HEMODYNAMIC EFFECTS OF ANESTHETIC INDUCTION IN PATIENTS TREATED WITH BETA AND CALCIUM CHANNEL BLOCKERS

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Summary

Background: The response to anesthetic induction and airway manipulation in the presence of cardiovascular disease and anti-hypertensive therapy has not been adequately investigated.

Methods: The blood pressure, pulse pressure and heart rate changes at induction and following tracheal intubation were compared in patients who were on either preoperative beta-adrenergic blocker therapy (BB group, n = 20) or a combination of beta-adrenergic blocker and calcium channel blocker therapy (BB + CCB group, n = 20). A standardized anesthesia induction protocol was followed, in the two gourps.

Results: No statistical difference was observed in the hemodynamic parameters between the two groups. The total number of hypotensive patients (SAP 90 <mmHg) and bradycardic episodes following induction of anesthesia were one in the BB group and eighteen in BB + CCB group and were treated with ephedrine (p = 0.000002). Two episodes of hypotension without bradycardia occurred in BB group and six in BB + CCB group and were treated with phenylephrine (p = 0.25).

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Conclusion: Hypotension requiring treatment in patients receiving a combination of BB + CCB is more frequent after induction of anesthesia.

Keywords: Intubation tracheal; cardiovascular system, responses; Beta adrenergic antagonists and calcium channel blockers.

Introduction

Anesthetic induction is associated with periods of hemodynamic instability and autonomic reflex activity. Hypotension can follow induction when the patient is unstimulated, whereas hypertension and tachycardia can follow laryngoscopy and tracheal intubation. These changes are of particular importance in patients with cardiovascular or neurovascular diseases[1]. Drugs used to prevent or attenuate the laryngoscopy and tracheal intubation response, may also cause hypotension and/or bradycardia in a significant numbers of patients post induction[2].

In current practice majority of patients with ischemic heart disease and hypertension are either on mono or multi therapy. Many of these patients are either treated with beta blockers (BB) or a combination of beta blockers and calcium channel blockers (BB+CCB)[3]. An increasing number of such patients are now scheduled for surgery.

A combination of beta blockers and calcium channel blockers may lead to varying degree of atrioventricular conduction block. Also, the negative inotropic effect of this combination may also cause profound hypotension and or bradycardia[4].

The purpose of this study was to find out the incidence and severity of hypotension after induction of general anesthesia in 40 patients receiving either beta blocker therapy a combination of beta blocker and calcium channel blocker until the morning of surgery. We also monitored the blood pressure response to laryngoscopy and intubation in these patients.

Methods and Materials

This prospective observational trial was conducted after approval of Ethical Committee of the University and obtaining informed written

patient consent. The protocol was rigidly defined and 40 consecutive adult patients (20 in each group) ASA II & III, 30-65 years, scheduled for elective surgery and requiring tracheal intubation, were prospectively included in the study. Power analysis based on previous data[5], suggested that 20 patients per group could detect a 205 difference in systolic blood pressure and heart rate between the two groups after induction and intubation ($\alpha = 0.05$, $\beta = 0.2$).

All patients were maintained either on beta blocker (BB) alone or on combined beta blocker and calcium channel blocker (BB + CCB) therapy for at least last two weeks (Table 1). Patients with preexisting arrhythmias, left ventricular ejection fraction less than 30%, or history of congestive cardiac failure, recent myocardial infarction (less than six weeks) symptomatic valvular heart disease, history of asthma, obesity (body mass index (BMI) >35), anticipated difficult intubation, chronic renal failure, history of gastroesophgeal reflux and presence of cardiac pacemaker, were excluded.

The anesthetic technique was standardized. Patients were divided into tow equal groups (20 each) on the basis of their treatment either with beta blockers alone group I (BB), or were being treated with a combination of beta blocker and calcium channel blockers, group 2 (BB + CCB).

Antihypertensive drugs were continued up till the morning of surgery.

