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Combination of music with lifestyle modification versus lifestyle modification alone on blood pressure reduction – A randomized controlled trial

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ABSTRACT

Objective: To evaluate the change in blood pressure (BP) after 3 months of music intervention combined with lifestyle modifications, in comparison with conventional lifestyle modifications.
Methods: A Prospective randomized control trial was conducted on hundred prehypertensives or stage I hypertensives who were randomly divided into two groups (n = 50 each). Both the groups were given lifestyle modifications while one had added music intervention (*raga bhimpalas*) for 3 months. Main outcome measures were 24 h ambulatory BP monitoring, stress levels, and biomarkers of hypertension.
Results: Mean (SD) of diastolic BP (DBP) pre and post intervention were overall = 85.1(6.8) and 83(8.7) {P = 0.004}, awake = 87.7(7.6) and 85.9(9.2){P = 0.021}. Regression analysis showed association between diastolic BP change and post-intervention stress score in the music intervention group. Significant change in BP was seen among those who were prehypertensives prior to intervention.
Conclusion: Music decreased DBP and when used as an adjunct benefitted subjects with initial BP in prehypertension range.

1. Introduction

Hypertension prevalence is increasing and globally, the number of hypertensives has been predicted to be 1.56 billion by 2025 [1]. The Seventh report of the Joint National Committee (JNC VII) has indicated lifestyle modifications (weight reduction, dietary modifications, salt restriction and physical activity) and pharmacological therapy for the management of hypertension [2].

Non-pharmacological modes aimed at reducing stress and promoting relaxation have been evaluated for the treatment of hypertension [3]. Listening to music, offers advantages of low cost, ease of administration, better compliance and safety. Music can be used for stress reduction through active music making, as well as passive listening.

Music as a non-pharmacological therapy for hypertension has been tried by a few investigators (listening to music, for durations ranging between 10 and 25 min for 1–3 months). Most of the studies have used clinical sphygmomanometric recordings and shown significant reduction in blood pressure (BP) [4–8]. Effect of music on 24 h ambulatory BP (ABP) measurements, with a prehypertension group and simultaneous measurements of biomarkers of hypertension has not been studied [9–13].

Raga, a word used to denote musical scale, is a set of musical notes presented in an orderly manner in order to generate a melody out of the same, in Indian music. Different ragas have the property of evoking different emotions among humans (example: *raga Mishra Mand* – refreshing light touch, *Neelambari* – sleep). According to *Sama veda and raga chikitsa* (Ancient Indian music literature), *ragas* that normalize BP are *Ahir bhairav, Bhupali, Puriya, Todi, Kausi Kanada, Hindol and Bhimpalas* [14,15]

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The objective of the present study was to evaluate the change in stress levels, 24 h ABP and biomarkers of hypertension after 3 months of music intervention (using *raga Bhimpalas*) combined with lifestyle modifications, in subjects with prehypertension or stage I hypertension, in comparison with conventional lifestyle modifications. The hypothesis was that there would be a decrease in 24 h ABP in subjects exposed to music and a concomitant change in the level of stress and biomarkers.

2. Methods

2.1. Inclusion and exclusion criteria

Subjects were recruited by the first author from the out-patient department patients and staff of a tertiary care centre. Inclusion criteria were as follows: Age group between 30 and 60 years; prehypertensives and stage I hypertensives as per JNC VII classification [2]. Pregnant women, subjects with body mass index (BMI) $\geq$35 kg/m^2, stage 2 hypertension, renal impairment, uncontrolled diabetes, stroke, epilepsy, hearing problems, psychiatric disorder, other cardiovascular and respiratory disorders were excluded.

The study period ranged from May 2012 to August 2013. The study protocol was approved by the institutional scientific committee on human research and ethical review board.

2.2. Sample size

The sample size was calculated (using nMaster 2.0 sample size software, Department of Biostatistics, CMC, Vellore) based on literature survey [7] which indicated that before lifestyle modifications the mean SBP was 133.03 $\pm$ 4.4 mm Hg. To calculate sample size, a SBP of 133.03 $\pm$ 4.4 mm Hg was predicted to reduce after lifestyle modification to 130 $\pm$ 8 mm Hg; and the group undergoing both lifestyle modifications and music intervention the SBP was predicted to reduce to 126 $\pm$ 8 mm Hg; expecting a decrease of 4 mm Hg due to music intervention. Using, independent t-test and considering a mean difference of SBP as 4 mm Hg (SD = 8) with 90% power and 5% level of significance the estimated sample size was 50 per group. A total of 100 prehypertensives and hypertensives were studied.

