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A NOVEL MODEL OF PSYCHOGENIC HYPERTENSION: EFFECT OF A YET ANOTHER PLEOTROPIC BETA BLOCKER OR JUST MIMICRY?

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ABSTRACT

Background: Hypertension is one of the leading causes of disability and death. Stress is a major etiology affecting both young and older age groups. Nebivolol is a 3rd generation beta blocker with additional vasodilatory effects due to endothelial NO production. **Objectives**: The current study aims to develop a model of stress induced chronic, psychogenic hypertension in male Swiss albino mice using restraint induced stress. This study also aims to evaluate the pharmacological effects of the beta blocker in this model. **Methods**: 4 groups (n=6) of albino male mice were selected and allowed immobilization for 2 hours daily using the restrainers. Weekly BP and HR were measured till there is maximum persistent increase in systolic BP more than 20 mm Hg from baseline level and observed for its hypertension persistence phase and how this declines due to adaptation that animals will undergo during stress phase. Among groups after inducing hypertension, one group was kept for hypertension control; the remaining three were used for influence of Nebivolol without stress, with stress and for the diluent control CMC. **Outcomes and Results:** A pilot development of a novel model of psychogenic hypertension was undertaken over nine weeks in the mice. Additionally the efficacy of the antihypertensive effects of nebivolol was compared with its other pleotropic effects in the cardiovascular and central nervous systems and was found to be significantly high. **Conclusion**: We have developed a novel psychogenic hypertension model induced by restraint stress in mice.

KEYWORDS: Nebivolol, Psychogenic hypertension, restraint-stress, hypertension model, Noninvasive blood pressure, beta receptors.

INTRODUCTION

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion.[1]

As per the World Health Statistics 2012, of the estimated 57 million global deaths in 2008, 36 million (63%) were due to non communicable diseases (NCDs). The largest proportion of NCD deaths is caused by cardiovascular diseases (48%). In terms of attributable deaths, raised blood pressure is one of the leading behavioral and physiological risk factor to which 13% of global deaths are attributed. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries.[3] There are large regional differences in cardiovascular mortality in India among both men and women. The mortality is highest in south Indian states, eastern and north eastern states and Punjab in both men and women, while mortality is the lowest in the central Indian states of Rajasthan, Uttar Pradesh and Bihar. The prevalence of hypertension in the last six decades has increased from 2% to 25% among urban residents and from 2% to 15% among the rural residents in India.[2]

Nebivolol is a third generation beta adrenergic blocker, with its dextro isomer being a potent β1 adrenergic blocker, responsible for most of its cardiovascular and nervous system effects, and the racemate being a vasodilator. This vasodilating action, in contrast to vasoconstriction produced by most non cardio selective beta blockers, has been attributed to coronary endothelial β3-activation in a NO-dependent manner that affords it a cardio protective property.[3, 4]

The animal models of hypertension used initially to evaluate the effects of such drugs included mostly renal

sympathectomy that altered Renin-Angiotensin-Aldosterone System (RAAS) – this hindered the development of essential hypertension in such models; also, neurogenic hypertension comprises > 50% of etiologies of hypertension.[5]

Hypertension can be induced by various methods. In animals, the methods of induction includes Reno vascular hypertension, Dietary hypertension, Endocrine hypertension, Neurogenic hypertension, Psychogenic hypertension, Genetic hypertension and some other minor methods.[6]

But to date, few models of psychogenic hypertension are in use to evaluate such drugs in animals, most of them being less efficient in outcome evaluation. One such model, though comparatively more validated than other models, incorporates noise-induced hypertension as a stress model.

The literature shows paucity of research on the effects of Nebivolol in psychogenic stress models of essential hypertension, especially with its additional vasodilating and anti-oxidant activities. Though its antihypertensive effects are well known, could these additional activities be responsible for its actions in psychogenic stress induced hypertension, was one of our research questions. To put this to an end we validated a novel model of restraint-induced hypertension in mouse.

MATERIALS AND METHODS

Ethical statement

The study was approved by animal ethics committee of PSGIMSR and was carried out under CPCSEA guidelines.

Mode of Study

This is an experimental observational pilot study.

Materials Required

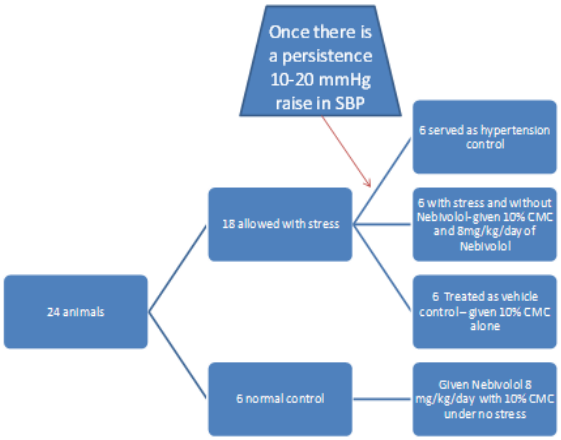
Swiss Albino mice (male), Nebivolol, carboxyl methyl cellulose, NIBP system, mouse restrainers, plastic syringe, 23-25 gauge needle, saline.

