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ORIGINAL ARTICLE

Attenuation of Cardiovascular response by ß-blocker esmolol during laryngoscopy and intubation

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Cardiovascular responses to laryngoscopy and intubation have long been recognized and various efforts have been made to attenuate this response. The aim of this study was to evaluate the efficacy and safety of ß-blocker esmolol in attenuating cardiovascular response to laryngoscopy and tracheal intubation in the Ghanaian population. After obtaining institutional ethical approval, 80 patients aged 18 to 65 years from either sex and classified as American Society of Anaesthesiologists (ASA) physical status I (normal healthy patients) or II (Patients with mild systemic disease) undergoing elective surgery under general anaesthesia were selected for the study. Participants were randomly allocated into two groups comprising 40 subjects each. Group I received esmolol 2 mg kg^{-1} I.V. bolus and group II (control) received a placebo 2 minutes prior to laryngoscopy. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product (RPP) were measured before induction as baseline, and at minute 1, 3 and 5 minutes respectively after tracheal intubation while they were also observed for any complications. There was a significant attenuation in HR, SBP, DBP, MAP and RPP in the experimental group as compared to the control group ($P < 0.05$) at 1 minute with onward decreases at 3 and 5 minutes respectively after intubation. However attenuation to baseline values at 5 minutes after intubation in the experimental group was significantly higher than that in the control group. Percentage changes in haemodynamic variables in experimental group versus control group at 5 minutes are as follows: HR = -2.90% vs 10.22%; SBP = 0.96% vs 6.21%; DBP = -3.54% vs 4.06%; MAP = -1.56% vs 4.94%; RPP = -1.86% vs 17.25%. Prophylactic therapy with esmolol was found to be safe and effective in attenuating cardiovascular responses to laryngoscopy and tracheal intubation among the Ghanaian population.

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INTRODUCTION

Laryngoscopy and tracheal intubation have been associated with haemodynamic changes (Bostana and Eroglu, 2012) such as transient hypertension (Manjunath *et al.*, 2008), tachycardia (Moon *et al.*, 2012), arrhythmias (Bae *et al.*, 2007), myocardial ischaemia or infarction (Landesberg *et al.*, 2009). These haemodynamic changes are of little consequence in healthy individuals but may be more severe and life threatening in patients with hypertension, coronary artery diseases and cerebrovascular diseases. Several attempts have been made to attenuate hemodynamic changes which include increase in blood pressure and heart rate in response to laryngoscopy and tracheal intubation. Pharmacological approaches involving the use of lidocaine (Manjunath *et al.*, 2008), remifentanil (Kaygusuz *et al.*, 2007), nitroglycerine (Fassoulaki and Kaniaris, 1983), diltiazem (Mikawa and Ikegaki, 1990), esmolol (Figueredo and Garcia, 2004), buprenorphine (Khan and Kamal, 1989), fentanyl (Bostana and Eroglu, 2012) and a combination of esmolol and nicardipine (Moon *et al.*, 2012) have been utilized

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to attenuate the pressure responses to laryngoscopy and tracheal intubation. Each of these drugs has a unique advantage and disadvantage in blunting the pressor response to intubation.

Reflex changes in the cardiovascular system are most marked after laryngoscopy and intubation and lead to an average increase in blood pressure by 40-50% and 20% increase in heart rate (Savio *et al.*, 2011). An increase in arterial pressure and heart rate following laryngoscopy and intubation can have deleterious effects on the heart as shown by Stoelting (1978). Esmolol is used to control periods of intense sympathetic stimulation (Hassan *et al.*, 1991) and plasma catecholamine release (Derbyshire *et al.*, 1983) in general anaesthesia. There has been no consensus regarding the optimum dose and timing of esmolol delivery (Gupta *et al.*, 2009).

