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Original Research Article

Comparative evaluation of propofol, thiopentone and etomidate on induction time, intubation response and recovery time during laparoscopic surgery under general Anaesthesia

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ABSTRACT

Background: Optimal choice of inducing agent can partially modify the post induction hypotension, having a reported incidence of 9-40% in various studies. So, we compared the induction and recovery profile of the routinely available induction agents.

Materials and Methods: This prospective randomized, comparative study was carried out on 120, ASA 1 and II patients undergoing routine laparoscopic cholecystectomy. Patient received either thiopentone 5 mg/kg, propofol 2.0 mg/kg or 0.3mg/kg injection etomidate at induction in group T, P and E respectively. The time taken from the administration of inducing agent to loss of eyelash reflex was noted. Heart rate, systolic, diastolic and mean arterial pressure, SpO2 was recorded at 1, 2, 3, 4, 5, 6 minutes and every five minutes after intubation. Steward score and the vitals were noted every 5 minutes after extubation till 30 minutes. It was noted that how long it took to get a Steward score of 6.

Results: The mean induction time (sec) was 49.85 ±2.54 in group T, 43.45 ±2.66 in group P and 52.675 ±2.11 in group E. ($p<0.0001$). The increase in mean heart rate from baseline upon induction and intubation was (10%, 31% in group T), (3%, 23% in group E) and (-7%, 16% in group P) ($p<0.0001$). Post induction decrease in systolic, diastolic and mean blood pressures observed in group T was (-9%, -4.5%, -6%), (-12.8%, -9.8%, -11%), in group P and (-4.6%, -1.7%, -2.9%) in group E. ($p<0.0001$). Post intubation increase in systolic, diastolic and mean blood pressures was (21.76%, 18%, 19.7%) in group T, (16%, 8.1%, 11.7%) in group E and (9.6%, 0%, 4%) in group P. Mean recovery time in min was 5.87 ±0.23 min with propofol, 6.97 ±0.28 with etomidate and 8.96 ±0.28 with thiopentone. ($p<0.0001$).

Conclusion: Amongst the three agents, we recommend propofol as preferred agent for induction due to faster induction, better attenuation of intubation response, faster recovery and stable hemodynamic parameters.

1. Introduction

Discovery of thiopentone in 1934 heralded the changes in safe intravenous anesthesia practice followed by discovery of etomidate and propofol.[1,2] Intravenous anaesthetics are used to induce general anaesthesia in patients, in addition they are used for sedation in the intensive care unit (ICU) and the management of status epilepticus.[2]

The quest for identification of an ideal intravenous anaesthetic persist due to the cardiorespiratory depression that all of these agents produce, despite their admirable

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safety records.[3,4]

Since its debut forty years ago, propofol has revolutionized the anaesthetic industry and is still regarded as an ideal anaesthetic. Its quick onset, short duration of action, and negligible side effects are the reasons for its success in the clinical setting. However undesirable hypotension (19-28%) may ensue after its use due to diminished cardiac contractility, systemic vascular resistance and preload.[4–6] As ventricular filling pressures and contractility are already reduced in some patients with impaired ventricular function, hence they are unable to endure reductions in cardiac output.[7] Propofol anaesthesia induction reduced LV and atrial contraction but did not impair baroreflex sensitivity, indicating that low heart rates can be maintained despite low arterial pressures thanks to effect on central sympatholytic and vagotonic mechanisms.[8,9] Due to the decrease in cardiac output and systemic vascular resistance, the heart rate rises in most of the scenarios but with propofol these baroreceptor-mediated compensatory mechanisms are not seen hence usually there is bradycardia that is observed.[10–13] Thiopentone sodium results in 10-15% incidence of reflex tachycardia thereby jeopardizing the myocardial O2 demand.[14] Etomidate is considered better for cardiac patients as its causes minimum alterations in hemodynamics, but it's expensive and the chances of adrenal cortical suppression of 6-8hrs duration, after single dose remains.[15–18]

Thus, in the present study induction characteristics, laryngotracheal response, perioperative stability and recovery profile of these agents was compared. As there is paucity of studies comparing all these characteristics together.

2. Materials and Methods

This prospective study was done from November 2020 to October 2021 after obtaining ethical clearance from the institution committee vide order no. No. HFW(MC-II) B (12) ETHICS/2020/-13926 and was registered with CTRI no. CTRI/2020/11/029093.

