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COMPARISON OF HAEMODYNAMIC RESPONSE TO INDUCTION WITH THIOPENTONE AND ETOMIDATE IN HYPERTENSIVE PATIENTS SCHEDULED FOR ELECTIVE SURGERY-A CLINICAL STUDY

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ABSTRACT

Aim: To compare the hemodynamic response to anaesthetic induction with thiopentone sodium or etomidate in adult treated hypertensive patients posted for elective surgeries.

Materials and methods:A prospective randomised blind clinical study conducted in 60 adult treated hypertensive patients(29-61 years) of ASA II posted for elective surgeries under general anaesthesia. Patients were randomly allocated to two groups of 30 each. **Group T**-Thiopentone sodium 5mg/kg body weight **Group E**-Etomidate 0.3mg/kg body weight. Pulse,systolic blood pressure, diastolic blood pressure and mean arterial pressure were noted down every minute for five minutes post induction.

Results: Both groups were comparable statistically for age, gender and weight.There was no statistically significant variation in the extent of over all change in heart rate, systolic, diastolic and mean arterial pressures between the two group of patients (p >0.05).All the studied hemodynamic variations with respect to HR,SBP,DBPand MAP in the two groups were self corrective and did not require any treatment. Patients in both groups did not have any side effects perioperatively and for 24 hours post operatively except for vomiting in one patient in group E.

Conclusion: Both thiopentone (5mg/kg) and etomidate (0.3mg/kg) have similar hemodynamic effects when used for induction of anaesthesia in adult treated hypertensive patients and can be safely used in them. However thiopentone comparatively has better cost effectiveness and ease of availability.

Key words: hypertension, anaesthesia induction, thiopentone, etomidate, hemodynamic changes

INTRODUCTION

Hypertension is extremely common, affecting over one billion people worldwide, and is responsible for over seven million deaths annually.In 2000 total number of hypertensive patient were 972 million and by 2025,1.6 billion will be suffering from hypertension.[1]Essential hypertension defined as chronic elevated blood pressure of unknown etiology is the most critical risk factor in predicting cardiovascular morbidity and mortality in general population. Patients with untreated or inadequately treated hypertension develop marked swings in blood pressure in situations such as anaesthesia, blood loss or pain. They may undergo profound fall in arterial pressure in response to induction and maintenance of anaesthesia and also exhibit an exaggerated hypertensive response to stimuli such as laryngoscopy and intubation.[2]They are prone to develop cardiac dysrrhythmias and ischaemia during anaesthesia. Induction is a critical phase of anaesthesia, especially in patients with limited coronary reserve. Hence induction agents should alleviate the stress response and cause minimal haemodynamic changes.

Thiopentone is the earliest intravenous ultra short acting barbiturate producing rapid induction and allows for high concentration of oxygen to be given. None the less, since it is being employed frequently, a precise definition of the haemodynamic changes it causes is important as the induction agents introduced later have gone through the phase of comparison with it.[3] Etomidate - a rapid acting non-barbiturate hypnotic, said to lack significant adverse cardiovascular and respiratory effects. Animal experiments and human studies have shown that it has fewer side effects on the cardiovascular and respiratory. Present study is done to compare the hemodynamic response to anaesthetic induction with thiopentone sodium or etomidate in adult treated hypertensive patients posted for elective surgeries.

MATERIALS AND METHODS

A Comparative prospective blind and randomised two group clinical study with 60 adult of ASA II adult treated hypertensive patients aged between 29-61 years scheduled for elective surgeries at Department of Anesthesiafor a period of oneyearsAugust 2019 to January 2020.

Inclusion criteria: patients aged between 29-61 years with treated essential hypertension.