Perioperative myocardial infarction is a leading cause of post-operative morbidity and mortality in normotensive patients due to hypertension and tachycardia (Savio *et al.*, 2011) following laryngoscopy and intubation. Studies from the African continent have shown avoidable anaesthesia mortality rates of 1:3000 in Zimbabwe (McKenzie, 1996), 1:1900 in Zambia (Heywood *et al.*, 1989), 1:500 in Malawi (Hansen *et al.*, 2000) and 1:150 in Togo (Bang'na Maman *et al.*, 2005). These demonstrate a serious and sustained absence of safe anaesthesia for surgery in developing countries. Deaths attributable to anaesthesia could be reduced by controlling the haemodynamic changes that occur during endotracheal intubation. There is increasing evidence that control of the heart rate and blood pressure response to endotracheal intubation is essential to prevent adverse cardiovascular outcomes (Korpinen *et al.*, 1998; Manjunath *et al.*, 2008)

Hypertension is known to occur more frequently in the black population and is associated with a higher incidence of cerebrovascular and renal complications. Strokes have been found to be more common in black hypertensives and hypertension associated end-stage renal failure occurs up to 20 times more commonly in black patients, compared to non-blacks (Gibbs *et al.*, 1999), therefore, the need for assessment in this study cohort.

Efforts are being made to practice safe anaesthesia in Ghana in an attempt to reduce intraoperative complications and mortality during anaesthesia. Esmolol is considered appropriate to attenuate haemodynamic changes in Caucasians during endotracheal intubation as it reduces heart rate as well as blood pressure. Specific racial differences need to be considered before treatment in view of a report that African-Americans respond much less to beta adrenergic receptor blocking drugs than whites (Materson *et al.*, 1993). Beta-blockers tend to be less effective in black hypertensives and thus higher doses are required to control blood pressure (Gibbs *et al.*, 1999). There is paucity of literature on studies to control haemodynamic changes during laryngoscopy and endotracheal intubation among the Ghanaian population. The purpose of this study was, therefore, to determine the efficacy and safety of intravenous esmolol in attenuating haemodynamic response to laryngoscopy and intubation in the Ghanaian population.

PATIENTS AND METHODS

Study site and participants

Eighty (80) adult patients of American Society of Anaesthesiologists (ASA) physical status I (normal healthy patients) or II (Patients with mild systemic disease) undergoing various elective surgeries at the Komfo Anokye Teaching Hospital (KATH) between November 2011 and May 2012 were divided into two groups of 40 patients each. Patients with a history of hypertension, diabetes, cardiac diseases, bronchial asthma and those on beta-blockers were excluded.

Dosing of Esmolol

Bolus dosing of esmolol was evaluated with doses varying between 1 mg kg^{-1} and 4 mg kg^{-1} (Savio *et al.*, 2011). The use of esmolol at 3 mg kg^{-1} (Korpinen *et al.*, 1995) and 4 mg kg^{-1} (Berg, 1998) respectively has been observed to have adverse effects such as unplanned hypotension and bradycardia during induction. Kumar *et al.* (2003) in their study claimed optimal results while using lesser doses of esmolol in Asian population (i.e. 2 mg kg^{-1}).

These findings were the basis for using smaller doses of esmolol in this study in a Ghanaian population.

Dosing procedure

Group I received injection esmolol (2 mg kg^{-1}) and Group II (control group) received injection normal saline as placebo. A preoperative history was taken prior to administration of the drug. Clinical examination and routine investigations such as haemoglobin, haematocrit, total lymphocyte count, differential lymphocyte count, serum electrolytes, blood group/ Rh typing, blood urea nitrogen, serum creatinine, fasting blood sugar, chest radiography and electrocardiogram in all patients. This study was undertaken at the Department of Anaesthesia and Intensive Care at KATH, Kumasi, following institutional approval by the Committee on Human Research Publications and Ethics (CHRPE), School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. The study objectives and procedure were explained to the participants and written informed consent was obtained.