We used the formula $n = \{(r+1)\ (Z_{\alpha/2} + Z_{\beta/2})^2\ \delta^2\}/rd^2$ for sample size calculation. Where "Z_{α} " is the normal deviate at a level of significance, "$Z_{1-\beta}$ " is the normal deviate at (1- β) % power with β% of type II error, "r = n1/n2" is the ratio of sample size required for 3 groups, "δ" is standard deviation and "d" is difference of means of 3 groups. We included 120 Adult Patients of ASA I and II physical status, based on previous study done by Meena et al.[19] for hemodynamic response to endotracheal intubation. Patients were aged 20-50 years, weighing between 45-65 kg undergoing routine laparoscopic cholecystectomy. Patients of ASA grade III and IV, with cerebrovascular accidents, coronary heart disease, diabetes mellitus, endocrinal dysfunction like hypo/hyperthyroidism, adrenal failure, patients on long term steroidal therapy, psychiatric, renal disorder, hepatic disorder, anticipated difficult intubation, history of drug allergy to egg and drugs under study, history of acute intermittent porphyria, alcoholism and drug addiction, patients with risk of regurgitation e.g., hiatal hernia, pregnancy, intestinal obstruction, anemia, hypoproteinemia, jaundice were excluded from the study. We took 145 patients initially for the study but 130 were randomly allocated into one of the three groups using computer generated randomization. Due to various reasons 10 patients were lost up in data collection hence 120 were finally analyzed at the end of study (Figure 1).

Group P patients received propofol: 2.0 mg/kg IV. Group T patients received thiopentone 5 mg/kg IV and group E patients received injection etomidate 0.3mg/kg at induction.

During routine preanesthetic examination thorough history and general physical examination of the patient was carried out, study protocol was explained to the patient and informed valid consent was obtained. The patients were examined in the preanesthetic room and informed consent to be part of the research was obtained. Premedication was done with tablet alprazolam 0.25 mg PO and tablet ranitidine 150 mg PO at bed time and in morning of the day of the surgery.

In the operation theatre, patient was connected to the monitor, intravenous line was secured with 18 G IV cannula on the dorsum of the hand and preinduction baseline ECG, heart rate, systolic, diastolic, mean arterial blood pressure (MABP) and SpO_2 were recorded. Preoxygenation of patient was done with 100% oxygen using face mask, injection fentanyl (2μg/kg) and injection diclofenac sodium 75 mg was given. There after as per group, patients were induced with either thiopentone, propofol or etomidate.

The time taken from the administration of inducing agent to loss of eyelash reflex was taken as time of induction and was noted. Intubation was achieved with injection succinylcholine 2mg/kg by direct laryngoscopy using Macintosh blade by an anesthetist of at least 5 yrs. experience. Heart rate, systolic, diastolic and mean arterial pressure, SpO_2 was recorded at 0, 1, 2, 3, 4, 5, 6 minutes and every five minutes after intubation. Anaesthesia was maintained with Inj. Cis-atracurium 0.2 mg/kg IV, nitrous oxide 66%, oxygen 33%, and halothane 0-0.75%. Cis-atracurium 0.02 mg/kg IV was repeated as and when required till end of surgery. Patients were ventilated with IPPV till reversal with injection glycopyrrolate (0.01 mg/kg) and neostigmine (0.05 mg/kg) at the end of surgery. Any patient with intubation time more than 30 seconds, more than 1 attempt and having failed intubation were excluded from this study. Inj. ondansetron 4 mg I.V. was given as antiemetic 30 min before end of surgery. Inj. atropine was given for any episode of bradycardia heart rate <50, hypotension of >30% from baseline was directed to be managed with intravenous fluid boluses of 100 ml or noradrenaline boluses of (5μg).

Blood pressure, $etCO_2$, heart rate & SpO2 was monitored every five minutes after intubation. After surgery, patients were shifted to the recovery room/PACU. Steward recovery score was recorded every five minutes till 30 minutes after extubation. This score assesses consciousness, airway and movement of the patients and all these are given 0-2 score each. A score of six (Steward Score) was taken as time to recovery from anaesthesia.