Exclusion criteria: Patients belonging to ASA III and above, end organ damage, emergency surgeries, co morbid conditions including epilepsy, COPD etc, Obstetric,paeditric and obese patients, shock and drug allergies

Methods:

Consequent to approval from institutional ethical committee and written informed consent from patients, this prospective blinded randomised study was conducted in sixty treated adult hypertensive patients (28males and 32 females) of ASA physical status II aged between 29-61 years who were to undergo elective general surgical, gynaecological and orthopaedic procedures. They were divided into two groups of thirty each.

Group E- Inj. Etomidate

Group T - Inj.Thiopental sodium

A thorough pre anaesthetic evaluation was done with particular attention to the duration of hypertension, treatment details, fundus examination for any change as well as pulse rate, blood pressures(systolic,diastolic and mean) recordings. Apart from general physical and systemic examination, routine investigations, blood urea, serum creatinine, serum electrolytes, ECG, x-ray chest and fundoscopy were performed in all patients.

All patients received Tab. Alprazolam 0.5 mg and Tab. ranitidine 150 mg on the night before surgery and all anti hypertensive medications were continued up to and on the day of surgery.

Upon arrival in the operating room , IV access was established and lactated Ringer's infusion started. Monitors included an automated blood pressure cuff, electrocardiogram with lead II monitoring, peripheral pulse oximeter, and capnometer.

Pre operative heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were recorded. After initial stabilisation for 2 minutes, patients in both groups received inj.glycopyrolate 0.2mg, inj. midazolam .02mg/kg and inj. fentanyl 1.5mcg/kg iv. Pre oxygenation was done with 100% oxygen for 3 minutes. The above parameters were recorded again and noted as at **level 0-** and considered for comparison with subsequent recordings Since it was a blind study the observer entered the OR after administration of the induction agent. General anaesthesia was induced in Group E with Inj.etomidate 0.3mg/ kg and in Group T with Inj. Thiopentone 5mg/kg . Inj. Vecuronium bromide(0.1mg /kg. body wt.), was injected after loss of eye lash reflex in both groups. Nitrous oxide, oxygen was used for mask ventilation in both study groups. Respiration was controlled with rate between 12 to 14 cycles per minute and tidal volume adjusted to maintain $EtCO_2$ between 30 to 35.

Subsequently, heart rate and blood pressure were and recorded at, one, two three, four and five minutes after induction **(level 1-5**). During this period patient was left undisturbed except for the mask ventilation in order to avoid alterations due to stimulation. Ecg was monitored through out to note

down any rhythm or ischaemic changes. Any untoward complications such as pain on injection ,myoclonus, hiccups during induction were noted down. Trachea was intubated at the end of 5 minutes. Patients were followed up for 24 hours for any untoward complications such as nausea, vomiting and haemodynamic changes.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

1. Sample Size estimation

Proportion Known populations

$n=[(z^2 *p*q)+ME^2]/[ME^2 +z^2 *p*q/N]$ Proportion Unknown population

$n=[(z^2 *p*q)+ME^2]/(ME^2)$

ME: is the margin of error, measure of precision. and Z is 1.96 as critical value at 95%CI

N: population size

n: Sample size

σ: Standard deviation

z: Critical value based on Normal distribution at 95% Confidence Interval

Results of the t-test: If the p-value associated with the t-test is small (< 0.05), there is evidence to reject the null hypothesis in favor of the alternative. In other words, there is evidence that the means are significantly different at the significance level reported by the p-value. If the p-value associated with the t-test is not small (> 0.05), there is not enough evidence to reject the null hypothesis, and you conclude that there is evidence that the means are not different.

+ Suggestive significance (P value: 0.05<P<0.10) * Moderately significant (P value:0.01<P ≤ 0.05) ** Strongly significant (P value : P≤0.01)

RESULTS

A Comparative prospective blind and randomised two group clinical study with 60 adult elective surgical hypertensive patients , 30 in Group T (Thiopental) and 30 patients in Group E(Etomediate)was undertaken to study the hemodynamic response to induction of anaesthesia with thiopentone or etomidate between January 2011 to September 2012.