Patients were premedicated with midazolam 7.5 mg orally one hour before surgery. Baseline non-invasive blood pressure and heart rate were monitored 5 minutes before induction of anesthesia along with ST segment analysis. Routine monitoring was done using Datex A/S5 Monitor (Helsinki, Finland) observing ECG lead CM5 (Right arm (RA) electrode placed on the middle part of the manubrium, left leg (LL) electrode at the V5 position, and the left arm electrode on the left shoulder for ground, and lead II was monitored) and ST segment analysis. Arterial oxygen saturation, non-invasive blood pressure monitoring, end tidal carbon dioxide concentration, fraction of inspired oxygen concentration (FiO_2) and end tidal inhalational agent concentration were recorded.

Table 1

Antihypertensives used with dosage

	Group I (Beta Blocker)		Group II (Beta Blocker and Calcium Channel Blocker)	
	Antihypertensive	Dosage	Anithypertensive	Dosage
1.	Atenolol	50 mg OD	Atenolol	25 mg OD
			Amilodipine	5 mg OD
2.	Atenolol	50 mg OD	Atenolol	25 mg OD
			Amilodipine	5 mg OD
3.	Atenolol	50 mg OD	Atenolol	25 mg OD
			Amilodipine	5 mg OD
4.	Atenolol	50 mg OD	Atenolol	50 mg OD
			Amilodipine	5 mg OD
5.	Atenolol	50 mg OD	Atenolol	50 mg OD
			Amilodipine	7.5 mg OD
6.	Atenolol	50 mg OD	Atenolol	50 mg OD
			Amilodipine	10 mg OD
7.	Atenolol	50 mg BID	Atenolol	50 mg OD
			Amilodipine	10 mg OD
8.	Atenolol	50 mg BID	Atenolol	100 mg OD
			Amilodipine	5 mg OD
9.	Atenolol	50 mg BID	Atenolol	100 mg OD
			Amilodipine	5 mg BID
10.	Atenolol	50 mg BID	Atenolol	100 mg OD
			Amilodipine	10 mg OD
11.	Atenolol	100 mg OD	Atenolol	100 mg OD
			Amilodipine	10 mg OD
12.	Atenolol	100 mg OD	Atenolol	100 mg OD
			Diltiazem	60 mg BID
13.	Metoprolol	50 mg OD	Metoprolol	25 mg BID
			Amilodipine	10 mg OD
14.	Metoprolol	75 mg OD	Metoprolol	50 mg BID
			Amilodipine	5 mg OD
15.	Metoprolol	50 mg BID	Metoprolol	50 mg BID
			Amilodipine	10 mg OD
16.	Metoprolol	50 mg BID	Metoprolol	100 mg OD
			Amilodipine	5 mg OD
17.	Metoprolol	100 mg OD	Metoprolol	100 mg OD
			Amilodipine	5 mg OD
18.	Metoprolol	100 mg OD	Metoprolol	50 mg TID
			Amilodipine	5 mg OD
19.	Metoprolol	100 mg BID	Metoprolol	100 mg OD
			Felodipine	5 mg OD
20.	Propranolol	40 mg BID	Metoprolol	50 mg TID
			Verapamil	80 mg TID

OD = Once daily, BID = Twice daily, TID = Thrice daily.

All patients received 5 ml/kg^{-1} ringer's lactate as bolus before induction of anesthesia over a period of 5-10 minutes. Following preoxygenation, fentanyl 2 μg/kg^{-1} bolus was given intravenously. An initial dose of intravenous thiopentone sodium 4 mg/kg^{-1} was then administered over a period of 1 minute. Loss of eyelash reflex was used as the induction end point. Additional dose of 0.5 mg/kg^{-1} thiopentone sodium was given if needed. Neuromuscular block was provided with atracurium 0.5 mg/kg^{-1}, and patients were ventilated manually by a face mask for two minutes before laryngoscopy and intubation. Anesthesia was maintained with end tidal isoflurane concentration of 0.6% and an oxygen/nitrous oxide ratio of 50:50.

Two anesthetists were involved in managing the cases. Bias was reduced by involving a third anesthetist who recorded the data and was unaware of the study groups. Macintosh blade size three was used for laryngoscopy. A polyvinylchloride tracheal tube internal diameter size 7.5 mm was used in females and size 8.5 mm in males. Laryngoscopy was accomplished within 15 seconds.

