

Failure of Psychological Interventions to Lower Blood Pressure; A Randomized Controlled Trial.

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ABSTRACT

Background

Previous studies have suggested that psychological intervention may be effective in reducing blood pressure. With rigorous methodology and the use of 24-h ambulatory BP monitoring we had the objective to compare the BP lowering efficacy of psychological interventions with that of a first-line antihypertensive drug in patients with mild primary hypertension.

Methods

In a prospective, open-label randomized controlled trial 65 adult patients with mild, uncomplicated hypertension were randomized to receive one of the following interventions for 12 weeks: 1) Individualized behavioral psychotherapy (IBT), 10 one-hour sessions of stress reduction training with a psychologist; 2) self-help psychotherapy (SHT), initial 1.5 hour session with psychologist and then reading of a self-help manual and listening to a relaxation audiotape daily, or 3) hydrochlorothiazide (HCTZ) 12.5-25 mg/day. The primary outcome was mean change in ambulatory blood pressure from baseline to week 12. Clinic resting blood pressure (BP) as well as adverse events were also measured

Results

Ambulatory blood pressure monitoring (ABPM) during 24 hours showed that hydrochlorothiazide significantly reduced both systolic and diastolic blood pressure as compared to baseline or IBT or SHT psychological therapies, ($-11.03 \pm 2.53 / -6.06 \pm 1.56$ mmHg vs. $-0.08 \pm 2.38 / 0.29 \pm 1.47$ mmHg vs. $-1.23 \pm 2.83 / -0.71 \pm 1.75$ mmHg, respectively, $p < 0.01$). Neither psychological therapy, IBT or SHT, statistically significantly lowered 24-hour ambulatory BP versus baseline.

Conclusions

In patients with primary elevated blood pressure, two psychological interventions failed to lower 24 hour ambulatory BP, whereas hydrochlorothiazide had its predicted BP lowering effect. The findings of this RCT are crucial addition to the evidence for health practitioners and patients seeking these types of non-pharmacological means to reduce their blood pressure.

Trial registration

Clinicaltrials.gov identifier: NCT00247910

INTRODUCTION

In patients with mild primary hypertension a number of options are available to attempt to lower the blood pressure. Non-pharmacological options include the DASH diet, low sodium diet, exercise, weight loss, and relaxation therapies. Relaxation therapies are based on the supposition that psychological stress may contribute to elevated blood pressure in some patients ^{1,2}. One link between stress and hypertension has been described as elevated sympathetic tone and vagal dysregulation ^{1,3}. There are several systematic reviews that have evaluated the value of diverse psychological or relaxation therapies in reducing blood pressure in patients with primary hypertension as compared with no therapy or sham therapy⁴⁻⁸. However, they have reported conflicting results. In a recent Cochrane systematic review of relaxation therapies, 25 RCTs (n=1,198) were evaluated. The review concluded that the BP lowering effect was questionable because of the poor quality of studies. In fact, when including only trials using blinded outcome assessment (9 RCT, n= 498), there was no significant reduction in either SBP or DBP⁹.

It remains important to know whether psychological interventions lower BP and what is the magnitude of the effect as many patients would choose this therapy over drug therapy if they were equally efficacious. We were therefore interested in rigorously evaluating the BP lowering effect of two psychological interventions. The first intervention, intensive behavioural therapy, involved 10 hourly psychological therapy sessions over a 10 week period. It has the advantage of allowing the therapist to tailor the therapy to the particular stressors in the individual patient.

The second intervention, self help therapy, involved 1.5 hour of therapist time plus daily relaxation exercises administered by the patient. It has the advantage of requiring less therapist time and more frequent and regular relaxation sessions.

To rigorously assess the effects of these two psychological interventions we compared them with a thiazide, a common first-line drug treatment of mild primary hypertension. There is a large amount of RCT data showing a BP lowering effect of thiazides and the magnitude of the short-term systolic/diastolic blood pressure lowering effect is approximately, 9/4 mm Hg¹⁰. There is considerable value in using a drug with a known effect as a comparator. As far as we know there are no previous RCTs comparing psychological interventions directly with a drug therapy control.