2.3. Randomization

This was a prospective, open labelled, parallel group, randomized controlled study. The study protocol was explained and informed consent was obtained. The subjects were informed about their rights to withdraw their participation from the study. The study's biostatistician randomly placed subjects in the control or treatment group in 1:1 ratio, by permuting the total sample size into 2 arms; the first 50 numbers were allotted to the music intervention combined with lifestyle modifications (group 1) by tossing the coin and the next 50 into the other group (for only lifestyle modifications – group 2). No stratification for age, sex, or BP range was performed. The random number indicating intervention or control was kept in an opaque and sealed envelope and the serial number of the patients were written on the top of the envelope. The envelope was opened by the research assistant after the baseline assessment of each participant had been completed and assigned the participants to both the arms. All the other investigators who did the outcome assessments were blinded to the interventions.

2.4. Baseline characteristics

Detailed baseline characteristics recorded on a pretested, semi-structured proforma, included general health questionnaire (GHQ12) [16], involvement in physical activity, diet history, family history, smoking, alcohol intake history and drug history and a short questionnaire that included questions related to music preference such as type of instrument, genre, and frequency of listening and formal training, if any. Standard questionnaires were used in this study. The research assistant was trained for 6 months prior to collection of data. Biostatistician analyzed this data collected after 6 months and assured uniformity in sample collection.

2.5. Experimental outcome measures (at the beginning and at the end of 3 months)

The primary end point of this study was change in 24 h ABP at the end of intervention. Secondary end points were change in stress levels (State Trait Anxiety Inventory (STAI)), biomarkers and correlation of this with change in BP.

Stress levels were assessed using STAI. It is a standardized tool with forty questions, with four possible responses to each [17,18]. On reliability generalization testing the measures of STAI demonstrated excellent internal consistency (average αs>0.89), and excellent test–retest reliability (average r = 0.88) at multiple time intervals [19]. The reliability of STAI in patients with anxiety disorder is found to be between 0.87 and 0.93 [20]. The BP (clinical sphygmomanometry), anthropometric measurements, BMI and waist hip ratio (WHR) were recorded according to standard protocol [21].

Those subjects satisfying our inclusion criteria (prehypertensive or stage I hypertensives) were now subjected to 24 h ABP recording using Schiller BR 102 Plus 24/48 h ABP monitor (ABPM), Schiller India. The device was programmed to measure half hourly BP between 07:00 to 22:00 h and hourly BP between 22:00 to 07:00 h. Subjects who had $\geq$18 readings (out of 39) were included for final analysis. The values of 24 h overall (average 24 h BP), awake and asleep SBP and DBP were recorded. This device has been standardized and validated by British Hypertension Society (BHS) and Association for the Advancement of Medical Instrumentation (AAMI) [22,23].

Five mL of whole venous blood was collected under aseptic conditions between 09:00 to 10:00 h to avoid diurnal variations. Plasma was separated and stored at −70 °C until further analysis. Plasma catecholamines were measured using CAT Enzyme linked immunosorbant assay (DLD Diagnostica GMBH, Germany) within one week of its collection. The intra-assay precision as measured by coefficient of variance (CV) was 8.35%, 9.7% and 9.6% for adrenaline, noradrenaline and dopamine respectively. Plasma Renin Activity (PRA) was determined via radioimmunoassay (Immunotech, Czech Republic). The inter-assay CV was <10.5%.

2.6. Intervention

2.6.1. Lifestyle modification (as per JNC VII) [2].

Counselling for lifestyle modifications and various non-pharmacological measures was given to all the subjects as per JNC VII guidelines. Handouts were given to enhance compliance and to help them recall the instructions.

2.6.2. Music intervention

Music was provided to the subjects based on their personal preference (compact discs, mobiles, i-pods). A 22 min instrumental (*Bansuri*) music, playing *raga Bhimpalas* without any accompaniments was used. According to study protocol, the subjects had to listen to this music for about 15 min daily (during the same time every day, preferably without interruptions) at least 5 days a week for 3 months, irrespective of the music which they listen to otherwise. The music intervention group also followed lifestyle modifications.