Non-invasive blood pressure and heart rate along with ST segment analysis was recorded immediately before induction of anesthesia and than every minute for two minutes following induction. Measurements were taken immediately after laryngoscopy and intubation and then every minute for 5 minutes. Measurements were then continued every minute for 5 minutes after incision. Any change in ST segment of more than 1 mm was also recorded.

Hypotension was defined as systolic blood pressure less than 90 mmHg and bradycardia less than 50 beats minute^{-1}. Treatment of episodes was defined prospectively, and ephedrine 5 mg intravenous bolus was administered if both hypotension and bradycardia were present. Intravenous phenylephrine 100 ug intravenous bolus was administered if only hypotension was present. For heart rate less than 50 beats/minute^{-1}, glycopyrrolate 200 ug intravenous bolus was used.

Statistical analysis

Statistical analysis was performed using a general linear model analysis of variance for repeated measures for continuous variables (with treatment group and time as between-and within-group factors). Chi-square test was applied to see the significance of hypotension, bradycardia and ST segment change between the groups. All analyses were performed using SPSS for Windows computer software (version 14.0).

Results

Patient's characteristics and baseline hemodynamics variable i.e. systolic arterial pressure (SAP), diastolic arterial pressure (DAP), pulse pressure (PP), mean arterial pressure (MAP) and heart rate (HR) were similar in both groups (Table 2).

Table 2

Patient's characteristics and baseline hemodynamic variables

	Group BB (n = 20)	Group BB+CCB (n = 20)	P Value
Age; years	51.5±8.5	55.8±7.9	NS
Sex; M: F	7: 13	11: 9	NS
Weight; kg	69.7±11.8	69.1±10.8	NS
Height; cm	158.1±9.9	161.3±8.7	NS
ASA Grade			
2	15 (75%)	12 (60%)	NS
3	5 (25%)	8 (40%)	NS
Baseline SAP; mmHg	133.9±18.6	135.9±17.1	NS
Baseline DAP; mmHg	82.5±11.9	80.1±10.5	NS
Baseline PP; mmHg	51.4±10.3	55.8±11.5	NS
Baseline MAP; mmHg	97.8±15	99.5±12.1	NS
Baseline HR; mmHg	72.6±12.6	70±11.9	NS

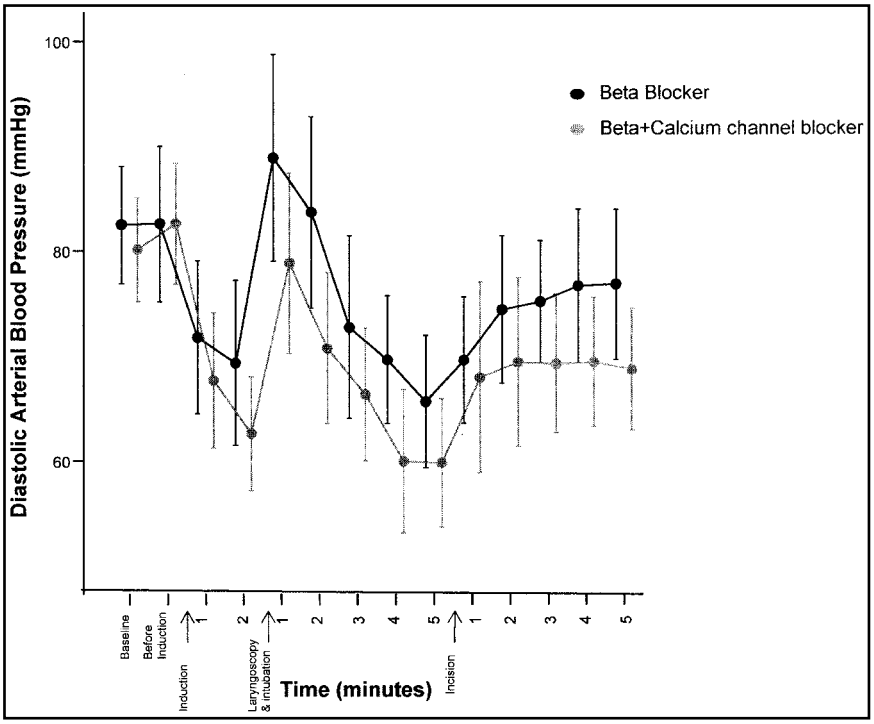
ASA = American Society of Anesthesiologists, SAP = Systolic arterial pressure, DAP = Diastolic arterial pressure, PP = Pulse pressure, MAP = Mean arterial pressure, HR = Heart rate.

