

Descriptive Controlled Study Regarding the Effects of Negative Chronotropic Agents on Lowering Heart Rate and Morning Surge in a Tertiary Care Hospital

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ABSTRACT: Objective: To determine the optimal therapy for lowering the heart rate (HR) of cardio-compromised patients by observing the effect of negative chronotropic agents.

Methods: The retrospective study was conducted at the 24 Holter monitoring data centre of Agha Khan University Hospital from August 2010 to July 2011. Data was extracted by using a predesigned Performa on individuals with compromised cardiovascular disease. The sample population was categorized into four groups. Furthermore, two time intervals were set which included an early morning and a later period.

Result: Of the 600 patients, 369 were males (61.5%) and 231 were females (38.5%) with a mean age of 54.9±19.2 years old. Average HR's for patients on BB, CCB, combination therapy and drug naïve were 71.14±11.4 bpm, 72.38±11.95 bpm, 66.88±10.37 bpm and 76.47±13.63 bpm respectively (p value<0.01). In period I, 42.5% of patients on BB had the lowest HR with a mean of 50.47±10.27 bpm, 36% on nCCB had a mean of 51.7±13.6 bpm, 50% on combination had a mean of 47.38± 8.3 bpm and 39.86% of drug naïve patients had a mean of 50.87±10.47 bpm (p-value <0.8). In period II, 57.5% on BB had the lowest HR with a mean of 49.87±9.15 bpm, 64% on nCCB had a mean of 50.75±10.23 bpm, 50% on combination had a mean of 50.5±5.01 bpm and 61.14% of drug naïve patients had a mean of 52.04±11.56 bpm (p value<0.61).

Conclusion: Negative chronotropic agents are highly effective in reducing a patient's HR as compared to those who were drug naïve.

Keywords: Beta blockers, non-dihydropyridine calcium channel blockers, morning surge, heart rate.
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INTRODUCTION

Cardiovascular disease (CVD) is perceived to be the leading of cause of morbidity and mortality not only in Pakistan, but worldwide [1-3] A significant portion of deaths and morbidity from cardiovascular diseases occur in developing countries. Countries such as India, Pakistan, Bangladesh, Sri Lanka, and Nepal comprising 20 per cent of the world's population have a very high prevalence of CVD [4].

The high burden of CVD in developing countries is attributable to urbanization and higher risk factor levels (such as obesity, diabetes, dyslipidaemia, hypertension, *etc.*) [5] Numerous physiological studies have indicated that since positive chronotropy increases the oxygen demand of the heart, it is likely to be associated with a negative outcome like Angina, Myocardial Infarction, and even death. Unfortunately, there has not been a single trial conducted to understand the effects of negative chronotropic drugs on the Pakistani patients.

Our study helps to understand the effect of giving negative chronotropic agents [Beta Blockers, Calcium Channel

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Blockers and a combination of therapy of the two drugs] on Pakistani patients with regards to controlling their heart rate and morning surge. It is seen that combination of non-dihydropyridine calcium channel blocker (NCCB) and beta blocker (BB) is more effective in reducing overall heart rate when compared to either beta blocker and non-dihydropyridine calcium channel blocker individually. One well-conducted double-blind study was done to confirm that diltiazem, verapamil, and nifedipine each can markedly improve both subjective and objective measures of efficacy when used in combination with a beta-blocker [6, 7]. Metoprolol monotherapy, as well as its combination with nifedipine, effectively reduces total ischemic activity compared with placebo and nifedipine monotherapy [8].

METHODS

Study Design and Settings

This was a retrospective single center study conducted at the Aga Khan University Hospital in Karachi, Pakistan. The hospital's Holter monitoring data center was approached to gather data on patients who were presented to the cardiopulmonary service. Holter monitor records various cardiac events throughout the day for the period of 24 hours such as average HR, lowest HR, highest HR and time at which minimum and maximum HR occurs. Data from August 2010 to July 2011 was collected from the centre; and patients were categorized into four groups in order to differentiate the effect of various negative chronotropic agents on HR. They included those using; only beta blockers, only non dihydropyridine calcium channel blockers, a combination of both nCCB and BB and drug naïve patients. Moreover, in order to assess the effects of different drugs on morning surge, the 24 hours monitoring period was divided into two intervals; an early morning period from 5:00A.M to 10:00A.M and a later period from 10:01A.M to 4:59A.M. Philips Zymed Holter was applied to these patients by trained technicians.

Ethical Statement

We acquired permission from The Ethics Review Committee of Aga Khan University Hospital. Patient confidentiality was strictly maintained throughout the study using medical record numbers rather than the patient's names for identification and data entry. In addition, informed consent was taken from head of the department of Holter monitoring centre and only the concerned students were allowed to participate for data collection.