METHODS

Design

Prospective, open-label randomized controlled trial.

Setting and Participants

Adult patients (≥ 18 years-old), from the community, with mild hypertension, defined as resting systolic blood pressure (SBP) ≥ 140 and or diastolic blood pressure (DBP) ≥ 90 mm Hg, were eligible. Patients were excluded if they had cardiovascular complications or any suspected medical condition that might have resulted in unacceptable risk of complications due to uncontrolled hypertension during the study period. Patients with uncontrolled hypertension (SBP ≥ 170 or DBP ≥ 100 on medication) or excessively high BP ($\geq 180/110$ off medication) were also excluded. Patients suspected of secondary hypertension were excluded, as well as patients who were pregnant or expecting to be pregnant, or who had a history of allergy, hypersensitivity or intolerance to thiazides.

Protocol

Patients who were taking medication at the time of initial screening underwent a washout of 3 to 5 weeks. Patients meeting the inclusion criteria and with baseline resting clinic BP off treatment ≥ 140 or DBP ≥ 90 mmHg were randomized to receive one of the following interventions for 12 weeks: 1) hydrochlorothiazide 12.5mg /day initially and then 25 mg if SBP was ≥ 140 or DBP ≥ 90 mmHg after 4 weeks of treatment. 2) Self-help psychological therapy, consisting of an initial 1.5 hour meeting with a psychologist and then daily sessions by reading a manual and listening to an audiotape; or 3) Individualized behavioral psychotherapy consisting of 10 one-hour sessions with a psychologist. Both psychological treatments for hypertension consisted of learning relaxation, biofeedback and stress management. Details of these psychological managements have been published elsewhere ¹¹. Centralized randomization using a random number table was done in blocks of 9 (based on gender and whether they were taking antihypertensive drugs). Intervention allocation was done via telephone by the Cochrane Hypertension Review Group Coordinator at the University of British Columbia, who was unaware of the baseline characteristics of patients other than gender and prior use of antihypertensive drugs. The study protocol was reviewed and approved by the Institutional Ethical Review Board at the University of BC. Written informed consent was obtained from all patients.

Clinical evaluation and follow-up

Before enrollment, patients provided a medical history and underwent a physical examination. A specific laboratory assessment was ordered if considered necessary. After enrollment patients attended the clinic every 4 weeks. At each visit resting BP was taken. All resting blood pressure measurements were the average of five readings with one-minute intervals in a seated position, after five minutes of rest and with the examiner out of the room [using the oscillometric VSM-100 automated BP machine- ¹²]. In patients randomized to hydrochlorothiazide, serum levels of

potassium were measured at week 7. Patients were instructed to report to the clinic immediately if they had any unusual symptom during the study.

A pre-treatment 24-hour ambulatory blood pressure monitoring (ABPM) was taken, using the Spacelabs Medical ABP monitor (model 90207, Spacelabs Inc, Redmond WA). This 24-hour ABPM measured blood pressure (BP) at 20-min intervals between 8:00 am and 8:00 pm (day time) and at 1-hour interval between 8:00 pm and 8:00 am (night time). This 24-hour ABPM was also performed at 12 weeks at the end of study.

Outcome measures

The primary efficacy outcome was the mean change in ambulatory blood pressure from baseline to week 12.

The secondary efficacy outcome was the mean change in resting clinic blood pressure, over 12 weeks of treatment.

All adverse events, regardless of the nature, were documented, reviewed and reported to the ethics committee.