Values are mean ± SD.

NS = Not Significant.

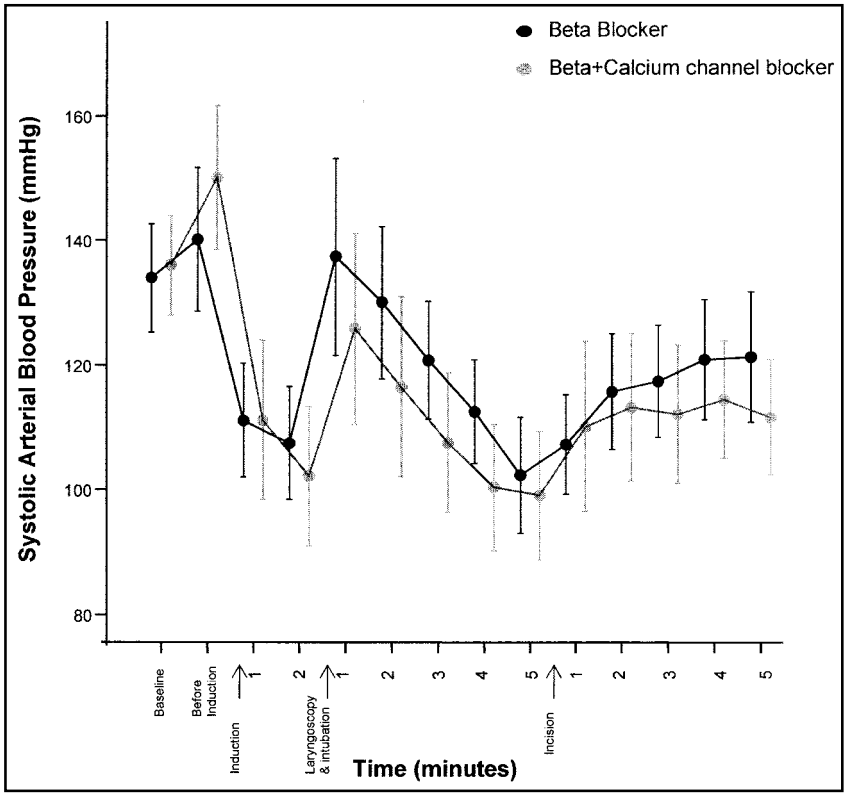
The SAP fell at 2 minute after induction in both groups (26 ± 21 in BB vs 33 ± 20 mm of Hg in BB + CCB groups). The SAP increase after laryngoscopy and intubation was obtunded in both groups (3 mm vs 10 mm of Hg) compared to baseline. Thereafter SAP fell in both group exceeding 20% of baseline at 5 minutes post intubation in BB group and at 3 minutes post intubation in BB + CCB group. The maximum mean fall in SAP was 32 ± 21 mm of Hg compared to the baseline in the BB group and 37 ± 26 mm of Hg in the BB + CCB group. No rise in BP compared to baseline was seen after incision. There was no statistical difference seen between the readings when the two groups when compared at corresponding time lines ($p>0.05$) (Graph 1).

Graph 1
Comparison of systolic arterial blood pressure between the two groups (mean and standard deviation).



The changes in DAP mirrored the SAP with a maximum fall in DAP of 13 ± 16 mm of Hg in BB group versus 18 ± 11 mm of Hg in the BB + CCB group. No statistical difference was seen between the two groups ($p>0.05$). Post incision no rise in DBP was seen (Graph 2).

