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ORIGINAL RESEARCH

Evaluation of hypotension following induction of general anaesthesia due to thiopentone, propofol and etomidate using perfusion index

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Background: Whether peripheral vasodilation or decrease in cardiac output causes the reduction in blood pressure (BP) following induction of anaesthesia, is not clearly understood. Therefore, an attempt was made to elucidate the mechanism of hypotension in terms of change in perfusion index (PI) and cardiac output.

Methods: With institutional ethics committee permission and consent, 66 patients were assigned equally to three groups. Each group received a titrated dose of a different induction agent, namely thiopentone (5 mg/kg), propofol (2 mg/kg) or etomidate (0.3 mg/kg). PI, heart rate (HR), and systolic, diastolic and mean arterial pressure were recorded at baseline and then every minute until 10 minutes post intubation. Echocardiography parameters (i.e. ejection fraction (EF), contractility and left ventricular end diastolic volume (LVEDV)) were measured at baseline, three minutes post induction and five minutes post intubation. Statistical analysis included one-way analysis of variance (ANOVA), Bonferroni test or Kruskal Wallis/Mann Whitney-U test.

Results: The EF and contractility remained stable after induction with all three induction agents. However, LVEDV and hence stroke volume increased significantly with etomidate ($p = 0.011$). There was gradual and continued increase in PI and reduction in the BP from the time of induction, which was minimal with etomidate and maximum with propofol. A marginal increase in HR was seen with thiopentone, while others caused a steady fall.

Conclusion: Vasodilation and reduced HR were responsible for the hypotension following induction of anaesthesia by intravenous agents. The effect was maximal with propofol with no evidence of myocardial depression. Etomidate lead to increase in stroke volume which explains its cardiovascular stability.

Keywords: general anaesthesia, induction, perfusion index, hypotension, blood pressure, echocardiogram, myocardial depression, ejection fraction

Introduction

Induction of anaesthesia is a vital part of general anaesthesia (GA), so is maintaining haemodynamic stability during induction. Intraoperative hypotension is a common complication that leads to tissue hypoperfusion and the subsequent consequences, which can raise postoperative morbidity and mortality, even following a brief period of hypotension.[1] Hypotension, secondary to induction of anaesthesia, is more common in the latter post-induction interval, between 5 and 10 minutes after induction.[2] As blood pressure (BP) is monitored at fixed intervals (every 3–5 minutes), short durations of intraoperative hypotension may go undiagnosed. The main risk factors for both post-induction hypotension and early intraoperative hypotension includes age, the existence of hypotension prior to induction, emergency surgery, and the type of induction drug being employed.[3]

Several factors, including the effect of anaesthetics on blood vessel walls that causes vasodilation and a decrease in systemic vascular resistance (SVR), direct myocardial depression, histamine release, or anaphylactic reaction, contribute to the reduction of BP during the induction of GA.[4]

In the context of critical care and perioperative care, perfusion index (PI) is invariably available to monitor patients. It is a very easy, affordable and non-invasive method to assess the perfusion of peripheries. PI is the proportion of pulsatile to the non-pulsatile blood flow in the peripheral tissue.[5] Since the value of PI is inversely linked to the peripheral vascular tone, a low baseline PI is correlated with higher incidence of hypotension.[6] Changes in the peripheral vascular tone or SVR are reflected as fluctuations in PI.[7]

However, the exact mechanism of hypotension is not well established. Therefore, this study was undertaken to ascertain the mechanism of post-induction hypotension with three induction agents by examining changes in the peripheral vascular resistance via PI and cardiac output (CO) via echocardiography. The primary outcome was the mechanism of hypotension following induction of anaesthesia with three intravenous (IV) induction agents. Secondary outcomes were to compare changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and any adverse effects after induction with thiopentone, propofol or etomidate.

Materials and methods

This prospective, randomised, double blind, observational study was conducted from April 2021 to September 2022 at a tertiary care teaching hospital in India after approval by the Institutional Ethics Committee (EC/NEW/INST/2020/834) through letter no.