2.1. Statistical analysis

The presentation of the categorical variables was done in the form of number and percentage. On the other hand, the quantitative data were presented as the means ± sd and as median with 25th and 75th percentiles (interquartile range). The comparison of the variables which were quantitative in nature were analyzed using anova and post hoc comparison was done using bonferroni correction. The comparison of the variables which were qualitative in nature were analyzed using chi-square test. If any cell had an expected value of less than 5 then fisher's exact test was used. The data entry was done in the Microsoft Excel spreadsheet and the final analysis was done with the use of statistical package for Social Sciences (SPSS) Software, IBM Manufacture, Chicago, USA, version 25.0.

3. Results

'In the study 145 patients were initially assessed for the study, but 15 were excluded due to various reasons like anticipated difficult intubation, preoperative hypotension, jaundice and patients undergoing gut preparation prior to surgery. Thus, 130 patients were randomized in their respective groups but during data collection further 10 patients were excluded and the final analysis was done on 120 patients. (Figure 1)

The demographic data i.e., age, weight, gender and ASA physical status of patients and mean duration of surgery were comparable amongst the groups ($p>0.05$. Mean duration of surgery in group T was 37.60±4.26 min, in Group P was 38.92±3.96 mins and in Group E it was 38.90±4.55 mins. ($p=0.3982$; Table 1)

The mean induction time in group T was 49.85±2.54 sec, 43.45±2.66 sec for group P and 52.67±2.11 sec for group E ($p<0.0001$). Recovery time (steward recovery score of 6) in group P was 5.87±0.23 mins, 8.96±0.28 mins in group T and 6.97±0.28 mins in group E ($p<0.0001$; Table 2).

The increase in HR at 2 min post induction was 31.65% in group T, 22.98% in group E and 16% in group P. There after it decreased in all the groups with becoming nonsignificant at 6 min but the group T patients still had 10% increase than the baseline values. Only in group P 7% decrease in heart rate at 1 min post induction was seen. ($p<0.0001$; Table 3).

The MAP decreased in all the groups post induction and it was 11% in group P, 7% in group T and 3% in group E at 1 min and there after it increased significantly in group T and E to 20%and 12% respectively at 2 min post induction. There after over next 8 min it returned to baseline values but the rise was always significantly more in group T followed by group E with group P having least difference from the baseline values. ($p<0.0001$; Table 4)

Amongst the three groups least incidence of transient confusion was in the propofol group (5%) compared to 10% in both group T and group E. There were no patients with nausea in group P compared to 10% with thiopentone and 12.5% with etomidate. 7.5% patients in both group T and P had shivering, whereas only 5% patients in group E had shivering Sore throat incidence was almost similar in all three groups and was 5% in both group T group P and 7.5% in Group E. Total incidence of adverse effects was highest with Group E (35%) compared to 32.5% in Group T and 17.5% in Group P($p>0.05$; Figure 2)

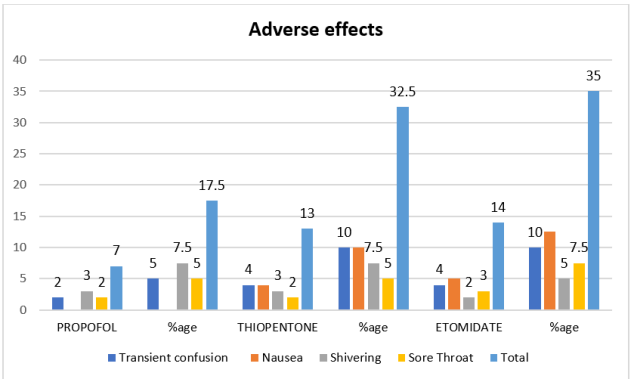

Fig. 2: Adverse effects of induction agents

4. Discussion

Peri-induction period in anaesthesia is a crucial time where hypotension or hypertension episodes may occur with disastrous consequences. Various factors like increasing age ≥ 50yrs, preoperative physical status ≥ASA II, associated comorbidity, baseline hypotension/hypertension are non-modifiable factors for its occurrence whereas choice of induction agent used can partially modify the degree of intubation response hence produced. Lethal sequalae such as pulmonary edema, cerebrovascular hemorrhage, myocardial infarction can develop as a consequence of pressor response to laryngoscopy or it can result in hypoperfusion induced myocardial ischemia and acute kidney injury due to inappropriate selection of induction agent.