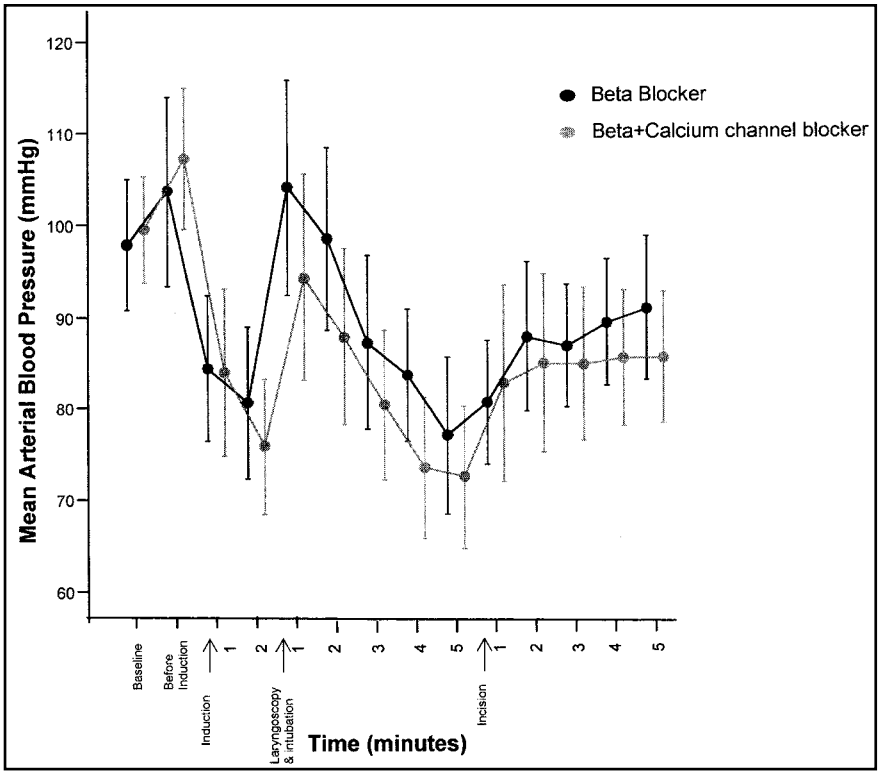
Graph 2
Comparison of diastolic arterial blood pressure between the two groups (mean and standard deviation).



The maximum fall in MAP after induction was at 2 minutes after induction (17 ± 18 mm of Hg in BB group versus 24 ± 13 mm of Hg in BB+CCB group). The increase in MAP after intubation was obtunded in BB group, (mean increase of 6 mm of Hg) and was obliterated in BB + CC group. No rise of pressure was seen after incision. There was no statistical difference seen between groups at corresponding time ($p>0.05$) (Graph 3).

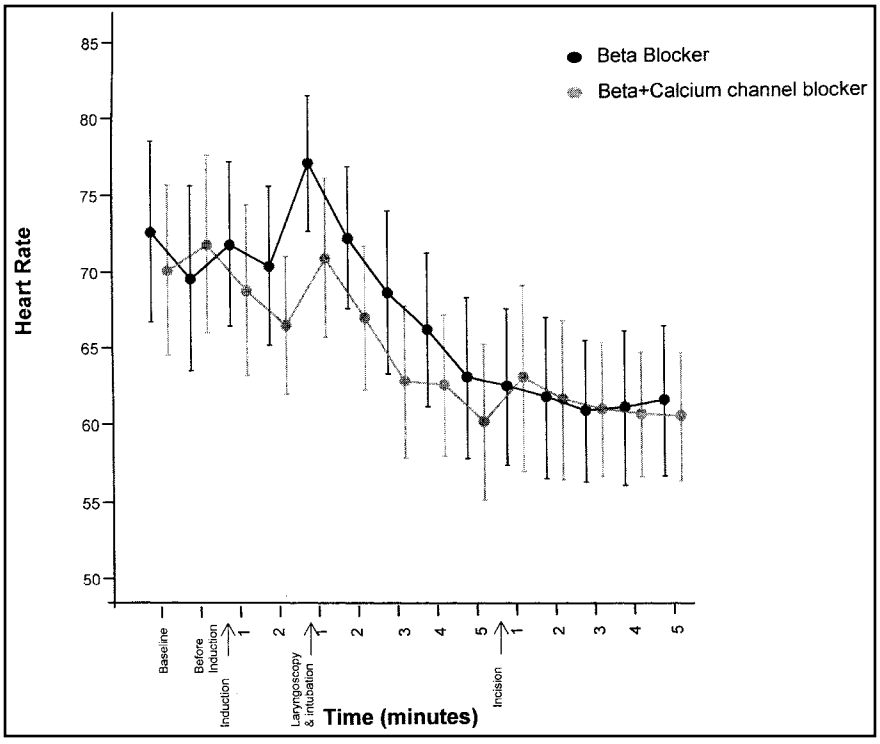
Graph 3

Comparison of mean arterial blood pressure between the two groups (mean and standard deviation).



