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Original Article

Anaesthesia Section

Comparison of Induction Characteristics of two Anaesthetic Agents: Etomidate-lipuro and Propofol for Day Care Surgery

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ABSTRACT

Introduction: Induction of anaesthesia is the most critical stage of anaesthesia. Thus, an induction agent with less side effect should be used.

Aim: To compare the newer formulation of Etomidate in lipid formulation (Etomidate-lipuro) and propofol-lignocaine admixture in patients undergoing day care gynaecological surgery.

Materials and Methods: Hundred ASA I and II patients in the age group 18-60 years, scheduled for dilatation and curettage procedure were randomly allocated to receive either Etomidate-lipuro 0.2 mg/kg or propofol 2 mg/kg. Both groups received intravenous midazolam 0.05 mg/kg and fentanyl 2 µg/kg as premedication. After induction with the desired agent titrated to Response Entropy (RE) 40, the time to achieve values to 40 (RE 40 time) were measured. Heart Rate (HR), Mean Arterial Pressures (MAP) were recorded at baseline, at induction and every minute for 15 minutes. Incidence of pain at injection site, myoclonus, apnea and thrombophlebitis were observed. Statistical analysis was done using Chi-square test and Student unpaired t-test.

Results: Haemodynamic parameters (HR and MAP) were well maintained with etomidate. There was a significant decline in HR and MAP with propofol as compared to etomidate ($p<0.001$). Onset of anaesthesia (Time to achieve RE 40) was 81.22±2.79 s and 77.60±230 s in propofol and Etomidate-lipuro respectively ($p<0.001$).

The incidence of pain was more with propofol-lidocaine admixture (40%) as compared to no pain with etomidate ($p<0.05$). None of the patients had myoclonus and postoperative thrombophlebitis in our study. Incidence of postoperative nausea was high with etomidate use (22%) than with propofol (14%) but statistically insignificant ($p>0.05$). None of the patient in our study had vomiting. Incidence of apnoea was higher with propofol (58%) as compared to etomidate (14%) ($p<0.001$).

Conclusion: Etomidate-lipuro can be a valuable induction agent due to its haemodynamic stability and lesser side effect profile for day care surgery.

Keywords: Entropy, Etomidate-lipuro, Haemodynamics, Propofol, Side effects

INTRODUCTION

The administration of a suitable drug by intravenous route for induction of anaesthesia is an important element of anaesthesia management. Currently, various anaesthetic induction agents with wide margin of safety are available. Propofol, a nonopioid, nonbarbiturate, sedative hypnotic agent has gained widespread popularity as an intravenous induction agent. It is highly lipophilic which accounts for its rapid and smooth onset of action. However, it is found to be the most profound cardiovascular depressant agent and causes pain at the injection site [1]. These drawbacks prompted the search for an intravenous induction agent devoid of these adverse effects. Etomidate, an imidazole derivative with stable haemodynamic profile, minimal respiratory depression and pharmacokinetics enabling rapid recovery can be a useful induction agent. However, due to adverse effects like pain on injection, thrombophlebitis, histamine release, haemolysis, myoclonus and nausea/vomiting the drug never became popular as induction agent [1,2]. These side effects were attributed to solvent propylene glycol. Newer formulation of etomidate contains medium chain triglyceride and soya bean (Etomidate-Lipuro) has been documented to reduce these untoward effects [3,4]. Hence, this study was devised to evaluate and compare the effects of newer formulation of etomidate and propofol with added lignocaine on haemodynamics (MAP and HR) and onset time as a primary outcome and side effects like pain on injection, myoclonus and thrombophlebitis as secondary outcome in patients undergoing day care gynaecological surgery.