2.7. Follow up

Weekly follow up was done to ensure compliance towards the intervention (by personal contact) (Fig. 1). Any change in pharmacological management was periodically monitored and recorded.

2.8. Statistical analysis

Quantitative data were expressed as mean, standard deviation (SD), median and inter-quartile ranges. Differences in the mean/median values between groups were tested by student t test/non-parametric tests of significance (Mann Whitney U test). Mean differences between pre and post intervention was assessed by paired Student t test/Wilcoxon signed rank test. Qualitative data was expressed as percentages. Chi square and Fischer's test was applied to test for associations between the categorical variables. Pearson's correlation coefficient was used to estimate the correlation between BP and biomarkers. Significant predictors in the univariate analysis were then included in a forward stepwise multiple logistic regression model to assess the independent predictors of change in BP. In order to study interaction effect, repeated measures ANOVA was used. P value of ≤ 0.05 was considered as the level of significance. The data was analyzed using SPSS software Version 18.0 (SPSS Inc., Chicago, USA).

3. Results

A total of 50 subjects were recruited in both the groups namely, music along with lifestyle modifications (group 1) and only lifestyle

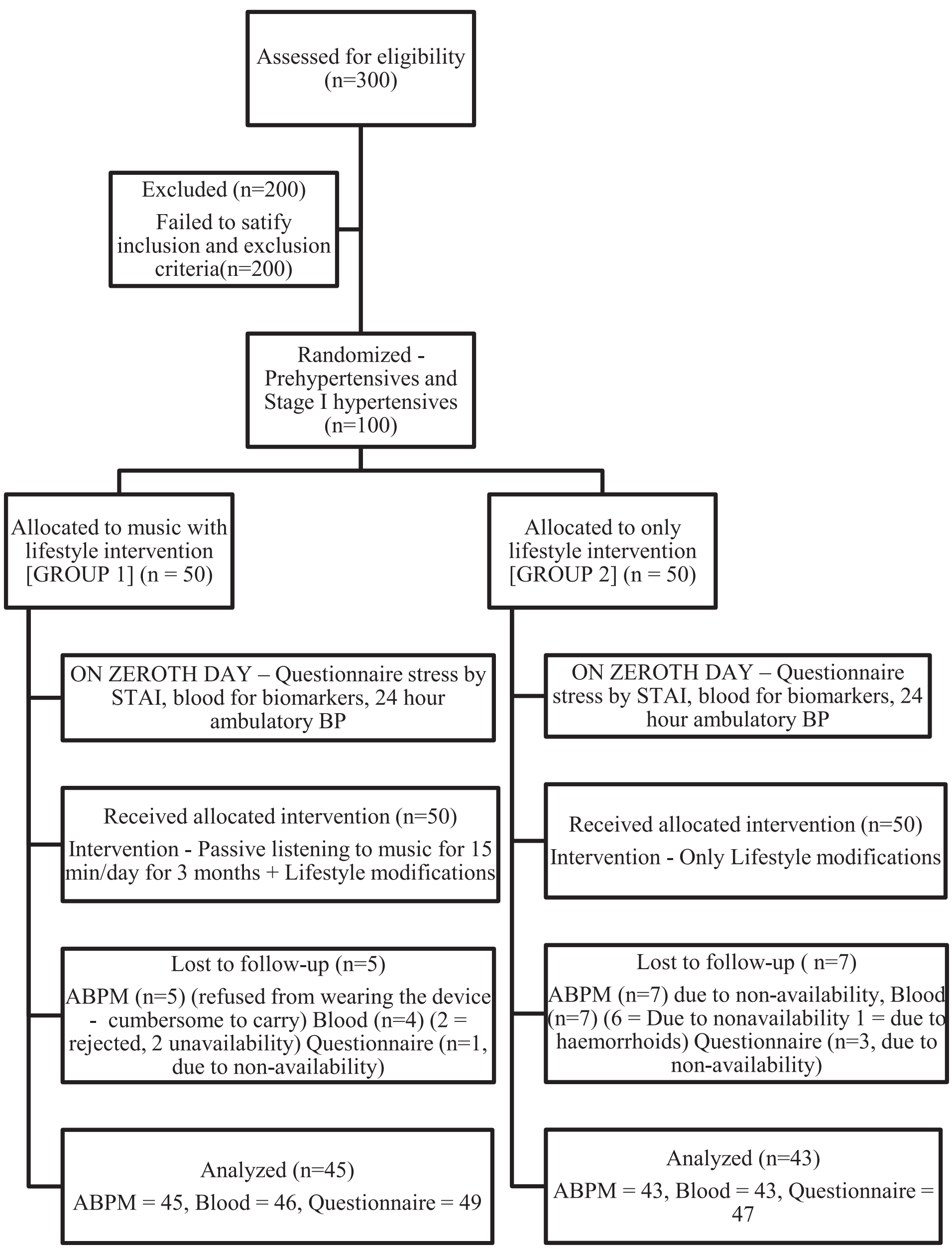

Fig. 1. Consort diagram of participant recruitment, distribution and follow up.

modification (group 2). Most of the subjects reported that they were following the lifestyle modifications recommended and that they were also listening to music as per instructions. A few subjects were lost due to various reasons during follow up. ABPM of twelve subjects could not be recorded (5-refused to wear, 7-due to non-availability). Blood sample was not drawn from 11 subjects (9-due to non-availability, 2-refused to give blood). Questionnaire recording was incomplete due to non-availability of 4 subjects. The final analysis was done on 49 subjects in group 1 and 47 in group 2.

3.1. Baseline characteristics

Mean age, gender, BMI and WHR were comparable between the two groups. Twelve and 14% of the subjects were smokers and 22 and 32% were current alcoholics in group 1 and group 2 respectively. History of smoking and consumption of alcohol did not differ significantly throughout the study in both the groups (Table 1). Other data in Supplementary file.

3.2. Blood pressure measured by ABPM

3.2.1. Baseline ABPM