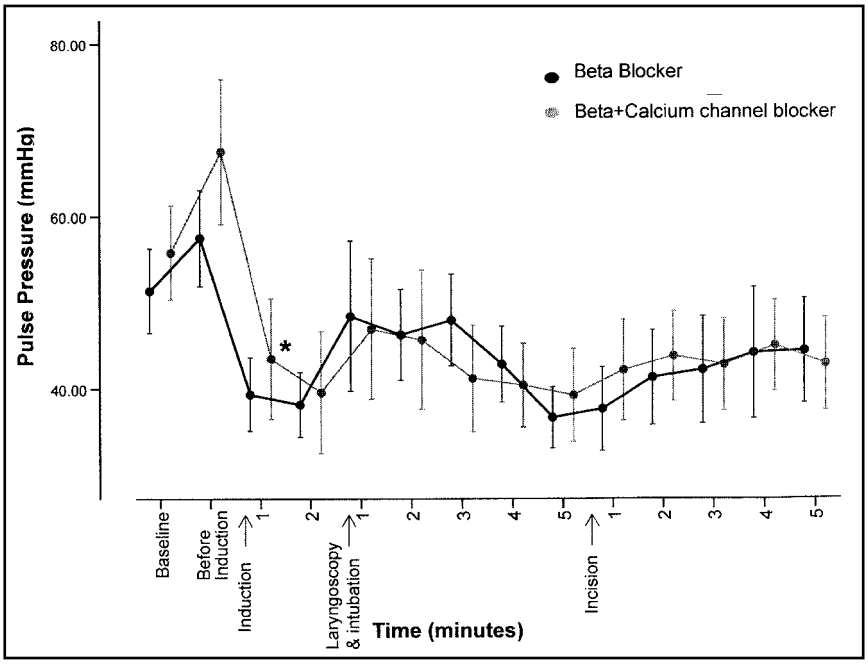
The heart rate showed a fall of 2 beats/min^{-1} in BB group vs 4 beats/min^{-1} in the BB + CCB group. Post tracheal intubation the heart rate increased by 4 beats/min^{-1} in BB and only 1 beat/min^{-1} in BB + CCB group. There was no change in post incision HR in BB and an increase of 3 beats/min^{-1} in the BB + CCB group. No difference was observed on comparing the two groups ($p>0.05$) (Graph 4).

Graph 4
Comparison of heart rate between the two groups (mean and standard deviation).



Pulse pressure changes mirrored the DAP but the pulse pressure was significantly lower in the BB group compared to the BB + CCB group at one minute after induction (p = 0.001) (Graph 5).

Graph 5
*Comparison of pulse pressure between the two groups (mean and standard deviation) * = p Value = 0.001.*



Episodes of hypotension and bradycardia: Overall three patients in BB group (15%) and eleven in BB + CCB group (55%) had one or more than one episode of hypotension. Total number of hypotensive episodes were three in the BB group and twenty four in the BB + CCB group (Table 3). One episode in the BB group and eighteen in BB + CCB group were associated with bradycardia and were treated with ephedrine ($p = 0.000002$). Two episodes in the BB group and six in BB + CCB group ($p = 0.25$) were not associated with bradycardia and were treated with phenylephrine. Patients in both groups became hypotensive around 2 minute after laryngoscopy.

Table 3
Total number of hypotensive episodes requiring administration of vasoconstrictor in the two groups after induction of anesthesia

Vasoconstrictor	Group		P Value
	BB n = 20	BB + CCB n = 20	
Ephedrine	1	18	0.000002
Phenylephrine	2	6	0.25

Four episodes of bradycardia alone occurred in the BB + CCB group compared to three in the BB group and were treated with glycopyrrolate only. Four patients in the BB group and two patients in the BB + CCB group showed ST segment depression of more than 1 mm ($p>0.05$).

