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Chronic Effects of Oral Cannabidiol Delivery on 24-h Ambulatory Blood Pressure in Patients with Hypertension (HYPER-H21-4): A Randomized, Placebo-Controlled, and Crossover Study

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View Article

Abstract

Background: Recent data indicate that cannabidiol (CBD), a nonintoxicating constituent of cannabis, is involved in several aspects of cardiovascular regulation, including blood pressure (BP). However, the impact of chronic CBD administration on 24-h BP and vascular health has not been previously examined in patients with hypertension. The primary aim of this randomized, triple-blind, placebo-controlled, and crossover study was to examine the influence of chronic CBD on 24-h ambulatory BP and arterial stiffness in hypertensive patients.

Methods: Seventy patients with mild or moderate primary hypertension, who were untreated or receiving standard of care therapy, were randomly assigned to receive either 5 weeks of oral CBD or placebo-matched controls. Following a >2-week washout period, patients were crossed over to alternate therapy. The primary outcome of the study was dynamic in 24-h ambulatory BP and was assessed using two-way repeated measure analysis of variance.

Results: Administration of CBD reduced average 24 h mean, systolic, and diastolic BP after 2.5 weeks (−3.22±0.90 mmHg [95% confidence interval −1.01 to −5.44 mmHg], −4.76±1.24 mmHg [−1.72 to −7.80 mmHg], and −2.25±0.80 mmHg [−0.30 to −6.01 mmHg], respectively (all $p<0.05$); however, these values largely remained stable following the uptitration of CBD dosing. There were no changes in liver enzymes or serious adverse events (AEs). There was no significant difference in pulse wave velocity (group×factor interaction: $F=1.50$, $p=0.226$) at different time points, regardless of the intervention arm.

Conclusions: In conclusion, chronic administration of CBD reduces ambulatory BP in those with untreated and treated hypertension. In addition, lack of serious AEs implies safety and tolerability of the above-noted CBD formulation. ClinicalTrials.gov ID: NCT05346562, Registered April 6th 2022.

Introduction

Arterial hypertension represents the biggest single cardiovascular risk factor contributing to the global all-cause mortality.[1–3] Emerging data indicate that cannabidiol (CBD), a nonintoxicating and well-tolerated constituent of cannabis, is involved in several aspects of cardiovascular regulation.[4] Specifically, CBD has been reported to cause vasodilation of isolated arteries, attenuate vascular inflammation, affect blood pressure (BP) and cardiac contractility mostly in animal models, but human studies have also demonstrated that CBD may affect vascular tone and BP.[5–7] Yet, most of these observations require further investigation to confirm effectiveness in a real-life clinical setting.

Data regarding the hypotensive effects of CBD, and mechanisms through which CBD exerts its effects in the cardiovascular system, are rather conflicting.[7–11] Furthermore, the impact of chronic CBD administration on 24 h BP and vascular health has not been previously examined in patients with untreated hypertension, nor it is known if CBD may further reduce BP and improve vascular function in patients already treated with standard of care antihypertensive medications. It is also noteworthy that influence of CBD on the cardiovascular system in humans might depend not only on a dose and duration of administration, but also on the delivery method of CBD.[12] Therefore, in the present trial, we used a DehydraTECH™2.0 CBD—a patented formulation that uses performance-enhancing dehydration process aimed to increase CBD bioavailability—as described in the study protocol.[13]

The principal aim of this randomized, triple-blind, placebo-controlled, and crossover study was to examine the influence of chronic DehydraTECH2.0 CBD administration on 24-h BP in individuals with mild or moderate primary hypertension who are either untreated or receiving standard of care therapy. Furthermore, secondary aim was to establish whether CBD will affect indices of arterial stiffness in these patients. Namely, secondary outcomes were changed in peripheral resistance, pulse wave velocity (PWV), and augmentation index at 75 bpm (AIx@75 bpm). Finally, the safety and tolerability profile of DehydraTECH2.0 CBD formulation during 5-week administration has been determined.

Methods

Trial design

HYPER-H21-4 was conducted as a single-center, randomized, triple-blind (Participant, Investigator, Outcomes Assessor), placebo-controlled, crossover study. The trial protocol was registered at the ClinicalTrials.gov (NCT05346562). The whole course of the study was conducted at the Department for Integrative Physiology, University of Split School of Medicine, Split, Croatia.

The trial design, alongside sample size calculation, has already been previously described in detail in the published study protocol.[13] The principal inclusion criteria were the presence of Grade 1 (140/90 to 159/99 mmHg) or Grade 2 hypertension (160/100 to 179/109 mmHg) treated with angiotensin-converting enzyme inhibitors (ACEi)/ACEi+diuretic/ACEi+Calcium Channel blockers or not receiving treatment; age 40–70 years, and body mass index 18.5–35.0 kg/m^2.[14] Detailed inclusion and exclusion criteria, adverse events (AEs) vigilance, and criteria for immediate termination of trial are outlined in the protocol.[13]