INST.EC/134/2020-21. The research was done in accordance with Helsinki Declaration of 1975 (revised in 2013). In total, 66 patients with American Society of Anesthesiologists (ASA) physical status class I and II, aged between 18 and 60 years who were undergoing elective surgery under GA with tracheal intubation, were included after written informed consent. Patients with hypertension, vasoactive medications, peripheral vascular disease, difficult airway, who were pregnant, or had an allergy to any of the drugs used, were excluded. Also, if the duration of laryngoscopy and intubation exceeded 20 seconds or if more than one intubation attempt were required, patients were excluded. After thorough pre-anaesthetic evaluation, participants were kept nil per os (NPO) eight hours for solids and two hours for clear liquids. Participants were pre-medicated with tablet diazepam (5 mg for < 50 kg, 10 mg for > 50 kg) at 10 pm on the preoperative night and 7 am on the operative day, and tablet pantoprazole 40 mg at 10 pm on the preoperative day. The participants were taken up as first cases as the procedure of echocardiography had to be performed by the expert. On the day of the surgery, after confirming the identity, consent and NPO status, the participant was connected to the monitor (non-invasive blood pressure, electrocardiogram and pulse oximetry) and baseline values were recorded. Patients were randomised into three equal groups of 22 participants each using computer-generated random number table to determine, which induction agent each participant will receive. Allocation concealment was ensured by using a closed opaque envelope. Transthoracic echocardiogram was done to assess the ejection fraction (EF), contractility and left ventricular end diastolic volume (LVEDV) before induction of anaesthesia. PI was measured in supine position using a pulse oximeter probe (Intellivue MP40 Anaesthesia monitor, Philips Medizin Systeme, GmbH 71034, Boeblingen, Germany) which was attached to the left index finger. After securing IV access, if not already done, Ringer's lactate infusion was started at 100 ml/h, just before induction of anaesthesia. Preoxygenation was done with 100% O_2 for three minutes. Inj. fentanyl 2 mcg/kg IV was administered followed by the IV induction agent, either thiopentone (Thiosol sodium, Neon laboratories Limited, Mumbai, India) 5 mg/kg (group T), propofol (Neorof 1%, Neon Laboratories Limited, Mumbai, India) 2 mg/kg (group P) or etomidate (Troymidate, Troikaa Pharmaceuticals Limited, Uttarakhand, India) 0.3 mg/kg (group E), according to the group allocation. The induction agent was injected slowly over one minute, titrated to loss of response to verbal communication in case of propofol and loss of eyelash reflex in case of etomidate or thiopentone, or to the maximum dose as already indicated. Three minutes post induction, EF, contractility and LVEDV were assessed with the help of transthoracic echocardiography. Inj. vecuronium 0.1 mg/kg was administered to facilitate laryngoscopy and endotracheal intubation. Lungs were ventilated with 100% oxygen for five minutes. Trachea was intubated with appropriate-sized endotracheal tube by the consultant anaesthesiologist. Sevoflurane was used for the initial 10 minutes post intubation and then switched over to isoflurane. Maintenance of anaesthesia with 50% N_2O in oxygen along with isoflurane 0.6%. End-tidal CO_2 was maintained between 35–45 mmHg. Five minutes post intubation, the participant's EF, contractility and LVEDV were reassessed with transthoracic echocardiography using the LOGIQ™ e ultrasound machine (GE Healthcare Technologies, Waukesha, Wisconsin). Haemodynamic parameters were recorded every minute until ten minutes after intubation. During this period surgical stimulus was avoided. Hypotension was defined as drop in SBP by < 30% of baseline or < 90 mmHg absolute or MAP to < 60 mmHg, whichever was less. Severe hypotension (MAP < 55 mmHg/MAP drop by > 20% from baseline) was treated immediately by rapid IV fluid administration (10 ml/kg) and Inj. ephedrine 3 mg IV bolus every three minutes. Bradycardia was defined as HR < 50/min or decrease by > 30% below baseline, whichever was less, which was treated by Inj. atropine 0.6 mg IV boluses. Any other adverse events were noted and managed adequately as per standard guidelines.

