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ORIGINAL ARTICLE

Is it Possible to Significantly Modify Blood Pressure with a Combined Nutraceutical on Top of a Healthy Diet? The Results of a Pilot Clinical Trial

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Abstract

Introduction Beyond the well-known effects on blood pressure (BP) of the dietary approaches to stop hypertension (DASH) and the Mediterranean diets associated to a correct lifestyle, often a lifestyle change is not simple and can show only long-time results: in this sense, a possible support might be derived from the use of some anti-hypertensive supplements or nutraceuticals, which may provide a significant reduction in blood pressure.

Aim We conducted a randomized, double-blind, placebo-controlled clinical trial in a group of 36 pre-hypertensive and first-degree hypertensive patients.

Methods The treatment period with a mix of bioactive substances (BPLN®, containing a donor of nitric oxide, magnesium, and vitamins) or placebo was 16-week long and was preceded by 4 weeks of diet stabilization.

Results At the end of the intervention, patients treated with the nutraceutical product showed a significant reduction of all morning pressure parameters and of evening systolic blood pressure, both versus the baseline and versus the group treated with placebo. These effects were maintained even after the first 16 weeks of treatment, confirming that the preliminary results were not due to simple changes in volume and do not lead to adaptation/tachyphylaxis. No patient complained of any side effects while taking the active treatment and placebo.

Conclusions The tested nutraceutical composite reduces systolic and diastolic blood pressure in the medium term, leading to a significant reduction in the estimated cardiovascular risk in a sample of patients with pre-hypertension or first-degree hypertension.

Keywords Hypertension · Blood pressure · Dietary supplements · Nutraceuticals · Clinical evidence · Clinical trial

1 Introduction

International guidelines for the management of hypertension and of the risk of cardiovascular disease suggest the improvement of lifestyle in a healthier way as the first step for the treatment of patients with pre-hypertension or first-grade hypertension [1]. There is no doubt that a correct dietary approach (especially if associated with a global lifestyle modification) is associated with a significant reduction in cardiovascular risk in the general population and in the hypertensive patient. However, often a lifestyle change is not simple and can show results after a long time. On one hand, this reduces compliance and persistence to the changes and, on the other hand, it reduces the expected efficacy of such interventions [2].

A possible support to lifestyle change might be derived from the use of some anti-hypertensive supplements or nutraceuticals, which, when effective, may provide a significant reduction in blood pressure, even on top of standard therapy [3]. In fact, meta-analyses of randomized placebo-controlled clinical trials have clearly shown that different substances of natural origin can individually induce pressure drops of 2-8 mmHg of systolic blood pressure and 2–5 mmHg of diastolic pressure [4]. Some of these require very high dosages (e.g. omega 3 fatty acids), others are too expensive (e.g. lactotripeptides), while others are burdened

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with side effects (e.g. aged garlic extracts) [5]. On the other hand, other nutraceuticals, such as precursors donor of nitric oxide, magnesium and folic acid, can improve endothelial function and consequently decrease the blood pressure levels [6].

In this context, we conducted a placebo-controlled pilot clinical trial to evaluate how the combination of evidence-based antihypertensive nutraceuticals could improve short- and medium-term blood pressure control at home in people with pre-hypertension or first-degree hypertension.

2 Methods

The study was conducted on 36 pre-hypertensive patients and first-degree hypertensive patients, not pharmacologically treated, with an estimated moderate cardiovascular risk, according to the SCORE algorithm.

The study was conducted according to the ethical rules of the Helsinki Declaration and all patients formally consented to the study.

At enrollment visit (T-1), patients were given standard behavioral and qualitative (not quantitative) dietary suggestions to correct unhealthy habits. Standard diet advice was given by a dietitian and/or specialist doctor. Dietitian and/or specialist doctor periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject's food diaries for counseling. In particular, subjects were instructed to follow general indication of a Mediterranean diet, avoiding salty products during the study, maintaining overall constant dietary habits. Individuals were also generically encouraged to increase their physical activity by walking briskly for 20–30 min, 3–5 times per week, or by cycling.

Thus, after 4 weeks of low-sodium Mediterranean stabilization diet, during which the patients were instructed to choose correct foods, to avoid excesses and to increase their daily physical activity, the same subjects were randomized to take a combined nutraceutical sachet or a placebo sachet indistinguishable in color and flavor, one every morning before breakfast.

The tested product contained a mix of bioactive substances (BPLN®, containing Beetroot dry extract—a donor of nitric oxide—500 mg, magnesium 300 mg, and vitaminàè C 400 mg, B1 25 mg and D 25 mcg per daily dose) with demonstrated antihypertensive and/or cardioprotective action (kindly provided by Pharmanutrition R & D, Milan, Italy).