Questionnaire

The questionnaire was designed with the help of the Department of Cardiology, Internal Medicine at Aga Khan University Hospital. A widespread search was completed

using PUBMED, MEDLINE and Google Scholar databases to extract relevant data to produce an accurate questionnaire. Data included 24 hours HR variations such as minimum HR, maximum HR and average HR. Other variables such as age, sex, comorbidity, names of different drugs used by patients, reasons for test, test date, analysis date and recording time were also collected. Data collection was completed within a two months time from August 2010 to July 2011. Although we were persistent regarding the completion of the entire questionnaire, 7 questionnaires had missing values and were excluded from the study.

Statistical Analysis

Data from the questionnaires was entered into Statistical Package for Social Sciences (SPSS) version 17 for analysis. Descriptive statistics such as means, standard deviations and percentages were used for the age, average HR, lowest HR and highest HR which formed the mainstay of our analysis. In addition, frequencies for each categorical variable were calculated. ANOVA and t-test were also used to compare HR variation among different groups in our study and the results were shown in the form of P-values.

Limitations

This was a single centre study and the number of patients on the combination study group was small. Also, this study cannot predict the effect of these drugs on every Pakistani patient. This means that further multi-institutional studies should be conducted in order to minimize bias. Furthermore, many of our patients were in the drug naïve group.

RESULTS

Demographics

A total of 600 patients were included in our study. Majority consisted of males 369 (61.5%) while 231 (38.5%) were females. The mean age of our patients was 54.9 ± 19.2 years. The mean average HR of all patients in our study was 75.16 ± 13.34 , mean lowest HR of all patients was 51.27 ± 10.87 and the mean highest HR of all patients was 121.01 ± 24.5 . After segregating the sample with respect to the drug intake, there were 80 (13.3%) patients on BB, 50 (8.3%) on nCCB, 16 (2.7%) on combination therapy and 454 (75.7%) were drug naïve. These results are shown in Table 1.

Effect of various drugs on lowest heart rate the mean lowest HR of all patients on BB was found to be 50.13 ± 9.5 bpm, those on nCCB was 51.10 ± 11.4 bpm, those on combination was 48.94 ± 6.85 bpm and those who were drug naïve as 51.57 ± 11.14 bpm (p value = < 0.57) as shown in Table 2A.

Effect of various drugs on highest heart rate on comparison, the mean highest HR of all patients on BB was found to be

112.88±21.9 bpm, those on nCCB was 113.88±18.4 bpm, those on combination was 104.31±25.3 bpm and those who were drug naïve was 123.82±24.8 bpm (p value<0.001) as shown in Table 2A.

Table 1. Microscopic Analysis.

Variables	Values
Total No. of Patients.	600
Male %(n)	61.5(369)
Female %(n)	38.5(231)
Mean Age(SD)	54.91(19.2)
Mean Average (SD)HR	75.16(13.34)
Mean inimum (SD)HR	51.27(10.87)
Mean Maximum (SD)HR	121.01(24.5)
No of Pt. on Beta blockers %(n)	13.3(80)
No of Pt. on CCB. %(n)	8.3(50)
No of Pt. on BB and CCB %(n)	2.7(16)
No of Drug Naïve Pt. %(n)	75.7(454)

Effect of various drugs on average heart rate the mean average HR of patients on BB was found to be 71.14±11.4 bpm, those on nCCB was 72.38±11.95 bpm, those on combination was 66.88±10.37 bpm and those who were drug naïve was 76.47±13.63 bpm (p value<0.01) as shown in Table 2A.

Effect of various drugs on morning surge in period I, from 5:00 a.m. to 10:00 a.m., 42.5% of patients on BB had the lowest HR with a mean of 50.47±10.27 bpm while 36% of patients on nCCB had a mean of 51.7±13 bpm.

Furthermore, 50% of patients on combination therapy had a mean of 47.38± 8.3 bpm while 39.86% of patients who were drug naïve had a mean of 50.87±10.47 bpm (p-value <0.801). These differences are demonstrated in Table IIB respectively. Conversely, in period II, from 10:01 a.m. to 4:59 a.m., 57.5% of patients on BB had the lowest HR with a mean of 49.87±9.15 bpm while 64% of patients on nCCB had a mean of 50.75±10.23 bpm. In addition, 50% of patients on combination therapy had a mean of 50.5±5.01 bpm while 61.14% of drug naïve patients had a mean of 52.04±11.56 bpm (p value<0.61).

DISCUSSION

Control of heart rate is regulated at many levels within the human body. It is under constant monitoring with various

Table 2A. Comparison of heart rate in patients on Beta Blocker, Calcium channel blocker, Calcium and Beta blocker both and drug naïve.