Intravenous access was secured and infusion of Ringer's lactate solution started. The patients were pre-medicated 30 minutes prior to surgery with glycopyrrolate-bromide (0.008 mg kg^{-1}) intramuscularly. Patients were then taken to the operating room after which routine non-invasive monitor Infinity Delta XL Drager was applied and vital signs monitored. Midazolam (0.04 mg kg^{-1}) was administered intravenously over 30 seconds as pre-medication and patients were pre-oxygenated with four to five breaths of 100% oxygen. The patients were induced with thiopentone sodium (6 mg kg^{-1} IV) in incremental doses until loss of eyelash reflex occurred, vecuronium bromide (0.12 mg kg^{-1} IV) was given over 20 seconds, followed by the administration of the study drugs (normal saline or esmolol) two minutes before laryngoscopy and intubation. The study drug was randomly allocated to patients in a double blinded manner.

Patients were ventilated with oxygen and halothane (1%) using intermittent positive pressure ventilation with a fresh gas flow of 6 litres per minute by Bain circuit until intubation. About 2 minutes after IV vecuronium, laryngoscopy was performed with a Macintosh laryngoscope blade and trachea intubated with an appropriate size cuffed endotracheal tube. After confirmation of correct placement of endotracheal tube, anaesthesia was then maintained with oxygen, halothane mixed with vecuronium (0.1 mg kg^{-1}). Heart rate (HR), systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial Pressure (MAP), Rate Pressure Product (RPP), Oxygen saturation (SpO_2) and Electrocardiogram (ECG) changes were recorded before induction (Basal) and after tracheal intubation at 1, 3 and 5 minutes for the purpose of this study. Manipulation (e.g. painting and draping) of the area of operation was not allowed until 5 minutes after the study drug has been administered. Injection fentanyl (2 μg kg^{-1}) was given before surgery.

Parameters and statistical analysis

Vital signs were recorded before induction (Basal) and after tracheal intubation at 1, 3 and 5 minutes respectively. Multi-channel monitor (Infinity Delta XL Drager, Draeger Medical Systems, Inc. Telford, PA 18969, USA) was used for recording HR, SBP, DBP, MAP, ECG, SpO_2. RPP was calculated by multiplying heart rate with systolic blood pressure. Patients were also observed for complications like hypotension, hypertension, arrhythmias, hypoxaemia and myocardial ischaemia. Haemodynamic variables were represented by mean ± standard deviation (SD). Means were compared with student *t*-test and p values were calculated. ANOVA with repeated measures was used to compare the changes in HR, SBP, DBP, MAP and RPP values. Bonferroni's multiple comparison tests were used to make intragroup comparisons. In all analyses, $p<0.05$ was considered statistically significant. All statistical analyses were performed using GraphPad prism 5.00 for windows (GraphPad software, San Diego, California, USA, www.Graphpad.com).

RESULTS

A comparison of the demographic profile of the study groups are as shown in Table 1. The male to female ratio of group I was 1:1.5 whereas that of group II was 1:2.6 ($p<0.34$). No significant difference was observed in the mean age for group I pa-

tients (40.8 ± 13.7 years) when compared to those in group II (41.8 ± 12.7 years) (p<0.74). The average weight was 70.1 ± 9.6 kg and 69.7 ± 9.8 kg in groups I and II respectively (p<0.85).The average height in group I was 164.2 ± 5.4 cm and group II was 163.3 ± 4.6 cm (p<0.47).

Table 2 shows a comparison of changes in mean haemodynamic variables in patients within the two groups at baseline and time (1, 3 and 5 minutes) after intubation. In group I, significant increases in the mean estimates for SBP, DBP, MAP, RPP were observed 1 minute after intubation when compared to the mean baseline estimates with the exception of the mean value for pulse which did not show any significant variation from the mean value at baseline. A time dependent decrease in the mean value for the parameter estimates was observed at 3 and 5 minutes respectively from first minute. Significant percentage decreases in the parameter estimates were observed at 5 minutes of intubation for group I patients (Table 3). In group II patients however, significant increases in all the mean estimates for the parameters were observed within the first minute after intubation and a time dependent decrease in the mean values for the parameter estimates was observed up to the fifth minute. A critical look at the percentage changes in the haemodynamic variables showed consistently higher percentage change values in the times after intubation in group II patients compared to group I patients (Table 3). It was evident that vital signs remained attenuated from 3 minutes to 5 minutess after intubation in group I patients, returning to baseline values after