Interventions, trial visits, and follow-up

Eligible subjects were randomized in a 1:1 allocation to one of two treatment sequences: Placebo (A)/DehydraTECH2.0 CBD (B) (AB sequence) or DehydraTECH2.0 CBD (B)/Placebo (A) (BA sequence). The participants that were allocated to the BA sequence group received CBD for 5 weeks, with increase in dose after 2.5 weeks. Specifically, in the first 2.5 weeks, participants were receiving 225 or 300 mg/day, depending on body weight, whereas in the next 2.5 weeks participants received 375 or 450 mg/day. Subsequently, the participants underwent a >2-week washout. After the washout period, the participants from the BA sequence group received placebo for 5 weeks. The detailed dosing regimen is outlined in Table 1. Conversely, participants from the AB sequence group first received placebo for 5 weeks, followed by 5 weeks of CBD supplementation using the above-noted dosing regimen. The DehydraTECH2.0 CBD capsule manufacturing process is outlined in detail in the study protocol.[13]

Table 1. Dosing Schedule

Intervention	Dose period 1 (2.5 weeks)	Dose period 2 (2.5 weeks)
DehydraTECH™2.0 CBD (Intervention B)	≤75 kg: CBD, 225 mg/day • 75 mg morning (1 capsule) • 75 mg afternoon (1 capsule) • 75 mg bedtime (1 capsule) >75 kg: CBD, 300 mg/day • 75 mg morning (1 capsule) • 75 mg afternoon (1 capsule) • 150 mg bedtime (2 capsules)	<100 kg: CBD, 375 mg/day • 75 mg morning (1 capsule) • 150 mg afternoon (2 capsules) • 150 mg bedtime (2 capsules) ≥100 kg: CBD, 450 mg/day • 150 mg morning (2 capsules) • 150 mg afternoon (2 capsules) • 150 mg bedtime (2 capsules)
Placebo (Intervention A)	Placebo, number of capsules matched to active treatment based on body weight	Placebo, number of capsules matched to active treatment based on body weight

CBD, cannabidiol.

Each patient visited the laboratory 6 times: at the start of each treatment period (CBD or placebo), in the middle of the period (after 2.5 weeks), and at the end of each period (after 5 weeks). Patients were equipped with an ambulatory BP monitoring system, Schiller BR-102 plus PWA (Schiller AG, Baar, Switzerland). As per contemporary guidelines, a minimum of 70% usable BP recordings were required for a valid ambulatory BP measurement session.[14] Ambulatory BP readings were edited using modified version of the Casadei method, and the analysis was performed by two independent investigators who were blinded to the allocation of the patient.[15] Data for pulse wave analysis were obtained from the same monitoring system.[13] In addition, during each visit, office BP was measured, in accordance with standards for BP measurement (three times) using WatchBP Home A (Microlife

AG Swiss Corporation, Widnau, Switzerland) BP monitor. The details of procedures from each visit were further described in the study protocol.[13]

Blood samples were obtained and analyzed from the cubital vein at each visit. An experienced biochemist who was blinded to the allocation of participants analyzed all blood samples, using standard operating procedures in a certified institutional biochemical laboratory.

Safety and tolerability of CBD formulation were continuously monitored during the whole course of the trial. Subjects were instructed to contact a study team member in case of AE occurrence. The principal investigator of the study, alongside two study investigators holding a medical degree, were responsible for monitoring of the safety of the study, including monitoring and tabulating AEs in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.

All SAEs would have been reported to the local Institutional Review Board according to good clinical practices within 5 business days for nonlife-threatening events and within 24 h for potentially life-threatening events, yet no such events have occurred. If they had occurred, the participant would immediately stop receiving treatment and would be excluded from study. The trial was to terminate immediately if ≥20% of involved participants report SAEs. Except from monitoring AEs, as per Food and Drug Administration guidance, we measured indices of possible drug-induced liver injury (aspartate transaminase [AST], alanine transaminase [ALT], gamma-glutamyl transferase, bilirubin) at each visit.

Namely, samples for safety analysis were obtained at six time points for each participant (three during CBD, and three during placebo period): at the start of the respective treatment period, in the middle of the period (after 2.5 weeks), and at the end of each period (after 5 weeks).

Outcomes

The primary outcome of this trial was change in 24-h ambulatory BP. Secondary outcomes included change in total peripheral resistance, PWV, and AIx@75 bpm. Finally, the safety and tolerability profile of DehydraTECH2.0 CBD formulation during 5-week administration has been determined.

Statistical analysis

Collected data were analyzed with the statistical software SPSS statistics (version 28.0; IBM, Chicago, IL) and Prism 6 for Windows® (version 6.01; GraphPad, La Jolla, CA). Kolmogorov–Smirnov test was used to estimate the normality of data distribution. A comparison of quantitative variables was conducted using Student's *t*-test, or Mann–Whitney *U* test, depending on normality of distribution, whereas categorical data were compared using chi-squared test.

Both primary and secondary outcomes were assessed using two-way repeated measure analysis of variance (ANOVA), in which time and treatment were set as within-subject factors. On the other hand, to explore the presence of carryover effect, order of treatment was set as a between-subject factor. For variables in which difference between groups (CBD vs. placebo) was significant, one-way repeated measures ANOVA with *post hoc* Bonferroni correction was used to estimate difference in measurements in the treatment group (baseline, after 2.5 weeks, and after 5 weeks, respectively). The difference between respective measurements was presented as mean difference (standard error) [95% confidence interval {CI}, *p*-value].