Discussion

A decrease in SAP follows induction of anesthesia with either propofol or thiopentone when used in combination with fentanyl and muscle relaxants[6]. Sparse data exists on the response to induction of anesthesia and majority of studies on the topic have concentrated on the effects of different induction agents in ASA 1 patients[7,8]. Hypotension occurring in patients with ischemic heart disease can be detrimental because

myocardial blood flow to regions supplied by narrowed coronary arteries is pressure dependent[9]. Whether intra-operative hypotension is a risk factor for postoperative myocardial infarction is till controversial[10]. Some studies have demonstrated that intra-operative hypotension increases the risk of post-operative cardiac and renal complications in high risk population[11].

Blood pressure (BP) and heart rate (HR) increases after tracheal intubation and has been extensively studied[12,13]. These hemodynamic changes are of little concern in relatively healthy patients but can be detrimental in high risk population[14,15]. Both hypotension or hypertension can lead to an imbalance of myocardial oxygen supply and demand and result in morbidity.

Diseases of the cardiovascular system, like hypertension, additionally affect the normal physiological response of the body to anesthesia induction and intubation. The changes associated with laryngoscopy and intubation can be more severe and more dangerous in hypertensive patients9,16. In addition this response is complicated by the anti hypertensive therapy.

A preoperative history of hypertension was strongly associated with perioperative cardiovascular death, odds ratio 4.14, 95% CI 1.63-11.6917, because hypertension is associated with end organ damage like ischemic heart disease, cardiovascular disease, heart and renal failure.

The BP lowering effect of anesthesia induction has been seen in patients chronically treated with angiotensin converting enzyme inhibitors (ACEI) till the morning of surgery18. A study of hypertensive, diabetic patients undergoing non cardiac surgery reported ischemic cardiac complications in 19% who had intra-operative decrease in MAP more than 20 mm of Hg lasting more than 60 minutes. Decreases more than 20 mm of Hg of 5-59 minutes increase incidence of post-operative ischemic cardiac complications11. Jin et al recommended that efforts be made to avoid intra-operative hypotension to less than 20% of awake values in elderly patients19. Brabant et al studied the prevalence and severity of hypotension after induction of anesthesia in hypertensive patients treated with either angiotensin II receptor subtype antagonists (ARA), combination of beta blockers (BB) and/or calcium channel blockers (CCB) and angiotensin converting enzyme inhibitors (ACEI)[20]. Hypotension (defined as systolic

BP decrease of 30% less than the preoperative value or a decrease to <90 mm of Hg) was seen in all patients (12/12) in the ARA group, in 27/45 patients in BB/CCB group and 18/27 in ACE group. The hypotension was most severe and refractory in the ARA group. On the other hand Sear et al[21] showed no difference in the degree of hypotension associated with anesthetic induction in four groups of hypertensive patients on chronic monotherapy with ACE inhibitors, beta blockers, calcium channel blockers or diuretics. The data from the two studies is not directly comparable as the anesthetic agents used in the two studies were different (sufentanil 0.5 mg/kg^{-1}, propofol 1.5 mg/kg^{-1} atracurium 0.5 mg/kg^{-1}) in the former, and fentanyl 1.5-2.0 $\mu g/kg^{-1}$, thiopentone 3-5 mg/kg^{-1} and rocuronium 0.1 mg/kg^{-1} were used in the later study.

Beta blockers have little effect on normal heart in a resting patient, but they decrease heart and myocardial contractility when sympathetic activity is decreased. Anesthesia imposes additional myocardial depression in beta blocked patients[22] but this is well tolerated as anesthesia is commonly accompanied by vasodilatation that unloads ventricles and facilitates forward flow[23]. In Stone study[9], hypotension (SAP <70 mmHg) occurred after induction in a substantial number of beta blocker group, but to a lesser extent in those treated with oxprenolol compared to labetalol and atenolol perhaps because of the intrinsic sympathetic activity. This fall in BP was not accompanied by myocardial ischemia.