The number of subjects in the prehypertension range (JNC VII Criteria) was higher in both the groups (Table 1) [2]. Prior to intervention none of the BP measures were statistically different between the two groups (Table 2).

3.3. Pre versus post intervention ABPM

The SBP decreased by 1.3 (overall) and 1.7 (awake) mm Hg in group 1, but this was not statistically significant. However, a statistically significant reduction in SBP was found in group 2 (overall − 3.2 mm Hg, $P = 0.015$ and awake − 3.7 mm Hg, $P = 0.026$). Diastolic BP decreased significantly in group 1 (overall − 2.1 mm Hg, $P = 0.004$ and awake DBP − 1.83 mm Hg, $P = 0.021$). In group 2, the overall DBP decreased significantly ($P = 0.015$) (Table 2).

On analysis of the data after excluding smokers and alcoholics the DBP decreased significantly in group 1 ($P = 0.05$), but not in group 2 ($P = 0.097$). Rest of the BP measurements did not vary significantly. Further, on exclusion of diabetics it was found that the decrease in DBP (overall, $P = 0.006$ and awake, $P = 0.021$) persisted in group 1 and the reduction in SBP remained in group 2 (overall, $P = 0.030$, awake, $P = 0.043$) and was statistically significant.

3.4. Factors affecting the change in DBP in multiple logistic regression analysis

All parameters that significantly changed after intervention on univariate analysis (Supplementary file − list of covariates) were further analyzed using multiple logistic regression analysis to confirm their effects on the post intervention overall DBP (overall DBP significantly declined in group 1 which was our main experimental group) in both the groups. The subjects were categorized into 2 groups based on change in overall DBP into those with <2 and > 2 mm Hg change after intervention (The association of the co-variates were studied with the dichotomized DBP levels). Post-intervention STAI state score was the only variable which showed association with the change in DBP in group 1 (Odds ratio 0.156; 95% CI = 0.03–0.84; $P = 0.03$). Those subjects who had lesser STAI state score after intervention (92.6%) showed a higher fall in DBP (>2 mm Hg) in group 1($P = 0.02$) (Chi-square analysis). In group 2 only BMI had a significant association with the DBP (Odds ratio 0.045; 95% CI = 0.003–0.61; $P = 0.02$). Those with BMI in normal range and pre-obese range had higher fall in DBP ($P = 0.02$) (Table 3). On combining both the groups, the only factor that had a significant association was BMI (Normal BMI − $P = 0.01$, Preobese BMI − P − 0.042).