The number of patients was 22 in general surgical category,18 in orthopaedic and 20 in gynaecological category.

Table-1: Demographic details in present study

Age in years	**Group T**		**Group E**	
	No	**%**	**No**	**%**
<30	1	3.3	1	3.3
31-40	5	16.7	4	13.3
41-50	11	36.7	11	36.7
51-60	13	43.3	13	43.3
>60	0	0.0	1	3.3
Total	30	100.0	30	100.0
Mean ± SD	48.93±7.80		49.90±8.83	
P-Value	1.000			

Gender				
Male	14	46.7	14	46.7
Female	16	53.3	16	53.3
P-Value	0.588			
Weight(kg)				
<50	15	50.0	18	60.0
51-60	13	43.3	7	23.3
61-70	0	0.0	5	16.7
>70	2	6.7	0	0.0
Total	30	100.0	30	100.0
Mean ± SD	52.43±9.53		50.63±9.40	
p-value	0.465 41			

Mean age in group T was 48.93±7.80 and in group E 49.90±8.83 .Maximum hypertensives in either group were in the age group of 51-60 years followed by age group of 41-50 years .Youngest patient was 29 years old and the oldest was 61 years in the present study.

There were 14 males (46.7%) and 16 females (53.3%) in group T. There were 14 males (46.7%) and 16 females (53.3%) in group E. Mean weight in group T - 52.43±9.53 Mean weight in group E - 50.63±9.40

Table-2: Duration and treatment of hypertension.

Duration of Hypertension	**Group T**		**Group E**	
	No	**%**	**No**	**%**
<6 months	22	73.3	26	86.7
6 months-1 year	4	13.3	3	10.0
1-2 years	2	6.7	0	0.0
3-5 years	1	3.3	1	3.3
>5 years	1	3.3	0	0.0
Total	30	100.0	30	100.0
P value	P=0.545			
Treatment:				
1.Calcium channel blockers	14	46.7	17	56.7
2.Calcium channel blockers with Beta blockers	0	0.0	4	13.3
3.Beta blockers	6	20.0	6	20.0
4.ACE inhibitors	2	6.7	2	6.7
5.ARB with Diuretics	4	13.3	1	3.3
6.ARB	3	10.0	0	0.0
7.Alpha blockers	1	3.3	0	0.0

Duration of hypertension is statistically similar in two groups studied with P=0.545

Maximum number of patients in our study were hypertensive for less than 6 months-- Group T-22(73.3%) , Group E- 26(86.7%).

Number of patients who were hypertensive for more than 5 years- Group T-1(3.3%), Group E-0.Among the patients in the study group, maximum patients were on treatment with Calcium channel blockers- Group T- 14 (46.7%) -Group E- 17 (56.7%) followed by Beta blockers -6 (20%) in each group.

Table-3: Fundus examination in present study

Fundus	**Group T (n=30)**		**Group E (n=30)**	
	No	**%**	**No**	**%**
No change	5	16.7	3	10.0
Change present	25	83.3	27	90.0
• Fundus I	11	36.7	9	30.0
• Fundus II	14	46.7	18	60.0