Study Method

The study comprised of two stages: Model development and validation, followed by evaluation of CVS effects of Nebivolol in this model. Initially, 24mice were selected. They were divided into 4 groups of 6 each. Group I (6 animals) served as the normal control in that they were not induced with any restraint stress. 18 animals were subjected to immobility only for 2hours per day using standard restrainers under standard conditions. Once there was a persistence rise in the systolic blood pressure, 18 animals were further divided into three groups.

12 animals (group III with Nebivolol, 10 % CMC, n=6, and stress), (Group IV with only 10% CMC) were grouped separately. Among the 2 groups, one was treated with oral Nebivolol (8mg/kg/day/single dose) to check the influence of stress in treatment group for BP, HR. Group II was the remaining 6 animals after hypertension induction kept as disease control group without Nebivolol.

Since there was no proper literature that explains the onset of hypertension, stable period of hypertension in small animal model to test the antihypertensive effect many drugs, this study was adopted as a new idea using immobility as a lead to induce psychogenic hypertension with help of standard animal (mice) restrainers.



Experimental procedure

The 24 mice were caged into 4 groups depending on the requirement. For the initial 4-5 days, the mice were acclimatized to restraint stress and measurement of the SBP by the tail cuff method. The SBP, HR of all the groups were measured and taken as the baseline BP and HR respectively. One of the groups was made as normal control (group I) and kept for observation. The remaining 3 groups were subjected to restraint induced stress for 2 hours daily with normal food and water. The restrainers were made of plastic tubes mounted over a wooden board and fixed tightly with screws for stability. The restrainers were made in such a shape that the mouse would not be able to freely move about and was made sure that the mice were immobilized within the restrainers and also had a conical head at one end in front to occupy the head of mouse. The conical head had perforations to allow the mouse to breathe. Every time when a mouse is put into a restrainer, it is done in such a way that the head and body of mouse is within the plastic container and the rear end is closed with a stopper and has a hole for the tail of the mouse. This restraint induced stress was carried out in the animal laboratory in morning when the sympathetic activity of the mice was maximum and placed in a dark, silent room at appropriate temperature.

In order to measure the restraint stress, the tail cuff method was used. The tail cuff method is a noninvasive technique to measure the BP and HR. In animals, the most common method of indirect BP measurement is by

using the tail cuff technique. This tail cuff measurement does have some advantages which would include.
(1) They are noninvasive and there is no necessity of surgery,
(2) Can be used to measure systolic blood pressure repeatedly in conscious animals
(3) Less expensive
(4) Can be used to screen for substantial differences in BP for a large number of animals.[7]

Further, it was also found that in the tail cuff noninvasive BP measurement,
(1). The tail cuff BP and the femoral arterial pressures measured using a photoelectric meter was almost the same.
(2). The tail cuff BP and the carotid artery pulse values also remained the same.[8]

During each of the weekly measurement of BP by this method, the mouse placed in a box with its tail passing out of it so that a tail cuff can be applied to the mouse's tail. The cuff had a sensor which measured the blood flow levels – when inflated, the blood flow stopped and when deflated, the blood flow returned. These inflation-deflation cycles were connected to a monitor and the readings were noted. The best 4 outcomes out of 6 were considered for each animal in each group every time it was measured. This procedure is similar to that done by Steven E. Whitesall et al.[9] Hypertension was induced continuously to check for any changes in the baseline BP and HR. And, it was found that the blood pressure gradually increased with every weekly measurement and also with significant changes in the heart rate levels. By around the 4th and 5th weeks when the BP and HR got stable with a persistent increase during weekly measurements, the 3 groups were further divided into.

Hypertension control (group ll)
Nebivolol,CMC with stress (group lll)
Only CMC with stress (group lV)
Hypertension was continued throughout although the administration of the drugs was done only in 2 of the groups(group lll & group lV).

Nebivolol was given in the does of 8 mg/kg/day by oral gavage using a 23-25 gauge needle. Nebivolol was mixed with 10% Carboxy Methyl Cellulose in water. The administration of Nebivolol was started at around mid-5th week and was continued every day from the time of stabilization of BP and was given after the restraint induced stress persistence of group lll. Further the Group IV(vehicle control) was given with 10% CMC in water alone, just to check whether the diluent had any effect on the mice and hence on the Nebivolol drug.

In order to check the efficacy of the 3rd generation beta blocker, Nebivolol in a normal mice without any hypertension, this was given as oral gavage to the group I (normal control) at the same time when group III was being given. The restraint induced stress was given for a period of 9 weeks.