MATERIALS AND METHODS

This prospective, randomised controlled, double blind trial (CTRI /2017/09/009613) was conducted after obtaining institutional ethics committee permission and written informed consent from the patients. Hundred adult females of American Society of Anaesthesiologists Physical Status (ASA PS) I and II and aged between 18 and 60 years scheduled to undergo elective dilatation and curettage during the period Nov 2010 to Nov 2012 were included. Patients refusing to participate, with known allergy to any of the study drug, history of seizure disorder, presence of primary and secondary steroid deficiency were excluded from the study. A computer generated randomisation table (Microsoft® Excel 2007 software, Microsoft Corp., Redmond, WA) was used to assign each patient into either Group “A” (patients receiving propofol) or Group “B” (patients receiving Etomidate-lipuro). For ensuring blinding, randomly allocated coded syringes of drugs containing 10 mL of either etomidate-lipuro 2 mg/mL (B. Braun) or propofol 1% (Neon) 10 mg/mL mixed with lignocaine 1mg/mL were prepared by an anaesthesiologist who was not involved either for induction or for monitoring during intraoperative and postoperative periods. A detailed preanaesthetic evaluation was done including airway assessment, clinical history, general and systemic examination and routine biochemical investigations. After adequate fasting confirmed, 20 G intravenous canula secured in a large peripheral vein of hand in operation theater and preloading was done with Ringer’s lactate 200 mL which infuse over 10 minutes. All Standard monitors including electrocardiogram, pulse oximeter, noninvasive blood pressure was attached. The onset time and depth of anaesthesia was

monitored using the entropy module (GE Healthcare) and recorded. The entropy sensor was appropriately applied on the forehead. All patients were premedicated with midazolam 0.05 mg/kg IV two minutes and fentanyl 2 µg/kg one minute prior to induction. During induction, the study drugs were injected slowly over a period of 60 seconds and were titrated until the target level of RE 40 was obtained and lithotomy position was given 40 seconds following induction. Anaesthesia was maintained on 50% nitrous oxide in oxygen and sevoflurane (1%) using face mask on Magill circuit with attached capnometer (sevoflurane was stopped when dilatation and curettage procedure was over). Haemodynamic parameters were noted every single minute for 15 minutes. Pain on injection was measured at the time of injection of study drug using 4 grade scale: 0-No pain, 1-Verbal complaint of pain, 2-Withdrawal of arm, 3-Both verbal complaint and withdrawal of arm.

The incidence and degree of myoclonus occurring at any time during the procedure was recorded using myoclonus scale as: 0-No myoclonic movement; 1-Minor myoclonic movement; 2-Moderate myoclonic movement; 3-Major myoclonic movement. The incidence of apnoea was also recorded. Patients, who went into apnoea for more than 15 seconds, were ventilated with positive pressure using bag and mask till return of spontaneous ventilation. Patients with blood pressure below 20% of preinduction value and HR below 50 beats per minute were treated with ephedrine and atropine, respectively. Patients were shifted to the Post Anaesthesia Care Unit (PACU) after complete clinical recovery where they received nasal oxygen supplementation, and were monitored for haemodynamic parameters and adverse effect like nausea/vomiting if any every 30 minutes for two hours till transferred to the surgical ward. In the ward injection site was assessed for any inflammation, oedema and erythema for the presence or absence of thrombophlebitis after 24 hours.

STATISTICAL ANALYSIS

The association was statistically analysed for age, weight, duration of surgery, incidence of apnoea, pain on injection scale and myoclonus scale, postoperative nausea and vomiting and ASA grades by applying chi-square test in both the groups. Pre and postinduction within group comparisons of quantitative parameters like HR, MAP, time taken for RE 40 were done by using Students unpaired t-test. A p-value <0.05 was considered statistically significant.