The recorded parameters were retrieved from the anaesthesia monitor except echo findings. Echocardiography was performed

Table I: Comparison of demographic data and baseline parameters (n = 66)

Parameters		Group T (n = 22)	Group P (n = 22)	Group E (n = 22)	p-value
Age in years (Mean ± SD)		42.8 ± 12.2	38.9 ± 12.8	41.7 ± 14	0.59
Gender (M/F) (n)		9/13	7/15	7/15	0.766
BMI (kg/m^2) (Mean ± SD)		26.5 ± 4.9	24.4 ± 3.7	26.5 ± 5.4	0.235
Type of procedure (n) ENT/General Surgery/Urology/Maxillo		13/8/1/0	8/10/2/2	8/10/1/3	0.505
ASA PS Class (n) I/II		12/10	13/9	11/11	0.832
Baseline	PI (Mean ± SD)	1.4 ± 1	1.1 ± 0.8	1.6 ± 1.1	0.235
	HR (BPM) (Mean ± SD)	76.5 ± 12.5	78.6 ± 10.9	80.4 ± 13.5	0.592
	SBP (mm Hg) (Mean ± SD)	131.1 ± 20.9	129.8 ± 13.4	129.2 ± 14.3	0.926
	DBP (mm Hg) (Mean ± SD)	78.8 ± 13	79.5 ± 9.3	77.9 ± 11.6	0.897
	MAP (mm Hg) (Mean ± SD)	92.7 ± 16.1	95.5 ± 9.6	94.7 ± 11.6	0.758
	EF (%) (Mean ± SD)	57.9 ± 9.3	57.3 ± 8.3	60.9 ± 9.4	0.365
	LVEDV (ml) (Mean ± SD)	109.5 ± 26.3	105.1 ± 22.1	114.7 ± 16.5	0.354

SD – standard deviation, BMI – body mass index, ENT – ear nose and throat, ASA PS – American Society of Anesthesiologists physical status, PI – perfusion index, HR – heart rate, BPM – beats per minute, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, EF – ejection faction, LVEDV – left ventricular end diastolic volume

by a consultant unaware of group allocation and induction drug. All the interventions were done by the consultant anaesthesiologist in charge of the patient.

There were no data available about changes in PI during induction of anaesthesia with thiopentone and etomidate. Hence, sample size was calculated on the basis of effect size using G*Power software version 3.1 (Heinrich Heine University Düsseldorf, Germany; 2009). Assuming 80% power, alpha error of 5%, effect size of 0.2 (as per Mehandale and Rajashekhar[7]) the samples required for three groups was 66 (i.e. 22 in each group). Data were computed on a Microsoft® Excel spreadsheet (Microsoft® Office professional 2013, Microsoft Corporation, Redmond, WA, USA) and analysed using Statistical Package for Social Sciences (SPSS) (International Business Machines (IBM), Armonk, USA). Comparisons were done using one-way analysis of variance (ANOVA), Bonferroni test, Kruskal Wallis/Mann Whitney-U test. To find correlation, Karl Pearson's coefficient correlation/Spearman's rank correlation were used. A p-value < 0.05 was considered statistically significant.