3.5. Stress (STAI)

Prior to intervention the stress levels among both the groups was comparable. It decreased significantly after intervention in both the groups ($P \leq 0.001$) (Tables 1 and 4).

Table 1
Comparison of baseline characteristics between the groups presented as mean (SD) and percentage.

Variable	Groups for analysis	Group 1 (N = 50)	Group 2 (N = 50)	P
Age (Years) as mean(SD)		46.50(8.5)	46.88(8.5)	0.824
BMI (kg/m^2) as mean(SD)		25.93(3.9)	25.86(3.1)	0.925
WHR		0.92	0.94	0.147
GHQ12 Score as mean(SD)		11.74(3.1)	12.72(2.9)	0.106
Males		60	74	0.137
Based on SBP (On the basis of Clinical BP measurement)	Pre hypertensive	86	72	0.086
	Stage I Hypertensive	14	28	
Hypertension present (Based on history)		46	34	0.221
Age at diagnosis as mean(SD)	Years	44.87(6.7)	44.12(7.5)	0.741
Non pharmacological measures followed to control hypertension	Diet modification	2	4	0.608
	Walking	4	8	
	Exercise	2	2	
	Yoga	2	0	
	Meditation	6	0	
Medication	β blockers	10	4	NC
	ACE inhibitors	0	2	
	Calcium channel blockers	4	4	
	β blockers + Calcium channel blockers	4	4	
	Angiotensin receptor blockers	16	6	
	Ayurvedic medicine	0	2	
STAI state score	<40	86	84	0.078
	≥40	14	16	
STAI trait score	<40	68	68	<0.001
	≥40	32	32	
STAI state score as mean(SD)		31.34(10.3)	34.76(8.4)	0.072
STAI trait score as mean(SD)		36.82(8.7)	38.3(8.4)	0.389

Note: N = sample size in each group, NC=Not computed, STAI=State Trait Anxiety Inventory, SD=Standard Deviation; $P < 0.05$ was considered significant.

Table 2
Comparative data of pre versus post intervention 24 h ABPM within group 1 and 2.

Group	Pressure	INT	SBP (mm Hg)			DBP (mm Hg)		
			Mean(SD)	95% CI	P	Mean(SD)	95% CI	P
Group 1 (n = 45)	Overall	Pre	130.74(8.7)	124.8–137	0.261	85.1(6.8)	81–87.3	0.004
		Post	130.02(12.2)	121–135.5		83(8.7)	77–89	
	Awake	Pre	133.34(9.1)	125.8–140.3	0.216	87.72(7.6)	83–91	0.021
		Post	132.18(12.9)	121.5–139.5		85.89(9.2)	78.5–92.5	
	Asleep	Pre	122.7(11.5)	115–126.5	0.506	76.4(6.8)	71.8–80.3	0.285
		Post	124.58(15.5)	113.5–132.5		75.6(10.3)	68.5–80	
Group 2 (n = 43)	Overall	Pre	133.12(11.8)	122.8–141.3	0.015	85.24(7.3)	79.5–92	0.015
		POST	129.91(11.5)	122–136		82.58(8.0)	76–88	
	Awake	Pre	136.36(11.9)	127–145.3	0.026	88.16(7.5)	82–94	0.084
		Post	132.53(11.5)	125–139		86.02(7.8)	79–91	
	Asleep	Pre	122.32(16.3)	109.8–132	0.483	75.42(10.9)	67–80.3	0.324
		Post	121.16(13.1)	112–130		74.14(8.4)	68–78	

Paired t test was employed to compare pre and post values within a group; Unit of BP is in mmHg; Values are given as mean (SD), P Value of <0.05 is considered significant.

Table 3
Multiple forward stepwise logistic regression analysis between change in DBP and factors which showed significant relation on (STAI state score and BMI) in both the groups.