In a subanalysis, difference with regard to previous antihypertensive treatment status was explored with two-way repeated measures ANOVA, using treatment status (i.e., whether patients were previously treated with antihypertensive medications) as a between-subject factor. Significance was set at $p<0.05$ for all comparisons.

Results

Baseline characteristics and randomization

The flow diagram of the study, including reasons for screening failure and dropout are presented in Supplementary Figure S1. Out of 70 randomized patients, one patient decided to withdraw from the trial before receiving the first dose, and was therefore excluded from subsequent analyses. Three participants decided to withdraw the trial after the first visit (two in BA, and one in AB sequence) due to personal reasons. Among 66 participants that successfully finished the trial, 5 patients had insufficient data to perform complete analysis owing to technical reasons (insufficient data for ambulatory BP analysis).

The baseline characteristics of the patients were compared in Table 2. The average age of our study population was 54.8±3.8 years, 58% were male participants, and average 24-h mean arterial pressure (MAP) was 103.3±10.1 mmHg. All participants were of Caucasian race. No significant differences in baseline characteristics were observed in age, sex, anthropometric characteristics, or standard laboratory measures between treated and untreated patients with hypertension, except in time since diagnosis ($p<0.001$).

Table 2. Baseline Characteristics of Patients

	Total (*n*=69)	Untreated hypertension (*n*=37)	Treated hypertension (*n*=32)	*p*
Age, years	54.8 (3.8)	55.3 (7.3)	54.4 (9.2)	0.154[a]
Male sex, *n* (%)	40 (58)	18 (48.6)	22 (68.8)	0.527[b]
Body mass index, kg/m^2	28.8 [27.2–30.2]	29.2 [26.2–30.2]	28.4 [27.4–30.2]	0.814[c]
Waist-to-hip ratio	0.94 (0.08)	0.95 (0.1)	0.93 (0.03)	0.206[a]
Family history of CV disease, *n* (%)	9 (13)	16 (50)	11 (29.7)	0.087[b]

	Total (*n*=69)	Untreated hypertension (*n*=37)	Treated hypertension (*n*=32)	*p*
Time since diagnosis, years	4 [2.0–6.0]	5.0 [3.0–7.5]	3 [2.0–4.3]	<0.001[c]
Total cholesterol, mmol/L	5.59 (0.9)	5.6 (0.9)	5.6 (1.1)	0.933[a]
Low-density lipoprotein, mmol/L	3.41 (0.8)	3.4 (0.7)	3.4 (0.9)	0.953[a]
High-density lipoprotein, mmol/L	1.4 [1.2–1.7]	1.4 [1.2–1.6]	1.4 [1.1–1.7]	0.728[c]
Triglycerides, mmol/L	1.30 [0.9–1.8]	1.1 [0.8–1.8]	1.4 [1.1–1.9]	0.409[c]
Aspartate transaminase, U/L	23 [19.7–27.2]	24.0 [20.0–28.0]	23.0 [19.0–26.0]	0.812[c]
Alanine transaminase, U/L	23.0 [18.0–31.3]	22.5 [17.5–29.0]	27.0 [18.7–33.0]	0.402[c]
Gamma-glutamyl transferase, U/L	18 [13.0–28.2]	17.5 [12.5–28.0]	21.0 [14.5–28.3]	0.474[c]
Creatinine, µmol/L	75.0 [61.0–84.0]	78.2 [59.7–78.2]	82.0 [71.9–87.5]	0.113[c]
Bilirubin, µmol/L	9.0 [7.0–11.8]	9.0 [7.0–11.5]	8.0 [7.0–11.7]	0.924[c]
Fasting blood	5.1 [4.8–	5.2 [4.8–5.8]	5.1 [4.8–5.5]	0.616[c]

	Total (*n*=69)	Untreated hypertension (*n*=37)	Treated hypertension (*n*=32)	*p*
glucose, mmol/L	5.6]			
Therapy, *n* (%)				
ACEi	15 (21.7)	N/A	15 (46.9)	N/A
ACEi + CCB	14 (20.2)	N/A	14 (43.8)	N/A
ACEi + thiazide diuretic	3 (4.3)	N/A	3 (9.4)	N/A
Ambulatory BP				
24 h MAP, mmHg	103.3 (10.1)	103.9 (10.5)	102.6 (9.7)	0.579[a]
24 h SBP, mmHg	134.6 (13.0)	134.5 (13.4)	134.7 (12.6)	0.938[a]
24 h DBP, mmHg	82.3 (9.3)	83.3 (9.7)	81.0 (8.7)	0.318[a]
Daytime MAP, mmHg	107.0 (9.2)	107.7 (9.4)	106.1 (9.0)	0.481[a]
Daytime SBP, mmHg	138.7 (11.8)	138.8 (12.3)	138.6 (11.5)	0.944[a]
Daytime DBP, mmHg	85.7 (8.7)	86.8 (9.0)	84.2 (8.3)	0.223[a]
Night-time MAP, mmHg	97.3 (13.5)	97.4 (14.3)	97.1 (12.8)	0.914[a]

	Total (*n*=69)	Untreated hypertension (*n*=37)	Treated hypertension (*n*=32)	*p*
Night-time SBP, mmHg	128.1 (17.6)	127.6 (18.3)	128.8 (17.0)	0.786[a]
Night-time DBP, mmHg	76.5 (11.7)	77.1 (12.5)	75.8 (11.0)	0.636[a]
PWV, m/s	8.1 (1.0)	8.0 (1.0)	8.2 (1.0)	0.493[a]
AIx@75 bpm, %	29.6 (6.4)	30.2 (6.5)	28.8 (6.4)	0.351[a]

Data are presented as mean (standard deviation), median [interquartile range], *n* (%).