Clinical and laboratory data have been obtained at the baseline (T0) and at the end of the trial (T1). Randomization was done using a drawing of envelopes containing randomization codes prepared by an independent statistician and specific software. The envelopes were then further mixed and distributed to the investigators who assigned the randomization code in a progressive way to the enrolled subjects. A copy of the code was provided only to the person responsible of performing the statistical analysis.

Throughout the study, we instructed patients to take the new product first dose on the day after they were given the study product in a blinded box. At the same time, all unused products were retrieved for inventory. Product compliance was assessed by counting the number of product doses returned at the time of specified clinic visits.

During the three previous days, the patients were requested to measure their pressure at home at 7:00 A.M. (before breakfast) and at 7:00 P.M. (before dinner), performing three consecutive measurements, as per guidelines. The pre-treatment and post-treatment parameters considered (systolic, diastolic, pulse and average blood pressure) were derived from the average of the data collected in the 3 morning and evening measurements of the 3 days prior to the visit.

The total cholesteraemia was monitored in order to estimate any risk variations with the SCORE algorithm, while the level of blood creatinine was used to evaluate possible variations of eGFR (estimated by the CKD-EPI formula), as a safety parameter.

All data were statistically analyzed with the help of SPSS 23.0 for Windows. The sample size suggested to detect a mean difference of 5% between treatments in term of systolic blood pressure reduction, with a power of 0.90 and an alpha error of 0.05, was of at least 20 subjects per group. As per protocol, we decided a priori to check the efficacy of treatments in subjects assuming at least the 90% of the tested products doses foreseen by the trial design. After a descriptive analysis, inferential comparison analyzes were performed for dependent and independent samples, using non-parametric tests for non-parametric data (Mann–Whitney test). A value of "p" lower than 0.05 was chosen as the significance threshold for all tests.

3 Results

A total of 36 subjects with an average age of 55 ± 8 years were enrolled, equally distributed between men and women. The baseline characteristics of patients assigned to the treatments were similar and no significant differences were observed regarding the studied parameters (Tables 1 and 2).

Diet compliance was monitored and evaluated as good throughout the duration of the study in both treatment groups.

No patient complained of any side effects while taking the active treatment and placebo. No significant changes in creatinine levels and eGFR were observed in either group.

Overall product acceptance was good in both groups and treatment compliance close to 100%.

The changes in the main efficacy parameters were summarized in Table 1 (placebo) and 2 (active treatment). Table 3 reports the between groups differences. In the placebo group, there was a small but significant reduction in morning systolic blood pressure compared to baseline ($p < 0.05$), compatible with the effect of the continuation of lifestyle change prescribed at the screening visit (also inferable from the slight but significant improvement in total cholesteraemia which showed a similar trend). Consequently, a small but significant improvement of estimated cardiovascular risk has been observed ($p < 0.05$).

The group treated with the nutraceutical product showed instead a significant reduction of all morning pressure parameters and of evening systolic blood pressure alone,

Table 1 Modifications in hemodynamic parameters, laboratory and estimated cardiovascular risk in the group treated with placebo

Parameters	Baseline (N = 18)	8 weeks (N = 18)	16 weeks (N = 18)
Morning SBP (mmHg)	146 ± 8	142 ± 9*	140 ± 7*
Morning DBP (mmHg)	91 ± 3	89 ± 4	89 ± 6
Morning PP (mmHg)	55 ± 4	53 ± 4	55 ± 3
Morning MAP (mmHg)	109 ± 11	106 ± 10	107 ± 8
Evening SBP (mmHg)	148 ± 7	146 ± 9	145 ± 9
Evening DBP (mmHg)	92 ± 4	91 ± 4	90 ± 3
Evening PP (mmHg)	56 ± 3	55 ± 4	55 ± 3
Evening MAP (mmHg)	111 ± 11	110 ± 9	109 ± 11
Total cholesterol (mg/dL)	192 ± 14	174 ± 13*	177 ± 12*
eGFR (mL/min)	82 ± 7	83 ± 6	82 ± 8
Estimated CV risk (%)	5.1 ± 0.8	4.7 ± 0.9*	4.7 ± 1.0*

CV cardiovascular, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *MAP* mean arterial pressure, *PP* pulse pressure, *SBP* systolic blood pressure

*P < 0.05 vs. baseline

Table 2 Modifications in hemodynamic parameters, laboratory and estimated cardiovascular risk in the group treated with combined nutraceutical

