	5 week	10 week	0 week	5 week	10 week
Placebo	167.8 ± 5.1	152.8 ± 4.1	155.6 ± 4.3	98.1 ± 2.6	90.4 ± 2.8	97.1 ± 6.7
Mg	168.3 ± 6.5	155.8 ± 4.5	176.4 ± 5.7	97.7 ± 6.7	91.9 ± 3.2	95.3 ± 1.6
Hawthorn	163.1 ± 9.2	162.6 ± 9.2	152.9 ± 6.6	108.1 ± 9.1	96.6 ± 6.6	95.0 ± 4.9
Mg and hawthorn	167.7 ± 6.9	163.7 ± 4.6	163.0 ± 5.0	95.2 ± 5.1	93.6 ± 5.7	94.9 ± 5.1

Figures are mean ± SE.

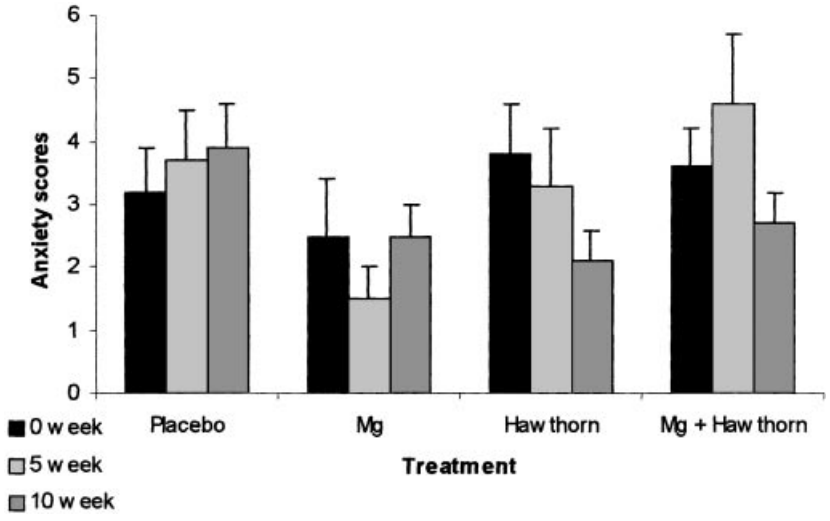

Figure 3. Mean anxiety score from well-being questionnaire (bars) and standard error of the mean (upper limit) of 36 mildly hypertensive subjects at baseline and 5 and 10 weeks after randomization to the following daily supplements: (a) placebo (b) 600 mg magnesium; (c) 500 mg extract of hawthorn leaves and flowers or (d) a combination of (b) and (c).

warrants further investigation, particularly as the French traditional use of hawthorn is as a mild sedative (Valnet, 1983).

In conclusion, Mg administration did not result in any notable effect on any of the variables examined. This is contrary to previous findings, but the lack of effect in our study may be attributable to the subjects being Mg-replete. Nevertheless, diastolic BP at rest showed a drop ($p = 0.081$) after 10 weeks of hawthorn administration, even though this effect did not reach statistical significance. Bearing in mind that both the numbers of volunteers in this pilot study and the dosage of hawthorn extract used were low, these results show promise. A larger, randomized, controlled study to fully assess the hypotensive and anxiolytic potential of hawthorn extract is now warranted.

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