Statistical analysis

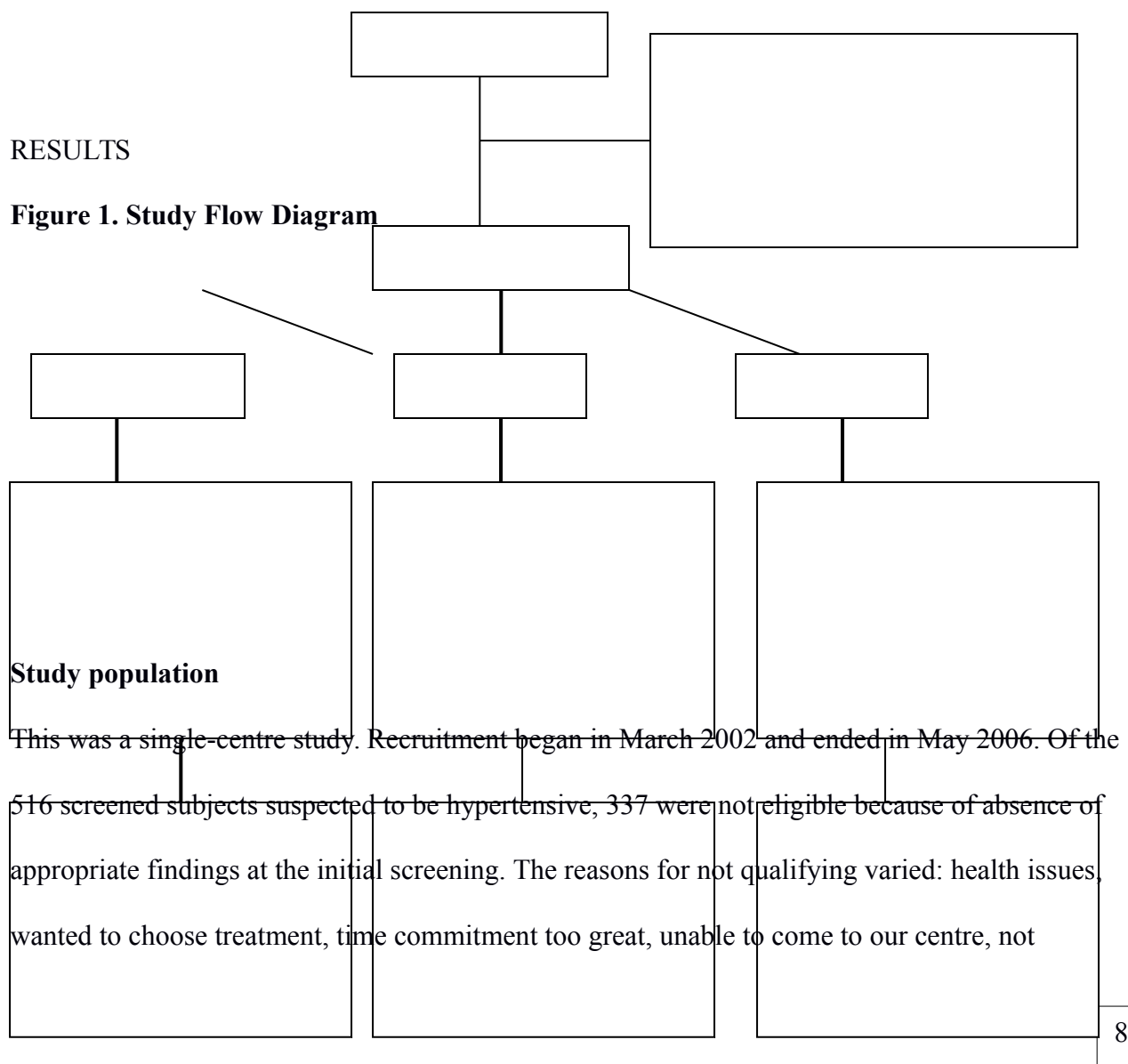
The analysis of the efficacy end-points was performed according to the intention-to-treat principles. All statistical analyses were performed using the statistical package NCSS 2007 (LLC Kaysville Utah USA). Unless otherwise indicated, data are reported as mean \pm standard error. Paired Student's t-test was used to compare continuous values before and after treatment within each group. Comparisons between groups were performed by analysis of variance (ANOVA) using the general linear model (GLM) approach for repeated measurements and Tukey's test for multiple comparisons. Using base-line values as a covariate, ANCOVA analysis was also performed. A p value less than 0.05 was considered to be statistically significant.

