PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hypertension Analysis of stress Reduction using Mindfulness meditatiON and Yoga (The HARMONY Study): study protocol of a randomized control trial
AUTHORS	Blom K, How M, Dai M, Baker B, Irvine J, Abbey S, Abramson B.L, Myers M, Perkins N and Tobe S.W.

VERSION 1 - REVIEW

REVIEWER	Joel W. Hughes, Ph.D. Associate Professor of Psychology
REVIEW RETURNED	30/01/2012

GENERAL COMMENTS	This manuscript describes the design of the HARMONY trial of MBSR for HTN. The design is a wait-list control randomized trial of a group stress management intervention for high BP. The study is well designed and overall a very strong contribution. I am eager to see the results. Minor points: • A wait-list control is a valid design, although an active control would have been more conservative. • Can research assistants be blinded to treatment condition? • How many screening BP's were conducted? If eligibility is essentially one 24-hour ABP, is that as prone to repeated measurement effects as in-office BP measurement? That is, previous behavioral interventions for BP have been criticized for inadequate baselines, and regression to the mean accounts for some of the treatment effect. ABP is more cumbersome than office BP, so perhaps one ABP can establish eligibility, whereas multiple sessions of office BP would be necessary. This is an empirical question. • The timeline is not clear—how long elapses between eligibility and baseline BP assessments, and between assessments and treatment? Is eligibility ABP also baseline ABP? • Unmedicated HTN: is this *newly diagnosed* or chronic unmedicated stage 1 HTN? Exclusion specifies no antihypertensives w/in 6 months, but did patients simply go off meds to be in the study? • Safety: I proposed this design in the USA and study section at NIH rejected the design, partly because of safety concerns. Specifically, they would not score the proposal in a fundable range if it was a behavioral intervention in patients with unmedicated stage 1 HTN. We had to move to prehypertension and an active control condition. I applaud you for getting a wait-list control with stage 1 HTN patients approved! • What is the funding source?

VERSION 1 – AUTHOR RESPONSE

For the reviewer:

1) A wait-list control is a valid design, although an active control would have been more conservative.

We chose to use a wait-list control design in an attempt to follow the methodology used by Linden. Using a wait-list control has the advantage of letting everyone in the study receive the same intervention and (if randomization was employed properly) ensures homogeneity between the two groups.

One of the limitations may be that expectations of improvement differ between the treatment and control group. The control group knows that they are not yet receiving an active treatment and has no reason to expect positive change. Other possible threats are that people content to sit on a waiting list may be atypical (unusually cooperative), or they may seek other "off-study" treatments on their own. However, as mentioned before, if randomization has been employed properly then different personality types should be equally distributed between treatment and control arms with the only difference between the two groups being the timeline for delivery of intervention.

2) Can research assistants be blinded to treatment condition?

Blinding is not possible as only one research assistant works on the study at a time. They are responsible for organizing and scheduling all study related visits, as well as sending participants necessary information for the MBSR course. They also MBSR collect homework logs and enter this data into the database. Due to the involved nature of their role and the fact that this was a wait-listed RCT (subjects were randomized to either “early” or “delayed”) it is impossible to blind participants or study personnel. However, those teaching the MBSR program are not informed of which group a participant is randomized to (ie whether they were early or delayed).

3) How many screening BP’s were conducted? If eligibility is essentially one 24-hour ABP, is that as prone to repeated measurement effects as in-office BP measurement? That is, previous behavioral interventions for BP have been criticized for inadequate baselines, and regression to the mean accounts for some of the treatment effect. ABP is more cumbersome than office BP, so perhaps one ABP can establish eligibility, whereas multiple sessions of office BP would be necessary. This is an empirical question.

To begin, two screening BP’s are conducted. First, screening is done using the BPTru, mostly with the aim of screening out those whose BP is too high to participate, as well as for practical reasons (ie high BP can make it too uncomfortable/painful for the participant to wear an ABPM for 24 hrs). Next, participants undergo 24 hr ABPM which is used to officially determine inclusion/exclusion from the HARMONY study.

With regards to ABPM and potential repeat measurements effects, it doesn’t seem to be as prone to repeat measurement effects when compared to other measurements. The following is a list (although not exhaustive) of the literature supporting the reproducibility of ABPM:

- Barnes at al (2002 – Reproducibility of ABPM in African American adolescents) found that reproducibility remained consistent over 4 months in a group of African American adolescents, however SBP remained only constant over 2 months.