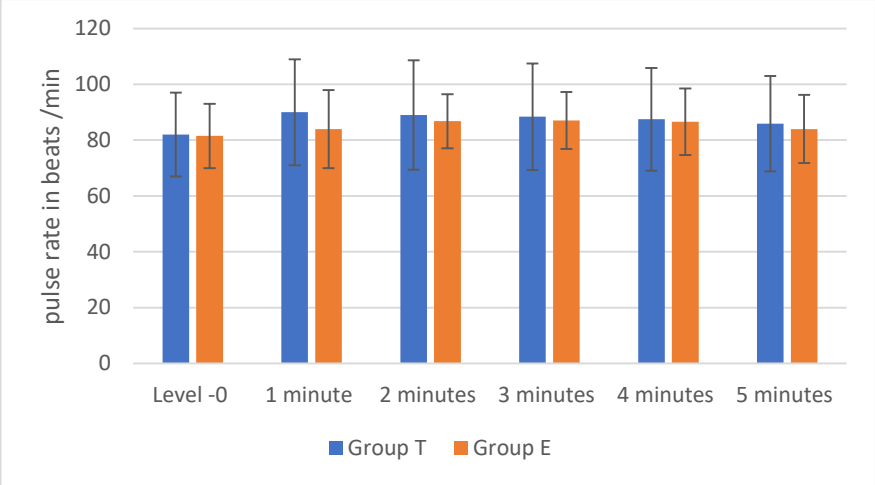
Findings of Fundus study was statistically similar with p=0.448. The number of patients with normal study of fundus- Group T - 5 (16.7%) Group E - 3 (10.0%).
The number of patients with hypertensive changes on fundus study- Group T -25 (83.3%) Group E - 27 (90.0%) .
The number of patients with grade I hypertensive changes- Group T – 11 (36.7%). Group E -9 (30.0%). The number of patients with grade II hypertensive changes- Group T -14 (46.7%) Group E- 18 (60.0%)

Table-4: Complications in present study

Complications	Group T (n=30)		Group E (n=30)	
	No	%	No	%
No complication	30	100.0	29	96.7
Complication present	0	0.0	1	3.3
• V omiting	0	0.0	1	3.3

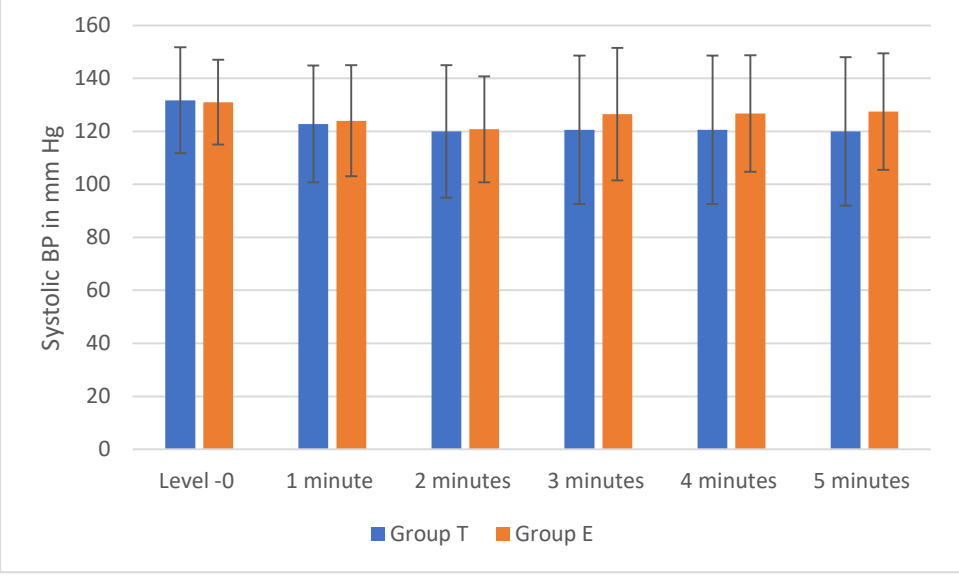
No patient in group T had any complication whileone patient in group E had post operative nausea and vomiting.