Thiopentone sodium is the oldest induction agent amongst the ones being studied in this study. It's known to increase the HR by 10-36% after peripheral vasodilation and

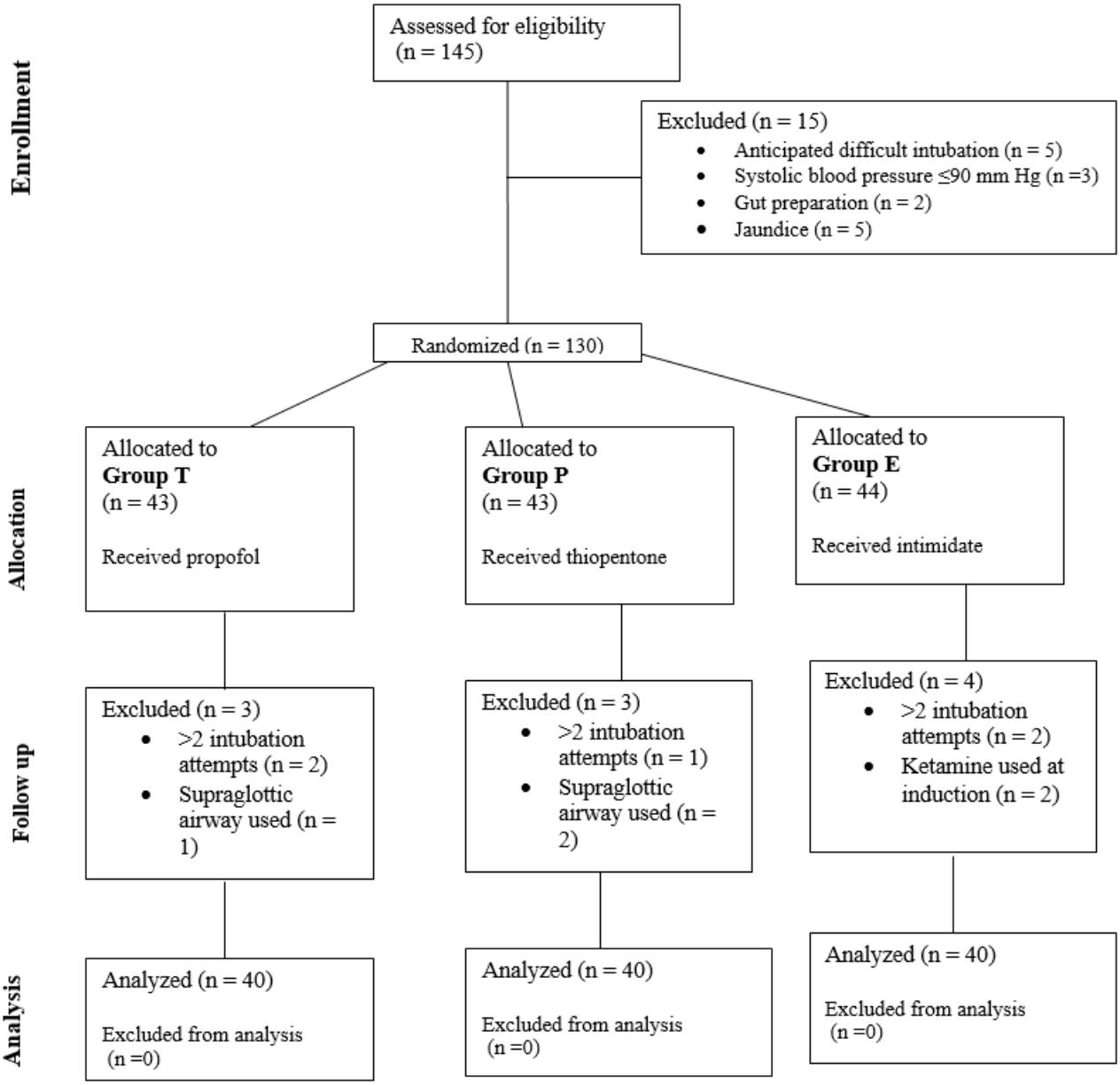

Fig. 1: Consort diagram

Table 1: Demographic profile & ASA status

N=40 in each group	Group P (Mean ± SD)	Group T (Mean ± SD)	Group E (Mean ± SD)	p-Value
Age (yrs.)	40.10±14.54	42.40±13.61	45.82±13.79	0.1958
Weight(kg)	60.37±5.63	61.8±6.04	59.70±5.44	0.2572
Male	9	5	8	
Female	31	35	32	
ASA physical status				
I	21	24	20	0.6463
II	19	16	20	