Results

In total, 66 patients were enrolled for the study and all were available for data analysis

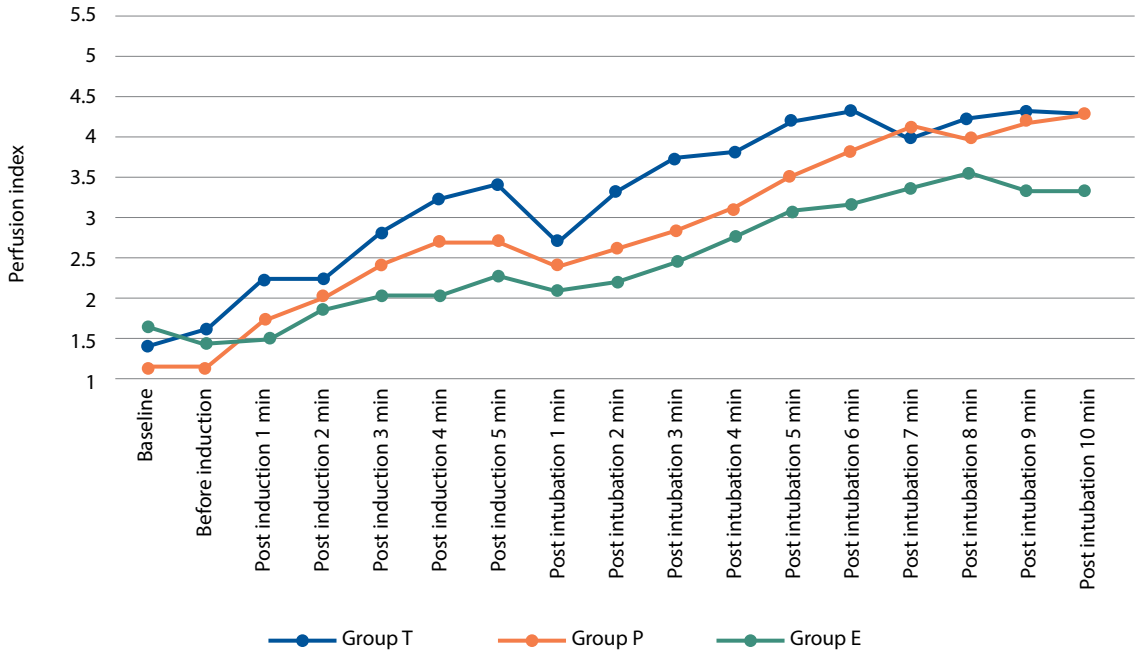

Figure 1: Perfusion index at different time points among three groups

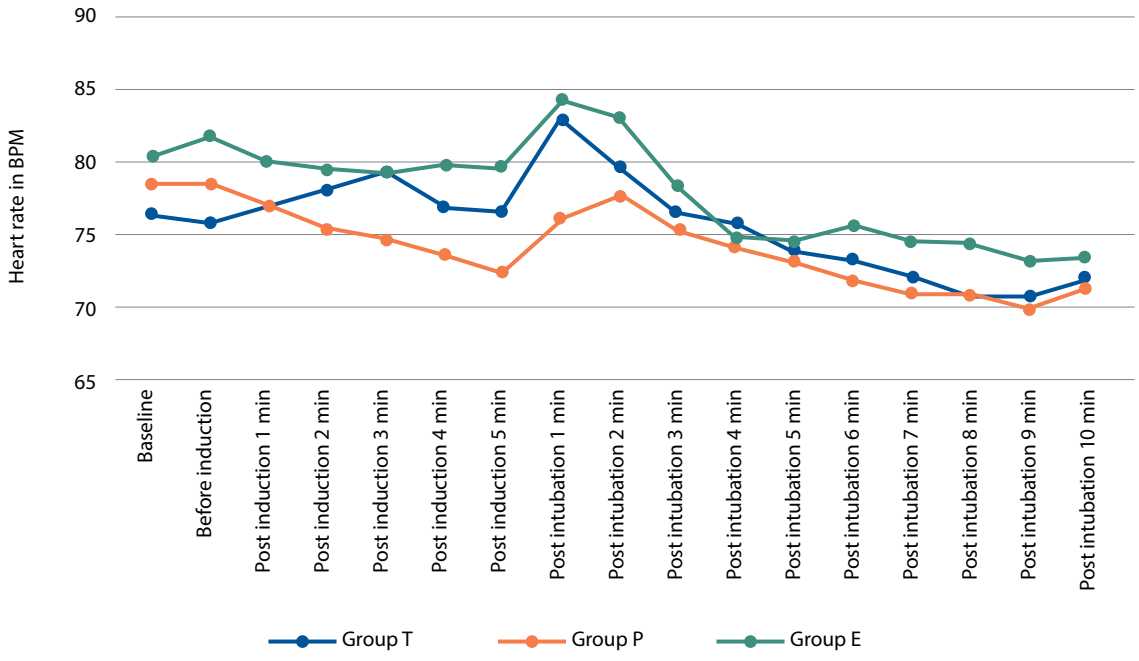

Figure 2: Heart rate at different time points among three groups
BPM – beats per minute