Table 1: Demographic profile of the study groups stratified by treatment

Variables	Group-I (n = 40)	Group-II (n = 40)	p-value
Age (yrs)	40.8 ± 13.7	41.8 ± 12.7	0.743
Weight (kg)	70.1 ± 9.6	69.7 ± 9.8	0.846
Height (cm)	164.2 ± 5.4	163.3 ± 4.6	0.465
Sex			
Males	16(40.0%)	11(27.5%)	0.344
M:F	1:1.5	1:2.6	

Data are presented as means ± SD, ratio and percentages. Group-I (Esmolol treated group), Group –II (Control group).

Table 2: Change in haemodynamic variables in the two study groups after intubation

parameter	Basal	1 minute	3 minutes	5 minutes	p-value
Group I					
Pulse (bpm)	90.8 ± 8.6	92.2 ±9.7	91.4 ±7.5	88.2 ± 8.8*†¥	0.0005
SBP (mmHg)	125.1 ± 8.3	137.5 ± 8.9*	131.9 ± 8.8*†	126.3 ± 8.7†¥	< 0.0001
DBP (mmHg)	81.9 ± 5.0	90.4 ± 5.7*	82.6 ± 5.2†	79.0 ± 5.9*†¥	< 0.0001
MAP (mmHg)	96.3 ± 4.3	106.1 ± 5.0*	99.0 ± 4.1*†	94.8 ± 4.9*†¥	< 0.0001
RPP	11355 ± 1229	12681 ± 1605*†	12062 ± 1352*	11144 ± 1401†¥	< 0.0001
Group II					
Pulse (bpm)	89.0 ± 9.3	116.1 ± 7.6*	109.5 ± 7.4*†	98.1 ± 9.3*†¥	< 0.0001
SBP (mmHg)	123.9 ± 6.5	153.1± 12.8*	145.0 ± 12.9*†	131.6 ± 10.1*†¥	< 0.0001
DBP (mmHg)	83.7 ± 6.7	99.4 ± 5.2*	94.3 ± 5.1*†	87.1 ± 5.5*†¥	< 0.0001
MAP (mmHg)	97.1 ± 5.0	117.3 ± 5.9*	111.2 ± 5.5*†	101.9 ± 4.8*†¥	< 0.0001
RPP	11012 ± 1196	17778 ± 1926*	15861 ± 1690*†	12912 ± 1574*†¥	< 0.0001

Data are presented as means ± standard deviation, and p value. ANOVA with repeated measures was used to compare the changes in HR, SBP, DBP, MAP and RPP values. Bonferroni's multiple comparison tests were used to make intragroup comparisons. Comparison symbols used - * with basal, † with 1min. and with ¥ 3min. Group-I- esmolol, bpm - beat per minute, B.P-Blood Pressure, MAP-Mean Arterial Pressure, mmHg- millimetre of mercury

5 minutes in both groups but attenuations in group I were more significant than those in group II. Patients in group II undergoing laryngoscopy and intubation showed an incidence of 8% ventricular ectopics and 5% dropped beats. However, the use of esmolol did not result in any kind of arrhythmias or hypotension.

Table 3: Percentage changes in haemodynamic variables from baseline and times after intubation in the study population stratified by treatment

Variables	1 min.	3 min.	5 min.
Group I			
Pulse (bpm)	1.50%	0.70%	-2.90%
Systolic (mmHg)	9.90%	5.40%	0.96%
Diastolic (mmHg)	10.40%	0.85%	-3.54%
MAP (mmHg)	10.20%	2.80%	-1.56%
RPP	11.68%	6.23%	-1.86%
Group II			
Pulse (bpm)	30.45%	23.03%	10.22%
Systolic (mmHg)	23.57%	17.03%	6.21%
Diastolic (mmHg)	18.76%	12.66%	4.06%
MAP (mmHg)	20.80%	14.52%	4.94%
RPP	61.44%	44.03%	17.25%