Figure-1: Comparison of heart rate variations in present study



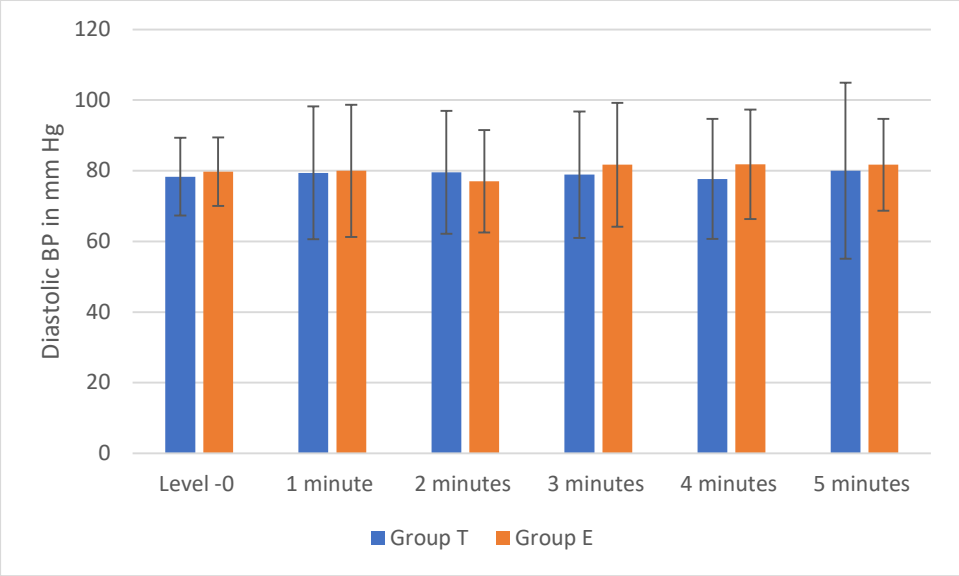
Comparison of the extent of heart rate variations from level-0 to post induction levels (1-5 minutes) between the two groups was insignificant.(p>0.05)

Figure-2: Comparisionof systolic blood pressure variations in present study



Comparison of the extent of systolic blood pressure variations from level - 0 to post induction levels(1-5) was insignificant.(p>0.05)

Figure-3: Comparison of diastolic blood pressure variations in present study



Maximum decrease from level –o was at- 2 minute post induction. Comparison of the extent of the diastolic blood pressure variation from level -0 to post induction levels(1-5) between the two groups was insignificant (p>0.05).Comparison of the extent of mean arterial pressure variation from level – 0 to post induction levels(1-5) between the two groups was insignificant .(p>0.05)

All the variations in heart rate,sbp,dbp and map remained within acceptable range and tended to return towards level-0 at the end of study period in both groups.All changes were self corrective without the need for intervention on our part.

DISCUSSION

Intravenous anaesthetic induction agents are drugs which when given intravenously in an appropriate dose cause loss of consciousness. Introduction of intravenous anaesthetic agents in 1930s caused a major shift in the concept of anaesthesia from that of production of anaesthesia to that of induction and maintenance of anaesthesia. The first licensing of the above such agents was for thiopentone sodium followed by several others. However, in the choice of the induction agent, apart from desirable characters like rapid onset and recovery, analgesia as well as lack of excitatory phenomenon, cumulation, interaction with relaxants, post op vomiting , delirium etc, one of the main considerations will centre on cardiovascular stability that the drug possesses; and this consideration becomes even more important in surgical patients whose cardiovascular system is compromised as in case of hypertensive disorder. When hypertensive patients require surgery, the management of hemodynamic variations poses considerable challenge to the anaesthesiologist.

Our patients in the two study groups T and E were well matched with respect to age, weight and gender. The recommended induction dose is 3-6mg/kg for thiopentone and 0.2-0.5 mg/kg for etomidate.[4] Many studies done in the past have used different doses of the above drugs on the basis of body weight -0.2 mg,[5]0.3 mg,[7]0.4 mg,[8]0.45 mg/kg foretomidate(Gauss[5],Colvin[6], of thiopentone(Gauss[5],Gooding[7] Geise[8] and Craido[9]) or 3mg,4 mg/kg

Equipotent doses of induction agents should be used in the comparison of hemodynamic effects. Compared with MAC(volatile anaesthetics) and MIR(intravenous anaesthetics by infusion, no equivalent exists for the bolus injection of induction agents. Induction doses of intravenous anaesthetics based on hypnotic potency alone usually differ from those found necessary by clinical experience.[5] Hence taking into account the relevant literature and clinical experience we have used etomidate 0.3 mg/kg and thiopentone 5mg/kg to do a comparative study of the hemodynamic effects of both drugs and any side effects during the 5 minutes following induction.