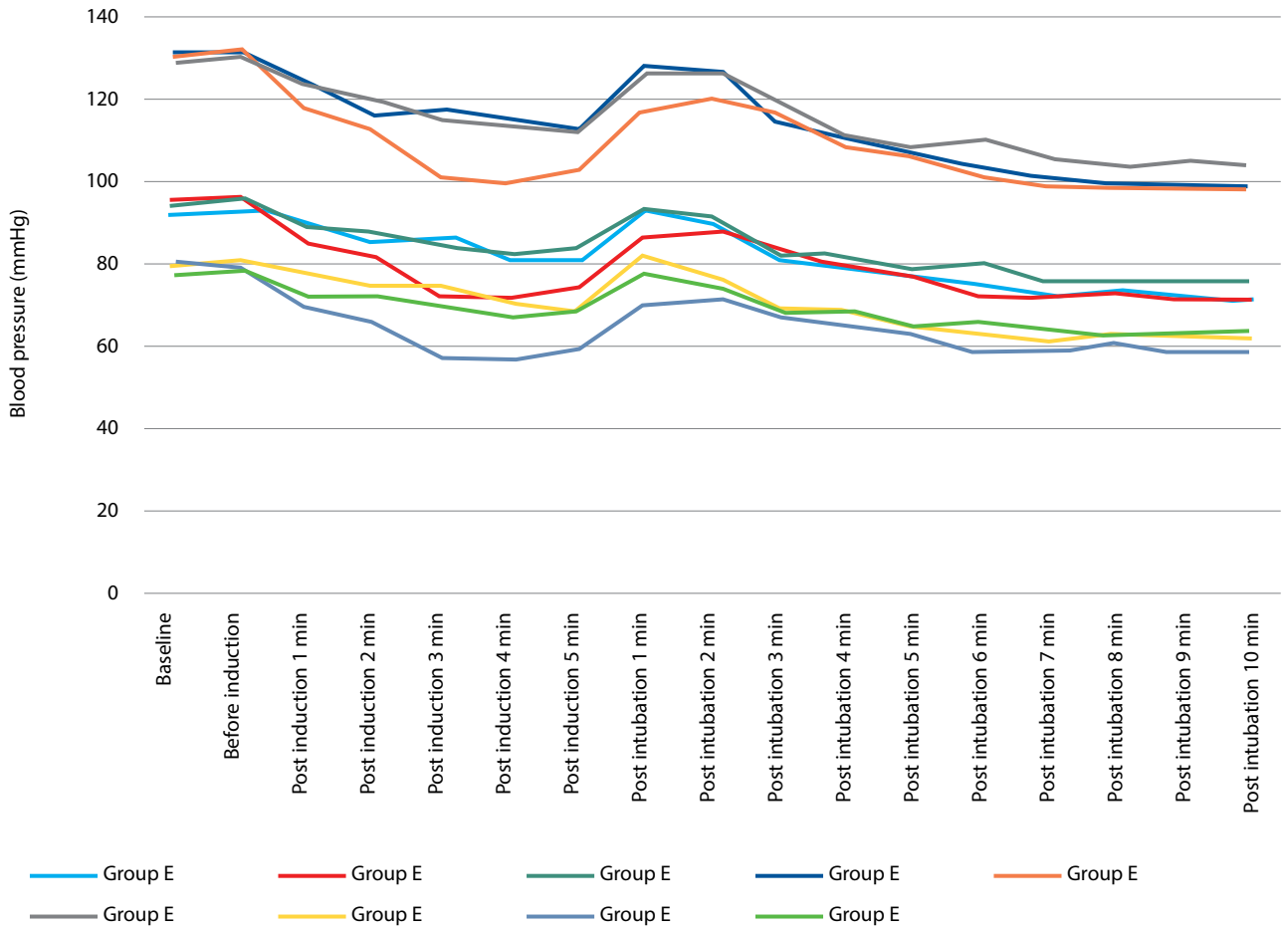

Figure 3: SBP, DBP and MAP at different time points between the groups
SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure

(Figure S1, in the supplementary files).

Demographic data including indication for surgery and baseline parameters were comparable among the groups (Table I).

There was a gradual increase in the mean PI from the time of induction of anaesthesia until after 10 minutes of endotracheal intubation. Also, there was a small dip noted in the mean PI just after completion of laryngoscopy and intubation, which was pronounced in the case of group T (Figure 1). Though the trend was similar among three groups, the difference was statistically significant ($p < 0.001$).

There was a decrease in the HR towards end of the study period. However, Group T showed a tendency for slight increase in the HR soon after the induction of anaesthesia, peaking at one minute post intubation and thereafter a gradual reduction. This was against the trend observed in the other two groups, which showed the decreasing trend followed by upswing and downswing in HR soon after tracheal intubation settling to below baseline values (Figure 2). This difference in the trend was statistically significant ($p < 0.001$).