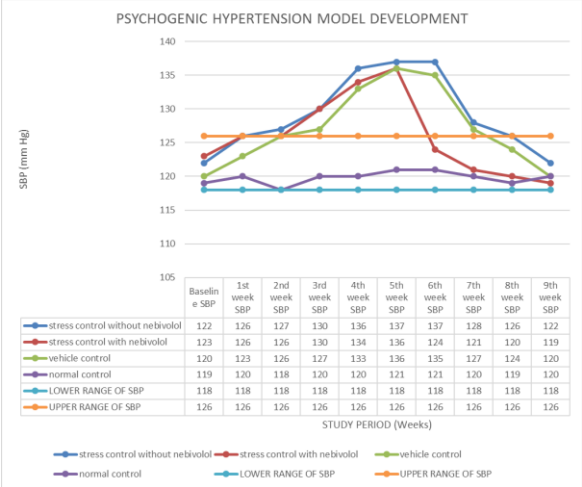
Experimental animals
The animals that were used are Swiss Albino male mice. All the mice were adults weighing 33-35 grams. The source of the animals was the PSGIMSR animal facility center. These mice had no genetic modifications done with the common genotype. The mice were healthy and normal.

Housing and husbandry
The mice were placed in standard housing conditions and the type of cage used for grouping are polypropylene shoe box cage. The bedding material for the animals were made of paddy husk with 3 mice in a single cage. They had normal light/dark cycle of 12 hours daylight and 12 hours in dark kept at 24 degree Celsius. They were provided with potable drinking water and food pellets and the access to food was ad libitum with no environmental enrichment.

Sample size
The total number of animals used in the experiment is 24 and each group had 6 animals. The number of animals per group was made to 6 in order to get a more accurate and conclusive result. The animals were weighed and separated in groups depending on the similarity of the weight measured.

Experimental outcomes
The primary outcome assessed is the reduction in the Blood pressure and Heart rate with the administration of the 3rd generation beta blocker, Nebivolol. The secondary outcome is to observe the change in the Blood pressure and Heart rate that occurs over a period of 9 weeks including a rise, a plateau and adaptation phase.

RESULTS
A) Psychogenic Stress model of essential hypertension
(i) *Model Development* – The mean Systolic blood pressure (SBP) of the normal control group I for the first 6 weeks (week 0 – V) was within the normal limit(118-126 mm Hg).It showed small fluctuations in the values but still just remained within the normal limit. The other 3 groups which were induced with restraint stress showed significant changes from the normal control group. These groups(II,III,IV) in the initial three weeks showed a fluctuation from their baseline but remained within the normal limits, more towards the upper limit: the mean BP of group II,III,IV for the first three weeks were 125,125,123 mm Hg. It gradually started rising over the next week and by the middle of the 4th week, the blood pressures of groups II,III,IV reached a new peak and remained constant over a plateau. The peak value was maintained around 133-137 mm Hg.



	Baseline SBP	1st week SBP	2nd week SBP	3rd week SBP	4th week SBP	5th week SBP	6th week SBP	7th week SBP	8th week SBP	9th week SBP
stress control without nebivolol	122	126	127	130	136	137	137	128	126	122
stress control with nebivolol	123	126	126	130	134	136	124	121	120	119
vehicle control	120	123	126	127	133	136	135	127	124	120
normal control	119	120	118	120	120	121	121	120	119	120
LOWER RANGE OF SBP	118	118	118	118	118	118	118	118	118	118
UPPER RANGE OF SBP	126	126	126	126	126	126	126	126	126	126

Figure 1: shows development of hypertension and persistence

(ii)*Model Termination* – The below shown graph clearly indicates the fall in SBP in all stress groups. The blood pressure of the normal control group remained within the normal range even after the treatment of Nebivolol and with no stress. The stress group without Nebivolol and the vehicle control group also show a return back towards the normal range. The stress group without Nebivolol or CMC (group II) shows an adaptation to the chronically induced restraint stress in such a way that the BP is gradually brought back to the baseline.

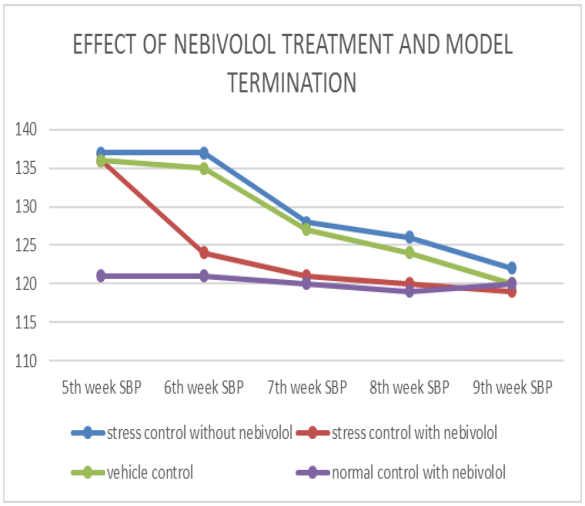


Figure 2: shows the reduction of SBP during the adaptation phase

B) Effect of Nebivolol in the Psychogenic Hypertension Model.