[a]Student's *t*-test for independent samples.

[b]Chi-squared test.

[c]Mann–Whitney *U* test.

ACEi, angiotensin-converting enzyme inhibitors; AIx@75 bpm, augmentation index at 75 bpm; BP, blood pressure; CCB, calcium channel blockers; CV, cardiovascular; DBP, diastolic blood pressure; MAP, mean arterial pressure; N/A, not applicable; PWV, pulse wave velocity; SBP, systolic blood pressure.

Primary outcome: effect of DehydraTECH2.0 CBD on ambulatory BP

Administration of CBD formulation reduced average 24-h MAP after the initial Period 1 (−3.22±0.90 mmHg [95% CI −1.01 to −5.44 mmHg, p=0.002]); however, average 24 h MAP remained stable following the up-titration of CBD dose (Dose Period 2; p=0.811; Fig. 1). Likewise, average 24-h systolic blood pressure (SBP) reduced after the first 2.5-week dose (−4.76±1.24 mmHg [95% CI −1.72 to −7.80 mmHg, p<0.001]), and remained stable with increased dosing (p=1.000; Fig. 1). Finally, the average 24-h diastolic blood pressure (DBP) was reduced after the initial Period 1 (−2.25±0.80 mmHg [95% CI −0.30 to −6.01 mmHg, p=0.019]), and did not change significantly following the uptitration of DehydraTECH2.0 CBD dose (p=0.590; Fig. 1). During the placebo trial, there were no significant changes in average 24 h MAP, SBP, or DBP (p=0.290, p=0.451 and p=0.330, respectively).

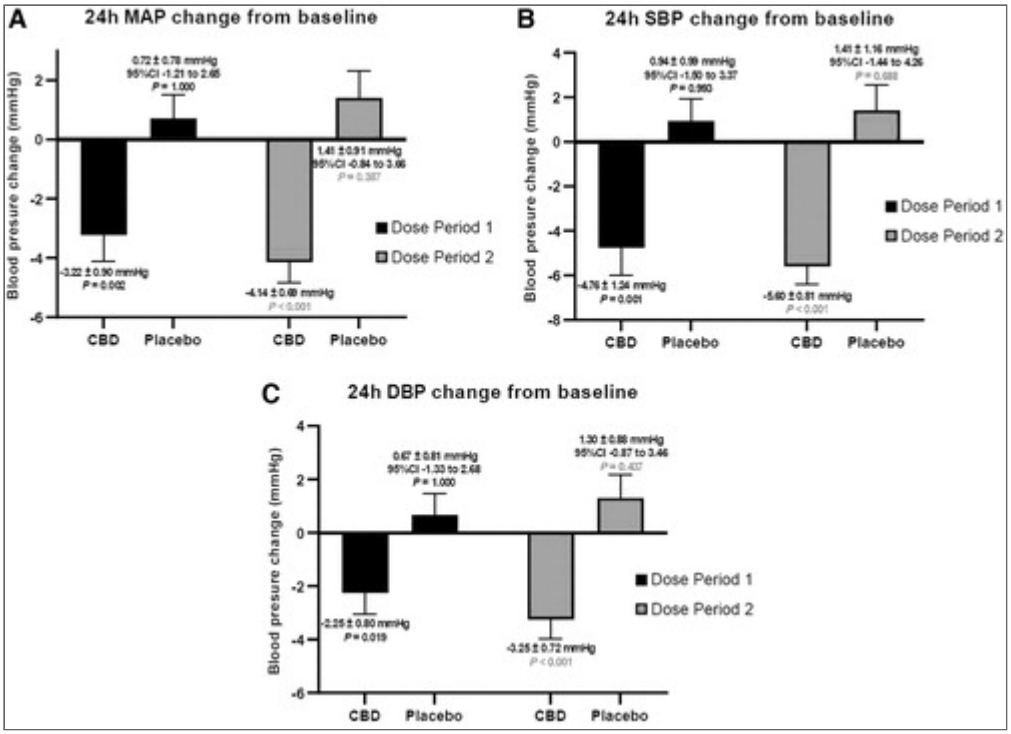

FIG. 1. Effect of chronic DehydraTECH™2.0 CBD administration on 24 h ambulatory blood pressure: **(A)** 24 h MAP; **(B)** 24 h SBP; **(C)** 24 h DBP. Data are presented as mean±SEM. Data were analyzed through repeated measure ANOVA. *p*-Values represent the difference between baseline BP and BP after 2.5 weeks (black) and BP after 5 weeks (grey), respectively. ANOVA, analysis of variance; BP, blood pressure; CBD, cannabidiol; CI, confidence interval; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; SEM, standard of the error mean.