The SBP, DBP, MAP started decreasing with time soon after induction of anaesthesia. The highest drop was noted in Group P. This trend was briefly reversed immediately post intubation, almost restoring the parameters to baseline. Maximum response was seen in Group P (Figure 3). This difference in the trend was statistically significant between the groups ($p < 0.001$).

The left ventricular myocardial contractility was well preserved as seen by direct observation.

When the ROC was constructed for PI and hypotension, there was no statistically significant correlation between PI and hypotension at post induction in the 5th minute and post

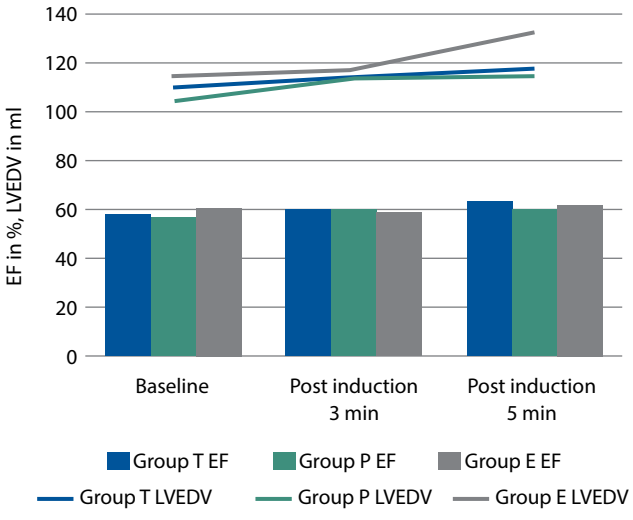

Figure 4: EF and LVEDV at different time points among three groups
EF – ejection fraction, LVEDV – left ventricular end diastolic blood pressure

intubation in the 10th minute (Figures S2 and S3, as mentioned in the supplementary files).

There was no statistically significant difference ($p = 0.366$) in the trend of change in the mean EF, whereas thiopentone showed a mild upward swing throughout the three points of measurement (Figure 4).

The mean LVEDV increased from baseline after induction and again after intubation (Figure 4). However, this was significant in the case of Group E (etomidate) which showed an increase in mean LVEDV by 17 ml (15%).