Parameters	Baseline (N = 18)	8 weeks (N = 18)	16 weeks (N = 18)
Morning SBP (mmHg)	147 ± 8	138 ± 7*°	139 ± 8*°
Morning DBP (mmHg)	92 ± 4	86 ± 3*°	85 ± 4*°
Morning PP (mmHg)	55 ± 4	52 ± 4*	54 ± 3*
Morning MAP (mmHg)	109 ± 10	106 ± 9*	107 ± 9*
Evening SBP (mmHg)	149 ± 9	145 ± 7*°	144 ± 8*°
Evening DBP (mmHg)	91 ± 5	89 ± 5	88 ± 3*
Evening PP (mmHg)	58 ± 5	56 ± 6	56 ± 5
Evening MAP (mmHg)	111 ± 10	108 ± 9	107 ± 9
Total cholesterol (mg/dL)	188 ± 16	167 ± 14*	166 ± 13*
eGFR (mL/min)	82 ± 7	83 ± 6	82 ± 8
Estimated CV risk (%)	5.2 ± 0.8	4.1 ± 0.9*°	4.2 ± 1.0*°

CV cardiovascular, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *MAP* Mean arterial pressure, *PP* pulse pressure, *SBP* systolic blood pressure

*P < 0.05 vs. baseline, °P < 0.05 vs. placebo

Table 3 Between-group comparison of significant modifications in hemodynamic parameters and estimated cardiovascular risk

	Δ 8 weeks	Δ 16 weeks
Morning SBP (mmHg)	− 2 (95% CI − 2.7 to − 0.4)	− 3 (95% CI − 4.1 to − 0.2)
Morning DBP (mmHg)	− 4 (95% CI − 5.8 to − 1.9)	− 5 (95% CI − 7.1 to − 1.8)
Evening SBP (mmHg)	− 2 (95% CI − 3.2 to − 0.3)	− 2 (95% CI − 3.1 to − 0.2)
Estimated CV risk (%)	− 0.7 (95% CI − 1.2 to − 0.1)	− 0.6 (95% CI − 1.1 to − 0.1)

CV cardiovascular, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

both versus the baseline ($p < 0.05$) and versus the group treated with placebo ($p < 0.05$). This resulted in a significant reduction in theestimated cardiovascular risk only in the group treated with nutraceuticals, both versus the baseline ($p < 0.05$) and versus the group treated with placebo ($p < 0.05$). The above reported effects were confirmed after both 8 and 16 weeks of treatment.

4 Discussion

The guidelines for the management of dyslipidemia already identified about ten years in nutraceuticals and functional foods with a cholesterol-lowering action a mean to control lipid levels in patients at lower risk [7]. Despite an equivalent (if not greater) amount of evidence in favor of antihypertensive supplements, this type of approach has not yet been clearly developed. Yet, the most recent American guidelines for the identification and management of hypertensive patients have particularly stressed the identification of patients with pressure previously defined as "normal-high" and the optimization of blood pressure control in subjects close to "normal" values [8]. This type of approach will involve on the one hand the identification of a much higher number of hypertensive subjects and on the other hand a high number of subjects with non-optimized pressure [9]. Since the same guidelines emphasize how this phenomenon does not necessarily have to be managed with a reinforcement of the pharmacological load, then it becomes more and more interesting to find alternatives that can make the patient more adherent to the modification of the lifestyle and to make such modifications more effective in reducing blood pressure levels without causing adverse events.

The moderate, but significant, antihypertensive effect observed in our study was in line with that expected based on the content of bioactive substances with vasodilator action present in the tested supplement.

These effects were maintained even after the first 4 weeks of treatment and they confirm, especially for the effects on blood pressure, that the preliminary results are not due to simple changes in volume and do not lead to adaptation/tachyphylaxis. The final result was a significant reduction in the cardiovascular risk estimated according to the SCORE algorithm of about one percentage point with an excellent tolerability profile. The attenuation of efficacy in the evening, compared to the morning post-assumption measurements, is probably linked to the short half-life of the active nutraceutical components. This fact also guarantees that accumulation phenomena are improbable and will allow shifting the administration time as needed. Finally, the active components lend themselves to association with other antihypertensive drugs and to perform extravascular functions of particular importance (see magnesium, vitamin D, etc.) [10].

The main limitations of this exploratory study were the reduced sample size and the short duration of the test, therefore it is not currently known whether we can have an adaptation to the effect and hence a reduction in long-term efficacy. However, the permanence of the effect over 16 weeks of treatment should exclude tachyphylaxis phenomena. Further studies must be conducted on more subjects and of longer duration. However, the efficacy and safety of use of the individual components included in the formulation tested in our study has already been extensively demonstrated in numerous studies of longer duration and adequately powerful.

In conclusion, the tested nutraceutical composite reduces systolic and diastolic blood pressure in the medium term, leading to a significant reduction in the estimated cardiovascular risk in a sample of patients with pre-hypertension or first-degree hypertension.

Compliance with Ethical Standards

Funding No specific funding were provided for the present study.

Conflict of Interest The authors state that they have not any conflict of interest to declare.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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