Percentage change was calculated as follows: [(Variable estimate for time after intubation – Basal estimate for variable)/Basal estimate for variable] X 100%, RPP = Rate pressure product

DISCUSSION

This study assessed the effect of esmolol on haemodynamic changes due to tracheal intubation in normotensive black population. Results from the study consistently showed that esmolol blunts unwanted haemodynamic responses to endotracheal intubation with significantly less circulatory responses experienced by patients receiving intravenous esmolol. In the control group, markedly high cardiovascular changes occurred after one minute following laryngoscopy and intubation. Esmolol (2mg kg^{-1}) given two minutes before intubation sufficiently reduced the circulatory responses in this cohort of normotensive black patients. ß- blockers minimize the increase in heart rate and blood pressure by attenuating positive chronotropic and ionotropic effects of the increase in adrenergic activity. Esmolol possesses several properties which makes it a valuable agent to obtund the cardiovascular response. It is a cardio selective agent, has ultra-short duration of action (9 minutes) and has not been reported to have significant drug interaction with commonly used anaesthetic drugs (Savio *et al.*, 2011).

Korpinen *et al.* (1998) reported that the administration of esmolol bolus 1 mg kg^{-1} and an infusion of 200 µg kg^{-1} $minute^{-1}$ IV 2 minutes before laryngoscopy and intubation suppressed the increase in heart rate rather than arterial blood pressures. Bostana and Eroglu (2012) reported that IV esmolol in doses of 1 mg kg^{-1} before intubation was effective in suppressing heart rate and arterial blood pressure in Caucasians. Kumar *et al.,* (2003) have reported optimal results while using higher doses of esmolol (2 mg kg^{-1}) in an Asian population, without any incidence of unplanned hypotension or bradycardia. In this normotensive cohort of black population, esmolol, at a dose of 2 mg kg^{-1} effectively decreased HR, SBP, DBP, MAP and RPP without any incidence of hypotension or bradycardia. This study further observed a reduction in DBP less than that in SBP resulting in a better control of the MAP in the study population. No consensus has however been reached regarding the optimum dose and timing of its delivery (Gupta *et al.*, 2009; Savio *et al.*, 2011) in Caucasian population.

The difference in the results of Korpinen *et al.* (1998) and Bostana and Eroglu (2012) involving esmolol 1 mg kg^{-1} to some extent, can be explained by differences in study designs including variations in patient population, age, racial differences, dose and timing of drug administration in relation to intubation. In addition, techniques used for induction, method of measurement of circulatory responses are contributing towards mixed effect of esmolol in these studies.

Increases in heart rate of patients receiving esmolol in this study was attenuated as compared to the

control group for a maximum duration of 5 minutes after intubation. Several studies have shown that there is increased incidence of myocardial infarction when intraoperative heart rate increases above 110 beats min^{-1} (Stone *et al.*, 1988; Slogoff and Keats, 1989). None of the patients in this study groups showed heart rate >110 beats min^{-1} (Table II).

RPP is a good estimate of myocardial oxygen requirement (Moon *et al.*, 2012). RPP levels close to 20,000 are normally associated with angina and myocardial ischemia (Cokkinos and Voridis, 1976). RPP one minute after intubation remained at 12,681 in the esmolol group thus confirming the cardioprotective effect of esmolol during laryngoscopy and intubation.

CONCLUSION

The use of esmolol for the control of haemodynamic responses to laryngoscopy and intubation has shown promising results in this cohort of black population. This study has established the prophylactic role of 2mg kg^{-1} dose of esmolol in attenuating hemodynamic responses to laryngoscopy and intubation in normotensive patients without any associated complications such as hypotension and bradycardia. However further studies needs to be done in high-risk patients, using longer duration infusions to investigate the safety and efficacy of esmolol in reducing the frequency of myocardial ischaemia after non-cardiac surgery.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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