The administration of Nebivolol was started by the 5th week. The graph shows that the drug brought the BP to normal ranges in almost a week within the administration. It gradually gets back to the baseline BP.

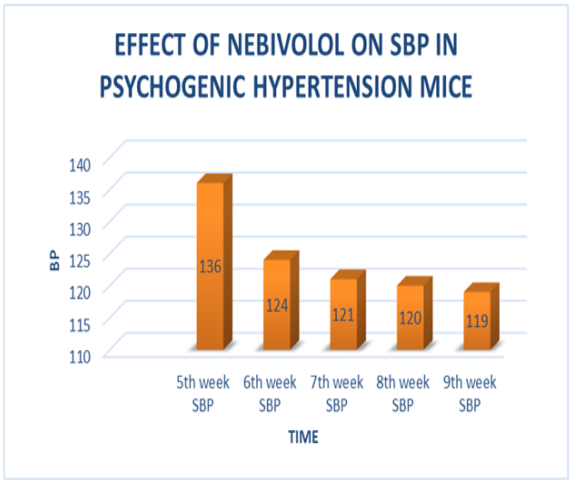


Figure 3: shows the effect of Nebivolol on SBP reduction

C) Effect of Nebivolol treatment on normal control mice without hypertension induction

When the Group I – normal control was given Nebivolol by the 5th week at the same time when the stress group was given the drug, it was seen that there was no significant reduction in BP to cause a hypotensive effect. However, there was a mild dip denoting the administration of the drug, it was not conclusive of the hypotensive effect as the normal range of BP of a mice is 118-126 mm Hg.This finding supports the article where it has been found that administration of Nebivolol to dogs does not cause hypotension.[24]

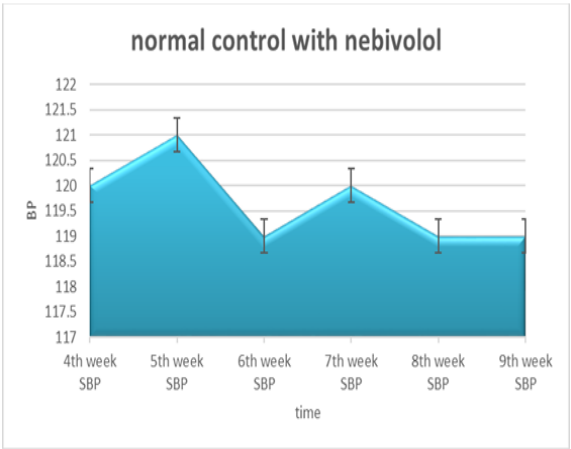


Figure 4: This graph shows the effect of Nebivolol on normal control group

D) Effect of Nebivolol Treatment in Stress Division on Heart Rate.

The heart rate seems to be in the normal range throughout the treatment period with Nebivolol, but it showed a downward trend with treatment at seventh week. At study termination at eight week, Nebivolol treated group showed an increase in heart rate compared to stress control division average heart rate – may be due to inefficacy of Nebivolol to act at the lower dose used in this study on reflex changes occurring at this period.

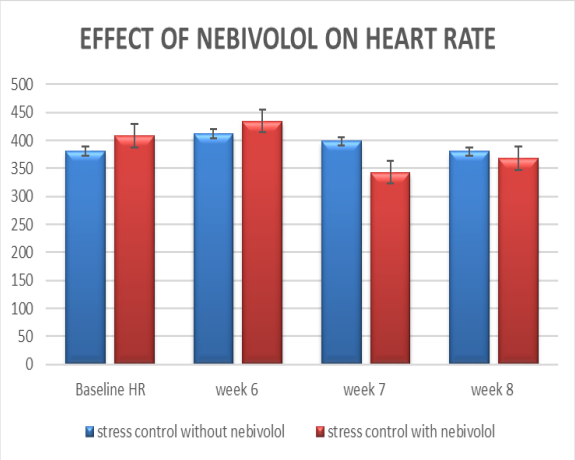


Figure 5: Bar chart depicting the effect of Nebivolol on Heart rate (bpm) in the model of psychogenic hypertension in stress division (Box plots indicate mean HR ± S.E.M.).

Statistical Analysis

The data was summarized using the weekly SBP measurements of all groups, their mean, and standard deviation. For normally distributed data, one way ANOVA was used followed by multiple comparison tests for significant F value in ANOVA followed by post hoc tests. This was further continued by unpaired t test to compare the significance between weekly intervals. A P value of <0.05 was considered significant. The overall P value measured for all groups is 0.015 which is statistically significant.