- Stergiou et al (2005 - Reproducibility of home and ABP in children and adolescents);another study

among adolescents and children found that between to visits (8 wks apart) 24 HR ABPM produced the most reproducible BP values

- Stenehjem & 0s (2004 - Reproducibility of BP variability, white coat effect and dipping pattern in untreated, uncomplicated and newly diagnosed essential htn) found that average ABP readings were reproducible among those with untreated, uncomplicated hypertension

- Palatini et al (1994 Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST Trial. Hypertension and Ambulatory Recording Venetia Study) demonstrated reproducibility was better for ambulatory than for office blood pressure among 508 hypertensive subjects over a 3 month period

- Mansoor et al (1994 – Long term reproducibility of ABP) looked at 25 patients with established hypertension (off antihypertensive therapy for at least 4 wks). They underwent office blood pressure readings measured by mercury column sphygmomanometry and then by ambulatory blood pressure monitoring. Study demonstrated "that long-term reproducibility of ambulatory blood pressure is superior to that for office measurement."

- Fotherby & Potter (1993 Reproducibility of ambulatory and clinic blood pressure measurements in elderly hypertensive subjects) also demonstrated the same among the elderly ("daytime ambulatory blood pressure monitoring significantly improve the reproducibility of blood pressure measurements compared with clinic blood pressure readings in elderly hypertensive subjects [however] more than 30 readings [were] needed during a daytime recording to significantly reduce variability compared with repeated clinic measurements").

- Eguchi et al (2010 Reproducibility of ambulatory blood pressure in treated and untreated hypertensive patients) "The good reproducibility of BP reduction means that each single ABPM, before and after the treatment, is acceptable for the assessment of drug efficacy."

It should be noted that one anonymous review (2010, Title: Ambulatory blood pressure measurement, Journal: Prescrire International) concluded that "There is no evidence that ambulatory blood pressure measurement is more reliable than repeated measurement during several office visits for predicting cardiovascular events". It is possible that some of the treatment effect is due to regression to the mean (see: Ben-Dov et al 2005 "In clinical practice, masked hypertension is as common as isolated clinic hypertension: predominance of younger men", see: Talleruphuus et al 2006 "Isolated systolic hypertension in an elderly Danish population. Prevalence and daytime ambulatory blood pressure"). These authors suggest that regression toward the mean may partially explain their results. We will have to take this into consideration when doing our analyses.

We agree, ABPM is more cumbersome than office BP. However, both ABPM and office BP are repeated at the various study visits to maintain consistency throughout our measures (this may also allow us to address the issues of regression to the mean). It is well known that ABPM is much better at predicting long term target organ damage compared to other measures and, according to the Canadian Hypertension Education Program (CHEP), it is equivalent to measuring BP at home 5 times for the diagnosis of HT. In our case, we measure both ABPM and automated office BP at each study visit (except for safety visits which are comprised of only an automated office BP measurement in-between their other study visits).

4) The timeline is not clear—how long elapses between eligibility and baseline BP assessments, and between assessments and treatment? Is eligibility ABP also baseline ABP?

There is no time elapsed between eligibility and baseline BP assessments; eligibility ABP is also used

as the baseline ABP. Asking participants to wear the monitor again would be unreasonable with regards to their time commitment. We also do not have additional funding for more visits. The time elapsed between baseline assessment and MBSR treatment varies depending on which arm a participant is randomized to. If they are randomized to “early”, they start MBSR within 4 weeks of their baseline ABPM, whereas if they are randomized to “delayed”, the participant repeats their ABPM 12 weeks from baseline and subsequently begins their MBSR within 4 weeks of that second ABPM. We have clarified this in the manuscript.

5) Unmedicated HTN: is this newly diagnosed or chronic unmedicated stage 1 HTN? Exclusion specifies no antihypertensives w/in 6 months, but did patients simply go off meds to be in the study?

The participants mostly consist of individuals who have some knowledge that their blood pressure is rising but have not yet been prescribed antihypertensives by their primary health care providers. Based on this description, participants can be either newly diagnosed or chronic unmedicated – we did not differentiate inclusion/exclusion based on that criterion. With regards to the few who were on antihypertensives at some point but discontinued (on their own accord before learning about HARMONY), are typically those with moderately high BP, were prescribed a diuretic and elected not to take their medication any more. No patients go off medication to be in the study. We recognize the possibility that someone may have choose to go off antihypertensives when they should not, and may potentially base that decision on wanting to be in the HARMONY Study. In these events, screening with both the BPTRU and ABPM should capture those individuals whose BP is too high and should be on antihypertensives. In a situation where screening BP is too high, these individuals are counselled on a one-on-one basis with the primary investigator, Dr Sheldon Tobe, about their blood pressure, antihypertensive drugs and why they could not be in the study. We have elaborated on this further in the manuscript.

6) What is the funding source?

Heart and Stroke Foundation of Ontario (can be found at end of manuscript under “Funding Statement)