Day-time ambulatory BP

Average daytime values of MAP were lower in comparison to baseline following the initial 2.5-week dose (−3.51±0.89 mmHg [95% CI −1.31 to −5.71 mmHg, $p<0.001$]), and remained unchanged following the second dosing period ($p=0.826$; Fig. 2). Daytime SBP and DBP followed the same pattern: day-time SBP was reduced by 4.51±1.24 mmHg [95% CI 1.47 to 7.55 mmHg, $p=0.002$] after Period 1, and remained stable following the final dosing period ($p=1.000$), and daytime DBP was reduced by 2.65±0.86 mmHg [95% CI −0.55 to −4.75 mmHg, $p=0.009$] after Period 1 and remained stable after the following dose ($p=0.618$; Fig. 2). During the placebo trial, there were no significant changes in average daytime MAP, SBP, or DBP ($p=0.813$, $p=0.994$ and $p=0.550$, respectively).

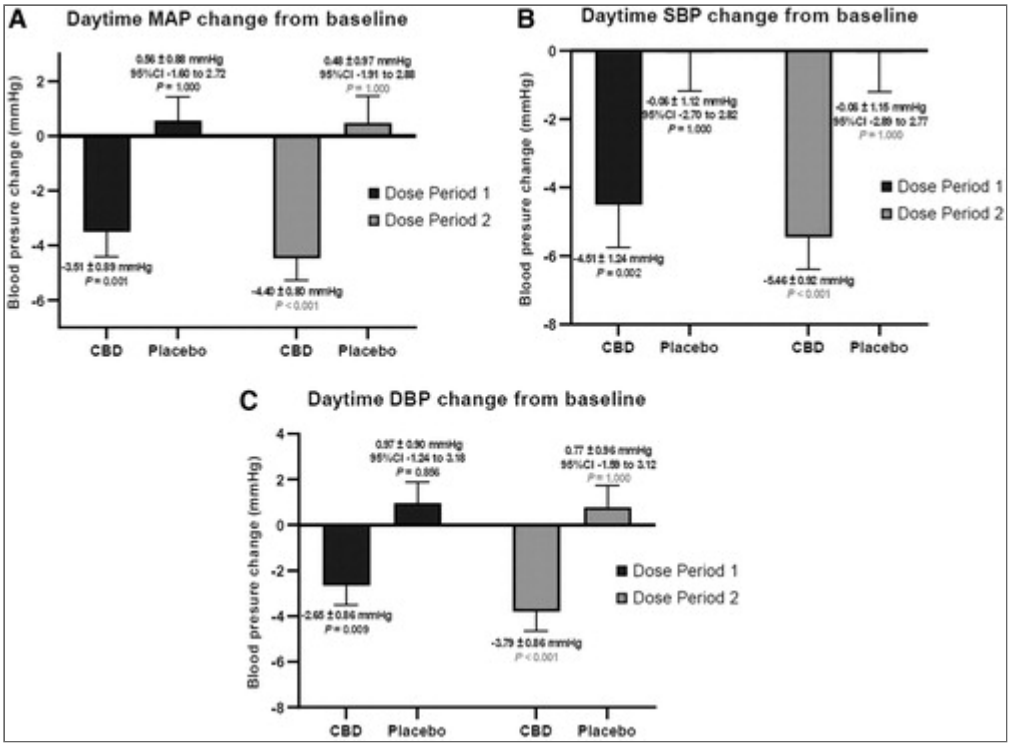

FIG. 2. Effect of chronic DehydraTECH2.0 CBD administration on daytime ambulatory blood pressure: **(A)** Daytime MAP; **(B)** Daytime SBP; **(C)** Daytime DBP. Data are presented as mean±SEM. Data were analyzed through repeated measures ANOVA. *p*-Values represent the difference between baseline BP and BP after 2.5 weeks (black) and BP after 5 weeks (grey), respectively.

Night-time ambulatory BP

Average night-time MAP was unchanged following 2.5-week administration of CBD (−3.37±1.38 mmHg [95%CI −0.03 to 6.77 mmHg, p=0.053]); however, following the 5 weeks of CBD dosing, it was reduced significantly in comparison to baseline (−3.81±1.08 mmHg [95% CI −1.15 to −6.47 mmHg, p=0.002]; Fig. 3). Night-time SBP reduced by 5.30±1.90 mmHg [95% CI 0.63 to 9.98 mmHg, p=0.021] following the initial 2.5-week dose and remained unchanged thereafter following the second doses (p=1.000; Fig. 3). On the other hand, there was no difference in night-time DBP at different time points, regardless of the intervention arm (CBD or placebo; group×factor interaction: F=2.93, p=0.058). During the placebo trial, there were no significant changes in average night-time MAP or SBP (p=0.193 and p=0.176, respectively).