Anaesthesia induction drugs are known to cause variations in heart rate. Craido et al in their study for assessing hemodynamic effects of etomidate observed significant increase in heart rate after administration of etomidate. Gooding et al noted 10% increase in heart rate was the only noteworthy change following induction of anaesthesia .[7] Prys Roberts in 10 treated hypertensive patients using thiopentone (mean dose 155 mg) found an increase in heart rate.[10] Colvin et al in their study of cardiorespiratory changes following induction of anaesthesia with etomidate observed no significant variation in heart rate even after administration of second dose of etomidate.[6] Price et al in their study of assessing change in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with etomidate found significant decrease in heart rate . Gauss et al in their study of echocardiographic assessment of hemodynamic effects of thiopentone and etomidate in 30 patients noted increase(11%) in heart rate following injection of thiopentone ,but not etomidate.[5]

In our study there was an increase in heart rate following induction of anaesthesia with both thiopentone(82.03±15.32 to 90.00±19.24) and etomidate(81.47±11.56 to 87.13±10.22).Maximum change occurred at 1 minute with thiopentone and at 3minutes with etomidate, the values returning back to almost level zero value in both groups. The comparison of the extent of change in heart rate from level zero to post induction levels(1-5) between the two groups was insignificant at all levels.($p>0.05$) .There was no bradycardia or rhythm disturbance at any time in the two groups.

The increase in heart rate noted by us following thiopentone was similar to that of Craido[9], Gooding,[7]Prys Roberts[10] but differed from the study of Colvin[6] where decrease in heart rate could be because of the use of digoxin as premedicant in their study.

Anaesthesia induction agents are known to cause fall in blood pressure following administration.(Morgan,s)Hypertensive patients whether treated or not are prone to much greater changes in arterial pressures than normotensive patients of the same age.(Prys Roberts) Robert J Fragen et al in their study of comparing new formulation of etomidate0.3mg/kg with thiopental 4mg/kg observed that blood pressures were stable in all patients with both drugs.Gooding et al in their study of the effects of etomidate on cardiovascular system observed no significant variation in systolic and diastolic blood pressures after induction with etomidate and mentioned that lack of significant effects on either the peripheral and pulmonary vascular beds or on the myocardium itself was the cause of cardiovascular stability.[7] Colvin et al in their study of cardiorespiratory changes following induction of anaesthesia with etomidate in 12 patients with mitral and aortic valve disease, observed a significant fall of 19% in the first 4 minutes in both systolic and diastolic blood pressures following induction after the first dose of etomidate 0.3 mg/kg ,and a further fall of 13% at 2 minutes after second dose and there after recovered. They mentioned that the likely cause of decrease in arterial pressure was vasodilation indicated by decrease in systemic vascular resistance.[6] Craido et al in their study with etomidate 0.45 mg/kg , observed a significant fall in systolic, diastolic and mean arterial pressures in almost all measurements(basal,3 and 10 min).MAP and diastolic blood pressures decreased which was thought to be a consequence of negative inotropism of etomidate.[9]

Gauss et al in their comparative study of echocardiographic assessment of hemodynamic effects of thiopentone 4mg/kg and etomidate0.2mg/kg i noted arterial systolic blood pressure decrease after thiopentone but not with etomidate. There were no significant changes in diastolic pressures.[5] Robert j Fragen et al in their comparative study of etomidate0.3mg/kg and thiopentone 4mg/kg iv found no significant difference between the drugs with respect to circulatory parameters.[11]

In our study there was decrease in systolic blood pressure in both study groups . The fall was upto 120±28.8 from the value at zero level of 131.70±20.73 in group T and upto 120.80±20.05 from level zero value of 131.23±16.03 in group E. Maximum post induction fall in systolic blood pressure from level zero occurred at 5 minutes in group T and at 2 minutes in group E.