Discussion

The induction agents caused vasodilation as evidenced by the increase in perfusion index in all three groups, though the magnitude differed. Similarly, the heart rate, as well as systolic, diastolic and mean arterial pressures also decreased gradually. The response to intubation manifested among all groups, though to a variable extent. It was most pronounced with thiopentone while least with etomidate. Changes in perfusion index and haemodynamic variables were to the same magnitude in a given group. Also, there was no apparent effect on the contractility of the myocardium in any of the groups, as observed by the observer, rather than measured by the left ventricular end diastolic pressure. The left ventricular end diastolic volume, also an indirect measure of contractility, did not significantly increase in either thiopentone or propofol group, while there was increase in LVEDV by 15% among participants who received etomidate.

In all cases, the PI recovered to pre-intubation values within the following minute and continued to increase. This trend continued even at the 10th minute in the case of propofol, whereas there was a plateau beyond the 6th minute with thiopentone and 8th minute in the case of etomidate.

This can be best described by the time to drug effector site half-life which is about 7 minutes for the haemodynamic depressing effect of propofol.[8] The duration of action of each induction agent may also have bearing on this trend which is approximately 10 minutes for propofol, 5–8 minutes for etomidate and about 15 minutes for thiopentone.[9]

Low PI usually reflects peripheral vasoconstriction with or without severe hypovolaemia while high PI usually reflects dilation of peripheral blood vessels. Therefore, it can be stated that maximal vasodilation was with propofol and minimal with etomidate.[10]

In the current study, there was minimal changes in the heart rate among all three groups, least being in thiopentone (no change). Post intubation, the change was minimal with propofol, which is known to cause abolition of baroreceptor reflexes. In contrast, as per the literature, at higher doses of propofol (at 2.5 mg/kg) there was significant decrease in HR post induction.[11-14] Interestingly, the change in the BP was in the negative direction among all three groups and of similar magnitude, by the 5th minute after induction. However, BP did not return to baseline in the propofol group, unlike in other two soon after intubation. This indicates that pressor response to laryngoscopy and endotracheal intubation was incapable of augmenting the BP to pre-induction levels in case of propofol. However, there is no congruence regarding the magnitude of fall in the BP with different induction agents at similar doses.[14-16]

The concomitant effect of the inhaled agent sevoflurane was also considered a contributing factor in the reduction of HR and BP towards the end of study period.

EF and contractility remained constant throughout the study period and there was no significant difference between the groups ($p = 0.366$). Therefore, the combination of fentanyl and induction agent did not exert much influence on the contractility of myocardium, at least during the initial few minutes. However, newer technologies in echocardiography have provided contradictory results.[17,18]

The LVEDV remained constant in Group P and Group T at two different points of observation (i.e., three minutes post induction and five minutes post intubation) indicating no evidence of myocardial depression. However, Group E showed statistically significant increase (15%; $p = 0.011$) in LVEDV at 5 minutes post intubation indicating increased stroke volume and `CO. However, etomidate was reported to cause decreased stroke volume and LVEDV which was partly compensated for by an increase in HR when given without any premedication.[19]

An attempt was made to find out whether there existed a correlation between post induction hypotension and PI. The basis for this argument was that increased PI meant vasodilation leading to fall in SVR leading to diastolic hypotension. Similarly, venodilation can produce decreased cardiac venous return effecting drop in preload, consequently CO and SBP. Both together or independently can result in drop in MAP. However, the receiver operating characteristic curve did not reveal any significant positive or negative correlation between PI and BP Hypotension being multifactorial, interplay of vasodilation (PI) and CO at different time points might have affected the BP.

It is well known that cardiac output is the product of heart rate and stroke volume ($CO = HR \times SV$).[20] Therefore, HR is one of the factors contributing to the variation in CO. The contractility, LVEDV and ejection fraction being unchanged, only heart rate could influence the CO.