Table 1: Shows the comparison between different groups and their significance

Group 1	Group 2	Critical	P	Significant?
stress control without nebivolol(group II)	normal control (group I)	0.008333	0.0000852	**Yes*** **
vehicle control (group IV)	normal control (group I)	0.01	0.001009	**Yes** **
stress control with nebivolol(group III)	normal control (group I)	0.0125	0.004123	**Yes** **
stress control without nebivolol(group II)	stress control with nebivolol(group III)	0.016667	0.231802	No
stress control without nebivolol(group II)	vehicle control (group IV)	0.025	0.450042	No
stress control with nebivolol(group III)	vehicle control (group IV)	0.05	0.649781	No

Note: *(P<0.05 – 0.01), ** (P<0.01 – 0.001), *** (P<0.001)

The results interpreted from it are.

- The mean systolic BP of the normal control group when compared to the mean systolic BP of the stress control group over a period of 9 weeks, the critical F value was found to be 0.008333 with a significant P value of 0.0000852.
- The mean systolic BP of the normal control group when compared to the mean systolic BP of the vehicle control group over a period of 9 weeks, the critical F value was found to be 0.01 with a significant P value of 0.001009.
- The mean systolic BP of the normal control group when compared to the mean systolic BP of the stress with Nebivolol group over a period of 9 weeks, the critical F value was found to be 0.0125 with a significant P value of 0.004123.

By the unpaired t test, the following significant results were obtained.

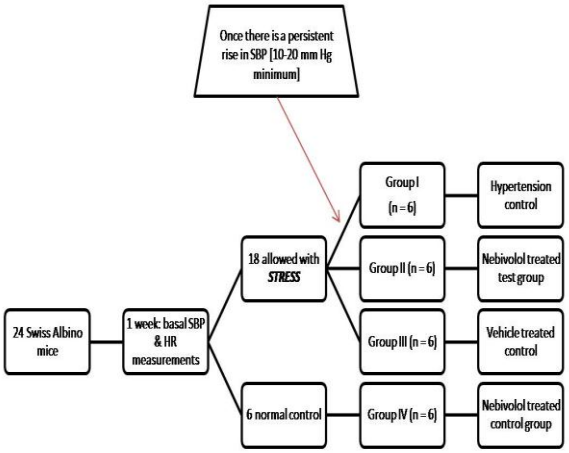
Table 2: This shows the results tabulated from the unpaired t test.

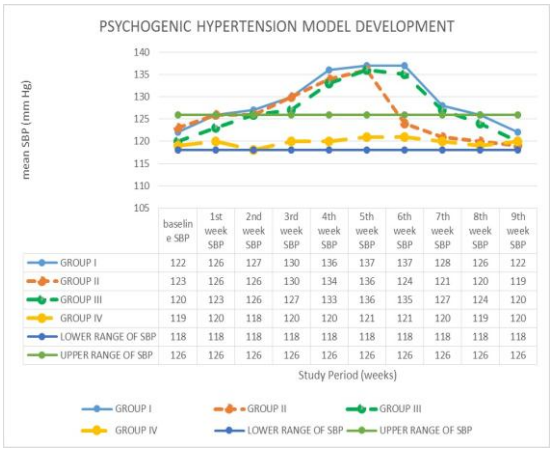
weeks considered	two tailed p value	significance
1st and 5th week	0.0259	yes
baseline and 3rd week	0.0193	yes
baseline and 4th week	0.0097	yes
baseline and 5th week	0.0051	yes
baseline and 6th week	0.0324	yes

The results interpreted from table 2 are

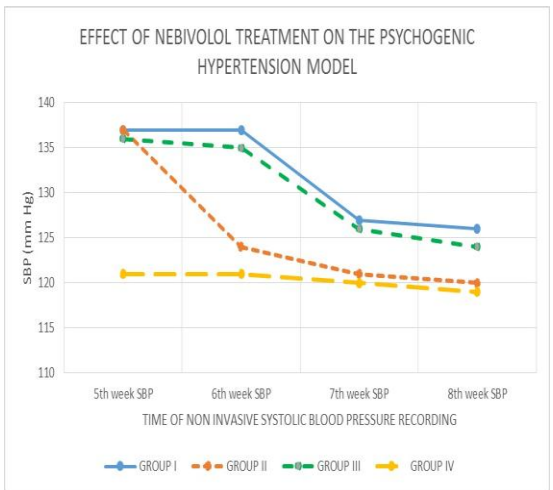
- The mean systolic BP values measured between the 1st and the 5th weeks shows significance meaning that there was a considerable variation between the afore-mentioned weeks. During the 1st week, just when the systolic BP is rising gradually it stays within the normal range 118-126.But, by the 5th week, the animal significantly raised to a high systolic BP which is denoted by the significant two tailed p value.