Group	Change in DBP (mm Hg)	STAI state score		χ^2	P	BMI categories (kg/m^2)			χ^2	P
		<26	>26			18.5–24.99	25–29.99	>30		
1	<2	65.2	34.8	5.82	0.016	39.1	52.2	8.7	4.11	0.122
	>2	92.6	7.4			51.9	25.9	22.2		
2	<2	61.9	38.1	0.512	0.474	42.9	57.1	0	5.8	0.022
	>2	51.7	48.3			51.7	31	17.2		

Total number of subjects was 50 in each group (100%); List of covariates that showed significant difference on univariate analysis is shown in appendix; P value of >0.05 was considered significant.

3.6. Biomarkers of hypertension

There was a statistically significant decrease in PRA (P = 0.046), noradrenaline (P = 0.049) and dopamine (P = 0.002) levels after intervention in group 1; but this significance was not observed after log conversion for noradrenaline and PRA (Table 4). It was hypothesized that the anticipated reduction in BP is likely to correlate with the levels of biomarkers. On analysis within the group a significant negative correlation between the post intervention overall and awake DBP with adrenaline (P < 0.05) was found. However only 16% (r^2) of the effect on overall DBP was explained by adrenaline values. None of the other biomarkers were correlating with the DBP.

Table 4
Comparison of pre versus post intervention stress scores and biomarkers of hypertension within group 1 and group 2.

Group	STAI Scores	Pre (n = 49) Mean(SD)	Post (n = 47) Mean(SD)	Pre vs post P
1	State	31.34(10.3)	27.69(6.1)	0.001
	Trait	36.82(8.7)	30.9(5.3)	<0.001
		PRE (N = 50)	Post (N = 47)	
2	State	34.76(8.4)	30.53(5.5)	<0.001
	Trait	38.3(8.4)	33.77(5.8)	<0.001
1	**Adrenaline**	PRE (n = 46)	POST (n = 43)	
	pg/mL	40.13(27.3)	40.29(19.8)	0.595
	Log_{10}	1.5(0.3)	1.55(0.2)	0.219
	Noradrenaline			
	pg/mL	467.87(294.9)	400.43(186.9)	0.049
	Log_{10}	2.51(0.5)	2.54(0.3)	0.376
	Dopamine			
	pg/mL	59.07(43.9)	40.43(38.4)	0.002
	Log_{10}	1.62(0.4)	1.45(0.4)	0.001
	PRA			
	ng/mL/hr	3.05(2.4)	2.67(2.4)	0.046
	Log_{10}	0.34(0.4)	0.31(0.3)	0.11
2	**Adrenaline**			
	pg/mL	43.2(25.7)	38.76(21.6)	0.349
	Log_{10}	1.54(0.3)	1.5(0.3)	0.558
	Noradrenaline			
	pg/mL	440.93(310.9)	434.26(246.1)	0.564
	Log_{10}	2.49(0.4)	2.56(0.3)	0.811
	Dopamine			
	pg/mL	50.8(27.9)	49.92(68.6)	0.124
	Log_{10}	1.62(0.3)	1.49(0.4)	0.073
	PRA			
	ng/mL/hr	1.75(1.9)	2.46(1.7)	0.012
	Log_{10}	0.06(0.4)	0.3(0.3)	0.002

P Value of <0.05 is considered significant; PRA, plasma renin activity.

3.7. Subgroup analysis

See supplementary file.

4. Discussion

In this study role of Indian music on BP was evaluated among prehypertensives and stage I hypertensives. We choose a particular *raga* after referring to ancient literature in music according to which a few *ragas* of Indian music could normalize BP. According to Swara shastra, there are 72 parent ragas (*melakartha ragas*) which transmit life energy through *nadis* [15] (energy channels – Ayurvedic concept) according to its *lakshana* (norms) and pitch. *Sama Veda*, music therapy and *Raga chikitsa* have identified specific *ragas* and their benefits. *Raga Bhimpalas* was chosen among all the ragas that normalize BP [14,15]. This *raga* is predominantly made of *komal* (soft) notes. *Komal* notes always create a positive impact on the mind with parasympathetic dominance, irrespective of the musical training of the person [24].

Instrumental music was used because it uses musical components like pitch, intensity, and timbre and it does not contain lyrics. So, the effect generated is exclusively by the musical components. Very little literature available on the most relaxing or soothing instrument, we chose bansuri/flute for this study. Flute is one of the most common instruments used in musical pieces meant for relaxation or meditation in India. The use of percussion instruments was avoided as tempo has been shown to significantly affect the heart in various ways [25].