Role of Funding Source

The Canadian Institutes of Health Research (CIHR) was the funding source. The authors' work was independent of CIHR. The Funding source had no financial or other interest in study outcome and had no role in study design, collection, analysis, interpretation or reporting of the data.

RESULTS

Figure 1. Study Flow Diagram



interested in stress management or in the drug, or living far away. The remaining 179 patients were sent to the clinic for an evaluation. Of those, 13 patients did not want to participate any longer after this evaluation, and 101 patients were ineligible due to the following reasons: Sixty five did not meet the minimum blood pressure inclusion criteria after going through the washout process. Eight patients had excessively high BP $\geq 180/110$ and 28 had a medical history, such as coronary artery disease, precluding them from being included (Fig. 1).

A total of 65 patients were randomized. Twenty-one patients were assigned to receive hydrochlorothiazide (HCTZ), 23 to individualized behavioral psychotherapy (IBT) and 21 to self-help psychotherapy (SHT). Table 1 shows the baseline characteristics for the three groups of patients. Except for the 24-h ABPM systolic blood pressure, in IBT group, the groups were similar for all variables. Six patients in the HCTZ group, 6 in the IBT and 9 in the SHT group withdrew from the study or did not have a second 24-h ABPM measurement.

Table 1. Base-line Characteristics of the Patients

Characteristic	Individualized		
	Hydrochlorothiazide treatment N=21	Behavioral Psychotherapy N=23	Self-Help Psychotherapy N=21

Mean age(yr)	58±1.76	54±1.88	60±1.89
Female			
N (%)	11(52%)	12(52%)	11(52%)
Taking anti-			
hypertensives	15(71%)	12(55%)	13(62%)
at screening			
N (%)			
CCB	4	1	3
BB	1	2	0
ACE-I	7	5	7
ATII	0	4	1
Thiazides	11	7	9
Duration of			
hypertension	7.64 ± 1.32	5.45 ±0.82	8.15 ± 1.86
(years)			
Resting			
baseline BP			
(mm Hg)			
SBP	154 ± 2.4	147 ± 2.2	154 ± 2.9
DBP	89 ± 1.6	89 ± 2.0	89 ± 2.1
24 h-ABPM			
(mm Hg)			
SBP	146 ± 2.8	143 ± 2.3	153* ± 2.1
DBP	88 ± 2.0	89 ± 2.0	92 ± 2.1
* p <0.05 IBT vs. SHT group; Continuous data are expressed as mean ± SE			

Primary outcome: Change in ambulatory blood pressure monitoring (ABPM)

Hydrochlorothiazide produced a significantly greater reduction in both, systolic and diastolic blood pressure during the 24-h ABPM as compared to baseline or either individualized or self-help psychological therapies (systolic: -11.03 ±2.53 vs. -0.08±2.38 vs. -1.23 ± 2.83, respectively, p = 0.006; diastolic: (-6.06 ± 1.56 vs. 0.29± 1.47 vs. -0.71 ± 1.75, respectively, p = 0.01; see

figure 2 A and B). Neither psychological therapy, IBT or SHT, statistically significantly lowered 24-h ABPM compared to baseline.