Table 2: Induction time and recovery time

Groups N=40	P Mean ±SD	T Mean ±SD	E Mean ±SD	P v s T	P vs E	T vs E	P value
Induction time (sec	43.45 ±2.66	49.85 ±2.54	52.67 ±2.11	<0.0001	<0.0001	<0.0001	0.000*
Recovery time (minutes)	5.87± 0.23	8.96 ±0.28	6.97 ±0.28	<0.0001	<0.0001	<0.0001	0.000*

*ANOVA one way

Table 3: Heart rate (HR) (beats per minute)

Time (min)	Group P N=40	%Change	Group T N=40	%change	Group E N=40	%change	p-value
Baseline (0)	81.57±12.02		84.35±12.78		82.12±12.71		0.6306
1	75.27±13.13	-7.72	93.07±13.22	10.34	84.8±13.10	3.25	<0.0001
2	94.65±8.41	16.02	111.05±8.43	31.65	101±8.73	22.98	<0.0001
3	89.57±12.56	9.8	104.5±10.93	23.88	92.72±12.49	12.9	<0.0001
4	87.65±8.76	7.44	101.6±8.25	20.45	90.32±10.16	9.98	<0.0001
5	85.05±12.09	4.25	98.2±12.33	16.41	87.5±14.05	6.54	<0.0001
6	84.3±9.33	3.34	92.92±8.94	10.16	86.32±9.48	5.11	0.0002
10	82.97±14.35	1.71	87.17±13.45	3.34	84.6±13.25	3.01	0.3964
15	80.72±12.95	-1.04	86.07±12.13	2.04	81.27±11.09	-1.03	0.1036
20	81.3±12.97	-0.33	81.27±11.79	-3.64	84.57±10.69	2.98	0.3712
25	83.72±13.36	2.63	84±12.41	-0.41	84.92±12.99	3.4	0.912
30	85.07±12.74	4.29	83.05±13.78	-1.54	84.72±13.43	3.16	0.7737
35	83.37±7.02	2.2	83.42±6.75	-1.1	82.12±7.31	0	0.6457
40	81.32±8.00	-0.3	82.4±7.34	-2.31	83.51±7.51	1.23	0.4405
POSTOP							
5	81.02±14.54	-0.67	81.9±10.92	-2.9	80.97±9.74	-1.4	0.9284
10	80.92±10.64	-0.79	82.2±12.70	-2.54	81±13.14	-1.36	0.8749
15	82.35±13.46	0.95	82.47±13.23	-2.22	83.6±11.61	1.79	0.8934
20	83.02±13.50	1.77	82.97±11.97	-1.63	80.62±11.17	-1.82	0.6149
25	78.97±13.92	-3.18	80.97±11.06	-4	83.17±11.56	1.27	0.3211
30	85.7±12.39	5.05	87.47±10.61	3.7	78.9±12.23	-3.92	0.0641

Table 4: Mean blood pressure (MBP) (mmHg)

Time(min)	Group P	% Change	Group T	% Change	Group E	% Change	p-value
Baseline (0)	86.57±5.99		87.42±6.29		86.25±5.29		0.6608
1	77.07±5.45	-10.97	81.65±5.58	-6.6	83.7±6.18	-2.95	<0.0001
2	90.2±3.80	4.18	104.62±4.03	19.67	96.35±4.78	11.71	<0.0001
3	87.45±5.45	1.01	97.92±5.89	12.01	92.72±6.37	7.5	<0.0001
4	86.77±3.43	0.23	96.05±4.28	9.86	91.9±4.57	6.55	<0.0001
5	87.77±5.36	1.38	90.5±5.96	3.51	89.07±5.53	3.27	0.1062
6	84.82±3.72	-2.02	88±4.15	0.65	86.77±4.60	0.6	0.0042
10	83.57±4.79	-3.46	87.77±5.88	0.4	85.9±6.62	-0.4	0.0075
15	85.22±6.74	-1.55	87.37±5.29	-0.05	86.62±6.52	0.43	0.305
20	86.92±5.24	0.4	88.02±6.46	0.68	87.37±6.26	1.3	0.72
25	86.1±5.14	-0.54	86.25±6.05	-1.34	87.37±5.92	1.3	0.5623
30	87.47±5.87	1.03	87.42±5.45	0	86.47±5.53	0.26	0.6771
35	88.35±2.66	2.05	87.35±2.83	0	86.79±3.25	0.6	0.0578
40	87.42±2.53	0.09	87.97±3.46	0.62	87.38±3.75	1.31	0.6698
Post Op							
5	90.62±5.00	4.67	91.12±6.22	4.23	91.15±5.42	5.68	0.8959
10	88.62±5.94	2.36	90.57±5.54	3.6	88.42±4.94	2.52	0.1665
15	91.95±5.46	6.2	91.1±4.82	4.2	91.4±5.93	5.97	0.7823
20	90.72±5.44	4.79	91.42±5.62	4.57	89.65±6.15	3.94	0.3925
25	92.57±5.71	6.93	89.62±5.09	2.51	89.9±5.65	4.23	0.0756
30	90.27±6.58	4.27	89.72±6.66	2.63	89.57±6.38	3.85	0.8839