Heart Rate	Beta Blockers	Calcium Channel Blocker	Beta & Calcium Channel Blocker	Drug Naïve	P values
Mean Average (SD)HR	71.14 (11.4)	72.38 (11.95)	66.88 (10.37)	76.47 (13.63)	< 0.01
Mean Minimum (SD)HR	50.13 (9.5)	51.1 (11.4)	48.94 (6.85)	51.57 (11.14)	< 0.57
Mean Maximum (SD)HR	112.88 (21.9)	113.88 (18.4)	104.31 (25.3)	123.82 (24.8)	< 0.00

Table 2B. Comparison of morning surge (5a.m. to 10a.m.) in Heart rate inpatients on Beta Blocker, Calcium channel blocker, Calcium and Beta blocker both and drug naïve.

Heart Rate	Beta Blockers	Calcium Channel Blocker	Beta & Calcium Channel Blocker	Drug Naïve	P values
Mean Average (SD)HR	74.94(12.04)	74.11(14.62)	64.88(12.22)	77.48(12.95)	<0.04
Mean Minimum (SD)HR	50.47(10.27)	51.72(13.61)	47.38(8.36)	50.87(10.47)	<0 .8
Mean Maximum (SD)HR	118.74(21.37)	117.61(19.9)	105(20.1)	126.72(24.07)	<0 .01

biological mechanisms such as local and neurological control which allows it to maintain hemostasis. Physiologically, elevation in an individual’s HR results in the rise of oxygen demand for the myocardial tissue due to an overall increase in the work load of the heart. Nowadays, novel pharmacological agents have been developed to

extrinsically regulate and control the HR for patients suffering from cardiovascular disease. However, failure to control the HR not only compromises cardiac function, it may potentially lead to life threatening conditions. Hence, it is necessary to have an efficient drug regimen to ensure adequate control of HR in compromised patients.

Our study was designed to observe the effects of various drugs on the HR among cardio-compromised selected individuals. We divided our investigation population into four groups which included: those consuming only beta blockers (BB), those taking non dihydropyridine calcium channel blockers (nCCB) only, patients on a combination therapy of both nCCB + BB and drug naïve patients. The data collected revealed that majority of the cardio-compromised patients were either drug naïve while the most commonly prescribed agent was BB monotherapy. Also, nCCB's were consumed by only 8.3% (n=50) patients, with combination therapy being the least commonly prescribed.

In our clinical trial, we offered an adjusted dose for comparison among different groups. The results showed no significant difference in the average lowest HR [$p > 0.05$]. However, in a separate analysis of our patient groups, there was a significant association between the chronotropic agent(s) used and the average highest HR [$p < 0.01$]. Thus, the mean maximum HR tends to be lowest with patients who were taking a combination of BB and nCCB while drug naïve patients recorded the highest. Various randomized control trials in literature have suggested that a combination therapy of two agents may prove to be more efficacious than any single agent therapy in regards to controlling an individual's HR [8], resulting in a more profound regulation and improvement in overall cardiovascular function. Egstrup *et al.* elaborated that BB reduced the HR early on in an ischemic episode while nCCB's provided control at a later stage [11]. He concluded that giving a combination of BB and nCCB therapy displayed a better outcome to nCCB alone for patients with cardiovascular disease, in which the latter were associated with limited long-term survival and likelihood of adverse effects [12]. These were similar results which we encountered in our patients. Therefore, the goal of this combination therapy is to provide an integrated control of the HR by actively participating on different physiological levels, enabling a cumulative action of these novel agents. The resulting alteration in the HR is of particular importance in patients with previous ischemic diseases or myocardial infarction with significant prognostic implications [9, 10]. Additionally, we assessed the morning surge from 5:00 a.m. to 10:00 a.m. in different groups as previously described. The mean minimum HR was insignificant in these groups [$p > 0.05$]. Nevertheless, the mean maximum heart rate was found to be highly significant [$p > 0.05$]. Data suggested that it was much lower with combination therapy as compared to individual use of these agents.

Interestingly, White mentioned that many cardiovascular events tend to follow a circadian rhythm, peaking early in the morning [13]. A similar study reported that labetalol, alpha and beta blocker, and nifedipine had a higher efficacy in controlling morning surge in a critical period from 6:00

a.m. to 12 p.m [14]. Moreover, Parmley *et al.* suggested that nCCB along with a BB were effective in blocking the circadian pattern of angina and ischemic events by regulating the HR and blood pressure [15]. These reports were followed by a Japanese study which indicated that a control of morning surge may potentially prevent adverse cardiovascular events [16]. Nevertheless, special emphasis should be given to understand the efficacy of prescribed therapeutic agents which aim to control the morning surge in HR.

CONCLUSION

In summary, our study revealed that combination therapy had the greatest efficacy in reducing the overall HR of our patients as compared to individual usage. Those who were placed on either BB or nCCB had their lowest HR recorded before 5 a.m., while 50% of patients on combination therapy had their lowest HR recorded in the early morning time period with mean values which were not only significantly lower than BB and nCCB in period I, but also lower in period II as shown in the results. Thus, patients with compromised heart disease will achieve greater results if they are placed on combination therapy rather than a single drug regimen.

CONFLICT OF INTEREST

Declared none.

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