Figure 2-A

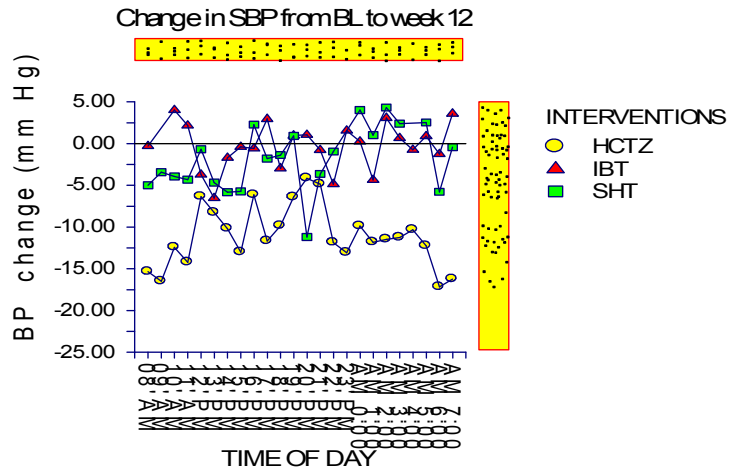
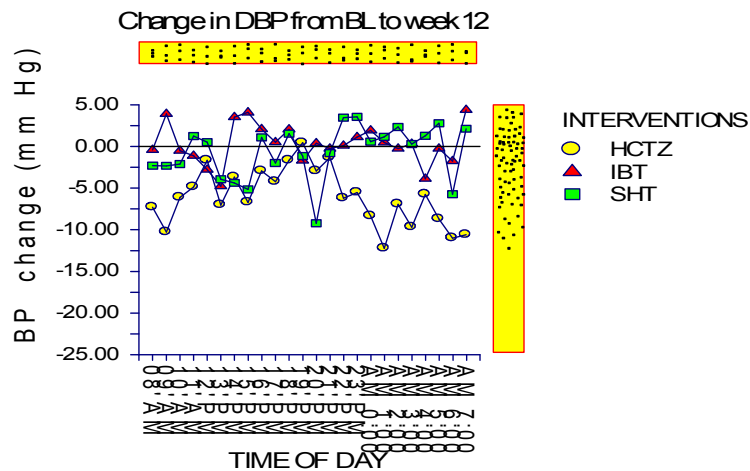


Figure 2-B



BP changes are shown in mmHg: n=15 for HCTZ, n=17 for IBT, n=12 for IBT. Data was not available for 6 patients in HCTZ (5 withdrawals, 1 missing ABPM report); 6 patients in IBT (all withdrawals); and 9 in SHT (8 withdrawals, 1 protocol violation).

Secondary outcome: Resting clinic blood pressure change

Data was available for more participants for this outcome: HCTZ n=19, IBT n=18 and SHT n=16. In this analysis both thiazide and IBT were associated with a statistically significant reduction in systolic and diastolic BP as compared to baseline (see Table 1) The BP lowering with the thiazide was numerically greater but the mean change in resting clinic Systolic or diastolic blood pressure over 12 weeks was not statistically different between HCTZ, IBT or SHT groups.

Table 1. Resting Clinic BP measurements at baseline and change (Δ) from baseline over 12 weeks

Resting BP Measurements	HCTZ		IBT		SHT	
	Baselin	Δ Baseline	Baselin	Δ Baseline	Baseline	Δ Baseline
	e	n= 19	e	n=18	n=21	n=16
	n=21		n=23			
SBP	154.42	-15.13*	147.22	-10.79*	154.38	-8.54
(SD)	(10.97)	(10.89)	(10.64)	(12.33)	(13.13)	(18.87)
DBP	89.23	-6.00*	89.43	-5.02*	88.62	-0.23
(SD)	(7.38)	(4.89)	(9.57)	(6.38)	(9.61)	(8.27)

BP values are expressed in mm Hg; * p <0.01 vs. baseline

Adverse events

There were a total of 5 withdrawals due to adverse events. Three participants withdrew because of intractable headache (one patient in the HCTZ group and two in the self-help behavioral treatment group). In all three cases, the headache subsided. One patient receiving HCTZ withdrew because of suspected allergic reaction to study medication (the patient stopped it because of sore in tongue and lips, at day 21). One patient receiving SHT withdrew because of palpitations. Another patient on 25 mg of hydrochlorothiazide developed hypokalemia, which was corrected with the addition of spironolactone. There were no serious adverse events during the trial.

DISCUSSION

In patients with primary hypertension, it has been hypothesized that psychological stress may contribute to the elevation of blood pressure and that psychological therapy lowers blood pressure. However, this has been called into question by a recent Cochrane systematic review when it was limited to studies that used blind outcome assessment⁹. This is the first randomized controlled trial comparing psychological therapy with a standard antihypertensive pharmacological treatment. Use of the thiazide as a control worked well in this study. The thiazide lowered blood pressure by 11/6 mmHg, which is similar to the reduction that has been shown in a meta-analysis of other thiazide studies at standard dose for a similar duration, 9/4 mmHg¹⁰. This is important as it demonstrates that the patients studied in this trial were representative of patients in other trials studying mild to moderate hypertension.