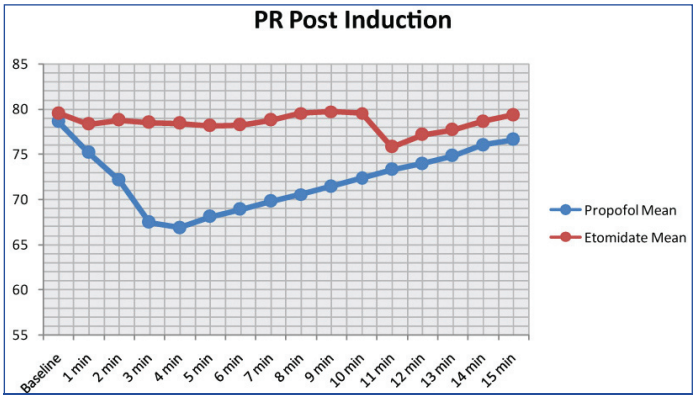
RESULTS

Both the groups were comparable with respect to age, weight, duration of surgery and ASA grades (p>0.05) [Table/Fig-1] Preoperative vitals (HR, SBP and MAP) were comparable in both groups. After premedication, statistically insignificant (p>0.05) fall in HR, Systolic Blood Pressure (SBP), Diastolic blood pressure (DBP), and MAP was noted in both the groups. After induction, fall in HR was noted in both the groups. In etomidate group HR almost returned to preinduction value after eight minutes but not in propofol group where it was always less than the preinduction value [Table/Fig-2]. There was a fall from baseline values for SBP beginning from the time of injection till 10 minutes of procedure in both the groups. However, on analysing the magnitude of fall, propofol group exhibited a greater fall compared to etomidate group. The mean fall of SBP in etomidate group (3%) was approximately one fourth of that seen in propofol group (13%) at 4th (p<0.001) minute. This fall in SBP was found to be statistically significant (p<0.001) between the groups till 10th minute as shown in [Table/Fig-3]. Similarly, a fall in DBP from baseline was noted in both the groups. The fall in DBP was much sharper in propofol group as compared to etomidate group. At fourth minute the fall in DBP was 22% in propofol group against 9% in etomidate group [Table/Fig-4]. Likewise, a much steeper fall in MAP was observed in propofol group as compared to etomidate group (p<0.01) [9,10]. At fourth minute postinduction the fall in MAP was 20% in group A as compared to 9% in group B (p<0.01). Surgical stimulus also failed to increase MAP which remained below the baseline throughout the procedure [Table/Fig-5]. Induction time (time to reach RE 40)

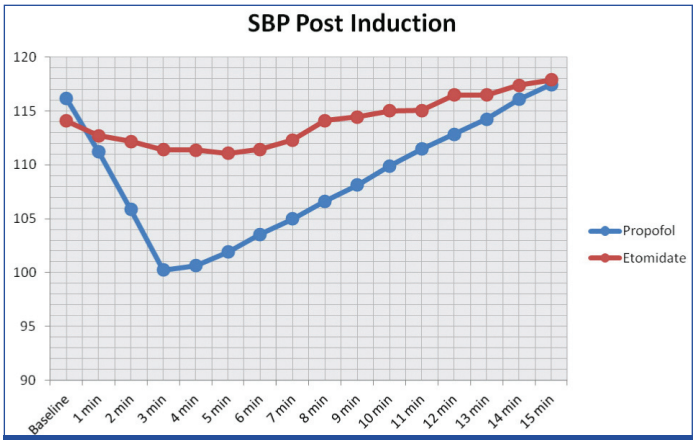
Variable	Propofol (Mean±SD)	Etomidate (Mean±SD)	Unpaired t-test	p-value
Age (years)	38.70±5.03	40.44±6.49	1.499	0.137
Weight (kg)	51.34±5.22	52.90±5.19	1.499	0.137
Duration of surgery	22.30±1.50	22.60±1.69	0.938	0.350

St Group		ASA Grade		Total (ASA I+ASA II)
		I	II	
Propofol	Count	42	8	50
	Percent	84.0%	16.0%	100.0%
Etomidate	Count	41	9	50
	Percent	82.0%	18.0%	100.0%
Total	Count	83	17	100

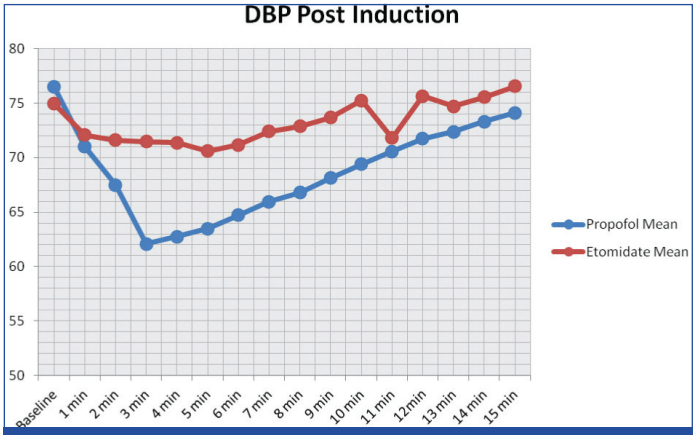
[Table/Fig-1]: Demographic data.
No association was found significant for baseline variables (p>0.05)



[Table/Fig-2]: Changes in heart rate after induction.