may lead to increase in myocardial oxygen demand; thus, has to be used cautiously.[19] Etomidate though is considered safe for CVS but produces relatively light anesthesia for laryngoscopy, moreover the risk of adrenocortical suppression with 32% risk of myoclonus coupled with increased cost has put a check on its use as a preferred agent for induction.[20] Propofol decreases the MAP by 10-40% but in normal clinical range the cardiac contractility is maintained. The hemodynamic response is mostly observed after patient loses consciousness that is after 5-10 min of induction.[21]

We conducted this comparative study to find the induction agent out of thiopentone, propofol and etomidate which can be used in routine surgery with minimal side effects. Invariably most of the studies like our study have reported better induction and recovery profile with propofol followed by etomidate or thiopentone use, though very few studies have compared all three agents and vitals during induction, intraoperatively and postoperatively.

Similar results were observed by Mir et al. but Rolly et al., Mackenzie et al.[21–23] Mollick et al. and Edelist et al. found shorter time of induction (30-35 sec for both propofol and thiopentone).[11,24] These different results are largely due to different defined end points of induction as most of the studies have taken cessation of counting as ends point of induction, while others have used higher dose of 2.5mg/kg propofol for induction over 2 mg /kg used in our study.

Edelist et al. and Mackenzie et al. observed shorter recovery times with propofol and thiopentone as the mean time to response to verbal command was 4.6 to 4.8±0.45min for propofol and 6.6 to 9.6±0.74 min for thiopentone. The difference in timing could be as they have used crude method of time to spontaneous opening of eyes to command as compared to stewards score used in our study. Mir et al, Rosa et al and Boysen et al used these drugs in different subset of un intubated patients undergoing either ECT or MTP procedure on bag and mask ventilation.[22,25,26] Mir and Rosa et al. observed shorter recovery time of 6.5-7.4 min with propofol, 8.2 -9.4 min with thiopentone use and 7.5-10.7 min in etomidate group in patients undergoing ECT procedure.[22,26] Boysen used these drugs in patients undergoing termination of pregnancy and observed longer time of response to verbal commands in patients receiving 2.5mg/kg propofol as it was 7 min (range 3-11 min) with propofol followed by 6 min (2-13 min) with thiopentone 4 mg/kg and shortest time with etomidate 0.3mg/kg as it was 5.3(3-9min).[25] The steward score at this time was similar and was 4 in all the groups. They observed the patients till 60 min post extubation and made them perform coin counting after every 15 min and observed significantly better results in propofol group as they took 16.5 min over 22.5 min in etomidate group and 31 min in thiopentone group to perform these tests. Kern et al evaluated recovery profile in day care knee arthroscopies, with the research revealing faster recovery with propofol (9.2 min) compared to thiopentone (12.3min) keeping ability to open eyes on verbal stimulation as the end point.[27]