Decreased CO due to reduced HR and vasodilation are probably the causes of this hypotension.[18] Despite significant increase in the PI (substantial vasodilation), especially with the propofol, which indicates better perfusion in the peripheries, the LVEDV was unchanged. Rather it increased in case of etomidate. In the absence of myocardial depression (unchanged EF and contractility), this points towards good cardiac venous return. Etomidate probably improved cardiac venous return and thereby increasing the CO with unchanged HR.

Thus, in clinically relevant doses, neither of the three agents affect myocardial contractility or EF in a significant way. The

reduction in the COt is primarily due to decreased HR. Along with decreased CO, vasodilation as indicated by increased PI might have contributed to the reduction in BP, especially with the thiopentone and propofol.

Adverse effects noted during the study period includes one case of severe hypotension requiring vasopressor in Group P; myoclonus in one case in Group E. The minimal incidence of hypotension requiring intervention was probably due to the dose of induction agent which was titrated to the requirement of each patient.

The strengths of this study includes the fact that thiopentone, propofol and etomidate are the drugs used in routine day-to-day practice. Though propofol is commonly used in most of the developed world, thiopentone is cheap and is still employed as an induction agent in resource-poor settings. For the first time, all the parameters responsible for the maintenance of blood pressure were studied together. Only non-invasive monitoring devices which are routinely available in the theatre, were used. Induction agents were titrated to the patients' requirements, the comparison and outcomes are clinically relevant. Known hypertensive patients and patients on vasoactive medications were excluded from the study to avoid untoward results. An adequate sample size was recruited. The number of attempts at and duration of intubation was also limited. The echocardiography is observer dependant. Therefore, trained cardiac anaesthesiologists, proficient in transthoracic echocardiography performed the trans thoracic echocardiography and inferred the results of the test.

The limitations of this study include the inability to perform echocardiography in left lateral position due to anaesthesia and intubation. Estimation of myocardial contractility could have been more objective if modern technology had been used (e.g. speckle tracking echocardiography and doppler derived indices). The perfusion index was correlated with non-invasive BP which has a time lag due to the technology involved in measurement. Measurement of CO with transthoracic echocardiography or dye dilution method and other haemodynamic parameters like SVR, would have given better insights. The effect of premedication and inhaled agent on haemodynamic parameters was neglected as these were common to all the groups. Ideally, it should have been avoided during the study period. However, to prevent awareness once the effect of the IV agent wore off, sevoflurane was used during intubation at a smaller concentration. PI is known to be affected by many factors including pre-existing illness, medication, anxiety, temperature and pain. Though preoperative factors were controlled by excluding patients, some of these factors were not addressed. Neither monitored nor specifically maintained, the peripheral temperature at the site of measurement of PI might have affected the outcomes of the study. Depth of the anaesthesia was also not monitored. Titrating the induction agent to the objectively measured depth of anaesthesia would have been more prudent.

Etomidate resulted in most stable haemodynamic conditions during induction of anaesthesia followed by thiopentone and propofol, respectively. Cardiac contractility and EF were unchanged with these drugs while HR decreased gradually. Though there was a steady increase in the PI and a decrease in BP, there was no significant correlation between these. Along with decreased CO, vasodilation as indicated by increased PI might have contributed to the reduction in the BP especially with thiopentone and propofol. These findings reinforce the existing recommendations to use etomidate in cases of significant cardiac disease or unstable haemodynamic status. Also, to be cautious while using propofol, and to have vasopressors ready to counter hypotension due to the vasodilation as this was the main reason for the hypotension observed following induction of anaesthesia.

Therefore, we found that vasodilation and reduced HR were responsible for the hypotension following induction of anaesthesia by intravenous agents. The effect was maximal with propofol with no evidence of myocardial depression. Etomidate lead to an increase in stroke volume which explains its cardiovascular stability.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee, KS Hegde Medical Academy, IRB number: EC/NEW/INST/2020/834.

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Supplementary file available online