Diastolic blood pressure in our study varied a follows. In group T it increased from (level zero) 78.30±11.00 to a maximum of 80.13±24.91 at level 5 and also showed decrease from 78.30±11.00 to 77.73±17.00 at level 4. In group E it increased from79.77±9.76 upto a maximum of 81.73±13.07 at

level 5 and showed decrease from 79.77±9.76 to 77.30±14.53.Maximum post induction variation in diastolic blood pressure from level '0' occurred at 5 minutes in group T and 3 minutes in group E.
Our findings of variation in diastolic blood pressure are similar to that of Gauss et al. [5]The comparison of the extent of change in systolic and diastolic blood pressure variations from level zero to post induction levels (1-5) between the two groups following induction was insignificant.($p>0.05$).
In John Gooding et al's study of cardiovascular and pulmonary responses following etomidate induction mean arterial pressure fell to 88 ± 21 from preinduction value of 9 1± 18 post etomidate (0.3mg)induction.[7] Craido et al in their study of etomidate observed fall in mean arterial pressure from basal value of 97.3 mm Hg to 87.1 mm Hg at 3 minutes and 92.1 mm Hg at 10 minutes .[9] Colvin et al in their study with etomidate observed a significant fall in mean arterial pressure in the first 4 minutes following induction.[6]
In our study, mean arterial pressure fell from 94.52±12.10 at level zero to 91.72±21.34 at 5 minutes in T group and fell from 96.96±12.96 at level zero to 90.37±17.51 at 2 minutes in group E. Maximum fall in MAP from zero level in group T was at 4 minutes post induction and at 2 minutes post induction in group E. This is similar to the findings of all above mentioned studies. The comparison of the extent of change in mean arterial pressure from level zero to post induction levels (1-5) between the two groups following induction was insignificant.($p>0.05$) All the variations in heart rate, sbp, dbp and map tended to return towards level-0 at the end of study period in both groups. All changes were self corrective without the need for intervention on our part.
Patients in our study did not have any myoclonus probably because of fentanyl premedication.In our study patients in either group did not complaint of any pain or injection probably because of use of etomidateLipuro-an advanced formulation.One patient in group E and none in group T had vomiting which was amenable to treatment.All patients in the present study were followed up for 24 hours post operatively and did not note any hemodynamic instability.
Thiopentone: 1 gm vial(Neon lab) with a maximum retail price of Rs 87/- for .Recommended dose for induction of anaesthesia is 5mg/kg which implies that a 1 gm vial can be used for 3 patients weighing about 60 kg after reconstitution. EtomidateLipuro(B Braun): supplied in a 20 mg(2mg/ml) ampoule costing Rs.490/- .Recommended dose being 0.3mg/kg which implies one ampoule can be used for only one patient weighing about 60 kgs. In our study considering the number of patients(30 in each group),we found thiopentone to have better cost effectiveness and ease of availability comparatively.

CONCLUSION

We conclude from our study that both thiopentone and etomidate have similar and safe hemodynamic profile when used in adult treated hypertensive patients. Thiopentone comparatively has better cost effectiveness and ease of availability. systems than other short acting IV induction agents.It has been introduced in India recently. In patients at risk because of hypertension it would appear that an induction agent that would provide a greatest margin of safety is desirable.Hence study was undertaken to assess the cardiovascular effects resulting from thiopentone and etomidate induction in 60 adult treated hypertensives scheduled for elective surgery, and also to assess any untoward side effect of either drug perioperatively with the available resources in our setup.A note was also made of cost effectiveness of each drug.

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