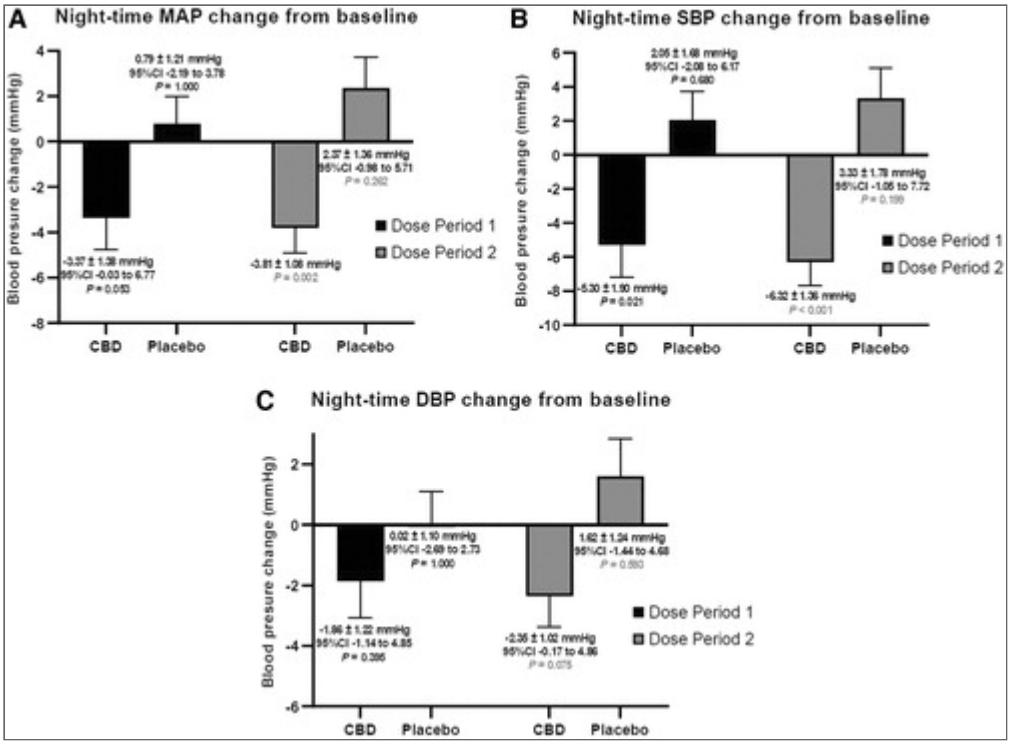

FIG. 3. Effect of chronic DehydraTECH2.0 CBD administration on night-time ambulatory blood pressure: **(A)** Night-time MAP; **(B)** Night-time SBP; **(C)** Night-time DBP. Data are presented as mean±SEM. Data were analyzed through repeated measures ANOVA. *p*-Values represent the difference between baseline BP and BP after 2.5 weeks (black) and BP after 5 weeks (grey), respectively.

In a subgroup analysis, there was no difference in any of the above-noted indices of ambulatory BP between treated and untreated group of patients with hypertension (Supplementary Table S1).

Office BP

Administration of CBD for 5 weeks reduced office MAP (−4.26±1.26 mmHg [95% CI −1.15 to −7.36 mmHg, p=0.004]); but significant difference was not reached in office MAP after first 2.5 weeks (p=0.054; Supplementary Fig. S2). However, 5-week CBD administration reduced office SBP (−4.80±1.50 mmHg [95% CI 1.12 to 8.49 mmHg, p=0.006]), and difference was already observed after Period 1 (−4.36±1.20 mmHg [95% CI −1.42 to −7.31 mmHg, p=0.002]; Supplementary Fig. S2). Difference in office SBP between Periods 1 and 2 has not been observed (p=1.000; Supplementary Fig. S2). Finally, administration of DehydraTECH2.0 CBD formulation did not significantly affect office DBP (group×factor interaction: F=0.98, p=0.378). During the placebo trial, when compared with baseline, there were no significant changes in office MAP, SBP, or DBP (Supplementary Fig. S2).

Secondary outcome: effect of DehydraTECH2.0 CBD on arterial stiffness

No significant difference was found between CBD and placebo in PWV (group×factor interaction: F=1.50, p=0.226) or AIx@75 bpm (group×factor interaction: F=1.51, p=0.223) at different time points, regardless of the intervention arm. In addition, difference between repeated measures was not present in a subgroup analysis (untreated vs. treated) either (Supplementary Table S1).

Safety profile

Only one patient did not receive the allocated intervention, and was hence excluded from the safety analyses. During the course of the intervention arm of trial (dose periods 1 and 2), eight participants in total experienced AEs. In the placebo trial, there were six reports of an AE. Based on MedDRA (Version 25.1) and CTCAE V.5.0 terminology, all reported AEs were classified as Grade I (mild, intervention not indicated) and were distributed over the first and second dosing periods. No serious AEs were reported, and no participant has discontinued treatment as a result of AEs. AEs reported/observed during dose periods are listed in Table 3. Finally, no participants demonstrated clinically relevant elevations in ALT, AST, or TBL that would lead to study exclusion.