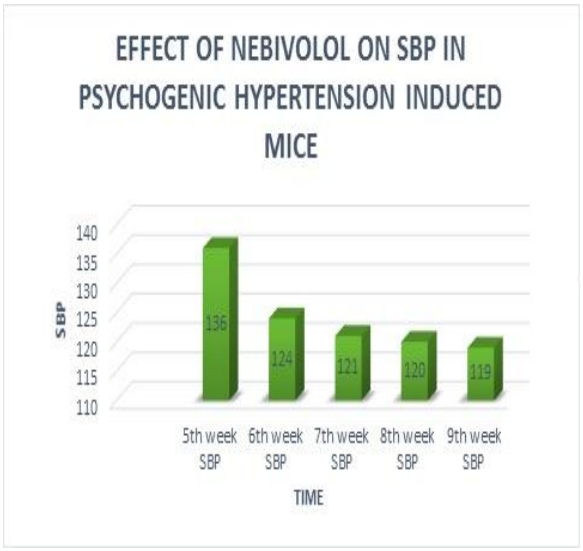
- The mean systolic BP of the baseline and the 3rd, 4th, 5th, 6th weeks are significant owing to the fact that there was a definitive increase in the systolic BP and its persistence over the 4th, 5th and 6th weeks. After which there was absence of significant two tailed P value (i.e., P>0.05) denoting the lowering of systolic BP and hence an adaptation in the mice inspire of a continued restraint induced stress 2 hours/daily.

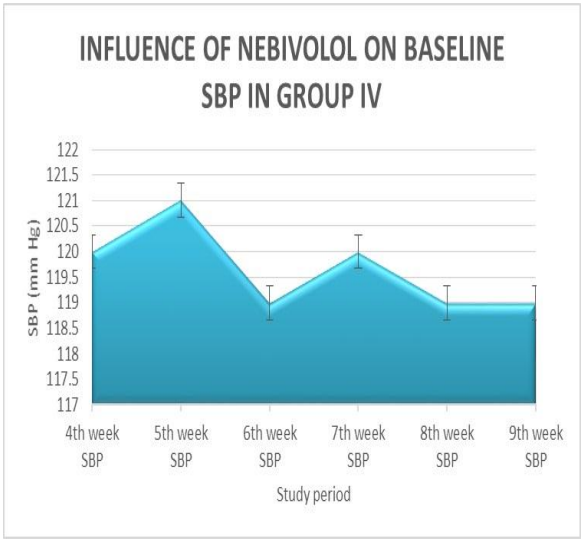


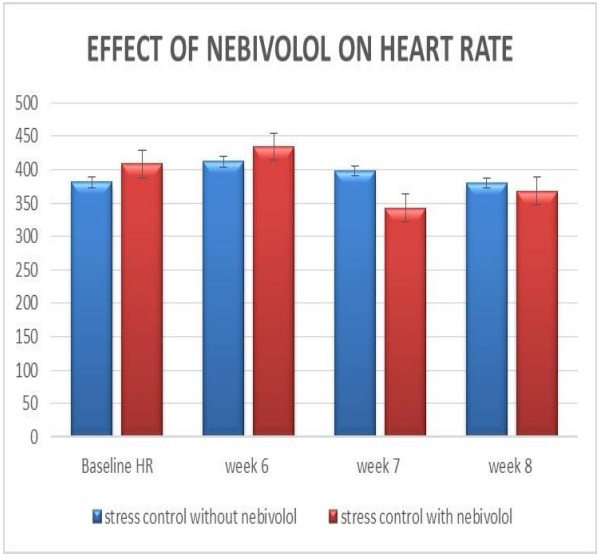


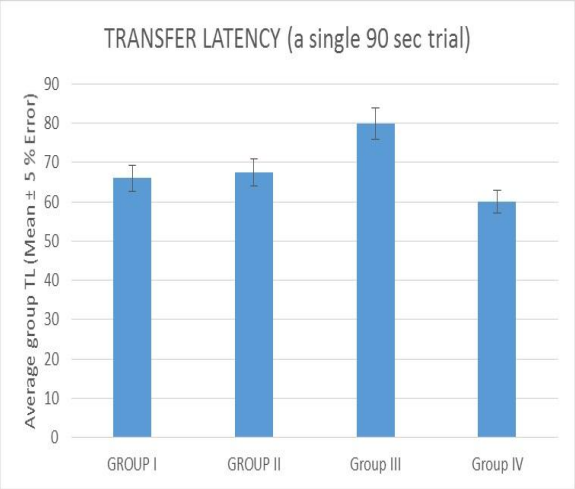
	baseline SBP	1st week SBP	2nd week SBP	3rd week SBP	4th week SBP	5th week SBP	6th week SBP	7th week SBP	8th week SBP	9th week SBP
GROUP I	122	126	127	130	136	137	137	128	126	122
GROUP II	123	126	126	130	134	136	124	121	120	119
GROUP III	120	123	126	127	133	136	135	127	124	120
GROUP IV	119	120	118	120	120	121	121	120	119	120
LOWER RANGE OF SBP	118	118	118	118	118	118	118	118	118	118
UPPER RANGE OF SBP	126	126	126	126	126	126	126	126	126	126