The hemodynamic profile measured as heart rate and blood pressure readings was done post induction in our patients. There was a brief period of fall of HR by 7% in propofol group followed by increase in all the groups but the rise was significantly more in thiopentone group over other groups. Boysen et al, Masoudifar et al. and Mollick MJH et al compared propofol with thiopentone or etomidate and observed no statistically significant change in HR with these drugs at induction.[11,25,28] McCollum et al., Price et al and Rolly G et al observed lower increase in heart rate with propofol(0-9%) than 9-14% rise seen with the use of thiopentone sodium at induction.[23,29,30] Mackenzie et al reported more increase in HR with the propofol group compared to thiopentone (15 beats/min vs 10.4 beats/min. This could be as the mean age of patients in their study was higher (41-47yrs) and they had reported more fall in blood pressure as compared to baseline, as they had used 2.5mg /kg dose of propofol.[21] Price et al studied cardiac index changes following induction and found that etomidate (0.29 mg/kg) lead to a fall in HR by 5%.[29]

Almost all researchers have observed decrease in MAP value from baseline values after propofol but the degree of this decrease varies amongst the studies. We observed 11% decrease in MAP with propofol and etomidate over around 20% decrease in thiopentone group over 10 min post induction period. Rolly G et al. observed 15% fall in blood pressure at 2 min post induction with no change in thiopentone group.[23] Mackenzie et al noticed that 55% (11 patients) had>20% fall in SBP at 2 min post induction as compared to 25% (5 patients) in thiopentone group.[21] McCollum et al reported 38% incidence of hypotension with 4% incidence of severe hypotension (>40 mm Hg fall) in propofol group over 20% incidence (6% severe hypotension) in thiopentone group.[30] Price et al in their study observed that mean arterial pressure fell by 4, 8 & 19% with thiopentone, etomidate and propofolrespectively.[29] Masoudifar et al also measured more hypotension in propofol group and it was 26.1% in Propofol group (6 of 23 patients) over 8% in Etomidate group (2 of 25 patients) (P = 0.09).[28] Mollick et al also observed almost 25% decrease in MAP with propofol over no fall in MAP with thiopentone sodium but the dose of thiopentone used was 4mg/kg which is less than used in our study.[11] Claeys et al reported that statistically significant decrease occurred in systolic and diastolic arterial pressures ; 2 min after induction (28% and 19%) and during infusion (30% and 25%).[31]

We observed the least incidence of various adverse effects in propofol group (17.5%) than 32.5% in thiopentone and 35% in etomidate group. Mir et al noticed 35% incidence of myoclonus by using etomidate and 3% with

propofol. They had used lower doses of these drugs so incidence of gag reflex, tears and coughing was more in their patients in all the groups as the patients were undergoing ECT. Edelist et al reported adverse effects in 38 per cent of the patients receiving propofol and 47 per cent of the patients receiving thiopentone.[24] Patients receiving propofol had more excitatory effects (musculoskeletal movement, hiccoughing) than did patients receiving thiopentone (p - 0.1). There were no significant differences in nausea and vomiting or injection site adverse experiences between groups adverse effects were found after the use of thiopental, etomidate and propofol in 7.5%, 9.07% and 5.1% of patients, respectively in the study by Djordjević et al.[32] Thus, the adverse effect like myoclonus is more in etomidate and cough and other effects more with thiopentone and these are least with the use of propofol. The primary requirement for an ideal anesthetic agent is the ability to cause cessation of consciousness without causing major hemodynamic fluctuations in vital parameters like heart rate and blood pressure. A fast recovery time is also desirable as it avoids the risk of post-operative respiratory depression.

Thus, in our study, propofol was associated with early induction, better hemodynamic profile and least adverse effects with early recovery hence we recommend its use in routine practice with a caution to measure the hemodynamic changes 10 min post induction when they are more commonly observed though they resolved by its own in our study. Propofol although decreases the blood pressure but it rarely causes myocardial dysfunction. Propofol is even known to cause protection against myocardial ischemic reperfusion injury (MIRI)possibly by increasing nitric oxide and reducing ET-1 & the inflammatory mediators. More studies are underway where high dose >6mg/kg propofol is being studied for myocardial protection during cardiac surgery. Thus, it is seen that though it decreases the blood pressure; the myocardial protection to this hypotension is there so the morbidity associated with this drug will be less.

There were some limitations of the study. We did not measure the depth of anesthesia, invasive blood pressure of the patients nor did we measure the serial glucocorticoid levels during the study.

5. Conclusion

Amongst propofol, thiopentone & etomidate, we recommend propofol as preferred agent for induction due to faster induction, better attenuation of intubation response, stable hemodynamic parameters, minimum side effects and faster recovery associated with its use.

6. Source of Funding

None.

7. Conflict of Interest

None.

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