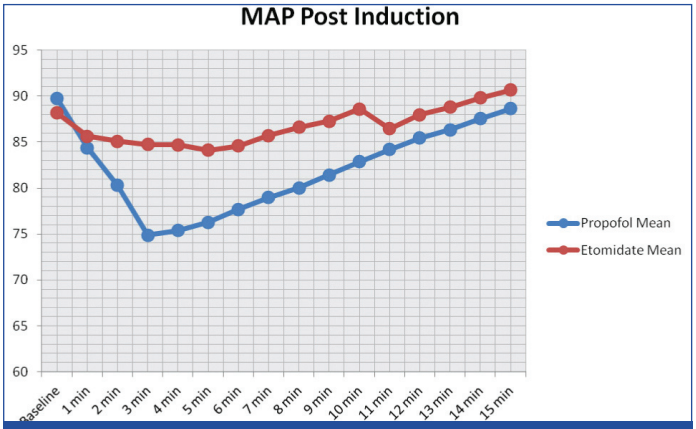


[Table/Fig-3]: Changes in systolic blood pressure with respect to time.

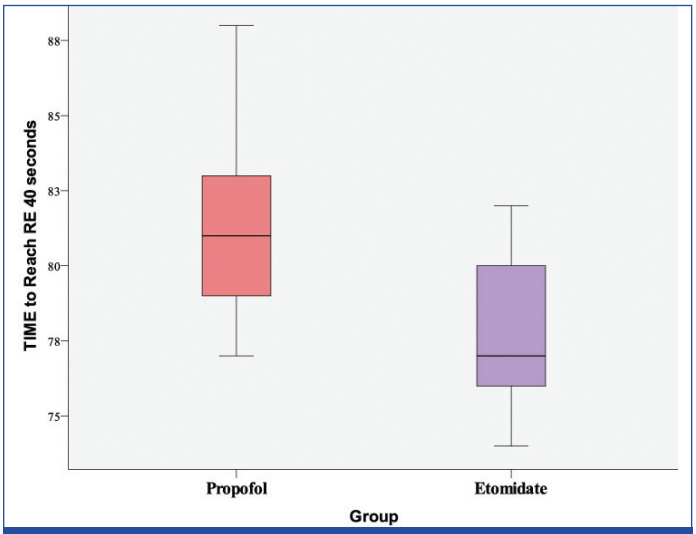


[Table/Fig-4]: Changes in diastolic blood pressure with respect to time.

was 81.22±2.88 s in propofol and 77.60±2.30 s in etomidate-lipuro group (p=0.000) [Table/Fig-6]. The incidence of injection pain was significantly higher in patients who received propofol. The incidence was (40%) in propofol and (0%) in etomidate-lipuro group (p<0.01). The distribution of pain scores is shown in [Table/Fig-7]. Higher incidence of apnoea was seen in propofol group (58%) compared to etomidate (14%) (p<0.001) [Table/Fig-7]. None of patients in our study group showed myoclonus, thrombophlebitis and hence were comparable. The incidence of postoperative nausea and vomiting was higher in etomidate (22%) group compared to propofol (14%), however, this difference was statistically not significant (p>0.05) [Table/Fig-7].



[Table/Fig-5]: Changes in mean arterial pressure with respect to time.



[Table/Fig-6]: Onset of action (Entropy 40) with propofol and etomidate.

Side effects	Propofol GR, n (%)	Etomidate, n (%)	p-value
Pain	20 (40%)	00 (0%)	<0.01
Apnoea	29 (58%)	07 (14%)	<0.001
Nausea and vomitting	07 (14%)	11 ((22%)	0.435

[Table/Fig-7]: Comparison of side effect profile of the two drugs.