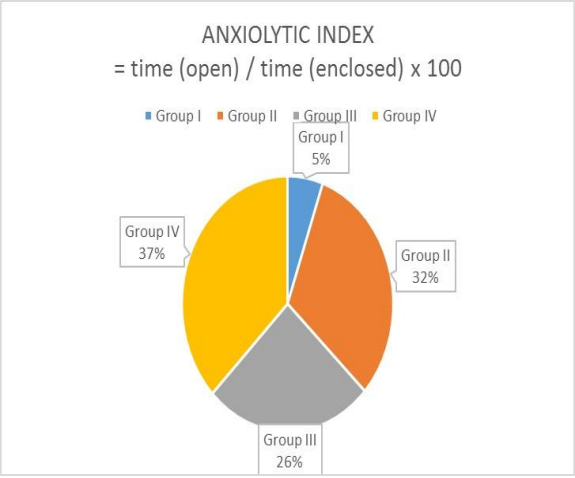


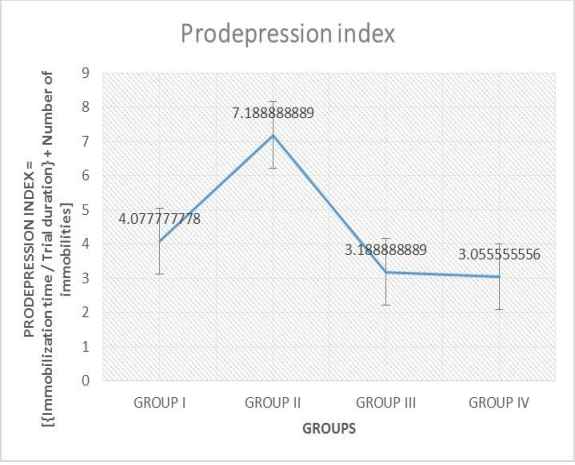












DISCUSSION

Stress induced hypertension is a common cause of hypertension in current scenario and commonly affect cognitive function especially in ageing. Stress significantly increases autonomic system function and related effects on various organs by raising the endogenous glucocorticoids and Norepinephrine & Epinephrine levels leading to vasospasm, hypertension, diabetes mellitus and poor concentration. Since stress is a common cause for hypertension and its proved in this animal study that persistent exposure with stress definitely lead to hypertension. Many studies explains the method of inducing psychogenic hypertension.[6] but the exact time frame of persistence in elevated SBP in animal models has not yet been measured. Many models exist explaining the acute stress for a short period as mentioned by D.K.Badyal et al.[6] where the borderline hypertensive rats were exposed to immobile sessions of short (20 min) or long (120 min) duration for 2 weeks. Similar models exist with chronic phase of immobilization over a period of 60 days done by Nayantara AK et al.[10] but the actual sequence of events as to what happens in each phase and the recording of BP and HR over the chronic immobilization period has not been done. Further studies on acute stress was also done by W.Sutanto and E.R. de Kloet.[11] where the mice were subjected to 1 hour and 24 hour immobilization periods by methods like restraint induced, forced swimming test and acute tail shock.

On the contrary, this experiment explains the development of a novel model for psychogenic hypertension in restraint induced immobility in mice measuring the chronically induced stress over a period of 9 weeks and gives an idea on how the systolic BP increases, raises to a plateau showing the adaptation phase and falls back to the baseline BP that was seen initially. In an experiment done by Fernanda Machado dos Santos et al[12], examination of the renal sympathetic nerve activity in rats with L-NAME(NOS inhibitor)-induced hyper- tension over the course of 2 and 14 days demonstrated that the sympathetic drive is not augmented in this hypertensive model. This shows the demonstration of the adaption phase in mice.

Nebivolol is a 3rd generation beta-blocker with the greatest sensitivity for cardiac $beta_1$ adrenergic receptors and the highest $beta_1/beta_2$ selectivity compared with other beta-blockers and because it has no effect on alpha-receptors, it is devoid of intrinsic sympathomimetic activity. It is a racemic mixture containing equal amounts of two isomers – d- and l- Nebivolol. $Beta_1$ blocking effects of Nebivolol reside in the d- isomer, while the inhibition of exercise induced tachycardia is evident in the racemic mixture. The nitric oxide releasing effect of Nebivolol is mainly due to its l- enantiomer.[4]

Uncontrolled hypertension affects all organs particularly brain & Heart causing stroke other than renal problems. But prior to such a major clinical event, hypertension exerts a more subtle impact on the brain that is revealed by diminished cognitive function, leading to proper performance on tests of attention, learning and memory, executive functions, visual spatial skills and psychomotor abilities.[13]