Table 3. Adverse Events

Symptom	Incidence of AEs, *n* (%)	
	CBD	Placebo
Diarrhea	3 (4.3)	—
Bloating	2 (2.9)	2 (2.9)
Headache	1 (1.4)	2 (2.9)
Nausea	1 (1.4)	—
Vomiting	—	—
Hypersomnia	1 (1.4)	1 (1.4)
Constipation	—	1 (1.4)

AEs, adverse events.

Discussion

To the best of our knowledge, this is the first study to explore chronic administration of CBD on ambulatory BP in patients with untreated and treated hypertension. Available data suggest that CBD, alongside other constituents of cannabis, exerts hemodynamic effects.[4–8] Despite the lack of agonistic properties of CBD on CB_1 and CB_2 receptors, hemodynamic effects of CBD may be attributed to increase in concentration of endogenous cannabinoids, anandamide, and 2-arachidonoylglycerol, as well as various other biologically active compounds such as adenosine, serotonin, and dopamine.[16–20] In addition, data suggest that CBD may act as an α2-adrenoreceptor agonist, thus altering the response of sympathetic nervous system.[21] In a preclinical setting, it was shown that CBD reduces BP in hypertensive rats, and that CBD causes endothelium-dependent vasorelaxation of

the human mesenteric artery *in vitro*.[22,23] Furthermore, it is well established that cannabis users are more prone to develop orthostatic hypotension.[24]

Interestingly, in a recent study, chronic administration of CBD (10 mg/kg o.d. for 2 weeks) failed to reduce BP in a model of primary and secondary hypertension in rats, despite the fact that significant CBD-induced effects on cardiac and plasma endocannabinoid system, oxidative stress, and lipid metabolism were noted.[25]

However, studies that examined the effect of CBD supplementation on BP yielded ambiguous results. A meta-analysis by Sultan et al. that summarized effects of CBD on BP in human and animal models demonstrated no clear effect on BP; however, at the time when analysis was performed, only one human study was conducted.[7]

More recently, several small-scale studies explored hemodynamic effects of CBD. For instance, in a randomized controlled trial (RCT) performed on healthy young volunteers (n=26), CBD (600 mg/day) significantly reduced resting MAP after acute dosing, but did not affect 24-h ambulatory BP values after repeated dosing (6 days).[9] In addition, healthy participants taking CBD had lower SBP in response to exercise stress after acute dosing in a randomized crossover study (n=9).[10] In a separate study, participants (n=17) taking CBD (200–800 mg) had lower SBP, but not DBP in response to an acute cold pressor test.[11] Finally, in our previous study, we showed that oral CBD at a dose of 90 mg did not affect BP; however, under similar formulation and dose of the DehydraTECH2.0 CBD used in the current study, MAP was attenuated.[26]

For the first time, the present study extended these acute findings in a chronic setting and revealed a sustained reduction in BP. The published thresholds for lowering BP that are reflected in decreased composite cardiovascular endpoints are ~4.6 mmHg for SBP and ~2.2 mmHg for DBP.[27] Thus, the averaged effect observed in these values in our study is approximately equal to both of these values. Although the clinical implications of even longer-term CBD use in hypertension remains to be established, the observed sustained reductions in BP are encouraging, given the fact that many antihypertensive drugs used to treat hypertension require several weeks of treatment and/or combination dosing before they produce clinically meaningful reductions in BP.[28]

It is noteworthy that even those on a standard-of-care antihypertensive also responded equally to the CBD dosing. It must be highlighted that mechanisms underlying the decrease in ambulatory BP were not explored in the present study. Nevertheless, owing to the pleiotropic nature of CBD, which involves agonistic, antagonistic, and inverse agonistic effects on various receptors, as well as the effect on endocannabinoid system and multiple other mediators, it is very challenging to do so.

In fact, large discrepancy with respect to the effect of CBD on BP is probably owing to the fact that no studies that were conducted were adequately powered to demonstrate a change in BP, not to mention the fact that acute, rather than chronic, effects of CBD dosing were explored in most studies. In this regard, it is worth mentioning that the required sample size to demonstrate a change in BP was calculated for the present trial. Also, in a subanalysis of the present trial, we debated that feasible basis for CBD-induced BP reduction may be a result of interaction between CBD and the sympathochromaffin system, as evidenced by concomitant reduction in serum catestatin levels, and the fact that the extent of BP reduction was heralded by baseline catestatin concentrations.[29]

Recently, Sultan et al. observed reduction in arterial stiffness after 7 days of repeated CBD administration.[9] As flow-mediated dilation was also improved after 7 days, and based on previous studies demonstrating that CBD causes endothelium-dependent vasodilation, the authors argued that the same mechanism may be responsible for the potential reduction in arterial stiffness.[23,30] However, considering that effects of CBD on vascular system are pleiotropic, and insufficiently explored in humans, these explanations should be interpreted with caution. As the previously reported effects were due to the functional, rather than structural adaptation of the vascular network, in

our study, we aimed to explore indices of arterial stiffness in a more chronic setting. However, our findings imply that chronic CBD does not affect arterial stiffness. The discrepancy could be explained by the fact that the acute response of CBD on stiffness is not sustained. On the other hand, as a study by Sultan et al.[9] was performed on healthy individuals, it is plausible that difference in vascular response between hypertensive and healthy patients may have blunted the effect of CBD.