This study shows that in a clinical setting where thiazide drug therapy lowers blood pressure by a magnitude similar to expected the two psychological therapies did not. This was particularly clear using ABPM blood pressure data. In the present study the individualized behavioral

therapy and self help psychotherapy had no effect on the mean change in 24-h ambulatory SBP/DBP blood pressure ($-0.08 \pm 2.38 / 0.29 \pm 1.47$; $-1.23 \pm 2.83 / -0.71 \pm 1.75$, respectively).

HCTZ also significantly lowered resting clinic blood pressure as compared to baseline. In this case IBT but not SHT produced a statistically significant change from baseline. For this outcome there was no statistically significant difference between the groups. This is probably partly due to the “placebo effect” that is known to be common in studies using clinic BP measurements. It is also possible that the IBT helped patients learn to relax particularly in the clinic setting. If so this would be unlikely to have any clinical value as there was no reduction in 24 hr BP measurements. This study was a good demonstration of the value of having 24 hour ambulatory BP measurements that lack a placebo effect and provide a better test of the treatment effect because of the increased power provided by the large number of BP measurements taken throughout the day.

One of the strengths of this study is that patients were properly randomized to the 3 treatment arms and that there was a full-proof method to conceal treatment allocation from the patients and investigators. A second strength is the use of automated BP measurements for both ambulatory BP and clinic BP and the absence of the presence of investigators at the time of BP measurements. . This substantially reduces bias in the blood pressure measurement. A further strength of this study is that all the available BP results were used in the analysis. There was no exclusion of any data thus preventing any selective reporting bias.

The limitations of this study are firstly, the small sample size, which undoubtedly contributed to the lack of power to detect differences in resting clinic blood pressures. A second limitation, which is linked to the previous one, is the high rate of withdrawals (23%, 26% and 38%; for the HCTZ, IBT and SHT, respectively). A third limitation is the fact that by chance the baseline blood pressure in the SHT group was higher than the IBT group. This could have reduced the

opportunity to achieve a blood pressure lowering effect in the IBT group to a small degree, but it is unlikely to change the overall conclusions. This was demonstrated when we performed a post-hoc ANCOVA analysis using baseline values as a covariate. The p values changed minimally when this covariate was added to both, ambulatory and resting clinic blood pressure outcomes.

When we planned our study there was no information on the blood pressure lowering effect of psychological therapy as compared with a pharmacological treatment. We chose hydrochlorothiazide because, in addition to its well known BP effects, thiazides have the most evidence for reduction in mortality and morbidity when used as a first-line drug¹³. The key important finding of this study is that compared with hydrochlorothiazide, psychological therapies do not appear to have any blood pressure lowering effect over a 12 week period as assessed by 24 hour ambulatory measurements. These results apply to patients with mild uncomplicated hypertension (SBP \geq 140 and or DBP \geq 90).

This new information needs to be put in context with other available RCT data. The best available evidence of the effect of relaxation therapies on BP is provided by a recent Cochrane systematic review. In this review, Dickinson et al., found that when including only RCTs in which the blood pressure was measured blindly, the psychological or relaxation techniques did not statistically significantly reduce BP. This led the authors to conclude “In view of the poor quality of included trials and unexplained variation between trials, the evidence in favor of causal association between relaxation therapy and blood pressure reduction is weak. Some of the apparent benefit of relaxation was probably due to aspects of treatment unrelated to relaxation.” The results from the present RCT are in agreement with that conclusion. If future trials of psychological interventions and other relaxation therapies are conducted, they must be carried out using rigorous designs to minimize bias.

COMPETING INTEREST

All authors have nothing to declare

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ETHICAL APPROVAL

Certificate of approval by the Clinical Research Ethics Board of University of British Columbia # C01-0175.

CONTRIBUTORS

MIP: was involved with the design, conduct, analysis and writing of the first draft of this manuscript; WL, LP and JMW were involved with the conception of the study, design, conduct and revisions of this manuscript, TPJr was involved with the conduct of the trial.

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