Stress decreased after intervention significantly in both the groups. Classical music is an effective stress buster and stress reduction can effectively reduce BP [26,27]. In this study subjects were educated about the ill effects of stress on health and emphasis was laid on the various methods of stress reduction.

In group 1, there was a significant decrease in overall and awake DBP (~2.5 mm Hg) after intervention. Previous studies have reported reduction in SBP by > 10 mm Hg and DBP by > 4 mm Hg after 2–3 months of music intervention [4–8]. These studies used one time sphygmomanometric BP monitoring. The magnitude of reduction in SBP and DBP was lesser in the present study. This can be attributed to 24 h ABP monitoring which is more accurate since it takes multiple measurements (>18/day) and averages them. Home BP and ABP measurements are lower than those obtained by clinic measurements [28].

After lifestyle modification (predominantly change in diet and stress; Supplementary file) in group 2, there was a statistically significant decrease in overall, awake SBP and overall DBP.

Subjects who had lesser post intervention state anxiety score had a higher fall in DBP (logistic regression) [29]. A significant negative correlation has been observed between the trait score and flow mediated dilation [30]. In group 2 and on combining both the groups, subjects with BMI in normal and pre-obese range had higher fall in DBP [31]. Thus, it is important to be less anxious and maintain an optimal BMI for effective control of BP.

Subgroup analysis (Supplementary file) showed that subjects with pre-intervention SBP in prehypertension range, overall DBP decreased by 3.18 mm Hg after intervention in group 1 and 2.54 mm Hg in group 2. Lifestyle modifications aided in reducing overall and asleep SBP significantly among stage I hypertensives in group 2. Group 1 subjects with DBP in prehypertension range prior to intervention, had a statistically significant decline after intervention, with fall in overall SBP (3.78 mm Hg), DBP (4.93 mm Hg); awake SBP (4.11 mm Hg), DBP (4.56 mm Hg) and asleep DBP (3.59 mm Hg). Group 1 had 86% of subjects in prehypertension range prior to intervention (with or without medication). Listening to music produced a significant reduction in BP among these subjects specifically. This proves that music can be a useful adjunct in normalizing the BP. Implementation of only lifestyle modifications did not completely normalize the BP in prehypertensives of group 2.

The plasma catecholamines and PRA decreased after music intervention, similar to previous reports [32]. The possible absence of the correlation between biomarkers with the change in DBP could be due to an attempt to establish correlation of biomarkers with 24 h BP levels. Instead, BP measured at the time of drawing blood might have given better correlation on analysis. However, monitoring these subjects for a longer period of time might have decreased these biomarkers significantly along with BP, as BP decrease follows the long term decrease in the causative factors.

4.1. Strengths of the study

For the first time a randomized trial of Indian music intervention was given to hypertensives. Music used here was exclusively recorded for this study after looking into the drawbacks in previous literature (eg: presence of percussion, lyrics, researcher selected music and notes used). Various studies have used other forms as control group (music on walkman or no audio). We used lifestyle modifications in order to avoid intervention bias for the second group of subjects. Music based intervention to study change in BP have not used ABPM [6–8].

4.2. Study limitations

Acute effect of music on BP, stress and biomarkers of hypertension was not studied. A better effect on BP could have been observed if we had used familiar rather than unfamiliar music intervention. However, music preference is purely subjective and varies widely among individuals. Music intervention combined with slow breathing may be a better intervention. Better compliance can be achieved in a laboratory. The study was conducted on a non-homogenous sample (prehypertensives and hypertensives in the same group; on or off treatment).

5. Conclusion

Music when used as an adjunct benefitted subjects with initial BP in prehypertension range. NPM for reduction of stress should be included in the recommendations given by JNC VII for better control of BP.

Authors' contributions

UKK, GJ, VJ, DV, VSP and NSM were responsible for the study conception and design. UKK, GJ, VJ and PAH performed the data collection and intervention. UKK, RK and NSM performed the statistical analysis and interpretation of data. UKK, GJ and NSM were responsible for drafting and editing the manuscript. All authors reviewed, edited and approved the final manuscript.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ctcp.2015.05.004.

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