DISCUSSION

In the present study, induction characteristics of two induction agents etomidate-lipuro and propofol were studied in patients undergoing day care gynaecological procedures. Induction dose of 0.2 mg/kg for etomidate and 2 mg/kg for propofol was used based on the literature and entropy monitoring [2]. Entropy has emerged as a useful device to monitor depth of anaesthesia. Values between 40 to 60 are recommended for adequate depth of anaesthesia. Unlike previous studies, where dose of induction drug required to reach entropy 40 was calculated, we studied the time required to achieve entropy level 40 as we wanted to compare the onset time of recommended doses of both induction agents [5]. Although propofol with its rapid onset of action is the gold standard drug in day care procedures, onset time in the present study was found to be similar in both the groups 81.22±2.88 s in propofol and 77.60±2.30 s in etomidate-lipuro (p≥0.5). Haemodynamic stability is the most desirable property of an induction agent. In the present study, propofol was associated with significant fall in HR, systolic, diastolic and MAP due to its direct myocardial depressant action, reduction of sympathetic nervous system activity and inhibition of baroreflex response [6]. On the other hand, lesser decline in HR and blood pressure associated with etomidate is due to its lack of effect on sympathetic nervous system, baroreceptor reflex system, myocardial depression even in patients with moderate cardiac dysfunction [2,6-8]. Propofol is associated with high incidence of pain on injection (28-90%). Despite addition of lidocaine, the incidence of pain on injection remains unacceptably high. It could be due to endothelial irritation, osmolality differences, and the activation of pain mediators, which can be reduced by lignocaine pretreatment [9]. Hence propofol premixed with lignocaine was used in the present study. In the present study propofol premixed with lignocaine was found to be associated with more pain on injection than etomidate (p<0.0006). Injection pain of mild (30%) to moderate (10%) severity was observed in 40% of patients in propofol group as compared to no pain (0%) in etomidate group. Lack of injection pain with etomidate could be due to replacement of propylene glycol with medam chain triglyceride as documented by Safavi M et al. In their study 60% of patients in etomidate with propylene glycol group experienced pain on injection which was alleviated with Magnesium sulphate and Lignocaine [9,10]. Additionally, low incidence of pain with Etomidate lipuro could be due to the concomitant use of fentanyl as premedication which decreases the pain with etomidate [2]. Incidence of myoclonus induced by etomidate induction has been reported to be as high as 50-80% which can be hazardous for the patients. A possible mechanism for myoclonus is transient disinhibition of subcortical structures during transition from consciousness to unconsciousness. Contrary to other studies, myoclonus was not observed in our patients in any of the groups. Low incidence with etomidate could be due to pretreatment with higher doses of midazolam (0.05 mg/kg) and fentanyl [2 µg/kg] which have been studied to reduce the incidence of myoclonus [11,12]. Do SH et al observed lower incidence and less severe myoclonus in slow injection group (S) (0.3 mg/kg over 2 minutes) than fast injection group (F) (0.3 mg/kg over 10 seconds) (28% vs 84%) [13]. Higher incidence myoclonus after etomidate administration in males compared to females was documented by Kelsaka E et al in their study [14]. Thus combined effect of higher doses of premedication i.e. midazolam and fentanyl, slower injection rate and female sex contributed 0% incidence of myoclonus in our study population [2,9,10].

Postoperative thrombophlebitis, leads to patient discomfort, increases hospital stay and morbidity. Venous sequelae (phlebitis and thrombophlebitis) are very common with etomidate in Propylene Glycol (hypnomidate) due to hyperosmolarity (4900 mosmol/L) and unphysiological pH.5 [1,2,10,15]. Eight cases of venous complications associated with etomidate in propylene glycol use were reported by Logan Kosarek et al [15]. Thrombophlebitis (venous sequelae) were not observed with the use of etomidate in lipid formulation in any of our patients in both the groups during 24 hours postoperatively.

In our study incidence of apnoea was more in propofol group (58%) compared to etomidate group (14%), (p<0.001). However, none of the patients required Positive Pressure Ventilation (PPV) and oxygen saturation never reduced below 95% in both the groups. Lesser incidence of apnoea with etomidate can be partly explained by the finding that etomidate produces CO_2 independent stimulation of ventilation [16,17].

We observed a higher incidence of postoperative nausea with etomidate (22%) as compared to propofol (14%), which was statistically not significant (p<0.05) [2,18].

LIMITATION

Although etomidate is known to cause adrenal suppression, study of Adrenocortical suppression was not a part of our study. We did not include this parameter in our study as effect of single bolus dose of etomidate on adrenal behaviour is not clear. There have been studies showing surgical stress overcomes the slight inhibitory effect of single dose of etomidate on adrenal function as well as studies showing adrenal inhibition for 48 hours with etomidate use which can be compensated by systemic steroids during this period [19]. But further studies need to be carried out. For day care procedures study of recovery characteristics (not done in our study) should be done.

CONCLUSION

From our study, we can conclude that etomidate-lipuro can be a suitable induction agent in day care surgeries due to its stable haemodynamic and lesser side effect profile and therefore should be welcomed for future use.

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