The reason for cognitive impairment is due to reduction in cerebral blood flow and impaired brain metabolism ie., utilization of glucose to obtain energy particularly in regions like frontal, temporal and sub cortical areas.[14] This finally results in pathological brain damage[15] and

structural alterations of large blood vessels.[16] leading to two main important clinical events like stroke and atherosclerosis accounting for major clinical events in mortality and morbidity. The process of cognitive impairment progresses by the release of vasoconstriction agent that affects neurochemical transmission within the brain and basic cellular functions.[17] These substances also damage blood brain barrier, thus allowing the entry of substances, that are toxic to the brain[18]This state of endothelial dysfunction can be reversed by Nebivolol, a beta blocker which releases nitric oxide, having vasodilating properties.[13] Nebivolol significantly reduces the infarct volume[19] and alleviates ischemia/reperfusion induced histopathological changes.[6] Nebivolol also corrects the disarrangements in vascular wall metabolism and function[13], an added benefit in patients with atherosclerosis.

Nebivolol dose-dependently relaxes rodent coronary resistance in micro arteries, an effect which is sensitive to NOS inhibition.. Nebivolol fails to relax microarteries from b3-AR-deficient mice. The cardiac protective effects of nebivolol was not observed in mice deficient in eNOS, nNOS, or b3-AR. Moreover, eNOS phosphorylation and nNOS expression were increased by nebivolol, causing an overall increase in the cardiac NO level. Nebivolol can also indirectly enhance NOS activity by decreasing the levels of ADMA, an endogenous competitive inhibitor of all three isoforms of NOS. Increased plasma levels of ADMA are associated with various cardiovascular disorders related to endothelial dysfunction and is considered as an important factor for mortality.[20]

The anti oxidant effect of Nebivolol is by scavenging the reactive oxygen species (ROS) by direct interaction with the free radicals and by acting as a chain-breaking antioxidant through proton donation and electron stabilization. HPLC analysis shows that the concentration of nebivolol declines after exposure to ROS in a medium without tissue being present, indicating that the compound is consumed following reaction with ROS. These important mechanisms of Nebivolol was put together by Paul M Vanhoutte and Yuansheng Gao[20] Its also seen that the NO and endothelin plays an important role in decreasing the arterial pressure and especially recovery from psychological stress.[21] The statistically significant mean systolic BP between the groups (1) normal control and stress control without Nebivolol (2) normal control and vehicle control and (3) normal control and stress with Nebivolol group can be attributed to the above mentioned effect of Nebivolol by a $beta_1$ blocking effect and $beta_3$ mediated NO vasodilatory effect.

In recent days, stress has accentuated surprisingly in human life that it could be a major cause manifesting as a heart ailment.This stress could be the major cause of psychogenic heart disease.As put by Murray Esler[5], acute and chronic stress and their subsequent activation of the sympathetic nervous system,cardiac sympathetic outflow and the coronary artery vasospasm are the major contributors for the development of the cardiac consequences and also, epidemiologic research shows strong support for the notion that behavioral and psychological factors may be important in the pathogenesis of essential hypertension.

This development of chronic stress in mice and their reduction with Nebivolol,a 3rd generation beta blocker is well shown in this experiment.
The Group I – the normal control group treated with Nebivolol showed that there was no hypotensive effect below the normal lower limit on the contrary to what was expected.This is similar to the results produced by Ward JE et al[22] which shows that there is no hypotensive effect of Nebivolol on normal animals.

Comparison of the efficacy of Nebivolol with some other drugs.

1) Nebivolol and atenolol: In humans,it has been demonstrated that treatment with nebivolol is more effective in improving exercise tolerance and time to onset of angina during exercise testing when compared with atenolol.[4]Compared with atenolol, nebivolol treatment reduced the maximal contraction of the resistant arteries in SHR markedly . . Nebivolol combines vasorelaxing properties with protection against oxidative stress-induce vasoconstrictions. Taken together, the results suggested that nebivolol, in contrast to atenolol, improved resistant arterial functio[n].[23]
2) Nebivolol and metoprolol: The target blood pressure reduction was effective in more number of patients given Nebivolol when compared to the group given Metaprolol and also,Nebivolol caused less adverse effects.[24]
3) Nebivolol when compared with Lisinopril, both showed equal tolerability.[24]
4) When Nebivolol was compared with the Calcium channel antagonist – Amlodipine, both showed good tolerability however the incidence of adverse effects of Amlodipine were more pronounced.[24]

Henceforth from the above references, it's shown that Nebivolol is well tolerable with better actions than many other drugs.

CONCLUSION

We have developed a novel psychogenic hypertension model induced by restraint stress in mice. We have also verified the efficacy of antihypertensive effects of a third generation beta adrenergic blocker in this model.

SUMMARY

This project gives an idea of induction of psychogenic hypertension in mice in a novel way. No other solid references were got for the chronically induced stress model. Henceforth, we have standardized this model. Nebivolol effectively reduces the blood pressure within a

specific period. This experiment gives an idea of the drug nebivolol with its anti-hypertensive and additional anti oxidant properties

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