Cardiac muscle and vascular smooth muscle contain small amounts of endoplasmic calcium and are more dependent on calcium influx than skeletal muscles[4] and are sensitive to the effects of calcium channel blockers. Concurrent treatment with calcium channel blockers was seen as a risk factor for perioperative silent myocardial infarction (MI) in one study, odds ratio 2.68; 95% CI 1.38-6.93[24]. No effect of chronic beta blockade was seen. Increased incidence of silent MI was also seen in patients on chronic calcium channel entry blockade for arterial hypertension or coronary artery disease[25].

In view of the conflicting evidence in literature, we decided to study the hemodynamic changes associated with induction in the group of patients who present for general anesthesia and are on combination therapy with

beta blocker and calcium channel blockers and compare it to changes in patients on monotherapy with beta blockers alone. There have been previous case reports of negative inotropic effects of a combination of CCB and BB resulting in profound hypotension specially in patients with compromised left ventricular function[26], which lead to varying types of atrioventricular conduction block[4]. Also combination of BB+CCB can lead to profound hypotension, especially in patients with left ventricular failure[26].

Both beta blockers and calcium channel blockers have been separately used for blunting the hemodynamic response to laryngoscopy and intubation in normotensive as well as hypertensive patients[27]. Beta blockers obtunded the heart rate response, whereas CCB obtunded the pressor response but not the increase in heart rate[21]. It is important to obtund these changes in hypertensive patients as they show an exaggerated pressor response to tracheal intubation compared to nomotensive patients[16,28], Sears found these pressor responses to be unaffected and of similar magnitude in treated hypertensive patients on monotherapy[21].

In our study the mean decrease in BP in each group following induction did not show statistical difference between the two groups. The hemodynamic response to laryngoscopy and tracheal intubation was minimal in the both groups 3% rise compared to baseline in BB and 7% rise compared to baseline in BB+CCB group, but this was at the expense of fall in the preintubation blood pressure. No changes in HR and BP were seen after incision. SAP instability of less than 20% of baseline was seen at two minutes post induction and 5 minutes post intubation before incision. The hypotensive episodes needing treatment were also significantly more in BB+CCB group ($P < 0.05$). Majority of these patients required vasoconstrictor support five minutes post laryngoscopy. This can be explained on the basis that majority of these patients at that time are left unstimulated for a brief period before incision. Myocardial ischemia as evidenced by ST depression of more than 1 mm was seen in 4 patients in BB and 2 patients in the BB+CCB group. Increased risk of myocardial ischemia was seen in a previous study in patients who received calcium channel blocker whether for hypertension or for coronary artery disease[4].

There is now increasing evidence that high pulse pressure, which is an indicator of large artery stiffness, is an independent risk factor for cardiovascular mortality, especially coronary mortality, in different populations[29]. In our study pulse pressure dropped significantly ($P < 0.05$) one minute after induction of anesthesia in BB group only. The short tem benefit of decrease in pulsatile stress need to be further studied in anesthesia.

There are some limitations to our study. Firstly, we used thiopentone as an induction agent whereas more cardiostable agents like etomidate are also available. Thiopentone is a less expensive drug and is easily available in developing countries. Though Etomidate is cardiostable yet there has been recent concern about its adrenal suppression action even with a single bolus dose[30]. Secondly, the duration of antihypertensie therapy may also influence the hemodynamic response. We did not look at the duration of therapy but only included patients who had been on therapy for at least past two weeks. Thirdly, we used noninvasive measurement of blood pressure instead of the more accurate direct arterial measurements and the use of an invasive method in a relatively stable patient was considered unethical by us.

In conclusion, antihypertensive therapy with beta blockers and calcium channel blockers can affect the hemodynamic responses at induction of anesthesia and expose patients to hypotension. The mean fall in SAP after induction exceeded 20% of baseline in both groups in the post induction period, whereas changes in HR were minimal. The hemodynamic response to laryngoscopy and intubation and incision were obtunded but at the expense of preintubation low pressures, but the SAP again fell to more than 20% of baseline 5 minutes post laryngoscopy. There is a further need to quantify these changes associated with different antihypertensive drugs, both alone and in different combinations and different induction techniques, and identify patients at risk of exaggerated responses so that timely appropriate measures are taken.

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