The use of DehydraTECH2.0 CBD over the course of 5 weeks turned out to be both safe and tolerable. Specifically, all the reported AEs were mild in nature, and were mostly associated with the gastrointestinal tract (diarrhea, bloating, nausea). Importantly, no drug–drug interactions with standard-of-care treatment for hypertension was found, implying that CBD may be a safe adjunct therapy for hypertension.

Unlike Δ9-tetrahydrocannabinol, CBD is devoid of adverse cardiovascular effects, such as tachycardia and acute coronary events associated with cannabis smoking.[4,31,32] Moreover, a recent meta-analysis that explored safety of acute and chronic CBD administration in 927 patients showed that most studies—20 of which were RCTs—reported no AEs with acute administration, and only mild-to-moderate AEs with chronic administration.[29] Furthermore, a recent Phase 1 trial revealed peak serum ALT values have risen over the upper limit of normal (ULN) in 44% participants, which exceeded the international criteria for drug-induced liver injury in 31% of these participants.[33]

The study included 16 participants, and all the reported AEs were mild or moderate. Notably, the final daily dose in the present study was two- to fourfold smaller than in the study by Watkins et al.[33] Although accumulated data suggest favorable safety profile, long-term safety data and uniform reporting of AEs are warranted to weight benefits and harms more appropriately.

The present study has some relevant methodological limitations to consider. First, the study was performed in a single center, and only Caucasian patients were enrolled, thus making it hard to infer about CBD antihypertensive effects in other populations. In addition, patients with Grade 3 hypertension were not included, and there was an uneven distribution of those with Stage 1 (n=57) and Stage 2 (n=12) hypertension; however, although exploratory, there was a selected relationship (r=0.340; p<0.001) between baseline BP and the magnitude of the related lowering during sleep following the 5-week intervention.

The possibility that CBD administration has a great antihypertensive influence on those with more severe hypertension should be explored in further studies. In this regard, it is also worth mentioning that although most within-subject factors were considered, BP might have been affected by factors that we could not influence, such as stress, amount of sleep, or variability in food intake. Interpretation of arterial stiffness indices is limited by the fact that these were not measured using gold-standard carotid–femoral PWV.

As in the present study, only DehydraTECH2.0 CBD formulation was used, it remains unknown whether the observed effects are applicable to other CBD formulations. Finally, despite the fact that the BP reduction was rendered clinically significant in light of existing evidence, it remains to be disclosed whether long-term CBD supplementation would result in significant improvement of cardiovascular outcomes.

The greatest strengths of the HYPER-H21-4 trial include measurement of ambulatory BP instead of office BP, which has so far been used in most studies that assessed CBD effect on BP. Furthermore, the crossover design enabled that both interventions are evaluated on the same participant, allowing comparison at individual, rather than the group level. Finally, careful exclusion criteria enabled that our study population is almost exclusively burdened by hypertension, and thus devoid of various other pathology that could confound the results.

It is noteworthy that hypertensive volunteers receiving standard care medication also experienced the antihypertensive effects of the chronic CBD administration. Although it is known that CBD is an inhibitor of the cytochrome P450 system and can therefore increase plasma concentrations of medicines already in use, we did not observe any drug-drug interactions between CBD and anti-hypertensive therapy.[34] The therapeutic potential of longer-term treatment with CBD, especially as a safe adjunct therapy for standard-care hypertensive treatment, should be explored in further studies.

Conclusion

In summary, the results of the present randomized, triple-blind, crossover study indicate that chronic administration of CBD encapsulated in form of DehydraTECH2.0 CBD reduces ambulatory BP. However, chronic CBD administration in the aforementioned form does not result in change of arterial stiffness. Importantly, no serious AEs or drug–drug interactions were reported during the whole course of the trial, thus proving safety and tolerability of DehydraTECH2.0 CBD. These findings should be confirmed in larger prospective cohorts to apply them into clinical practice.

Authors' Contributions

G.D.: Participated in conceptualization, methodology, investigation, formal analysis, and original draft preparation. M.K. and J.V.: Participated in visualization, investigation, formal analysis, and original draft preparation. Z.D. and J.B.: Participated in conceptualization, funding acquisition, resources, project administration, and reviewing and editing of the article.

Ethics Considerations

The Ethics Committee of the University of Split School of Medicine approved the study on December 15, 2021 (Class: 003-08/21-03/0003; Reg. No.: 2181-198-03-04-21-0091), and all patients signed a written informed consent after they were informed about the procedures, safety, and purpose of this research.

Author Disclosure Statement

Not applicable.

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Supplementary Material

Supplementary Table S1

Supplementary Figure S1

Supplementary Figure S2

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Abbreviations Used

ACEi	angiotensin-converting enzyme inhibitors
AEs	adverse events
AIx@75 bpm	augmentation index at 75 bpm
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
BP	blood pressure
CBD	cannabidiol
CCB	calcium channel blockers
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DBP	diastolic blood pressure

MAP	mean arterial pressure
PWV	pulse wave velocity
RCT	randomized controlled trial
SBP	systolic blood pressure
SEM	standard of the error mean